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

Section A: Comments on the Diagnostics Assessment Report

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
Great Lakes NeuroTechnologies Inc.	1	28	1.3.3	The KinesiaU motor assessment system has now received the UKCA mark.	No response needed
Great Lakes NeuroTechnologies Inc.	2	145-146	7.3	The report highlights how the devices considered are different and therefore assumes that clinical benefits cannot be compared. While the specific device functionalities differ, the overall scope of remote management remains the same and the utility would likely be similar. Therefore, the supporting evidence should be considered in aggregate to determine if this type of technology useful for various clinical care applications.	The EAG does not agree with this position, as stated in our report.
Great Lakes NeuroTechnologies Inc.	3	102	5.6	The report states, "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." While this is one use case, there are several other use cases for which these types of technologies could be quite useful. For example, patients who experience motor fluctuations, wearing off, dyskinesias, etc. would likely benefit more from RPM than the PD population as a whole. This could lead to changes in dosage and timing, providing more "on time." Additionally, for patients whose doctor has already determined a treatment change is necessary, RPM could help with dose optimization as many PD therapies require a lengthy titration process. A specific example where remote monitoring was used specifically for optimizing rotigotine dosage is described in Isaacson et al., 2019. Additional use cases could include screening patients for when an in-person visit with a movement disorder specialist is truly necessary and identifying candidates for advanced Parkinson's therapies such as deep brain stimulation and drug pumps at described in Heldman et al., 2016. Finally, patients who live far from movement disorders centres or are unable to travel may benefit more from remote monitoring than the PD population as a whole.	Not a factual inaccuracy. We think our simple text covers these issues.
Great Lakes NeuroTechnologies Inc.	4	130	6.3	KinesiaU continuous monitoring includes nearly identical data processing to the Kinesia 360 for its continuous passive monitoring as described in Pulliam et al., 2018. Kinesia 360 was designed for the clinical trial market and KinesiaU was designed to be a more cost-effective version of Kinesia 360 by allowing patients to use their own compatible smartphone and smartwatch instead of our proprietary sensor hardware. Therefore, the same economic analysis applied to Kinesia 360 should be applied to KinesiaU but reflecting the lower costs of KinesiaU. As an added benefit, the KinesiaU also includes optional task-based assessment of tremor, bradykinesia, and dyskinesia, thus providing the best of Kinesia 360 passive monitoring and a subset of Kinesia ONE task-based	Not a factual inaccuracy. EAG's conclusion regarding the clinical evidence for KinesiaU below: "Evidence on KinesiaU was limited to one small study (16 patients).[92] The EAG

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

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
				assessment. This gives the treating physician the ability to closely monitor the patient subsequent to a titration change using task-based assessments. To ensure maximal clinical applicability, all Kinesia systems' outputs are based on algorithms developed with clinician ratings as the ground truth and use the same scoring scales to facilitate clinical understanding and interpretation. In essence these new results are an extension of the clinical standard care being applied for many years.	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." p75 The EAG has undertaken evidence-based considerations for the technologies under evaluation. In the absence of clinical evidence or the demonstration of the broader logistical considerations for implementing KinesiaU in NHS practice (i.e. smartphone/smart watch provision) the EAG does not believe the economic analysis applied to Kinesia 360 is indeed applicable to KinesiaU.
Great Lakes NeuroTechnologies Inc.	5	117	5.11.1	The cost model of KinesiaU was misunderstood. The EAG is correct that 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). However, the £59 per month for clinician access to the portal is only for months that the clinician accesses the portal to view and/or download patient data, which based on the model design, would be only three times per year per patient. So, the model should have had the patient uses the device all year (£5/month x 12 months) but the clinician only access patient data three times per year (£59/month x 3 months) so total costs for KinesiaU would be only £237 per patient per year.	KinesiaU does not fall within the purview of the economic analysis given the distinct lack of clinical evidence (see comment 4). Note that it remains unclear to the EAG how the NHS may deliver monitoring that requires repeatedly subscribing and unsubscribing a clinicians

