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Assessment Group's Report

Devices for remote continuous monitoring of people with Parkinson's disease

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Edward Cox (Research Fellow in Health Economics) contributed to the protocol, developed the economic model, contributed to the writing of the cost-effectiveness sections of the report and performance of the economic analysis.

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Mark Simmonds (Senior Research Fellow and Statistician) contributed to the protocol, undertook analyses using the individual patient data supplied by Global Kinetics Corporation and oversaw the conduct and writing of the clinical effectiveness sections and takes joint responsibility for the report as a whole.

Note on the text

This report does not contain any confidential information.

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ABSTRACT

Background

Parkinson's disease is a brain condition causing a progressive loss of coordination and movement problems. Around 145,500 people have Parkinson's disease in the UK. Levodopa is the most prescribed treatment for managing motor symptoms in the early stages. Patients should be monitored by a specialist every 6 to 12 months for disease progression and treatment adverse effects.

Wearable devices may provide a novel approach to management by directly monitoring patients for bradykinesia, dyskinesia, tremor and other symptoms. They are intended to be used alongside clinical judgement.

Objectives

To determine the clinical and cost-effectiveness of five devices for monitoring Parkinson's disease: Personal Kinetigraph (PKG), STAT-ON, Kinesia 360, KinesiaU and PDMonitor.

Methods

We performed systematic reviews of all evidence on the five devices, outcomes included: diagnostic accuracy, impact on decision making, clinical outcomes, patient and clinician opinions and economic outcomes. We searched MEDLINE and 12 other databases/trial registries to February 2022. Risk of bias was assessed.

Narrative synthesis was used to summarise all identified evidence, as the evidence was insufficient for meta-analysis. One included trial provided individual-level data, which was re-analysed.

A de novo decision analytic model was developed to estimate the cost-effectiveness of PKG and Kinesia 360 compared to standard of care (SoC) in the UK NHS over a 5-year time horizon. The base case analysis considered two alternative monitoring strategies: One-time use and routine use of the device.

Results

Fifty-seven studies of PKG, fifteen of STAT-ON, three of Kinesia 360, one of KinesiaU and one of PDMonitor were included.

There was reasonable evidence to suggest that PKG can accurately measure bradykinesia and dyskinesia, leading to treatment modification in some patients, and a consequent improvement in clinical outcomes when measured using the Unified Parkinson's Disease Rating Scale (UPDRS).

The evidence for STAT-ON suggested it may be of value for diagnosing symptoms, but there is currently no evidence on its clinical impact. The evidence for Kinesia 360, KinesiaU and PDMonitor is insufficient to draw any conclusions on their value in clinical practice.

The base case results for PKG compared to SoC for one-time and routine use resulted in incremental cost-effectiveness ratios (ICERs) of £67,856 and £57,877 per quality-adjusted life year (QALY) gained, respectively, with a beneficial impact of the PKG on UPDRS domains III and IV. The ICER results for Kinesia 360 compared to SoC for one-time and routine use were £38,828 and £67,203 per QALY gained, respectively.

Limitations

The evidence was limited in extent and often low quality. For all devices except PKG there was little to no evidence on the clinical impact of the technology.

Conclusions

PKG could reasonably be used in practice to monitor patient symptoms and modify treatment where required. There is too little evidence on STAT-ON, Kinesia 360, KinesiaU or PDMonitor to be confident that they are clinically useful.

The cost-effectiveness of remote monitoring appears to be largely unfavourable with ICERs in excess of £30,000 per QALY across a range of alternative assumptions. The main driver of cost-effectiveness was the durability of improvements in patient symptoms.

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PLAIN ENGLISH SUMMARY

Parkinson's disease is a brain condition causing loss of coordination and movement problems. Levodopa is the most prescribed treatment for early disease. Patients should be seen by a specialist every 6 to 12 months to assess their treatment needs. Wearable devices (like smart watches) may aid management by directly monitoring patients for disease symptoms including tremor and slowness of movement (bradykinesia), or side effects of treatment like involuntary movement (dyskinesia).

This assessment considered the clinical and economic value of five wearable devices: Personal Kinetigraph (PKG), STAT-ON, Kinesia 360, KinesiaU and PDMonitor. We searched medical databases to find all studies of the five devices. We assessed the quality of these studies and reviewed their results.

We found 77 studies of the devices. There was evidence to suggest that PKG can accurately measure bradykinesia and dyskinesia, leading to treatment modification in some patients, and a consequent improvement in symptoms.

The evidence for STAT-ON suggested it may be of value for diagnosing symptoms, but there is currently no evidence on its clinical value. There was insufficient evidence for Kinesia 360, KinesiaU and PDMonitor to draw any conclusions.

An economic analysis was conducted to investigate whether using any of these technologies is economically viable. The economic analysis found that the quality of life benefits generated by remote monitoring devices were small relative to the additional costs of implementing them in the NHS. As such, none of the remote monitoring devices were good value for money when compared with the current standard of care.

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SCIENTIFIC SUMMARY

Background

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). There are around 145,500 people living with Parkinson's disease in the UK. The risk of developing the disease increases sharply with age.

Levodopa is the most prescribed treatment for managing the motor symptoms of Parkinson's disease in the early stages. However, it may be associated with significant motor complications, including response fluctuations and dyskinesias (involuntary movements). 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. Deep brain stimulation and levodopa–carbidopa intestinal gel can be considered in people with advanced Parkinson's disease whose symptoms do not respond adequately to best medical therapy.

NICE recommends that people with Parkinson's disease (PwP) 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.

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. Results of the monitoring are analysed remotely, and a summary provided to the specialist physician and/or to the patient. The data should be used to determine whether any changes in treatment regimen are desirable, in consultation with the patient.

This assessment considers only wearable remote monitoring devices that produce results with no input, or limited input, from the user. Five relevant devices were identified for consideration:

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

Objectives

To determine the clinical and cost-effectiveness of the five included remote monitoring devices in people with Parkinson's disease.

Methods

Systematic review

Systematic reviews were conducted following the general principles recommended in the Centre for Reviews and Dissemination (CRD) guidance and reported in accordance with the PRISMA statement.

Comprehensive searches of the literature were conducted to identify all studies relating to the use of the five remote continuous monitoring devices. MEDLINE, EMBASE, CENTRAL, ClinicalTrials.gov and other databases and registries were searched on 1st February 2022. Two reviewers independently screened all titles and abstracts.

All clinical studies of any of the five included devices, where used in PwP (of any severity or stage), were eligible for inclusion. The key comparator was clinical judgement of disease symptoms without the use of remote monitoring devices; however, included studies did not have to have a comparator group. Outcomes of interest included:

- Association and diagnostic accuracy between outputs of remote monitoring (such as bradykinesia score, dyskinesia score) and clinical measures (such as Unified Parkinson's Disease Rating Scale [UPDRS] score or clinical judgment of symptoms).
- All impacts on clinical decision-making: such as changes in therapy and dose modification.
- All clinical outcomes: such as UPDRS or Hoehn and Yahr scores, morbidities, and mortality.
- All patient, carer or clinician opinions on the technologies.

Data reported in publications were extracted by one reviewer and independently checked by a second reviewer. Study quality was assessed using suitable tools, such as QUADAS-2 for diagnostic accuracy studies and the Cochrane Risk-of-Bias tool for clinical trials.

Evidence was synthesised using a narrative synthesis approach. The results of data extraction were presented in structured tables and as a narrative summary. A broad thematic synthesis was used to identify key issues arising from the extracted evidence. Due to the diversity of reporting across studies, meta-analysis was not feasible for any outcomes. One clinical trial provided its individual participant data; this was re-analysed for this report.

Economic analysis

Two cost-effectiveness reviews were conducted: i) A review of remote monitoring devices for PwP, and ii) a review of existing decision models evaluating treatments for PwP. The titles and abstracts of all reports identified by the bibliographic searches were screened independently by two researchers. Key findings were summarised narratively.

A de novo decision analytic model was developed to assess the potential health gains and costs associated with implementing remote monitoring in the NHS. The base case analysis considers only the cost-effectiveness of PKG and Kinesia 360, which are compared on a pairwise basis with current standard of care (SoC). The cost-effectiveness of other remote monitoring technologies was explored in scenario analysis. Based on company information, real-world applications of PKG and expert clinical advice, the External Assessment Group (EAG) assessed two alternative monitoring strategies: i) One-time use: Remote monitoring implemented at model baseline and as a one-time aid to clinical assessment, and ii) Routine use: Remote monitoring used at every follow-up assessment (i.e., over the review period at regular intervals) to routinely assist clinical judgement.

The EAG model was based on a Markov model structure which sought to capture changes in the MDS-UPDRS domain scale scores, as an indicator of the level of symptom control associated with the use of remote continuous monitoring devices relative to SoC. These changes in MDS-UPDRS were informed by the clinical literature and were linked to health-related quality of life (HRQoL) to assess quality adjusted life year (QALY) changes associated with remote monitoring. The economic analysis also captured cost differentials between SoC and alternative remote monitoring strategies considering: (i) costs associated with using each remote monitoring device; (ii) changes in levodopa-equivalent medication use; (iii) implementation costs; (iv) follow-up consultations. The costs applied were independent of MDS-UPDRS scores modelled. Changes in levodopa-equivalent medication were, however, informed by the relevant clinical effectiveness literature so as to align with the applied treatment effects.

Clinical Effectiveness Results

Seventy-seven studies of clinical effectiveness were included in the systematic review.

There were 57 studies of PKG. The diagnostic accuracy studies suggested that PKG has good accuracy for assessing bradykinesia, dyskinesia and tremor, but lower accuracy to detect sleep disturbance. Studies reporting changes in management found that PKG provided additional information leading to a change in the clinical management plan in 31.8% to 79% patients (depending on study), most commonly an increase in treatment dose.

One comparative trial provided individual participant data to the EAG. The results show that the use of PKG appears to improve UPDRS scores, particularly UPDRS III (by around 3.1 points) and UPDRS IV (by around 1.2 points). This is likely to be because PKG use is reducing time with bradykinesia (by 2.1 percentage points) dyskinesia (by 1.5 percentage points) and tremor (by 0.6 percentage points), although none of these reductions achieved statistical significance. The trial data suggested that PKG use predominately improves symptoms (particularly bradykinesia and UPDRS scores) in people who were not "in target" and whose condition was not adequately controlled. Other

trials reporting clinical outcomes were not comparative, but generally supported the evidence that PKG use improves UPDRS scores.

Patient opinion was broadly supportive of PKG use, particularly as a reminder to take medication. Patients mostly felt that PKG provided additional useful information on their symptoms (59% to 79% felt this), but clinicians were more equivocal; only 33% to 47% felt PKG provided additional information.

There were 15 included studies of the STAT-ON device. STAT-ON had high diagnostic accuracy to detect treatment "On-Off" times and bradykinesia, and high sensitivity, but lower specificity, to detect freezing of gait. There were no studies that presented evidence on the intermediate or clinical impact of STAT-ON.

There were 3 included studies for the Kinesia 360 motor assessment system. It had moderate to good diagnostic accuracy to detect bradykinesia, dyskinesia and tremor. Two small RCTs (64 patients) found some inconclusive evidence that Kinesia 360 improved UPDRS III and PDQ-39 scores when compared to standard management.

One small cohort study (16 patients) of KinesiaU motor assessment system was included. The EAG consider that this was too small to draw any meaningful conclusions.

For PDMonitor only one conference abstract and one small case study were included. The EAG consider that this was insufficient to draw any meaningful conclusions.

Cost-Effectiveness Results

Estimated changes in UPDRS associated with PKG, show that PKG is associated with small unfavourable changes in UPDRS domains I and IV. In consideration of these highly uncertain results, the base case analysis considered two alternative efficacy configurations for PKG: (i) an unrestricted analysis (considering all UPDRS domains); and (ii) a restricted analysis (considering only UPDRS domains III and IV).

The deterministic base case incremental cost effectiveness ratio (ICER)'s for PKG using a one-time use strategy was £67,856 and £202,363 per QALY for the restricted and unrestricted analysis, respectively. Considering a routine strategy, the deterministic base case ICER was £57,877 per QALY in the restricted analysis and £172,602 per QALY in the unrestricted analysis. The deterministic base case ICER's for Kinesia 360 using one-time use and routine remote monitoring strategies were £38,828 and £67,203 per QALY, respectively. Probabilistic results for PKG and Kinesia 360 aligned with the deterministic values.

Sensitivity analysis demonstrated that cost-effectiveness results were sensitive to assumptions regarding the durability of modelled treatment effects. Scenarios with low or zero waning of the treatment effect improved cost-effectiveness markedly. Results were otherwise broadly robust to a range of alternative assumptions and parameter inputs.

The EAG was not able to evaluate the cost-effectiveness of STAT-ON, KinesiaU or PDMonitor due to lack of comparative clinical effectiveness evidence. In a cost comparison (assuming a 5-year time horizon), modelled device costs were lowest for PKG provided three devices or less were ordered per annum, followed by KinesiaU, STAT-ON, Kinesia 360 and PDMonitor.

Discussion

This assessment includes a comprehensive investigation of diagnostic accuracy and clinical efficacy of remote monitoring devices for Parkinson's disease. The review used extensive database searches to identify all published evidence on the included technologies and followed rigorous recommended review methods to identify relevant publications, assess their risk of bias and undertake a narrative synthesis of the results.

The review identified a substantial literature on the diagnostic accuracy of PKG, and a smaller literature on clinical efficacy. Evidence for other remote monitoring devices was generally limited. PKG appears to accurately measure several symptoms of Parkinson's disease including dyskinesia, bradykinesia, tremor and treatment-related outcomes. PKG also appears to generate clinical benefits compared with clinical management alone, with improvements in UPDRS III and IV scores. However, the available evidence was generally low quality, particularly for diagnostic accuracy. This casts some doubt on the validity of the results reported in the identified studies.

The cost-effectiveness of remote monitoring appears to be largely unfavourable with ICERs in excess of £30,000 per QALY. Cost-effectiveness results were largely robust to alternative assumptions and parameter inputs. The key drivers identified were: (i) the direction and magnitude of changes on the UPDRS scale associated with remote monitoring strategies; (ii) the persistence in changes to UPDRS (treatment waning); and (iii) the number of devices requested (PKG).

Insurmountable limitations in the evidence base meant that the EAG were unable to assess the cost-effectiveness of STAT-ON, KinesiaU or PDMonitor. Comparative evidence for Kinesia 360 was also extremely limited and unlikely to be comparable with that used for PKG, thereby making comparisons problematic. This essentially limits comparisons across alternative monitoring devices to a cost-minimisation exercise, which necessarily implies strong assumptions about relative efficacy.

Conclusions

The EAG considers that the evidence for PKG shows that it could be of use in clinical practice, provided it can be made cost-effective. It provides useful information on key symptoms of Parkinson's disease, including bradykinesia, dyskinesia and tremor. The use of PKG leads to changes in treatment management for at least some patients, and consequent improvement in symptoms.

Although there is some promising evidence for STAT-ON and Kinesia 360, the EAG considers that the evidence is currently not sufficient to be confident that these technologies will produce clinical benefits for patients. The EAG considers that there is too little evidence for KinesiaU or PDMonitor to draw any conclusions as to their clinical value.

Almost all current evidence relates to patients receiving pharmacological therapy, mainly levodopa. The EAG notes that, at present, it is unclear whether PKG, or other technologies, offer any clinical benefit in other patients, such as those receiving advanced therapies.

Concerns about potential bias, together with the other limitations in the available evidence, means that cost-effectiveness estimates are highly uncertain. Key uncertainties relate to the magnitude and durability of treatment effects. The results of the economic analysis are largely unfavourable, with ICERs in excess of thresholds typically adopted by NICE.

Suggested research priorities

The primary research priority should be to conduct further studies into the clinical impact of remote monitoring devices. This should focus on expanding the evidence base for PKG and Kinesia 360, where there is currently limited evidence on clinical effects, as well as conducting studies of STAT-ON, KinesiaU and PDMonitor, where there is currently no evidence of clinical effects.

Any future studies of comparative effectiveness should address the methodological limitations of the current evidence, as identified by this report. These would preferably be RCTs with pre-specified outcome measures. Studies should be carefully designed to consider the most applicable remote monitoring schedules and settings, as there is significant potential for variation in how remote monitoring devices could be used in practice. Specific consideration should be given to longer-term routine use of remote monitoring devices; currently all evidence pertains to short-term applications. Future studies of remote monitoring devices for Parkinson's disease may also consider patients with early and advanced disease. There is currently no evidence in these populations for any device.

Implementing remote monitoring may have a range of resource consequences which are currently not fully understood and may impact significantly on cost-effectiveness. This may include impacts on health care professionals' time and administration of the devices, as well as risks such as loss, damage

or theft of devices. Where possible future studies should seek to address these uncertainties by collecting appropriate data on resource implications.

Collecting further diagnostic accuracy evidence is considered a lower priority, but could be useful for Kinesia 360, KinesiaU and PDMonitor, where evidence is lacking. Diagnostic accuracy studies should evaluate the accuracy of these technologies for measuring bradykinesia and dyskinesia. Care should be taken to ensure the reference standard is robust and at a low risk of bias. It may be helpful for such studies to compare the technologies to PKG.

Word count: 2384

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List of abbreviations

ADL	Activities of daily living
AIMS	Abnormal Involuntary Movements Scale
AS	Apathy Scale
AUC	Area under the curve
BDI	Beck Depression Inventory
BIS/BAS	Behavioural Inhibition Scale/Behavioural Activation Scale
BKS	Bradykinesia Score
BMT	Best medical treatment
CD/LD	Carbidopa/levodopa
CGI-I	Clinician Global Impression of Improvement
COMT	Catechol O methyl transferase
DBS	Deep brain stimulation
DKS	Dyskinesia Score
EAG	External Assessment Group
EQ VAS	EuroQol Visual Analogue Scale
ESS	Epworth Sleepiness Score
FDS	Fluctuations Dyskinesia Score
FS	Fluctuation score
GKC	Global Kinetics Corporation
HADS	Hospital Anxiety and Depression Scale
H&Y	Hoehn & Yahr
ICER	Incremental cost-effectiveness ratio
LED	Levodopa Equivalent Dose
LEDD	Levodopa Equivalent Daily Dose
MAO-B	Monoamine oxidase Type B
MDS-UPDRS	Movement Disorder Society-Unified Parkinson's Disease Rating Scale
MOCA	Montreal Cognitive Assessment
NMSQ	Non-Motor Symptom Questionnaire
NMSQuest	Non-Motor Symptom Questionnaire
PD	Parkinson's disease
PDCS	Parkinson's Disease Composite Scale
PDQ-8	Parkinson's Disease Questionnaire-8
PDQ39	Parkinson's Disease Quality of Life 39 Questions
PDSS	Parkinson's Disease Sleep Scale
PGI-I	Patient Global Impression of Improvement

PKG	Personal KinetiGraph
PSG	Polysomnography
PTB	Percent time in bradykinesia
PTD	Percent time in dyskinesia
PTI	Proportion of time immobile
PTOT	Percent time over target
PTT	Percent time tremor
PwP	People with Parkinson's disease
QUIP	Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease
ROC	Receiver operator characteristic (curve)
SENS PD	Severity of predominantly Non-dopaminergic Symptoms in Parkinson's Disease
SoC	Standard of care
STAI	State Trait Anxiety Inventory
SVM	Support Vector Machines
UDysRS	Unified Dyskinesia Rating Scale
UPDRS	Unified Parkinson's Disease Rating Scale
WOQ9	9-item Wearing-Off Questionnaire

Glossary

Area under the curve: Area under a receiver operator characteristic curve (for assessing diagnostic accuracy).

Bradykinesia: Slowness of movement.

Cost-effectiveness analysis: An economic analysis that converts effects into health terms and describes the costs for additional health gain.

Decision modelling: A theoretical construct that allows the comparison of the relationship between costs and outcomes of alternative health-care interventions.

Dyskinesia: Involuntary and uncontrollable movement.

False negative: Incorrect negative test result – number of diseased persons with a negative test result.

False positive: Incorrect positive test result – number of non-diseased persons with a positive test result.

Incremental cost-effectiveness ratio: The difference in the mean costs of two interventions in the population of interest divided by the difference in the mean outcomes in the population of interest.

Index test: The test whose performance is being evaluated.

Markov model: An analytic method particularly suited to modelling repeated events or the progression of a chronic disease over time.

Sensitivity: Proportion of people with the condition of interest who have a positive test result.

Specificity: Proportion of people without the condition of interest who have a negative test result.

True negative: Correct negative test result – number of non-diseased persons with a negative test result.

True positive: Correct positive test result – number of diseased persons with a positive test result.

1 BACKGROUND AND DEFINITION OF THE DECISION PROBLEM

1.1 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]

1.2 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.

1.2.1 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]

1.2.2 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]

1.3 Description of the technologies under assessment

People with Parkinson's disease (PwP) 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.

This assessment considers 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) were identified for consideration:

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

1.3.1 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 wrist-worn PKG watch/logger that continuously measures movement, over a period of at least 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 at least 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 for 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 states that the PKG is suitable for 70-80% of PwP, particularly managing patients remotely, managing complex patients and those being considered for (or already on) advanced therapy. The company does not recommend use of the technology for patients who have restricted movement (for example, patients confined to bed or wheelchair users) 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.

1.3.2 Kinesia 360 motor assessment system (Great Lakes Neurotechnologies)

The Kinesia 360 motor assessment system (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 bradykinesia, dyskinesia and tremor. Whilst the device can be worn at night, the motor sensors can record up to 16 hours of motion data continuously before they need to be recharged. Typical use involves wearing the sensors during the day and recharging/data upload overnight. 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.

Healthcare staff can be trained in Kinesia 360 in approximately 30 minutes.

1.3.3 KinesiaU motor assessment system (Great Lakes Neurotechnologies)

The KinesiaU motor assessment system (Great Lakes Neurotechnologies) measures tremor, slowness and dysKinesiaUsing a smartwatch and smartphone application. Patient symptoms can be monitored continuously during activities of daily living (iOS only as of February 2022) and discretely during standardized tasks (iOS and Android). Patients can view reports in real-time and healthcare professionals can view their patients' data remotely through the KinesiaU provider portal. 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. A number of new features are planned to be added to the KinesiaU system, including

additional data reports, enhanced patient diaries, electronic health record integration, patient medication reminders and continuous monitoring for Android smartwatches.

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.

Healthcare staff can be trained in KinesiaU in approximately 30 minutes.

1.3.4 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.

An "Induction and Usage Training" is offered to healthcare professionals, either in groups or in person, to help them understand the PDMonitor system. There is also a physician user manual for the physician tool.

1.3.5 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 PwP 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.

Training sessions last an hour and a half. Quick guides are provided for healthcare professionals and quick videos to understand how the system is configured. A complete graphical document is also provided with user cases, examples and how to interpret the report.

1.4 Populations and relevant subgroups

The population of interest is people with Parkinson's disease (PwP). The subgroups relevant to this appraisal are:

- 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.

Global Kinetics Corporation informed NICE that there are 34 hospitals across the UK using the PKG. However, use is limited by funding constraints within the care pathway (personal communication)[7]. PD Monitor is available in the UK and is currently in demo use at King's College, St George's and Belfast Trusts.[8] Kinesia 360 and STAT-ON are available in the UK,[9, 10] although there is no indication that they are currently being used in NHS practice. KinesiaU is not yet available in the UK.[11]

1.5 Comparators

The comparator is clinical judgement of symptoms and need for treatment modification, without the use of remote monitoring devices.

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 (UPDRS) – 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.

1.6 Care pathways

Management of Parkinson's disease depends on the stage of the disease. In the early or diagnosis stage patients may not require any medical treatment or will be managed with non-pharmacological

treatment, such as physiotherapy. The maintenance stage is when symptoms are controlled, perhaps by medication. Levodopa is the most prescribed treatment for managing the motor symptoms of Parkinson's disease, but dopamine agonists, MAO-B inhibitors or COMT inhibitors may also be used. Advanced Parkinson's disease is defined by the presence of more complex symptoms that significantly impact daily living, including anxiety, depression and dementia. In this stage levodopa may still be beneficial, but patients might be given deep brain stimulation or levodopoa-carbodopa intestinal gel.

It is important to regularly monitor PwP to assess disease progression and adverse effects of treatment. NICE recommends that PwP should be seen by a specialist every 6 to 12 months initially, then more often with increasing disease complexity (every 2 to 3 months), although this is often difficult because of the increasingly ageing population and demands on Parkinson's disease services.[12] The remote monitoring technologies considered in this assessment (see Section 1.3) have all been proposed as a means of supporting clinical and patient evaluation of symptoms.

This assessment evaluates whether remote continuous monitoring devices are effective and reliable for monitoring motor symptoms, tremors and sleep disturbance in PwP. 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 some in-person reviews (including remote management, remote appointments, and where a patient might be unable to attend in person).

1.7 Outcomes

Outcomes 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 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:

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 UPDRS, 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 was considered, including: sensitivity and specificity, measure of correlation, or results of regression models.

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.

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.

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 was expected that data would be unavailable for many of these outcomes. They are listed here to present a complete list of outcomes of interest.

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).

1.8 Aims and 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 1.3.

To achieve this, the following objectives were set:

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). If feasible and appropriate, 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 ASSESSMENT OF CLINICAL EFFECTIVENESS

2.1 Methods for reviewing clinical effectiveness

The systematic review was conducted following the general principles recommended in the Centre for Reviews and Dissemination (CRD) guidance and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[13]

2.1.1 Search strategies

Comprehensive searches of the literature were conducted to identify all studies relating to the use of the remote continuous monitoring devices PKG, Kinesia 360, KinesiaU, PDMonitor and STAT-ON for monitoring motor symptoms in PwP. An Information Specialist (HF) designed the search strategy in Ovid MEDLINE in consultation with the research team. The strategy consisted of terms for the population which were then combined with specific interventions of interest, or broader terms that reflect remote monitoring technologies. Text word searches for terms appearing in the title, abstract or keyword fields of database records were included in the strategy alongside searches of relevant subject headings. Date, language, and study design limits were not applied. The final MEDLINE strategy was adapted for use in all resources searched.

The searches were carried out on 1st February 2022. The following databases were 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 were searched for ongoing, unpublished, or grey literature: ClinicalTrials.gov; EU Clinical Trials Register; and the WHO International Clinical Trials Registry Platform. All search strategies are presented in full in Appendix 9.1.

Search results were imported into EndNote 20 (Clarivate Analytics, US) and deduplicated. As a supplementary search method, reference lists of relevant reviews were scanned in order to identify additional potentially relevant studies. Company submissions and company websites were also searched for additional relevant studies.

2.1.2 Selection criteria

Two reviewers (RW and NM) independently screened all titles and abstracts using Covidence systematic review management software. Full papers of any titles and abstracts that were thought to be relevant were obtained where possible and independently screened by the two reviewers according to the criteria below. Any disagreements were resolved by consensus or by consulting a third reviewer (MS). Conference abstracts were included where sufficient data were reported to confirm eligibility.

Population

People with Parkinson's disease (PwP).

Interventions

Five remote monitoring devices with CE marks (or in the process of seeking CE-marking) for monitoring motor and non-motor symptoms in PwP:

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

Comparators

Clinical judgement of disease symptoms without the use of remote monitoring devices, which may include the use of rating scales. Single arm studies without use of a comparator were eligible for inclusion.

Outcomes

See Section 1.7 for a full list of relevant outcomes.

Study designs

All study designs were eligible for inclusion, provided they reported evidence on the outcomes listed.

2.1.3 Scoping eligible studies

Studies that met the inclusion criteria were scoped in order to prioritise studies reporting the most relevant outcomes for full data extraction. Studies reported only as abstracts were not subject to full data extraction, but are tabulated in appendices.

2.1.4 Data extraction

A data extraction form was developed, piloted and finalised to data extract study and patient characteristics and eligible outcomes. Data were extracted by one reviewer and independently

checked by a second reviewer, with discrepancies resolved by discussion. Data from relevant studies with multiple publications were extracted and reported as a single study, where it was possible to determine that the publications included the same patients. The most recent or most complete publication was used in situations where we could not exclude the possibility of overlapping populations across separate study reports.

2.1.5 Quality assessment

The quality of the diagnostic accuracy studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool.[14] QUADAS-2 evaluates both risk of bias (associated with the population selection, index test, reference standard and patient flow) and study applicability (population selection, index test and reference standard) to the review question.

Risk of bias in RCTs was assessed using the latest version of the Cochrane risk of bias tool.[15] A tool for assessing the risk of bias of non-randomised studies was developed using relevant criteria as outlined in CRD's guidance on undertaking systematic reviews.[16]

Quality assessment was performed by one reviewer and independently checked by a second reviewer. Disagreements were resolved through discussion. Quality assessment was performed only for included studies with full publications. Conference abstracts were not quality assessed due to lack of information to merit a full assessment. Quality assessment was not performed for studies reporting association outcomes without reporting diagnostic accuracy.

2.1.6 Methods of data synthesis

The results of data extraction were presented in structured tables and as a narrative summary. A broad thematic synthesis was used to identify key issues arising from the extracted evidence, including key areas of agreement or disagreement across the included literature.

A statistical synthesis using meta-analysis was proposed in the protocol. However, due to the substantial diversity in study populations, conduct, and outcomes reported, it was not possible to combine any studies in meta-analyses. Therefore, a narrative and thematic synthesis approach was used throughout.

2.1.7 Analysis of individual participant data

One clinical trial of PKG has deposited its original trial data on a repository for reanalysis.[17] The authors of the study gave permission to the EAG to reanalyse the trial data, and have supplied it to the EAG.

The supplied data was checked, compared to the published results and reanalysed. Linear regression was used to analyse continuously distributed outcomes (e.g. UPDRS score) by considering the change from baseline to follow-up time for each outcome, and analysing the mean difference in change from baseline between PKG and non-PKG patients. Logistic regression was used for dichotomous outcomes (e.g. change in medication), analysing the odds ratio between PKG and non-PKG patients. Analyses were adjusted for potential confounding factors, chiefly number of clinical visits and duration of PD (see Section 3.3.4.1 for further details).

2.1.8 Methods for estimating quality of life

Health-related quality of life associated with disease severity was estimated. It was expected that measures of disease severity would 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 pragmatic review of utility studies was 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 RESULTS OF THE REVIEW OF CLINICAL EFFECTIVENESS

3.1 General summary of evidence

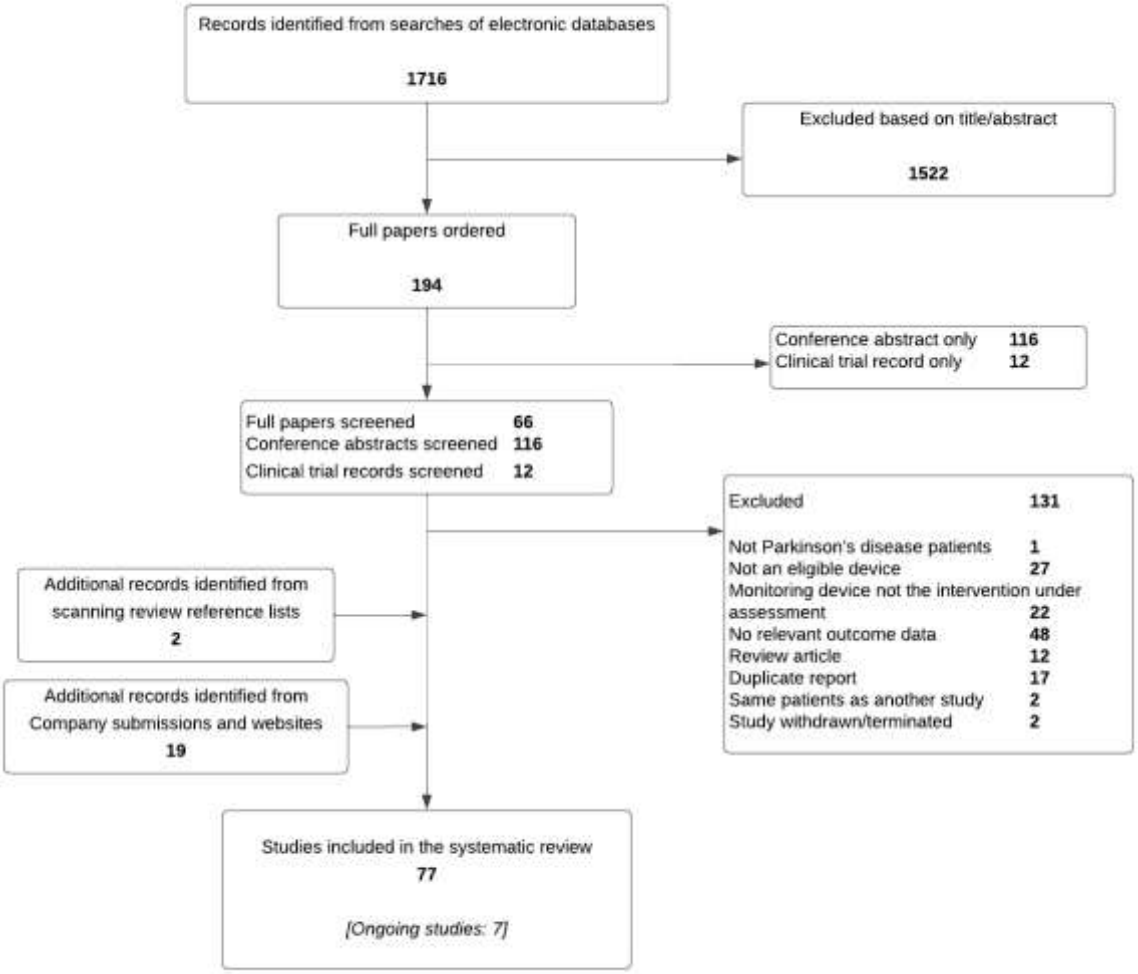
The literature searches of bibliographic databases identified 1716 references. After initial screening of titles and abstracts 194 were considered to be potentially relevant and ordered for full paper screening. Sixty-three studies were eligible for inclusion in the review and 131 studies were excluded. Two additional studies were identified from scanning systematic review reference lists and 19 additional studies were identified from Company submissions and websites. The full study selection process is illustrated in the PRISMA diagram in Figure 1. The 131 studies excluded at full paper stage are listed in Appendix 9.2 Table 49, along with the reasons for their exclusion.

A total of 84 studies met eligibility criteria; 7 ongoing studies with no results available (summarised in Appendix 9.3 Table 50) and 77 studies included in the systematic review. Complete details of all included studies are given in Appendix 9.4 (Table 51 to Table 66). Where stated, most studies of PKG were conducted in Australia or the USA, most studies of STAT-ON were conducted in Spain, studies of Kinesia 360 and KinesiaU were conducted in USA or Canada and the study of PDMonitor was conducted in Greece and Italy. Few studies were conducted in the UK.

Fifty-seven studies evaluated PKG.[17-73] Fifteen studies evaluated STAT-ON.[74-88] Three studies evaluated Kinesia 360.[89-91] One study evaluated KinesiaU.[92] One study evaluated PDMonitor.[93] There were no studies that directly compared one remote continuous monitoring device against another.

Additional ongoing studies and planned studies are reported in the Company submissions.[8-11, 94]

Figure 1 Flow diagram of the study selection process



3.2 Classification of studies by outcome reported

The included studies varied substantially, both within and across technologies, as to what outcomes were reported. To simplify the assessment of the studies they have been arranged into six categories by type of outcome reported as follows:

Diagnostic accuracy studies

Studies reporting whether the devices can predict symptoms and outcomes (such as bradykinesia, dyskinesia, sleep disturbance or tremor), or predict the need for medication change or similar. Studies must report sensitivity and specificity, or other diagnostic accuracy statistics.

Association studies

Studies reporting whether device output is associated with symptoms and outcomes, that report correlations, model fit, or other measures of association, without reporting diagnostic accuracy.

Intermediate impact of monitoring studies

Studies reporting how devices impact changes in treatment, treatment adherence, adherence to appointments, and all outcomes listed in Section □.

Clinical outcome studies

Studies reporting how devices impact outcomes for patients, including changes in UPDRS, quality of life, and all outcomes listed in Section 0.

Patient and carer opinion studies

Studies reporting how patients or carers viewed the device, such as whether it was easy to use and useful; including all outcomes listed in Section 0.

Clinician opinion studies

Studies reporting opinions of clinicians on the devices, such as whether they provide useful information to inform treatment and management.

Table 1 illustrates the number of studies reporting the different types of outcomes according to technology, for all studies reported in full journal articles. The numbers in this table exceed the total number of papers because some papers reported on multiple classes of outcome.

Table 2 summarises the same data for studies reported only as conference abstracts.

Table 1 Summary of full papers by technology and outcomes reported

	PKG	STAT-ON	Kinesia 360	KinesiaU	PDMonitor
Diagnostic accuracy	7	8	1	0	0
Association study	11	3	0	0	0
Intermediate impact	8	0	1	1	0
Clinical outcomes	6	0	2	1	0
Patient and carer opinions	4	1	1	1	0
Clinician opinions	4	1	0	0	0

Table 2 Summary of conference abstracts by technology and outcomes reported

	PKG	STAT-ON	Kinesia 360	KinesiaU	PDMonitor
Diagnostic accuracy	1	1	0	0	0
Association study	10	1	0	0	1
Intermediate impact	17	0	0	0	0
Clinical outcomes	4	0	0	0	0
Patient and carer opinions	4	1	0	0	0
Clinician opinions	2	2	0	0	0

It can be seen from Table 1 and Table 2 that most of the published evidence is for the PKG device; there is a modest amount of primarily diagnostic accuracy evidence for STAT-ON, and almost no evidence for Kinesia 360, KinesiaU or PDMonitor. Much of the evidence is categorised as either diagnostic accuracy or association studies. These were generally proof-of-concept studies to demonstrate that the devices could provide clinically viable measurements. Evidence on the intermediate impact of the devices, such as whether their use led to changes in treatment, was generally only available for PKG. Studies reporting clinical outcomes were few, and only three (one for PKG,[17] two for Kinesia 360 [89, 90]) were comparative studies, comparing device use to standard clinical practice. There was limited evidence on patient, carer or clinical opinions, mostly for PKG.

In the sections below the included studies are summarised for each of the five monitoring technologies, and for each outcome class described above. The following sections provide a general summary of the evidence. Where additional data were available in publications the complete data extraction is presented in Appendix 9.4 (Table 51 to Table 66).

3.3 PKG

This section considers the results of all the studies that assessed the PKG device. Studies are summarised narratively, according to the type of outcomes reported. This section also presents the analysis of the IPD supplied for one trial (Woodrow).[17]

3.3.1 Diagnostic accuracy

Seven papers reporting diagnostic accuracy data (sensitivity and specificity, or area under the curve [AUC]) for PKG were identified.[23, 41, 44, 49, 50, 61, 72] One further conference abstract was found,[46] which is not discussed here due to limited reporting of data.

The QUADAS-2 risk of bias assessment of these studies is summarised in Table 3.

Table 3 QUADAS-2 Risk of Bias assessment of PKG studies

Study	Risk of Bias				Applicability Concern		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Braybrook 2016[23]	High	Unclear	High	Unclear	Low	Unclear	Low
Horne 2015[44]	High	High	High	Unclear	Low	Unclear	Low
Horne 2016[41]	High	High	Unclear	Low	Low	High	Low
Khodakarami 2019 A[49]	High	High	High	Unclear	Unclear	Unclear	Unclear
Khodakarami 2019 B[50]	High	High	Unclear	Unclear	Low	Unclear	Low
McGregor 2018[61]	High	High	Low	Low	Low	Unclear	Low
Watts 2021[72]	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low

The risk of bias assessment identified substantial concerns with the included diagnostic accuracy studies. Reporting was frequently poor, leading to an "Unclear" assessment and, where risk could be assessed, studies were often at high risk of bias. Four of the studies were case-control studies,[41, 44, 50, 61] which are generally accepted as having high risk of bias, as the patient's condition is known before the PKG assessment is performed. In most studies the reference standard was not described in detail, often limited to just stating that it was clinical opinion. Similarly, the exact test being assessed was rarely described. The EAG have assumed that it was the output of the PKG device in some form, but it is unclear whether the output or algorithm used is the same as for the current device in actual use, hence our "Unclear" classification for the applicability of the index test in these studies. There were also concerns with the flow and timing component of risk of bias assessment, because it was generally not clear when the reference standard and index tests were performed, and whether each was assessed blinded to the results of the other.

It should be noted, however, that some of these risk-of-bias issues may be due to the nature of the studies and the condition. There is no clearly established reference standard for measuring PD symptoms beyond clinician and patient assessment (e.g. by using UPDRS). This is unlikely to be a

perfect reference standard. Indeed, a possible benefit of PKG (and the other technologies) is that they may provide a more accurate evaluation of symptoms than patient recall or clinical opinion; this cannot be easily determined from a diagnostic accuracy study. Also, the studies do not appear to have been designed as formal diagnostic accuracy studies. Most were proof-of-concept studies where diagnostic accuracy data were reported alongside other information. This may explain why some aspects of bias risk were not clearly reported.

A summary of the diagnostic accuracy data reported in the included studies is shown in Table 4. None of the studies were from the UK, but most were from Australia or the USA, and so are likely to have results that generalise to the UK population. Studies varied substantially in size: from 26 to 373.

Table 4 Diagnostic accuracy reported in PKG studies

Study	Study type	N	Reference standard	Outcome	Sensitivity	Specificity	AUC
Braybrook 2016[23] Australia	Prospective cohort	85 (cohort 1) 87 (cohort 2)	Clinical judgement	Tremor	92.5 90.3	92.9 * 92.7	92%
Horne 2015[44] Australia	Case-control	36 cases, 16 controls	AIMS and UPDRS	Fluctuation (wearing off of DK)	97.1	87.5 *	98%
Horne 2016[41] Australia	Case-control	18 cases, 35 controls	AIMS and UPDRS	BKS	100	83	96%
Khodakarami 2019 A[49] Australia	Cohort	172	Clinical opinion	Suitability for Device Assisted Therapy	89	86.6	93%
Khodakarami 2019 B[50] Holland, USA and Australia	Case-control	199 cases, 174 controls	Levodopa challenge test (clinic assessed)	Levodopa response			92%
McGregor 2018[61] Australia	Case-control	72 cases; 46 controls	Polysomnography	Sleep disturbance and quality	80	86 *	
Watts 2021[72] USA	Cohort	26	UPDRS	Treatment classification accuracy	84.5 (±0.7)	81.7 (±2.2)	83.1% (±1.1)

** reported as "selectivity" in the publications*

Diagnostic accuracy results were generally poorly reported. None reported actual numbers of true positives, etc., and most did not report confidence intervals or standard errors for the reported estimates. Each study examined a different outcome, with no replication of outcome across different studies. Most studies used some form of clinical judgment as the reference standard, generally using UPDRS to measure symptoms.

The three studies that reported bradykinesia, dyskinesia and tremor[23, 41, 44] showed high diagnostic accuracy of PKG to detect these, with sensitivities above 90% and specificities ranging from 83% to 92.9%. This suggests that PKG is able to measure key Parkinson's disease outcomes. The one study of sleep disturbance showed slightly poorer diagnostic accuracy (80% sensitivity, 86% specificity),[61] suggesting that PKG may not be as effective at identifying people with sleep disturbance.

Three studies examined the diagnostic accuracy of PKG for making treatment decisions.[49, 50, 72] The two studies by Khodakarami showed that PKG had a reasonably good ability to identify patients' levodopa response (92% AUC) or need for device assisted therapy (AUC 93%). One small study showed slightly poorer performance for accuracy of treatment classification (AUC 83.1%),[72] but the clinical relevance of this classification was unclear.

3.3.2 Association outcomes

Eleven papers reporting association outcomes for PKG were identified.[24, 31, 37-39, 51, 52, 54, 55, 63, 69] Ten further conference abstracts were found, but are not discussed here due to limited reporting (see Appendix 0 Table 54).[19, 21, 22, 26, 27, 36, 42, 43, 58, 60] A summary of the results of studies reporting association data for PKG is reported in Table 7. One study was from the UK; others were mostly from Europe, Australia or the USA. Studies varied in size; from 18 to 228 patients.

Table 5 Association data reported in PKG studies

Study	Study type	N	Reference standard	Outcome	Correlation/Result	P-value
Chen, 2020[24] China	Prospective cohort	100	UPDRS III total	BKS	0.546	<0.001
			UPDRS III tremor	% time tremor	0.434	<0.05
			WOQ-9	DKS	Very weak	>0.05
			WOQ-9	FDS	Very weak	>0.05
Evans, 2014[31] Australia	Prospective cohort	25	QUIP	Impulse control behaviour	0.79 in 19 patients (6 patients were clear outliers)	Not significant
Griffiths, 2012[37] Australia	Prospective cohort	44	Modified AIMS	DKS	0.8	<0.0001
			UPDRS IV (n=25 with bilateral PD)	Global median DKS	Not stated	<0.05
			UPDRS III (n=25 with bilateral PD)	Global median BKS	0.64	<0.0005
			'Dot slide' test	BKS	0.63	<0.001
Guan, 2021[38] USA	Prospective cohort	18	On/Off (using UPDRS III)	BKS	-0.547 (6 months)	0.019
				DKS	0.133 (6 months)	0.598
				PTT	-0.523 (6 months)	0.1
			PDQ39 (ADL domain)	BKS	0.381	0.119
				DKS	-0.057	0.824
				PTT	0.16	0.526
Hoglund, 2021[39] Sweden	Prospective cohort	53	Motor and non-motor (mood and anxiety) fluctuations	Daytime sleep	Daytime sleepiness correlated with motor symptoms, mood and anxiety amongst motor fluctuators (n=28)	Significant
			Sleepiness diary	Daytime sleep	Weak	Not significant
Khodakarami, 2021[51] Australia	Retrospective cohort	228	UPDRS III	% time bradykinesia	0.4	<0.0001
			UPDRS Total	% time bradykinesia	0.34	<0.0001
			PDQ39	% time bradykinesia	0.35	<0.0001

Klingelhoefer, 2016[52] UK	Prospective cohort	63	NMSQuest (n=30 with excessive daytime sleepiness)	PKG sleep assessment	Significant correlation (no significant correlation in 'non-sleepy' patients)	Significant
			PDQ8 (n=30 with excessive daytime sleepiness)	PKG sleep assessment	0.46 to 0.6	Not significant
Knudson, 2020[54] Denmark	Prospective cohort	34	UPDRS II	BK change score	Not stated	0.006
				DKS	Not stated	0.007
Kotschet, 2014[55] Australia	Case control	98	Polysomnography (n=7 with >30 mins immobile/day)	Sleep disturbance (immobility)	85.2% concordance	<0.0001
			Epworth sleepiness score	% time immobile	Not stated	0.01
Ossig, 2016[63] Germany	Prospective cohort	24	Patient diary	BKS, DKS, On-Off periods (calibrated)	0.404 to 0.658	<0.05
Tan, 2019[69] USA	Prospective cohort	54	Patient diary	Fluctuation score	PKG fluctuator scores significantly differentiated early and troublesome fluctuators, as well as dyskinetic and non-dyskinetic patients, but not subtler motor fluctuations.	-

In general, PKG bradykinesia (BKS), percent time bradykinesia (PTB) and percent time tremor (PTT) scores were moderately correlated with UPDRS III scores. BKS and PTB was also moderately correlated with PDQ39 scores. There was a statistically significant correlation between PKG dyskinesia score (DKS) and UPDRS II. PKG DKS was also significantly correlated with modified AIMS and PKG BKS was significantly correlated with bradykinesia measured by the 'dot slide' test. In a subgroup of patients with bilateral PD, there was significant correlation between 'global median DKS' and UPDRS IV, and 'global median BKS' and UPDRS III.

However, the Wearing-off Questionnaire-9 (WOQ-9) had a very weak, non-significant correlation with the PKG fluctuation and dyskinesia score (FDS) and DKS. Another study found that PKG fluctuator scores significantly differentiated early fluctuators and troublesome fluctuators, as well as dyskinetic and non-dyskinetic patients, but could not discriminate subtler motor fluctuations.

Results relating to sleep outcomes were more mixed. High Epworth Sleepiness Score was correlated with PKG proportion of time immobile (PTI). Correlations between PKG variables and 3-day daytime sleepiness diaries were generally weak and non-significant. In a subgroup of patients with excessive daytime sleepiness, the PKG's parameters for quantity and quality of night-time sleep correlated significantly with the total burden of non-motor symptoms of PD as measured by NMSQuest. In non-sleepy patients there was no significant correlation. There was also a moderate to high (though non-statistically significant) correlation between PKG night-time sleep markers and the PDQ8 in the excessive daytime sleepiness group. In a subgroup of patients who were immobile for >30

minutes/day and underwent ambulatory daytime polysomnography (n=7), periods of immobility on PKG was highly correlated with detection of sleep by polysomnography.

The ratio of medication acknowledgements/number of doses was strongly correlated with ratings of Impulsive-Compulsive Behaviours in 19/25 patients, however 6 patients were clear outliers and fell into the false negative group; these patients had normal response ratios, but high Impulsive-Compulsive Behaviour scores.

The Bergquist (2018) conference abstract is worthy of note; it describes preliminary data from the ongoing WestPORTS registry study which compares randomly selected PwP in West Sweden (n=154) with retrospective data from clinically motivated recordings in PwP suspected to have motor fluctuations (n=248). The PKG scores were significantly different between the two populations: median BKS 30.4 vs 23.0 (p=0.014) and DKS 1.0 vs 3.0 (p<0.0001) in the randomly selected population and clinically motivated recordings, respectively.

3.3.3 Intermediate impact of monitoring

Twenty-five studies reporting on the intermediate impact of monitoring were identified; eight reported in full publications[28, 32, 35, 48, 56, 62, 66, 68] and 17 as conference abstracts.[18, 20, 25, 29, 30, 33, 34, 40, 45, 47, 53, 57, 59, 64, 70, 71, 73] The conference abstracts are not discussed here due to limited reporting (see Appendix 0 Table 57), however, results were largely consistent with those of the full papers.

The eight studies reported in full were assessed for quality using a tool developed for the review using relevant criteria. The results are summarised in Table 6.

Table 6 Quality assessment of PKG intermediate impact of monitoring studies

Study	Dominey, 2020[28]	Evans, 2020[32]	Farzanehfar, 2018[35]	Joshi, 2019[48]	Krause, 2021[56]	Nahab, 2019[62]	Santiago, 2019[66]	Sundgren, 2021[68]
Inclusion criteria clearly defined	Yes	No	Yes	Yes	Yes	Yes	No	Yes
Representative sample from relevant population	Yes	Unclear	Yes	Yes	Yes	Yes	Unclear	Yes
Clearly described and consistently delivered intervention	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Clearly described and consistently	N/A	N/A	Yes	Yes	Yes	Yes	Yes	Yes

delivered comparator (if applicable) *								
Outcome measures pre-specified, reliable and consistently assessed	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Yes
Outcome assessors blinded	N/A	N/A	Yes	Yes	Yes	Yes	Unclear	Yes
Attrition low and accounted for in analysis	No	Yes	Yes	Yes	Yes	Yes	No	Yes
Free from suggestion of selective reporting	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Overall judgement of risk of bias	High	High	Low	Low	Low	Low	High	Low

** Comparator here refers to comparing treatment actions that would have been undertaken without PKG, to those decided on using PKG results*

Five of the six comparative studies (where PKG was compared against clinical assessment prior to reviewing the PKG data) had a low overall risk of bias.[35, 48, 56, 62, 68] However, one of the comparative studies did not clearly define the study inclusion criteria, attrition was high and it was unclear whether the clinician was blinded to PKG results at the time of outcome assessment.[66] The two uncontrolled studies had a high risk of bias.[28, 32]

A summary of the results of studies reporting the intermediate impact of monitoring is reported in Table 7. Two studies were from the UK; others were from Australia, the USA and Sweden.

Table 7 Intermediate impact of monitoring reported in PKG studies

Study	Study type	N	PKG use	Comparator	Intermediate impact of monitoring
Dominey, 2020[28] UK	Retrospective cohort	166 (78 new patients and 88 follow-up)	PKG for 6 days.	None.	Treatment recommendations were made for 92% (152/166) patients; most commonly relating to dopamine replacement and advice on sleep hygiene and bowel management. Treatment recommendations were implemented for 73% (83/114) patients (where data available); including advanced therapy (n=6), additional motor agent (n=34) and additional non-motor agent (n=16). Information from the PKG confirmed initial judgement in 54.5% cases and provided additional information in 45.5% cases.
Evans, 2020[32] UK	Pilot cohort	61	PKG in a virtual clinical appointment.	None.	79% (48/61) appointments were deemed successful (the clinician felt the outcome of the consultation was likely to have been the same as a face-to-face clinic). Reasons for unsuccessful consultations included complex phase of disease (n=5), problems with the PKG (n=5), needing a blood pressure reading (n=2) and speech problems (n=1).
Farzanehfar, 2018[35] Australia	Prospective cohort	103	PKG for 6-7 days.	Clinical assessment by a neurologist.	The neurologist agreed with the PKG in 90% (93/103) cases. In 61% (63/103) cases the PKG added to the clinical findings to the extent that the therapeutic decision was influenced. Adjustment of oral therapy was attempted in 40/80 patients with uncontrolled motor function, 9/80 were referred for advanced therapy, no change was made in 5 cases because of risk of contraindications and 26/80 did not complete the study (protocol violations).
Joshi, 2019[48] USA	Prospective cohort	63 (85 routine care visits)	PKG for 6 days.	Clinical assessment.	In 48% of patients the PKG reported a symptom not reported by the patient (24% bradykinesia, 16% dyskinesia, 8% tremor). 24% of patients reported a symptom that didn't appear in the PKG report. PKG data was used to make changes in treatment plans in 79% (50/63) patients; most commonly addition of at least one medication or changed dosage and timing of medications.
Krause, 2021[56] USA	Retrospective cohort	104 (170 PKG reports)	PKG for 7 days.	Clinical assessment by a movement disorder specialist.	PKG complemented patient input in 82.9% (141/170) PKG reports and led to medication changes in 71% (100/141) of the complimented inputs; 79 led to increase in medications, 6 led to decrease in medications and 23 led to introduction of a new drug (some encounters led to more than one medication change).
Nahab, 2019[62] USA	Prospective cohort	28 (clinically stable patients using levodopa)	PKG for 6 days at 2 routine visits.	Clinical assessment by a movement disorder specialist.	PKG revealed a higher degree of symptom severity than was noted by clinical history alone in 18 patients (64%) at visit 1 and 8 patients (29%) at visit 2, resulting in clinical management plan changes. Medication changes included adding a new medication (6 instances), stopping a medication (2), increasing (14) or decreasing (1) medication dose or adjusting dose timing (5). 64% of patients had an increase in levodopa dose; 11% had a dose reduction.
Santiago, 2019[66] USA	Physician survey	89 (patients considered to benefit from continuous objective measurement;	PKG for 6 days.	Clinical assessment by a movement disorder specialist.	32% (36/112) had an alteration to patient care as a result of PKG. The PKG most commonly yielded new information on daily off time [50% (18/36)].

		112 assessments)			
Sundgren, 2021[68] Sweden	Prospective cohort	66	PKG for 6 days.	Clinical assessment by a neurologist.	After clinical assessment, a treatment change was recommended for 52/66 PwP; for the remaining 14 patients the current treatment was planned to be left unchanged. After PKG review, the treatment plan proposed after the clinical assessment was changed in 31.8% (21/66) PwP. The clinical assessment and the PKG review differed frequently, mainly regarding overall presence of motor problems (67%), characteristics of bradykinesia/wearing off (79%), dyskinesia (35%) and sleep (55%). Almost all patients reported good compliance and no tendency to impulse control disorder. For these items there were few disagreements between the clinical and PKG assessments (3% for impulse control disorder and 5% for compliance).

Three studies reported the level of agreement between the PKG and clinical assessment/initial judgement; there was agreement in 54.5% to 90% of cases.[28, 35, 56] Hence there appears to be considerable cross-study uncertainty in the consistency between PKG assessments and standard clinical assessments.