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

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
					access to a portal on an individual patient basis.
Great Lakes NeuroTechnologies Inc.	6	117	5.11.1	The report states, "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)." That study was 12 weeks long and overestimates the required duration of use. Per patient titration should be much faster for different types of therapies (e.g., days for levodopa-carbidopa intestinal gel (Lew et al., 2015), weeks for extended-release carbidopa/levodopa (Espay et al., 2017)). However, data is collected whenever the patient uses the KinesiaU, so all data is collected and stored, even when not accessed by the physician.	Not a factual inaccuracy. The EAG has undertaken evidence-based considerations for the technologies under evaluation.
Great Lakes NeuroTechnologies Inc.	7	40	3.1	The remote patient monitoring devices evaluated by the EAG only include systems that provide continuous monitoring. However, studies of devices that use tasked-based assessment (e.g., Kinesia ONE, Great Lakes NeuroTechnologies Inc.) still provide insightful information on both the usefulness and cost-effectiveness of remote monitoring for PD and should be considered in the economic analysis even if those specific devices are not eligible for inclusion. For example, in a study of Kinesia ONE for remote monitoring, for a subset of participants, the neurologist successfully used information in the Kinesia ONE reports, such as quantified responses to treatment or progression over time, to make therapy adjustments (Heldman et al., 2017). Likewise, Kinesia ONE remote monitoring was shown to help with identifying candidates for advanced Parkinson's therapies such as deep brain stimulation and drug pumps (Heldman et al., 2016), which would be another useful application for continuous remote monitoring.	Not a factual inaccuracy. Kinesia ONE does not form part of this assessment. The EAG does not agree that task-based assessment is relevant.
Great Lakes NeuroTechnologies Inc.	8	98	4.5	While Kinesia ONE does not provide continuous monitoring, home-based motor monitoring with Kinesia ONE was cost-effective in terms of improvement of functional status, motor severity, and motor complications (UPDRS II, III; IV subscales), with an ICER/UPDRS ranging from €126.72 to €701.31, respectively (Cubo et al., 2017). Even though the Kinesia ONE device is not eligible for inclusion, the results are relevant and this study should be considered by the EAG for consideration of the value of this remote monitoring technology as a whole.	Not a factual inaccuracy. Kinesia ONE does not form part of this assessment and falls outside the remit of the economic evaluation.
Great Lakes NeuroTechnologies Inc.	9	147	8.2	While the KinesiaU system is ready now to be used in clinical care applications, we welcome further studies and would be happy to participate.	No response needed
Great Lakes NeuroTechnologies Inc.	10	40	3.1	Review articles were excluded as were the opinions of key opinion leader clinicians in the field. However, clinicians who use the technologies could describe specific use cases where remote monitoring can help in their clinical care that are not adequately captured in research publications.	Not a factual inaccuracy

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

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
Great Lakes NeuroTechnologies Inc.	11	139	6.8	Although the physician might download the data one to three times a year and pay only for those times, Great Lakes NeuroTechnologies would be happy to work with NHS on a program so that other NHS researchers could download all the KinesiaU scores for tremor, bradykinesia, and dyskinesia for every two minutes of use. This will give the NHS researchers 30 data sets every hour, which over an estimated 16 hours/day and 365 days/year equates to 175,200 data sets per patient per year. With scores of tremor, bradykinesia, and dyskinesias for each data set, along with diary information on therapy dosage, this is millions of data points for every patent that can be tied back to how the patient is doing. When used by tens of thousands of patients, this will provide researchers billions of accurate data points for use in artificial intelligence and machine learning algorithm development to allow new discoveries as to the most effective treatments, saving the NHS millions or billions of pounds in the future.	No response needed
Great Lakes NeuroTechnologies Inc.	12			References: Cubo, E., Mariscal, N., Solano, B., Becerra, V., Armesto, D., Calvo, S., Arribas, J., Seco, J., Martinez, A., Zorrilla, L., & Heldman, D. (2017). Prospective study on cost-effectiveness of home-based motor assessment in Parkinson's disease. Journal of Telemedicine and Telecare, 23(2), 328–338. https://doi.org/10.1177/1357633X16638971 Espay, A. J., Pagan, F. L., Walter, B. L., Morgan, J. C., Elmer, L. W., Waters, C. H., Agarwal, P., Dhall, R., Ondo, W. G., Klos, K. J., & Silver, D. E. (2017). Optimizing extended-release carbidopa/levodopa in Parkinson disease: Consensus on conversion from standard therapy. Neurology: Clinical Practice, 7(1), 86. https://doi.org/10.1212/CPJ.0000000000000316 Heldman, D. A., Giuffrida, J. P., & Cubo, E. (2016). Wearable sensors for advanced therapy referral in Parkinson's disease. Journal of Parkinson's Disease, 6(3), 631–638. https://doi.org/10.3233/JPD-160830 Heldman, D. A., Harris, D. A., Felong, T., Andrzejewski, K. L., Dorsey, E. R., Giuffrida, J. P., Goldberg, B., & Burack, M. A. (2017). Telehealth Management of Parkinson's Disease Using Wearable Sensors: An Exploratory Study. Digital Biomarkers, 1, 43–51. https://doi.org/10.1159/000475801	No response needed