Six studies reported the proportion of patients for whom the PKG provided additional information leading to a change in the clinical management plan; this was the case in 31.8% to 79% patients.[28, 35, 48, 62, 66, 68] The most common treatment changes were the addition of at least one medication or a change in dosage; a small proportion of patients were referred for advanced therapy. This suggests that there will be a proportion of patients for whom PKG will lead to changes in management, but also a substantial proportion where management will be unchanged. There is considerable uncertainty as to exactly how many patients will have changes to management if PKG is used. It was unclear from the publications how a decision to change, or not change, management was related to patient symptoms, nor exactly what the changes were (such as how much levodopa dosage was adjusted).

One study assessed PKG use in virtual clinical appointments; 79% of virtual appointments were deemed successful (the outcome of the consultation was likely to have been the same as a face-to-face appointment).[32] Reasons for unsuccessful consultations included complex phase of disease, problems with the PKG, needing a blood pressure reading and speech problems.

3.3.4 Clinical outcomes

We identified ten studies that reported on clinical outcomes related to PKG. As the original trial data were supplied for the Woodrow trial it is analysed in Section 3.3.4.1. The remaining studies are summarised in Section 3.3.4.2.

3.3.4.1 Woodrow Individual Participant Data

Full data was made available for the Australian trial of PKG by Woodrow et al.[17] This was not randomised; rather, twelve centres were selected to either use PKG for the management of patients, or to use standard clinical practice. PKG clinics were generally those with existing experience of using PKG in practice. Patients were assigned to clinics based on location and convenience. Hence the trial can be thought of as a quasi-randomised cluster trial. All patients wore the PKG smartwatch, and so were blind to which arm they were in.

PKG measurements were taken for all patients, but only given to clinicians in the PKG arm. Patients were seen every five weeks, with PKG measurements taken before each visit, until their PKG measurements were judged to be "in target" (defined as BKS < 26 and DKS < 7 from PKG assessment); with a maximum of five consultations.

The risk of bias of the trial was assessed using the Cochrane Risk of bias tool, and is reported in Table 8. Although Cochrane risk of bias is intended for RCTs, it was decided to be the most suitable tool for assessing the Woodrow trial. The main risk of bias in the trial was because it was not strictly randomised. Other aspects of the trial were judged to be at low risk of bias.

Table 8 Risk of Bias assessment for the Woodrow trial

Study	Woodrow[17]
Risk of bias arising from the randomisation process	High
Risk of bias due to deviations from the intended interventions	Low
Missing outcome data	Low
Risk of bias in measurement of the outcome	Low
Risk of bias in selection of the reported result	Low
Overall judgement of risk of bias	Some concerns

The supplied IPD was checked for potential bias problems, including imbalances across trial arms. When examining patient characteristics at recruitment the EAG could not exactly match results presented in the trial publication,[17] but inconsistences were small, and most likely due to differences in how excluded patients were evaluated. The EAG found no substantial imbalance in patient characteristics between PKG and non-PKG patients; so, although the trial was not randomised, there does not appear to be any bias due to imbalance between arms. Missing data was largely confined to

patients who were excluded or withdrew from the trial. There was no evidence of imbalance in missing data between arms.

The IPD included the following outcomes, which are reanalysed here:

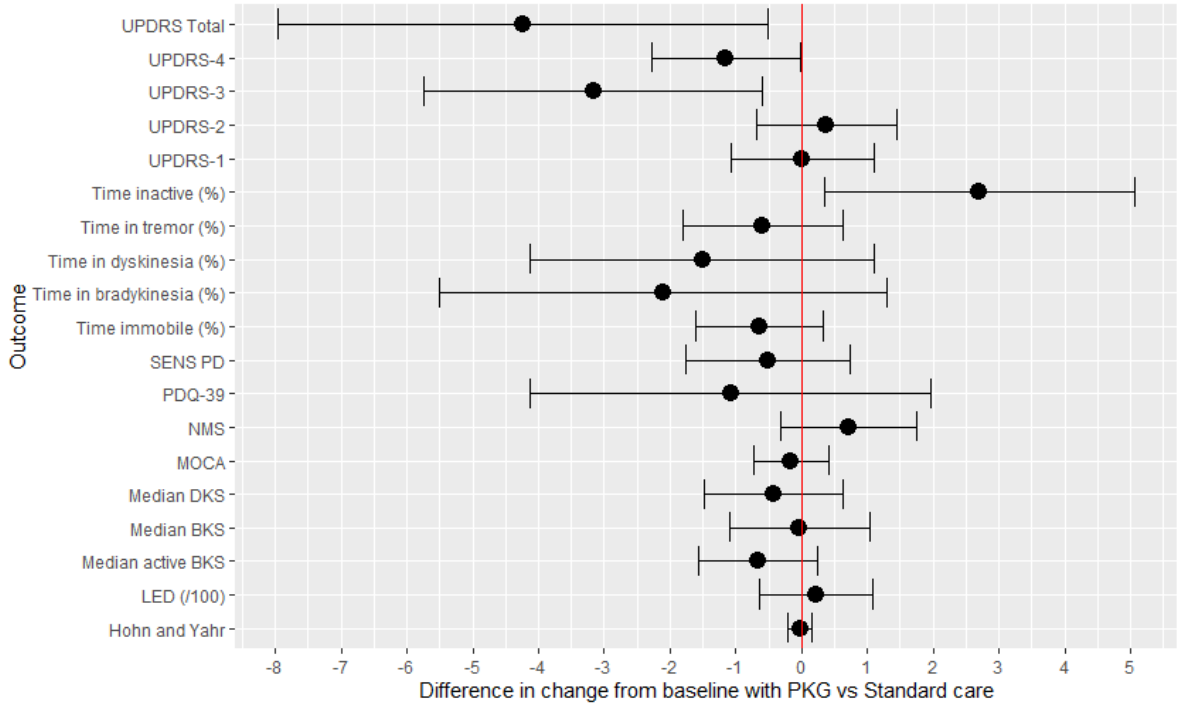
- UPDRS (I, II, III, IV and Total)
    - Part I covers non-motor aspects of daily living (e.g. depression and anxiety)
    - Part II covers motor aspects of daily living (e.g. walking and eating)
    - Part III is the full motor assessment
    - Part IV covers motor complications (dyskinesia and "On-Off" times)
- Levodopa equivalent dose (LED)
- Hoehn and Yahr
- Median BKS, active BKS and DKS
- Montreal Cognitive Assessment (MOCA)
- Non-Motor Symptoms Questionnaire (NMS)
- PDQ-39
- Severity of predominantly Non-dopaminergic Symptoms in Parkinson's Disease (SENS PD)
- Percentage time with bradykinesia, dyskinesia or tremor
- Percentage time inactive or immobile

These are broadly the same outcomes reported in the trial publication, except time inactive was not reported in the paper, so there is no clear evidence of reporting bias. Figure 2 shows the difference between PKG and non-PKG patients in terms of change in outcome from baseline, for all the outcomes reported above. The circles show the estimated difference between PKG and non-PKG arms, and the horizontal lines are 95% confidence intervals. Results to the left of the red line indicate those favouring PKG. Results for levodopa equivalent dose (LED) are divided by 100, to fit on this plot. Full numerical results for this analysis are given in Appendix Table 67.

The results show that the use of PKG appears to improve UPDRS scores, particularly UPDRS III (by around 3.1 points) and IV (by around 1.2 points) and hence total score. This is likely to be because PKG use is reducing time with bradykinesia (by 2.1 percentage points) dyskinesia (by 1.5 percentage points) and tremor (by 0.6 percentage points), although none of these reductions achieved statistical significance. Results for other outcomes are mostly in the direction of favouring PKG, but effect sizes are mostly small and confidence intervals wide. Use of PKG appears to improve symptoms, without requiring substantial increases in levodopa dose.

The main exception to the general trend favouring PKG was for time inactive, which was higher in PKG patents than in non-PKG patients, by about 2.7% points. It is not clear why this discrepancy might occur. It was notably not reported in the original trial publication.

Figure 2 Results from the Woodrow trial - Difference between PKG and standard care



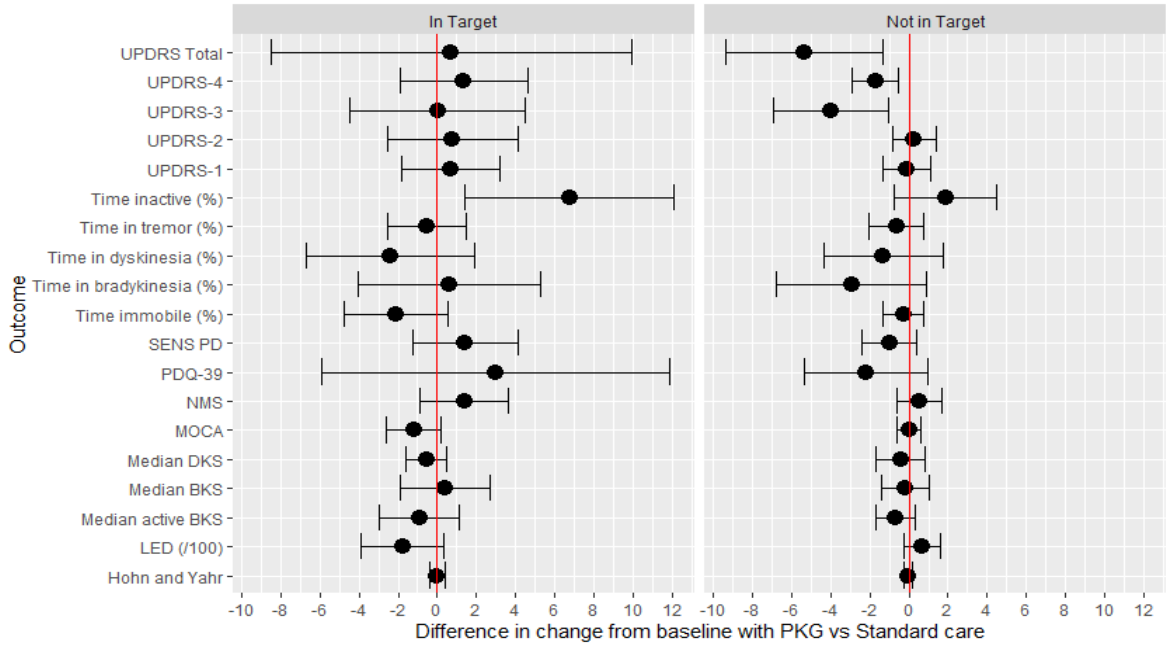
We examined models that adjusted for potential confounding factors, namely: age, sex, PD duration, UPDRS III at baseline and number of clinic visits during follow-up. This found that sex and age had no impact on results, but the other factors could alter outcomes. We reanalysed the data for all outcomes adjusting for PD duration, UPDRS III at baseline and number of clinic visits during follow-up. Results of this analysis are given in Appendix Figure 11 and Appendix Table 67.

Overall, the results for the adjusted analyses were similar to the original analysis (Figure 2). The benefit of PKG was marginally reduced for some outcomes. For example, the benefit of PKG on UPDRS IV declined from 1.2 points to 0.7 points. This might suggest that some of the observed benefit of PKG is because people in the PKG arm had more clinic visits.

Further analysis of the impact of both number of visits and baseline UPDRS III on outcomes were performed, by analysing outcomes separately for each number of visits and by quartiles of UPDRS III score at recruitment. These analyses are summarised in Appendix Figure 12 and Figure 13. These show that the benefits of PKG were mostly in patients who had poor UPDRS III scores initially and those who required more visits before symptoms became in target. This suggests that PKG may be of most benefit to patients with more severe, and less manageable, symptoms.

To match analyses performed in the trial publication we also performed a subgroup analysis, examining the impact of PKG on all outcomes according to whether patients were judged to be "in target" or "out of target" at baseline, using their PKG results. The results of this analysis are summarised in Figure 3, and given in full in Appendix Table 68.

Figure 3 Impact of PKG in the Woodrow trial, by "in target" status at baseline



These results suggest PKG use predominately improves symptoms (particularly bradykinesia and UPDRS scores) in people who were not "in target" and whose condition was not adequately controlled. For people whose condition was "in target" there are no improvements in UPDRS or time in bradykinesia. However, for "in target" patients on PKG the percentage time in dyskinesia and LED were lowered compared to non-PKG patients, although neither result was statistically significant.

This suggests that using PKG can be useful in improving UPDRS, by reducing bradykinesia, in patients whose disease is not being adequately controlled, while possibly allowing for levodopa dose reduction, and consequent reduction in dyskinesia, in patients whose condition was already well-controlled.

The supplied IPD permitted analysis for three further dichotomous outcomes: change in medication, referral for device assisted therapy (exact therapies were not reported) and "in target" status. The first two were not included in the trial publication, but of relevance to this assessment. Odds ratios for these three outcomes are given in Table 9. Models adjusted for PD duration, UPDRS III at baseline and number of clinic visits during follow-up gave broadly similar results. The data were insufficient for analyses by target status at baseline.

The results suggest that patients using PKG were substantially more likely to be "in target" at follow-up and to be referred for device-assisted technologies. There was no clear evidence that patients using PKG were more likely to have a change in medication.

Table 9 Results for analysis of dichotomous outcomes in the Woodrow trial

Outcome	Number with PKG	Number with standard care	Odds ratio	95% CI	
Change in medication	49	39	1.18	0.52	2.68
Referral for device assisted technology	36	13	4.01	1.82	8.85
In Target at follow-up	34	14	3.43	1.67	7.03

3.3.4.2 Other studies reporting results for clinical outcomes

Nine cohort studies reported on clinical outcomes related to PKG; five reported in full publications[35, 48, 56, 62, 68] and four reported as conference abstracts.[34, 43, 45, 59]. The quality assessment results for the five studies that were reported in full are presented in Table 6 above, as these studies also reported intermediate outcomes. All five had a low overall risk of bias.[35, 48, 56, 62, 68] Quality assessment was not undertaken for the conference abstracts, owing to limited reporting.

A summary of the results of studies reporting clinical outcomes related to PKG are reported in Table 10, including results for the conference abstracts, given the importance of clinical outcomes to the assessment of PKG.

Table 10 Clinical outcomes reported in PKG studies

Study	Study type	N	PKG use	Comparator	Clinical outcomes
Studies reported in full publications					
Farzanehfar, 2018[35] Australia	Prospective cohort	103	PKG for 6-7 days.	Clinical assessment by a neurologist.	33/80 uncontrolled PwP were treated with oral therapy; motor scores and function were brought under control in 14 cases. In 19/33 cases it was not possible to reach therapeutic targets by the end of the study; 7 were reclassified - 3 were referred to advanced therapy and 4 were classed as 'treatment contraindicated'. Significant improvements from baseline to final visit were observed in the 33 treated patients: UPDRS I (effect size=2, p=0.0007) UPDRS II (effect size=4, p=0.03) UPDRS III (effect size=3, p=0.0009) UPDRS IV (median did not change, p=0.01) Total UPDRS (effect size=8, p<0.0001)

					NMS questionnaire (median did not change, p=0.02) MOCA (effect size=2, p=0.02) Improvements in quality of life (PDQ39) were significant in the subgroup of 14 patients whose symptoms were brought under control (effect size=8.5, p=0.03), but not the full population of 33 treated patients (effect size=10, p=0.08).
Joshi, 2019[48] USA	Prospective cohort	63 (85 routine care visits)	PKG for 6 days.	Clinical assessment.	No serious adverse events or adverse device effects were reported.
Krause, 2021[56] USA	Retrospective cohort	104 (170 PKG reports)	PKG for 7 days.	Clinical assessment by a movement disorder specialist.	Out of 104 patients, 49 had more than 1 PKG encounter; 37 had 2 encounters (mean interval 6.3 months between encounters), 7 had 3 encounters (mean interval 11.4 months between first and last encounter) and 5 had 4 encounters (mean interval 15.8 months between first and last encounter). Most patients undergoing 3 or 4 PKG encounters did not reach a controlled state as defined by PKG until the 3rd or 4th encounter.
Nahab, 2019[62] USA	Prospective cohort	28 (clinically stable patients using levodopa)	PKG for 6 days at 2 routine visits.	Clinical assessment by a movement disorder specialist.	Mean MDS-UPDRS III summary score significantly reduced (improved) from 28.9 at visit 1 to 24.1 at visit 2 (p<0.028). Mean MDS-UPDRS IV summary score reduced from 4.1 at visit 1 to 3.0 at visit 2 (p=0.07). BKS, DKS, percentage time immobile and percentage time in tremor showed no clear evidence of change from visit 1 to visit 2. Hoehn and Yahr ratings were similar between visit 1 and visit 2; at visit 2, 5 patients (18%) were rated as having improved one Hoehn and Yahr stage and 6 had worsened one stage. On the Clinician Global Impression of Improvement (CGI-I) scale, 17/28 patients (61%) showed improvement, 9 (32%) no change and 2 (7%) minimally worse. On the Patient Global Impression of Improvement (PGI-I) scale, 13/24 patients (54%) indicated improvement, 9 (38%) no change, 2 (8%) minimally worse and 4 patients did not respond.
Sundgren, 2021[68] Sweden	Prospective cohort	66	PKG for 6 days.	Clinical assessment by a neurologist.	There were no significant differences in clinical variables when repeated after 3-6 months (mean score at baseline and follow-up) in PDCS (18.5, 18.8), NMSQ (9.0, 8.8), PDQ-8 (22.7, 21.5), EQ VAS (66.0, 66.7), BKS (27.9, 27.4), DKS (3.5, 3.2), FDS (8.5, 8.6). Overall change at follow-up (assessed using CGI-I Scale) was 3.6; a score of 4 represents no change, a lower score represents improvement.
Studies reported as conference abstracts					
Farzanehfar, 2017[34] Location not stated	Prospective feasibility study	28 (with controlled symptoms)	PKG.	Clinical assessment.	Patients with uncontrolled bradykinesia (n=21) showed statistically significant improvements in UPDRS III and Total UPDRS following intervention. In the 8 patients recognised as poorly controlled by PKG alone, there were statistically significant

					improvements in UPDRS III and Total UPDRS following intervention (median improvement = 13; p=0.01).
Horne, 2016[43] Location not stated	Interim findings of prospective cohort study	19 (considered well controlled by general neurologists)	PKG.	Assessment by a movement disorder specialist.	Clinically significant changes in patient outcomes were noted in the UPDRS, PKG scores and PDQ8.
Horne, 2018[45] Australia	Pilot prospective cohort study	103	PKG.	Clinical assessment.	At the end of the study 48% patients were in target (22% at outset and 26% by treatment change, not including those referred for advanced therapy). In those in whom oral therapy was changed, total UPDRS and PDQ39 improved (effect size 8 and 10 respectively). MOCA scores also improved significantly.
Lynch, 2018[59] Australia	Cohort study	80 (uncontrolled patients)	PKG.	None.	Among 33 patients treated with oral therapy, decreases were observed in: mean UPDRS II (-4; 9-13), mean UPDRS III (-3; 36-39), Percent Over Target (-8; 64-73) and PDQ39 (10; 19-29).

Two full papers reported results for UPDRS changes.[35, 62] One study, which reported that PKG resulted in clinical management plan changes in 64% patients at visit 1 and 29% patients at visit 2, reported a significant reduction (improvement) in mean MDS-UPDRS III summary score between visit 1 and visit 2 (from 28.9 to 24.1, p=0.028). Mean MDS-UPDRS IV summary score was also reduced (from 4.1 to 3.0, p=0.07).[62]

Another study reported the proportion of 'uncontrolled' patients whose symptoms were brought under control after changes in oral therapy following assessment using PKG; 14/33 patients were brought under control (within 2-4 visits), whilst it was not possible to reach therapeutic targets by the end of the study in 19/33 patients. Significant improvements were observed in UPDRS I, UPDRS II, UPDRS III, UPDRS IV and total UPDRS.[35]

Four conference abstracts reported limited data on UPDRS and other outcomes.[34, 43, 45, 59] One study randomised patients to clinical examination followed by PKG or PKG followed by clinical examination.[34] Twenty-four patients were identified as uncontrolled; 16 by both clinical history and PKG, 8 by PKG alone. Following intervention there were statistically significant improvements in UPDRS III and Total UPDRS amongst all patients with uncontrolled bradykinesia and amongst the 8 patients identified as uncontrolled by PKG alone.[34] Another study that randomised patients to clinical examination followed by PKG or PKG followed by clinical examination also reported clinically significant changes in PKG scores, UPDRS and PDQ8 after treatment for bradykinesia or fluctuations; the movement disorder specialist recognised the same symptoms as PKG in 10 patients, but would not have recognised 6 patients at poorly controlled without the PKG.[43] In one study, oral therapy was recommended in 74% patients due to PKG scores being outside the target range; there

were significant improvements in Total UPDRS, PDQ39 and Montreal Cognitive Assessment scores in patients whose oral therapy was changed.[45] The final conference abstract reported improvements in UPDRS II, UPDRS III, Percent Over Target and PDQ39 amongst 33 patients treated with oral therapy, who were found to have uncontrolled disease with the assistance of PKG.[59] Whilst these results appear promising, two of the studies were very small and it was not possible to assess their quality owing to limited reporting.

Other clinical outcomes were less thoroughly reported and outcomes reported varied amongst the studies reported as full publications. In the study which reported that PKG resulted in clinical management plan changes in 64% patients at visit 1 and 29% patients at visit 2, PKG scores and Hoehn and Yahr ratings were similar between visit 1 and visit 2.[62] On the Clinician Global Impression of Improvement (CGI-I) scale, 61% patients showed improvement, 32% no change and 7% minimally worse. On the Patient Global Impression of Improvement (PGI-I) scale, 54% respondents indicated improvement, 38% no change, 8% minimally worse (4 patients did not respond).[62] However, it is not clear how many patients would have had a change in treatment anyway, regardless of PKG; reporting was unclear.

In the study that reported the proportion of 'uncontrolled' patients whose symptoms were brought under control after changes in oral therapy following PKG assessment, there were significant improvements in Non-Motor Symptom Questionnaire and Montreal Cognitive Assessment between baseline and the final visit amongst the 33 patients who had a change in therapy. Improvement in quality of life, measured using PDQ39, was not statistically significant amongst the full population who had a change in therapy, however, there was a statistically significant improvement in the subgroup of 14 patients whose symptoms were brought under control.[35]

Another study, which reported that PKG resulted in treatment plan changes in 31.8% patients, reported that there were no significant differences in clinical variables (PKG Bradykinesia Score, PKG Dyskinesia Score, PKG Fluctuations Dyskinesia Score, Parkinson's Disease Composite Scale, Non-Motor Symptom Questionnaire, Parkinson's Disease Questionnaire-8 and EuroQoL Visual Analogue Scale) when repeated after 3-6 months.[68] However, the Clinician Global Impression of Improvement (CGI-I) scale showed a slight overall improvement at follow-up (mean score = 3.6).[68]

A retrospective cohort study reported that 49/104 patients required more than 1 PKG encounter to reach a controlled state; 37 patients had 2 encounters, 7 patients had 3 encounters and 5 patients had 4 encounters. Most patients undergoing 3 or 4 PKG encounters did not reach a controlled state as defined by PKG until the 3rd or 4th encounter.[56]

One study merely reported that there were no serious adverse events or adverse device effects reported.[48]

3.3.5 Patient and carer opinions

A total of eight studies reported patient or carer opinions on PKG.[25, 28, 32, 48, 62, 65, 67, 71] The four studies reported in full also reported intermediate or clinical outcomes, so the quality assessment of these studies is reported in Table 6.[28, 32, 48, 62] Four conference abstracts only reported survey results.[25, 65, 67, 71] These have not been assessed for quality due to lack of information in abstracts.

The results are summarised in Table 11, with further data in Appendix 9.4 Table 63.

Table 11 Patient and carer opinions of PKG

Study	N	Topic / Question asked	Agreed	Disagreed	Neutral	Don't know
Full papers						
Dominey 2020[28] UK	62	Introductory information and instructions were helpful	79.0%			
		Process of returning the device simple	98.0%			
		Valued the medication reminders	80.0%			
		Perceived the results as reflective of their lived experience	60.0%			
		Valuable in providing additional information to their clinical team	59.0%			
		Willing to continue using it as part of their management	97.0%			
		Satisfaction at not having to travel to clinic	40.0%		44.0%	
Evans 2020[32] UK	46	Satisfied with virtual clinic	89.0%	7.0%	7.0%	
Joshi 2019[48] USA	63	PKG medication reminders assisted me with taking my medication on time	75.3%	2.4%	11.8%	10.6%
		PKG data assisted me with explaining my symptoms to my doctor	61.4%	4.8%	24.1%	9.6%
		The PKG provided additional data that assisted my doctor with making decisions about my care	78.6%	1.2%	10.7%	9.5%
		The PKG was easy to use	85.7%	3.6%	0.0%	10.7%
		I was able to wear the PKG and complete medication use confirmations as instructed by my doctor	84.3%	4.8%	0.0%	10.8%
		I would be willing to use the PKG again to assist in the management of my PD in the future	86.9%	1.2%	1.2%	10.7%

		Other questions omitted due to similarity. Results presented as proportion of visits (n=85)				
Nahab 2019[62] USA	28	PKG was easy to use	93.0%			
		Performed as expected	96.0%			
		Would use it again (if not charged)	100.0%			
		Would use it again (if payment required)	32.0%			
		Device assisted with explaining symptoms to the physician	79.0%			
		Assisted with taking medication on time	100.0%			
		Valuable in providing data to the physician they could not provide	89.0%			
Abstracts						
Chhabria 2018[25] Location not stated	50	Overall, patients reported high satisfaction with wearing the device.				
Rasul 2017[65] USA	28	PKG was very easy to use (*strongly agreed*)	68.0%			
		Able to wear PKG and complete medication use confirmations as instructed by doctor	96.0%			
		The feature of PKG for reminder was very helpful for medication compliance	97.0%			
Spengler 2016[67] USA	5	Patients felt that PKG was helpful with medication reminders and helped explain the symptoms better.				
Thomas 2019[71] UK	NR	98% of patients reported a positive/neutral user experience.				

In surveys of patients and carers most agreed that PKG was generally easy to use. PKG appeared most useful to patients as a reminder to take medication, with between 75.3% (in Joshi 2019[48]) and 100% (in Nahab 2019[62]) agreeing that PKG was useful for that purpose. Results were more equivocal for whether PKG provided useful information on symptoms that the patients or carers could not themselves provide; between 59% (Dominey 2020[28]) and 79% (Nahab 2019[62]) of patients agreed this was the case. It is unclear whether this was because people felt the device was not providing useful information, or because their symptoms were such that the device did not provide extra information.

Patients were generally willing to use the PKG device again, although less so if required to cover the costs themselves (Nahab 2019[62]). In the study that used PKG for remote management of patients

(Evans 2020[32]), patients were generally happy with the virtual clinic approach, suggesting that PKG could reasonably be used for fully remote monitoring and assessment.

3.3.6 Clinical opinions

A total of six studies reported clinicians' opinions on the value of PKG.[48, 57, 62, 66, 68, 70] These are summarised in Table 12. The studies reported in full also reported intermediate or clinical outcomes, so the quality assessment of these studies is reported in Table 6. Two conference abstracts only reported survey results.[57, 70] These have not been assessed for quality due to lack of information in abstracts.

Table 12 Clinical opinions of PKG

Study	N	Question asked	Agreed	Disagreed
Full papers				
Joshi 2019[48] USA	63	Improved dialogue with patient	59%	
		Improved ability to assess impact of a therapy	38%	
		Improved ability to assess need for additional tests or treatments	7%	
		Improved ability to assess patient PD symptoms	33%	
		Some questions omitted due to similarity		
Nahab 2019[62] USA	28	Improved dialogue with patient	89% (visit 2)	
		Improved ability to assess impact of a therapy	89% (visit 2)	
		Improved ability to assess need for additional tests or treatments	4% (visit 2)	
Santiago 2019[66] USA	112	Did PKG provide additional information?	41%	59%
		Was a clinical management plan change made?	32%	9%
Sundgren 2021[68] Sweden	66	PKG improved the dialogue with the participant	88%	
Abstracts				
Langston 2017[57] USA	89	PKG provided additional information not available from clinical consultation alone	38%	
Thakur 2017[70] USA	51	PKG provided information not available from the clinical consultation that drove a clinical management plan change	47%	

Clinicians' opinions of PKG were generally less favourable than patient opinions. Most clinicians agreed that use of PKG improved dialogue with patients.[48, 62, 68] They were generally less convinced that PKG improved their assessment of symptoms or need for changes in therapy. Four of the studies found that PKG provided additional useful information in only 32% to 47% of patients.[48, 57, 66, 70] Nahab 2019 was an outlier, where 89% of clinicians felt that PKG improved their ability to assess impact of therapy.[62]

It should be noted that these clinical opinions somewhat contradict the actual evidence on changes in treatment (Section 3.3.3 and Table 7), where many patients did have a change in treatment as a result of PKG use.

3.3.7 Summary of PKG evidence

Much of the published evidence for PKG consists of either diagnostic accuracy or association studies, mostly designed as proof-of-concept studies to show that PKG can usefully measure symptoms associated with Parkinson's disease. This evidence broadly suggests that PKG can accurately measure dyskinesia, bradykinesia and tremor. Sensitivity estimates (for bradykinesia and fluctuations in dyskinesia) were high (near 100%), but specificity estimates were generally lower (83-87.5%), suggesting a possibility that PKG may slightly over-diagnose symptoms. PKG appears to have lower accuracy for measuring sleep disturbance. Diagnostic accuracy studies also suggest that PKG has reasonable accuracy when diagnosing clinical factors, such as levodopa response and need for device assisted therapy. It should be noted that the quality of diagnostic evidence is low, and lacks replication, with most outcomes studied in only one study. This is partly due to the limitations of performing formal diagnostic accuracy studies in this field, as all outcomes are usually assessed by clinicians and patients, with no clear objective reference standards.

The results of the association studies generally supported those of the diagnostic accuracy studies; PKG bradykinesia, dyskinesia and tremor scores were generally moderately correlated with UPDRS scores, whilst the evidence for sleep and impulse control behaviours was less promising.

The studies investigating the intermediate impact of PKG were generally of good quality (5/8 studies had a low risk of bias). The evidence from those studies indicates that PKG is being used by clinicians to guide treatment decisions, primarily the addition of a new therapy or increase in treatment dose. PKG use is likely to lead to change in management for a sizeable proportion of patients (plausibly 31.8% to 79% of patients). However, this also means that many patients will have no change in management after PKG use, although its use may still be helpful for confirming that no change is required. As these studies were not formal comparative studies there is a possibility that some medication changes made because of PKG results were unnecessary, or helpful medication changes may have been missed. The population of these studies was newly diagnosed PwP, those attending

routine follow-up, clinically stable patients and those considered to benefit from continuous objective measurement, where stated. There was no comparison of different patient populations, therefore, no indication of which patients are more likely to have management changes as a result of PKG use.

The key evidence on the clinical value of PKG came from a single trial (Woodrow et al.).[17] This trial compared centres using PKG to those using standard assessment methods. It was not randomised but was otherwise at low risk of bias. The Woodrow trial demonstrated that patients managed with PKG appear to benefit more than those on clinical management alone, with improvements in UPDRS III and IV scores (by around 3.1 and 1.2 points respectively), and plausibly reductions in bradykinesia and dyskinesia. This benefit seems to depend on whether patients were "in target" (i.e. condition was under control with current treatment) before PKG use. Patients not "in target" saw improved UPDRS scores, but those "in target" did not. Patients "in target" may, however, benefit from reduced levodopa dose and consequent reduction in dyskinesia, but this was inconclusive. It should be noted that the Woodrow trial included multiple uses of the PKG device over a short period of time (once every five weeks); hence the clinical benefits that might occur if PKG is used less frequently might be different.

Other clinical evidence was more limited and drawn from non-comparative studies, although these studies generally had low risk of bias. This additional evidence supports PKG giving improvements in UPDRS scores; study populations varied, with some studies including clinically stable patients with well controlled symptoms, whilst others included uncontrolled patients. It also suggested improvements in outcomes in the majority of patients as assessed by patients and clinicians using PGI-I and CGI-I scales. As these studies were not comparative it is unclear how much of the benefit can be ascribed to PKG use specifically.

There was limited evidence on patient, carer or clinician opinions of PKG. Patients had generally favourable opinions as to the value of PKG, particularly valuing its ability to remind them to take medication. Patients often found that PKG helped with discussing or reporting symptoms with their clinician. Clinicians were more equivocal about the value of PKG, with many thinking that PKG provided no additional clinical information over their own judgement, although the majority agreed that PKG improved dialogue with the patient.

There was some evidence, from one study, that PKG can be used for remote management of Parkinson's disease.[32] In that study, clinicians judged that most remote assessments were successful, and patients were generally satisfied with a remote assessment of their condition.

Overall, the EAG concludes that there is a good body of evidence to support the use of PKG in practice. PKG appears to be able to reliably measure bradykinesia and dyskinesia, and provides useful information that leads to changes in clinical management for at least some patients. There is

reasonable evidence that using PKG leads to genuine clinical improvements for patients when compared to standard management, in terms of reductions in UPDRS scores. However, multiple clinic visits and PKG assessments may be required before patients reach a controlled state.

3.4 STAT-ON

This section considers the results of the 15 publications that reported evidence on the STAT-ON device. It should be noted that several included publications, particularly those reporting diagnostic accuracy taken from the manufacturer website, did not explicitly name the device used as STAT-ON. However, as the papers were listed as relating to STAT-ON on the manufacturer website, they are included in this assessment.

3.4.1 Diagnostic accuracy

A total of eight papers reporting on diagnostic accuracy for STAT-ON were identified.[74, 77, 78, 80, 82, 84, 86, 87] None of these explicitly identified the device used as STAT-ON; however, all were listed on the device website, so it is assumed that the device is the same as STAT-ON. Many of the papers overlap in authorship, and most report data from the REMPARK study, or related studies, supported by the manufacturer. All studies are reported here for completeness, but it should be noted that they are not independent and may have overlapping populations. One further conference abstract was found, which is not discussed here due to limited reporting of data (this study reported that no device-related adverse events were reported).[75]

The quality assessment of the papers is given in Table 13.

Table 13 QUADAS-2 risk of bias assessment for STAT-ON studies of diagnostic accuracy

Study	Risk of Bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Bayes 2018[74]	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Perez-Lopez 2016 (AIM)[78]	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Perez-Lopez 2016 (Sensors)[77]	Unclear	Unclear	Unclear	High	Low	High	Unclear
Rodriguez-Martin 2017 (PlosOne)[80]	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low
Rodriguez-Molinero 2015[82]	Unclear	Unclear	Unclear	High	Low	High	Low
Rodriguez-Molinero 2018[84]	Unclear	Unclear	Unclear	Low	Low	Unclear	Low

Sama 2017 A[86]	Unclear	Unclear	Unclear	Low	Low	High	Unclear
Sama 2018 B[87]	Unclear	Unclear	Unclear	Low	Low	High	Unclear

As the STAT-ON diagnostic accuracy papers were mostly reporting the REMPARK study, and/or had overlapping authorship, the QUADAS-2 assessment was very similar across publications. Risk of bias for the index test was considered unclear as papers did not generally describe the index test directly, and in some it appeared to be derived as part of the data analysis itself. Hence it was also unclear whether these index tests are part of the current device in commercial use. Although effort was made to have robust reference standards, such as by video recording patients for clinical assessment, or adjusting patient diaries for possible errors, it remains unclear whether clinical or patient assessment represents a robust reference standard for the outcomes considered. Flow and timing risk was often rated as high or unclear due to lack of reporting as to exactly when index tests and reference standard assessments were performed, and whether all included patients were analysed.

Table 14 presents a summary of the diagnostic accuracy data from the STAT-ON publications. No studies were from the UK; studies were mostly conducted in Spain, or in various European countries, as part of the REMPARK study. Sample sizes varied from 12 to 102.

Table 14 Diagnostic accuracy data reported in STAT-ON studies

Study	Study type	N	Reference standard	Outcome	Sensitivity	Specificity
Bayes 2018[74] Spain, Italy, Israel and Ireland	Cohort	41	Patient diaries + UPDRS correction	On-Off times	97	88
Perez-Lopez 2016 (AIM) [78] Spain, Ireland, Italy and Isreal	Cohort	102	Clinical assessment based on video	DK (all n=35)	57	81
				DK (strong trunk n=4)	100	98
Perez-Lopez 2016 (Sensors) [77] Spain	Cohort	35	Clinical assessment and patient diaries	On-Off times	90.28 (by outputs)	92.11
Rodriguez-Martin 2017[80] Spain, Ireland, Italy and Isreal	Cohort	21	Clinical assessment based on video	Freezing of gait (SVM generic)	74.7	79
				(SVM personalised)	88.1	80.1
Rodriguez-Molinero 2015[82] Spain	Cohort	20 (total 35 in study, exact number unclear)	Trained observer	On-Off times	96 (IQR: 93 to 100)	94 (IQR: 90 to 100)
Rodriguez-Molinero 2018[84] Spain	Cohort	23 (with advanced PD)	Patient diaries	On-Off times	PPV: 92 95% CI: 87.33 to 97.3	NPV: 94 95% CI: 90.71 to 97.1
Sama 2017 (CBM)[86] Spain	Cohort	12	Clinical assessment based on video	BK	92.52	89.07
Sama 2018 (PRL)[87] Spain	Cohort	15	Clinical assessment based on video	Freezing of gait	91.7	87.4

Reporting of diagnostic accuracy data was limited, with only two studies reporting numbers of true positives, etc.,[77, 78] and most studies not reporting confidence intervals. Four studies evaluated whether STAT-ON can diagnose "On-Off" times.[74, 77, 82, 84] These all found that STAT-ON had high diagnostic sensitivity (between 90.3% and 97%) and high specificity (88% to 94%), and also high PPV and NPV (92% and 94%, respectively[84]). Two studies evaluated freezing of gait and found that STAT-ON had high sensitivity (88.1% and 91.7%), but lower specificity (80.1% and 87.4%).[80, 87]

One study found that STAT-ON had high accuracy for predicting bradykinesia,[86] and one study found that STAT-ON had high accuracy for predicting strong trunk dyskinesia, but poor diagnostic accuracy for predicting dyskinesia in general.[78]

Overall, these results suggest that STAT-ON is good at determining "On-Off" times, and symptoms in the lower limbs and trunk, such as freezing of gait and trunk dyskinesia.

3.4.2 Association outcomes

Three small cohort studies (n=11 to 75) reported only association outcomes.[79, 83, 85] One conference abstract that reported patient satisfaction/usability also reported limited association outcome data, but is not considered further here (see Appendix 0 Table 55 for data).[76] A summary of the association data reported in the included studies is shown in Table 15.

Table 15 Association data reported in STAT-ON studies

Study	Study type	N	Reference standard	Outcome	Correlation/Result	P-value
Perrote, 2021[79] Argentina	Cohort	11	Patient diary	Mean hours monitored	60±9.89 vs 40±16.4	<0.001
				Freezing of gait	Higher with STAT-ON	0.003
				Hours in ON state	Higher with STAT-ON	0.002
Rodriguez-Molinero, 2017[83] Spain, Italy, Israel and Ireland	Cohort	75	UPDRS III	STAT-ON output	-0.56	<0.001
			Gait (UPDRS III)	STAT-ON output	-0.73	<0.001
Rodriguez-Molinero, 2019[85] Spain, Italy, Israel and Ireland	Cohort	13	UDysRS (based on video)	DKS	0.7	0.01
				Trunk and leg DKS	0.91	<0.001

We note that the study by Perrote did not strictly report correlation between STAT-ON and patient diaries, however, the study meets inclusion criteria for the review and fits better within 'association outcomes' than any of the other outcomes of interest.[79]

There was a significant correlation between STAT-ON and clinical assessment using UDysRS (0.70, 95% CI: 0.33 to 0.88), which was higher for trunk and legs scale sub-items (0.91, 95% CI: 0.76 to 0.97), since the sensor is located on the waist.[85] In the largest study (n=75) there was moderate correlation between UPDRS III and STAT-ON outputs (rho -0.56); correlation between STAT-ON outputs and the gait item in the UPDRS III was good (rho -0.73).[83] The other study reporting association data on STAT-ON simply reported that mean hours monitored was greater by STAT-ON than that recorded by the movement diary (60 ± 9.89 vs 40 ± 16.4, p<0.001) and that reporting of freezing of gait episodes and hours in the ON state were higher with STAT-ON compared to the patient movement diary.[79]

3.4.3 Clinical outcomes and intermediate impact of monitoring

No studies reporting either intermediate impact or clinical outcomes were identified for STAT-ON.

3.4.4 Patient-, carer-, and clinician-reported opinions

One paper[74] and one conference abstract[81] reported patient or carer opinions on STAT-ON and one paper[88] and two conference abstracts[76, 81] reported clinicians' opinions.

Due to the limited reporting of these studies, quality assessment was not performed. Results of the studies are summarised in Table 16, and are given in full in Appendix 9.4 Table 64.

Table 16 Patient, carer and clinical opinions of STAT-ON

Study	N	Topic / Question asked	Agreed	Disagreed	Neutral
Full papers					
Bayes 2018[74] Spain, Italy, Israel and Ireland	33	Satisfaction with device (QUEST results)	76.0%	5.0%	20.0%
Santos-Garcia 2020[88] Spain *(Clinician survey)*	27	STAT-ON was considered better than the diaries	70.3%		
		A useful device for identifying advanced PD patients	81.5%		
		STAT-ON was considered from quite to very useful	74%		
		STAT-ON was considered very useful	11%		
		See also Appendix 0			
Conference abstracts					
Rodriguez-Martin 2021[81]	30	Caregivers find it a good or very good solution	80%		
		Caregivers found it easy to use	76%		

Location not stated	41	Patients found it very easy to use	77.5%		
	19	Neurologists think it can detect advanced PD symptoms	88%		
		Neurologists find the information useful or very useful	100%		
Caballol 2020[76] Spain	39	Patient satisfaction was high (most items scored 'quite satisfied' to 'very satisfied') *See also Appendix 0*			

Based on the limited evidence available, patients and caregivers generally found STAT-ON easy to use and were satisfied with the device (over 75% in two studies[74, 81]). The majority of neurologists considered the device/information 'quite' to 'very useful' and considered it a useful tool for identifying patients with advanced PD symptoms.[88]

One small cohort study (n=39) reported that patient satisfaction with STAT-ON was high (assessed using Quebec User Evaluation of Satisfaction with assisted Technology) and the system was found to be easy to use (assessed using System Usability Scale).[76]

3.4.5 Summary of STAT-ON evidence

While a substantial body of evidence on STAT-ON has been published, this evidence is largely restricted to diagnostic accuracy studies. The diagnostic accuracy studies were of uncertain risk of bias, largely because of lack of clarity in the exact index tests being used, and difficulties in establishing a robust reference standard. In general, the studies suggest that STAT-ON can accurately determine "On-Off" times and bradykinesia. STAT-ON may have particular benefits in identifying trunk and lower limb symptoms. It appears to have reasonably good accuracy for diagnosing freezing of gait, and possibly trunk dyskinesia, but not dyskinesia elsewhere. However, most of these results are based on very small numbers of patients. A larger study reporting association outcomes suggests that there is moderate correlation between STAT-ON outputs and the UPDRS III; there was good correlation between STAT-ON outputs and the gait item in the UPDRS III.[83]

A key limitation in the STAT-ON evidence base is that there is currently no evidence on the intermediate impact of STAT-ON (i.e. whether its use changes clinical management of patients) or on the clinical impact of STAT-ON (such as whether it leads to improved UPDRS scores). It is therefore unclear whether STAT-ON use will lead to treatment modification, and whether patients will see a benefit in terms of reduction in bradykinesia and dyskinesia, and improvements in UPDRS scores and quality of life.

There was limited evidence on patient, carer or clinical opinions of STAT-ON; most was generally favourable.

Overall, the EAG considers that the diagnostic accuracy evidence suggest that STAT-ON is a promising technology, that is likely to be able to identify "On-Off" periods, bradykinesia and freezing of gait. As it is worn on the waist it may be particularly useful for detecting lower limb and trunk symptoms. However, the lack of clinical evidence for STAT-ON means that it is not currently possible to determine if its diagnostic value will translate into a real clinical value for patients. The EAG considers that, because STAT-ON is a waist-worn device, and because diagnostic accuracy data relates mostly to "On-Off" times and freezing if gait, it cannot be safely assumed that the clinical benefits observed when using PKG will also apply when using STAT-ON.

3.5 Kinesia 360 and KinesiaU motor assessment systems

This section considers the Kinesia 360 and KinesiaU technologies together, as they are produced by the same Company. Overall, there were three eligible studies for Kinesia 360 and one for KinesiaU. All were conducted in the USA or Canada.

3.5.1 Diagnostic accuracy

One study reported diagnostic accuracy for a technology judged to be equivalent to Kinesia 360.[91] It should be noted that the device used was not explicitly named as Kinesia 360, and so may not be exactly the same as the true Kinesia 360 motor assessment system. The QUADAS-2 assessment is presented in Table 17 and the results are summarised in Table 18.

No diagnostic accuracy studies for KinesiaU were identified.

Table 17 QUADAS-2 assessment for Kinesia 360

Study	Risk of Bias				Applicability concern		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Pulliam 2018[91]	Unclear	Low	Low	Low	Low	High	Low

Table 18 Diagnostic accuracy of Kinesia 360

Study	Study type	N	Reference standard	Outcome	Sensitivity	Specificity	AUC
Pulliam, 2018[91] USA	Prospective cohort	13	Clinical assessment based on video	DK	74	85	86%
				BK	80	66	82%
				Tremor	90	80	89%

The risk of bias for the study was generally rated as low because the index test was clearly described, although it was not explicitly named as Kinesia 360. The index test and reference standard were assessed in a blinded fashion.

Kinesia 360 was found to have moderate to good diagnostic accuracy to detect bradykinesia, dyskinesia and tremor, with AUCs ranging from 82% for bradykinesia to 89% for tremor.

3.5.2 Association outcomes

There were no studies reporting association outcomes for Kinesia 360 or KinesiaU.

3.5.3 Clinical outcomes and intermediate impact of monitoring

Two studies of Kinesia 360[89, 90] and one study of KinesiaU[92] were eligible for inclusion. The studies were assessed for quality using tools appropriate to their study design; the two RCTs were assessed using the Cochrane risk of bias tool and the cohort study was assessed using a tool developed for the review using relevant criteria. The quality assessment results are summarised in Table 19 and

Table 20.

Table 19 Quality assessment of Kinesia 360 RCTs

Study	Isaacson, 2019[89]	Peacock, 2021[90]
Risk of bias arising from the randomisation process	Some concerns	High
Risk of bias due to deviations from the intended interventions	Low	Low
Missing outcome data	Low	Low
Risk of bias in measurement of the outcome	Low	Low
Risk of bias in selection of the reported result	Low	Some concerns
Overall judgement of risk of bias	Some concerns	High

Table 20 Quality assessment of KinesiaU cohort study

Study	Hadley, 2021[92]
Inclusion criteria clearly defined	Yes
Representative sample from relevant population	Unclear
Clearly described and consistently delivered intervention	Unclear
Outcome measures pre-specified, reliable and consistently assessed	Unclear

Outcome assessors blinded	No
Attrition low and accounted for in analysis	No
Free from suggestion of selective reporting	Yes
Overall judgement of risk of bias	High

Each of the included studies had a high risk of bias or some concerns regarding bias, limiting the reliability of their results.

A summary of the results of studies reporting clinical outcomes related to Kinesia 360 and KinesiaU is reported in Table 21.

Table 21 Clinical outcomes reported in Kinesia 360 and KinesiaU studies

Study	Study type	N	Intervention	Comparator	Intermediate impact of monitoring	Clinical outcomes
Isaacson, 2019[89] USA	Pilot RCT	PwP (n=39) with insufficiently controlled motor symptoms, prescribed transdermal rotigotine.	Kinesia 360 data used to supplement standard care in adjusting rotigotine dosage (n=19). Kinesia 360 was worn throughout the day on at least 2 consecutive days in weeks 1, 2, 3, 4 and 11.	Standard care to titrate the optimal rotigotine dosage (n=20).	Mean rotigotine dose (Kinesia 360 vs standard care): 4.8 vs 3.9 mg/24 hours. Mean rotigotine dosage increase (Kinesia 360 vs standard care): +2.8 vs +1.9 mg/24 hours. Mean number of dosage changes (Kinesia 360 vs standard care): 2.8 vs 1.8 changes.	Change in UPDRS II at week 12 (Kinesia 360 vs standard care): -2.1 vs 0.5; p=0.004. Change in UPDRS III at week 12 (Kinesia 360 vs standard care): -5.3 vs -1.0; p=0.134 (no significant difference between groups). Change in PAM-13 score at week 12 (Kinesia 360 vs standard care): -4.6 vs -0.2; p=0.164 (no significant difference between groups). There was no significant change in PDQ-39 in either group. Mean rotigotine dosage increase from baseline to week 12 (Kinesia 360 vs standard care): +2.8 vs +1.9 mg/24 h. Mean number of dosage changes: 2.8 vs 1.8. 3 patients in the Kinesia 360 arm and 2 patients in the standard care arm discontinued rotigotine due to treatment-emergent adverse events.
Peacock, 2021[90] Canada	RCT	PwP (n=25) with bothersome	Telehealth follow-up care with data from in-home	In-person follow-up care with clinical	None	Average change in PDQ-39 Summary Index score from baseline to

		tremor or dyskinesia identified as a treatment target.	Kinesia 360 (n=13). Kinesia 360 was worn for 3 days.	examination and 3-day symptom diary (n=12).		completion (telehealth follow-up vs usual care): 4.7 points (95% CI: -10.2 to 0.7) vs +0.9 (95% CI: -3.6 to 5.5). LEDD change from baseline (mean 32 mg vs 52 mg) and appointments per participant (mean 2.2 vs 1.8) were not significantly different between groups.
Hadley, 2021[92] USA	Prospective cohort study	PwP (n=16) undergoing therapy changes.	KinesiaU alongside clinical judgement. KinesiaU was worn for 3 days.	None.	Therapy recommendation made based on KinesiaU and clinical judgement.	8/13 patients who successfully used KinesiaU and returned for follow-up demonstrated improvements from their new therapy and were instructed to continue with it, while 5 were instructed to discontinue (due to lack of benefit or side effect) and return to previous therapy/dose. 3 patients were prescribed levodopa inhalation powder (2 improved, 1 discontinued), 1 patient was prescribed trihexyphenidyl (discontinued), 3 patients were prescribed istradefylline (1 improved, 2 discontinued), 1 was prescribed increased melatonin dose (improved), 2 were prescribed exercise (improved), 2 were prescribed an increase in carbidopa-levodopa dose (1 improved, 1 discontinued) and 1 patient was prescribed increased doses of carbidopa-levodopa and trihexyphenidyl (improved).

A small pilot RCT (n=39) compared Kinesia 360 to supplement standard care versus standard care alone to titrate the optimal rotigotine dosage in PwP with insufficiently controlled motor symptoms, prescribed transdermal rotigotine.[89] Mean rotigotine dose, mean rotigotine dosage increase and mean number of dosage changes were higher in the Kinesia 360 arm than the standard care arm. At week 12 there was a statistically significant improvement in UPDRS II in the Kinesia 360 arm compared with a slight worsening in the standard care arm (-2.1 vs 0.5, p=0.004). The difference in improvement in

UPDRS III was not statistically significant between groups (-5.3 vs -1.0; p=0.134). There was no significant change in PDQ-39 or PAM-13 score at week 12 in either study group.

A small RCT that was suspended due to Covid-19 (n=25) compared telehealth follow-up care using data from Kinesia 360 with usual in-person follow-up care in PwP with bothersome tremor or dyskinesia identified as a treatment target at their most recent visit.[90] The average change in PDQ-39 Summary Index score from baseline to completion (primary outcome) was -4.7 points in the telehealth group (95% CI: -10.2 to +0.7) and +0.9 (95% CI: -3.6 to +5.5) in the usual care group (mean baseline PDQ-39 score was 29 in the telemedicine group and 25 in the usual care group). Secondary outcomes were not significantly different between groups. Repeat measurement of MDS-UPDRS Part III was not completed due to suspension of face to face clinical and research visits, due to Covid-19.

A small cohort study (n=16) assessed KinesiaU in PwP undergoing therapy changes.[92] Fourteen patients successfully used the KinesiaU system, whilst two did not complete the recordings due to user difficulty or technical issues. Thirteen of the patients who successfully used the KinesiaU system returned for a follow-up visit; the clinician reviewed the KinesiaU report with each patient and made a therapy recommendation based on the report and clinical judgement. Eight patients demonstrated improvements with their new therapy and were instructed to continue with it while five were instructed to return to their previous therapy.

3.5.4 Patient-, carer-, and clinician-reported outcomes

One paper reported patient opinions of Kinesia 360, and one paper reported patient opinions of KinesiaU. The quality assessment results of these studies are presented in Table 19 and

Table 20. Table 22 summarises the patient opinion data from the two studies.

Table 22 Patient opinions of Kinesia 360 and KinesiaU

Study	Study type	N	Topic / Question asked	Agreed	Disagreed	Neutral
Peacock 2021[90] Kinesia 360 Canada	RCT	13	Comfortable or very comfortable using motion sensors	54.0%	8.0%	39.0%
			Telehealth patients would have preferred to be in the usual care group	46.0%	8.0%	46.0%
Hadley 2021[92] KinesiaU USA	Prospective cohort	16	The KinesiaU system was easy to understand and use	88.0%	12.0%	
			I looked at the KinesiaU reports often	32.0%	37.0%	31.0%
			The KinesiaU reports were useful to look at	38.0%	19.0%	44.0%
			The periodic tasks were easy to perform	88.0%	6.0%	6.0%

			I would continue to use the system on my own if it was available to me	44.0%	31.0%	25.0%
			I would recommend this device to a friend	53.0%	14.0%	33.0%
			The KinesiaU reports made me more aware of changes in my symptoms	44.0%	13.0%	44.0%

In the RCT of telehealth follow-up care with data from in-home Kinesia 360,[90] 54% telehealth patients reported feeling comfortable or very comfortable using motion sensors and 8% were uncomfortable or very uncomfortable using motion sensors. 46% telehealth patients would have preferred to be in the usual care group, 8% would not and 46% were undecided. 8% usual care patients would have preferred to be in the telehealth group, 67% would not and 25% were undecided.

In the cohort study of KinesiaU,[92] 88% patients agreed or strongly agreed that the KinesiaU system was easy to understand and use, while 12% disagreed or strongly disagreed. Only 32% patients agreed or strongly agreed that they looked at the KinesiaU reports often and only 38% agreed or strongly agreed that they were useful to look at. 44% patients agreed or strongly agreed that they would continue to use the system if it was available to them, 25% were neutral and 31% disagreed.

3.5.5 Summary of Kinesia 360 and KinesiaU evidence

The evidence on Kinesia 360 was mostly from two small RCTs (64 patients in total). These suggested favourable results when using Kinesia 360, with reductions in UPDRS scores, and improvements in quality of life comparable to those seen for PKG. However, neither study used the device during routine clinical visits for PwP; in one study patients with insufficiently controlled motor symptoms were being assessed to titrate the optimal rotigotine dosage,[89] and in the other study Kinesia 360 was used in remote telehealth assessments.[90]

One diagnostic accuracy study found that Kinesia 360 had moderate to good accuracy for diagnosing dyskinesia, bradykinesia and tremor.[91]

Given the limited evidence base, the EAG considers that Kinesia 360 is a promising technology, but there is too little evidence at present to be confident about its clinical value.

Evidence on KinesiaU was limited to one small study (16 patients).[92] The EAG considers this to be too little evidence to draw any conclusions on the clinical value of KinesiaU. Patient opinion of the KinesiaU system was not particularly favourable.

3.6 PDMonitor

One paper[95] and one conference abstract[93] discussing the PDMonitor technology were identified.

3.6.1 Diagnostic accuracy and association outcomes

One small cohort study (n=30), reported only as an abstract, reported that PDMonitor accurately detected and estimated the severity of arm bradykinesia, dyskinesia, gait impairment, wrist tremor, leg tremor and freezing of gait compared with clinical assessment by a PD expert physician using UPDRS III and AIMS.[93]

3.6.2 Clinical outcomes and intermediate impact of monitoring

One case series described two cases where PDMonitor revealed information leading to medication changes and improvement in symptoms.[95] As this study only included two patients the EAG do not think it represents useful evidence for PDMonitor, and do not consider it further.

3.6.3 Patient-, carer-, and clinician-reported outcomes

No studies reporting patient, carer or clinical opinion for PDMonitor were identified.

3.6.4 Summary of PDMonitor evidence

As there are currently no fully published studies of PDMonitor, the EAG considers that no conclusion as to the clinical value of PDMonitor can be drawn. It cannot be safely assumed that the benefits of PKG (or other technologies) will apply if PDMonitor is used.

3.7 Discussion

3.7.1 Summary of key results

A full summary of the EAG's conclusions for each technology is reported in the sections of the report for each technology (See Sections 3.3 to 3.6). Here we present a broad summary of all evidence.

Overall, the EAG considers that only PKG has a body of research evidence sufficient to fully assess its clinical potential. PKG appears to accurately measure dyskinesia and bradykinesia, with very high sensitivity and reasonably high specificity. Diagnostic accuracy was also reasonably high for measuring tremor and treatment-related outcomes. However, its accuracy for measuring sleep disturbance was lower.

PKG is being used by clinicians to guide treatment decisions, primarily the addition of a new therapy or increase in treatment dose; PKG use led to a change in management for 32-79% patients. The key evidence on the clinical value of PKG came from a single trial by Woodrow et al. The trial demonstrated that patients managed with PKG appear to benefit more than those on clinical management alone, with improvements in UPDRS III and IV scores. This benefit seems to depend on whether patients were "in target" (i.e. condition was under control with current treatment) before PKG use. Patients not "in target" saw improved UPDRS scores, but those "in target" did not. Also, PKG

was used frequently (every five weeks) in the trial, and benefits may be different if PKG is used less frequently.

There is therefore reasonable evidence that using PKG leads to genuine clinical improvements for some patients. However, multiple clinic visits and PKG assessments may be required before patients reach a controlled state.

For STAT-ON, evidence is almost entirely limited to diagnostic accuracy studies. These suggest that STAT-ON can accurately diagnose "On-Off" times and bradykinesia. STAT-ON also seems to have reasonably good accuracy for diagnosing freezing of gait and possibly trunk dyskinesia (as a waist-worn device), but not dyskinesia elsewhere.

There is currently no evidence on the intermediate impact of STAT-ON or on the clinical impact of STAT-ON, therefore, it is unclear whether STAT-ON use will lead to treatment modification and subsequent improvements in symptoms and quality of life. Overall, the EAG concludes that whilst STAT-ON is a promising technology, the lack of clinical evidence means that it is not currently possible to determine if its diagnostic value will translate into real clinical value for patients.

Two small RCTs suggest favourable clinical outcomes with Kinesia 360 use in populations receiving rotigotine or when Kinesia 360 was used for remote telehealth assessments. In view of the extremely limited evidence base, the EAG considers that Kinesia 360 is a promising technology in certain situations, but that there is currently too little evidence to be confident about its clinical value.

Evidence on KinesiaU and PDMonitor are too limited to draw any conclusions on their clinical value.

The EAG considers that, because of the very different natures of the technologies assessed, such as the specific symptoms they measure, the position of the sensors on the body and the characteristics of PwP that the devices have been assessed in, it should not be assumed that any clinical benefits observed for PKG would also be found with the other technologies.

There were no studies that directly compared one remote continuous monitoring device against another. In addition, there was limited evidence on the use of remote monitoring devices in different patient subgroups. Therefore, it is unclear which patients are more likely to have management changes and subsequent improvements in clinical outcomes as a result of their use. The only evidence relating to adverse events was that there were no device-related adverse events reported (PKG and STAT-ON).

3.7.2 Generalisability of results

The EAG considers that the results observed in the included studies are likely to be broadly generalisable to patients with Parkinson's disease in the UK. Although few studies were conducted in the UK itself, most were conducted in Europe, North America or Australia, and so their results are likely to be broadly applicable to the UK. Most studies recruited patients with Parkinson's disease without any further limitations on inclusion criteria, and without focus on specific subgroups. This would suggest that the results will be generally applicable to other patients with Parkinson's disease.

A key generalisability concern is that almost all studies were conducted in patients receiving pharmacological therapy, primarily levodopa. The clinical evidence for PKG is largely focussed on how PKG use can modify levodopa therapy, and the clinical impacts of those therapy changes. Consequently, there is little to no evidence on the possible benefits of the technologies in other types of patients, such as those receiving non-pharmacological therapy, or on more advanced therapies such as deep brain stimulation. The EAG does not think it safe to assume that the benefits of PKG, or other technologies, will necessarily apply to these other patient groups.

There was no evidence relating to most patient subgroups of interest. In particular, there was no evidence specifically related to people with communication barriers or difficulties, and no evidence for specific ethnicities, or by socio-economic status. It is unclear how PKG, or other technologies, might work in those key populations.

As noted elsewhere, because of the very different natures of the technologies assessed, the EAG does not consider that any clinical benefits observed for PKG would also be found with the other technologies.

3.7.3 Strengths and limitations of analysis

This is the first complete systematic review of all available diagnostic and clinical evidence for PKG, Kinesia 360, KinesiaU and PDMonitor (a review of STAT-ON was published while this project was underway). This review used extensive database searches to identify all published evidence on the included technologies and followed rigorous recommended review methods to identify relevant publications, assess their risk of bias and undertake a narrative synthesis of the results. As such, this is the first fully rigorous review of these technologies, and also the first to compare the technologies in one review.

The review was strengthened by the provision of individual-level data for the key clinical trial of PKG, which permitted a more thorough examination of the clinical impact of PKG than would otherwise have been possible.

A key limitation of the analyses is due to the lack of replication across studies. In general, most outcomes were reported in only one or two studies, or outcomes were reported in inconsistent ways across studies. This meant that no meta-analysis was possible for any included studies, and the narrative synthesis was severely limited by the consequent difficulties in comparing different studies. This lack of replicability raises some concerns as to how robust the findings of the review are. It should be noted that many of the review conclusions are based on individual studies.

A further limitation is the low quality of much of the evidence, particularly for diagnostic accuracy. This casts some doubt on the validity of the diagnostic accuracy evidence. It should be noted that few studies were formal diagnostic accuracy studies, and there are innate difficulties in this field in robustly assessing diagnostic accuracy, given the lack of clear reference standards, and lack of clarity over the exact algorithms used to convert device output into diagnostic assessments.

4 ASSESSMENT OF EXISTING COST EFFECTIVENESS EVIDENCE

This section provides an overview of existing cost-effectiveness evidence relating to the use of remote continuous monitoring devices (PKG, Kinesia 360, KinesiaU, PDMonitor and STAT-ON) as an adjunct to clinical judgement for the assessment of motor and non-motor symptoms in PwP. Given that all technologies under assessment have only recently been commercialised, it was anticipated that there would be a dearth of relevant economic evidence for the remote monitoring devices. Therefore, to inform the development of a new decision-analytic model in Parkinson's disease, a broader review of published 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 PwP was undertaken.

4.1 Methodology of the cost-effectiveness review of remote continuous monitoring devices for people with Parkinson's disease

4.1.1 Searches

The bibliographic search detailed in Section 2.1 was used to identify studies reporting on the cost-effectiveness of PKG, Kinesia 360, KinesiaU, PDMonitor and STAT-ON devices.

4.1.2 Selection process

The review considered a broad range of economic studies including trial-based economic evaluations, modelling studies and analyses of administrative databases. The inclusion criteria considered were full economic evaluations comparing two or more alternative interventions in terms of both costs and consequences, i.e., cost-minimisation, cost-effectiveness, cost-utility and cost-benefit analyses.

The protocol for the selection of relevant studies defined two selection stages: i) assessment and screening for possible inclusion of titles and abstracts identified by the search strategy, and ii) acquisition and screening for inclusion of the full texts of potentially relevant studies. Two researchers (RW and NM) independently screened the titles and abstracts of all reports identified by the bibliographic searches. Full-text papers were subsequently obtained for assessment and screened by at least two researchers, with any disagreement resolved by consensus.

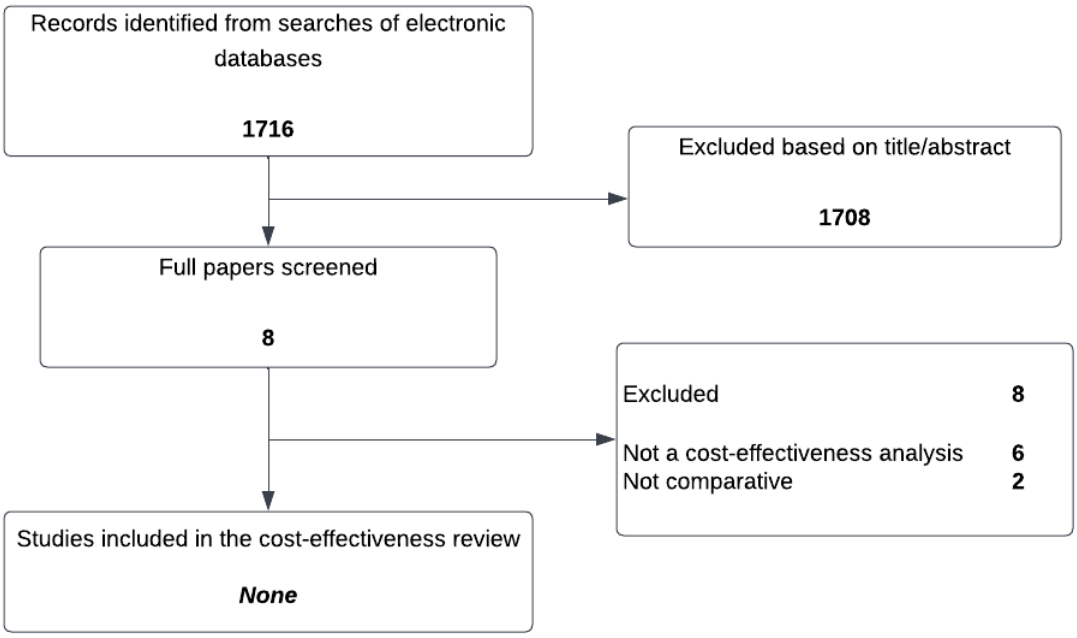
4.2 Results of the cost-effectiveness review for remote continuous monitoring devices

A PRISMA diagram of the review of studies identified in the main systematic review is presented in Figure 4. The initial search identified a total of 1716 (after deduplication). A total of 8 studies were identified as potentially relevant from their titles and/or abstracts. Following full text assessment none were considered to meet the full inclusion criteria. Two excluded studies, Lynch et al. (2018) and Rao et al. (2019), were retrospectively included in the review because both aimed to assess the cost

savings and quality-adjusted life year (QALY) gains associated with PKG but were non-comparative assessments of cost-effectiveness, i.e., no comparator was considered in the analysis.[59, 64]

Following completion of the systematic review of previous cost-effectiveness studies for remote continuous monitoring devices, the company for PKG (Global Kinetics) made the EAG aware of a company-sponsored study examining the cost-effectiveness of PKG and clinical assessment in the management of Parkinson's disease. This study by Chaudhuri et al., (2022) was published online on 14th June 2022.[96] The study is directly relevant to the decision problem addressed in this report as it represents the first cost-effectiveness analysis performed for a continuous objective measurement system in Parkinson's disease in the context of the UK NHS. A detailed description and critique of Chaudhuri et al. (2022) is presented below.

Figure 4 Flow diagram of the study selection process for the cost-effectiveness review



4.2.1 *Lynch et al., 2018*

Lynch et al. was a cost-consequence analysis considering the cost savings and QALY gains in people whose oral therapy was adjusted following assessment with the PKG and did not consider any comparator.[59] The analysis was based on a before and after study enrolling 103 PwP in Australia, all of which were evaluated using the PKG. The economic evaluation focused specifically on a subgroup of 33 of these patients who had their oral therapy adjusted. In this subgroup, patients were observed to have experienced reductions in UPDRS II and UPDRS III scores and improvements in the PDQ39 quality of life instrument. No formal modelling was implemented as part of the economic analysis. Instead, the UPDRS domain scores were used to directly estimate reductions in costs and QALYs

using evidence from published sources considering a one-year time horizon. Cost savings were estimated using an algorithm reported in McCrone et al. (2007), which suggested that a one-point reduction in UPDR-II is associated with a $430 cost saving.[97] Based on reported changes in UPDRS-II, this resulted in cost savings of $1,719.42 per patient (exclusive of the cost of the PKG monitoring device). Benefits were estimated using regression models reported in the NICE Parkinson's disease Guideline, which linked EQ-5D with several clinical measures.[98] Using reported improvements in UPDRS II, UPDRS III, Percent Over Target and PDQ39, QALY gains of between 0.10-0.12 were estimated.

4.2.2 *Rao et al.*

Rao et al. sought to assess the impact of PKG on pharmacological treatment and decisions to initiate advanced treatment.[64] The study reports on 37 PwP attending a movement disorder clinic and who were clinically assessed as requiring advanced treatment. Following PKG, 5 of these were considered to need advanced treatment with the remaining 5 patients managed via dose adjustments to pharmacological care. On the basis of this finding, the study estimated potential cost savings associated with postponing advanced treatment. This assumed transition to apomorphine either administered by pump or by pen. Cost savings associated with Apo-go pump were estimated as £5,400 per pump per year leading to a saving of £27,000 per year for 5 patients. For Apo-go-pen treatment, equivalent cost savings were estimated as £3,200 per year leading to a saving of £16,000 per year. Sources used to inform the costs were not stated.

4.2.3 *Chaudhuri et al.*

Chaudhuri et al. (2022) explored the cost-effectiveness of the PKG and clinical assessment in the management of PD compared to standard of care (SoC) in the context of the UK NHS.[96] A cost-utility model was developed using a Markov model structure. The model was comprised of three health states: (1) uncontrolled; (2) controlled; and (3) death, with the ability to transition bidirectionally between the uncontrolled and controlled health states. The uncontrolled and controlled health states were based on the Movement Disorder Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS) domain scales of II (motor experiences of daily living) and III (motor examination). All individuals entering the model start in an uncontrolled state. The transitions between the uncontrolled and controlled health states are dependent on the improvement in MDS-UPDRS II and III with either the PKG, in addition to clinical assessment, or with clinical assessment alone (considered to represent SoC). The transition to the death state was based on UK all-cause mortality rates, with an elevated mortality risk of 2.22 associated with PD-specific relative mortality risk (based on Xu et al., 2014).[99] The Markov model had a cycle length of one year and a lifetime horizon of 22 years in the base-case analysis. A discount rate of 3.5% was used for both costs and effects, in line with NICE recommendations.[100]

The clinical efficacy of the PKG and clinical assessment compared with SoC was based on the study by Woodrow et al. (2020).[17] Full details of this study are described in Section 3.3.4 of this report. In summary, the study is based on a population in Australia and evaluated comparative outcomes in a PKG+ arm (use of the PKG and clinical assessment) compared to a PKG- arm (clinical assessment without the use of the PKG). At the first screening visit, individuals were assessed to decide whether their PD motor features were in-target (no further treatment required) or out-of-target. In the latter case, a plan for changing treatment was provided until the next consultation five weeks later. The same assessment protocol was followed until the PD motor features were in-target. A maximum of five visits were permitted, inclusive of the first screening visit. The primary study outcome was the difference in MDS-UPDRS total score from baseline to the end of the study. Woodrow et al. (2020) provides the outcomes of Total MDS-UPDRS score, as well as the sub-scores for domains I-IV, at the first and last study visit in the PKG+ and PKG- arms. In the PKG+ arm, MDS-UPDRS total score and MDS-UPDRS domain scale III significantly improved by 8.5 points and 6.4 points, respectively, between the first and last study visit, while in the PKG- arm the change in MDS-UPDRS total score and MDS-UPDRS III failed to reach statistical significance.

The patient population used in the model by Chaudhuri et al. (2022) is based on the Woodrow et al. (2020) study. The baseline patient characteristics for age, gender, levodopa equivalent daily dose, MDS-UPDRS domain scales II and III and Hoehn and Yahr (H&Y) stage are the same as those reported in Table 1 of Woodrow et al. (2020). For each intervention strategy in the model (i.e., PKG and clinical assessment, represented by PKG+ in Woodrow et al., or SoC, represented by PKG- in Woodrow et al.), individuals in the uncontrolled health state were assumed to have a MDS-UPDRS score in line with the MDS-UPDRS score obtained at the first screening visit in the corresponding arms of Woodrow et al., while individuals in the controlled health state were assumed to have a MDS-UPDRS score in line with the final study visit in Woodrow et al. The probabilities of transitions between the uncontrolled and controlled health states in the first six months of the model were derived from the proportion of patients that were identified as controlled after the initial use of the PKG in Woodrow et al. After six months, transition probabilities were estimated using a bootstrap approach, but no details on the methods used are provided in Chaudhuri et al. (2022). The model did not include adverse events.

The treatment effectiveness was assumed to be maintained for a period of five years. This was based on a systematic literature review on the impact of levodopa-carbidopa intestinal gel (LCIG) in patients with advanced PD, where the results of the review suggest that LCIG extends the benefits of levodopa (in terms of reduced 'OFF-time') for at least 2-5 years.[101] From 6 years onwards, a long-term gradual waning of effectiveness was assumed in line with the natural disease progression of PD. The authors acknowledge that long-term progression rates are heterogeneous as they vary from person to person.

Therefore, the authors used two alternative estimates for rates of progression: (1) a rate of progression based on a bootstrap analysis of published UPDRS III progression data based on a study by Holden et al. (2018),[102] which equates to an average annual rate of progression of 10.9%; and (2) a published annual rate of progression of 2 - 7% based on a prospective study by Schrag et al. (2007).[103]

The base-case analysis was modelled to mitigate the benefit observed in the Woodrow et al. study to 75%. This is because participating clinicians assigned to the PKG+ arm in Woodrow et al. received an additional 1-day training in interpreting the PKG for the assessment of PD compared to participating clinicians who were not assigned a PKG. The base case also assumed that PKG+ patients who are controlled will use two PKGs per year, while of the uncontrolled patients, 50% will use three PKGs per year and the other 50% will use four PKGs per year.

To derive health-related quality of life, the MDS-UPDRS domain scores for II and III obtained from the Woodrow et al. study were used in a published mapping algorithm to predict EQ-5D index values. The mapping algorithm was derived from a study population of 121 patients with idiopathic PD from study centres in Hessia, Germany.[104] The EQ-5D values were derived based on weights from a European population, valued by a visual analogue technique (European index) for the base-case analysis. Alternative values for a scenario analysis were based on weights derived from a German population, valued with the time trade-off approach (German index). The authors also conducted a scenario analysis using utility values derived from a model developed for the NICE PD guidelines, which estimated that health-related quality of life increases by 0.04 for every point reduction in UPDRS II and 0.02 for every point reduction in UPDRS III.[98] The resulting health state utility values from the alternative sources and approaches differed significantly.

PKG costs were based on the manufacturer's list price of £225, equating to a total cost of £450 per year for controlled patients (2 PKGs per year), and £787.50 per year for uncontrolled patients (50% with three PKGs per year and 50% with four PKGs per year). An outpatient and telephone visit with a Movement Disorder Specialist was costed at £384 and £60 per year, respectively. Health state costs associated with PD progression were based on direct medical and non-medical costs associated with the H&Y scale from the NICE PD guidelines.[98] The authors state that the MDS-UPDRS scores in the model were applied to derive average annual costs by H&Y stage (see Table 23), but no details are provided.[96]

Table 23 Annual costs by Hoehn & Yahr (H&Y) stage and percentage of patients by intervention in Chaudhuri et al. (2022)

H&Y stage	Annual costs	Intervention (PKG+) % of patients	Standard of care (PKG-) % of patients
1	£3,918	13.85%	11.65%
2	£7,417	49.30%	40.35%
3	£14,150	33.55%	38.85%
4	£28,660	3.30%	8.85%
5	£53,335	0%	0.30%

The cost-effectiveness results from Chaudhuri et al. (2022) showed that the intervention of PKG and clinical assessment is associated with lower total costs compared to SoC (£141,950 versus £159,312) and improved total QALYs (7.88 versus 7.61) over a lifetime horizon, which resulted in an incremental difference of £17,362 and 0.267 QALYs per patient and an incremental cost-effectiveness ratio (ICER) of -£64,979 per QALY. Sensitivity analysis by the authors indicated that the ICER was most sensitive to the annual cost of H&Y stage 4.

4.2.4 *Critique of Chaudhuri et al.*

Chaudhuri et al. (2022) represents the first cost-effectiveness analysis of the PKG remote continuous monitoring system in PD. The study appears to be well conducted and has been performed from the perspective of the UK NHS, which makes it directly relevant to the decision problem addressed in this report. The study accounts for direct medical costs only and QALYs are accumulated over the lifetime of an individual with PD. The population is with moderate disease based on the inclusion criteria of Woodrow et al. (idiopathic PD of ≥ 4 years or taking ≥ 4 doses of levodopa per day because of a much greater likelihood of being out-of-target at baseline; aged 59-75 years because less likely to be candidates for deep brain simulation and less likely to have a high incidence of contraindications to increasing dopaminergic therapy; not receiving treatment with, or under consideration for, device-assisted therapy), while the intervention's effectiveness is based on outcomes from the only comparative study for the PKG, where the PKG, in addition to clinical assessment, is compared to clinical assessment alone in Woodrow et al. In the absence of alternative sources of data for clinical efficacy, the data source, population and intervention strategies used by the authors are considered appropriate; however, it is not clear that individuals' suitable for PKG in the UK NHS would use as many PKGs as assumed in Chaudhuri et al., i.e., patients with PD classified as controlled and in-target are assumed to use two PKGs and have two Movement Disorder Specialist visits per annum, while patients with PD classified as uncontrolled and out-of-target are assumed to use 3-4 PKGs with 3-4 visits per annum.

The clinical effectiveness of the PKG is based on the MDS-UPDRS domain scores II and III, while the primary endpoint of the Woodrow et al. study was Total MDS-UPDRS.[17] Chaudhuri et al. justified

the choice of domains II and III based on the availability of published mapping algorithms that use domains II and III to predict EQ-5D utility values for the model and on the basis that these domains constitute the largest components of the Total MDS-UPDRS score. The EAG notes that this means that the results of Chaudhuri et al. do not reflect the impact of the PKG on non-motor experiences of daily living (MDS-UPDRS I) or on the most severe motor complications (MDS-UPDRS IV) associated with PD.

The model considered a lifetime horizon of 22 years in the base-case analysis. The study justified the choice of 22 years to approximate lifetime treatment and to capture the long-term costs and health effects of treatment. Whilst the EAG acknowledges that a lifetime horizon is an appropriate time horizon to capture the effect of treatment on the long-term progression of PD, the EAG also has a major concern about the use of a lifetime horizon to capture the difference in costs and health effects of PKG compared to SoC when there is an absence of evidence to suggest that the benefits of PKG equates to changes in treatment that are sustained over the long-term, into a future of 22 years, particularly in recognition of the fact that there are no disease-modifying treatments available for PwP. The model by Chaudhuri et al. makes a number of strong assumptions about sustaining the 6-12month benefits observed in Woodrow et al. over the long-term:

- In the model by Chaudhuri et al. the change in the MDS-UPDRS II and III scores between the first (uncontrolled) and last study visit (controlled) for the PKG+ arm compared to the PKG- arm in Woodrow et al. is used to capture a 6-12month treatment effect. Although the authors mitigate this benefit to 75% to account for additional support provided to clinicians in the PKG+ arm and the effect of participating in a clinical trial, the benefits are assumed to be sustained in full (i.e., without any waning effect) for a period of five years. This assumption is not supported by any treatment data in patients with moderate PD and only justified by the authors as a proxy on the basis of data for the use of LCIG in patients with advanced PD.
- It is only from year 6 onwards in the model that a long-term waning of treatment effect is included. The waning effect is assumed to gradually decline in line with the natural history of disease progression for PD; however, the authors acknowledge that the long-term progression rate of PD is heterogeneous and highly uncertain. An average progression rate of 10.9% per annum was used by the authors based on the progression of MDS-UPDRS III scores over five years from the Parkinson's Progression Markers Initiative, which is an international, multicentre study in patients with de novo PD (early, initially untreated PD).
- The transition probabilities representing the bidirectional movement between the uncontrolled and controlled health states in the model over time were based on the proportion of patients that were identified as controlled at the first visit in the Woodrow et al. study. The exact proportion used in the model at six months does not appear to be reported in Woodrow et al.

(2020) but, more importantly, this proportion at six months, with an estimate of uncertainty, is used to establish the transition probabilities between the health states over a lifetime horizon.

The authors state that their modelling approach is conservative because they have mitigated the benefit from Woodrow et al. to 75% and have included the benefit of using the PKG for one year, whereas the cost of provision of the PKG for the following years is included in the model. However, the EAG notes that the benefits of using the PKG in the first year are sustained in full for a period of five years; it is simply that no additional 'top-up' benefit from using PKGs in the following years is included in the model. Furthermore, the changes in MDS-UPDRS scores from first to last visit in Woodrow et al. are based on up to five consultation visits, where a PKG was worn prior to each visit in the PKG+ arm. At each visit (5 weeks apart), a plan for changing treatment was provided until the motor features of the disease were considered to be in-target and no further treatment required. The EAG considers it unlikely that UK clinical practice would follow a similar protocol.

The movement between the uncontrolled and controlled health states over time, based on the MDS-UPDRS II and III scores from the Woodrow et al. study, affects the costs and utility values at each model cycle over the lifetime horizon of the model. The MDS-UPDRS II and III scores from Woodrow et al. are used in a mapping algorithm to predict EQ-5D index values for the uncontrolled and controlled health states in the model. The mapping algorithm by Dams et al. (2013) is based on a small study population of 121 patients with PD in Germany, where the health states identified by the EQ-5D were converted into EQ-5D indices employing weights from a pooled European population valued by a visual analogue technique.[104] The EAG notes that this method does not align with the NICE Reference case, where the valuation of health-related quality of life measured by patients (or their carers) should be based on a valuation of public preferences from a representative sample of the UK population using a choice-based method.[100] The mapping algorithm in Dams et al. is also based on UPDRS scores, rather than MDS-UPDRS scores. Chaudhuri et al. does not provide details on whether any conversion was made between UPDRS and MDS-UPDRS scales to derive the EQ-5D values. Furthermore, the resulting estimates of health state utility values differed substantially from other alternative sources and approaches considered by the authors. Therefore, even in spite of the concerns about the long-term extrapolation of benefits in the model, the health state utility values themselves are uncertain. This means that the accumulated total QALYs over a lifetime horizon are subject to considerable uncertainty.

The health state-related costs used in the model were based on MDS-UPDRS scores from Woodrow et al. and costs associated with the H&Y scale. The authors refer to the costs reported in the NICE PD guidelines Appendix F for the H&Y scale; however, despite a thorough review of the NICE PD guidelines,[98] the EAG was unable to identify or validate the costs reported in Chaudhuri et al. No details are provided on how the annual costs by H&Y stage were derived in the model. Importantly, it

is unclear how the MDS-UPDRS scores were converted onto the H&Y scale. The costs associated with the H&Y stages and the proportion of individuals in each stage by intervention strategy is a key driver of the total costs over a lifetime horizon. This is evident from Table 23, where the distribution of patients by intervention (PKG+) and SoC (PKG-) shows a greater proportion of patients in the less severe H&Y stages 1 and 2 and a smaller proportion in the higher stages of 3 to 5 for PKG+, whereas a smaller proportion are in stages 1 and 2 and a higher proportion in stages 3 to 5 for SoC. The annual cost associated with H&Y stages 1 and 2 is £3,918 and £7,417, respectively, whereas the annual cost associated with H&Y stages 3 to 5 varies from £14,150 to £53,335. Given that the annual health state costs are considerably larger than the annual cost of PKG and consultation visits (by an approximate order of magnitude of 10 for the lower H&Y stages and 100 for the higher stages), it is expected that the key driver of total costs in the model is the difference in the proportion of individuals in the H&Y stages by intervention over a lifetime horizon.

The base case results suggest that PKG and clinical assessment compared to clinical assessment alone reduces the total costs to the NHS by £17,362 per patient. The cost savings for PKG+ are driven by a lower likelihood, on average, that a patient will end up in one of the more severe H&Y stages 3 to 5 (36.9%) compared to standard of care (48%) over a lifetime horizon. The base case results also suggest that PKG+ increases the total QALYs by 0.267 QALYs per patient compared to standard of care. This is driven by a higher increment in utility for the controlled versus uncontrolled health states for PKG+ (0.036) compared to the increment in utility for the controlled versus uncontrolled health states for SoC (0.021), and a greater likelihood of being in the controlled health state versus uncontrolled health state for PKG+ compared to SoC over a lifetime horizon. Results of sensitivity and scenario analyses by the authors showed that the cost-effectiveness results were robust to the base case conclusions; however, the EAG notes that the majority of these analyses did not address the key structural assumptions affecting the long-term efficacy, health-related quality of life and costs over a lifetime horizon in the model.

4.3 Methodology of the review of decision models evaluating interventions used in Parkinson's disease

Given the very limited number of cost-effectiveness studies evaluating remote continuous monitoring devices in Parkinson's disease, a review of published cost-effectiveness studies evaluating broader interventions (both pharmacological and non-pharmacological) for the management of symptoms in people living with Parkinson's disease was conducted. The review targeted cost-effectiveness studies that included a decision analytic model rather than economic evaluations conducted alongside clinical trials with no consideration of longer-term disease progression. The specific aims of the review were:

- To help inform the conceptualisation of the decision problem for PwP and long-term progression of the disease;
- To identify important structural assumptions used in previous models in PD; highlighting key areas of uncertainty and outlining the potential issues of generalising from the results of existing models;
- To identify any relevant sources of evidence. In particular, attention was given to identifying important parameter estimates and sources of data inputs for linking evidence on short- and long-term outcomes for PwP.

The studies identified from the review were not subject to a formal assessment using checklists to assess the quality of the included studies. Instead, a narrative review of key model features and modelling approach used, key assumptions and data sources underpinning 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 or disease progression and mortality in these studies was assessed.

4.3.1 *Searches*

The bibliographic search detailed in Section 2.1 was used to identify relevant studies.

4.3.2 *Study selection*

Cost-effectiveness studies using decision analytic modelling published after the year 2000 were considered for inclusion. Only cost-effectiveness, cost-utility and cost-benefit analyses were considered eligible. The population of this review was defined as people with diagnosed Parkinson's disease. Studies in people with other neurological disorders were excluded. The inclusion criteria further specified that only titles in English would be considered eligible. Titles that were books, editorials, letters to the editor, and reviews that did not include a *de novo* model were excluded from the review.

Two researchers (EC, THP) conducted the two-step selection process consisting of first screening studies for inclusion based on the titles and abstracts of studies identified by the bibliographic searches, and then reviewing the full-text articles identified at the previous step as potentially relevant.

4.4 Results of the systematic review of decision models evaluating interventions in Parkinson's disease

A total of 1,285 records were identified during the initial search of the economic databases of which 744 remained after deduplication. The initial screening identified 41 titles as potentially relevant

based on their titles and/or abstracts. The full text articles of 32 of these records were obtained and assessed for eligibility. All were considered to meet the selection criteria and included in the review. The studies are summarised in detail in Appendix 9.6, Table 69 and Table 70.

The majority of studies used a Markov cohort model with Hoehn & Yahr (H&Y) stages 1-5,[105-115] OFF-time (e.g. ≥25% "OFF" time/day),[116-122] dyskinesia,[123, 124] [Haycox et al. (2009), Farkouh (2012)], and motor fluctuation[125, 126], being the most popular discrete health-states used to characterise disease progression in Parkinson's disease. In 11 studies, composite health-states (i.e., health states encompassing multiple disease measures) were adopted; 10 combined H&Y stages and OFF-time [127-135], and one study combined OFF-time and cognitive function.[136] Two studies modelled disease progression according to treatment-specific health-states within a Markov model framework, where interventions confer changes in UPDRS domain scores,[137] and risk of developing dyskinesias.[124] Only one study used a decision tree, which was used to model operative complications associated with Deep Brain Simulation (DBS) and MR-guided focused ultrasound thalamotomy for tremor-dominant Parkinson's disease relative to medical therapy.[138] Two studies conducted individual-level simulation approaches, one implementing the total time spent without OFF episode symptoms as the mechanism of treatment benefit,[139] and the other changes in Movement Disorder Society (MDS)-UPDRS domain scores (among other measures).[140]

In summary, most models in Parkinson's disease have adopted a Markov structure where the evaluation of treatment effectiveness and costs of different pharmacological or surgical interventions is modelled by transitions between health states. In most studies to date, these transitions between health states are used to track disease progression, which is predominantly measured by the H&Y scale (stages 1-5) and/or OFF-time per day. In most of the earliest studies, the mechanism of benefit from the interventions is derived by providing a difference in disease progression via treatment-specific transition probabilities between H&Y stages. In some studies, these are applied as 'one-time' shifts in the H&Y stage of disease (i.e., the treatment effect produces a one point in time shift in the H&Y stage of disease), while in other studies progression through the H&Y stages may occur in each model cycle over the course of the disease. In the latter case, the longer-term transition probabilities for each stage are typically derived from longitudinal studies of people with PD. The use of discrete health states (e.g. ≥25% or <25% 'off' times per day) is considered to be quite a crude measure in the context of modelling complex diseases such as PD.

In the most recent studies, there has been a move away from the use of the H&Y stages to measure the severity of disease progression because H&Y only measures motor symptoms of PD. More recently, the UPDRS or MDS-UPDRS domain scales (where the MDS-UPDRS is the revised version of the original UPDRS by the Movement Disorder Society) have been used in models to track disease progression over time because the UPDRS/ MDS-UPDRS measures both motor and non-motor

symptoms and is composed of four distinct parts: MDS-UPDRS I (non-motor aspects of experiences of daily living), MDS-UPDRS II (motor aspects of experiences of daily living), MDS-UPDRS III (motor examinations) and MDS-UPDRS IV (motor complications), where higher scores indicate increased severity of the disease. The UPDRS has been shown to have excellent internal consistency across multiple studies and stages of disease severity as measured by the H&Y staging system. The use of the UPDRS or MDS-UPDRS domain scales to track disease progression over time is also aligned with the outcomes reported in short-term clinical trial data of symptomatic therapies and devices used for PwP, where the primary or secondary efficacy outcome measures include the UPDRS or MDS-UPDRS domain scale.

Of the 32 studies reviewed, two analyses were considered good examples of contemporary modelling approaches that considered outcomes available from the clinical review (see Section 3.3.4). The first study by Fundament et al. (2016) was a Markov model where health states were based around treatment interventions and, for each treatment, disease progression was modelled according to changes in the UPDRS domain scores (parts I-IV).[137] The changes in UPDRS domain scores were recorded over time within the model, but they were not explicitly used to derive the health states. In the second study by Chandler et al. (2021), disease progression was characterised in terms of changes in MDS-UPDRS, UPDRS and H&Y stages over a lifetime horizon.[140] Unlike Fundament et al., the model was a discrete event simulation, which was constructed to represent the individual-level heterogeneity observed in disease progression rates and capture the potential benefits of novel disease-modifying drugs when they become available for PD. A summary of both models is presented below.

4.4.1 *Fundament et al.*

Fundament and colleagues developed a Markov model to represent the progression of PD as rated using the UPDRS over time in patients with early onset of motor complications. The model was developed to evaluate the cost-effectiveness of Deep Brain Stimulation (DBS), compared to best medical therapy (BMT), for PD with early motor complications from a UK payer perspective. The study population was based on baseline characteristics for patients included in the Controlled Trial With Deep Brain Stimulation in Patients With Early Parkinson's Disease (EARLYSTIM) trial, who all were assumed to have motor complications at model entry. The base case analysis used a 15-year time horizon to capture the long-term progression to more advanced stages of PD.

Health states in the Markov model were based only on the treatment interventions (DBS and BMT) and death, but disease progression over time was modelled according to changes in UPDRS domain scores I-IV by treatment. DBS patients were assumed to continue therapy until withdrawal, after which they would continue with BMT until the end of the modelled time horizon or death. For the

first two years of the model, clinical efficacy estimates in terms of changes in UPDRS scores for each intervention were derived from the EARLYSTIM trial, which collected UPDRS domain scores at treatment initiation and at 5, 12, and 24 months follow-up. These were used to calculate the percentage change in UPDRS from baseline in each domain for each intervention. Rates of disease progression beyond two years was modelled to be the same for both interventions (with the exception of UPDRS domain score IV) due to a lack of consistent long-term data on UPDRS outcomes by treatment. Annual rates of progression for each UPDRS domain were based on data pooled from various studies because the authors did not identify a single study that reported all domains of the UPDRS consistently. Supplemental appendix table S1 provides the annual rates of progression in UPDRS scores by treatment group.

Mortality was incorporated into the model using a two-step approach. Firstly, age- and gender-specific baseline mortality was applied using UK all-cause mortality rates based on the baseline characteristics of patients in the EARLYSTIM trial. In the second step, a hazard ratio for mortality risk of 1.31 was applied to the baseline mortality for patients with more advanced disease. Using data from studies reporting on the relationship between UPDRS III and mortality, a per 10-point increase in UPDRS III score was associated with an increased risk of mortality, which was applied only in patients with a UPDRS III score above 15 to reflect the increased mortality associated with more advanced disease.

The model accounted for both treatment-specific and disease-related adverse events. The incidence of adverse events reported in the EARLYSTIM trial was used to inform the treatment-specific rates. For the disease-related adverse events, the authors highlighted that PD progression is associated with increasing postural instability, which may lead to falls and serious injury in some patients. To reflect the incidence of falls and associated hospitalisation rate, the authors pooled data from a series of studies to define a baseline proportion of patients falling per year of 42.8% based on patients with a UPDRS III score of 12 points. An odds ratio of 1.07 for each point increase in UPDRS III score was then applied to the baseline risk based on three studies reporting incidence of falls.[141] Of these falls, 50.9% were assumed to require hospitalisation.

Health-related quality of life was accounted for, in the short term, using a published mapping algorithm to map from the 39-item Parkinson's Disease Questionnaire (PDQ-39) data from the EARLYSTIM trial to the EQ-5D, since EQ-5D was not collected in the trial. The corresponding utility weights by intervention were applied in the first two years of the model. For the longer term, after two years, the authors developed a new algorithm to link UPDRS scores to EQ-5D. The authors used an iterative approach to identify a statistical model which could accurately predict the EQ-5D index from the explanatory variables available from the EARLYSTIM trial (including UPDRS domain scores). The resulting EQ-5D function was given by Fundament et al.:

$$EQ\text{-}5D = 1.59 * e^{(0.01721*Male + 0.001448*Age - 0.0198*UPDRS\ I - 0.00049*(UPDRS\ II)^2 - 0.0178*UPDRS\ IV - 0.2468)} - 0.594$$

This algorithm was applied to changes in UPDRS scores over time in the model (beyond two years) to estimate the health-related quality of life by treatment group.

For resource use and costs used in the model, data were sourced from price lists, national drug prices, hospital payment tariffs and social care cost data. Due to a lack of standardised drug protocols for the management of PD, the authors analysed data from the UK Clinical Practice Research Datalink (CPRD) of 297 PD patients for the period April 2003 to March 2012 to derive information on drug formulations administered. Dosing information and the number of patients receiving each drug was combined with unit costs from the British National Formulary to calculate a drug cost per day for each treatment option of £4.16 for BMT and £2.28 for DBS. The costs of regular neurology outpatient appointments were accounted for by assuming four visits per year in the first year of treatment with DBS and two visits per year thereafter, while patients on BMT were assumed to have two visits per year. Home visits by a PD nurse were applied in both treatment groups with the same frequency as the neurology outpatient appointments. The unit costs associated with hospitalisation for falls and follow-up appointments were based on hospital payment tariffs and social care cost data. Supplemental appendix table S1 provides a list of the unit costs used in the model.

The results of the cost-effectiveness analysis indicate that DBS leads to improved QALY outcomes and increased costs compared with BMT in patients with early onset of motor complications from a UK NHS perspective, leading to an incremental cost-effectiveness ratio (ICER) of £19,887 per QALY gained. Device costs made up the largest percentage of costs in the DBS treatment group, while in the BMT group, drug therapy and management of co-morbidities were the main cost drivers. The model results were most sensitive to the time horizon used to model long-term costs and outcomes; when this was limited to five years, the ICER increased beyond £30,000 per QALY gained for DBS. The key uncertainty in the model was the lack of long-term follow-up data beyond five years for the interventions.

4.4.2 *Chandler et al.*

Chandler and colleagues developed a modelling framework to facilitate the estimation of long-term health and economic outcomes in PD.[140] The model was structured to simulate the long-term progression of PD from diagnosis through to a lifetime horizon, capturing both motor and non-motor symptoms and associated outcomes. The model was developed to support the cost-effectiveness evaluation of new disease-modifying drugs in PD when they become available. The authors recognise that there are currently no disease-modifying therapies available for the treatment of PwP, but new therapies are being studied and results from clinical trials are expected in the future. The objective of the study by Chandler et al. was to develop and validate a novel model that addresses the unmet need

to simulate the disease progression from diagnosis over a lifetime horizon. The authors also recognised the limitations of previous models in PD, where most have typically modelled transitions between health states defined based on the H&Y staging system and very few have tracked disease progression using UPDRS domain scores. The authors emphasised the need to reflect non-motor aspects of PD and therefore the need to develop models using the revised version of the original UPDRS: MDS-UPDRS. The model by Chandler et al. represents the first novel model in PD to track disease progression over a lifetime horizon using MDS-UPDRS domain scores (amongst others).

The model by Chandler et al. provides a conceptual modelling framework of long-term disease progression in PD but it also simulates the progression of disease along the MDS-UPDRS and UPDRS subscales over time using predictive equations that capture the intercorrelation between MDS-UPDRS/ UPDRS subscales and baseline population characteristics. The predictive equations for the simulation of disease progression for newly diagnosed PwP were developed from an analysis of longitudinal, observational data from the Parkinson's Progression Markers Initiative (PPMI), which is an international multicentre study that follows individuals from diagnosis (treatment naïve, age >30 years) up to six years of follow-up. The data were analysed using a mixed-effect repeated measures (MMRM) model to predict change from previous values of MDS-UPDRS I (non-motor experiences of daily living), MDS-UPDRS II (motor experiences of daily living) and MDS-UPDRS III (motor examinations). In the MMRM model, the initiation of treatments for PD symptoms was identified as a predictor of MDS-UPDRS II and MDS-UPDRS III scores. For people treated with levodopa and/or dopamine agonists, MDS-UPDRS III was assessed both pre- and post-dose in the PPMI dataset, while for other medications (e.g., monoamine oxidade-B inhibitors) MDS-UPDRS III was assessed post-dose. Additional predictors in the model included age, gender, disease duration, time, baseline MDS-UPDRS scores and prior MDS-UPDRS scores. The form of the predictive equations was a general linear model. Supplementary Table 2 of Chandler et al. (2021) provides the mean predictor coefficients (with standard error) for change within each MDS-UPDRS subscale (I-III) from prior visit for people with newly diagnosed PD based on baseline values for age, gender, disease duration and MDS-UPDRS scores, time from previous visit in days, MDS-UPDRS scores at prior visit and PD medication. The mean scores within each MDS-UPDRS subscale increased year on year, which was indicative of greater levels of severity in both motor (subscales II and III) and non-motor (subscale I) symptoms in newly diagnosed PD. The authors also noted a significant difference in MDS-UPDRS II and III scores between people on no PD medication, people treated with levodopa and/or dopamine agonists, and other PD medications alone (e.g., monoamine oxidade-B inhibitors).

In addition to the predictive equations for newly diagnosed PD, the model by Chandler et al. also simulates disease trajectories when people initiate treatments for PD symptoms via a separate set of predictive equations for changes in UPDRS subscales. This second set of predictive equations was

developed from an analysis of the National Institute of Neurological Disorders and Stroke Exploratory Trials of Parkinson Disease Long-term Study 1 (NET-PD LS-1), which was a large multicentre, randomised placebo-controlled efficacy trial of creatine, where eligible participants were within five years of PD diagnosis and treated with levodopa and/or dopamine agonists. The data from this study (1,720 people with PD with five years of follow-up) was used to develop equations to predict changes over time in UPDRS subscales I-IV, levodopa-equivalent doses (LED), and percent OFF-time. Supplementary Table 3 of Chandler et al. (2021) provides the mean predictor coefficients (with standard error) for change within each UPDRS subscale (I-IV) from a prior visit based on baseline values for age, gender, disease duration, and UPDRS scores, levodopa-equivalent daily dose, time from the previous visit in days, OFF-time, UPDRS scores at prior visit, rate of change in prior UPDRS scores, and interactions between variables. In the predictive model, LED is predicted to increase over time and impact on the UPDRS sub scores I-IV.

Using the predictive equations for disease progression, Chandler et al. developed an individual patient-level simulation model to represent the heterogeneity observed in progression rates and capture the potential long-term benefits of new disease-modifying drugs when they become available, as distinct from symptomatic improvements. Disease progression was characterised in terms of changes in MDS-UPDRS, UPDRS and H&Y stages from diagnosis through to a lifetime horizon. Through the prediction equations, the simulation captures the benefits of starting symptomatic treatments, dose adjustments, increases in OFF-time, and the associated complications of dopaminergic therapies. A target population of newly diagnosed PwP was analysed by the authors to understand the potential value of treatment with new DMTs. A profile of risk factors to predict disease progression, treatment changes and mortality was generated for each simulated individual in the model using the PPMI dataset. When individuals progressed to MDS-UPDRS or UPDRS subscale III, a UPDRS III threshold was used to predict the time to H&Y stage 3. Because H&Y was not collected in NET-PD LS-1, the PRECEPT and PostCEPT studies, which are longitudinal, randomised placebo-controlled efficacy trials in early-stage PD (average duration of PD of less than one year) were used to predict time to H&Y stage 3. Conversions between the UPDRS and MDS-UPDRS subscales were based on the linear relationship published in Goetz et al. (2012).[142] The progression between H&Y stages 3 to 5 was based on published transition probabilities from a previous economic model in PD.[108] General population mortality estimates were adjusted to capture the impact of PD on mortality by applying hazard ratios by H&Y stage.

The model was validated in two ways: (1) the predictive equations developed for the MDS-UPDRS and UPDRS subscales were used to compare the predicted and observed scores each year post-baseline in the corresponding PPMI and NET-PD LS-1 datasets; and (2) the simulated outcomes from the model with the predictive equations implemented within the model were compared to the

observed data in the datasets. Supplementary Figures 1 and 2 demonstrated good validity between the simulated disease progression of UPDRS scores predicted over time and observed outcomes.

Chandler et al. also used their model to conduct an economic analysis for a new hypothetical DMT, in addition to the current SoC, compared to SoC alone. The analysis was conducted from a UK NHS perspective. The model was used to simulate newly diagnosed patients starting a DMT in addition to standard of care. For the DMT, a 50% change in MDS-UPDRS progression compared to the natural history without the DMT was assumed, while a 5% discontinuation rate was included in the first year and a 2.5% in subsequent years. Patients who discontinued DMT were assumed to experience a gradual loss of treatment effect over two years, reverting to the natural history of progression on standard of care.

For health-related quality of life, a MMRM model was developed by the authors to predict EQ-5D-3L utility values based on an analysis of data collected in the NET-PD LS-1 study and using the UK preference weights. This study had up to six years of follow-up with EQ-5D-3L index scores of 1,741 observations at baseline and 330 at year six. The statistical model was used to identify predictors of the association between EQ-5D utility values and PD severity; it found that gender, non-motor and motor aspects of PD (i.e., all four UPDRS subscales) were all significant predictors of EQ-5D-3L utility values. Supplementary appendix Table 4 provides the mean values (with standard error) for the coefficients of gender and each of UPDRS I-IV subscales to predict EQ-5D-3L index scores, while Supplementary Figure 3 demonstrates that the utility equation performs well when validated with the observed data. In the authors' hypothetical economic analysis for a new DMT, the predictive equation was used to derive utility values up to H&Y stage 3. Once individuals transition to H&Y stage 3, utility values are assigned conditional on H&Y stage and OFF-time using an approach adopted in a previous economic model in PD.[129] Caregiver disutilities were also assigned conditional on H&Y stage from a study reporting caregiver decrements by H&Y while controlling for age and gender.[130]

For resource use and costs, the initiation of medications (levodopa and/or dopamine agonists or other PD medications such as monoamine oxidade-B inhibitors) for newly diagnosed PD was based on data observed in PPMI for the likelihood of starting PD treatments over time. This was supplemented by symptomatic treatment costs from a study by Kalilani et al. (2019) who identified treatment patterns in the UK CPRD database for the period 2004 to 2015 based on 7,775 PD patients.[143] The most common PD medications included in the CPRD database (levodopa, 43%; pramipexole, 30.34%; ropinirole, 21.52%; and bromocriptine, 4.78%), the average cost per mg and LED conversion factors for each treatment were used to derive a weighted average annual cost per LED mg of £5.01. The percentage of patients receiving advanced therapies and associated treatment durations were based on the OBSERVE-PD (OBSERVational, cross-sEctional PD) study,[144] while direct medical and non-

medical costs per annum by H&Y stage were derived from a UK healthcare survey published by Findley et al. (2011).[145]

The results of the cost-effectiveness analysis for the hypothetical DMT indicate that over a lifetime horizon, DMT in addition to standard of care leads to improved discounted (at 3.5% per annum) QALY outcomes of 1.1 QALYs compared to standard of care alone. Patients treated with standard of care were projected to incur discounted costs of £232,619 over a lifetime (26% related to treatment costs and 55% from non-medical costs including respite care and nursing home costs). For the hypothetical DMT, without including acquisition and administration costs of the DMT, the total discounted costs were predicted to be lower than standard of care by 16% due to reductions in hospitalisations, nursing home admissions and at home care.

4.5 Conclusions of the assessment of existing cost-effectiveness evidence

The review did not identify any studies that evaluated the cost-effectiveness of PKG, Kinesia 360, KinesiaU, PDMonitor and STAT-ON devices. However, one study for PKG, which was published online after the cut-off date of our searches, was identified.[96]

A supplementary review of decision models evaluating interventions in PD identified 32 studies with model-based economic evaluations in PD. Most studies adopted a Markov model that typically modelled the progression of PD according to transitions between health states defined by the H&Y staging system, OFF-time per day, or a combination of both these measures. Only two models directly tracked disease progression using the UPDRS domain scores and considered both motor and non-motor aspects of PD;[137, 140] one of these models used the MDS-UPDRS domain scores.[140] The most relevant model to support the cost-effectiveness assessment of remote continuous monitoring devices in PD is the model by Chandler et al. (2021).[140] This model provides a new foundation for evaluating interventions in PD by taking account of motor and non-motor aspects of the disease and provides progression rates over time, which capture the benefits of starting symptomatic treatments, dose adjustments and longer-term implications of increasing OFF-time per day and the associated complications of dopaminergic therapies. The model is constructed as an individual patient level simulation for a target population of newly diagnosed, treatment naïve patients at baseline and is developed to aid the evaluation of new disease modifying drugs in the future. Despite the fact that the population likely to use remote continuous monitoring devices in PD does not match that of Chandler et al. (2021), the model developed in this study provides a foundation for the underlying disease progression risk over time and associated complications of symptomatic therapies. In particular, the risk prediction equations from this study provide an invaluable source of the rate of progression of motor and non-motor symptoms that capture multiple factors and dependencies, including age,

gender, duration of disease, PD medications and LED, as well as leveraging prior values and rates of change of the UPDRS domain subscales.

5 INDEPENDENT ECONOMIC ASSESSMENT: YORK MODEL

5.1 Overview

At the time of the systematic literature review of cost-effectiveness studies (Section 4.2), no studies evaluating the cost-effectiveness of remote continuous monitoring devices (PKG, Kinesia 360, KinesiaU, PDMonitor and STAT-ON) were identified. Therefore, a de novo decision analytic model was developed to formally estimate the cost-effectiveness of remote continuous monitoring devices, as an adjunct to clinical judgement, for the assessment of motor and non-motor symptoms in people with maintenance-phase Parkinson's disease, relative to clinical judgement alone (standard of care, SoC) in the NHS. Due to not having identified any comparative evidence of clinical effectiveness for STAT-ON, KinesiaU, PDMonitor, or for any device within an advanced disease settings (see Section 3.3.4), the full economic evaluation was limited to establishing the cost-effectiveness of PKG and Kinesia 360 compared to SoC in the maintenance-stage of Parkinson's disease. However, the costs associated with STAT-ON, KinesiaU, and PDMonitor are descriptively assessed, alongside a number of threshold analyses based on uninformed assumptions about clinical efficacy. The conceptualisation, development and parameterisation of the economic model was informed by existing economic modelling studies described in Section 4.4, and clinical findings reported in Section 3. The model provides a framework for combining and evaluating the impacts alternative remote monitoring schedules have across a range of parameters relevant in establishing patient outcomes, NHS costs and overall cost-effectiveness.

Three issues were considered central in developing and populating the decision analytic model:

1. The need to link data from the use of remote continuous monitoring devices to meaningful changes in patient outcomes.
2. The need to model the underlying disease progression over time, whilst incorporating and extrapolating the potential benefits observed from the remote monitoring devices relative to SoC.
3. The need to consider and assess the impacts of alternative monitoring schedules (e.g., one-time use or repeated use of the devices over time).

The decision analytic model provides a link between intermediate outcomes from remote continuous monitoring devices and final health outcomes expressed in terms of quality-adjusted life years (QALYs). The model provides a comparison between the potential health gains achieved by a remote monitoring intervention schedule, relative to their additional costs to NHS providers. Costs are expressed in UK £ sterling (2019/20) and evaluated from the perspective of the NHS and Personal Social Services (PSS). Both costs and outcomes are discounted at a 3.5% annual discount rate, in line

with current NICE guidelines.[100] The model was evaluated over a 5-year time-horizon to reflect maintenance-stage Parkinson's disease. The model is developed using Microsoft Excel.

The model is probabilistic, meaning that the uncertainty in the input parameters are reflected through the use of appropriate probability distributions, rather than using fixed mean parameter estimates.[146] Monte Carlo simulation is used to propagate uncertainty in input parameters through the model in order to capture the uncertainty in overall results. Scenario analyses are undertaken to explore the robustness of the cost-effectiveness results to changes in the parameter inputs and assumptions of the model.

The following sections outline the decision problem, the structure of the model and provide an overview of the key assumptions and data sources used to populate the model.

5.2 Decision problem and population

The decision problem the economic model seeks to address is whether devices for remote continuous monitoring of people with Parkinson's disease (PKG, Kinesia 360, KinesiaU, STAT-ON or PDMonitor) represent a cost-effective use of NHS resources.[147]

Parkinson's disease is a heterogeneous disease with many different patterns of progression, outcomes, and associated cognitive decline. This complexity, combined with individual patient and service-specific circumstances, has led to considerable variation in the methods used in current clinical practice to assess Parkinson's disease symptoms. Monitoring methods include history taking, patient reported diaries, activity data (e.g. mobile activity trackers, pedometers, etc.) and use of the UPDRS, Hoehn and Yahr, and MBRS scales.[147] The NICE guideline for Parkinson's disease (NG71) recommends that people diagnosed with Parkinson's disease should be seen at regular intervals of 6 to 12 months to review their diagnosis.[2] The position of remote continuous monitoring device technologies within this clinical pathway remains uncertain. Remote technologies lend themselves to a variety of settings and configurations and can be applied at different stages of Parkinson's disease to routinely assist review appointments, as a means of substituting or screening the need for patient consultation, or as one-off applications in circumstances considered particularly beneficial for helping decisions about care. Specific circumstances may include patients having difficulties communicating symptoms, when motor fluctuations are not being adequately managed, where response to treatment is unclear, or to inform the calibration of device-assisted therapies (e.g. deep brain stimulation).