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

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
				Isaacson, S. H., Boroojerdi, B., Waln, O., McGraw, M., Kreitzman, D. L., Klos, K., Revilla, F. J., Heldman, D., Phillips, M., Terricabras, D., Markowitz, M., Woltering, F., Carson, S., & Truong, D. (2019). Effect of using a wearable device on clinical decision-making and motor symptoms in patients with Parkinson's disease starting transdermal rotigotine patch: A pilot study. Parkinsonism & Related Disorders, 64, 132–137. https://doi.org/10.1016/j.parkreldis.2019.01.025 Lew, M. F., Slevin, J. T., Krüger, R., Martínez Castrillo, J. C., Chatamra, K., Dubow, J. S., Robieson, W. Z., Benesh, J. A., & Fung, V. S. C. (2015). Initiation and dose optimization for levodopa-carbidopa intestinal gel: Insights from phase 3 clinical trials. Parkinsonism & Related Disorders, 21(7), 742–748. https://doi.org/10.1016/J.PARKRELDIS.2015.04.022 Pulliam, C. L., Heldman, D. A., Brokaw, E. B., Mera, T. O., Mari, Z. K., & Burack, M. A. (2018). Continuous assessment of levodopa response in Parkinson's disease using wearable motion sensors. IEEE Transactions on Biomedical Engineering, 65(1). https://doi.org/10.1109/TBME.2017.2697764	
Global Kinetics PTY	13	3. 7. 8. 10. Etc…	Methods Methods (systematic review) Clinical Effectiveness results Discussion	"Diagnostic accuracy" of the PKG is regularly referenced throughout the report. Additionally, page 10 states that the available evidence was of "*generally low quality… for diagnostic accuracy".* The "low quality" statement appears to be attributable to the "high" risk of bias assessment in Table 3, but as noted on p45, 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. Moreover, the intended purpose of the PKG is as a *monitoring* device. Diagnostic accuracy was not a primary outcome of the clinical trials, and any conclusions drawn regarding the quality of such – low, or otherwise, is tangential, as the PKG is utilised in the **detection** of uncontrolled symptoms in order to facilitate a correction in clinical management. • As referenced in Woodrow et al, 2020 – 72% of patients were not "in target" (i.e., uncontrolled) at the initiation of the study • As referenced in Farzanehfar et al, 2018 – 78% of patients were not "in target" (i.e., uncontrolled) at the initiation of the study	Not a factual inaccuracy. As noted, this is discussed in the EAG report.

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

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
Global Kinetics PTY	14	8	Clinical Effectiveness results	The report claims "none of these reductions achieved statistical significance". In the original report from Woodrow et al, 2020, the referenced outcomes are statistically significant values Per **Table 2** (PKG+; all participants): o Change in UPDRS Total = 8.5 points (p = 0.001) o Change in UPDRS III = 6.4 points (p = 0.01) o Change in UPDRS IV = 1.5 points (p <0.001) • Per **Table 4** (PKG+ arm; only out of target): o Change in UPDRS Total = 11.6 points (p <0.001) o Change in UPDRS III = 7.9 points (p <0.001) o Change in UPDRS IV = 2.3 points (p <0.001) And in the re-analysis using the IPD, Figure 2 shows improvement with standard error bars for UPDRS Total, -4 and -3 not overlapping baseline and "Overall, the results for the adjusted analyses were similar to the original analysis" p55	Not a factual inaccuracy. "none of these reductions achieved statistical significance" refers only to the sentence in which it appears; i.e, relating to bradykinesia etc, not UPDRS.
Global Kinetics PTY	15	118.	5.11.3	The EAG/York model assumes 45% of SoC review appointments will be conducted remotely without any objective measurement facility. This is direct contrast to the PKG remote monitoring strategy, where all remote 6-monthly review appointments benefit from objective measurement leading to an improvement in clinical outcomes (as referenced on page 3 [Results]). The NHS Long Term Plan sets out to define a series of measures that will enable the NHS move to a new service model in which patients get more options, better support, and properly joined-up care at the right time in the optimal care setting. One of the key objectives is to enact a person-centred care model, including the use of personalised digital technologies to allow up to one-third of face-to-face outpatient appointments to be shifted to a remote monitoring care context. PKG, which is already well established within the NHS, offers a simple route to achieving this goal, whilst maintaining clinical standards. This is distinct from simply substituting telephone follow-up in the absence of objective patient assessment., Many NHS trusts have been compelled to adopt this approach during the Covid-19 lockdown – however it risks compromising monitoring quality, as accurate assessment of clinical condition is difficult in the absence of face-to-face contact and/or objective assessment. We consequently believe that a clear	The base case model settings assume approximately a 34% increase in the proportion of appointments conducted remotely.