The target population of the model consists of PwP in the maintenance phase of disease, where symptoms have increased significantly since diagnosis and medication is routinely required and regularly reviewed. Although remote continuous monitoring devices may be used in advanced stages of Parkinson's (e.g. to aid programming DBS and to monitor the impact of advanced treatments), no

evidence on the comparative effectiveness of the devices beyond the maintenance stage of Parkinson's disease was available.

The clinical sub-population of patients experiencing uncontrolled motor symptoms ("in-target" and "out-of-target" - see Section 3.3.4) were considered potentially relevant subpopulations but were not incorporated into the design of the analysis due to the ex-post nature of the population definition, i.e. patients can only be identified as out-of-target *after* the use of a remote continuous monitoring device. It may be plausible that people with uncontrolled (out-of-target) motor symptoms are identified without the use of a continuous monitoring device, for example, following an assessment that is triggered due to self-referral; however, it is unclear how this population would be defined in practice and to what extent it would overlap with one identified as out-of-target using a remote continuous monitoring device. No other subpopulations were considered.

5.3 Strategies/comparators

The principal aim of remote continuous monitoring devices is to provide 'objective' ambulatory measurement and identify uncontrolled Parkinson's disease symptoms in order to inform necessary changes in treatment, thereby leading to improvements in patient outcomes. Other objectives include enhancing medication adherence, improving patient-physician dialogue, reducing unnecessary clinic visits, aiding patient autonomy and improving on broader elements of patient health and wellbeing (e.g., educational materials, strength and fitness training). Given the complex and multi-faceted nature of Parkinson's disease, as reflected by the broad range of information provided by remote monitoring devices, symptom status does not lend itself to a singular dichotomous primary endpoint (e.g. positive or negative status) or conventional assessments of diagnostic accuracy (e.g. sensitivity and specificity, predictive values, likelihood ratios). Instead, diagnostic evaluation studies have examined correlations between specific recorded variables (e.g. bradykinesia score) and broader symptom measures (e.g. disease-specific rating scales), the impact of diagnostic information on clinician decision making, patient and clinician feedback, and the direct clinical benefits associated with remote monitoring on patient outcomes (see Section 3). Due to the inability to reliably link diagnostic accuracy, changes in treatment, or clinician/patient feedback to patient outcomes, the EAG considered strategies on the basis of relevant models of care delivery and the extant evidence on comparative clinical impact.

Comprehensive searches of the literature identified three studies reporting comparative clinical outcomes for the remote monitoring devices under consideration (Section 3.3.4):

- Woodrow et al. (2020): a quasi-randomised cluster trial (n=154) assessing PKG's ability to guide therapy and improve outcomes in people with Parkinson's disease compared to SoC practice (see Section 3.3).[17]

- Issacson et al. (2019): a small pilot RCT (n=39) evaluating Kinesia 360's capability to inform optimal rotigotine dosage and improve outcomes in Parkinson's disease for people with insufficiently controlled motor symptoms, versus SoC alone (see Section 3.5).[89]
- Peacock et al. (2021): A suspended small RCT (n=25) comparing telehealth follow-up care using Kinesia 360 to SoC follow-up in Parkinson's disease for patients with bothersome tremor or dyskinesia (identified at prior visit).[90]

Due to the early termination of the trial, Peacock et al. did not provide any comparative outcomes measures relevant to the analysis.[90] No comparative clinical effectiveness evidence could be identified for STAT-ON, KinesiaU or PDMonitor. Consequently, the full economic evaluation only considered intervention strategies using either PKG or Kinesia 360. To assess the potential cost-effectiveness of STAT-ON, KinesiaU and PDMonitor, an exploratory scenario analysis was presented using evidence from Woodrow et al. (2020) to model treatment effects across all interventions (including Kinesia 360). This scenario should be interpreted with caution as it is purely exploratory in nature due to the differences between the alternative remote continuous monitoring devices and the lack of evidence to suggest equivalence in outcomes.

In both Woodrow et al. (2020) and Issacson et al. (2019), the remote continuous monitoring devices were used to optimise current treatment as part of initial assessments and did not consider longer-term repeated use of remote continuous monitoring devices. However, based on company information, real world applications of PKG and expert clinical advice, the EAG assessed two alternative monitoring strategies for PKG and Kinesia 360 within the decision analytic model:

- One-time use: Remote monitoring (PKG or Kinesia 360) implemented at model baseline as a one-time aid to clinical assessment
- Routine use: Remote monitoring (PKG or Kinesia 360) as an adjunct to SoC applied at every follow-up period to routinely assist regular clinical assessments

One-time use attempts to approximate the use of the remote monitoring devices as used in Woodrow et al. (2020) and Issacson et al. (2019). Consequently, it is expected to most closely reflect the available clinical evidence. Routine use assumes repeat use of remote monitoring devices as an adjunct to SoC. This strategy broadly reflects the use of remote monitoring devices as anticipated in the relevant company submissions for PKG and Kinesia 360.

A third strategy of recurrent use was considered in a scenario analysis and is presented as a variation to the routine use strategy. It explores the potential for remote monitoring assessments to replace SoC appointments. In this scenario, remote monitoring (PKG or Kinesia 360) was implemented at model baseline as an adjunct to SoC and, in the follow-up pathway, conducted 6 months between annual

consultations to reduce the number of consultations and facilitate treatment titration prior to the next annual review. This strategy attempts to capture an approach to using remote monitoring devices reported in Dominey et al. (2020).[28]

In the full economic evaluation, PKG and Kinesia 360 were compared to SoC within each alternative monitoring strategy delivery schedule. Further details of the alternative monitoring strategies are provided in Section 5.5.2.

5.4 Model structure

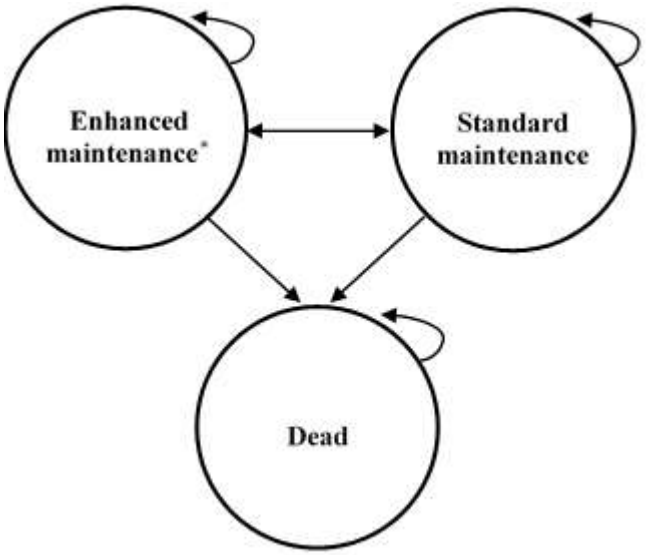
A de novo economic analysis was developed to estimate the costs and health outcomes (in terms of QALYs) associated with alternative remote monitoring strategies and SoC. The economic analysis was designed to capture PwP experiences during the maintenance phase of disease, and is predicated on the assumption that remote monitoring provides a degree of symptomatic relief via improvements in clinical assessment and therapeutic decisions. The economic analysis does not attempt to explicitly model this link and instead directly captures improvements in symptom relief. Specifically, the model uses changes in MDS-UPDRS observed in Woodrow et al. (2020) and Issacson et al. (2019) as an indicator of the degree of symptom control and to capture any health benefits resulting from remote continuous monitoring.[17, 89]

The economic analysis uses a Markov cohort structure consisting of three health states: enhanced maintenance, standard maintenance, and death. Enhanced maintenance and standard maintenance are associated with a specific set of MDS-UPDRS domain scores (I to IV) representing the degree of symptom control associated with remote monitoring (enhanced monitoring health state) and standard of care (standard monitoring health state). The difference between enhanced and standard maintenance is informed via evidence on comparative clinical efficacy and also linked to the changes in levodopa-equivalent titration associated with remote monitoring (see Sections 5.5 for further details of efficacy assumptions and Section 5.11 for resource assumptions).

For any remote monitoring strategy, the cohort enters the model in the enhanced maintenance health-state. During the first cycle of the model (6-months) patients are assumed to either: (i) remain in the enhanced maintenance state; (ii) transition to the standard maintenance health-state; or (iii) transition to an absorbing death state. Transitions between the enhanced and standard maintenance health states are used to capture the waning of treatment effect, with the proportions in each health state determined by the proportion of treatment effect remaining, see Section 5.6 for further details on assumptions associated with the waning of treatment effect. Consequently, the monitoring schedule is determined by the monitoring strategy, rather than state membership (i.e. patients within the standard maintenance health-state can still be undertaking remote monitoring).

Depending on the monitoring strategy and extrapolation assumptions, patients within the standard maintenance state can also transition back into the enhanced maintenance health-state. This is assumed to only occur in strategies where repeat use of remote monitoring devices is permitted and represents a return to enhanced disease management for these patients. At base case model settings, such back-transitions do not occur. For SoC, patients enter the model in the standard maintenance health-state and can either: (i) remain in the standard maintenance health-state or (ii) transition to an absorbing death state. The Markov model structure is presented in Figure 5.

Figure 5 Markov model structure



*Only applicable to patients receiving remote monitoring.

Since Parkinson's disease is a degenerative condition with no available cure or disease modifying treatments, the model considers disease progression exogenous, meaning each monitoring strategy has no influence on disease progression. Disease progression is modelled according to changes in UPDRS domain scores (I-IV), where changes in UPDRS domain scores associated with remote monitoring differentiate the health states. Patients within the enhanced maintenance health-state progress along the same disease trajectory as those within the standard maintenance health-state but experience an intermediate shift in UPDRS scores from alternative maintenance therapy representing the symptomatic relief associated with enhanced management.

The Markov cycle length is 6 months to align with the frequency of consultations made during the maintenance phase of Parkinson's disease. As indicated above, the base case analysis uses a time horizon of 5-years. The NICE reference guide indicates that the time horizon used for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs and

benefits between the technologies being compared.[100] In considering the appropriate time horizon the EAG considered the following points.

- The primary benefits of monitoring result from the optimisation of treatment. The impact of monitoring devices on benefits and costs is therefore contingent upon the availability of alternative treatment strategies. As discussed previously, this is likely to be predominantly confined to the early and maintenance stages of the disease, where alternative treatment strategies can offer improved symptom control
- Comparative clinical evidence on the use of remote continuous monitoring devices is confined to the maintenance stage of the disease, with only limited/no evidence in early and advanced populations
- The symptomatic benefits associated with improved monitoring relative to SoC are likely to be brief as a consequence of further disease progression and catch-up amongst patients receiving current SoC
- The lack of disease-modifying treatments (i.e., treatments that change how PD develops over time) means that improved monitoring cannot impact the long-term trajectory of patients.
- The time horizon of the data used in the literature to establish key relationships (i.e. progression and health-related quality of life models use data with up to 6-years follow-up).

Reflecting on these points, the EAG considered a short time 5-year horizon most appropriate. A lifetime horizon (more typically modelled in NICE appraisals) would require the model to extrapolate relationships beyond the time horizon of the data and would need to account for transitions to more advanced stages of disease including the modelling of advanced treatments such as deep brain stimulation, apomorphine injections and levodopa-carbidopa intestinal gel. While it is plausible that, monitoring devices may impact on transitions to advanced therapies, the available clinical evidence to inform this is limited (see Section 3.3.2). Moreover, the lack of disease modifying drugs implies convergence between patients on SoC with and without remote monitoring. Any impacts on costs and benefits would therefore be transitory, and most likely only impact the timing of when advanced treatments are initiated. The economic analysis also implicitly assumes that remote monitoring will not continue beyond the maintenance disease stage reflecting the available clinical evidence. The 5-year time horizon therefore assumes that remote monitoring devices will be used for a maximum of 5-years (reflecting the approximate duration of the maintenance phase) with no lasting differences to costs and benefits after this time.

5.5 Model input parameters

5.5.1 Patient population

The target population in the model consists of patients in the maintenance phase of Parkinson's disease, where the management of symptomatic motor and non-motor features of the disease is routinely required. Patients in the model consist of the average characteristics of participants enrolled in the Woodrow et al. (2020) study,[17] given that this study represents the largest comparative assessment of clinical effectiveness for remote continuous monitoring devices. Table 24 summarises the values used for the baseline patient characteristics in the model. Disease duration, levodopa daily dose, HY-stage and baseline MDS-UPDRS scores all constitute key characteristics in determining baseline disease progression in the model. Sex and age characteristics establish disease progression, patient's HRQoL and mortality risk. Expert clinical advice obtained by the ERG indicates the Australian study setting does not preclude its relevance to the UK context. Expert clinical advice sought by the EAG did not preclude the relevance of this population to the UK context. However, compared to the patient population in the UK, the trial population may represent a younger and more sex-balanced cohort than seen in UK clinical practice with the average age of Parkinson's diagnosis in the UK occurring between 70-79 years of age and prevalence is notably higher amongst men.[4, 148] The model population aims to reflect the average characteristics of patients with maintenance stage PD; however, the study by Isaacson et al (2019) represents a more severe subpopulation of those experiencing clinically significant motor symptoms insufficiently controlled by current therapy. The EAG acknowledges these limitations.

Table 24 Baseline characteristics

Characteristics	Value
Female	47%
Disease duration	6.35 years
Age	67.8 years
Levodopa daily dose	718.6 mg
HY-stage	2
Baseline MDS-UPDRS1	10.86
Baseline MDS-UPDRS2	10.12
Baseline MDS-UPDRS3	35.46
Baseline MDS-UPDRS4	4.79

5.5.2 Monitoring schedules and settings

Patients with Parkinson disease require regular follow-up care. Appointments serve as an opportunity for health care professionals to review, test and treat a wide range of Parkinson's-specific and age-related symptoms, events, and complications (e.g. motor issues, behavioural abnormalities, falls,

dementia, blood pressure, constipation, etc.). In UK clinical practice, appointments are conducted with a consultant or community Parkinson's disease nurse specialist either via face-to-face consultations or remotely using phone or video appointments. At present, no standard template exists for monitoring within current care pathways with or without the introduction of remote monitoring devices. Remote monitoring devices have the potential to be introduced in a variety of ways, including on a targeted basis, where clinicians believe specific circumstances warrant its application; as a clinical aid used across all follow-up periods; or as an intermediary tool to improve clinical understanding while facilitating targeted follow-up (only assessing those in need). After consultation with experts, reviewing real world applications of remote monitoring devices and considering company responses, the EAG modelled one-time and routine applications of remote monitoring devices, with an alternative recurrent use assessed in a scenario analysis. The assumed schedules and settings for SoC and for the alternative remote monitoring strategies are detailed below.

Standard of care

Patients receiving SoC are assumed to undertake review appointments every 6-months, representing the lower bound of the recommended schedule in NICE clinical guidelines (every 6 to 12 months).[2] It is assumed 55% of consultations are conducted face-to-face and 45% remotely, in line with activities reported in the 2019/20 NHS reference costing schedule (from 158,768 recorded specialist Parkinson's and Alzheimers nursing/liaison activities).[149]

One-time use

Patients receiving a one-time remote monitoring assessment using PKG or Kinesia 360 are assumed to undertake remote assessment in conjunction with baseline consultation. Thereafter, patients' follow-up schedule and setting align with SoC (Table 25).

Routine use

Aligned with the companies' positioning of the technologies, routine use strategies include remote monitoring (PKG or Kinesia 360) as an adjunct to SoC applied at every follow-up period to routinely assist clinical assessments. The model assumes that routine use of remote monitoring devices increases the rate of remote consultations up to 79% (versus 45% in SoC).[32]

Recurrent use (scenario)

In line with the management approach outlined in Dominey et al. (2020),[28] the recurrent use scenario analysis introduces remote management as an intermediary assessment solution, replacing consultations between annual appointments where possible. In this scenario it was assumed that a proportion of intermediate consultations would not be required and that only 21% of patients would require interim (those between annual consolations) face-to-face consultations. This was based on the proportion of virtual clinic appointments deemed unsuccessful in Evans et al. (2020) (issues include

the PKG, speech or hearing problems, complex care needs).[32] This strategy was only considered as scenario due to its stylised nature. For simplicity, this scenario assumes equivalent effectiveness to the routine use strategy, see Section 5.6 for discussion.

Table 25 Base case follow-up schedules for each monitoring strategy

Base case schedules	Baseline		6-months		12-months		18-months		...	Time horizon	
	RMD FU	SoC FU	RMD FU	SoC FU	RMD FU	SoC FU	RMD FU	SoC FU		RMD FU	SoC FU
SoC	✗	✓✓	✗	✓✓	✗	✓✓	✗	✓✓	…	✗	✓✓
One-time use:											
PKG	✓✓	✓✓	✗	✓✓	✗	✓✓	✗	✓✓	…	✗	✓✓
Kinesia 360	✓✓	✓✓	✗	✓✓	✗	✓✓	✗	✓✓	…	✗	✓✓
Routine use:											
PKG	✓✓	✓✓	✓✓	✓✓	✓✓	✓✓	✓✓	✓✓	…	✓✓	✓✓
Kinesia 360	✓✓	✓✓	✓✓	✓✓	✓✓	✓✓	✓✓	✓✓	…	✓✓	✓✓
Recurrent use (scenario):											
PKG	✓✓	✓✓	✓✓	✗*	✗	✓✓	✓✓	✗*	…	✗	✓✓
Kinesia 360	✓✓	✓✓	✓✓	✗*	✗	✓✓	✓✓	✗*	…	✗	✓✓

*Intermediary consultations withdrawn, with exception to patients with exceptional clinical need (assumed to be 21% in base case analysis)
RMD FU: Remote monitoring device follow-up; SoC FU: Standard of care follow-up

5.6 Efficacy

The clinical efficacy of remote monitoring devices is modelled according to changes in UPDRS domain scores relative to SoC. The EAG considered changes in UPDRS to offer a broader and more appropriate measure of symptomatic benefit compared to changes in H&Y scales or other measures used in previous Parkinson's'-related economic evaluations (e.g. <25% 'off' times per day, Section 4.4). The model considers the efficacy of remote monitoring devices as the health benefits attained via improved symptom control and management of the disease relative to SoC. These health benefits are confined to the enhanced maintenance health-state of the model and are conferred via a one-time shift in the disease progression curve (independent of the rate of progression over time). Given the time horizon of the model, the benefits are considered to only occur within the management phase of Parkinson's disease. The magnitude of the changes in UPDRS associated with PKG and Kinesia 360 was informed by Woodrow et al. (2020) and Isaacson et al. (2019), respectively.[17, 89]

To consider a common outcome measure across interventions, and to align with the progression risk and utility equations from Chandler et al. (2020) (Section 5.7, Section 0),[140] MDS-UPDRS scores from Woodrow et al. (2020) were converted onto the UPDRS scale using the linear relationships published by Goetz et al.[142] The EAG notes that Goetz et al. (2012) maps from UPDRS to MDS-UPDRS, and it is unclear how appropriate it is to apply this conversion in the reverse order; however,

the EAG considers it preferable to use the conversion rather than assume that MDS-UPDRS and UPDRS are equivalent. As undertaken in Section 3.3.4.1, changes in UPDRS associated with PKG remote monitoring were adjusted for potential confounding factors (age, sex, PD duration, UPDRS III at baseline and number of clinical visits during follow-up).

Changes in UPDRS associated with Kinesia 360 were derived from the reported difference in difference in UPDRS II and UPDRS III scores between baseline and 12-week follow-up. Due to an absence in reporting UPDRS I and UPDRS IV outcomes in Isacsson et al. (2019), the EAG assume Kinesia 360 has no impact beyond the daily living (UPDRS II) and motor-symptom (UPDRS III) domains of the UPDRS. Without access to individual patient level data, the EAG were not able to adjust for potential confounding factors in Issacson et al. (2019). It is also important to note that the study population in Issacson et al. (2019) represents an enriched population compared to Woodrow et al. (2020), recruiting patients with more severe disease all of whom presented with clinically significant motor symptoms. Given these differences in the study populations, comparisons between PKG and Kinesia 360 should be interpreted with caution.

Estimated changes in UPDRS associated with PKG and Kinesia 360 are reported in Table 26. In line with findings on the MDS-UPDRS scale (Section 3.3.4.1), PKG is associated. PKG is also associated with a negligible and unfavourable impact on the UPDRS I and UPDRS II domains. In consideration of these highly uncertain results, the base case analysis considered two efficacy configurations for PKG: (i) an unrestricted analysis which considers changes across all domains of the UPDRS; and (ii) a restricted analysis that considers only UPDRS domains III and IV, with the average efficacy on UPDRS domains I and II set to zero (i.e. PKG having no detrimental impact on average) (Table 26).

Table 26 Efficacy estimates

Intervention	Method	Source	UPDRS I	UPDRS II	UPDRS III	UPDRS IV
Base case						
PKG	Unrestricted and adjusted UPDRS changes (Section X)	Woodrow et al. (2020)[17]	0.02	0.33	-2.65	-1.16
PKG	Restricted and adjusted UPDRS changes (Section X)	Woodrow et al. (2020)[17]	0	0	-2.65	-1.16
Kinesia 360	Observed UPDRS difference in differences (Table X)	Isaacson et al. (2019) [89]	0	-2.6	-4.3	0
Scenarios						
PKG	Unadjusted UPDRS changes	Woodrow et al. (2020)[17]	-0.83	0.22	-3.35	-1.18
Kinesia 360	Scaled (observed changes in UPDRS	Woodrow et al. (2020)[17]	-1.23	0.12	-3.42	-1.26

Section 3.3.4.1 reports the significance of "target" status in determining outcomes associated with remote monitoring devices. On the basis that "target" status, as defined in Woodrow et al. (2020), cannot be established a priori (i.e. in the absence of a remote monitoring device), the EAG apply average treatment-effects from the trial (i.e. considering all participants, with and without controlled disease). In practice however, health care professionals may, to an extent, be able to identify and focus remote monitoring on "out-of-target" patients (e.g. patients with insufficiently controlled symptoms). The EAG does not present cost-effectiveness results by, or averaged across, "target" status on the basis that patients' "target" status, as defined in Woodrow et al (2020), does not represent, at the point of care, a valid ex-ante sub-group.

Low quality diagnostic accuracy studies suggest that PKG and Kinesia 360 offer moderate short-term systematic benefits from remote monitoring, as observed though improvements in UPDRS II (Kinesia 360), III (PKG and Kinesia 360) and IV (PKG) scores. However, in the absence of any evidence on the efficacy of devices beyond the immediate term, the EAG explores alternative extrapolations in treatment-effect that directly informs transitions between enhanced maintenance and standard maintenance health-states in the model. In the base case analysis, the EAG assume equal rates of treatment waning for PKG and Kinesia 360 with routine remote monitoring strategies and a recurrent scenario strategy incurring no waning in benefit over the maximum 5-year model time horizon (i.e. all patients remain within the enhanced maintenance health-state), and one-time strategies a 50% waning rate per cycle (i.e. every 6-months 50% of patients within the enhanced maintenance health-state transition to the standard maintenance health-state). Modelled strategy-specific efficacy on the UPDRS III domain is displayed in Figure 7 and Figure 8. A wide range of potential values for the exponential waning rates were explored in sensitivity analysis (0-90%).

5.7 Progression of disease

The model uses UPDRS domain scale scores to measure disease severity (behavioural problems, non-motor and motor symptoms, and therapy complications) and progression over the analysis time-horizon. Patients are assumed to progress across all four UPDRS domains according to the prediction equations published in Chandler et al. (2020), which incorporate: patient characteristics (age, gender), treatment factors (PD medications, LED, time since previous follow-up), condition (baseline severity, disease duration) and structural dependencies (rates of change and interactions). Patients in the enhanced maintenance health-state progress along the SoC defined curve but with a decrement associated with their monitoring device (Section 5.6). Details regarding the data informing these equations are provided in Section 4.4. See Table 27 for model coefficients and Figure 6-Figure 8 for progression predictions applicable to the model population.

Table 27 Progression model coefficients

	UPDRS I		UPDRS II		UPDRS III		UPDRS IV	
	β	SE	β	SE	β	SE	β	SE
Intercept	0.19780	0.17220	0.65960	0.50540	-2.78020	0.63200	2.50260	0.16600
Female	-	-	-0.19450	0.08112	-0.75140	0.17200	0.21230	0.03852
Current disease duration (years)	-0.00350	0.01669	0.02299	0.03824	0.05820	0.07809	-0.00107	0.01563
Current age (years)	-0.00048	0.00260	-0.00924	0.00763	0.06763	0.00896	-0.00522	0.00249
Levodopa equivalent daily dose	-0.00001	-0.00010	0.00029	0.00024	-0.00109	0.00047	0.00036	0.00010
Time since last visit (days)	0.00101	0.00016	0.00476	0.00039	0.00868	0.00079	0.00078	0.00015
No off time	-0.17240	0.03450	-0.57840	0.07832	-0.48480	0.16470	-2.34110	0.03305
Baseline score: UPDRS 1	0.25560	0.01893	0.00000	0.00000	-0.07360	0.07479	0.08418	0.01601
Baseline score: UPDRS 2	-	-	0.06945	0.01612	0.05421	0.02600	0.00000	0.00000
Baseline score: UPDRS 3	-0.00624	0.00311	0.02960	0.00563	0.17110	0.01695	0.00000	0.00000
Baseline score: UPDRS 4	-	-	-	-	-	-	0.08793	0.01472
Prior visit score: UPDRS 1	-1.08650	0.07079	0.20450	0.02509	0.33830	0.05784	0.05258	0.01142
Prior visit score: UPDRS 2	-	-	-0.55090	0.05427	-	-	-	-
Prior visit score: UPDRS 3	0.01518	0.00245	-	-	-0.30470	0.01428	-	-
Prior visit score: UPDRS 4	0.03870	0.00927	-	-	-0.09407	0.04415	-0.62510	0.05252
Prior slope: UPDRS 1	-37.06080	3.49530	-	-	-	-	-	-
Prior slope: UPDRS 2	-	-	-48.64770	5.25890	-	-	-	-
Prior slope: UPDRS 3	-	-	-	-	-89.65470	15.97280	-	-
Prior slope: UPDRS 4	-	-	-	-	-	-	-12.06010	1.98680
Current disease duration (years) * levodopa equivalent daily dose	0.00005	0.00002	0.00000	0.00005	0.00006	0.00009	0.00005	0.00002
Baseline score: UPDRS 1 * Prior slope: UPDRS 1	4.70130	1.00190	-	-	-	-	-	-
Baseline score: UPDRS 2 * Prior slope: UPDRS 2	-	-	1.61260	0.49860	-	-	-	-
Prior visit score: UPDRS 1 * Current age (years)	0.00809	0.00105	-	-	-	-	-0.00193	0.00081
Prior visit score: UPDRS 2 * Current age (years)	-	-	0.00494	0.00078	-	-	-	-
Prior visit score: UPDRS 3 * Prior slope: UPDRS 3	-	-	-	-	-1.44400	0.23940	-	-

Figure 6 Predicted disease progression in standard of care

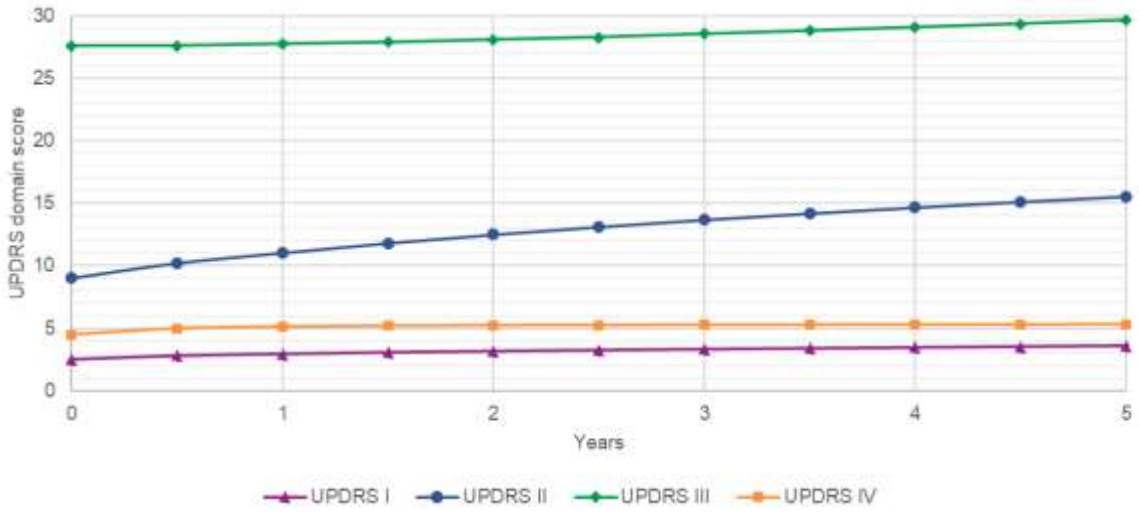


Figure 7 Estimated one-time use monitoring-specific UPDRS III scores (50% decay rate)

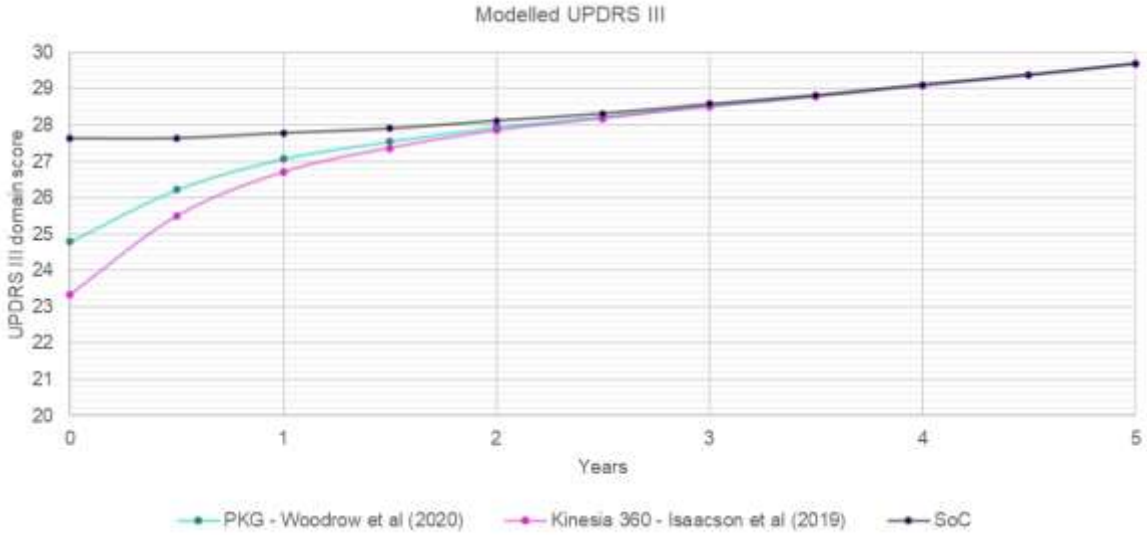
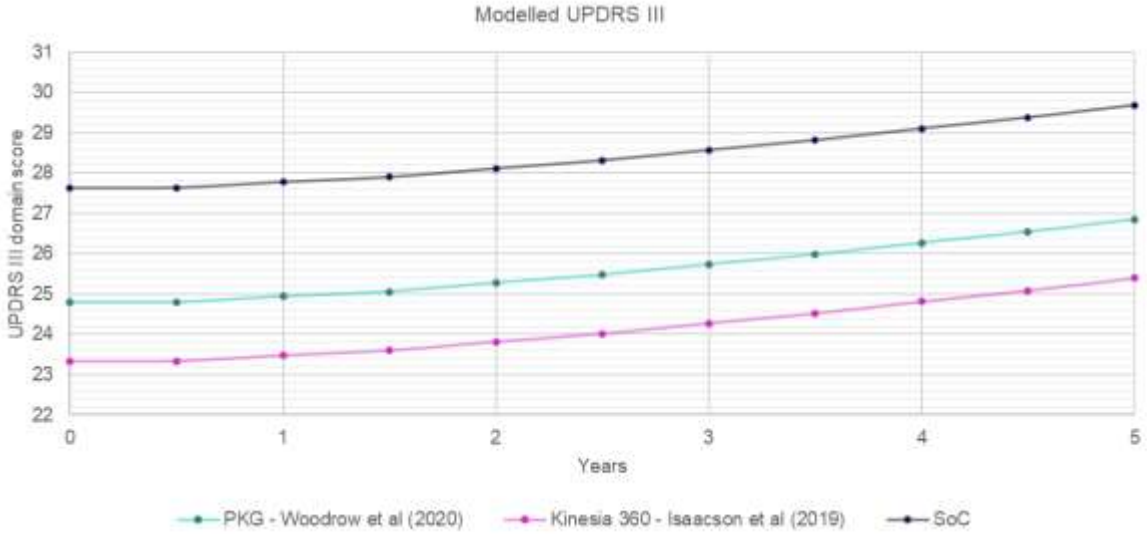


Figure 8 Estimated routine monitoring-specific UPDRS III scores (0% decay rate)



5.8 Adverse event costs

None of the studies identified in the systematic review reported any adverse events directly linked to the use of remote monitoring device. It was therefore not possible to include adverse effects in the economic analysis.

5.9 Mortality

Mortality in the model is based on age- and sex-adjusted all-cause mortality probabilities from the UK Office of National Statistics Interim Life Tables 2018–2020.[150] PD is generally associated with increased mortality; however, survival is highly dependent on the stage and characteristics of the Parkinson's disorder.[151] Patients with Parkinson's presenting with normal cognitive function seem to have a largely normal life expectancy.[151] A recent large, UK population-based study of more than 10,000 patients with PD and more than 50,000 in the control group without PD, however, showed a modest elevation in mortality risks for PwP.[148] Informed by this analysis, the base case analysis adopts an elevated 1.14 hazard ratio for management-stage Parkinson's patients, representing a modest overall increase in mortality associated with the condition compared to the general population. The model applies common mortality rates within patient traces, meaning no differential mortality impact is associated with SoC or the alternative remote monitoring strategies compared.

5.10 Health-related quality of life

5.10.1 Patient health-related quality of life

As previously discussed, health benefits from monitoring devices are assumed to be as a consequence of better symptom control and improved management of the disease. This is captured in the model via changes in UPDRS domain scores. In order to estimate HRQoL benefits associated with the monitoring devices changes in UPDRS domain score were linked to HRQoL improvements using an algorithm reported in Chandler et al. (2020).[140] The Chandler et al. (2020). algorithm was based on a regression analysis using EQ-5D-3L data from the NET-PD LS-1 database which includes 1,741 PD patients from the United States and Canada followed-up for maximum of 6 years. Data was analysed using UK preference weights for the EQ-5D-3L responses and a mixed-effect repeated measures model to account for repeat measurement and included gender and UPDRS domain covariates (having tested for the impact of other patient covariates).

The EAG also considered two alternative sources of HRQoL data: NICE CG71 and Fundament et al. (2020).[98, 137] Both alternative value sets were, however, based on data from patients with advanced disease and therefore did not reflect the modelled population. In the case of Fundament et al. (2020), there were also specific methodological concerns with how the value set was generated, see Section 4.4. The EAG, therefore, deemed Chandler et al.'s (2020) algorithm the most appropriate source for

estimating HRQoL within the UK decision-making context for management-phase Parkinson's disease. Table 28 reports the modelled coefficients.

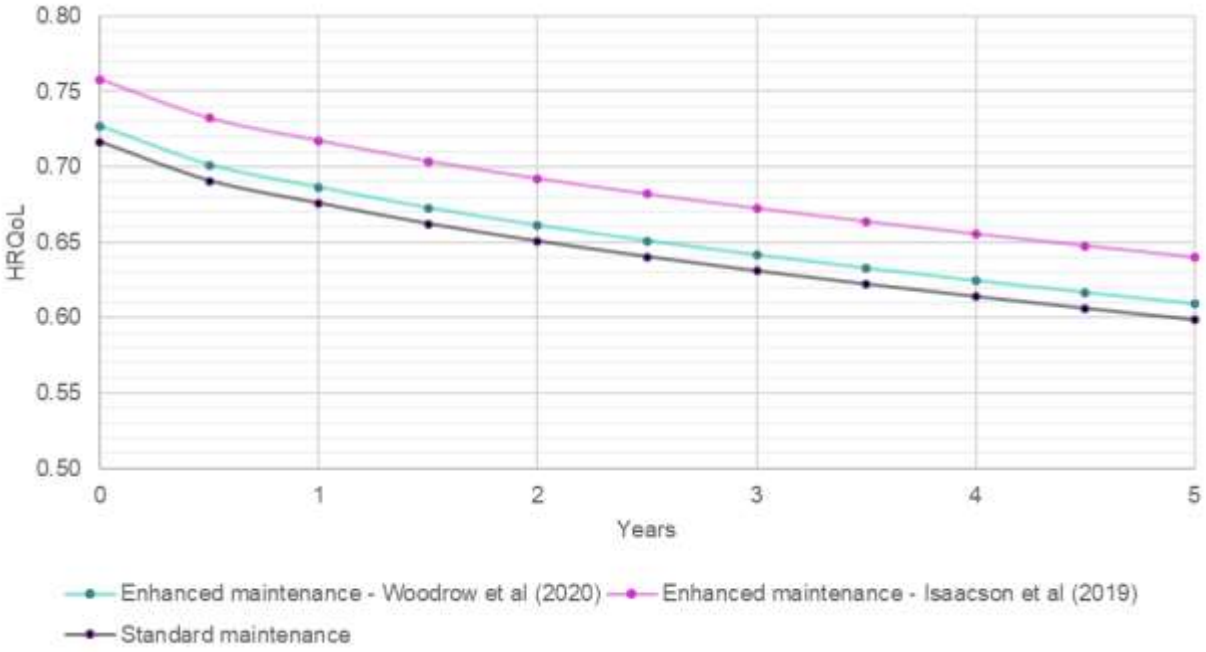
Table 28 Chandler EQ-5D-3L regression

Parameter	Co-efficient	Standard error
Constant	0.9434	0.006414
Male	0.03955	0.006045
UPDRS I	-0.01913	0.001267
UPDRS II	-0.0133	0.000537
UPDRS III	-0.00161	0.00026
UPDRS IV	-0.00813	0.000966

The total incremental QALY gains for the remote continuous monitoring devices compared to SoC are derived from the magnitude of treatment effect (Table 26), persistence of effect over time (Section 5.6) and HRQoL gains (Table 28) associated with the UPDRS differentials between the alternate monitoring strategies. Differentials in UPDRS and associated HRQoL are estimated on a per cycle basis in the model (see Section 5.7). The average HRQoL utility values in the enhanced maintenance health state (using the restricted approach for estimating the efficacy of PKG) is displayed in Figure 9.

Although Parkinson's Disease Questionnaire 39 (PDQ-39) summary scores were available in Woodrow et al. (2020), the omission of dimension-level individual participant data precluded the EAG from generating treatment-specific utility values by mapping the PDQ-39 onto EQ-5D.[152]

Figure 9 Modelled HRQoL in the standard maintenance and in the treatment-specific enhanced maintenance health-states for the remote monitoring devices



5.10.2 Carer quality of life

Caring for people with Parkinson's disease can place a burden on informal caregivers, negatively impacting their (health-related) quality of life.[153] Studies have shown that functional status is an important determinant of carer quality of life, with several studies emphasising mobility and cognitive impairment as drivers of carer quality of life. There is, however, no direct evidence linking the use of remote monitoring devices to carer quality of life. Moreover, the broader literature does not show any consistent relationship between relevant clinical outcomes such as UPDRS.[154] It was therefore not possible to account for any impacts on carer quality of life within the economic analysis. This may represent an uncaptured benefit given the observed improvements in UPDRS and other clinical outcomes.

5.11 Resource use and costs

This section details the resource use and costs applied in the model. The EAG did not establish a relationship between disease severity and costs. The model considers the costs of the remote continuous monitoring devices, implementation costs, follow-up consultations and medication costs. Details of each resource use and cost in the model are presented in the sections below.

5.11.1 Remote monitoring device costs

The costs of PKG, Kinesia 360, STAT-ON, KinesiaU and PDMonitor devices were based on company responses to the NICE request for information. The alternative devices had three types of

payment mechanism: (i) pay per use; (ii) subscription model; or (iii) outright purchase of the device. VAT was not applied to device costs as outlined in the NICE Diagnostics Assessment Programme manual.[100] The costs of the devices are reported in Table 29.

Table 29 Remote continuous monitoring device costs

	Cost (exc. VAT)	Unit	Modelled cost per year	Modelled cost per 5 years (base case time horizon)
PKG	£225	Per use per patient	£450*	£2250*
Kinesia 360	£224	Monthly device subscription	£2,688†	£13,440†
STAT-ON	£1,600	Annual device subscription	£1,920†	£9,600†
KinesiaU	£64	Monthly subscription per patient	£768†	£3,840†
PDMonitor	£12,000	Outright device purchase	£12,000†	£12,000†

* Excludes initial assessment(s), †assumes one patient per subscription/device

The PKG device requires a payment of £225 per application. The cost is inclusive of the postage of the data logger to the patient, postage back to GKC and the PKG report made available via the online portal. Kinesia devices use a subscription service cost model with monthly fees of £224 and £64 for Kinesia 360 and KinesiaU products, respectively. KinesiaU comprises patient-level costs for access to the company's smartphone/smartphone app (£5 per month) and clinician-specific costs for access to the KinesiaU portal (£59 per month). STAT-ON uses a subscription model with an annual licence fee (£1,600). This grants the user(s) a device, charger kit and adjustable belt with clinical and technical support as well as a 2-year warranty. Kinesia 360, STAT-ON, and PDMonitor allow multiple users to access the subscribed or purchased devices (albeit with new straps required). Besides PKG, it is unclear whether broader costs for the delivery and management of devices are included in the company costs (e.g. device delivery, administration, relevant support, etc.). The costs of potential loss or damage to devices is not stated by the companies and for simplicity is not included in the model.

The EAG assumes subscription models (Kinesia 360, KinesiaU and STAT-ON) continuously run over the course of the model time horizon for routine strategies and for the recurrent monitoring scenario. PDMonitor is treated as a one-time up-front cost, with no additional intervention costs for repeated use. The EAG believe this to be reasonable on the basis that the model time horizon falls within the company stated lifetime of the device (approximately 7-years). For one-time use remote monitoring strategies, it was assumed that a 3-month subscription was required for Kinesia products (in line with the 12-week follow-up in Isaacson et al. (2019)[89]), and a one-year subscription for STAT-ON. The EAG acknowledges that the one-time monitoring strategy does not align with the companies positioning of purchased (PDMonitor) or subscription-based services (Kinesia 360, KinesiaU and STAT-ON) and may incur further administrative burden and implementation costs relative to one-time PKG use.

5.11.2 Implementation costs

The costs required to successfully implement remote monitoring strategies into service pathways was divided into fixed implementation costs, those irrespective of device use, and variable costs, those specifically incurred from using a remote monitoring device in clinical practice.

Fixed implementation costs were calculated in accordance with staff training times noted in company responses, with the mid-point selected within ranges (PKG & STAT-ON: 90 minutes; Kinesia 360, KinesiaU and PDMonitor: 30 minutes). This equated to a £56 cost per patient assuming clinician-level fixed costs are distributed over 8 patients.[32, 155] Implementation costs may include clinician training (participating clinicians in the Woodrow study received a day of training in interpreting the PKG), and a variety of process factors (e.g. administration, procurement, etc.).

Variable implementation costs may exist given the potential for remote monitoring devices to require additional patient support and health-care professional time required to arrange its application and review findings. The base case analysis applies zero variable implementation costs, assuming consultation costs sufficiently cover potential broader service factor costs. Scenario analyses considered the removal of implementation costs and the addition of variables costs (an additional £39 cost per consultations using a remote monitoring device, equivalent to 15 minutes of general practitioner time).

5.11.3 Consultation costs

In line with Woodrow et al. (2020), it was assumed that several initial face-to-face consultations would be required. For all remote monitoring strategies patients were assumed to undertake 2.57 initial visits, while patient receiving SoC were assumed to receive 2.17 visits.

For subsequent visits the consultation setting, and their associated costs, are dependent on the monitoring strategy (i.e. one-time use or routine monitoring). As described previously (see Section 5.5.2), patients receiving SoC are assumed to undertake review appointments every 6-months, with 55% of consultations conducted face-to-face and 45% remotely. This split was informed by activities reported in the 2019/20 NHS reference costing schedule (from 158,768 recorded specialist Parkinson's and Alzheimer's nursing/liaison activities).[149] Face-to-face and remote consultations were assumed to cost the NHS £81.41 and £56.41 respectively, in line with NHS reference costs 2019/20.[149]

The one-time use remote monitoring strategies were assumed to align to the setting and follow-up schedule received with SoC. Relative to SoC and one-time use strategies, the routine and recurrent remote monitoring strategies are assumed to increase the proportion of consultations which can be conducted remotely based on evidence from Evans et al. (2020).[32] To incorporate this cost-saving, the

routine and recurrent (scenario analysis) strategies assume 79% of consultations are conducted remotely (compared to 45% in SoC). The recurrent scenario strategy also allows 79% of patients to avoid an interim review between annual appointments (with the remaining 21% requiring face-to-face consultation). To consider the potential for remote monitoring strategies to mitigate the need for consultation, alternative consultation savings were explored in sensitivity analysis. Table 30 provides an overview of the costs and patient consultation settings for SoC and each monitoring strategy.

Table 30 Consultation setting, cost and schedules

	Face-to-face consultations		Cost source	Remote consultation		Cost source	Schedule
	Proportion of patients	Cost per consult		Proportion of patients	Cost per consult		
Standard of care	55%	£81.41	Tariff: N22AF	45%	£56.41	Tariff: N22AN	Every 6-months
One-time use	55%	£81.41	Tariff: N22AF	45%	£56.41	Tariff: N22AN	Every 6-months
Routine use	21%	£81.41	Tariff: N22AF	79%	£56.41	Tariff: N22AN	Every 6-months
Scenario:							
Recurrent use	21%	£81.41	Tariff: N22AF	79%	£56.41	Tariff: N22AN	Annual*

*21% patients receiving intermediary face-to-face consultations

5.11.4 Medication costs

Medication costs in the model were based on the average cost per mg of levodopa equivalent daily dose (LED) regimens reported in Chandler et al. (2021).[140] The study calculates the average cost per mg of LED in the UK to be £5.01 per year, from the medication composition published in an analysis of the UK Clinical Practice Research Datalink (CPRD) database between 2004-2015 (levodopa 43%, pramipexole 30.34% , ropinirole 21.52%, and bromocriptine 4.78%) and drug costs from the Monthly Index of Medical Specialties database.[143]

Across all remote monitoring strategies, patients within the enhanced maintenance health state in the model were prescribed an additional 22mg LED, in line with the EAG adjusted estimates of the differences in LEDD consumption from the Woodrow et al. study (Section 3.3.4.1). Based on previous economic evaluations, it was assumed LED doses increase at a rate of 10% per annum.[156-158] Differentials in LED between remote monitoring strategies diminish at the assumed rate of decay in treatment benefit, whereby differences are maintained over the model time horizon in the base case routine and recurrent remote monitoring strategies (assuming no efficacy decay), and diminish at an assumed positive rate in the one-time remote monitoring strategies (50% base case).

5.12 Analytical methods

5.12.1 Base case analysis

The base case analyses present deterministic and probabilistic pairwise comparisons between PKG and SoC and Kinesia 360 and SoC for one-time use and routine remote monitoring strategies. Cost-effectiveness analyses of PKG were presented both with restricted and unrestricted efficacy (i.e. restricted to only assessing UPDRS domains III and IV). A base case analysis with an incremental comparison of SoC, PKG and Kinesia 360 was also presented. The base-case parameters and their associated assumptions and sources are detailed in Table 31.

Table 31 Base case parameters and assumptions

Parameter	Values	Source/Assumptions	Probabilistic model setup
Patient characteristics			
Age	67.8	Woodrow et al. (2020)	NA
Proportion of male individuals	53%	Woodrow et al. (2020)	NA
Disease duration	6.35 years	Woodrow et al. (2020)	NA
Levodopa equivalent daily dose	718.60mg	Woodrow et al. (2020)	NA
Proportion of patients experiencing no off-time	0%	Woodrow et al. (2020)	NA
Baseline MDS-UPDRS I	10.86	Woodrow et al. (2020)	NA
Baseline MDS-UPDRS II	10.12	Woodrow et al. (2020)	NA
Baseline MDS-UPDRS III	35.46	Woodrow et al. (2020)	NA
Baseline MDS-UPDRS IV	4.79	Woodrow et al. (2020)	NA
Efficacy			
PKG: unrestricted adjusted estimates			
UPDRS I	0.00469	Woodrow et al. (2020)	Gaussian distribution: Mean: 0.00469 SE: 0.24960
UPDRS II	0.51770	Woodrow et al. (2020)	Gaussian distribution: Mean: 0.51770 SE: 0.52475
UPDRS III	-2.84362	Woodrow et al. (2020)	Gaussian distribution: Mean: -2.84362 SE: 1.00518
UPDRS IV	-0.72765	Woodrow et al. (2020)	Gaussian distribution: Mean: -0.72765 SE: 0.58011

PKG: restricted adjusted estimates			
UPDRS I	0	Woodrow et al. (2020)	Gaussian distribution: Mean: 0 SE: 0.24960
UPDRS II	0	Woodrow et al. (2020)	Gaussian distribution: Mean: 0 SE: 0.52475
UPDRS III	-2.84362	Woodrow et al. (2020)	Gaussian distribution: Mean: -2.84362 SE: 1.00518
UPDRS IV	-0.72765	Woodrow et al. (2020)	Gaussian distribution: Mean: -0.72765 SE: 0.58011
PKG: unrestricted unadjusted estimates			
UPDRS I	-0.01318	Woodrow et al. (2020)	Gaussian distribution: Mean: -0.01318 SE: 0.26946
UPDRS II	0.23822	Woodrow et al. (2020)	Gaussian distribution: Mean: 0.23822 SE: 0.52958
UPDRS III	-3.33473	Woodrow et al. (2020)	Gaussian distribution: Mean: -3.33473 SE: 1.27556
UPDRS IV	-1.72282	Woodrow et al. (2020)	Gaussian distribution: Mean: -1.72282 SE: 0.60529
PKG: restricted unadjusted estimates			
UPDRS I	-0.01318	Woodrow et al. (2020)	Gaussian distribution: Mean: -0.01318 SE: 0.26946
UPDRS II	0	Woodrow et al. (2020)	Gaussian distribution: Mean: 0 SE: 0.52958
UPDRS III	-3.33473	Woodrow et al. (2020)	Gaussian distribution: Mean: -3.33473 SE: 1.27556
UPDRS IV	-1.72282	Woodrow et al. (2020)	Gaussian distribution: Mean: -1.72282 SE: 0.60529
Kinesia 360			
UPDRS I	0	Isaacson et al. (2019)	Gaussian distribution: Mean: 0 SE: 0
UPDRS II	-2.60	Isaacson et al. (2019)	Gaussian distribution: Mean: -2.60 SE: 0.6
UPDRS III	-4.30	Isaacson et al. (2019)	Gaussian distribution: Mean: -4.30 SE: 2.0
UPDRS IV	0	Isaacson et al. (2019)	Gaussian distribution: Mean: 0 SE: 0
Long-term decay rate in efficacy (i.e. transitions between enhanced maintenance and standard maintenance health-state)			

One-time use remote monitoring	50%	Assumption	NA
Routine remote monitoring	0%	Assumption	NA
Recurrent remote monitoring (scenario)	0%	Assumption	NA
Disease progression			
Disease progression model	Table 27	Chandler et al. (2021)	Table 27
HRQoL			
UPDRS I	-0.01913	Chandler et al. (2021) (see Section 5.10 for full model)	Gaussian distribution: Mean: -0.01913 SE: 0.001267
UPDRS II	-0.01330	Chandler et al. (2021) (see Section 5.10 for full model)	Gaussian distribution: Mean: -0.01330 SE: 0.000537
UPDRS III	-0.00161	Chandler et al. (2021) (see Section 5.10 for full model)	Gaussian distribution: Mean: -0.00161 SE: 0.00026
UPDRS IV	-0.00813	Chandler et al. (2021) (see Section 5.10 for full model)	Gaussian distribution: Mean: -0.00813 SE: 0.000966
Costs			
Intervention costs			
PKG	£225 (per use)	Company response	NA
STAT-ON	£1600 (per year)	Company response	NA
Kinesia 360	£224 (per month)	Company response	NA
KinesiaU	£64 (per month)	Company response	NA
PDMonitor	£12,000 (one-time)	Company response	NA
Fixed implementation cost per patient			
PKG	£29.25	Calculated based on company reported clinician training time and general practitioner time costs. It was assumed costs were distributed over an eight patient cohort (in line with the eight-patient template in Evans et al. (2020)).	NA
STAT-ON	£29.25		NA
Kinesia 360	£9.75		NA
KinesiaU	£9.75		NA
PDMonitor	£9.75		NA
Initial baseline consultations			
SoC	2.17	Woodrow et al. (2020)	Gamma distribution: α: 4.15630 β: 0.52138
PKG	2.57	Woodrow et al. (2020)	Gamma distribution:

			α: 3.84598 β: 0.66797
STAT-ON	2.57	Woodrow et al. (2020)	Gamma distribution: α: 3.84598 β: 0.66797
Kinesia 360	2.57	Woodrow et al. (2020)	Gamma distribution: α: 3.84598 β: 0.66797
KinesiaU	2.57	Woodrow et al. (2020)	Gamma distribution: α: 3.84598 β: 0.66797
PDMonitor	2.57	Woodrow et al. (2020)	Gamma distribution: α: 3.84598 β: 0.66797
Consultation costs			
Office appointment	£81.41	NHS Reference costs (19/20): Specialist Nursing, Parkinson's and Alzheimers Nursing/Liaison, Adult, Face to face [N22AF]	NA
Remote appointment	£56.41	NHS Reference costs (19/20): Specialist Nursing, Parkinson's and Alzheimers Nursing/Liaison, Adult, Non face to face [N22AN]	NA
Medication costs			
LED dosage change associated with remote monitoring	21.62mg	Woodrow et al. (2020)	Gaussian distribution: Mean: 21.62mg SE: 43.95mg
Dopaminergic medication costs (per LED mg)	£5.01	Chandler et al. (2021)	Gaussian distribution: Mean: 5.01 mg SE: 1.00 mg (20% mean)
Non-dopaminergic medication costs (per annum)	£192.10	Chandler et al. (2021)	Gaussian distribution: Mean: 192.10 SE: 38.42 (20% mean)
Mortality			
Disease-specific all-cause mortality hazard ratio	1.14	Okunoye et al. (2021)	Log normal distribution: Mean: 1.14 SE: 0.11

The core structural assumptions underlying the economic analysis are detailed in Table 32.

Table 32 Core structural model assumptions

Structural assumptions		
Assumption	**Element**	**Description**
1	Costing	Cost differentials between SoC and alternative remote monitoring strategies only result from: (1) costs associated with using each remote monitoring device (PKG, Kinesia 360, etc.); (2) changes in LED medication use; (3) implementation costs; (3) follow-up care setting (face-to-face or remote consultation); (4) The model considers the costs of the remote monitoring devices, implementation costs, follow-up consultations and medication costs. Costs were independent of disease progression. One-time applications of Kinesia devices and STAT-ON require a 3-month and annual subscription, respectively.
2	Efficacy	Treatment efficacy is represented via a one-time shift in severity (defined by UPDRS and used to differentiate the enhanced and standard maintenance health-states) and linked in the model via changes in medication alone. The base case analysis assumes a 0% and 50% per cycle waning in treatment benefit (i.e. transition from enhanced maintenance to standard maintenance health-state and associated outcomes) for one-time use and routine remote monitoring strategies, respectively.
3	HRQoL	Health-related quality of life is only dependant on the UPDRS score and gender over the time horizon of the analysis.
4	Disease progression	Disease progression is defined on the UPDRS scale, with rates of progression deemed independent to remote monitoring.
5	Time horizon	5 years is a sufficient time-horizon for assessing the application of remote monitoring devices within the management phase of Parkinson's disease
6	Adverse events	Patients do not experience adverse events.
7	Mortality	Patients experience an elevated 1.14 times greater all-cause mortality risk compared to the UK age- and sex-adjusted general population. On death all device remote monitoring device subscriptions are assumed cancelled.

5.12.2 Scenario analyses

A number of scenario analyses are considered in which the alternative strategies and assumptions are inputted into the economic model and results compared to base case findings. These analyses are undertaken to assess the robustness of the base case results to key uncertainties. Details of each scenario, including applicable model element, the relevant position taken in the base case analysis, which strategies the scenario is applicable to, and the alternative assumption applied is presented in Table 33.

Table 33 Details of the key elements of the base-case analysis and the variations made in scenario analysis

Scenario	Element	Position in base case analysis	Strategies	Variation in scenario analysis
1	Remote monitoring strategies	One-time use and routine applications of remote monitoring devices considered (see Section 5.5.2).	PKG, Kinesia 360 (recurrent strategies using PKG or the Kinesia 360 remote monitoring device)	An alternative remote monitoring strategy (recurrent) which places remote monitoring between annual clinic appointment, in line with the schedule reported in Dominey et al. (2020).
2	PKG efficacy	Adjusted analysis of UPDRS data from Woodrow et al. (2020)	PKG (one-time use and routine remote monitoring strategies)	Unadjusted analysis of UPDRS data from Woodrow et al. (2020)
3	Implementation costs	a) Fixed implementations costs distributed over 8 patients, aligned to company recommended training times and general practitioner time costs	PKG, Kinesia 360 (one-time use and routine remote monitoring strategies)	Removing all implementation costs
		b) Assumes no variable implementation costs		£39 variable cost (15 minutes of general practitioner time applied at each consultation with a corresponding remote monitoring device).
4	Consultation setting	SoC and one-time use remote monitoring strategies: 55% face-to-face; 45% remote appointment Routine remote monitoring strategies: 79% online; 21% remote	PKG, Kinesia 360 (one-time use and routine remote monitoring strategies)	Equal consultation setting across all alternatives under investigation: 55% face-to-face; 45% remote appointment
5	Routine follow-up schedule	Follow-up schedule for one-time and routine monitoring strategies set to every 6-months (representing the lower bound of NICE guideline recommendations NG61).	PKG, Kinesia 360 (one-time use and routine remote monitoring strategies)	Follow-up schedule set to 12-months (representing the upper bound of NICE guideline recommendations).[2] PKG routine remote monitoring strategy assumed to align with annual follow-up with other subscription and purchase models unaffected.
6	Incremental approach	Pairwise comparisons using base case model settings	PKG, Kinesia 360, KinesiaU, STAT-ON, PDMonitor (routine remote monitoring strategies only)	A fully incremental comparison of routine remote strategies for PKG, Kinesia 360, KinesiaU, STAT-ON and PDMonitor assuming equal efficacy as estimated from Woodrow et al. (2020).

5.12.3 Model validation

The model was developed in Excel by EC and validated by a second analyst (RH). As part of an overall quality assurance process, the internal validity of the model was assessed by extensively exploring logical consistency in the model results.

6 RESULTS OF THE INDEPENDENT ECONOMIC ASSESSMENT

Economic assessments comprised: (i) pairwise comparisons of PKG remote monitoring strategies with SoC; (ii) pairwise comparisons between Kinesia 360 remote monitoring strategies and SoC; (iii) incremental comparison with PKG, Kinesia 360 and SoC; (iv) a cost comparison of all alternative monitoring derives including STAT-ON, KinesiaU and PDMonitor; and, (v) a fully incremental exploratory scenario analysis that assumes equal efficacy across all the remote monitoring devices, but differences in costs of the devices. Scenarios analyses applicable to each economic assessment are described in Table 33. Additional sensitivity analyses considered further uncertainties.

6.1 PKG base-case scenario

Deterministic and probabilistic base case findings for one-time use and routine PKG remote monitoring strategies are reported in Table 34 and Table 35, respectively. Base case ICER's for the PKG relative to SoC were dependant on monitoring strategy and whether efficacy estimates were restricted (those only considering UPDRS domains scales that demonstrated a beneficial impact of the PKG, see Table 26). The deterministic base case ICER's for PKG one-time use and routine remote monitoring strategies were £67,856 (£202,363) per QALY and £57,877 (£172,602) per QALY when using a restricted (unresstricted) analysis, respectively. Incremental costs were markedly higher for the routine remote monitoring strategy (£2,640) versus one-time use (£339). In both the restricted and unrestricted analyses, QALY gains were approximately 9.15 times greater for the routine remote monitoring strategy relative to one-time use. Restricted analyses significantly increased the HRQoL and consequent QALY-gain associated with PKG, increasing HRQoL gains in the enhanced maintenance health-state from approximately 0.0036 to 0.0105 relative to SoC. In the restricted analysis, 44% of the HRQoL benefits associated with PKG were conferred via changes on the UPDRS III domain and the remainder via the UPDRS IV domain (56%). Mean and incremental probabilistic results were broadly comparable to deterministic values, albeit with minor reductions in estimated mean QALYs.

Table 34 PKG one-time use remote monitoring strategy base case cost-effectiveness results

One-time use remote monitoring strategy				Incremental		ICER
		Costs	QALY	Costs	QALYs	(£/QALY)
Deterministic analysis	*Restricted analysis*					
	Standard of care	£21,939	2.788			
	PKG	£22,278	2.793	£339	0.00499	£67,856
	Unrestricted analysis					
	Standard of care	£21,939	2.788			
	PKG	£22,278	2.790	£339	0.00167	£202,363
Probabilistic analysis	*Restricted analysis*					
	Standard of care	£21,886	2.760			
	PKG	£22,225	2.765	£339	0.00504	£67,260
	Unrestricted analysis					
	Standard of care	£21,953	2.755			
	PKG	£22,291	2.757	£338	0.00171	£197,475

Table 35 PKG routine remote monitoring strategy base case cost-effectiveness results

Routine remote monitoring strategy				Incremental		ICER
		Costs	QALY	Costs	QALYs	(£/QALY)
Deterministic analysis	*Restricted analysis*					
	Standard of care	£21,939	2.788			
	PKG	£24,580	2.834	£2,640	0.04562	£57,877
	Unrestricted analysis					
	Standard of care	£21,939	2.788			
	PKG	£24,580	2.804	£2,640	0.01530	£172,602
Probabilistic analysis	*Restricted analysis*					
	Standard of care	£21,951	2.756			
	PKG	£24,578	2.801	£2,627	0.04553	£57,702
	Unrestricted analysis					
	Standard of care	£21,875	2.756			
	PKG	£24,527	2.771	£2,652	0.01509	£175,711

In order to help understand the incremental results, the disaggregated incremental results for total expected costs for the PKG one-time use and routine remote monitoring strategies compared to SoC are presented in Table 36. The total incremental cost per strategy (relative to SoC) is £338.47 and £2,640.34, respectively. Cost differentials were predominantly as a result of device-related costs, which made up 66% (one-time) and 83% (routine) of the cost differentials. PKG one-time remote monitoring incurred device and implementation costs while incurring additional consultation and medication costs relative to SoC. PKG routine remote monitoring found consultation cost savings via a higher proportion of remote consultations compared to face-to-face consultations and incurred additional costs relative to SoC via device-, implementation- and medication-related costs.

Table 36 PKG disaggregated incremental discounted costs

	PKG incremental costs versus SoC				
Strategy	Device costs	Consultation costs	Implementation costs	Medication costs	Total
One-time use	£225.00	£32.73	£29.25	£51.47	£338.47
Routine monitoring	£2,181.25	-£41.13	£29.25	£470.97	£2,640.34

6.2 PKG scenario results

Table 37 shows the restricted (considering only UPDRS III and IV domains) and unrestricted (considering all UPDRS domains) results of each EAG scenario analysis. As for the base case analysis, both one-time and routine use strategies where considered.

Scenario 1 considers the recurrent monitoring strategy, a variation on the routine strategy in which interim consultations are avoided in a proportion of patients, see Section 5.5.2 for details. The recurrent remote monitoring strategy scenario generated ICER's of £32,417 and £96,675 per QALY when using the restricted and unrestricted analyses, respectively. This is substantially lower than the base case routine strategy. This is driven by reductions in both the number of PKGs administered (approximately 50% reduction compared to routine use), as well as reductions in consultation costs which are averted under this strategy.

Scenario 2 presents results using the naive unadjusted estimates from Woodrow et al. (2020). This scenario increases the QALY gains associated with remote monitoring. These are a result of greater efficacy on the UPDRS IV domain (adjusted: Δ-0.73; unadjusted Δ-1.16). The ICER's for the one-time use and routine remote monitoring strategies were £52,071 (£80,239) and £44,413 (£68,438) per QALY, respectively, for the restricted (unrestricted) analyses.

Scenario 3(a) and 3(b) consider alternative assumptions regarding model implementation costs. Scenario 3(a) removes the initial (fixed) implementation costs (£29.25), while scenario 3(b) adds variable implementation costs (£39 per PKG). Reflecting the removal of fixed implementation costs associated with PKG, scenario 3(a) results in a modest reduction in the ICER compared to the base case analysis. The ICER's for the one-time use and routine remote monitoring strategies were £61,992 (£184,875) and £57,263 (£170,690) per QALY, respectively, for the restricted (unrestricted) analyses. These contrast with the results from scenario 3(b) where the respective ICERs increase. The ICER's for the one-time use and routine remote monitoring strategies were £75,675 (£225,680) and £66,164 (£197,317) per QALY, respectively, for the restricted (unrestricted) analyses.

Scenario 4, and the alignment of consultation setting (55% face-to-face, 45% remote) had a relatively minor impact on cost-effectiveness findings.

Scenario 5 explores annual (as opposed to 6-monthly) routine follow-up and PKG applications. This scenario results in significantly reduced incremental costs compared to base case findings, primarily driven by reduced device costs compared to the base case. Consequently, this scenario resulted in lower ICERs compared to the base case analysis, £36,973 and £110,260 per QALY when using the restricted and unrestricted analyses, respectively. Note this scenario assumes equivalent outcomes to the base case routine remote monitoring strategy configuration (i.e. bi-annual consultations with no waning in treatment efficacy).

Table 37 Scenario analyses for PKG remote monitoring strategies

	PKG – restricted analysis					*PKG – unrestricted analysis*				
			Incremental		**ICER**			**Incremental**		**ICER**
	Costs	**QALY**	**Costs**	**QALYs**	**(£/QALY)**	**Costs**	**QALY**	**Costs**	**QALYs**	**(£/QALY)**
Scenario 1: Recurrent monitoring strategy										
Routine use										
Standard of care	£21,939	2.788				£21,939	2.788			
PKG	£23,418	2.834	£1,479	0.04562	£32,417	£23,418	2.804	£1,479	0.01530	£96,675
Scenario 2: Unadjusted efficacy estimates Woodrow et al. (2020)										
One-time use										
Standard of care	£21,939	2.788				£21,939	2.788			
PKG	£22,278	2.795	£338	0.00650	£52,071	£22,278	2.792	£338	0.00422	£80,239
Routine use										
Standard of care	£21,939	2.788				£21,939	2.788			
PKG	£24,580	2.848	£2,640	0.05945	£44,413	£24,580	2.827	£2,640	0.03858	£68,438
Scenario 3 a): Removal of implementation costs										
One-time use										
Standard of care	£21,939	2.788				£21,939	2.788			
PKG	£22,248	2.793	£309.22	0.00499	£61,992	£22,248	2.790	£309.22	0.00167	£184,875
Routine use										
Standard of care	£21,939	2.788				£21,939	2.788			
PKG	£24,550	2.834	£2,611	0.04562	£57,236	£24,550	2.804	£2,611	0.01530	£170,690
Scenario 3 b): Inclusion of variable implementation costs (£39 per PKG)										
One-time use										
Standard of care	£21,939	2.788				£21,939	2.788			
PKG	£22,317	2.793	£377.47	0.00499	£75,675	£22,317	2.790	£377.47	0.00167	£225,680
Routine use										
Standard of care	£21,939	2.788				£21,939	2.788			
PKG	£24,958	2.834	£3,018	0.04562	£66,164	£24,958	2.804	£3,018	0.01530	£197,317
Scenario 4: Consultation settings aligned across all strategies										
One-time use										
Standard of care	£21,939	2.788				£21,939	2.788			
PKG	£22,278	2.793	£338.47	0.00499	£67,856	£22,278	2.790	£338.47	0.00167	£202,363
Routine use										

Standard of care	£21,939	2.788				£21,939	2.788			
PKG	£24,653	2.834	£2,714	0.04562	£59,496	£24,653	2.804	£2,714	0.01530	£177,430
Scenario 5: Annual routine follow-up (and annual PKG remote monitoring)										
Routine use										
Standard of care	£21,630	2.672				£21,630	2.672			
PKG	£23,317	2.718	£1,687	0.04562	£36,973	£23,317	2.687	£1,687	0.01530	£110,260

6.3 Kinesia 360 base-case results

Deterministic and probabilistic base case results for one-time use and routine Kinesia 360 remote monitoring strategies are reported in Table 38 and Table 39, respectively. The deterministic base case ICER's for one-time use (3-month subscription) and routine remote monitoring strategies were £38,828 and £67,203 per QALY per QALY, respectively. Incremental costs were markedly higher for the routine remote monitoring strategy (£12,125) versus one-time use (£766). QALY gains were approximately 9.15 times greater for the routine remote monitoring strategy (0.18) relative to one-time use (0.02). HRQoL benefits associated with Kinesia 360 remote monitoring were accrued via changes in the UPDRS II (83% of HRQoL gain) and UPDRS III (17% of HRQoL gain) domains. Mean and incremental probabilistic results were broadly comparable to deterministic values, albeit with minor reductions in estimated mean QALYs.

Table 38 Kinesia 360 one-time use remote monitoring strategy base case cost-effectiveness results

One-time use remote monitoring strategy			Incremental		ICER
	Costs	QALY	Costs	QALYs	(£/QALY)
Deterministic					
Standard of care	£21,939	2.788			
Kinesia 360	£22,705	2.808	£766	0.01973	£38,828
Probabilistic					
Standard of care	£21,886	2.760			
Kinesia 360	£22,651	2.780	£765	0.01977	£38,722

Table 39 Kinesia 360 routine remote monitoring strategy base case cost-effectiveness results

Routine remote monitoring strategy			Incremental		ICER
	Costs	QALY	Costs	QALYs	(£/QALY)
Deterministic					
Standard7of care	£21,939	2.788			
Kinesia 360	£34,064	2.969	£12,125	0.18042	£67,203
Probabilistic					
Standard of care	£21,951	2.756			
Kinesia 360	£34,061	2.936	£12,110	0.17973	£67,376

The disaggregated total expected costs for the Kinesia 360 one-time use and routine remote monitoring strategies versus SoC are presented in Table 40. The total incremental cost of Kinesia 360 one-time use relative to SoC is £765.97, and for routine remote monitoring is £12,124.90. Total incremental costs were almost entirely driven by device-related subscription costs which made up 88% (one-time) and 96% (routine) of the cost differentials. As observed in the PKG analysis, small incremental cost savings are accrued in the consultation cost category when using a routine use strategy.

Table 40 Kinesia 360 disaggregated costs

	PKG incremental costs versus SoC				
Strategy	Device costs	Consultation costs	Implementation costs	Medication costs	Total
One-time use	£672.00	£32.73	£9.75	£51.49	£765.97
Routine monitoring	£11,685.31	-£41.13	£9.75	£470.97	£12,124.90

6.4 Kinesia 360 scenario results

Table 41 reports the results of each EAG scenario analysis applicable to Kinesia 360 one-time use and routine remote monitoring strategies. Note that Scenario 2 is not relevant to this comparison as only unadjusted effectiveness inputs are available for Kinesia 360. In all other respects the scenario analysis reflects those conducted for PKG.

Results for scenarios 3(a), 3(b) and 4 demonstrate a similar pattern to those observed for PKG in all cases resulting in only minor variations in the ICER. Results for scenarios 1 and 5, however, contrast sharply with those reported for PKG. In the PKG comparisons, both Scenarios 1 and 5 resulted in significant reductions in the ICER relative to the base case, primarily as a consequence of reductions in device acquisitions costs. Similar reductions in device costs are, however, not generated for the respective Kinesia 360 scenarios and consequently only have minor impacts on incremental costs and overall cost-effectiveness. This is largely due to the EAG's assumption that subscription services could not be repeatedly cancelled and re-initiated (i.e. continual subscription assumed), meaning device costs only varied across the predefined remote monitoring strategies considered (i.e. one-time use and routine use). ICER's varied between £38,334-£40,805 per QALY for one-time use. When considering the routine remote monitoring strategy ICER's ranged between £66,115-£69,298 per QALY gained.

Table 41 Kinesia 360 scenario analyses

	Kinesia 360				
		Incremental		ICER	
	Costs	QALY	Costs	QALYs	(£/QALY)
Scenario 1: Recurrent monitoring strategy					
Routine use					
Standard of care	£21,939	2.788			
Kinesia 360	£33,868	2.969	£11,929	0.18042	£66,115
Scenario 3 a): Removal of implementation costs					
One-time use					
Standard of care	£21,939	2.788			
Kinesia 360	£22,695	2.808	£756	0.01973	£38,334
Routine use					
Standard of care	£21,939	2.788			
Kinesia 360	£34,054	2.969	£12,115	0.18042	£67,149
Scenario 3 b): Inclusion of variable implementation costs (£39 per consultation using remote monitoring)					
One-time use					
Standard of care	£21,630	2.672			
Kinesia 360	£22,744	2.808	£805	0.01973	£40,805
Routine use					
Standard of care	£21,939	2.788			
Kinesia 360	£34,442	2.969	£12,503	0.18042	£69,298
Scenario 4: Consultation settings aligned across all strategies (55% face-to-face; 45% remote)					
One-time use					
Standard of care	£21,939	2.788			
Kinesia 360	£22,705	2.808	£766	0.01973	£38,828
Routine use					
Standard of care	£21,939	2.788			
Kinesia 360	£34,138	2.969	£12,199	0.18042	£67,612
Scenario 5: Annual routine follow-up					
Routine use					
Standard of care	£21,630	2.672			
Kinesia 360	£33,793	2.852	£12,162	0.18042	£67,410

6.5 Incremental analysis of PKG and Kinesia 360

Table 42 and Table 43 display the fully incremental deterministic and probabilistic base case cost-effectiveness results for PKG and Kinesia 360 for one-time use and routine remote monitoring strategies, respectively. In each analysis PKG is extendedly dominated by Kinesia 360, suggesting Kinesia360 offers better value relative to PKG. The extended dominance of PKG occurs due to Kinesia 360 generating health benefits at a lower incremental cost per QALY gained (i.e. has lower ICER for PKG vs Soc). Note that caution must be taken when comparing the cost-effectiveness of PKG versus Kinesia 360 given the fundamental differences in the underlying evidence base that informs the expected improvements in patient outcomes.

Table 42 Fully incremental comparison between SoC and PKG and Kinesia 360 one-time use remote monitoring strategies

One-time use remote monitoring strategies				Incremental		ICER
		Costs	QALY	Costs	QALYs	(£/QALY)
Deterministic analysis	*Restricted analysis*					
	Standard of care	£21,939	2.788			
	PKG	£22,278	2.793	£338	0.00499	Ext. dominated
	Kinesia 360	£22,705	2.808	£766	0.01973	£38,828
	Unrestricted analysis					
	Standard of care	£21,939	2.788			
	PKG	£22,278	2.790	£338	0.00167	Ext. dominated
	Kinesia 360	£22,705	2.808	£766	0.01973	£38,828
Probabilistic analysis	*Restricted analysis*					
	Standard of care	£21,886	2.760			
	PKG	£22,225	2.765	£339	0.00504	Ext. dominated
	Kinesia 360	£22,651	2.780	£765	0.01977	£38,722
	Unrestricted analysis					
	Standard of care	£21,869	2.768			
	PKG	£22,291	2.757	£338	0.00171	Ext. dominated
	Kinesia 360	£22,651	2.780	£765	0.01977	£38,722

Table 43 Fully incremental comparison between SoC and PKG and Kinesia 360 routine remote monitoring strategies

Routine remote monitoring strategy				Incremental		ICER
		Costs	QALY	Costs	QALYs	(£/QALY)
Deterministic analysis	*Restricted analysis*					
	Standard of care	£21,939	2.788			
	PKG	£24,580	2.834	£2,640	0.04562	Ext. dominated
	Kinesia 360	£34,064	2.969	£9,485	0.13480	£67,203
	Unrestricted analysis					
	Standard of care	£21,939	2.788			
	PKG	£24,580	2.804	£2,640	0.01530	Ext. dominated
	Kinesia 360	£34,064	2.969	£12,125	0.18042	£67,203
Probabilistic analysis	*Restricted analysis*					
	Standard of care	£22,116	2.765			
	PKG	£24,601	2.810	£2,485	0.04549	Ext. dominated
	KinesiaU	£34,087	2.947	£9,486	0.13643	£65,800
	Unrestricted analysis					
	Standard of care	£22,325	2.750			
	PKG	£24,783	2.767	£2,458	0.01658	Ext. dominated
	Kinesia 360	£34,087	2.947	£9,486	0.13643	£65,800

6.6 KinesiaU, STAT-ON and PDMonitor base case results

In the absence of any evidence of comparative effectiveness for KinesiaU, STAT-ON and PDMonitor, a cost comparison was conducted between all devices. Figure 10 displays the discounted device costs over a 5-year time-horizon for all the remote monitoring devices under consideration. Costs were markedly different between the remote monitoring devices, with a 5-year subscription to Kinesia 360 the most expensive alternative (£12,136) followed by purchasing a PDMonitor (£12,000), then by five-year subscriptions of STAT-ON (£7,224) and KinesiaU (£3,468), and PKG with the lowest device costs provided being applied tri-annually or less (at four PKG's per annum KinesiaU has the cheapest 5-year device costs).

Figure 10 Discounted remote monitoring device costs

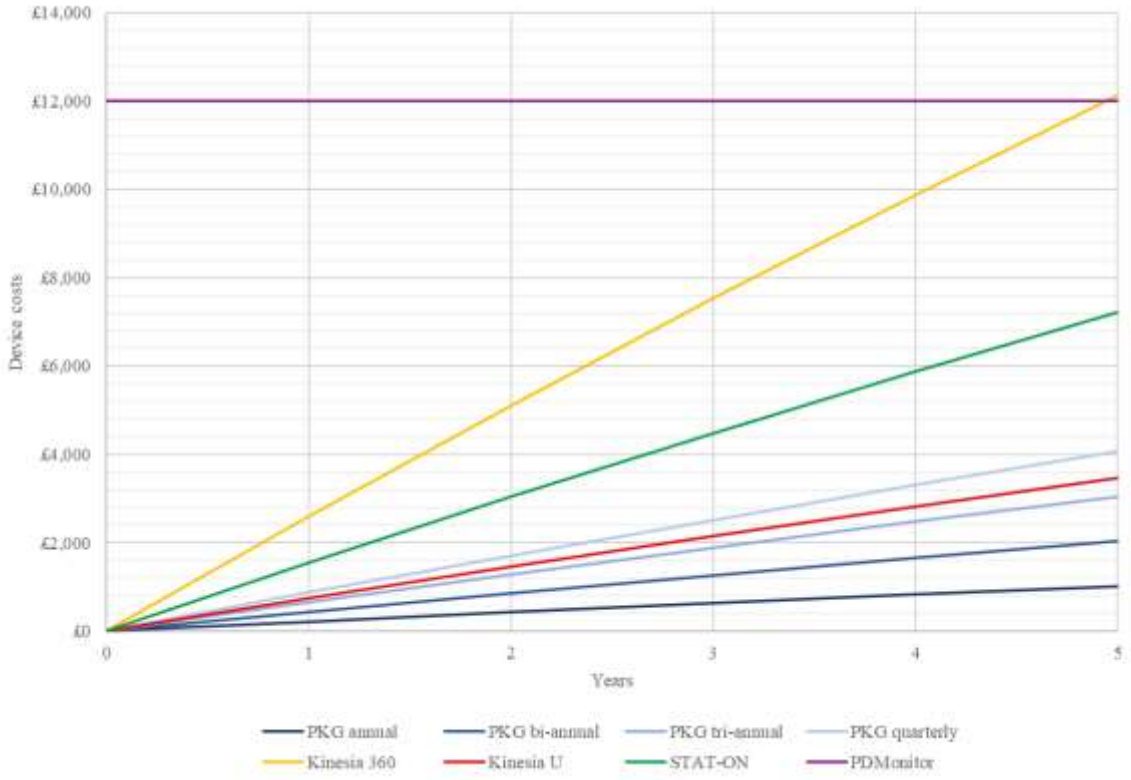


Table 44 reports modelled disaggregated pairwise incremental costs (relative to SoC) for each alternative device. Across all alternative devices and remote monitoring strategies device-related costs constituted the largest share of incremental costs. Note that the modelled device costs marginally differ from those aforementioned and reported in Figure 10 due to mortality effects. The EAG acknowledges that one-time use strategies may be illogical (e.g. PDMonitor) and potentially infeasible in some cases. Furthermore, PDMonitor and Kinesia 360 devices have the potential to be shared between patients, which would significantly reduce the average device costs per patient, but may also incur transfer costs (e.g. strap changes) as well as other costs due to the administrative burden associated with a shared usage model. Given uncertainties in how sharing models for remote

monitoring strategies would occur in practice, the EAG only considered individual patient-level applications for devices.

Table 44 Modelled incremental costs for KinesiaU, STAT-ON and PDMonitor relative to SoC

	PKG incremental costs versus SoC at base case settings				
Strategy	Device costs	Consultation costs	Implementation costs	Medication costs	Total
One-time use					
KinesiaU	£192.00	£32.73	£9.75	£51.49	£285.97
PKG	£225.00	£32.73	£9.75	£51.49	£337.47
Kinesia 360	£672.00	£32.73	£9.75	£51.49	£765.97
STAT-ON	£1,600	£32.73	£29.95	£51.49	£1713.47
PD-Monitor	£12,000.00	£32.73	£9.75	£51.49	£12093.97
Routine use					
PKG	£2,181.25	-£41.13	£29.95	£470.97	£2,640.34
KinesiaU	£3,338.66	-£41.13	£9.75	£470.97	£3,778.25
STAT-ON	£6,955.54	-£41.13	£29.95	£470.97	£7,414.63
Kinesia 360	£11,685.31	-£41.13	£9.75	£470.97	£12,124.90
PD-Monitor	£12,000.00	-£41.13	£9.75	£470.97	£12,439.59

Table 45 and Table 46 show the results of Scenario 6, a fully incremental comparison of the one-time and routine remote monitoring device strategies respectively. In this scenario analysis all monitoring derives are assumed to be equally effective, as calculated using adjusted efficacy estimates from Woodrow et al. (2020). The EAG presents this scenario for purely exploratory purposes and advises caution interpreting the results given the lack of evidence to suggest equivalence in outcomes across remote monitoring devices. Exploratory results were presented for both restricted and unrestricted adjusted estimates from Woodrow et al. (2020). Using a one-time use strategy, KinesiaU (assuming a 3-month subscription) had the lowest costs and an ICER of £53,331 per QALY when using the restricted analysis. This increased to £170,975 per QALY in the unrestricted analysis. As KinesiaU was the cheapest alternative it dominated all other equally efficacious one-time use alternatives. For the routine remote monitoring strategy, PKG had the lowest costs and an ICER of £57,877 per QALY when using the restricted analysis. This increased to £172,602 in the unrestricted analysis. Again, as PKG was the cheapest alternative, all other equally efficacious alternatives were dominated.

Table 45 Scenario analysis 6 - fully incremental comparison of one-time use PKG, Kinesia 360, KinesiaU, STAT-ON and PDMonitor remote monitoring strategies assuming equal efficacy (Woodrow et al. (2020))

One-time use remote monitoring strategies			Incremental		ICER
	Costs	QALY	Costs	QALYs	(£/QALY)
Scenario 6: fully incremental comparison of all remote monitoring strategies assuming equal efficacy					
Restricted analysis					
Standard of care	£21,939	2.788			
KinesiaU	£22,225	2.793	£286	0.00499	£57,331

PKG	£22,278	2.793	£53	0.00000	Dominated
Kinesia 360	£22,705	2.793	£480	0.00000	Dominated
STAT-ON	£23,653	2.793	£1,428	0.00000	Dominated
PDMonitor	£34,033	2.793	£11,808	0.00000	Dominated
Unrestricted analysis					
Standard of care	£21,939	2.788			
KinesiaU	£22,225	2.790	£286	0.00167	£170,975
PKG	£22,278	2.790	£53	0.00000	Dominated
Kinesia 360	£22,705	2.790	£480	0.00000	Dominated
STAT-ON	£23,653	2.790	£1,428	0.00000	Dominated
PDMonitor	£34,033	2.790	£11,808	0.00000	Dominated

Table 46 Scenario analysis 6 - fully incremental comparison of routine use PKG, Kinesia 360, KinesiaU, STAT-ON and PDMonitor remote monitoring strategies assuming equal efficacy (Woodrow et al. (2020))

Routine remote monitoring strategies			Incremental		ICER
	Costs	QALY	Costs	QALYs	(£/QALY)
Scenario 6: fully incremental comparison of all remote monitoring strategies assuming equal efficacy					
Restricted analysis					
Standard of care	£21,939	2.788			
PKG	£24,580	2.834	£2,640	0.04562	£57,877
KinesiaU	£25,717	2.834	£1,138	0.00000	Dominated
STAT-ON	£29,354	2.834	£4,774	0.00000	Dominated
Kinesia 360	£34,064	2.834	£9,485	0.00000	Dominated
PDMonitor	£34,379	2.834	£9,799	0.00000	Dominated
Unrestricted analysis					
Standard of care	£21,939	2.788			
PKG	£24,580	2.804	£2,640	0.01530	£172,602
KinesiaU	£25,717	2.804	£1,138	0.00000	Dominated
STAT-ON	£29,354	2.804	£4,774	0.00000	Dominated
Kinesia 360	£34,064	2.804	£9,485	0.00000	Dominated
PDMonitor	£34,379	2.804	£9,799	0.00000	Dominated

6.7 Sensitivity analyses

As discussed in Section 5.6, there is limited evidence to evaluate the impacts of remote monitoring on patient outcomes beyond the immediate term. To explore this uncertainty, a sensitivity analysis assessed the impact of alternative waning rates (0%-90%). Table 47 reports pairwise ICERs for PKG and Kinesia 360, considering both one-time use and routine remote monitoring strategies. The results of this analysis show that the ICER is highly sensitive to the assumed waning rate. The restricted analysis for one-time PKG found ICER's of below £20,000 per QALY when assuming a waning rate of 10% or less, while a 20% waning rate resulted in an ICER of less than £30,000 per QALY (£29,755). When using an unrestricted analysis, PKG's one-time use ICER did not fall below £49,548. Kinesia 360 ICER's fell below £20,000 per QALY for waning rates of 30% or less while a

40% waning rate resulted in ICER below £30,000 per QALY (£28,080). Since the base case analysis assumes routine remote monitoring strategies maintain treatment-specific reductions in UPDRS (i.e. no waning of the treatment effect), alternative waning rates only made PKG and Kinesia 360 remote monitoring strategies less favourable.

Table 47 Sensitivity analysis surrounding alternative efficacy decay rates

Pairwise ICER's (vs SoC)	Efficacy decay rates									
One-time use	0%	10%	20%	30%	40%	50%*	60%	70%	80%	90%
PKG -*restricted analysis*	£16,614	£20,816	£27,174	£36,352	£49,310	£67,856	£95,853	£142,573	£236,032	£516,422
PKG -*unrestricted analysis*	£49,548	£62,078	£81,039	£108,410	£147,054	£202,363	£285,854	£425,185	£703,902	£1,540,087
Kinesia 360	£6,570	£9,215	£13,218	£18,996	£27,153	£38,828	£56,452	£85,863	£144,697	£321,206
Routine use	0%*	10%	20%	30%	40%	50%	60%	70%	80%	90%
PKG -*restricted analysis*	£57,877	£90,786	£140,284	£211,507	£311,919	£455,559	£672,355	£1,034,136	£1,757,838	£3,929,031
PKG *unrestricted analysis*	£172,602	£270,743	£418,357	£630,760	£930,214	£1,358,581	£2,005,114	£3,084,027	£5,242,268	£11,717,253
Kinesia 360	£67,203	£110,636	£176,285	£270,991	£404,667	£595,972	£884,745	£1,366,650	£2,330,650	£5,222,771

*Base case value

As discussed in Section 5.11.3, remote monitoring may reduce the number of consultations required between patients and health care practitioners. To consider this uncertainty, the EAG have explored the impact of assuming fewer consultations are required when using remote monitoring. Table 48 displays the pairwise ICERs for PKG and Kinesia 360 across a 0%-50% range of face-to-face and remote consultation cost savings. The EAG did not believe this sensitivity analysis was applicable for one-time use strategies and therefore this analysis only considers the routine remote monitoring strategy. The results of this analysis show that the ICER is broadly insensitive to this parameter. This was likely due to two reasons: (i) consultation costs represent a relatively small proportion of total overall costs; (ii) routine strategies were assumed to predominantly undertake cheaper remote appointments (79%), thus providing less scope for cost saving.

Table 48 Sensitivity analysis surrounding alternative consultations saving rates

Pairwise ICER (vs SoC)	Remote monitoring consultation savings					
Routine use	0%*	10%	20%	30%	40%	50%
PKG *-restricted analysis*	£57,877	£56,702	£55,527	£54,351	£53,176	£52,001
PKG *unrestricted analysis*	£172,602	£169,097	£165,593	£162,088	£158,583	£155,079
Kinesia 360	£67,203	£66,906	£66,609	£66,311	£66,014	£65,717

*Base case value

6.8 Discussion of the independent economic assessment

The decision problem addressed by the model relates to the cost-effectiveness of remote monitoring devices in providing 'objective' ambulatory measurements to aid in the identification and treatment of uncontrolled Parkinson's disease symptoms. In the absence of any evidence to reliably establish the clinical value of remote monitoring within early- or advanced-stage Parkinson's disease, or that using STAT-ON, KinesiaU or PDMonitor, cost-effectiveness assessments were confined to PKG and Kinesia 360 technologies during management-stage Parkinson's disease. The cost-effectiveness analysis assessed two remote monitoring strategies for PKG and Kinesia 360: (i) one-time use (one PKG, three-month Kinesia 360 subscription); and (ii) routine use (bi-annual PKG assessment, continuous subscription to Kinesia 360). The clinical efficacy for PKG was established using restricted (considering only the clinical benefit associated with UPDRS domains III and IV) and unrestricted analyses (considering the impact on all UPDRS domains I-IV) of trial data (see Section 3.3.4.1), and for Kinesia 360 via a difference-in-difference analysis of UPDRS outcomes reported in a small pilot study.[89] Base case cost-effectiveness estimates considered the costs and consequences associated with PKG (restricted and unrestricted) and Kinesia 360 remote monitoring strategies. The analysis also considered the cost of each technology together with relevant consultation, medication, and implementation costs over a 5-year time-horizon.

The base case ICER's for PKG one-time use and routine remote monitoring strategies were £67,856 (£202,363) per QALY and £57,877 (£172,602) per QALY gained, respectively, when using a restricted (unrestricted) analysis. The base case ICER's for Kinesia 360 one-time use (3-month subscription) and routine remote monitoring strategies were £38,828 and £67,203 per QALY, respectively. Cost-effectiveness results were largely insensitive to the number and type of consultations and to the implementation costs considered. The main drivers of cost-effectiveness identified were: (i) the direction and magnitude of changes on the UPDRS scale associated with remote monitoring strategies; (ii) the persistence in changes to UPDRS over time (treatment waning); and (iii) the number of devices requested (PKG). Over a 5-year time horizon, PKG incurred the lowest device-related costs (provided that the number of devices ordered per annum was ≤ three), followed by Kinesia U, STAT-ON, Kinesia 360 and PDMonitor. On a one-time use basis, KinesiaU incurred the lowest device costs (provided subscription ≤3 months) followed by PKG, Kinesia 360 (subscription ≤3 months), STAT-ON (1-year minimum subscription) and PDMonitor.

Despite evaluating the PKG remote monitoring system within the same context and utilising the same efficacy data, EAG findings significantly differed from those reported in Chaudhuri et al. (2022) who found PKG to be highly cost-effective. This misalignment could be due to a number of reasons. First the EAG model considered a 5-year time horizon, meaning costs and benefits were broadly limited to management-stage Parkinson's disease and ensured the model cohort was aligned to the populations and follow-up horizons used to inform key relationships within the model (i.e. efficacy, progression and health-related quality of life). In contrast Chaudhuri et al. (2022) considered a lifetime horizon that allows treatment effects to accrue over the entire lifetime of a Parkinson's patient (up to 22 years into the future). Second, this economic assessment only considered PKG-related cost savings via facilitating more remote consultations and potentially reducing the number of consultations overall (e.g. recurrent strategy). In contrast, Chaudhuri et al. (2022) incorporated PKG cost-savings as those directly related to the associated shifts in disease severity (defined on the H&Y scale). Third the utilities associated with changes on the UPDRS scale, and the sources and methods used to calculate them, are markedly different between the analyses. Fourth different PKG schedules are assumed (EAG: one-time and routine bi-annual applications; Chaudhuri et al. (2022) controlled patients 2 PKG's, uncontrolled 3-4 PKGs) and consider different UPDRS domains (Chaudhuri et al. (2022) only considers changes in MDS-UPDRS domains II and III). Lastly, differences in model structure and the estimation methods used to derive efficacy estimates may also contribute to differential findings.

With respect to each of the differences above, the EAG takes the following position. First the EAG believes assessing costs and outcomes within a shorter-term horizon allows for a more internally consistent assessment of remote monitoring strategies in the context of the clinical evidence (confined

to the maintenance stage of the disease), therapeutic options (no disease-modifying treatments to impact the long-term trajectory of patients) and disease progression (where treatment strategies may progressively converge between remote monitoring and SoC). Second, it's not clear whether the moderate reductions in MDS-UPDRS associated with remote monitoring translate into meaningful reductions in NHS costs at the management-stage of Parkinson's disease. In line with Chandler et al.'s conceptual model (for potential disease modifying therapies), Chaudhuri et al.'s (2022) analysis suggests remote monitoring can shift disease status on the H&Y scale and consequently delay patients' progression through progressively costly H&Y states. The EAG appreciate the potential for symptomatic benefits from remote monitoring to reduce health-care utilisation, but question whether such changes can reliably prompt changes on the H&Y scale (progression on the H&Y scale often takes years under normal circumstances)[159] and whether such changes can be reliably extrapolated over a lifetime horizon. The EAG's approach to omit any disease-related cost savings could be considered conservative, nevertheless the EAG has concerns regarding Chaudhuri et al.'s (2020) approach to modelling cost-savings given the uncertainties surrounding the validity of the methodological approach taken (i.e. conversion from MDS-UPDRS to H&Y, the derivation of differential H&Y distributions and their life-time extrapolation) and the H&Y health-state costs used (note that the EAG could not validate the values reported due to a lack of details). Third the utilities in this analysis align with NICE methods guidelines by representing robust estimates of the association between UPDRS scores and UK EQ-5D-3L preference weights (see Section 5.10.1).[100, 140] The base case utilities from Chaudhuri et al. (2020) mapped UPDRS scores onto EQ-5D values using an algorithm derived using weights from a European population valued by a visual analogue technique, thereby not aligning with NICE methods guidelines. The authors do not state whether efforts were made to convert Woodrow et al. (2020) MDS-UPDRS scores onto the UPDRS scale.[104]

The current findings suggest that one-time use and routine applications of PKG and Kinesia 360 remote monitoring devices are not cost-effective relative to SoC at a £30,000 per QALY threshold. This finding is, however, subject to significant uncertainty.

First, remote monitoring devices are not confined to management-stage Parkinson's disease or to any single monitoring strategy configuration. Applications in an advanced disease setting (e.g. deep brain stimulation), to patients receiving non-pharmacological therapies, or delivered using alternative configurations than those modelled in the EAG analysis may significantly alter study findings. In the absence of any comparative clinical evidence on the longer-term and/or repeated use of the technologies, the base case treatment effectiveness for alternative remote monitoring strategies was assumed rather than based on empirical data. While explored in sensitivity analysis this remains a key uncertainty.

Second, consultation costs associated with SoC and remote monitoring in the model may be underestimated. Parkinson's patients interact with a variety of health care professionals. A UK survey analysis reports Parkinson's patient engagement across eighteen alternative health-care professions. The authors calculate the average NHS consultation cost for Parkinson's to be £443.04 per annum (2015), markedly larger than standard of care consultation costs in this analysis (£140.31 per annum from face-to-face and remote specialist nurse consultations).[160] A broader consideration of the health care professions involved with patient consultation may provide more information on potential cost savings from facilitating remote appointments or averting consultations.

Third, several broader cost and benefit factors related to remote monitoring strategies were considered beyond the scope of this analysis. These include the potential risks and costs associated with the loss, damage or theft of devices (not outlined in company responses); carer quality-of-life, the alleviation of capacity constraints on service providers and indirect costs to Parkinson's patients and their carers (e.g., travel, out-of-pocket payments for private services, informal care, etc.). The benefits of remote monitoring may be amplified for those with particular difficulties attending consultations or those accessing care from services at full capacity.

The cost-effectiveness of PKG and Kinesia 360 was largely contingent on uncertain estimates in the magnitude and persistence of the symptomatic benefits (as defined according to UPDRS domains I-IV) patients can achieve with each remote monitoring technology. The average costs associated with each technology is largely dependent on its configuration within a remote monitoring strategy (e.g. one-time use, routine use, recurrent use, etc.). From a resourcing perspective, the PKG technology appears most flexible to cost considerations, albeit with Kinesia 360 and PDMonitor offering avenues for potential cost sharing between patients. From an efficacy perspective, subscription and purchase models may be advantageous relative to PKG ordering provided patients benefit from more regular remote self-assessments.

7 DISCUSSION

7.1 Statement of principal findings

7.1.1 Clinical effectiveness

Overall, the EAG considers that only PKG has a substantial body of research evidence. PKG appears to accurately measure dyskinesia and bradykinesia, with very high sensitivity and reasonably high specificity. Diagnostic accuracy was also reasonably high for measuring tremor and treatment-related outcomes. However, its accuracy for measuring sleep disturbance was lower.

PKG is being used by clinicians to guide treatment decisions, primarily the addition of a new therapy or increase in treatment dose; PKG use led to a change in management for 32-79% patients. Patients managed with PKG appear to benefit more than those on clinical management alone, with improvements in UPDRS III and IV scores. This benefit seems to depend on whether patients were "in target" (i.e. condition was under control with current treatment) before PKG use. Patients not "in target" saw improved UPDRS scores, but those "in target" did not.

For STAT-ON, evidence is almost entirely limited to diagnostic accuracy studies. These suggest that STAT-ON can accurately diagnose "On-Off" times and bradykinesia. STAT-ON also seems to have reasonably good accuracy for diagnosing freezing of gait and possibly trunk dyskinesia (as a waist-worn device), but not dyskinesia elsewhere.

There is currently no evidence on the intermediate impact of STAT-ON or on the clinical impact of STAT-ON, therefore, it is unclear whether STAT-ON use will lead to treatment modification and subsequent improvements in symptoms and quality of life.

Two small RCTs suggest favourable clinical outcomes with Kinesia 360 use in populations receiving rotigotine or when Kinesia 360 was used for remote telehealth assessments. However, the EAG considers that there is currently too little evidence to be confident about its clinical value.

Evidence on KinesiaU and PDMonitor are too limited to draw any conclusions on their clinical value.

The only evidence relating to adverse events was that there were no device-related adverse events reported (PKG and STAT-ON).

7.1.2 Cost-effectiveness

The base case cost-effectiveness results for one-time use and routine PKG and Kinesia 360 remote monitoring strategies found ICER's exceeding £30,000 per QALY gained. The EAG were not able to

evaluate the cost-effectiveness of STAT-ON, KinesiaU or PDMonitor. Over a 5-year time horizon, modelled device costs for routine use were lowest for PKG provided three devices or less were ordered per annum, followed by KinesiaU, STAT-ON, Kinesia 360 and PDmonitor. Base case QALY gains from PKG remote monitoring strategies were highly sensitive to the inclusion of associated small, unfavourable and statistically insignificant changes on the UPDRS II domain.

Scenarios analyses considered an additional monitoring strategy and alternative model assumptions from those used as part of the base case analysis. Cost-effectiveness results were largely robust to changes in consultation setting (face-to-face versus remote), fixed implementation costs, and potential consultation savings. The scenarios were also used to identify the main drivers of cost-effectiveness. The key drivers identified were: (i) the direction and magnitude of changes on the UPDRS scale associated with remote monitoring strategies; (ii) the persistence in changes to UPDRS (treatment waning); and (iii) the numbers of devices requested (PKG).

The EAG was not able to evaluate the cost-effectiveness of STAT-ON, KinesiaU or PDMonitor due lack of comparative clinical effectiveness evidence. In a cost comparison (assuming a 5-year time horizon), modelled device costs were lowest for PKG provided three devices or less were ordered per annum, followed by Kinesia U, STAT-ON, Kinesia 360 and PDMonitor.

7.2 Strengths and limitations of the assessment

7.2.1 Strengths

This is the first complete systematic review of all available diagnostic and clinical evidence for PKG, Kinesia 360, KinesiaU and PDMonitor. This review used extensive database searches to identify all published evidence on the included technologies and followed rigorous recommended review methods to identify relevant publications, assess their risk of bias and undertake a narrative synthesis of the results. As such, this is the first fully rigorous review of these technologies, and also the first to compare the technologies in one review.

The review was strengthened by the provision of individual-level data for the key clinical trial of PKG, which permitted a more thorough examination of the clinical impact of PKG than would otherwise have been possible.

This is also the first study to review and estimate the cost and cost-effectiveness of PKG, Kinesia 360, KinesiaU, STAT-ON and PDMonitor technologies relative to SoC and each other (where possible). A de-novo economic model was developed to assess the costs and consequences associated with one-time and routine applications of each technology within management-stage Parkinson's disease. The model has made best use of systematically identified evidence of clinical effectiveness, considered a

broad and sensitive measure of Parkinson's disease severity, progression and symptomatic benefit, and utilised contemporary evidence of disease progression, health-related quality of life and NHS service utilisation associated with Parkinson's disease and remote monitoring.

7.2.2 Limitations

There was a lack of replication across studies. In general, most outcomes were reported in only one or two studies, or outcomes were reported in inconsistent ways across studies. This meant that no meta-analysis was possible for any included studies, and the narrative synthesis was severely limited by the consequent difficulties in comparing different studies. This lack of replicability raises some concerns as to how robust the findings of the review are. It should be noted that many of the review conclusions are based on individual studies.

A further limitation is the low quality of much of the evidence, particularly for diagnostic accuracy. This casts some doubt on the validity of the diagnostic accuracy evidence. It should be noted that few studies were formal diagnostic accuracy studies, and there are innate difficulties in this field in robustly assessing diagnostic accuracy, given the lack of clear reference standards, and lack of clarity over the exact algorithms used to convert device output into diagnostic assessments.

Cost-effectiveness results were limited for a number of reasons and should be interpreted with caution. The EAG identified no evidence to reliably establish the clinical value of STAT-ON, KinesiaU or PDMonitor, thereby restricting any meaningful assessments of cost-effectiveness for these devices. The evidence used to inform the clinical effectiveness of Kinesia 360 is extremely limited and unlikely to be comparable with that used for PKG, making comparisons problematic. Conversions made between MDS-UPDRS scores and UPDRS are at risk of bias. Cost-effectiveness results were highly sensitive to the persistence in initial clinical improvements, a variable which could not be informed with current evidence. Furthermore, cost-effectiveness assessments were confined to management-phase Parkinson's disease assessments only. Remote monitoring devices are applicable to a wide variety of potential schedules, contexts and settings. The consequences, implementation costs (e.g. health care professional time, administration) and risks (e.g. loss, damage or theft of devices) associated with alternative delivery model configurations is unknown and likely to impact cost-effectiveness.

7.3 Uncertainties

The primary clinical uncertainty in this review is the clinical value of STAT-ON, KinesiaU and PDMonitor, as these technologies currently have no evidence, and particularly no formal comparison with standard care, to demonstrate that they produce clinical benefit for patients. The trial evidence for Kinesia 360 is currently too limited to be confident of its clinical value. Because of the very

different natures of the technologies assessed, the EAG does not consider that any clinical benefits observed for PKG would also be found with the other technologies. Even for PKG the comparative evidence with standard care is limited to one trial that was not strictly randomised.

Almost all studies were conducted in patients receiving pharmacological therapy, primarily levodopa. The clinical evidence for PKG is largely focussed on how PKG use can modify levodopa therapy, and the clinical impacts of those therapy changes. Consequently, there is little to no evidence on the possible benefits of the technologies in other types of patients, such as those receiving non-pharmacological therapy, or on more advanced therapies such as deep brain stimulation. The EAG does not think it safe to assume that any clinical benefits observed will necessarily apply to these other patient groups.

There were no studies that directly compared one remote continuous monitoring device against another. In addition, there was limited evidence on the use of remote monitoring devices in different patient subgroups. Therefore, it is unclear which patients are more likely to have management changes and subsequent improvements in clinical outcomes as a result of their use.

There is currently no evidence on the long-term use or repeated use of the technologies. It is currently uncertain for how long the observed clinical benefits with PKG will persist, or how frequently PKG (or other technologies) should be used to maintain clinical benefit (e.g. every six months, or every year).

Uncertainties in the economic analysis largely reflect the limitations of available clinical evidence. Additionally, uncertainties relate to upcaptured costs and benefits associated with remote monitoring strategies. These include additional administration and training costs; potential risks and costs associated with the loss, damage or theft of devices; carer quality-of-life benefits; capacity constraints on service providers; and, indirect costs to Parkinson's patients and their carers.

8 CONCLUSIONS

8.1 Implications for service provision

The EAG considers that the evidence for PKG shows that it could be of use in clinical practice, provided it can be made cost-effective. It provides useful information on key symptoms of Parkinson's disease, including bradykinesia, dyskinesia and tremor. This leads to changes in treatment management for at least some patients, and consequent improvement in symptoms. There is some evidence that PKG provides most clinical benefits in patients whose symptoms are inadequately controlled by their current treatment, and PKG use may be best used if targeted at such patients. The ERG notes, however, that PKG may be required to identify such patients.

Although there is some promising evidence to support the clinical value of STAT-ON and Kinesia 360, the EAG considers that the evidence is currently not sufficient to be confident that these technologies will produce clinical benefits for patients. The EAG considers that there is too little evidence for KinesiaU or PDMonitor to draw any conclusions as to their clinical value.

Almost all current evidence relates to patients receiving pharmacological therapy, mainly levodopa. The EAG notes that, at present, it is unclear whether PKG, or other technologies, offer any clinical benefit in other patients, such as those receiving advanced therapies.

Concerns about potential bias, together with the other limitations in the available evidence mean that cost-effectiveness estimates are highly uncertain. Uncertainties regarding the magnitude and durability of treatment effects are a primary concern and are key drivers of cost-effectiveness. Moreover, concerns about uncaptured implementation costs and benefits further increase uncertainties. Taken at face value the results of the economic analysis are largely unfavourable, with ICERs in excess of thresholds typically adopted by NICE. Given the current clinical evidence base, establishing the cost-effectiveness of remote monitoring devices is likely to require either a reduction in total device costs (the primary driver of total costs) or the identification of additional cost savings not accounted for in the EAG's analysis.

8.2 Suggested research priorities

The primary research priority should be to conduct further studies into the clinical impact of remote monitoring devices. This should focus on expanding the evidence base for PKG and Kinesia 360, where there is currently limited evidence on clinical effects, as well as conducting studies of STAT-ON, KinesiaU and PDMonitor, where there is currently no evidence of clinical effects. This requires RCTs comparing the devices to standard clinical management without the use of remote continuous monitoring devices. Cluster RCTs (clustered by centre or clinic) and quasi-randomised trials would

also be of value. Non-randomised comparative studies would also be useful, provided they can be shown to be free of selection biases.

These trials should, at least, record the following outcomes:

- Numbers of patients with changes in clinical management
- Changes in treatment, such as levodopa equivalent dose
- UPDRS (all sub-scales), Hoehn and Yahr, bradykinesia and dyskinesia
- Patient opinions and patient-centred outcomes, including quality of life (e.g. PDQ-39)

All trials should examine whether clinical benefits vary according to key patient subgroups, such as by symptom severity at randomisation. Studies should be carefully designed to consider the most applicable remote monitoring schedules and settings, as there is significant potential for variation in how remote monitoring devices could be used in practice. Specific consideration should be given to longer-term routine use of remote monitoring devices; currently all evidence pertains to short-term applications. Future studies of remote monitoring devices for Parkinson's disease may also consider patients with early and advanced disease. There is currently no evidence in these populations for any device.

Implementing remote monitoring may have a range of resource consequences which are currently not fully understood and may impact significantly on cost-effectiveness. This may include impacts on health care professionals' time and administration of the devices, as well as risks such as loss, damage or theft of devices. Where possible future studies should seek to address these uncertainties by collecting appropriate data on resource implications.

The EAG considers that collecting further diagnostic accuracy evidence is a lower priority, but would be useful for Kinesia 360, KinesiaU and PDMonitor. Diagnostic accuracy studies should evaluate the accuracy of these technologies for measuring bradykinesia and dyskinesia. Care will have to be taken to ensure the reference standard is robust and at low risk of bias. It may be helpful for such studies to compare the technologies to PKG.

If deemed clinically useful, observational studies to investigate the value of all technologies in patients receiving advanced therapies (such as deep brain stimulation), or patients receiving non-pharmacological therapies, may be worthwhile.

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9 APPENDICES

9.1 Literature search strategies

Search strategies for identification of clinical studies (February 2022)

Ovid MEDLINE(R) ALL

via Ovid http://ovidsp.ovid.com/
Date range searched: 1946 to January 31, 2022
Date searched: 01 February 2022
Records retrieved: 687

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:
/ = indexing term (Medical Subject Heading: MeSH)
* = truncation
ti,ab,kw = terms in either title, abstract, or keyword fields
rn = registry number/name of substance field
adj3 = terms within three words of each other (any order)

Embase

via Ovid http://ovidsp.ovid.com/
Date range searched: 1974 to 1974 to 2022 January 31
Date searched: 01 February 2022
Records retrieved: 1108

1 Parkinson disease/ (170324)
2 (parkinson* adj2 (disease* or syndrom* or disorder* or complex)).ti,ab,kw. (159760)
3 or/1-2 (200059)
4 wearable sensor/ (966)
5 telemetry/ (19025)
6 remote sensing/ (11647)
7 ((continuous* or remote*) adj2 (measure* or monitor* or sensor*)).ti,ab,kw. (71013)
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. (3192)
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. (2334)
10 telemetr*.ti,ab,kw. (15101)
11 ((smart watch* or smart-watch* or smartwatch*) and (remote* or continuous*)).ti,ab,kw. (231)
12 (((mobile adj (health* or app*)) or (e-health or eHealth or m-health or mHealth)) and (remote* or continuous*)).ti,ab,kw. (2726)
13 ((remote* or continuous*) and ((ambulatory or outpatient* or patient* or physiologic*) adj2 (monitor* or manage*))).ti,ab,kw. (15311)
14 or/4-13 (116848)
15 3 and 14 (962)
16 KinetiGraph*.ti,ab,kw,dv. (131)
17 (PKG* not "protein kinase").ti,ab,kw,dv. (1714)
18 (kineti* adj graph*).ti,ab,kw,dv. (112)
19 Kinesia*.ti,ab,kw,dv. (213)
20 (STAT ON* or STAT-ON*).ti,ab,kw,dv. (65)
21 (PDMonitor* or (PD adj monitor*)).ti,ab,kw,dv. (73)
22 or/16-21 (2178)
23 3 and 22 (299)

24 15 or 23 (1203)
25 animal/ (1551022)
26 exp animal experiment/ (2794289)
27 nonhuman/ (6785311)
28 (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep).ti,ab,sh. (6074833)
29 or/25-28 (9600168)
30 exp human/ (23201428)
31 human experiment/ (563905)
32 30 or 31 (23203414)
33 29 not (29 and 32) (6877011)
34 24 not 33 (1132)
35 remove duplicates from 34 (1108)

Key:
/ or .sh. = indexing term (Emtree Subject Heading)
* = truncation
ti,ab,kw = terms in either title, abstract, or keyword fields
dv = device trade name field
adj3 = terms within three words of each other (any order)

APA PsycInfo

via Ovid http://ovidsp.ovid.com/
Date range searched: 1806 to January Week 4 2022
Date searched: 01 February 2022
Records retrieved: 134

1 Parkinson's Disease/ (24607)
2 Parkinson Disease.mh. (13837)
3 (parkinson* adj2 (disease* or syndrom* or disorder* or complex)).ti,ab. (31456)
4 or/1-3 (33506)
5 wearable devices/ (444)
6 Wearable Electronic Devices.mh. (121)
7 Telemetry.sh,mh. (746)
8 Remote Sensing Technology.mh. (66)
9 ((continuous* or remote*) adj2 (measure* or monitor* or sensor*)).ti,ab. (4631)
10 (((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. (172)
11 (((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. (351)
12 telemetr*.ti,ab. (1062)
13 ((smart watch* or smart-watch* or smartwatch*) and (remote* or continuous*)).ti,ab. (21)
14 (((mobile adj (health* or app*)) or (e-health or eHealth or m-health or mHealth)) and (remote* or continuous*)).ti,ab. (269)
15 ((remote* or continuous*) and ((ambulatory or outpatient* or patient* or physiologic*) adj2 (monitor* or manage*))).ti,ab. (494)
16 or/5-15 (7495)
17 4 and 16 (104)
18 KinetiGraph*.ti,ab. (8)
19 (PKG* not "protein kinase").ti,ab. (70)
20 (kineti* adj graph*).ti,ab. (2)
21 Kinesia*.ti,ab. (33)
22 (STAT ON* or STAT-ON*).ti,ab. (0)
23 (PDMonitor* or (PD adj monitor*)).ti,ab. (2)
24 or/18-23 (106)
25 4 and 24 (36)
26 17 or 25 (135)
27 remove duplicates from 26 (134)

Key:
/ = indexing term (Thesaurus of Psychological Index Terms)

mh = indexing term MeSH
* = truncation
ti,ab = terms in either title or abstract fields
adj3 = terms within three words of each other (any order)

Econlit

via Ovid http://ovidsp.ovid.com/
Date range searched: 1886 to January 27, 2022
Date searched: 01 February 2022
Records retrieved: 0

1 (parkinson* adj2 (disease* or syndrom* or disorder* or complex)).ti,ab,kw. (36)
2 ((continuous* or remote*) adj2 (measure* or monitor* or sensor*)).ti,ab,kw. (363)
3 (((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. (3)
4 (((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. (7)
5 telemetr*.ti,ab,kw. (15)
6 ((smart watch* or smart-watch* or smartwatch*) and (remote* or continuous*)).ti,ab,kw. (0)
7 (((mobile adj (health* or app*)) or (e-health or eHealth or m-health or mHealth)) and (remote* or continuous*)).ti,ab,kw. (7)
8 ((remote* or continuous*) and ((ambulatory or outpatient* or patient* or physiologic*) adj2 (monitor* or manage*))).ti,ab,kw. (10)
9 KinetiGraph*.ti,ab,kw. (0)
10 (PKG* not "protein kinase").ti,ab,kw. (1)
11 (kineti* adj graph*).ti,ab,kw. (0)
12 Kinesia*.ti,ab,kw. (0)
13 (STAT ON* or STAT-ON*).ti,ab,kw. (1)
14 (PDMonitor* or (PD adj monitor*)).ti,ab,kw. (0)
15 or/2-14 (402)
16 1 and 15 (0)

Key:
* = truncation
ti,ab,kw = terms in either title, abstract, or keyword fields
adj3 = terms within three words of each other (any order)

Cochrane Central Register of Controlled Trials (CENTRAL)

via Wiley http://onlinelibrary.wiley.com/
Date range: Issue 2 of 12, February 2022
Date searched: 01 February 2022
Records retrieved: 125

#1 [mh ^"Parkinson Disease"] 4556
#2 (parkinson* NEAR/2 (disease* or syndrom* or disorder* or complex)):ti,ab,kw 10982
#3 {OR #1-#2} 10982
#4 [mh ^"Wearable Electronic Devices"] 115
#5 [mh ^Telemetry] 257
#6 [mh ^"Remote Sensing Technology"] 50
#7 ((continuous* or remote*) NEAR/2 (measure* or monitor* or sensor*)):ti,ab,kw 8741

#8	(((wear* or worn or wrist* or ankle* or body* or waist* or belt*) NEAR/2 (tech* or device* or sensor*)) and (remote* or continuous*)):ti,ab,kw	396
#9	(((inertia* or kinetic* or motor or gait or bradykine* or dyskine* or tremor* or shaking or instability or stability or balance or sleep*) NEAR/2 (tech* or device* or sensor*)) and (remote* or continuous*)):ti,ab,kw	466
#10	telemetr*:ti,ab,kw	843
#11	((smart NEXT watch* or smartwatch*) and (remote* or continuous*)):ti,ab,kw	37
#12	(((mobile NEXT (health* or app*)) or (eHealth or mHealth)) and (remote* or continuous*)):ti,ab,kw	694
#13	((remote* or continuous*) and ((ambulatory or outpatient* or patient* or physiologic*) NEAR/2 (monitor* or manage*))):ti,ab,kw	3248
#14	{OR #4-#13}	12526
#15	#3 and #14	83
#16	KinetiGraph*:ti,ab,kw	13
#17	(PKG* not "protein kinase"):ti,ab,kw	93
#18	(kineti* NEXT graph*):ti,ab,kw	11
#19	Kinesia*:ti,ab,kw	37
#20	("STAT ON"):ti,ab,kw	1265
#21	(PDMonitor* or (PD NEXT monitor*)):ti,ab,kw	7
#22	{OR #16-#21}	1406
#23	#3 and #22	50
#24	#15 or #23 in Trials	125

Key:
mh = exploded indexing term (MeSH)
mh ^ = unexploded indexing term (MeSH)
* = truncation
ti,ab,kw = terms in either title or abstract or keyword fields
near/3 = terms within three words of each other (any order)
next = terms are next to each other

Cochrane Database of Systematic Reviews (CDSR)

via Wiley http://onlinelibrary.wiley.com/
Date range: Issue 2 of 12, February 2022
Date searched: 01 February 2022
Records retrieved: 4

#1	[mh ^"Parkinson Disease"]	4556
#2	(parkinson* NEAR/2 (disease* or syndrom* or disorder* or complex)):ti,ab,kw	10982
#3	{OR #1-#2}	10982
#4	[mh ^"Wearable Electronic Devices"]	115
#5	[mh ^Telemetry]	257
#6	[mh ^"Remote Sensing Technology"]	50
#7	((continuous* or remote*) NEAR/2 (measure* or monitor* or sensor*)):ti,ab,kw	8741
#8	(((wear* or worn or wrist* or ankle* or body* or waist* or belt*) NEAR/2 (tech* or device* or sensor*)) and (remote* or continuous*)):ti,ab,kw	396
#9	(((inertia* or kinetic* or motor or gait or bradykine* or dyskine* or tremor* or shaking or instability or stability or balance or sleep*) NEAR/2 (tech* or device* or sensor*)) and (remote* or continuous*)):ti,ab,kw	466
#10	telemetr*:ti,ab,kw	843
#11	((smart NEXT watch* or smartwatch*) and (remote* or continuous*)):ti,ab,kw	37
#12	(((mobile NEXT (health* or app*)) or (eHealth or mHealth)) and (remote* or continuous*)):ti,ab,kw	694
#13	((remote* or continuous*) and ((ambulatory or outpatient* or patient* or physiologic*) NEAR/2 (monitor* or manage*))):ti,ab,kw	3248
#14	{OR #4-#13}	12526
#15	#3 and #14	83
#16	KinetiGraph*:ti,ab,kw	13
#17	(PKG* not "protein kinase"):ti,ab,kw	93
#18	(kineti* NEXT graph*):ti,ab,kw	11
#19	Kinesia*:ti,ab,kw	37
#20	("STAT ON"):ti,ab,kw	1265
#21	(PDMonitor* or (PD NEXT monitor*)):ti,ab,kw	7

#22	{OR #16-#21}	1406
#23	#3 and #22	50
#24	#15 or #23 in Cochrane Reviews	4

Key:
mh = exploded indexing term (MeSH)
mh ^ = unexploded indexing term (MeSH)
* = truncation
ti,ab,kw = terms in either title or abstract or keyword fields
near/3 = terms within three words of each other (any order)
next = terms are next to each other

International HTA database

via https://database.inahta.org/
Date range: Inception – 01 February 2022
Date searched: 01 February 2022
Records retrieved: 36

((((continuous* OR remote*) AND (measure* OR monitor* OR sensor*)))[Title] OR (((continuous* OR remote*) AND (measure* OR monitor* OR sensor*)))[abs] OR (((continuous* OR remote*) AND (measure* OR monitor* OR sensor*)))[Keywords] OR ((((wear* OR worn OR wrist* OR ankle* OR body* OR waist* OR belt*) AND (tech* OR device* OR sensor*)) AND (remote* OR continuous*)))[Title] OR ((((wear* OR worn OR wrist* OR ankle* OR body* OR waist* OR belt*) AND (tech* OR device* OR sensor*)) AND (remote* OR continuous*)))[abs] OR ((((wear* OR worn OR wrist* OR ankle* OR body* OR waist* OR belt*) AND (tech* OR device* OR sensor*)) AND (remote* OR continuous*)))[Keywords] OR ((((inertia* OR kinetic* OR motor OR gait OR bradykine* OR dyskine* OR tremor* OR shaking OR instability OR stability OR balance OR sleep*) AND (tech* OR device* OR sensor*)) AND (remote* OR continuous*)))[Title] OR ((((inertia* OR kinetic* OR motor OR gait OR bradykine* OR dyskine* OR tremor* OR shaking OR instability OR stability OR balance OR sleep*) AND (tech* OR device* OR sensor*)) AND (remote* OR continuous*)))[abs] OR ((((inertia* OR kinetic* OR motor OR gait OR bradykine* OR dyskine* OR tremor* OR shaking OR instability OR stability OR balance OR sleep*) AND (tech* OR device* OR sensor*)) AND (remote* OR continuous*)))[Keywords] OR ((telemetr* OR ((smart watch* OR smart-watch* OR smartwatch*) AND (remote* OR continuous*))))[Title] OR ((telemetr* OR ((smart watch* OR smart-watch* OR smartwatch*) AND (remote* OR continuous*))))[abs] OR ((telemetr* OR ((smart watch* OR smart-watch* OR smartwatch*) AND (remote* OR continuous*))))[Keywords] OR ((((mobile AND (health* OR app*)) OR (e-health OR eHealth OR m-health OR mHealth)) AND (remote* OR continuous*)))[Title] OR ((((mobile AND (health* OR app*)) OR (e-health OR eHealth OR m-health OR mHealth)) AND (remote* OR continuous*)))[abs] OR ((((mobile AND (health* OR app*)) OR (e-health OR eHealth OR m-health OR mHealth)) AND (remote* OR continuous*)))[Keywords] OR (((remote* OR continuous*) AND ((ambulatory OR outpatient* OR patient* OR physiologic*) AND (monitor* OR manage*))))[Title] OR (((remote* OR continuous*) AND ((ambulatory OR outpatient* OR patient* OR physiologic*) AND (monitor* OR manage*))))[abs] OR (((remote* OR continuous*) AND ((ambulatory OR outpatient* OR patient* OR physiologic*) AND (monitor* OR manage*))))[Keywords] OR ((KinetiGraph* OR PKG* OR Kinesia* OR STAT ON* OR STAT-ON* OR PDMonitor* OR (kineti* AND graph*) OR (PD AND monitor*)))[Title] OR ((KinetiGraph* OR PKG* OR Kinesia* OR STAT ON* OR STAT-ON* OR PDMonitor* OR (kineti* AND graph*) OR (PD AND monitor*)))[abs] OR ((KinetiGraph* OR PKG* OR Kinesia* OR STAT ON* OR STAT-ON* OR PDMonitor* OR (kineti* AND graph*) OR (PD AND monitor*)))[Keywords]) AND (("Parkinson Disease"[mh]) OR ((parkinson* AND (disease* OR syndrom* OR disorder* OR complex)))[Title] OR ((parkinson* AND (disease* OR syndrom* OR disorder* OR complex)))[abs] OR ((parkinson* AND (disease* OR syndrom* OR disorder* OR complex)))[Keywords])

Key:
[mh] = indexing term: Medical Subject Heading (MeSH)
[Keywords] = search of keywords field
[abs] = search of abstract field
[Title] = search of title field
* = truncation

Database of Abstracts of Reviews of Effects (DARE)

via https://www.crd.york.ac.uk/CRDWeb/
Date range searched: Inception to 31st March 2015
Date searched: 01 February 2022
Records retrieved: 2

1	MeSH DESCRIPTOR Parkinson Disease IN DARE	144

2 (parkinson* NEAR2 (disease* or syndrom* or disorder* or complex)) IN DARE 256
3 #1 OR #2 256
4 MeSH DESCRIPTOR Wearable Electronic Devices IN DARE 0
5 MeSH DESCRIPTOR Telemetry IN DARE 6
6 MeSH DESCRIPTOR Remote Sensing Technology IN DARE 1
7 ((continuous* or remote*) NEAR2 (measure* or monitor* or sensor*)) IN DARE 190
8 (((wear* or worn or wrist* or ankle* or body* or waist* or belt*) NEAR2 (tech* or device* or sensor*)) and (remote* or continuous*)) IN DARE 2
9 (((inertia* or kinetic* or motor or gait or bradykine* or dyskine* or tremor* or shaking or instability or stability or balance or sleep*) NEAR2 (tech* or device* or sensor*)) and (remote* or continuous*)) IN DARE 3
10 telemetr* IN DARE 14
11 ((smart watch* or smart-watch* or smartwatch*) and (remote* or continuous*)) IN DARE 0
12 (((mobile NEAR (health* or app*)) or (e-health or eHealth or m-health or mHealth)) and (remote* or continuous*)) IN DARE 2
13 ((remote* or continuous*) and ((ambulatory or outpatient* or patient* or physiologic*) NEAR2 (monitor* or manage*))) IN DARE 35
14 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 233
15 #3 AND #14 2
16 KinetiGraph* IN DARE 0
17 (PKG* NOT protein kinase) IN DARE 0
18 (kineti* NEAR graph*) IN DARE 0
19 Kinesia* IN DARE 1
20 (STAT ON* or STAT-ON*) IN DARE 0
21 (PDMonitor* or (PD NEAR monitor*)) IN DARE 0
22 #16 OR #17 OR #18 OR #19 OR #20 OR #21 1
23 #3 AND #22 0
24 #15 OR #23 2

Key:
MeSH DESCRIPTOR = indexing term: Medical Subject Heading (MeSH)
* = truncation
NEAR3 = terms within three words of each other (only in the order specified)

NHS Economic Evaluation Database (NHS EED)

via https://www.crd.york.ac.uk/CRDWeb/
Date range searched: Inception to 31st March 2015
Date searched: 01 February 2022
Records retrieved: 1

1 MeSH DESCRIPTOR Parkinson Disease IN EED 33
2 (parkinson* NEAR2 (disease* or syndrom* or disorder* or complex)) IN EED 46
3 #1 OR #2 46
4 MeSH DESCRIPTOR Wearable Electronic Devices IN EED 0
5 MeSH DESCRIPTOR Telemetry IN EED 14
6 MeSH DESCRIPTOR Remote Sensing Technology IN EED 2
7 ((continuous* or remote*) NEAR2 (measure* or monitor* or sensor*)) IN EED 36
8 (((wear* or worn or wrist* or ankle* or body* or waist* or belt*) NEAR2 (tech* or device* or sensor*)) and (remote* or continuous*)) IN EED 0
9 (((inertia* or kinetic* or motor or gait or bradykine* or dyskine* or tremor* or shaking or instability or stability or balance or sleep*) NEAR2 (tech* or device* or sensor*)) and (remote* or continuous*)) IN EED 0
10 telemetr* IN EED 26
11 ((smart watch* or smart-watch* or smartwatch*) and (remote* or continuous*)) IN EED 0
12 (((mobile NEAR (health* or app*)) or (e-health or eHealth or m-health or mHealth)) and (remote* or continuous*)) IN EED 8
13 ((remote* or continuous*) and ((ambulatory or outpatient* or patient* or physiologic*) NEAR2 (monitor* or manage*))) IN EED 34
14 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 89
15 #3 AND #14 0
16 KinetiGraph* IN EED 0
17 (PKG* NOT protein kinase) IN EED 0
18 (kineti* NEAR graph*) IN EED 0

19 Kinesia* IN EED 0
20 (STAT ON* or STAT-ON*) IN EED 0
21 (PDMonitor* or (PD NEAR monitor*)) IN EED 1
22 #16 OR #17 OR #18 OR #19 OR #20 OR #21 1
23 #3 AND #22 1
24 #15 OR #23 1

Key:
MeSH DESCRIPTOR = indexing term: Medical Subject Heading (MeSH)
* = truncation
NEAR3 = terms within three words of each other (only in the order specified)

Health Technology Assessment (HTA)

via https://www.crd.york.ac.uk/CRDWeb/
Date range searched: Inception to March 2018
Date searched: 01 February 2022
Records retrieved: 0

1 MeSH DESCRIPTOR Parkinson Disease IN HTA 66
2 (parkinson* NEAR2 (disease* or syndrom* or disorder* or complex)) IN HTA 86
3 #1 OR #2 86
4 MeSH DESCRIPTOR Wearable Electronic Devices IN HTA 0
5 MeSH DESCRIPTOR Telemetry IN HTA 17
6 MeSH DESCRIPTOR Remote Sensing Technology IN HTA 5
7 ((continuous* or remote*) NEAR2 (measure* or monitor* or sensor*)) IN HTA 66
8 (((wear* or worn or wrist* or ankle* or body* or waist* or belt*) NEAR2 (tech* or device* or sensor*)) and (remote* or continuous*)) IN HTA 2
9 (((inertia* or kinetic* or motor or gait or bradykine* or dyskine* or tremor* or shaking or instability or stability or balance or sleep*) NEAR2 (tech* or device* or sensor*)) and (remote* or continuous*)) IN HTA 1
10 telemetr* IN HTA 23
11 ((smart watch* or smart-watch* or smartwatch*) and (remote* or continuous*)) IN HTA 0
12 (((mobile NEAR (health* or app*)) or (e-health or eHealth or m-health or mHealth)) and (remote* or continuous*)) IN HTA 1
13 ((remote* or continuous*) and ((ambulatory or outpatient* or patient* or physiologic*) NEAR2 (monitor* or manage*))) IN HTA 19
14 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 92
15 #3 AND #14 0
16 KinetiGraph* IN HTA 0
17 (PKG* NOT protein kinase) IN HTA 018 (kineti* NEAR graph*) IN HTA 0
19 Kinesia* IN HTA 0
20 (STAT ON* or STAT-ON*) IN HTA 0
21 (PDMonitor* or (PD NEAR monitor*)) IN HTA 1
22 #16 OR #17 OR #18 OR #19 OR #20 OR #21 1
23 #3 AND #22 0
24 #15 OR #23 0

Key:
MeSH DESCRIPTOR = indexing term: Medical Subject Heading (MeSH)
* = truncation
NEAR3 = terms within three words of each other (only in the order specified)

ClinicalTrials.gov

via https://clinicaltrials.gov/
Date searched: 01 February 2022
Records retrieved: 271
Advanced search screen used. 2 separate searches were used, retrieving 271 records in total, which were imported into EndNote 20 and deduplicated.

Search Strategies:
1. **Condition or disease:** Parkinson

Other terms: ("Kineti Graph" OR KinetiGraph OR PKG OR Kinesia OR "STAT ON" OR PDMonitor OR "PD Monitor") = 46 hits

2. **Condition or disease:** Parkinson
   Other terms: ((continuous OR remote) AND (measure OR monitor OR sensor)) = 225 hits

European Union Clinical Trials Register

via www.clinicaltrialsregister.eu/ctr-search/search
Date searched: 01 February 2022
Records retrieved: 11
Advanced search screen used. 2 separate searches were used, retrieving 11 records in total, which were imported into EndNote 20 and deduplicated.

Search Strategies:

1. (Parkinson AND ("Kineti Graph" OR KinetiGraph OR PKG OR Kinesia OR "STAT ON" OR PDMonitor OR "PD Monitor")) = 6 hits
2. Parkinson AND ((continuous OR remote) AND (measure OR monitor OR sensor)) = 5 hits

World Health Organization International Clinical Trials Registry Platform

via https://trialsearch.who.int/AdvSearch.aspx
Date searched: 01 February 2022
Records retrieved: 12
Advanced search screen used. 2 separate searches were used, retrieving 12 records in total, which were imported into EndNote 20 and deduplicated.
Search Strategies:

1. **Condition:** Parkinson
   Intervention: (Kineti Graph OR KinetiGraph OR PKG OR Kinesia OR STAT ON OR STAT-ON OR PDMonitor OR PD Monitor)
   Recruitment Status: ALL
   = 11 records for 11 trials found

2. **Condition:** Parkinson
   Intervention: ((continuous OR remote) AND (measure OR monitor OR sensor))
   Recruitment Status: ALL
   = 1 records for 1 trials found

Search strategies for identification of economic studies (March 2022)

Ovid MEDLINE(R) ALL

via Ovid http://ovidsp.ovid.com/
Date range searched: <1946 to March 01, 2022>
Date searched: 02 March 2022
Records retrieved: 529

1 Parkinson Disease/ (75106)
2 (parkinson* adj2 (disease* or syndrom* or disorder* or complex)).ti,ab,kw. (112396)
3 1 or 2 (125301)
4 *economics/ (10787)
5 exp *"costs and cost analysis"/ (78000)
6 (economic adj2 model*).mp. (14362)
7 (cost minimi* or cost-utilit* or health utilit* or economic evaluation* or economic review* or cost outcome* or cost analys?s or economic analys?s or budget* impact analys?s).ti,ab,kf,kw. (38225)
8 (cost-effective* or pharmacoeconomic* or pharmaco-economic* or cost-benefit or costs).ti,kf,kw. (80925)
9 (life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s).ab,kf,kw. (35175)
10 (cost or economic*).ti,kf,kw. and (costs or cost-effectiveness or markov or monte carlo or model or modeling or modelling).ab. (75922)
11 or/4-10 (205434)
12 3 and 11 (546)
13 exp animals/ not humans/ (4965507)
14 12 not 13 (544)

15 letter.pt. (1170841)
16 editorial.pt. (596777)
17 historical article.pt. (367835)
18 or/15-17 (2114647)
19 14 not 18 (529)

Key:
/ = indexing term (Medical Subject Heading: MeSH)
* before a MeSH term = focussed subject heading
* = truncation
ti,ab,kw = terms in either title, abstract, or keyword fields
mp = multipurpose field
pt = publication type
? = optional wild card character - stands for zero or one letters
adj3 = terms within three words of each other (any order)

Embase

via Ovid http://ovidsp.ovid.com/
Date range searched: <1974 to 2022 March 01>
Date searched: 02 March 2022
Records retrieved: 548

1 Parkinson Disease/ (171312)
2 (parkinson* adj2 (disease* or syndrom* or disorder* or complex)).ti,ab,kw. (160723)
3 1 or 2 (201252)
4 *economics/ (27548)
5 *"cost benefit analysis"/ (12396)
6 *"cost effectiveness analysis"/ (34235)
7 *"cost utility analysis"/ (2741)
8 *"cost minimization analysis"/ (817)
9 (economic adj2 model*).mp. (8770)
10 (cost minimi* or cost-utilit* or health utilit* or economic evaluation* or economic review* or cost outcome or cost analys?s or economic analys?s or budget* impact analys?s).ti,ab,kw. (56649)
11 (cost-effective* or pharmacoeconomic* or pharmaco-economic* or cost-benefit or costs).ti,kw. (111273)
12 (life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s).ab,kw. (54031)
13 (cost or economic*).ti,kw. and (costs or cost-effectiveness or markov).ab. (93389)
14 or/4-13 (232822)
15 3 and 14 (872)
16 animal/ (1558504)
17 exp animal experiment/ (2806299)
18 nonhuman/ (6815251)
19 (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep).ti,ab,sh. (6095552)
20 or/16-19 (9639196)
21 exp human/ (23327515)
22 human experiment/ (567633)
23 or/21-22 (23329520)
24 20 not (20 and 23) (6898393)
25 15 not 24 (864)
26 letter.pt. (1213039)
27 editorial.pt. (718624)
28 note.pt. (885196)
29 conference abstract.pt. (4333669)
30 or/26-29 (7150528)
31 25 not 30 (548)

Key:
/ or .sh. = indexing term (Emtree Subject Heading)
* before an Emtree term = focussed subject heading
* = truncation
ti,ab,kw = terms in either title, abstract, or keyword fields

mp = multipurpose field
pt = publication type
? = optional wild card character - stands for zero or one letters
adj3 = terms within three words of each other (any order)

Econlit

via Ovid http://ovidsp.ovid.com/
Date range searched: 1886 to February 24, 2022
Date searched: 02 March 2022
Records retrieved: 36

1 (parkinson* adj2 (disease* or syndrom* or disorder* or complex)).ti,ab,kw. (36)

Key:
* = truncation
ti,ab,kw = terms in either title, abstract or keyword fields
adj3 = terms within three words of each other (any order)

NHS Economic Evaluation Database (NHS EED)

via https://www.crd.york.ac.uk/CRDWeb/
Date range searched: Inception to 31st March 2015
Date searched: 02 March 2022
Records retrieved: 46

1	MeSH DESCRIPTOR Parkinson Disease IN EED	33
2	(parkinson* NEAR2 (disease* or syndrom* or disorder* or complex)) IN EED	46
3	#1 OR #2	46

Key:
MeSH DESCRIPTOR = indexing term: Medical Subject Heading (MeSH)
* = truncation
NEAR2 = terms within three words of each other (only in the order specified)

Health Technology Assessment (HTA)

via https://www.crd.york.ac.uk/CRDWeb/
Date range searched: Inception to March 2018
Date searched: 02 March 2022
Records retrieved: 86

1	MeSH DESCRIPTOR Parkinson Disease IN HTA	66
2	(parkinson* NEAR2 (disease* or syndrom* or disorder* or complex)) IN HTA	86
3	#1 OR #2	86

Key:
MeSH DESCRIPTOR = indexing term: Medical Subject Heading (MeSH)
* = truncation
NEAR2 = terms within three words of each other (only in the order specified)

International HTA database

via https://database.inahta.org/
Date range: Inception – 02 March 2022
Date searched: 02 March 2022
Records retrieved: 95

(("Parkinson Disease"[mh]) OR ((parkinson* AND (disease* OR syndrom* OR disorder* OR complex)))[Title] OR ((parkinson* AND (disease* OR syndrom* OR disorder* OR complex)))[abs] OR ((parkinson* AND (disease* OR syndrom* OR disorder* OR complex)))[Keywords])
Key:
[mh] = indexing term: Medical Subject Heading (MeSH)
[Keywords] = search of keywords field

[abs] = search of abstract field
[Title] = search of title field
* = truncation

9.2 Excluded studies with rationale

Table 49 Table of excluded studies

Study	Reason for exclusion
Abou, 2021[161]	Not an eligible device
Adams, 2021[162]	Not an eligible device
AlMahadin, 2020[163]	Not an eligible device
Ancona, 2022[164]	Review article
Barrachina-Fernandez, 2021[165]	Not an eligible device
Battista, 2020[166]	Not an eligible device
Battista, 2021[167]	Not an eligible device
Bendig, 2020[168]	No relevant outcome data
Blaze, 2016[169]	Monitoring device not the intervention under assessment
Brillman, 2015[170]	No relevant outcome data
Canento, 2019[171]	No relevant outcome data
Carroll, 2019[172]	Duplicate report
Channa, 2020[173]	Review article
DavidPrakash, 2013[174]	Not an eligible device
DelPrete, 2019[175]	No relevant outcome data
DelPrete, 2022[176]	Monitoring device not the intervention under assessment
Dominey, 2018[177]	Duplicate report
Edwards, 2020a[178]	Monitoring device not the intervention under assessment
Edwards, 2020b[179]	No relevant outcome data
Evans, 2014[31]	Monitoring device not the intervention under assessment
Evans, 2019[180]	Duplicate report
Evans, 2020[181]	Duplicate report
Evans, 2021[182]	No relevant outcome data
Farley, 2018[183]	Not an eligible device
Farzanehfar, 2017b[184]	Duplicate report
Farzanehfar, 2017c[185]	Review article
Flisar, 2016a[186]	No relevant outcome data
Flisar, 2016b[187]	No relevant outcome data
Flisar, 2018[188]	No relevant outcome data
Gao, 2018[189]	Not an eligible device
Gernon, 2018[190]	No relevant outcome data
Ghoraani, 2021[191]	Review article
Giuffrida, 2009a[192]	Not an eligible device
Giuffrida, 2009b[193]	Not an eligible device
Griffiths, 2012[194]	Duplicate report
Heldman, 2014[195]	Not an eligible device
Heldman, 2016[196]	Not an eligible device
Horne, 2014[197]	No relevant outcome data
Isaacson, 2018[198]	Duplicate report
Jansa, 2016[199]	No relevant outcome data
Johansson, 2019[200]	Monitoring device not the intervention under assessment
Joshi, 2019[201]	Duplicate report
Karl, 2020[202]	Monitoring device not the intervention under assessment

Keogh, 2021[203]	Review article
Kilincalp, 2022[204]	Monitoring device not the intervention under assessment
King, 2021[205]	Not an eligible device
Klingelhoefer, 2015[206]	Duplicate report
Klingelhoefer, 2016c[207]	No relevant outcome data
Koivu, 2017[208]	No relevant outcome data
Kostikis, 2021[209]	No relevant outcome data
Kotschet, 2012[210]	No relevant outcome data
Krause, 2019[211]	Same patients as another study
Leake, 2019[212]	No relevant outcome data
Lynch, 2016[213]	No relevant outcome data
Lynch, 2018b[214]	No relevant outcome data
Lynch, 2018c[215]	No relevant outcome data
Lynch, 2019[216]	No relevant outcome data
Malhotra, 2020[217]	No relevant outcome data
Metta, 2021[218]	No relevant outcome data
Mirelman, 2020[219]	Not an eligible device
Mohamed, 2020[220]	No relevant outcome data
Morgan, 2020[221]	Review article
Morgante, 2019[222]	Monitoring device not the intervention under assessment
Mostile, 2010[223]	Not an eligible device
Nahab, 2018[224]	Duplicate report
Pahwa, 2018[225]	No relevant outcome data
Pahwa, 2019[226]	No relevant outcome data
Pahwa, 2020[227]	No relevant outcome data
Pai, 2020[228]	No relevant outcome data
Papapetropoulos, 2016[229]	Not an eligible device
Phillips, 2013[230]	Monitoring device not the intervention under assessment
Podlewska, 2019[231]	No relevant outcome data
Potter, 2020[232]	No relevant outcome data
Powell, 2020[233]	Not Parkinson's disease
Pulliam, 2015[234]	Not an eligible device
Robertson, 2020[235]	Not an eligible device
Rodriguez-Martin, 2019[236]	Review article
Rodriguez-Martin, 2021b[237]	No relevant outcome data
Rovini, 2019[238]	Review article
Sachdev, 2017[239]	No relevant outcome data
SantosGarcia, 2020b[240]	Duplicate report
Sasaki, 2018[241]	No relevant outcome data
Sica, 2021[242]	Review article
Sringean, 2014[243]	No relevant outcome data
Stuijt, 2016[244]	Monitoring device not the intervention under assessment
Stuijt, 2017[245]	Duplicate report
Stuijt, 2018[246]	Monitoring device not the intervention under assessment
Sundgren, 2019[247]	Duplicate report
Sung, 2018[248]	No relevant outcome data
Suttrup, 2016[249]	No relevant outcome data

Taddei, 2018[250]	Monitoring device not the intervention under assessment
Tan, 2017[251]	No relevant outcome data
Thomas, 2017a[252]	Duplicate report
Thomas, 2017b[253]	Monitoring device not the intervention under assessment
Thomas, 2019a[254]	Monitoring device not the intervention under assessment
Thomsen, 2019[255]	No relevant outcome data
Titova, 2020[256]	No relevant outcome data
vandenBergh, 2021[257]	Review article
VanUem, 2016[258]	Not an eligible device
VanUem, 2018[259]	Not an eligible device
VanWamelen, 2019[260]	Monitoring device not the intervention under assessment
VanWamelen, 2020[261]	Monitoring device not the intervention under assessment
VanWamelen, 2021[262]	Monitoring device not the intervention under assessment
VanWamelen, 2021[263]	Review article
Watts, 2021a[72]	Same patients as another study (although this paper was used to supplement data extraction of diagnostic accuracy outcomes)
Watts, 2021b[264]	No relevant outcome data
Williamson, 2021[265]	Not an eligible device
Zampogna, 2020[266]	Not an eligible device
Zhang, 2020[267]	Not an eligible device
Zhang, 2021[268]	Review article
#2178 (no author name or year or abstract){, #314}	No relevant outcome data
#2120 (no author name or year or abstract){, #316}	No relevant outcome data
#2075 (no author name or year or abstract){, #315}	No relevant outcome data
#1616 (no author name or year or abstract){, #317}	No relevant outcome data
#1971 (no author name or year or abstract){, #313}	Not an eligible device
#1581 (no author name or year or abstract){, #310}	No relevant outcome data
#1580 (no author name or year or abstract){, #308}	No relevant outcome data
#1434 (no author name or year or abstract){, #318}	No relevant outcome data
#552 (no author name or year or abstract){, #312}	Not an eligible device
#1319 (no author name or year or abstract){, #309}	No relevant outcome data
Euctr-000346-19-Se, 2018{Euctr-000346-19-Se, 2018 #301}	Monitoring device not the intervention under assessment
Euctr-005170-19-Se, 2018{Euctr-005170-19-Se, 2018 #300}	Monitoring device not the intervention under assessment
NCT04381065, 2020{Nct, 2020 #302}	Study withdrawn
NCT03984305, 2019{Nct, 2019 #297}	Study terminated
NCT03152721, 2017{Nct, 2017 #305}	Duplicate report
NCT03103919, 2017{Nct, 2017 #296}	Duplicate report

NCT04653688, 2020{NCT04653688, 2020 #307}	Monitoring device not the intervention under assessment
NCT031305959	Duplicate report
NCT04719468, 2021{Nct, 2021 #299}	Monitoring device not the intervention under assessment
NCT02152319, 2014{Nct, 2014 #306}	Not an eligible device
NCT03531060, 2018{Nct, 2018 #303}	Monitoring device not the intervention under assessment

9.3 Ongoing studies

Table 50 Table of ongoing studies

Study details	Study design and funding source	Population	Intervention	Comparator(s)	Outcomes
Price, 2016[269] UK	Prospective cohort study Funding: not stated	PwP (n=5 to date)	PKG	-	Patient satisfaction
Price, 2017[270] Location: not stated	Prospective cohort study Funding: not stated	PwP (n=6 to date)	PKG to assess tremor	Patient report	Patient satisfaction
Rodriguez-Molinero, 2019[271] Spain	Randomised controlled trial Funding: not stated (2 authors' affiliations are Sense4Care)	PwP	STAT-ON	Patient diary Clinical assessment in clinic	Change in clinical management and number of visits to the doctor for medication adjustment Motor fluctuations diary, UPDRS, Freezing of Gait Questionnaire
UK PKG Registry: Multi-centre real-world registry of Personal KinetiGraph in 441 patients with Parkinson's disease. NIHR portfolio study ID: 35053[272] UK	Registry Funding: not stated	PwP (n=441)	PKG	-	
#1692 (NCT05153356){, #311} USA	Prospective cohort study Funding:	PwP (estimated enrolment n=20)	PKG Kinesia 360	Patient questionnaires and clinician rating scales	Correlation, patient satisfaction
NCT04176302, 2019[273] Spain	RCT (MoMoPa-EC) Funding:	PwP	STAT-ON	Clinical assessment Patient diary	Clinical outcomes, change in clinical management, physician and patient satisfaction

NCT03741920, 2018[274] USA	RCT (APPRISE) Funding: not stated	PwP (n=231)	PKG	Clinical assessment	Change in clinical management

Abbreviations: PKG, Personal KinetiGraph; PwP, people with Parkinson's disease; UPDRS, Unified Parkinson's Disease Rating Scale.

9.4 Data extraction tables

9.4.1 Diagnostic accuracy

For diagnostic accuracy results (sensitivity/specificity etc.) see Table 4 of main report.

PKG (7 full papers, 1 abstract)

Table 51 Data from PKG diagnostic accuracy studies

Study details	Study design and funding source	Population (incl. N)	Reference standard
Full papers			
Braybrook, 2016[23] Australia	Prospective cohort study Funding: Global Kinetics Corporation	PwP (n=172)	Examination, UPDRS III, history
Horne, 2015[44] Australia	Case-control Funding: Global Kinetics Corporation	PwP (n=36) and healthy controls (n=16)	UPDRS part III Abnormal Involuntary Movement Score (AIMS)
Horne, 2016[41] Australia	Case-control Funding: not stated	PwP (n=18) and healthy controls (n=35)	UPDRS part III Abnormal Involuntary Movement Score (AIMS)
Khodakarami, 2019 A[49] Australia	Retrospective cohort study Funding: Global Kinetics Corporation (1 author is employed by GKC, 1 author has financial interests in GKC)	PwP (construction set n=112) and PwP (test set n=60)	Clinical assessment for selecting patients for DAT referrals (including MDS-UPDRS)
Khodakarami, 2019 B[50] Holland, USA and Australia	Case-control Funding: None (1 author is employed by GKC, 1 author has financial interests in GKC)	PwP (n=199), people without PD (n=174) and PwP who underwent DBS (n=24)	Levodopa challenge test (LDCT) as part of routine clinical care (including UPDRS III)

Study details	Study design and funding source	Population (incl. N)	Reference standard
McGregor, 2018[61] Australia	Case-control Funding: Global Kinetics Corporation	PwP (n=72), healthy controls (n=155) and healthy people undergoing polysomnogram (n=46)	Parkinson's Sleep Score 2 (PDSS 2) in PwP Polysomnogram (PSG) in non-Parkinson's disease controls (n=46)
Watts 2021[72] USA	Cohort Funding: Partially supported by the Science Alliance, The University of Tennessee, The Parkinson's Alliance and by the Laboratory Directed Research and Development Program of Oak Ridge National Laboratory managed by UT-Battelle, LLC, for the U.S. Department of Energy (1 author is employed by GKC)	PwP (n=26)	MDS-UPDRS III
Abstracts			
Horne, 2017[46] Germany and France	Cohort Funding: Not stated	PwP (n=36) under consideration for DBS	Clinical assessment

Abbreviations: AIMS, Abnormal Involuntary Movements Scale; DAT, device assisted therapy; DBS, deep brain stimulation; LDCT, Levodopa challenge test; MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; PD, Parkinson's disease; PwP, people with Parkinson's disease; UPDRS, Unified Parkinson's Disease Rating Scale.

STAT-ON (8 full papers, 1 abstract)

Table 52 Data from STAT-ON diagnostic accuracy studies

Study details	Study design and funding source	Population (incl. N)	Reference standard	Additional results
Full papers				
Bayes, 2018[74] Spain, Italy, Israel and Ireland	Prospective pilot cohort study Funding: European Community	PwP (n=41)	Patient diaries and clinical assessment	

Study details	Study design and funding source	Population (incl. N)	Reference standard	Additional results
Perez-Lopez, 2016 (AIM) [78] Spain, Ireland, Italy and Israel	Prospective cohort study Funding: European Community	PwP (n=92) and historical PwP patients (n=10)	Clinical assessment (video recording used for labelling the signal by a trained expert)	
Perez-Lopez, 2016 (Sensors) [77] Spain	Prospective cohort study Funding: Instituto de Salud Carlos III-Ministerio de Economia y Competividad and the European Regional Development Fund (6 authors are shareholders of Sense4Care)	PwP (n=15) and historical PwP patients (n=20)	Clinical assessment, using UPDRS Patient diaries	
Rodriguez-Martin, 2017 [80] Spain, Ireland, Italy and Israel	Prospective cohort study Funding: La Fundacio La Marato de TV3 20140431 and European Community (6 authors are shareholders of Sense4Care)	PwP (n=21) Subgroup of patients from Perez-Lopez, 2016b who had Freezing of Gait score above 6	Clinical assessment (video recording used for labelling the signal by an experienced clinician)	
Rodriguez-Molinero, 2015[82] Spain	Prospective cohort study Funding: Instituto de Salud Carlos III – Ministerio de Economia y Competitividad and the European Regional Development Fund	PwP (n=20) and PwP (n=15)	Clinical assessment (video recording used for labelling the signal by experienced clinicians) and patient report	
Rodriguez-Molinero, 2018[84] Spain	Prospective cohort study Funding: Instituto de Salud Carlos III (4 authors are shareholders of Sense4Care)	PwP - advanced (n=23)	Patient diaries	
Sama, 2017[86] Spain	Prospective cohort study Funding: Instituto de Salud Carlos III-Ministerio de Economia y Competividad and the European Regional Development Fund (6 authors are shareholders of Sense4Care)	PwP (n=12)	Clinical assessment (video recording used for labelling the signal by a trained expert) UPDRS	

Study details	Study design and funding source	Population (incl. N)	Reference standard	Additional results
Sama, 2018[87] Spain	Prospective cohort study Funding: La Fundacio La Marato de TV3 436/C/2014 (3 authors are shareholders of Sense4Care)	PwP (n=15)	Clinical assessment (video recording used for labelling the signal by a trained expert)	
Abstracts				
Bougea, 2021[75] Location: not stated	Prospective cohort study Funding: not stated	PwP with motor fluctuations and dyskinesia, treated with Levodopa Carbidopa Intestinal Gel (n=51)	Patient diary completed once every hour	STAT-ON demonstrated 93.4% sensitivity and 89% specificity in detecting OFF state, 94% sensitivity and 87% specificity in dyskinesia and 94.2% sensitivity and 87.1% specificity in falls compared with patient-completed diaries (OFF: 71.6% and 80.3%, dyskinesia: 78.2% and 81.4%, Falls: 78.2% and 81.4%). The overall classification accuracy was 92.2%. No device-related adverse events were reported.

Abbreviations: PwP, people with Parkinson's disease; UPDRS, Unified Parkinson's Disease Rating Scale.

Kinesia 360 (1 full paper, 0 abstracts)

Table 53 Data from Kinesia 360 diagnostic accuracy studies

Study details	Study design and funding source	Population (incl. N)	Reference standard
Full papers			
Pulliam, 2018[91] USA	Prospective cohort study Funding: National Institutes of Health (4 authors are employees of Great Lakes Neuro-Technologies)	PwP (n=13)	Clinical assessment (clinician ratings based on video recordings) UPDRS-III

Abbreviations: PwP, people with Parkinson's disease; UPDRS, Unified Parkinson's Disease Rating Scale.

KinesiaU (0 papers/abstracts)

PDMonitor (0 papers/abstracts)

9.4.2 Association outcomes

PKG (11 full papers, 10 abstracts)

Table 54 Data from PKG association studies

Study details	Study design and funding source	Population	Intervention	Comparator(s)	Results
Full papers					
Chen, 2020[24] China	Prospective cohort study Funding: Joint Funds for the innovation of Science and Technology, Fujian province and the Central Government Directs Special Funds for Local Science and Technology Development	PwP (n=100)	PKG for ≥6 days	UPDRS III Wearing-off Questionnaire-9 (n=75 PwP receiving stable levodopa treatment 125mg tid)	The PKG bradykinesia score (BKS) was moderately correlated with UPDRS III scores: UPDRS III total score (r=0.546, p<0.0001), UPDRS III-B (r=0.588, p<0.001) and UPDRS III-R (r=0.479, p<0.001), especially in the early stage (Hoehn-Yahr stage 1-2) group (r=0.682, p<0.001). The PKG percent time tremor (PTT) scores and UPDRS tremor scores were also significantly correlated: UPDRS III-T (r=0.434, p<0.05) and UPDRS II-T (r=0.269, p<0.05). However, the Wearing-off Questionnaire-9 (WOQ-9) had a very weak, non-significant correlation with the PKG dyskinesia score (DKS) and fluctuation and dyskinesia score (FDS); p>0.05.
Evans, 2014[31] Australia	Prospective cohort study Funding: Medical Research Council Funds (4 authors have a financial interest in Global Kinetics Corporation)	PwP (n=25)	PKG worn for 10 days (acknowledgement of medication consumption)	A blinded examiner administered the Starkstein Apathy Scale (AS) and the Questionnare for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP) Patients also completed the Beck Depression Inventory (BDI),	A Response Ratio, representing the number of acknowledgements/number of doses (expressed as a percentage) was strongly correlated with ratings of Impulsive-Compulsive Behaviours (r^2=0.79) in 19/25 patients. However, 6 patients were clear outliers and fell into the false negative group; these patients had normal Response Ratios, but high Impulsive-Compulsive Behaviour Scores, as well as higher apathy scores and low levels of dyskinesia.

Study details	Study design and funding source	Population	Intervention	Comparator(s)	Results
				Behavioural Inhibition Scale/Behavioural Activation Scale (BIS/BAS) and the State Trait Anxiety Inventory (STAI)	
Griffiths, 2012a[37] Australia	Prospective cohort study Funding: Florey Neuroscience Institute, the Pfizer Neuroscience Research grant, Medical Research Council Research Funds and the Victorian Government's Operational Infrastructure Support Program (4 authors have financial interest in Global Kinetics, Global Kinetics provided the PKG devices)	PwP (n=34) and age-matched controls (n=10)	PKG worn for up to 10 days	Conventional clinical rating methods: rapid alternating movements, AIMS and UPDRS III and IV	There was a significant correlation between modified AIMS (assessed by three Movement Disorder Specialists) and PKG dyskinesia score (DKS) ($r=0.80$, $p<0.0001$). The margin of error in predicting the AIMS from DKS was 3.2 AIMS units compared with -3.4 to +4.3 AIMS units by the neurologists (with a maximum score of 20). The PKG 'global median DKS' was obtained from 25 patients with established bilateral PD over 10 days; there was a significant correlation between Global DKS and UPDRS IV ($p<0.05$). The Global DKS predicted the UPDRS IV with a margin of error of 3.9 over a possible range of 0-8. PKG bradykinesia score (BKS) correlated well with bradykinesia measured by the 'dot slide' test ($r=0.63$, $p<0.001$), with a specificity of 88% and sensitivity of 95%. The PKG 'global median BKS' was obtained from the 25 patients with established bilateral PD in the ON state; there was a significant correlation between Global BKS and UPDRS III ($r=0.64$, $p<0.0005$). The margin of error in predicting the UPDRS III from BKS was 18 UPDRS III units.
Guan, 2021[38] USA	Prospective cohort study (substudy of ATLaS-PD)	PwP (n=18)	PKG worn for 6 days	Traditional in-clinic off/on testing using MDS-UPDRS part III	There was a moderate inverse correlation between off/on improvement and BKS at baseline ($r=-0.552$, $p=0.017$) and 6-month ($r=-0.547$, $p=0.019$) visits. There were no significant associations between off/on improvement and the remaining PKG

Study details	Study design and funding source	Population	Intervention	Comparator(s)	Results
	Funding: National Institute of Neurological Disorders and Stroke and Neurodegenerative Disorders Development Trust				scores (DKS: r=0.133, p=0.598 and PTT: r=-0.523, p=0.1 at 6 months). There was a moderate positive linear association between bradykinesia and the ADL domain of the PDQ39 (coefficient of 0.38). However, this did not reach statistical significance. There were no other significant associations between the PKG scores and off/on improvement to the ADL and mobility domains of the PDQ39.
Hoglund, 2021[39] Sweden	Prospective cohort study Funding: The Swedish Parkinson Foundation (Global Kinetics provided the PKG devices)	PwP (n=53)	PKG worn for 6 days (during the daytime: 09:00 to 18:00)	3-day home diary of daytime sleepiness, other non-motor (mood and anxiety) and motor fluctuations	28 patients were classified as motor fluctuators and 24 as non-fluctuators. Daytime sleepiness correlated significantly with motor symptoms, mood and anxiety amongst motor fluctuators (n=28). Motor fluctuators showed stronger correlations between the individual mean level of all diary variables (daytime sleepiness, anxiety, mood and motor symptoms) when compared to the non-fluctuators (n=24). Stronger positive within-individual correlations were found among fluctuators in comparison to non-fluctuators. Correlations between diary variables and PKG variables were generally weak and non-significant.
Khodakarami, 2021[51] Australia	Retrospective cohort study (patient overlap with Farzanehfar, 2018 and Woodrow, 2020) Funding: None (2 authors are employed by Global Kinetics, 1 author	PwP (n=228) and People without PD (n=157)	PKG worn for 6 days	MDS-UPDRS III, UPDRS Total and PDQ39	A normal range of % time in bradykinesia (PTB) and % time in dyskinesia (PTD) based on control subjects was developed. The level of PTB and PTD experienced by PwP was compared with their levels of fluctuation. There was a correlation (Pearson's ρ=0.4, $p<0.0001$) between UPDRS III scores and PTB. The correlation between PDQ scores and UPDRS Total scores and PTB was slightly lower (Pearson's ρ=0.35, $p<0.0001$ and Pearson's ρ=0.34, $p<0.0001$, respectively).

Study details	Study design and funding source	Population	Intervention	Comparator(s)	Results
	has financial interests in Global Kinetics)				PTB and PTD fell in response to treatment for bradykinesia or dyskinesia (respectively) with greater sensitivity than clinical scales.
Klingelhoefer, 2016a[52] UK	Prospective cohort study Funding: not stated	PwP (n=63)	PKG worn for 6 days and 5 nights	Hauser diaries and scales of motor state (including UPDRS part IV and AIMS), non-motor state and sleep assessments (including Non-Motor Symptom Questionnaire (NMSQuest), Epworth Sleepiness Score (ESS), Parkinson's Disease Sleep Scale (PDSS 1) and Hospital Anxiety and Depression Scale (HADS)) and health related quality of life (PDQ8)	In patients with excessive daytime sleepiness (n=30) the PKG's parameters for quantity and quality of night-time sleep correlated significantly with the total burden of non-motor symptoms of PD as measured by NMSQuest as well as overall sleep disturbances as measured by PDSS. In 'non-sleepy' PD patients (n=33) there was no significant correlation. There were no significant correlations of night-time sleep quantity parameters of the Hauser diary with subjective sleep perception (NMSQuest and PDSS) in either patient group. A moderate to high correlation of quantitative and qualitative night-time sleep markers of the PKG was noted with the PDQ8 (r_s=0.46-0.60) in the excessive daytime sleepiness group.
Knudson, 2020[54] Denmark	Prospective cohort study Funding: Carleton College, DIS Copenhagen, and the Department of Clinical Neurophysiology and Neurology at Zealand University Hospital	PwP (n=34)	PKG worn for 6 days and patient questionnaire	MDS-UPDRS part II	There was a significant correlation between MDS-UPDRS part II and PKG bradykinesia change score (P=0.006), PKG dyskinesia score (p=0.007) and subjective score (p=0.0009).

Study details	Study design and funding source	Population	Intervention	Comparator(s)	Results
Kotschet, 2014[55] Australia	Prospective cohort study Funding: Medical Research Council Funds and Global Kinetics Corporation	PwP (n=68) and healthy controls (n=30)	PKG	Daytime polysomnography (PSG; 7 patients) Epworth Sleepiness Score (ESS)	7 PwP whose time immobile was >30 minutes/day (measured on a previous PKG recording) had daytime PSG performed; periods of immobility on PKG had an 85.2% concordance with the detection of sleep by ambulatory daytime PSG (p<0.0001). High ESS was associated with proportion of time immobile (PTI) (p=0.01). PD patients had a higher PTI than healthy controls (p<0.0001). PD patients with a high PTI had more bradykinesia, less dyskinesia and higher PDQ39 scores than those with low PTI. There was no relationship between PTI and dose or type of PD medications, although in 53% patients PTI increased in the 30-60 minutes after levodopa, confirming that in some patients levodopa results in increased sleepiness.
Ossig, 2016[63] Germany	Prospective cohort study Funding: Global Kinetics Corporation	PwP inpatients (n=24)	PKG data recorded between 6am and 10pm	Patient diaries completed every hour for 5 consecutive days	Distribution of total motor state hours per day measured by PKG showed moderate-to-strong correlation to those assessed by diaries for the different motor states (Pearson's correlations coefficients: 0.404-0.658). Inter-rating method agreements on the single-hour-level were only low-to-moderate (Cohen's κ: 0.215-0.324).
Tan, 2019[69] USA	Prospective cohort study Funding: not stated	PwP (n=54). Patients were split into different fluctuator groups (non-fluctuators (n=14), early fluctuators (n=15), moderate fluctuators (n=15) and troublesome fluctuators (n=10)) according	PKG fluctuator scores (worn for 6 days)	Patient two-day motor symptom diary (39 patients returned valid two-day motor diaries)	PKG fluctuator scores significantly differentiated early fluctuators and troublesome fluctuators, as well as dyskinetic and non-dyskinetic subjects, but could not discriminate subtler motor fluctuations. Patient diaries could not distinguish the four study groups on the basis of average OFF time. The diaries distinguished non-fluctuators from moderate fluctuators for average dyskinesia time.

Study details	Study design and funding source	Population	Intervention	Comparator(s)	Results
		to WOQ9 and MDS-UPDRS IV scores			
Abstracts					
Bergquist, 2016[21] Sweden	Retrospective cohort study Funding: not stated	PwP (n=258)	PKG	Visual assessment by a trained specialist	The agreement between visual assessment and assessments based on median PKG scores was low (Cohen Kappa 0.11). In particular, the PKG fluctuation dyskinesia score (FDS) identified fewer OFF-fluctuators than visual assessment by a trained specialist as 25% of the population had significantly increased FDS, but visual assessment identified OFF-fluctuations in an additional 45% of the population. Patients tolerated the PKG well and only 8% had problems handling the reminder function or wearing the device.
Bergquist, 2018[19] Sweden	Prospective cohort study (WestPORTS study) Funding: not stated	PwP (n=154) and historical PwP patients (n=248)	PKG in a randomly selected population of PwP	Clinically motivated PKG recordings in a historical cohort of PwP suspected to have motor fluctuations	PKG bradykinesia scores (BKS) and dyskinesia scores (DKS) were significantly different between a randomly selected population of PwP and a historical PwP population with clinically motivated PKG recordings; median BKS 30.4 and 23.0 (p=0.014), median DKS 1.0 and 3.0 (p<0.0001), respectively.
Bogdanova-Mihaylova, 2016[22] Location: not stated	Prospective cohort study Funding: not stated	PwP (n=20 with advanced disease)	PKG for 6 days	Patient diaries, patient derived dyskinesia severity data (UPDRS IV) and patient perception of motor disability (ranging from 1 to 5)	By history, the mean total daily duration of the OFF time was 3 hours. There was no significant correlation between PKG derived bradykinesia score (BKS) with subjectively reported OFF time (r=0.29, p=0.25) and UPDRS IV part B Fluctuations (r=0.25, p=0.28). 47% patients, who completed the diary (n=17) reported troublesome dyskinesia with a mean duration of 17.85% of the waking day. Correlation between PKG derived dyskinesia score (DKS) and UPDRS IV part A Dyskinesias was approaching significance (r=0.38, p=0.09).

Study details	Study design and funding source	Population	Intervention	Comparator(s)	Results
					A statistically significant association was found between patients' perception of disability due to motor fluctuations and fluctuation score (FS) derived from variations in DKS and BKS (r=0.52, p=0.018).
Dahlen, 2014[26] Location: not stated	Prospective cohort study Funding: not stated	PwP (n=15 with suspected motor fluctuations)	PKG worn for 10 days	Hauser style patient diaries for 3 days	A positive linear correlation (slope 0.73+/-0.33) was found for sleep time (r^2=50.275, p=0.0447), but not for time spent in OFF, ON or Bad ON. Seven patients reported ONtime that correlated with PKG recordings, two patients reported OFF-time that correlated, and two reported Bad ON time correlating with high DK.
Dominey, 2018a[27] Location: not stated	Prospective or retrospective cohort study Funding: not stated	PwP (n=62 newly diagnosed patients)	PKG	Non-Motor Symptoms Questionnaire (NMS Quest)	Patients were allocated to one of five phenotypic subgroups based on PKG data and NMS Quest data. 19% of patients met full criteria for inclusion in one of the five subgroups. Of the remaining patients 51% failed to be allocated to a subgroup due to missing one of the required criteria for inclusion.
Fowler, 2017[36] Location: not stated	Prospective cohort study Funding: not stated	PwP (n=26 patients being evaluated for advanced therapy)	PKG worn for 6 days	Clinical assessment by a movement disorder specialist	All patients met clinical criteria for advanced therapy. 16/26 patients (61.54%) met criteria by PKG for additional therapy. Of the 10 patients who did not meet the criteria, the BKS score ranged from 18.6 to 25.9, the DKS score ranged from 0.6 to 7.3 and the FDS score ranged from 7.3 to 11.5.
Horne, 2016b[42] Location: not stated	Prospective cohort study Funding: not stated	PwP (n=45), additional PwP (n=35) and age matched non-PD controls (n=24)	PKG worn for 6 nights	Polysomnography (PSG) for sleep assessment and Parkinson's Disease Sleep Scale 2 (PDSS-2) questionnaire (n=35 PwP)	The PKG score combining the % time asleep and the median time immobile predicted normal and abnormal sleep (according to the polysomnography) with 100% selectivity and sensitivity. 2/24 non-PD controls had abnormal sleep according to the PKG, one of which gave a history of restless legs. Amongst PD patients 28% had normal sleep according to the PKG criteria. In those interviewed, PKG values had a good correlation with the PDSS-2 scale (r=250.49).

Study details	Study design and funding source	Population	Intervention	Comparator(s)	Results
Horne, 2016c[43] Location: not stated	Retrospective cohort study Funding: not stated	PwP (n=200)	PKG worn for 6 days	Clinical assessment for the presence and nature of tremor	A % time that tremor was present (between 09:00 and 18:00) ≥0.8 provided a high sensitivity (92.5%) and selectivity (92.9%) in identifying tremor. False negatives were mainly low amplitude kinetic or postural tremor which were frequently not apparent to the patient or tremors that did not affect the upper limb. A % time that tremor was present ≥1 indicated a high likelihood of the presence of clinically meaningful tremor and a "grey zone" was identified between 0.6 and 1.0. Tremor did not produce false increase in dyskinesia score in this sample of 200.
Lina, 2020[58] Location: not stated	Prospective or retrospective cohort study Funding: not stated	PwP (n=100)	PKG worn for ≥6 days	UPDRS III	There was significant correlation between PKG bradykinesia score and UPDRS III, including UPDRS III total scores, UPDRS III-bradykinesia scores and UPDRS III-rigidity scores (Pearson's correlations coefficients: 0.479-0.588, $p<0.05$). There was also significant correlation between PKG percent time tremor score and UPDRS III-tremor scores and UPDRS II-tremor scores ($r=0.223$, $r=0.343$, $p<0.05$). Subgroup analysis showed that early stage (H-Y stage 1-2) or early disease course (<3 years) PKG bradykinesia score and UPDRS III scores were better correlated ($r^2=0.465$, $r^2=0.441$, $p<0.05$).
Margolesky, 2017[60] Location: not stated	Prospective or retrospective cohort study Funding: not stated	PwP on continuous enteral carbidopa/levodopa (CD/LD) infusion therapy (n=2)	PKG worn for 6 days prior to initiation of CD/LD therapy and after a 3-month titration period of enteral CL/LD therapy	Patient report	Patients' subjective results were not fully reflected in the objective PKG results. Patient 1 noted mild dyskinesias and the PKG noted an increase in dyskinesia. Patient 2 noted moderate dyskinesias and the PKG device noted no change in dyskinesia but an increase in percent time with tremor.

Abbreviations: ADL, activities of daily living; AIMS, Abnormal Involuntary Movements Scale; AS, Apathy Scale; BDI, Beck Depression Inventory; BIS/BAS, Behavioural Inhibition Scale/Behavioural Activation Scale; BKS, bradykinesia score; CD/LD, carbidopa/levodopa; DKS, dyskinesia score; ESS, Epworth Sleepiness Score; FDS, fluctuations dyskinesia score; FS, fluctuation score; HADS, Hospital Anxiety and Depression Scale; MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease

Rating Scale; NMSQuest, Non-Motor Symptom Questionnaire; PD, Parkinson's disease; PDQ8, Parkinson's Disease Questionnaire-8; PDQ39, Parkinson's Disease Quality of Life 39 Questions; PDSS, Parkinson's Disease Sleep Scale; PKG, Personal KinetiGraph; PSG, polysomnography; PTB, percent time in bradykinesia; PTD, percent time in dyskinesia; PTI, proportion of time immobile; PTT, percent time tremor; PwP, people with Parkinson's disease; QUIP, Questionnare for Impulsive-Compulsive Disorders in Parkinson's Disease; STAI, State Trait Anxiety Inventory; UDysRS, Unified Dyskinesia Rating Scale; UPDRS, Unified Parkinson's Disease Rating Scale; WOQ9, 9-item Wearing-Off Questionnaire.

STAT-ON (3 full papers, 1 abstract)

Table 55 Data from STAT-ON association studies

Study details	Study design and funding source	Population (incl. N)	Intervention	Reference standard/ comparator(s)	Brief results
Full papers					
Perrote, 2021[79] Argentina	Retrospective cohort study Funding: None	PwP (n=11)	STAT-ON (not stated in paper, but in Sense4Care submission)	Self-administered movement diary	The mean hours monitored was greater by the Holter than that recorded by the movement diary (60 ± 9.89 vs 40 ± 16.4, p<0.001). The report of freezing of gait episodes and hours in the ON state were higher with the Holter compared to the movement diary.
Rodriguez-Molinero, 2017[83] Spain, Italy, Israel and Ireland	Prospective cohort study Funding: The European Commission and partially supported by the Instituto de Salud Carlos III-Ministerio de Economia y Competividad and the European Regional Development Fund (5 authors are shareholders of Sense4Care)	PwP (n=75) asked to walk both in the Off and the On state in the patient's home	STAT-ON (not stated in paper, but on Sense4Care website)	Motor section of the UPDRS III administered in both motor phases	Correlation between UPDRS III and algorithm outputs was moderate (rho -0.56, p<0.001). Correlation between the algorithm outputs and the gait item in the UPDRS III was good (rho -0.73, p<0.001). The factorial analysis of the UPDRS III has repeatedly shown that several of its items can be clustered under the so-called Factor 1: "axial function, balance, and gait." The correlation between the algorithm outputs and this factor of the UPDRS III was -0.67 (p<0.01).
Rodriguez-Molinero, 2019[85]	Prospective cohort study	PwP (n=13) performing normal daily life activities	STAT-ON (not stated in paper, but in	Clinical assessment (video recording used for labelling the signal by a trained	The correlation coefficient between the sensor output and UDysRS result was 0.70 (95% CI: 0.33 to 0.88, p=0.01). Since the sensor was located on the waist,

Study details	Study design and funding source	Population (incl. N)	Intervention	Reference standard/ comparator(s)	Brief results
Spain, Italy, Israel and Ireland	Funding: Instituto de Salud Carlos III-Ministerio de Economia y Competividad and the European Regional Development Fund (5 authors are shareholders of Sense4Care)	(for an average period of 30 minutes) at home Possible patient overlap with other REMPARK studies	Sense4Care submission)	expert) determining the severity of dyskinesia through the Unified Dyskinesia Rating Scale (UDysRS)	the correlation between the sensor output and the results of the trunk and legs scale sub-items was calculated: 0.91 (95% CI: 0.76 to 0.97, p<0.001).
Abstracts					
Caballol, 2020[76] Spain	Prospective cohort study Funding: not stated	PwP (n=39) Dates: not stated	STAT-ON worn for one week (device not stated in abstract, but abstract in Sense4Care submission)	Patient report	74% of patients reported having motor fluctuations, 31% freezing of gait and 54% dyskinesia. According to the information provided by the sensor, 100% of patients had motor fluctuations, 61% freezing of gait and 79% dyskinesia. The proportion of patients reporting motor fluctuations increased to 79% after returning the device. According to PD specialist experience, all patients who still reported not having motor fluctuations actually presented with them, when analysing clinical symptoms and data provided by the sensor.

Abbreviations: PD, Parkinson's disease; PwP, people with Parkinson's disease; UDysRS, Unified Dyskinesia Rating Scale; UPDRS, Unified Parkinson's Disease Rating Scale.

Kinesia 360 (0 full papers, 0 abstracts)

KinesiaU (0 full papers, 0 abstracts)

PDMonitor (0 full papers, 1 abstract)

Table 56 Data from PDMonitor association studies

Study details	Study design and funding source	Population (incl. N)	Intervention	Reference standard/ comparator(s)	Brief results
Abstracts					
Kostikis, 2020[93] Greece and Italy	Prospective cohort study Funding: not stated	PwP (n=30)	PDMonitor in the clinic for 3 hours	Clinical assessment by a PD expert physician every half hour using UPDRS part III and AIMS	The device accurately detected and estimated the severity of arm bradykinesia (r^2=0.46 with UPDRS items 23, 24, 25), dyskinesia (accuracy 90% compared to AIMS score), gait impairment (r^2=0.6 with UPDRS item 29), wrist tremor (accuracy 89% and r^2=0.67 with UPDRS item 20), leg tremor (accuracy 93%) and freezing of gait (accuracy 93% compared to UPDRS item 14). 900-hour wearability study was also conducted with PwP (n=10) and healthy volunteers (n=19) who wore PDMonitor at home. Users found it relatively easy to wear the device.

Abbreviations: AIMS, Abnormal Involuntary Movements Scale; PD, Parkinson's disease; PwP, people with Parkinson's disease; UPDRS, Unified Parkinson's Disease Rating Scale.

9.4.3 Intermediate impact

PKG (8 full papers, 17 abstracts)

Table 57 Data from PKG studies of intermediate impact

Study details	Study design and funding source	Population	Intervention	Comparator(s)	Results
Full papers					
Dominey, 2020[28] (some data extracted from Dominey, 2018b abstract[177] and Carroll, 2019 letter[172] which have overlapping patients with this study) UK	Retrospective cohort study Funding: not stated (PKG recordings were provided by GKC or funded by a licence arrangement with GKC)	PwP (n=166; 78 new patients and 88 follow up) Dates: July 2015 to January 2018 Reported in Dominey, 2018b abstract[177]: PwP (n=216; 104 new patients, 5 complex care and 107 follow up). Dates: July 2015 to January 2018 Reported in Carroll, 2019 letter[172]: PwP (n=209). Dates: July 2015 to July 2017	PKG worn for 6 days	-	Treatment recommendations were made by reporters for 152/166 patients (92%) with the most common changes relating to dopamine replacement and advice on sleep hygiene and bowel management, for example upon detection of dose failure. Final treatment outcomes obtained retrospectively from follow-up letters were available for 133/166 reports (80%); treatment recommendations were implemented for 83/114 patients (73%), with advanced therapy in 6, additional motor agent in 34 and additional non-motor agent in 16. Reported in Dominey, 2018b[177] (abstract): The most frequent purpose of the PKG was to investigate medication response (55%). There were remotely-implemented treatment changes made in 93% of cases. Costs calculated by the NHS business advisory service: implementation of the PKG in routine PD care has the potential to reduce routine consultant follow-up appointments by 50%, leading to an estimated saving of £104,000pa per 250 patients. Reported in Carroll, 2019[172] (letter): Information from the PKG confirmed initial judgement in 54.5% cases and provided additional information in 45.5% cases.

Study details	Study design and funding source	Population	Intervention	Comparator(s)	Results
Evans, 2020a[32] (some data extracted from Evans, 2019b abstract[180] which has overlapping patients with this study) UK	Pilot cohort study (PKG recordings taken prior to enrolment) Funding: Bevan Commission	PwP (n=61 who had a PKG within the last 2 months and face-to-face appointment due in 1-2 months) Dates: From September 2018	PKG (used in a virtual clinic appointment)	Face-to-face clinic appointment	A consultation was deemed successful if the clinician felt that the outcome of the consultation was likely to have been the same as a face-to-face clinic. This could include a decision to change medications, a referral to another multidisciplinary team member or a decision to follow-up only. If the face-to-face clinic appointment was required within 8 weeks after the virtual clinic, it was considered unsuccessful. By this definition 48/61 appointments (79%) were successful. Reasons that the consultation was unsuccessful included complex phase of disease (n=5), problems with the PKG (n=5), needing a blood pressure reading (n=2) and speech problems (n=1). Face-to-face clinic template has a combination of 40 minute new patient and 20 minute follow-up slots. Virtual clinic appointments had an average phone consultation length of 12 minutes, but an administration time (PKG to be reviewed and interpreted prior to the call, pro-forma filled in and letter typed) of 10 minutes per patient; total clinic time of 22 minutes, compared with a regular follow-up slot of 20 minutes (not including dictation and typing of the clinic letter). Colleague consensus is that face-to-face appointments often run late, longer than the 20 minute slot allocated and the extra administration time can vary from 30 minutes to 2 hours. Of the 61 consultations, 35 of the previously planned face-to-face contacts could be postponed a median time of 6 months. A face-to-face follow-up appointment in movement disorder clinic costs £116 including the premises, support staff and clinician time. Currently the cost of each PKG is £225, including the postage of the data logger to the patient, postage back to GKC and the PKG report made available via the online portal. Even without accounting for the cost of a clinician's session, this makes virtual clinics using PKG appear more expensive than a normal clinic. However, this does not take into account the value-added

Study details	Study design and funding source	Population	Intervention	Comparator(s)	Results
					features mentioned above, reduced use of ambulance transport and new patient slots created to reduce waiting lists.
Farzanehfar, 2018[35] Australia	Prospective cohort study Funding: Global Kinetics Corporation	PwP (n=103) Dates: not stated	PKG worn for 6-7 days	Clinical assessment by neurologist	After reviewing the patient in conjunction with the PKG, the study neurologist agreed with the pre-reporting of the PKG in 93/103 cases (90%). In 63 (61%) of these cases the PKG added to the clinical findings to an extent that the therapeutic decision was influenced. There was artefactual elevation of the BKS or DKS plot in 10 cases, mostly due to exercise (3 cases) and increased somnolence (5 cases). In 9 cases, these artefacts were noted and reported and thus would not have affected therapeutic decisions. If the PKG had not been acted on without consideration of the interpretation, then it may have led to the changing of a dose at the time that sleep or exercise occurred. A low frequency tremor caused artefactual elevation of the dyskinesia score in one case but this was noted by the PKG reporter. The PKG did fail to detect truncal dyskinesia in one case but this did not alter the therapeutic decision making. At the beginning of the study 23/103 PwP had controlled motor function, according to the neurologist's clinical judgement (based on history, examination and inspection of the PKG), and 80 PwP had uncontrolled motor function. Adjustment of oral therapy was attempted in 40 of these 80 PwP (uncontrolled), 9 were immediately referred for advanced therapy, no attempt was made in 5 cases because of risk of contraindications and 26 did not complete the study (protocol violations).
Joshi, 2019a[48] USA	Prospective cohort study Funding: Global Kinetics Corporation	PwP (n=63; 85 routine care visits) Dates: Not stated	PKG worn for 6 days	Clinical assessment (discussion of PD symptoms with patient and a motor examination)	In 48% of patients the PKG reported a symptom not reported by the patient. 24% of patients reported a symptom that didn't appear in the PKG report.

Study details	Study design and funding source	Population	Intervention	Comparator(s)	Results
					Data from the PKG was used to make changes in treatment plans in 50 patients (79%). The most common treatment changes included the addition of at least one medication or changed dosage and timing of medications.
Krause, 2021[56] USA	Retrospective cohort study Funding: None (1 author serves as a consultant for Global Kinetic Corporation)	PwP (n=104; 170 PKG reports) Dates: 1 December 2016 to 30 October 2018	PKG worn for 7 days	Clinical assessment by a movement disorders specialist	PKG complemented patient input in 141/170 PKG reports (82.9%) and led to medication changes in 100/141 (71%) of the complimented inputs. Of these medication changes, 79 led to increase in medications and 23 led to the introduction of a new drug; 7 of which were amantadine immediate or extended release for dyskinesia. 6 PKG encounters led to decrease in medication; 4 because of levodopa induced dyskinesia and 2 for lack of response. Some encounters led to more than one medication change (hence 108 medication changes resulting from 100 encounters resulting in medication change).
Nahab, 2019[62] USA	Prospective cohort study Funding: not stated	PwP (n=28) clinically stable patients using levodopa who attended both routine visits Dates: 2 June 2016 to 16 March 2017	PKG worn for 6 days	Routine clinical assessment by a movement disorder specialist (including symptom review, medication review and routine clinical exams), undertaken twice, with UPDRS data reviewed by the movement disorder specialist after the second visit	PKG revealed a higher degree of symptom severity than was noted by clinical history alone in 18 patients (64%) at visit 1 and 8 patients (29%) at visit 2, resulting in clinical management plan changes. Medication changes included adding a new medication (6 instances), stopping a medication (2), increasing (14) or decreasing (1) medication dose or adjusting dose timing (5). 64% of patients had an increase in levodopa dose; 11% had a dose reduction.
Santiago, 2019[66] USA	Prospective physician survey Funding: Global Kinetics Corporation	Physicians of PwP (n=4 movement disorder specialists who	PKG worn for 6 days	Clinical consultation alone (routine clinic visit before reviewing PKG data)	Physicians targeted PKG use in patient populations they believed continuous objective measurement would improve the value of clinical encounters. Patients generally fell into one of four categories: first patient visit in clinic; patients with PD symptom

Study details	Study design and funding source	Population	Intervention	Comparator(s)	Results
	provided PKG System product for use in this research project, research service support and funds for manuscript submission	ordered 143 PKGs on 89 patients; 112 completed surveys on 81 patients were included in the analysis) Dates: December 2015 to July 2016			fluctuations; patients with indeterminate history; and patients considering or using DBS or Duopa. Of 112 completed physician surveys, 46 (41%) indicated the PKG provided relevant additional information sufficient to consider adjusting their therapeutic management plan; 66 (59%) indicated the PKG provided no further information to support a therapeutic decision differing from that made during a routine clinic visit. Upon further review of these 46 surveys, 36 surveys (78%) stated that the information provided by the PKG ultimately resulted in an alteration in patient care, whereas 10 surveys stated the PKG provided additional information but that no alteration in patient care occurred based on this information. Overall, 36/112 patients (32%) had an alteration to patient care as a result of PKG. The PKG most commonly yielded new information on daily off time [50% (18/36)].
Sundgren, 2021[68] Sweden	Prospective cohort study Funding: Global Kinetics Corporation	PwP (n=66) Dates: March 2018 to February 2020	PKG worn for 6 days	Clinical assessment (before reviewing PKG data)	After clinical assessment, a treatment change was recommended for 52/66 PwP; for the remaining 14 patients the current treatment was planned to be left unchanged. After PKG review, the treatment plan proposed after the clinical assessment was changed in 21/66 PwP (31.8%). The clinical assessment and the PKG review differed frequently (defined as non-identical choices among the pre-defined options), mainly regarding overall presence of motor problems (67%), characteristics of bradykinesia/wearing off (79%), dyskinesia (35%) and sleep (55%). Almost all patients reported good compliance and no tendency to impulse control disorder. For these items there were few

Study details	Study design and funding source	Population	Intervention	Comparator(s)	Results
					disagreements between the clinical and PKG assessments (3% for impulse control disorder and 5% for compliance).
Abstracts					
Andriola, 2017[18] USA	Prospective cohort study Funding: not stated	PwP (n=49) Dates: May 2016 to March 2017	PKG worn for 6 days	Clinical assessment conducted during a routine PD follow-up visit	3 patients were excluded from the analysis because the recording was not complete. Reason for PKG: confirm need for DBS (n=11), optimisation of DBS (n=12), other routine therapy assessment (n=23). PKG confirmed the need for DBS in 10/11 patients (91%). 8/12 post-DBS patients (67%) had clinical management adjustments post-PKG. 14/23 non-DBS patients (61%) subsequently had clinical management plan changes post-PKG and 3 (13%) were identified as DBS candidates. Overall, clinical management changes were made in 34/46 patients (74%) after PKG.
Bergquist, 2019[20] Sweden	Randomised controlled trial (substudy of the WestPORTS study) Funding: not stated	PwP (n=121 [stated in abstract, however, 61+59=120]) Dates: not stated	Managing physician provided with PKG report (n=61)	Managing physician received results of patients' self-rating using PD Quality of life (PDQ8) and Non Motor Symptom Questionnaire (NMSQ) self rating (n=59)	Patients were re-evaluated with PKG and self-ratings 3 months after the visit, changes in medication between the visit and follow up were identified based on medical records and reported use. Over 2/3 patients could be classified as 'uncontrolled' based on the PKG. There was no difference in the frequency or type of management change between the two groups.
Chhabria, 2018[25] Location: not stated	Retrospective cohort study Funding: not stated	PwP (n=50) Dates: not stated	PKG	-	Reason for prescribing the PKG watch was most commonly difficulty distinguishing timing of tremor and dyskinesia, unclear off periods, unclear response to doses of levodopa, and periods of somnolence.

Study details	Study design and funding source	Population	Intervention	Comparator(s)	Results
					Over 50% of patients that wore the PKG watch had changes made to their medications. Compliance with individual doses of medications seemed improved.
Duja, 2021a[29] Location: not stated	Retrospective cohort study Funding: not stated	PwP (n=50), described as advanced disease Dates: not stated but it was 'the last four years and during pandemic…'	PKG worn for 7 days	-	As a result of PKG 31.11% patients had their L-Dopa increased, 22.22% had their medication timing adjusted. 4.44% had COMT inhibitor added, another 4.44% had MAO B inhibitor added and 2.22% had dopamine agonist increased. 4.44% had their Apo-morphine dose adjusted and 17.78% were referred for advance treatment (half for apo-morphine, rest for Duodopa and DBS). 22.22% had more than one adjustment. Patient satisfaction was high.
Duja, 2021b[30] Location: not stated	Retrospective cohort study Funding: not stated	PwP (83 patients had PKG; currently data is available for 48 patients) Dates: not stated	PKG worn for 7 days	-	Changes in medical management were made for 41 patients (85.42%). 18 (43.9%) had their medications increased, 16 (39%) had medication changed to a different group of medication. 4 (9.7%) were referred for advance treatment and 3 (7.3%) had their treatment reduced in view of failure to respond and alternate diagnosis was made. No changes were made in the management of 7 patients (14.58%).
Evans, 2019a[33] UK	Retrospective cohort study Funding: not stated	PwP (n=28) Dates: not stated	PKG (used in a virtual clinic appointment)	-	82% of appointments are successful, where a clinical decision could be made. This could be a medication change (n=13), or no action required (n=10). The reasons that clinical decisions could not be made included needing a BP reading (n=2) and complex stage of disease (n=2).
Farzanehfar, 2017a[34] Location: not stated	Prospective feasibility study Funding: not stated	PwP (n=28 where patient and doctor perceived that PD symptoms were controlled) Dates: not stated	PKG	Clinical assessment	4/28 patients were identified as optimally controlled by both the clinical history and PKG. 24 were uncontrolled (3 with dyskinesia and 21 with bradykinesia); 16 were identified as uncontrolled by both the clinical history and PKG, 8 were identified as uncontrolled only via the PKG.

Study details	Study design and funding source	Population	Intervention	Comparator(s)	Results
Horne, 2016a[40] Location: not stated	Interim findings of a prospective cohort study Funding: not stated	PwP (n=19 considered to be well controlled by general neurologists) Dates: not stated	PKG	Assessment by a movement disorder specialist	3 patients were considered well controlled and 16 patients were considered poorly controlled and consequently treatment was changed. The movement disorder specialist would have not recognised 6 patients as poorly controlled without the PKG and in 10 patients the movement disorder specialist recognised the same symptoms as the PKG. There were no examples in which the PKG failed to recognise treatment symptoms. 15/16 poorly controlled patients (94%) were treated for bradykinesia or fluctuations (wearing-off).
Horne, 2018[45] Australia	Pilot prospective cohort study Funding: not stated	PwP (n=103) Dates: not stated	PKG	Clinical assessment	The PKG motor scores of 78% of participants were outside the target for optimum control and changes in oral therapy were recommended in 74%, advanced therapy in 12% and treatment was contraindicated in 9%. At the end of the study 48% were in target (22% at outset and a further 26% by treatment change and not including those referred for advanced therapy – 19%). Advanced therapy had not previously been discussed in these patients. Contraindications prevented therapy change in 17%.
Jones, 2018[47] Location: not stated	Retrospective cohort study Funding: not stated	PwP (n=70) with either self-reported severe or worsening symptomatology or an uncertain response to a treatment change and a clinical query over the	PKG	Clinical assessment	Increasing symptoms and wearing-off were the commonest reasons for undertaking PKG. PKG was consistent with clinical impression in 53 patients (76%). It gave additional clinically-relevant information (unidentified bradykinesia or dyskinesia) in 18 patients (25%). Clinical decision changed in 24 patients (34%) based on the results of PKG. 4 patients (6%) clinically considered to require an advanced treatment had current medication titrated instead. 5

Study details	Study design and funding source	Population	Intervention	Comparator(s)	Results
		next best management course Dates: December 2015 to February 2017			patients (7%) in whom advanced treatments were not being considered pre-PKG were deemed to require them and were subsequently referred. In 2 patients the PKG demonstrated a poor response to medication which led to revision of the diagnosis.
Klingelhoefer, 2016b[53] Location: not stated	Prospective cohort study Funding: not stated	PwP (n=82) Dates: Not stated	PKG worn for 6 days	Routinely completed self-ratings (Hauser diary and other measures)	68.3% patients were compliant with PKG and Hauser diary assessment, 15.9% were not compliant concerning both PKG and Hauser diary. 11% patients were compliant with PKG but not Hauser diary assessment, whereas 4.9% were compliant concerning Hauser diary but not PKG assessment.
Langston, 2017[57] USA	Prospective or retrospective cohort study Funding: not stated	PwP (n=89; 123 movement disorder surveys completed, 44 patients had multiple PKGs) Dates: Not stated	PKG worn for 6 days	Clinical assessment by a movement disorders specialist	Physicians reported that the PKG provided additional information not available from clinical consultation alone in 38% of visits overall and in 53% of visits for patients noted as having fluctuations and/or unclear histories. Overall clinical management changes were made in 58% of visits. Physicians were more likely to make a change when the PKG provided additional information (78%) compared to only 44% of cases when PKG did not provide additional information.
Lynch, 2018a[59] Australia	Prospective or retrospective cohort study Funding: not stated	PwP (n=80 uncontrolled patients) Dates: not stated	PKG	-	33 of 80 uncontrolled patients were treated with oral therapy, with the assistance of PKG.
Rao, 2019[64] UK	Retrospective cohort study Funding: not stated	PwP (n=37; 45 PKG reports) Dates: February 2016 to May 2018	PKG	Clinical assessment	There were multiple indications for PKG for most patients, including dose failure (14 patients), off periods and wearing off (11 patients), possible off dystonia or dyskinesia (5 patients), freezing, falls and relationship with medication (6 patients), bradykinesia and pain (7 patients) and to quantify dyskinesia (3 patients).

Study details	Study design and funding source	Population	Intervention	Comparator(s)	Results
					On clinical grounds, it was felt that 10/36 patients were likely to need complex treatment before PKG (one was already on apomorphine – Apo-go pen). After PKG, 4 patients started complex treatment (Apo-go pen), 1 is being assessed for DBS, 5 did not need complex treatment but changed their medication with increase in dosage of L-dopa in 4 patients and a reduction in dosage in 1 patient. The authors envisage that 2 of these 5 patients are likely to need a form of complex treatment in the near future. Cost of postponing advanced treatment for 5 patients: Apo-go pump (average cost of £5,400/pump/year) led to a saving of £27,000/year. Postponement of apomorphine (Apo-go) pen treatment (average cost of £3,200/year) led to a saving of approx. £16,000/year. 35 patients changed their PD medication after PKG. Furthermore, 13 were found to have mild to significant dyskinesia with 6 needing a reduction in drug doses. 26 patients were under treated, mostly with off-periods, with 23 needing an increase in drug dosage.
Thakur, 2017[70] USA	Retrospective cohort study Funding: not stated	PwP (n=51) Dates: November 2015 to November 2016	PKG worn for 6 days	Clinical assessment during routine PD follow-up by Movement Disorder Specialists	2 patients did not tolerate the PKG due to wristband irritation and 5 patients were lost to follow up or their appointment was delayed. Physicians reported that the PKG provided information not available from the clinical consultation that drove a clinical management plan change in 21/44 patients (47%). Common clinical management changes were increase or reduction in medication dose and/or frequency in 19/21 patients (91%). The PKG provided supporting evidence in 2 patients for recommending advanced therapies with DBS.
Thomas, 2019b[71]	Retrospective cohort study	PwP (n=256 evaluations)	PKG	Clinical assessment	209 completed evaluations provided information about the impact of the PKG test on clinical decision making. The most frequent

Study details	Study design and funding source	Population	Intervention	Comparator(s)	Results
UK	Funding: not stated	Dates: not stated			reasons for performing a PKG were 'increased symptoms' and 'wearing-off'. Information from the PKG confirmed initial clinical judgement in 54.5% of cases and provided additional information to inform the clinical decision in 45.5% cases. Changes in decision making included 10 patients where the PKG results prompted a treatment change when clinicians initially predicted no changes were necessary, and 15 patients who went on to receive advanced therapies where oral medication titration had initially been considered. Conversely, information from the PKG prompted clinicians to try other options in 18 patients originally considering advanced therapies.
Wilson, 2017[73] Location: not stated	Prospective cohort study Funding: not stated	PwP (n=10 where follow-up data available) Dates: not stated	PKG worn for 7 days	Patient 7 day symptom diary	In 2 patients with early stage disease bradykinesia was over reported by PKG; on clinical assessment and with patient diaries there was no reported bradykinesia. 1 patient who felt under treated was identified as having significant periods of dyskinesia, and PKG report was used to explain he was in fact overtreated. 1 patient who had reported freezing episodes was found to have significant episodes of bradykinesia; PKG helped guide apomorphine use. In 3 patients with advanced disease PKG showed significant bradykinesia; 1 patient had previously declined increase in medication dose and subsequently was persuaded to comply, following PKG study. 1 of these patients had recurrent erroneous activation of the medication sensor, which may reflect impulse control disorder. 1 patient with cognitive impairment failed to report his bradykinesia, which was detected by PKG.

Abbreviations: BKS, Bradykinesia Score; BP, blood pressure; DBS, deep brain stimulation; DKS, Dyskinesia Score; GKC, Global Kinetics Corporation; MAO-B, monoamine oxidase Type B; NMSQ, Non Motor Symptom Questionnaire; PD, Parkinson's disease; PKG, Personal KinetiGraph; PwP, people with Parkinson's disease; UPDRS, Unified Parkinson's Disease Rating Scale.

STAT-ON (0 full papers, 0 abstracts)

Kinesia 360 (1 full paper, 0 abstracts)

Table 58 Data from Kinesia 360 studies of intermediate impact

Study details	Study design and funding source	Population	Intervention	Comparator(s)	Results
Full papers					
Isaacson, 2019[89] USA	Pilot randomised controlled trial Funding: UCB Pharma	PwP with insufficientl y controlled motor symptoms, prescribed transdermal rotigotine (n=39) Dates: March 2017 to January 2018	Kinesia 360 data used to supplement standard care in adjusting rotigotine dosage (n=19). Kinesia 360 was used throughout the day on at least two consecutive days in weeks 1, 2, 3, 4 and 11	Standard care to titrate the optimal rotigotine dosage (n=20)	Mean rotigotine dose was higher in the Kinesia 360 arm than the usual care arm (4.8 vs 3.9 mg/24 hours). Mean rotigotine dosage increase (+2.8 vs +1.9 mg/24 hour) and mean number of dosage changes (2.8 vs 1.8 changes) during the study were also higher in the Kinesia 360 arm.

Abbreviations: PwP, people with Parkinson's disease.

KinesiaU (1 full paper, 0 abstracts)

Table 59 Data from KinesiaU studies of intermediate impact

Study details	Study design and funding source	Population	Intervention	Comparator(s)	Results
Full papers					
Hadley, 2021[92] USA	Prospective cohort study Funding: National Institutes of Health (2 authors are employees of and own stock in Great Lakes Neuro-Technologies)	PwP (n=16) undergoing therapy changes	KinesiaU (alongside clinical judgement) worn for at least 3 days in the week prior to instituting a therapy change and for at least 3 days during weeks 3 and 5 after the therapy change	N/A	14 patients successfully used the KinesiaU system for the duration of the study; 2 did not complete the recordings due to user difficulty or technical issues. The 14 participants averaged 4.9 assessments per day for 3 days per week during the study. 13 of the patients who successfully used the KinesiaU system returned for the follow-up visit with the clinician; 1 patient could not return due to Covid-19 travel difficulties. The clinician reviewed the KinesiaU reports with each patient and made a therapy recommendation based on the reports and clinical judgement. 8 patients demonstrated improvements from their new therapy and were instructed to continue with it, while 5 were instructed to discontinue (due to lack of benefit or side effect) and return to their previous therapy/dose. 3 patients were prescribed levodopa inhalation powder (2 improved, 1 discontinued), 1 patient was prescribed trihexyphenidyl (discontinued), 3 patients were prescribed istradefylline (1 improved, 2 discontinued), 1 was prescribed increased melatonin dose (improved), 2 were prescribed exercise (improved), 2 were prescribed an increase in carbidopa-levodopa dose (1 improved, 1 discontinued) and 1 patient was prescribed increased doses of carbidopa-levodopa and trihexyphenidyl (improved).

Abbreviations: PwP, people with Parkinson's disease.

PDMonitor (0 full papers, 0 abstracts)

9.4.4 Clinical outcomes

PKG (6 full papers, 4 abstracts)

Table 60 Data from PKG studies with clinical outcomes

Study details	Study design and funding source	Population	Intervention	Comparator(s)	Results
Full papers					
Farzanehfar, 2018[35] Australia	Prospective cohort study Funding: Global Kinetics Corporation	PwP (n=103) Dates: not stated	PKG worn for 6-7 days	Clinical assessment by neurologist	33/80 PwP (uncontrolled) were treated with oral therapy and it was possible to bring the motor scores and function under control in 14 cases. In 19/33 cases it was not possible to reach therapeutic targets by the end of the study. After attempting treatment 7 of these cases were reclassified: 3 were referred for advanced therapy and 4 were reassigned to the 'treatment contraindicated' group because they could not tolerate any change in medications. Significant improvements from baseline to final visit were observed in the 33 treated patients: UPDRS I (effect size=2, p=0.0007) UPDRS II (effect size=4, p=0.03) UPDRS III (effect size=3, p=0.0009) UPDRS IV (median did not change, p=0.01) Total UPDRS (effect size=8, p<0.0001) NMS questionnaire (median did not change, p=0.02) MOCA (effect size=2, p=0.02) Improvements in quality of life (PDQ39) were significant in the subgroup of 14 patients whose symptoms were brought under control (effect size=8.5, p=0.03), but not the full population of 33 treated patients (effect size=10, p=0.08).

Study details	Study design and funding source	Population	Intervention	Comparator(s)	Results
Joshi, 2019a[48] USA	Prospective cohort study Funding: Global Kinetics Corporation	PwP (n=63; 85 routine care visits) Dates: Not stated	PKG worn for 6 days	Clinical assessment (discussion of PD symptoms with patient and a motor examination)	No serious adverse events or adverse device effects were reported.
Krause, 2021[56] USA	Retrospective cohort study Funding: None (1 author serves as a consultant for Global Kinetic Corporation)	PwP (n=104; 170 PKG reports) Dates: 1 December 2016 to 30 October 2018	PKG worn for 7 days	Clinical assessment by a movement disorders specialist	Out of 104 patients, 49 had more than 1 PKG encounter; 37 had 2 encounters (mean interval 6.3 months between encounters), 7 had 3 encounters (mean interval 11.4 months between first and last encounter) and 5 had 4 encounters (mean interval 15.8 months between first and last encounter). Most patients undergoing 3 or 4 PKG encounters did not reach a controlled state as defined by PKG until the 3rd or 4th encounter, suggesting that repeated use of PKG might be needed to optimise motor control as therapy changes done after one encounter might not be enough.
Nahab, 2019[62] USA	Prospective cohort study Funding: not stated	PwP (n=28) clinically stable patients using levodopa who attended both routine visits Dates: 2 June 2016 to 16 March 2017	PKG worn for 6 days	Routine clinical assessment by a movement disorder specialist (including symptom review, medication review and routine clinical exams), undertaken twice, with UPDRS data reviewed by the movement disorder specialist after the second visit	Mean MDS-UPDRS III summary score significantly reduced (improved) from 28.9 at visit 1 to 24.1 at visit 2 ($p<0.028$). Mean MDS-UPDRS IV summary score reduced from 4.1 at visit 1 to 3.0 at visit 2 ($p=0.07$). Overall, PKG scores were similar between visit 1 and 2; 16 patients (57%) had improvement and 12 patients (43%) had worsening median BKS scores. Overall Hoehn and Yahr ratings were similar between visit 1 and visit 2; at visit 2, 5 patients (18%) were rated as having improved one Hoehn and Yahr stage and 6 had worsened one stage. On the Clinician Global Impression of Improvement (CGI-I) scale, the movement disorder specialist ranked 17/28 patients (61%) as having improvement, 9 (32%) as no change and 2 (7%) as minimally worse.

Study details	Study design and funding source	Population	Intervention	Comparator(s)	Results
					On the Patient Global Impression of Improvement (PGI-I) scale, 13/24 patients (54%) indicated their PD was improved, 9 (38%) as no change, 2 (8%) as minimally worse and 4 patients did not respond.
Sundgren, 2021[68] Sweden	Prospective cohort study Funding: Global Kinetics Corporation	PwP (n=66) Dates: March 2018 to February 2020	PKG worn for 6 days	Clinical assessment (before reviewing PKG data)	There were no significant differences in clinical variables when repeated after 3-6 months (mean score at baseline and follow-up) in PDCS (18.5, 18.8), NMSQ (9.0, 8.8), PDQ-8 (22.7, 21.5), EQ VAS (66.0, 66.7), BKS (27.9, 27.4), DKS (3.5, 3.2), FDS (8.5, 8.6). Overall change at follow-up (assessed using CGI-I Scale) was 3.6; a score of 4 represents no change, a lower score represents improvement.
Woodrow, 2020[17] Australia (12 clinics; 6 using PKG)	Blinded controlled trial (allocated based on convenience of clinic location) Funding: Parkinson's Victoria, Shake It Up Australia Foundation and the Michael J Fox Foundation (GKC provided the PKG and loggers as a grant in aid). One of the authors is the inventor of the PKG and a paid consultant to GKC. Two authors have a financial interest in GKC	PwP, ≥4 year duration or taking ≥4 doses of levodopa/day (n=154). Patients referred for device-assisted therapies were excluded from the study Dates: March 2018	Assessment using history, examination and PKG information (worn for 6 days) (PKG+; n=75) At the first consultation patients were assessed to decide whether their motor features were 'in target' (BKS target <26, DKS	Assessment using history and examination alone (patients wore the PKG logger for blinding purposes) (PKG-; n=79) As per the PKG+ arm, patients were assessed at the first consultation to decide whether treatment was adequate or whether further treatment was required. Patients requiring a treatment change were assessed again 5 weeks later; this was repeated until patients were 'in target' (with a maximum of 5 visits permitted), with the same	54/75 patients (72%) in the PKG+ arm and 57/79 patients (72%) in the PKG- arm were 'out of target' at the first consultation, therefore, had a treatment change and were re-assessed after 5 weeks. The median number of visits (2) was the same in both arms, however, there were significantly more visits in the PKG+ arm (p=0.01). In the subgroup of patients who were 'out of target' at the first consultation, the median number of visits in the PKG+ arm was 3 (IQR=3) vs 2 (IQR=2) in the PKG- arm (p=0.0009). There was a statistically significant improvement in mean UPDRS Total score (primary outcome) between the first and last visit in the PKG+ arm (59.6 vs 51.1; p=0.001), but the improvement in the PKG- arm (62.3 vs 57.4; p=0.10) did not reach statistical significance. A direct comparison of the final MDS-UPDRS Total score

Study details	Study design and funding source	Population	Intervention	Comparator(s)	Results
		to December 2019	target <7) or 'out of target'. If 'out of target', a plan for changing treatment was provided and patients were assessed again 5 weeks later; this was repeated until PKG data were 'in target' (with a maximum of 5 visits permitted) See paper for full 'out of target' criteria and treatment change caveats	caveats to changing treatment that applied to the PKG+ arm (see paper for further information)	between treatment groups (51.1 vs 57.4; p=0.02) was statistically significant. There was also a statistically significant improvement in MDS-UPDRS IV score (5.0 vs 3.5), MDS-UPDRS III score (35.1 vs 28.6) and PTOT score (19.9 vs 13.0) between the first and last visit in the PKG+ arm. However, there was no significant difference in PDQ39, SENS PD, NMSQ (amongst others) between the first and last visit in the PKG+ arm. Scores in the PKG- arm improved between the first and last visit, although none of the differences were statistically significant. 12% of the PKG+ group who were 'out of target' were not treated, compared with 30% of the PKG- group, suggesting that PKG had a larger influence on clinical decisions than history and examination alone. Similarly, in the PKG- arm, 52% of cases reported as 'in target' were treated, compared with 17% in the PKG+ arm. Clinical scores of 'in target' cases were similar between the two treatment groups and remained unchanged 3 months later (data not shown). In the subgroup of patients who were 'out of target' at the first consultation in the PKG+ arm (n=54), there was a statistically significant improvement in mean MDS-UPDRS Total (62.8 vs 51.1; p<0.001), MDS-UPDRS IV (5.6 vs 3.3; p<0.001), MDS-UPDRS III (36.5 vs 28.6; p<0.001), PDQ39 (28.1 vs 22.1; p=0.045) and PTOT

Study details	Study design and funding source	Population	Intervention	Comparator(s)	Results
					(23.8 vs 14.3; p=0.001) scores between the first and final visit. None of the scores changed significantly from first to final visit in the subgroup of patients who were 'out of target' at the first consultation in the PKG- arm (n=57). There were statistically significant increases in Levodopa Equivalent Daily Dose (LEDD) between the first and last visit in the PKG+ arm (675 vs 799; p=0.04) and the 'out of target' subgroup of the PKG+ arm (669 vs 823; p=0.02). The increases in LEDD between the first and last visit in the PKG- arm (760 vs 870) did not reach statistical significance (p=0.06) but the increase in LEDD was statistically significant in the 'out of target' subgroup of the PKG- arm (760 vs 933; p=0.02). There was no significant difference in final LEDD score between treatment groups. However, there was a statistically significant difference in the change in D2 agonist use between treatment groups (change in 33% patients in the PKG+ arm and 18% patients in the PKG- arm; p=0.0001). Subgroup results are also presented for the subgroup of patients who were 'out of target' due to bradykinesia.
Abstracts					
Farzanehfar, 2017a[34] Location: not stated	Prospective feasibility study Funding: not stated	PwP (n=28 where patient and doctor perceived that PD symptoms	PKG	Clinical assessment	Analysis of the 21 patients with uncontrolled bradykinesia showed statistically significant changes in the UPDRS III (p=0.005; median improvement = 7) and Total UPDRS (p=0.002; median improvement = 15) following intervention. In 8 patients recognised as poorly controlled only via the PKG, there was a statistically significant improvement in the UPDRS III (p=0.01; median

Study details	Study design and funding source	Population	Intervention	Comparator(s)	Results
		were controlled) Dates: not stated			improvement = 13) and Total UPDRS (p=0.01, median improvement = 13).
Horne, 2016a[40] Location: not stated	Interim findings of a prospective cohort study Funding: not stated	PwP (n=19 considered to be well controlled by general neurologists) Dates: not stated	PKG	Assessment by a movement disorder specialist	Clinically significant changes in patient outcomes were noted in the UPDRS, PKG scores and PDQ8.
Horne, 2018[45] Australia	Pilot prospective cohort study Funding: not stated	PwP (n=103) Dates: not stated	PKG	Clinical assessment	At the end of the study 48% patients were in target (22% at outset and 26% by treatment change, not including those referred for advanced therapy). In those in whom oral therapy was changed, total UPDRS and PDQ39 improved (effect size 8 and 10 respectively). MOCA scores also improved significantly.
Lynch, 2018a[59] Australia	Prospective or retrospective cohort study Funding: not stated	PwP (n=80 uncontrolled patients from Farzanehfar, 2018 – excluded as doesn't report data	PKG	-	Among the 33 patients treated with oral therapy after PKG, decreases were observed in: mean UPDRS II (-4; 9-13), mean UPDRS III (-3; 36-39), Percent Over Target (-8; 64-73) and PDQ39 (10; 19-29). It was estimated that over the relevant range of UPDRS II scores, a one-point reduction in UPDRS II correlates with an average of $430 in cost savings from lower resource utilisation. Improved disease management contributed to total resource utilisation cost savings of $1,719.42 per

Study details	Study design and funding source	Population	Intervention	Comparator(s)	Results
		on relevant outcomes) Dates: not stated			patient over a 12-month period. Using PKG efficacy for UPDRS III (-3), UPDRS II (-4), PTO (-8) and PDQ39 (-10), a QALY gain of between 0.10-0.12 was estimated over a 12-month period.

Abbreviations: BKS, Bradykinesia Score; CGI-I, Clinical Global Impressions – Improvement Scale; DBS, deep brain stimulation; DKS, Dyskinesia Score; EQ VAS, EuroQol Visual Analogue Scale; FDS, Fluctuations Dyskinesia Score; GKC, Global Kinetics Corporation; LEDD, Levodopa Equivalent Daily Dose; MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; MOCA, Montreal Cognitive Assessment; NMSQ, Non-Motor Symptom Questionnaire; PD, Parkinson's disease; PDCS, Parkinson's Disease Composite Scale; PDQ-8, Parkinson's Disease Questionnaire-8; PDQ39, Parkinson's Disease Quality of Life 39 Questions; PGI-I, Patient Global Impression of Improvement; PKG, Personal KinetiGraph; PTOT, percent time over target; PwP, people with Parkinson's disease; QALY, quality adjusted life year; SENS PD, Severity of predominantly Non-dopaminergic Symptoms in Parkinson's Disease; UDysRS, Unified Dyskinesia Rating Scale; UPDRS, Unified Parkinson's Disease Rating Scale.

STAT-ON (0 full papers, 0 abstracts)

Kinesia 360 (2 full papers, 0 abstracts)

Table 61 Data from Kinesia 360 studies with clinical outcomes

Study details	Study design and funding source	Population	Intervention	Comparator(s)	Results
Full papers					
Isaacson, 2019[89] USA	Pilot randomised controlled trial Funding: UCB Pharma	PwP with insufficientl y controlled motor symptoms, prescribed transdermal rotigotine (n=39) Dates: March 2017	Kinesia 360 data used to supplement standard care in adjusting rotigotine dosage (n=19). Kinesia 360 was used throughout the day on at least two	Standard care to titrate the optimal rotigotine dosage (n=20)	At week 12, there was a statistically significant improvement in UPDRS II in the Kinesia 360 arm compared with a slight worsening in the standard care arm (-2.1 vs 0.5; p=0.004). The difference in improvement in UPDRS III was not statistically significant between groups (-5.3 vs -1.0; p=0.134). There was no significant change in PDQ-39 score at week 12 in either study group (-5.1 vs -3.5; p=0.471).

Study details	Study design and funding source	Population	Intervention	Comparator(s)	Results
		to January 2018	consecutive days in weeks 1, 2, 3, 4 and 11		Change in PAM-13 score at week 12 (Kinesia 360 vs standard care): -4.6 vs -0.2; p=0.164 (no significant difference between groups). Mean rotigotine dosage increase from baseline to week 12 (Kinesia 360 vs standard care): +2.8 vs +1.9 mg/24 h. Mean number of dosage changes: 2.8 vs 1.8. 3 patients in the Kinesia 360 arm and 2 patients in the standard care arm discontinued rotigotine due to treatment-emergent adverse events.
Peacock, 2021[90] Canada	Randomised controlled trial Funding: not reported	PwP (n=25 – study suspended due to Covid-19) with bothersome tremor or dyskinesia identified as a treatment target at their most recent clinic visit Dates: May 2019 to March 2020	Telehealth (video-conference) follow-up care with data from in-home Kinesia 360 (worn for 3 days), by movement disorder neurologist, at baseline, 6 weeks, 3 months and 6 months (n=13)	Usual in-person follow-up care with clinical examination and review of 3 days of symptom diaries, by movement disorder neurologist, at baseline, 6 weeks, 3 months and 6 months (n=12)	The average change in PDQ-39 Summary Index score from baseline to completion (primary outcome) was -4.7 points in the telehealth group (95% CI: -10.2 to +0.7) and +0.9 (95% CI: -3.6 to +5.5) in the usual care group. Note: mean baseline PDQ-39 score was 29 in the telemedicine group and 25 in the usual care group. Secondary outcomes were not significantly different between groups (LEDD change from baseline (mean 32mg vs 52mg) and appointments per participant with sensor or diary data available (mean 2.2 vs 1.8)). Repeat measurement of MDS-UPDRS Part III was not completed due to suspension of face to face clinical and research visits, due to Covid-19.

Abbreviations: MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; PAM-13, 13-Item Patient Activation Measure; PDQ-39, 39-Item Parkinson's Disease Questionnaire; PwP, people with Parkinson's disease; UPDRS, Unified Parkinson's Disease Rating Scale.

KinesiaU (1 full paper, 0 abstracts)

Table 62 Data from KinesiaU studies with clinical outcomes

Study details	Study design and funding source	Population	Intervention	Comparator(s)	Results
Full papers					
Hadley, 2021[92] USA	Prospective cohort study Funding: National Institutes of Health (2 authors are employees of and own stock in Great Lakes Neuro-Technologies)	PwP (n=16) undergoing therapy changes	KinesiaU (alongside clinical judgement) worn for at least 3 days in the week prior to instituting a therapy change and for at least 3 days during weeks 3 and 5 after the therapy change	N/A	14 patients successfully used the KinesiaU system for the duration of the study; 2 did not complete the recordings due to user difficulty or technical issues. The 14 participants averaged 4.9 assessments per day for 3 days per week during the study. 13 of the patients who successfully used the KinesiaU system returned for the follow-up visit with the clinician; 1 patient could not return due to Covid-19 travel difficulties. The clinician reviewed the KinesiaU reports with each patient and made a therapy recommendation based on the reports and clinical judgement. 8 patients demonstrated improvements from their new therapy and were instructed to continue with it, while 5 were instructed to discontinue (due to lack of benefit or side effect) and return to their previous therapy/dose. 3 patients were prescribed levodopa inhalation powder (2 improved, 1 discontinued), 1 patient was prescribed trihexyphenidyl (discontinued), 3 patients were prescribed istradefylline (1 improved, 2 discontinued), 1 was prescribed increased melatonin dose (improved), 2 were prescribed exercise (improved), 2 were prescribed an increase in carbidopa-levodopa dose (1 improved, 1 discontinued) and 1 patient was prescribed increased doses of carbidopa-levodopa and trihexyphenidyl (improved).

Abbreviations: PwP, people with Parkinson's disease.

PDMonitor (0 full papers, 0 abstracts)

9.4.5 Patient, carer and clinician opinions

PKG (6 full papers, 6 abstracts)

Table 63 Data from PKG studies of patient, carer and clinical opinions

Study details	Study design and funding source	Population	Intervention	Comparator(s)	Results
Full papers					
Dominey, 2020[28] UK	Retrospective cohort study Funding: not stated (PKG recordings were provided by GKC or funded by a licence arrangement with GKC)	PwP (n=166; 78 new patients and 88 follow up) Dates: July 2015 to January 2018	PKG worn for 6 days	-	Patient opinion (n=62): 41/51 respondents (80%) valued the medication reminders and 23/39 (59%) rated use of the PKG as valuable in providing additional information to their clinical team. 24/40 respondents (60%) perceived the PKG results as reflective of their lived experience. 57/59 respondents (97%) were willing to continue using the PKG as part of their management, while 19/48 (40%) reported satisfaction at not having to travel to clinic.
Evans, 2020[32] UK	Pilot cohort study (PKG recordings taken prior to enrolment) Funding: Bevan Commission	PwP (n=61 who had a PKG within the last 2 months and face-to-face appointment due in 1-2 months) Dates: From September 2018 Reported in Evans, 2019b[180] abstract: PwP (n=30 patients who returned questionnaires).	PKG (used in a virtual clinic appointment)	Face-to-face clinic appointment	Patient satisfaction questionnaire (n=46): 41/46 respondents (89%) agreed or strongly agreed they were satisfied with the virtual clinic. Reported in Evans, 2019b[180] (abstract): 27/30 patients (90%) agreed or strongly agreed that they were satisfied with the virtual clinic and that their concerns were suitably addressed. 23/30 (77%) felt they could talk to the doctor as if it were a regular consultation and 19/30 (63%) would recommend a virtual clinic consultation to other PwP.

Study details	Study design and funding source	Population	Intervention	Comparator(s)	Results
		Dates: From September 2018			
Joshi, 2019[48] USA	Prospective cohort study Funding: Global Kinetics Corporation	PwP (n=63; 85 routine care visits) Dates: Not stated	PKG worn for 6 days	Clinical assessment (discussion of PD symptoms with patient and a motor examination)	Patient and caregiver satisfaction: 82% agreed or strongly agreed that the PKG was easy to learn, easy to use, enabled them to confirm medication administration, performed as expected and would use it again. Physician's assessment of global impact on patient care: the PKG improved dialogue with the patient in 59% visits, improved ability to assess impact of a therapy in 38% visits, improved ability to assess need for additional tests or treatments in 7% visits, improved ability to assess PD symptoms in 33% visits, and improved patient education about symptoms in 29% visits.
Nahab, 2019[62] USA	Prospective cohort study Funding: not stated	PwP (n=28) clinically stable patients using levodopa who attended both routine visits	PKG worn for 6 days	Routine clinical assessment by a movement disorder specialist (including symptom review, medication review and routine clinical exams), undertaken twice, with UPDRS data reviewed by the movement disorder specialist after the second visit	The movement disorder specialist assessed the PKG as having an overall positive impact on patient care with high responses (79-100%) across clinical visits in improved dialogue, improved patient education and improved ability to assess the impact of therapy. Patients had a positive response on the use of the PKG; they agreed it was easy to use (93%), performed as expected (96%) and they would use it again (100%). Patients assessed the PKG as having an overall positive impact on their care; the device assisted with explaining symptoms (79%), in providing data to the physician they could not provide (89%), in assessing their daily activity levels (96%), and in providing data that contributed to the overall management of their PD (93%). When asked if they would be willing to pay for the device if their insurance didn't cover the cost, 32% patients said they would, 25% said it would depend on cost and 43% said they would not pay for the device.

Study details	Study design and funding source	Population	Intervention	Comparator(s)	Results
Santiago, 2019[66] USA	Prospective physician survey Funding: Global Kinetics Corporation provided PKG System product for use in this research project, research service support and funds for manuscript submission	Physicians of PwP (n=4 movement disorder specialists who ordered 143 PKGs on 89 patients; 112 completed surveys on 81 patients were included in the analysis) Dates: December 2015 to July 2016	PKG worn for 6 days	Clinical consultation alone (routine clinic visit before reviewing PKG data)	Of 112 completed physician surveys, 46 (41%) indicated the PKG provided relevant additional information sufficient to consider adjusting their therapeutic management plan; 66 (59%) indicated the PKG provided no further information to support a therapeutic decision differing from that made during a routine clinic visit.
Sundgren, 2021[68] Sweden	Prospective cohort study Funding: Global Kinetics Corporation	PwP (n=66) Dates: March 2018 to February 2020	PKG worn for 6 days	Clinical assessment (before reviewing PKG data)	Physicians considered that the PKG improved the dialogue with the patient in 58/66 visits (88%).
Abstracts					
Chhabria, 2018[25] Location: not stated	Retrospective cohort study Funding: not stated	PwP (n=50) Dates: not stated	PKG	-	Overall, patients reported high satisfaction with wearing the device.
Langston, 2017[57] USA	Prospective or retrospective cohort study Funding: not stated	PwP (n=89; 123 movement disorder surveys completed, 44	PKG worn for 6 days	Clinical assessment by a movement disorders specialist	38% agreed that the PKG provided additional information not available from clinical consultation alone.

Study details	Study design and funding source	Population	Intervention	Comparator(s)	Results
		patients had multiple PKGs) Dates: Not stated			
Rasul, 2017[65] USA	Prospective cohort study Funding: not stated	PwP (n=51; 28 provided feedback regarding their experience of using PKG) Dates: Not stated	PKG worn for 6 days	-	68% patients strongly agreed that PKG was very easy to use. 96% agreed or strongly agreed that they were able to wear PKG and complete medication use confirmations as instructed by doctor. 97% found that the feature of PKG for reminder was very helpful for medication compliance.
Spengler, 2016[67] USA	Pilot prospective cohort study Funding: not stated	PwP with newly implanted STN leads for DBS therapy (n=5) Dates: not stated	PKG	-	Patients felt that PKG was helpful with medication reminders and helped explain the symptoms better.
Thakur, 2017[70] USA	Retrospective cohort study Funding: not stated	PwP (n=51) Dates: November 2015 to November 2016	PKG worn for 6 days	Clinical assessment during routine PD follow-up by Movement Disorder Specialists	2 patients did not tolerate the PKG due to wristband irritation. 47% clinicians agreed that the PKG provided information not available from the clinical consultation that drove a clinical management plan change.
Thomas, 2019[71] UK	Retrospective cohort study Funding: not stated	PwP (n=256 evaluations) Dates: not stated	PKG	Clinical assessment	Patient feedback on the PKG was favourable, with 98% patients reporting a positive or neutral user experience.

Abbreviations: DBS, deep brain stimulation; PD, Parkinson's disease; PKG, Personal KinetiGraph; PwP, people with Parkinson's disease.

STAT-ON (2 full papers, 2 abstracts)

Table 64 Data from STAT-ON studies of patient, carer and clinical opinions

Study details	Study design and funding source	Population	Intervention	Comparator(s)	Results
Full papers					
Bayes, 2018[74] Spain, Italy, Israel and Ireland	Prospective pilot cohort study and patient survey Funding: European Community	PwP (n=41)	STAT-ON	Patient diaries and clinical assessment	Usability and user satisfaction: Median SUS in this study was 70 (IQR 25). A SUS score >50 is considered acceptable and above 68-70 is good. In the QUEST-questionnaire no patient was 'not satisfied at all' with the system, 5% were 'not very satisfied', 20% 'more or less satisfied' and 76% 'satisfied' or 'very satisfied'. Comfort is the element with the lowest score and security with the highest.
SantosGarcia, 2020a[88] Spain	Prospective physician survey Funding: not stated (STAT-ON was provided by Sense4Care)	Physicians of PwP (n=27 neurologists treating 114 patients) Dates: October to December 2019 (survey sent in February 2020)	STAT-ON	-	74% neurologists rated STAT-ON 'quite' to 'very useful'. Subjective general opinion about the device (from 0 to 10) was 6.9 ± 1.7. On a scale of 1 (unhelpful) to 7 (very helpful) 'On-Off daily distribution' was the best scored item (5.5 ± 1.5), whereas 'falls detection' (3.6 ± 2.0) and 'number of freezing of gait episodes and duration' (3.7 ± 1.7) were the worst. 70.3% neurologists rated STAT-ON better than diaries and 81.5% considered it a useful tool for the identification of patients with advanced PD. Most frequently reported limitations of the information provided by the device were 'problems with the interpretation of time inactive' (n=6 neurologists) and

Study details	Study design and funding source	Population	Intervention	Comparator(s)	Results
					'proper identification of freezing of gait episodes and/or falls' (n=5 neurologists). 89% neurologists would use the device in their daily clinical practice.
Abstracts					
Rodriguez-Martin, 2021a[81] Location: not stated	Prospective survey Funding: not stated	PwP (n=41), caregivers (n=30), neurologists (n=17), health professionals (n=19) Dates: not stated	STAT-ON	-	88% of neurologists surveyed think that the medical device can detect advanced PD symptoms. The average score of the sensor is 7.9/10 and all neurologists find the information useful or very useful. Health professionals scored the sensor 8.6/10 and all of them see the sensor as a good or very good solution. Patients rate the sensor 8.5/10 and 77.5% think it is very easy to use. The belt is rated 8.1/10. 80% caregivers find the sensor a good or very good solution and no-one dislikes the sensor. 76% think it is easy to use and no caregiver thinks the belt is difficult to wear and adjust.
Caballol, 2020[76] Spain	Prospective cohort study Funding: not stated	PwP (n=39) Dates: not stated	STAT-ON worn for one week (device not stated in abstract, but abstract in Sense4Care submission)	Patient report	Satisfaction with the device (assessed using Quebec User Evaluation of Satisfaction with assistive Technology (QUEST)) was high: all items scored between 4 'quite satisfied' and 5 'very satisfied', except for the item 'easy in adjusting' which had a lower score. The system was found to be easy to use (assessed using System Usability Scale (SUS)).

Abbreviations: IQR, interquartile range; PD, Parkinson's disease; PwP, people with Parkinson's disease; QUEST, Quebec User Evaluation of Satisfaction with assistive Technology; SUS, System Usability Scale.

Kinesia 360 (1 full paper, 0 abstracts)

Table 65 Data from Kinesia 360 studies of patient, carer and clinical opinions

Study details	Study design and funding source	Population	Intervention	Comparator(s)	Results
Full papers					
Peacock, 2021[90] Canada	Randomised controlled trial Funding: not reported	PwP (n=25 – study suspended due to Covid-19) with bothersome tremor or dyskinesia identified as a treatment target at their most recent clinic visit Dates: May 2019 to March 2020	Telehealth (video-conference) follow-up care with data from in-home Kinesia 360 (worn for 3 days), by movement disorder neurologist, at baseline, 6 weeks, 3 months and 6 months (n=13)	Usual in-person follow-up care with clinical examination and review of 3 days of symptom diaries, by movement disorder neurologist, at baseline, 6 weeks, 3 months and 6 months (n=12)	54% telehealth patients reported feeling comfortable or very comfortable using motion sensors, 39% were neither comfortable nor uncomfortable and 8% were uncomfortable or very uncomfortable using motion sensors. 50% usual care patients reported feeling comfortable or very comfortable using symptom diaries, 50% were neither comfortable nor uncomfortable. 85% telehealth patients felt comfortable or very comfortable talking to their doctor through a computer screen, whilst 15% felt uncomfortable or very uncomfortable. 46% telehealth patients would have preferred to be in the usual care group, 8% would not and 46% were undecided. 8% usual care patients would have preferred to be in the telehealth group, 67% would not and 25% were undecided.

Abbreviations: PwP, people with Parkinson's disease.

KinesiaU (1 full paper, 0 abstracts)

Table 66 Data from KinesiaU studies of patient, carer and clinical opinions

Study details	Study design and funding source	Population	Intervention	Comparator(s)	Results
Full papers					
Hadley, 2021[92] USA	Prospective cohort study Funding: National Institutes of Health (2 authors are employees of and own stock in Great Lakes Neuro-Technologies)	PwP (n=16) undergoing therapy changes	KinesiaU (alongside clinical judgement) worn for at least 3 days in the week prior to instituting a therapy change and for at least 3 days during weeks 3 and 5 after the therapy change	N/A	88% patients agreed or strongly agreed that the KinesiaU system was easy to understand and use, while 12% disagreed or strongly disagreed. 88% agreed or strongly agreed that the periodic tasks were easy to perform, while 6% were neutral and 6% disagreed. Only 32% patients agreed or strongly agreed that they looked at the KinesiaU reports often and only 38% agreed or strongly agreed that they were useful to look at (44% were neutral and 19% disagreed or strongly disagreed). 44% patients agreed or strongly agreed that they would continue to use the system if it was available to them, 25% were neutral and 31% disagreed.

Abbreviations: PwP, people with Parkinson's disease.

PDMonitor (0 full papers, 0 abstracts)

9.5 Further results from Woodrow IPD analysis

Table 67 Woodrow IPD analysis: Continuous outcomes using unadjusted and adjusted models

Variable	Unadjusted analysis		Adjusted analysis	
	Mean difference	Standard error	Mean difference	Standard error
Median active BKS	-0.665	0.457	-0.412	0.449
Median BKS	-0.028	0.544	0.289	0.527
Median DKS	-0.432	0.540	-0.516	0.561
Hohn and Yahr	-0.025	0.095	-0.044	0.097
LED (/100)	0.216	0.440	-0.224	0.413
MOCA	-0.164	0.292	-0.200	0.300
NMS	0.717	0.522	0.829	0.540
PDQ-39	-1.077	1.553	-0.650	1.600
Time in bradykinesia (%)	-2.106	1.734	-1.223	1.699
Time in dyskinesia (%)	-1.507	1.344	-2.059	1.390
Time immobile (%)	-0.636	0.495	-0.558	0.516
Time inactive (%)	2.701	1.203	2.685	1.252
Time in tremor (%)	-0.589	0.615	-0.325	0.616
SENS PD	-0.514	0.631	-0.391	0.655
UPDRS-1	0.012	0.555	-0.015	0.577
UPDRS-2	0.381	0.541	0.589	0.557
UPDRS-3	-3.166	1.300	-3.300	1.172
UPDRS-4	-1.151	0.578	-0.719	0.576
UPDRS Total	-4.236	1.884	-3.540	1.810

Figure 11 Woodrow IPD analysis: Continuous outcomes using unadjusted and adjusted models

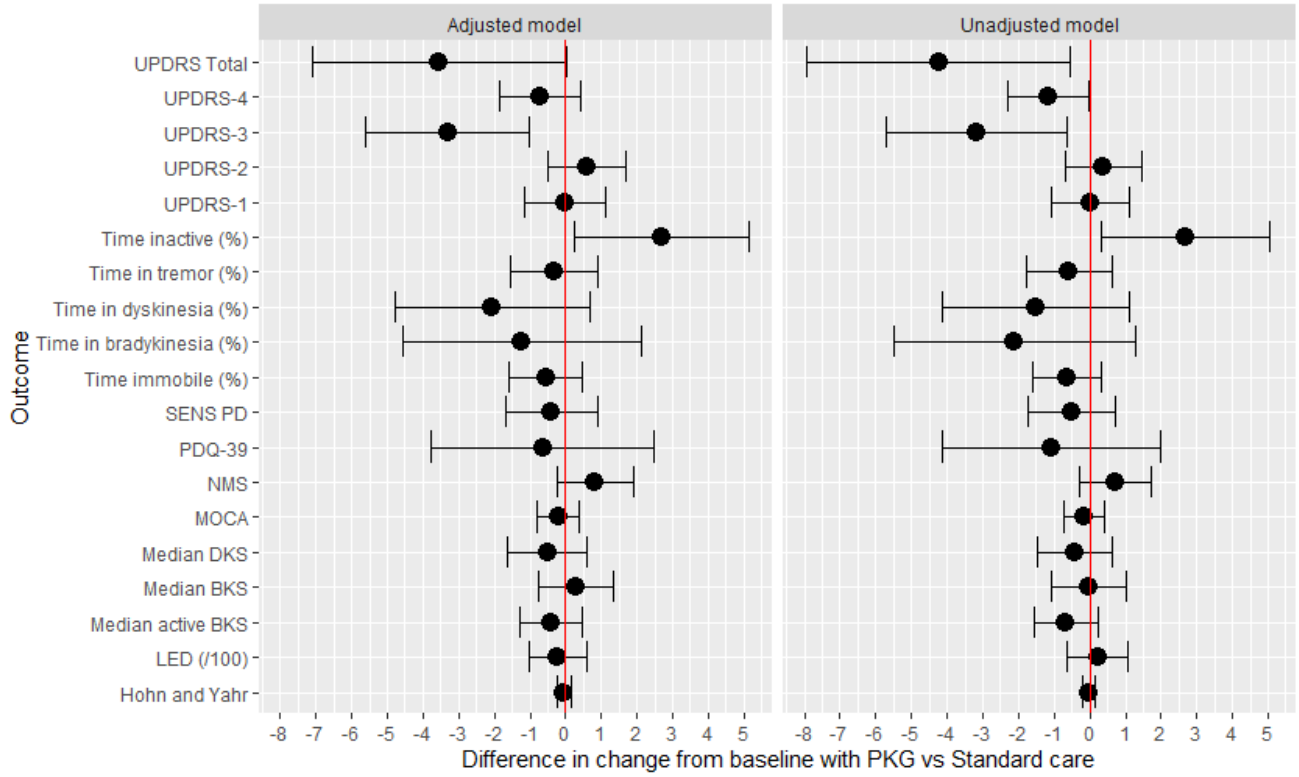

Figure 12 Woodrow IPD analysis: Continuous outcomes by number of visits required

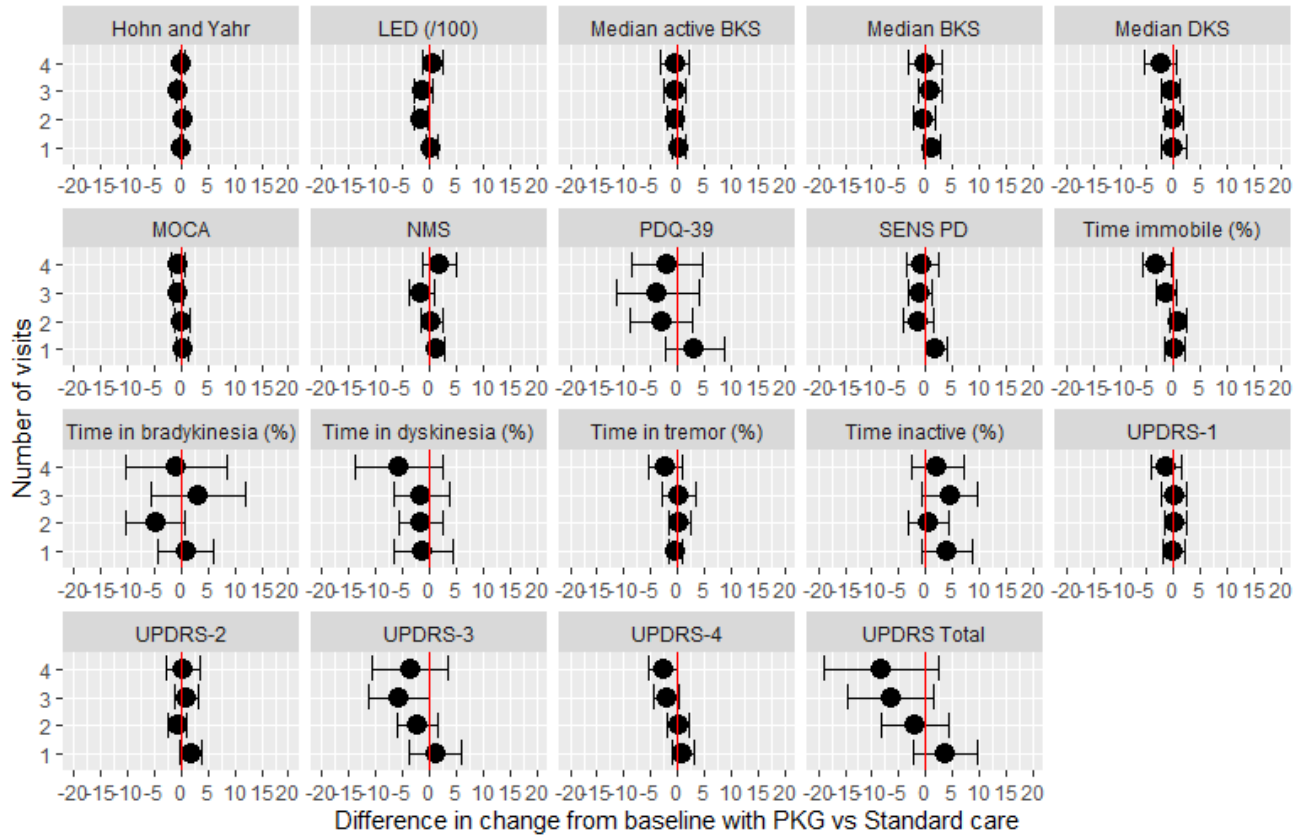

Figure 13 Woodrow IPD analysis: Continuous outcomes by UPDRS III score at baseline

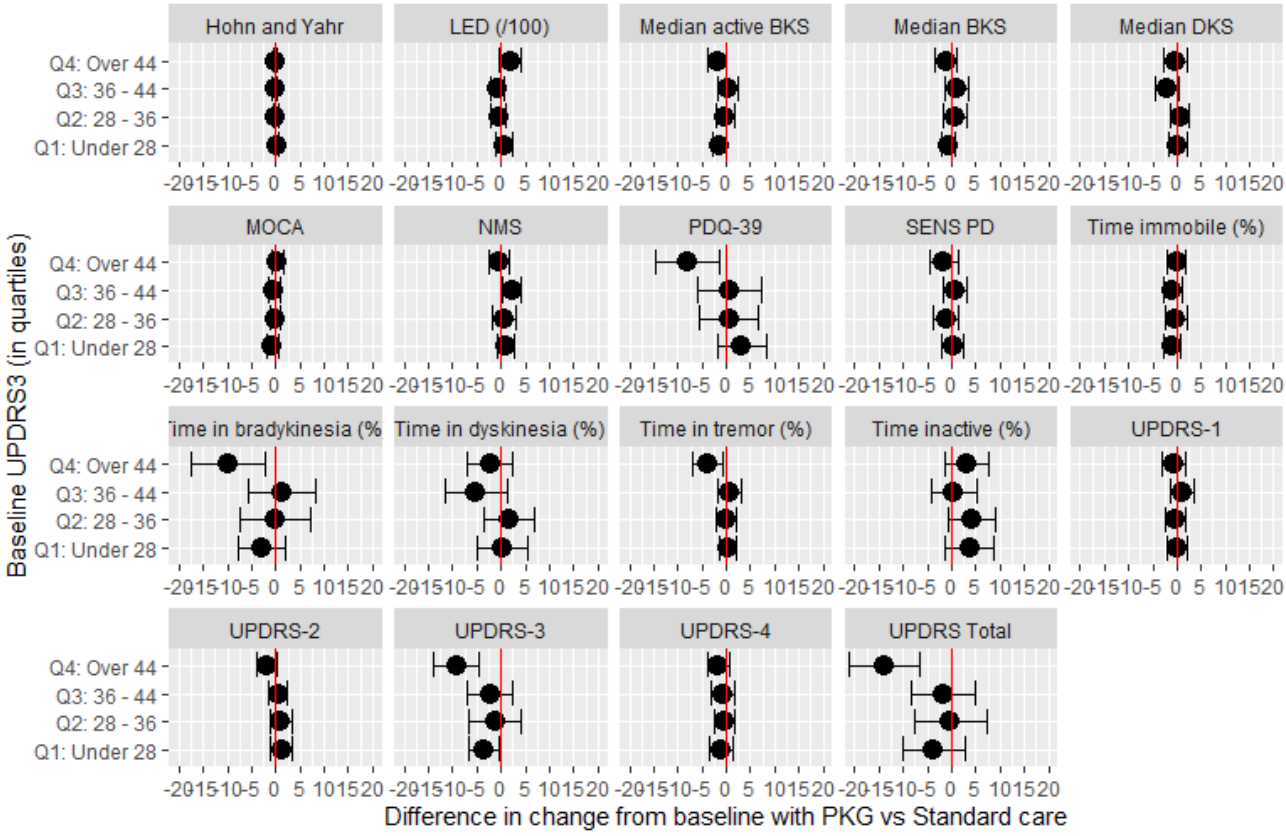

Table 68 Woodrow IPD analysis: Continuous outcomes by target status

Variable	Target	Odds ratio	Standard error	95% CI	
Median active BKS	In Target	-1.585	1.101	-3.743	0.574
Median active BKS	Not in Target	-0.073	0.510	-1.073	0.928
Median BKS	In Target	-0.845	1.172	-3.142	1.452
Median BKS	Not in Target	0.524	0.613	-0.677	1.725
Median DKS	In Target	-0.426	0.590	-1.581	0.730
Median DKS	Not in Target	-0.637	0.685	-1.979	0.705
Hohn and Yahr	In Target	-0.029	0.228	-0.476	0.418
Hohn and Yahr	Not in Target	-0.035	0.113	-0.258	0.187
LED (/100)	In Target	-1.000	1.126	-3.207	1.208
LED (/100)	Not in Target	-0.192	0.466	-1.105	0.722
MOCA	In Target	-1.692	0.760	-3.182	-0.201
MOCA	Not in Target	-0.010	0.335	-0.666	0.646
NMS	In Target	1.374	1.415	-1.399	4.147
NMS	Not in Target	0.381	0.630	-0.853	1.616
PDQ-39	In Target	0.893	5.475	-9.838	11.624
PDQ-39	Not in Target	-2.438	1.724	-5.818	0.941
Time in bradykinesia (%)	In Target	0.463	2.783	-4.992	5.918
Time in bradykinesia (%)	Not in Target	-0.711	1.996	-4.624	3.202
Time in dyskinesia (%)	In Target	-2.356	2.578	-7.410	2.698
Time in dyskinesia (%)	Not in Target	-2.337	1.637	-5.546	0.871

Time immobile (%)	In Target	-2.766	1.466	-5.640	0.108
Time immobile (%)	Not in Target	-0.093	0.559	-1.189	1.003
Time inactive (%)	In Target	6.777	3.162	0.579	12.975
Time inactive (%)	Not in Target	2.009	1.422	-0.778	4.795
Time in tremor (%)	In Target	-1.409	1.068	-3.502	0.685
Time in tremor (%)	Not in Target	0.003	0.744	-1.454	1.461
SENS PD	In Target	2.242	1.449	-0.599	5.083
SENS PD	Not in Target	-0.858	0.748	-2.323	0.607
UPDRS-1	In Target	1.448	1.477	-1.447	4.344
UPDRS-1	Not in Target	-0.319	0.661	-1.614	0.977
UPDRS-2	In Target	0.115	1.628	-3.076	3.307
UPDRS-2	Not in Target	0.323	0.599	-0.851	1.498
UPDRS-3	In Target	-0.856	2.437	-5.633	3.921
UPDRS-3	Not in Target	-3.179	1.551	-6.219	-0.140
UPDRS-4	In Target	-0.379	1.645	-3.603	2.845
UPDRS-4	Not in Target	-1.236	0.627	-2.464	-0.008
UPDRS Total	In Target	-5.111	4.431	-13.796	3.574
UPDRS Total	Not in Target	-4.110	2.154	-8.331	0.111

9.6 Supplementary material from review of cost-effectiveness

Table 69 Supplementary review of decision analytic models evaluating PD interventions

Study, country	Interventions under consideration	Patient population (base-case where clearly stated)	Model type	Model design	Mechanism of benefit
All Wales Medicines Strategy, 2007 UK	1. Levodopa-carbidopa intestinal gel (Duodopa®) 2. SoC (conventional oral/topical medication with subcutaneous apomorphine infusion for 20% of patients)	Advanced Parkinson's disease (H&Y≥3) 64-years old	Markov model	The company's economic model has a Markov structure consisting of 25 health states representing a combination of HY stage (1–5) and the proportion of the waking day spent in the OFF state (OFF 0–4, with higher score signifying greater OFF time).	Treatment-specific (Duodopa®) transition probabilities differ between the alternatives throughout the model time-horizon. Transitions in the first year of the model are informed according to clinical data. Thereafter SoC transition probabilities are derived from published natural history studies on Parkinson's disease progression, with Duodopa® assumed to experience a 0.5 relative risk (50% lower risk) of progression to OFF states than SoC over the remainder of the model time horizon Delaying transitions into higher HY and OFF score health-states accrues more QALYs (from higher HRQoL) and lower NHS costs. This model structure permits a distinction between the natural progression of the disease (HY) and a key symptomatic element of disease (motor fluctuation status/OFF-time) which is susceptible to longer-term alleviation via treatment.
Arnold et al., 2017 US	1. Immediate-release carbidopa-levodopa and entacapone 2. Extended-release carbidopa-levodopa	Advanced Parkinson's disease 60-years old.	Markov model	Markov model representing the progression and management of PD with health states defined according to two levels of "off" time in a day: ≤25% versus >25% of waking hours.	Intervention strategies are associated with transition probabilities for patients to (i) remain in the >25% "off" time health state (where all patients begin in the model), (ii) transition to an improved health state (≤25% "off" time), or (iii) die. Note the probability of death was assumed to be independent of treatment or health-state. Treatments that enhance the time spent in the ≤25% "off" time health-state accrue more QALYs (from higher HRQoL) and lower costs over a 5-year time-horizon

					This model structure permits a distinction between the natural progression of the disease (exogenous to the model) and a key symptomatic element of disease (motor fluctuation status) which is susceptible to longer-term alleviation via treatment.
Chandler et al., 2021 UK	1. Hypothetical disease-modifying therapy (DMT) as a new treatment for PD (as an add-on to SOC) 2. Current SOC (symptomatic treatments for PD)	Newly diagnosed, treatment-naïve patients who were, on average: 61 years old, 65% male, 6-months disease history, and with disease severity MDS-UPDRS I 5.8, MDS-UPDRS II 5.9, MDS-UPDRS III 21.1 HY-1: 44% HY-2: 56% HY3-5: 0%	Individual patient simulation study	Individual patient-level simulation which represents the progression and management of PD as changes in the sub-scales of MDS-UPDRS, UPDRS and HY stages according to patient characteristics (age, disease duration, gender). For further details see Section 4.4.	DMT was assumed to provide a 50% change in MDS-UPDRS progression compared to natural history with a 5% discontinuation in treatment effect in the first year and an annual rate of discontinuation of 2.5% in subsequent years. Patients discontinuing DMT revert to SOC trajectories following a gradual loss of treatment effect over two years. Advanced therapies were assumed to have an initial, one-time shift in HY stage and no subsequent benefit. Changes in MDS-UPDRS were associated with… For further details see Section XXX.
Dams et al., 2016 Germany	1. Deep brain stimulation of the subthalamic nucleus 2. Best medical treatment	52 years of age, 52.6% male, average 1.7 years' experience with motor complications and disease severity: H&Y OFF I: 5% H&Y OFF II: 65% H&Y OFF III: 20%; and H&Y OFF IV: 10%	Markov model	Uses the same model as Dams et al., 2013 (see below).	Same model as Dams et al., 2013 (see below).
Dams et al., 2013	1. Deep brain stimulation 2. Best medical treatment	60 years of age, 52.6% male, with all patients experiencing motor fluctuations and dyskinesias and disease severity: H&Y OFF III: 50% H&Y OFF IV: 30% H&Y OFF V: 20%	Markov model	Markov model representing the progression and management of PD as changes in Hoehn-Yahr scale and OFF and ON-states. The distribution of individuals between ON- and OFF-states at each severity stage is contingent on treatment. Patients are assumed to progress through six discrete Hoehn-Yahr OFF stages (equivalent without treatment) 1–5 and death. HY-ON states are nested within each discrete HY-OFF state and represent cases of treatment response where patients improve clinically within a given HY severity scale. All Hoehn-Yahr	Treatment-specific differentials in costs and outcomes were determined in the model via differential probabilities to develop motor complications (transitions between ON- and OFF-states) alongside treatment-associated resources and utility decrements. This model structure permitted a distinction between the natural progression of the disease and non-disease symptom modifying treatment effectiveness.

				stages are transitional states and death is an absorbing stage.	
Davey et al., 2001 Australia	1. Pergolide dopamine receptor agonist 2. Bromocriptine dopamine receptor agonist	Not reported.	Markov model	Markov model representing the progression and management of PD as changes in the Hoehn-Yahr scale, where the distribution of individuals starting in each Hoehn-Yahr severity stage, and the probability of moving between stages, is contingent on treatment strategy. Patients are assumed to progress through six discrete Hoehn-Yahr stages 1–5 and death. All Hoehn-Yahr stages are transitional states and death is an absorbing stage.	Treatment-specific effects were determined in the model via the time spent in H&Y states (primary model outcome), with those in higher stages incurring greater costs and lower HRQoL (where differentials in the initial H&Y distribution and the probability of transitioning between H&Y severity states occur in the first two years in the base case analysis). This model structure does not permit a distinction between the natural progression of the disease and non-disease modifying treatment effectiveness.
Eggington et al., 2014	1. Deep brain stimulation 2. Best medical treatment	Advanced PD	Markov model	Markov model representing the progression and management of PD as changes in Hoehn-Yahr scale and nested OFF-time sub-states. The distribution of individuals between OFF-states (0-25%, 26-50%, 51-75%, and 76%-100%) at each H&Y severity stage is contingent on treatment. Patients are assumed to progress through Hoehn-Yahr stages 1–5 and death where PD patients could worsen by one H&Y stage, progress by one level of 'OFF' time, or both/neither in each cycle. HY-OFF states are nested within each discrete HY state and represent cases of treatment response/wearing-off where patients improve/deteriorate clinically within a given HY severity scale. All Hoehn-Yahr stages are transitional states and death is an absorbing stage.	Treatment-specific effects were determined in the model via the time spent in H&Y states and nested OFF-time sub-states (with operative mortality from DBS, with those in higher H&Y stages and more severe OFF-time sub-states incurring greater costs and larger decrements in HRQoL. Differentials in time spent in each state were determined via differences in H&Y stage and level of 'OFF' time between baseline and 6 months, with patients' underlying disease stage thereafter extrapolated equally between arms. This model structure permits a distinction between the natural progression of the disease (H&Y stage) and non-disease modifying (OFF-time) treatment effectiveness.
Espay et al., 2010	1. Early STN DBS: Subthalamic nucleus deep brain stimulation (STN DBS) applied to patients with PD at an "early" stage	45-year-old with normal cognitive function and between 10 and 20% OFF-time (base case)	Markov model (with tree based elements for procedural outcomes)	Markov model representing the progression and management of PD according to combinations of both cognitive (normal, severe) and motor functioning (<10%, 10-20%, 21-39%, ≥40% OFF-time), with considerations made to DBS procedural complications (no complications, major complications, mortality). Early STN DBS receive immediate intervention, while Delayed STN DBS receive intervention in the	Treatment-specific effects were determined in the model via differentials in the times spent in alternative cognitive function and nested OFF-time sub-states. Treatment-associated aversions of time spent in more severe health states (i.e. those with higher proportion of OFF-times and/or more severe cognitive function) reduced costs and conferred gains in HRQoL.

	(OFF-time 10–20%) 2. Delayed STN DSB: STN DBS applied to patients with PD at a "delayed" stage (OFF-time>40%)			model once OFF-time ≥40%. Thus delayed STN DBS strategy enters the Markov model within the normal cognitive function 10-20% OFF-time health-state, whereas Early STN DBS enters the Markov model in the normal cognitive function <10% OFF-time state (assuming an approximate 50% reduction in OFF-time). After entering the Markov model, subjects may remain in, improve or have progression both before and after DBS placement; develop surgical/medical complications, or die.	This model structure permits a distinction between the natural progression of the disease (cognitive functions) and non-disease modifying (OFF-time) treatment effectiveness. The probability of disease progression was not altered by STN DBS.
Fann et al., 2020	1. Subthalamic nucleus deep brain stimulation 2. medication, in which patients took medication after being diagnosed with PD	Late PD	Markov model (with tree-based elements)	Markov model representing the progression and management of PD as changes in the Hoehn-Yahr scale, where the distribution of individuals starting in each Hoehn-Yahr severity stage, and the probability of moving between stages, is contingent on treatment strategy. Patients are assumed to progress through six discrete Hoehn-Yahr stages 1–5 and death via each subject's treatment-specific UPDRS motor score (drawn from a normal distribution). All Hoehn-Yahr stages are transitional states and death is an absorbing stage.	Treatment-specific effects were determined in the model via the time spent in H&Y states, with treatment-associated reductions in UPDRS motor scores associated with lower H&Y states, and in turn reduced costs and improved HRQoL. This model structure does not permit a distinction between the natural progression of the disease (UPDRS~H&Y) and non-disease modifying treatment effectiveness.
Farkouh et al., 2012	1. Rasagiline mesylate (rasagiline) first-line therapy 2. Dopamine antagonist (DA) first-line therapy 3. Levodopa first-line therapy (LD)	61 years-old H&Y stage 1.5 in early PD requiring pharmacologic intervention.	Markov model	Markov model representing the progression and management of PD as the onset of dyskinesia and treatment switching between alternative therapeutic regimens (rasagiline, DA's and LD). The model consists of treatment-specific health-states with transitions to alternative subsequent-line therapies, nested dyskinesia health-states and death possible. Patients on DA or LD are at risk of transitioning to treatment-specific nested dyskinesias health-states. Death could occur from any health state.	Treatment-specific effects were determined in the model via the time spent in treatment-specific 1st line, 2nd line, and dyskinesia health-states. Treatments extending time until subsequent lines of therapy or dyskinesia accrued cost savings and improved HRQoL. This model structure did not provide a natural progression of the disease but rather the treatment sequencing associated with disease progression and non-disease modifying treatment effectiveness (time to dyskinesia symptoms).
Fundament et al., 2016	1. Deep brain stimulation	PD with early motor complications (i.e. those with motor fluctuations	Markov model	Markov model representing the progression and management of PD as changes in UPDRS domain scores (I-IV) and treatment switching within and between treatment-specific health-	Interventions associated with reductions in UPDRS scores conferred significant cost savings, reductions in adverse events (i.e. falls), improved HRQoL and reduced risk of mortality (in advanced disease).

	2. Best medical therapy (BTS)	or dyskinesias present for 3 years or less).		states. Patient either remain in their treatment-specific health-state, transition to an absorbing health state, or in the case of DBS patients, patients may withdrawal from DBS therapy and transition to the DMT health state (i.e., where they would continue with BMT until the end of the model horizon or until death). For further details see Section XXX.	For further details see Section XXX.
Groenendaal et al., 2010	1. Rasagiline as adjunctive therapy to levodopa 2. Entacapone as adjunctive therapy to levodopa 3. Levodopa/carbidopa/entacapone (LCE) 4. Levodopa monotherapy	Idiopathic PD (defined as the presence of two or more cardinal signs). With a modified (H&Y) scale score of <5 in the OFF-state.	Markov model	Markov model representing the progression and management of PD over two-years, with health states defined according to two levels of OFF-time in a day: ≤25% versus >25% of waking hours. Patients could transition to an absorbing death health-state from either OFF-time health-state over the two-year model time horizon. The shorter model time frame precluded modelling longer-term treatment switching.	Interventions accruing less time within the >25% OFF-time health-state (i.e. relatively favourable transition probabilities) confer savings in medical care expenses, and reduced HRQoL decrements (i.e. higher utility values). Mortality risks in the model were independent of treatment or health-state. This model structure did not provide a natural progression of the disease but rather the immediate impacts on non-disease modifying treatment effectiveness (OFF-time).
Hensen et al., 2021	1. Opicapone 2. Entacapone	64-year old PD patients (aligned to those enrolled in the BIPARK-1 trial)	Markov model	Markov model representing the progression and management of PD over 25-years, with health states defined according to two levels of OFF-time in a day: <25% versus ≥25% of waking hours. Patients could transition to an absorbing death health-state from either OFF-time health-state.	Interventions accruing less time within the >25% OFF-time health-state (i.e. relatively favourable transition probabilities) confer cost savings (reduced likelihood of hospitalisation and length of stay), and averted HRQoL decrements (via health-state specific differences in utilities and via averting decrements applied per additional number of hours of OFF-time). The enhanced mortality risks associated with PD applied in the model were independent of treatment or health-state. The natural progression of the disease was characterised via progression of symptoms (OFF-time), providing a narrow definition with non-disease modifying treatment effectiveness.
Haycox et al., 2009	1. First-line rasagiline monotherapy 2. Pramipexole	Patient characteristics made treatment-specific:	Markov model	Markov model representing the progression and management of PD as the onset of dyskinesia and treatment switching between alternative therapeutic regimens (rasagiline, pramipexole or levodopa). The model consists of treatment-	Treatment-specific effects were determined in the model via the time spent in treatment-specific 1st line, 2nd line, 3rd line and dyskinesia health-states. Treatments extending time until dyskinesia and

		Rasagiline (pramipexole): age 61 (62), male 62% (64%), disease duration 12 months (18 months), H&Y stage 1.9 (1.9), UPDRS baseline score for ADL 6 (9) and motor function 18 (22)		specific health-states with transitions to alternative subsequent-line therapies occurring at the onset of dyskinesia (with all transitions possible between rasagiline, pramipexole, and levodopa, with exception to pramipexole to rasagiline which was deemed to make "*little sense*"). The appearance of levodopa-induced dyskinesia was considered the 'absorbing' state (endpoint) of the model. Death was not considered.	subsequent lines of therapy accrued cost savings and improved HRQoL. This model structure did not provide a natural progression of the disease but rather the treatment sequencing associated with disease progression and non-disease modifying treatment effectiveness (via time to dyskinesia symptoms).
Hjelmgren et al., 2006	Hypothetical novel therapeutic procedures	PD patients 58.6 years at diagnosis, 4.3 years at first neurological assessment with disease severity: Initial OFF-time and HY stage I: 34.2% HY stage II: 31.6% HY stage III 22.8% HY stage IV 10.1% HY stage V:1.3%	State transition model	Markov model representing the progression and management of PD as changes in the H&Y scale, where transitions between H&Y health states was assumed to follow an estimated continuous estimated temporal function.	Treatment-specific effects were determined in the model via the time spent in H&Y states, with those in higher stages incurring greater costs and reduced HRQoL. Interventions were assumed to see reductions in the progression rate for 2 years, followed by a stationary period up to 5 year, after which disease progression was assumed to progress at an estimated pre-operative disease progression rate. All Hoehn-Yahr stages are transitional states and death is an absorbing stage. This model structure does not permit a distinction between the natural progression of the disease and non-disease modifying treatment effectiveness.
Kalabina et al., 2019	1. Levodopa carbidopa intestinal gel (LCIG) 2. Standard of care	Advanced PD patients unsuitable for apomorphine or deep brain stimulation (S187.3.004 study). Patients enter the model at age 64 years, with 59% of the cohort being male. Patients are distributed across health states at baseline as follows: H&Y 3-OFF III: 62%, H&Y 3-OFF IV: 3%, H&Y 4-OFF III: 32%,	Markov model	Markov model representing the progression and management of PD as changes in composite H&Y scale and OFF-time health-states. Patients can transition between OFF-time (0%, 1-25%, 26-50%, 51-75%, and 76%-100%) and H&Y severity stage health-states or transition to an absorbing death health-state. The probabilities of transitioning between states is contingent on treatment. Patients are assumed to only progress to more severe health-states overtime with the exception to the first cycle, where patients can transition to less severe-states as a result of treatment.	Treatment-specific effects were determined in the model via the time spent in H&Y and OFF-time health-states. LCIG is modelled as having a short-term 1-year treatment effect on the composition of patients within H&Y and OFF-time health-states. Thereafter the rate of progression in OFF-time is reduced in the LCIG arm (halved). No improvement on H&Y scale was assumed after the first year for either intervention. Individuals in higher H&Y stages/OFF-time health-states incur greater costs and larger decrements in HRQoL in the model. Mortality was determined independently of treatment in the model. This model structure permits a distinction between the natural progression of the disease (H&Y stage) and a

		H&Y 4-OFF IV: 3%, H&Y 5-OFF III: 0%, H&Y 5-OFF IV: 0%.			key symptomatic element of disease (OFF-time) which are susceptible to treatment.
Lindgren et al., 2003	1. Cabergoline 2. Levodopa	Early PD age 61.9 years, aligned to trial data	Markov model	Markov model representing the progression and management of PD as changes in the H&Y scale (omitting HY stage 5), and a state for patients with motor complications (no distinction between HY stage) and an absorbing state for dead patients. Transitions to the death state are not treatment-related (equal to Swedish general population rates).	Treatment-specific effects were determined in the model via the time spent in H&Y states and motor complication state, with health-care costs rising in higher stages and for those transitioning into the motor complications health-state. The efficacy measure within the model corresponded to time spent with motor complications, with no consideration made with respect to H&Y stages. This model structure permitted a distinction between the natural progression of the disease (H&Y stage) and non-disease modifying treatment effectiveness (onset of motor complications).
Lowin et al., 2011	1. Levodopa carbidopa intestinal gel (LCIG) 2. Standard of care	Advanced PD patients (H&Y 3, OFF-time>50%)	Markov model	Markov model representing the progression and management of PD as changes in composite H&Y scale and OFF-time health-states. Patients can transition between OFF-time (0%-25%, 26-50%, 51-75%, and 76%-100%) and H&Y stage III-V health-states or transition to an absorbing death health-state. The model was largely focused on individuals with OFF-time>50%. Patients are assumed to only remain in the same state or deteriorate (and transitioning to more severe health-states) overtime with the exception to the first cycle, where patients can transition to less severe-states as a result of treatment (both with respect to H&Y stage and OFF-time).	Treatment-specific effects were determined in the model via the time spent in H&Y and OFF-time health-states. LCIG is modelled as having a short-term 6-month treatment effect on the composition of patients within H&Y and OFF-time health-states. Thereafter the rate of progression in OFF-time is reduced in the LCIG arm (halved) for five years (wherefrom patients revert back to standard care). No further treatment efficacy with respect to changes in H&Y stages is assumed thereafter. Individuals in higher H&Y stages/OFF-time health-states incur greater costs and larger decrements in HRQoL in the model. Thus, interventions which defer time spent in the more severe health-states achieve gains in HRQoL and discounted health-care cost savings. Mortality was determined independently of treatment in the model. This model structure permits a distinction between the natural progression of the disease (H&Y stage) and a key symptomatic element of disease (OFF-time) which is susceptible to longer-term alleviation via treatment.

Lowin et al., 2017	1. Levodopa carbidopa intestinal gel (LCIG) 2. Standard of care	Advanced PD patients, H&Y 3, OFF-time>50% and mean age 64 years	Markov model	Uses the same model as Lowin et al., 2017 albeit with H&Y states I and II included (see above.)	Uses the same model as Lowin et al., 2017 albeit with H&Y states I and II included (see above.)
Meng et al., 2020	1. MR-guided focused Ultrasound thalamotomy (MRgFUS) 2. Medical therapy alone 3. Deep brain stimulation (DBS)	Tremor-dominant Parkinson's disease	Decision tree	Decision tree representing the three-year horizons for patients using each alternative (decision node) with operative chance nodes for DBS and MRgFUS operative outcomes. Chance nodes for DBS and MRgFUS included probabilities of no complications, some complications, and major complications, while DBS includes chance nodes for the options of undergoing re-operation at each complication branch (for cases of hardware malfunction or infection). Reoperation of MRgFUS was not modelled (although possible). Death was not modelled as perioperative death and long-term mortality were deemed "*negligible*".	Treatment-specific differentials in the model were determined via treatment-specific input parameters, with different interventions incurring different costs, utilities and alternative likelihoods of different events (e.g. perioperative complication) which incur costs and impacts on HRQoL.
Nuijten et al., 2004	Comparison of hypothetical interventions: 1. a hypothetical new antiparkinsonian (AP) drug 2. Usual practice	Not reported (hypothetical)	Markov model	Markov model representing the progression and management of PD via fluctuation status alone. Disease progression characterised as the deterioration in fluctuations after initial treatment responses, with all other factors exogenous in the model. Individuals on usual practice remain within a fluctuation health-state, while those on AP may transition to a "no fluctuations" health-state before eventually returning to the fluctuation state according to the natural disease progression. Death was not modelled.	Treatment-specific differentials in the model were determined via the impact a theoretical intervention may have on transitioning and maintaining patients from the "fluctuating" health-state into the "no fluctuations" health-state. Increasing the time spent in the no-fluctuations health-state conferred lower health-care costs and considerably higher HRQoL relative to time-spent with fluctuations. This model structure permits a distinction between the natural progression of the disease (exogenous to the model) and a key symptomatic element of disease (motor fluctuation status) which is susceptible to longer-term alleviation via treatment.
Nuijten et al., 2003	Comparison of hypothetical interventions: 1. a hypothetical new	Not reported (hypothetical)	Markov model	Markov model representing the progression and management of PD as changes in the H&Y scale, where transitions between H&Y health states were assumed to follow an trajectory of natural disease progression with a hypothetical AP drug reducing the rate of disease progression over the life-time of the model. All	Treatment-specific effects were determined in the model via the time spent in H&Y states, with those in higher stages incurring greater costs and reduced HRQoL. Interventions were assumed to see reductions in the progression rate (10% annual reduction) which retards the progression on patients onto more costly and lower utility health-states.

	antiparkinsonian (AP) drug 2. Usual practice			Hoehn-Yahr stages are transitional states and death is an absorbing stage.	This model structure does not permit a distinction between the natural progression of the disease (H&Y) and non-disease modifying treatment effectiveness (i.e. the drug is a disease modifying therapy).
Nuijten et al., 2002	Comparison of hypothetical interventions: 1. a hypothetical new antiparkinsonian (AP) drug 2. usual practice	Not reported (hypothetical)	Markov model	First a simple markov model structure was used to validate epidemiological data, then a main markov model was developed for the cost-effectiveness analysis of a hypothetical intervention for patients with PD. The primary model represents the progression and management of patients being prescribed a hypothetical PD drug via PD status and fluctuation status. Individuals can transition into three health-states in accordance with their characteristics (age and gender): patients without Parkinson's (NP), patients with no fluctuations (P-No-fluc) and patients with fluctuations (P-Fluc). Thereafter transitions follow the Nuijten et al., (2004) model (see above). Disease progression is characterised by the deterioration in fluctuations after initial treatment responses and dependant on modelled age and gender status. Other non-fluctuation related progression factors are exogenous in the model.	The same mechanism of treatment benefit as detailed in Nuijten et al., (2004) (see above).
Nuijten et al., 2001	1. Entacapone as complementary therapy to standard of care 2. Usual care (consists of levodopa therapy for all patients and extra add-on medication for some)	Aligned to trial data with ≥25% off time, 62-64 years old, 7.9-9 years levodopa treatment, 55-67% male (range across nonecomt and seesaw trial arms)	Markov model	Markov model representing the progression and management of PD with health states defined according to two levels of "off" time in a day: ≤25% versus >25% of waking hours.	Intervention strategies are associated with transition probabilities for patients to (i) remain in the >25% "off" time health state (where all patients begin in the model and where usual care patients remain), (ii) transition to an improved health state (≤25% "off" time, only possible with the entacapone treatment strategy), or (iii) die. Note the probability of death was assumed to be independent of treatment or health-state and was not impacted by Parkinson's disease (i.e. aligned to population values).

					Treatments that enhance the time spent in the ≤25% "off" time health-state accrue more QALYs (from higher HRQoL) and lower costs over a 5-year time-horizon relative to time-spent in the >25% health-state (as occurs in usual care).
Palmer et al., 2002	1. Entacapone as complementary therapy to standard of care 2. Standard therapy (consists of levodopa therapy for all patients and extra add-on medication for some)	Aligned to trial data with ≥25% off time, 62-64 years old, 7.9-9 years levodopa treatment, 55-67% male (range across nonecomt and seesaw trial arms)	Markov model	The same markov model design as detailed in Nuijten et al., (2001) (see above).	The same mechanism of treatment benefit as detailed in Nuijten et al., (2001) (see above).
Pietzsch et al., 2016	1. Deep brain stimulation 2. Best medical treatment	Advanced PD - 60.5 years; 64% male; H&Y staging based on patient-level data	Markov model	The same markov model design as detailed in Eggington et al. (2014) (see above).	The same mechanism of treatment benefit as detailed in Eggington et al., (2014) (see above).
Postma et al., 2012	N/A (illustrative study for modelling cost-effectiveness in early Parkinson's	N/A	Markov model	Markov model representing the progression and management of PD as changes in the H&Y scale, with a distinction made between asymptomatic (H&Y I-II state) and symptomatic status (H&Y I-II, H&Y III-IV, H&Y V states). Transitions between health states were assumed to follow a trajectory of natural disease progression where interventions would be seen to prolong time spent in the `early' asymptomatic stage. There is also the potential for tunnel states to track the history of patients. All Hoehn-Yahr stages are transitional states and death is an absorbing stage.	Treatment-specific effects would be determined in the hypothetical model via the time spent in H&Y states, with those in higher stages incurring greater costs and reduced HRQoL. Interventions that prolonged the time spent in the asymptomatic H&Y state would retard the progression of patients onto more costly and lower utility health-states, thereby generating benefit. This model structure permits a distinction between the natural progression of the disease (H&Y) and non-disease modifying treatment effectiveness (i.e. transitions to the symptomatic health-state).
Shimbo et al., 2001	1. Levodopa plus bromocriptine 2. Levodopa plus pergolide	Male (base case) 60-year old Parkinson's patients	Markov model	Markov model representing the progression and management of PD as changes in the H&Y scale (I-V), where the first year in the model allows transitions to less severe H&Y health states on account of treatment-specific	Treatment-specific effects were determined in the model via the time spent in H&Y states, with those in higher stages incurring greater costs and reduced HRQoL. Interventions were assumed to see reductions

	3. Levodopa alone			therapeutic effect. Following the first-year transition probabilities only allowed individuals to remain or progress through H&Y health-states according to an assumed disease progression. All Hoehn-Yahr stages are transitional states and death is an absorbing stage.	in the progression rate for 1 year, represented by a one-time treatment-specific shift in H&Y stage. This model structure does not permit a distinction between the natural progression of the disease and non-disease modifying treatment effectiveness.
Smala et al., 2003	1. Cabergoline monotherapy 2. Levodopa monotherapy	Parkinson's in H&Y stage I-III	Markov model	Markov model representing the progression and management of PD via a series of composite health states, consisting of age (≤60 years, >60 years), intervention, H&Y scale (I-V), and the development of motor complications (dyskinesia, motor functions and dyskinesia + fluctuations). Patients were simulated through the different sets of health-states via treatment-specific transition probabilities. Disease progression (defined by H&Y) was not dependant on treatment. All age-, intervention-, H&Y-, and motor complication-specific health-states were transitional states with death an absorbing stage.	The mechanism of treatment benefit stemmed from treatment-specific differentials in the initial distribution of patients following treatment, and the treatment-specific probabilities of developing motor complications. Interventions which can provide a more favourable (less severe) distribution of initial H&Y scores and/or reduce the likelihood of transitioning into health-states with motor complication accrue less costs and superior UPDRS outcome weights in the model. This model structure permits a distinction between the natural progression of the disease (H&Y over-time) and non-disease modifying treatment effectiveness (motor complications).
Thach et al., 2021	1. Apomorphine sublingual film 2. Apomorphine hydrochloride injection 3. Levodopa inhalation powder	Parkinson's disease patient, mean age 62.7 years, mean OFF-time 3.9 hours per day, H&Y I: 0.9% HY2: 73.3% HY3: 25.9% (aligned to CTH-300 study)	Microsimulation model	Microsimulation model representing the management and progression of PD via the disease course of "OFF" episodes alongside the intended effect of "on-demand" treatments over a ten-year time horizon. Random patients (age, baseline disease severity (H&Y) and OFF-time per day) enter the model at baseline, where after patients may transition to death in any 3-month cycle (conditional of individual-level factors), or remain alive with a simulated number of "OFF" hours per day in a cycle (informed via treatment option). Over the model horizon, the progression of "OFF" time and mortality is modelled with patients assigned costs and utility values depending on their simulated "OFF" hours. Mortality was estimated separately from "OFF"-hours or treatment.	The mechanism of treatment benefit stems from treatment-specific impacts on the number of "OFF" hours patients experience. Treatments that reduce the number of "OFF" hours are expected to achieve reductions in the number of adverse events, avert medical costs and achieve superior HRQoL. This model structure permits a distinction between the natural progression of the disease (H&Y over-time) and non-disease modifying treatment effectiveness (OFF-time).

Van Boven et al., 2014	1. Ropinirole prolonged release (PR) 2. Ropinirole immediate release (IR)	65 year-old PD patients with a time from PD diagnosis of almost 8 years, a mean duration of L-dopa use of 5.5 years and dosing at 670 mg per day at study entry on average (reflective of PREPARED trial)	Markov model	Markov model representing the progression and management of PD via changes between two alternative sets of H&Y stages, one relevant to those experiencing <25% "OFF"-time/day and the other for those experiencing ≥25% "OFF"-time/day. During the first cycle (6-months) individuals could transition to an equivalent H&Y stage <25 % "OFF"-time health-state. Thereafter patients could only remain or progress to a more severe HY stage / "OFF"-time" Health-state, where patients would maximally move one HY stage ahead per cycle.	The model did not incorporate any benefits for interventions in HY progression, but rather via the probabilities of moving between the alternative "OFF"-time health-states. Differentials in costs and outcomes between treatment-arms stemmed from differences in the times spent in "OFF"-time states, where interventions able to achieve higher probabilities of transitioning too and maintaining time within a "OFF-time <25% equivalent H&Y state accumulated greater HRQoL benefits for patients and achieved cost savings. This model structure permits a distinction between the natural progression of the disease (H&Y over-time) and non-disease modifying treatment effectiveness (OFF-time).
Walter et al., 2015	1. Continuous subcutaneous apomorphine infusion (CSAI) 2. Infusion of levodopa/carbidopa intestinal gel (LCIG) 3. Deep brain stimulation (DBS) 4. Standard of care (SOC)	Advanced Parkinson's disease (H&Y stage 3-5, see below) 59.1 years old,experiencing more than 50% of waking time (14 h) in OFF-time H&Y III 25% HY IV: 50% HY V: 25% (patient characteristics from a synopsis of 19 open label Studies)	Markov model	Markov model representing the progression and management of PD via health states defined by H&Y staging and the amount of time spent in OFF experienced per waking hours. Patients can transition between OFF-time (0%-25%, 26-50%, 51-75%, and 76%-100%) and H&Y stages I-V health-states or transition to an absorbing death health-state. Patients are assumed to only remain in the same state or deteriorate (and transitioning to more severe health-states) overtime with the exception to the first cycle, where patients can transition to less severe-states due to treatment (both with respect to H&Y stage and OFF-time). All Hoehn-Yahir stages are transitional states and death is an absorbing stage.	Treatment benefit is expressed as delayed disease progression due to improvement in the first cycle. One-time recession in disease severity (with respect to OFF-time and H&Y stage) reduces the time patients spent in more severe H&Y and OFF-time health-states. Individuals in higher H&Y stages/OFF-time health-states incur greater costs and larger decrements in HRQoL in the model. Thus, interventions which defer time spent in the more severe health-states achieve gains in HRQoL and discounted health-care cost savings. Mortality was determined independently of treatment in the model. This model structure permits a distinction between the natural progression of the disease (H&Y stage) and a key symptomatic element of disease (OFF-time) which is susceptible to longer-term alleviation via treatment

Table 70 Studies excluded from the supplementary review of decision analytic models evaluating PD interventions

Study	Reason for rejection
Francois et al. (2016)	Different patient population (neurogenic orthostatic hypotension)
Dodel et al. (2021)	No de novo decision analytic model
Pizarro et al. (2013)	Non-English full text
Rudakova et al. (2017)	Non-English full text
Johnson et al. (2013)	Unable to access full text paper
Findley et al. (2005)	Unable to access full text paper
Hudry et al. (2006)	Unable to access full text paper
Linna et al. (2002)	Unable to access full text paper
Tomaszewski et al. (2001)	Unable to access full text paper