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

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
				distinction should be made in the report between simple remote follow-up and the PKG-enabled approach.	
Global Kinetics PTY	16	5	Plain English Summary	Published evidence has confirmed wearable medical devices (like the PKG) absolutely aid in the management of the symptoms of PwP[1] the use of the phrase "*may* aid management" is imprecise. Additionally, the paragraph implies smartwatches and UKCA/CE-marked medical devices are homogenous, whereas smartwatch wearable technology and medical device wearables exist in two completely discrete legislative classes. It's important to make the distinction between wearables and the entirely separate regulatory specifics of wearable medical devices (e.g., the PKG and other wrist-worn CE/UKCA-marked medical devices). [1]Viewpoint and practical recommendations from a movement disorder specialist panel on objective measurement in the clinical management of Parkinson's disease; Per Odin, K. Ray Chaudhuri, Jens Volkmann, Angelo Antonini, Alexander Storch, Espen Dietrichs, Zvezdan Pirtošek, Tove Henriksen, Malcolm Horne, David Devos and Filip Bergquist; *npjParkinsonâ s Disease* (2018) 4:14; doi:10.1038/s41531-018-0051-7	The EAG disagrees that "medical devices (like the PKG) absolutely aid in the management…" The purpose of a DAR is precisely to determine the value of a technology: it cannot be assumed to be valuable a priori. The reference to smartwatches is to aid understanding for non-specialists (as this is a Plain English summary).
Global Kinetics PTY	17	6.	Scientific Summary (Background) 3rd paragraph	While *"NICE recommends that people with Parkinson's disease should be seen by a specialist every 6 to 12 months initially, then more often with increasing disease complexity… this is often difficult because of the increasingly ageing population and demands on Parkinson's disease services".* Because of overloaded pathways and under-resourced departments, this NICE guidance cannot be routinely complied with. Compounding these issues has been the pandemic response resulting in a significant backlog[2]. The latest NHS waiting times data shows that there were currently 162,522 (September 2021) people waiting for a neurology appointment, up 4,932 from the previous month and a 48% increase on the same time the previous year. Of these 2,732 were waiting more than a year, which is an increase of 11% on the previous month[2]. The EAG report omits acknowledging the NHS Long-Term Plan (LTP)[3] objectives requiring that patients get joined up care, at the right time, in the optimal setting. To accurately assess the PKG's clinical and cost benefits, the wider strategy for patient management must be considered. Failing to include key strategic elements from the LTP	Not a factual inaccuracy Consideration of the NHS LTP is outwith the expertise of the EAG.

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

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
				when assessing new digital services could result in incomplete conclusions. Additionally, the LTP includes a pledge to redesign outpatients services and free up staff time. The LTP stresses the importance of Digital technology and how it underpins some of the plans/objectives. By the end of the 10-year period covered by the plan, the vision is for people to be increasingly cared for and supported at home using remote monitoring and digital tools (such as wearable devices). Digital technology will also facilitate service transformation, including the redesign of outpatient services[3]. Further benefits of the PKG aligned with the LTP include elements for which cost savings are difficult to quantify, such as improved flow-through via greater patient throughput, staff efficiency gains, improvement in patient QoL, increasing work capacity etc. PwP numbers have been increasing annually, "by 2025, because of population growth and an increasingly ageing population, the estimated prevalence of Parkinson's disease is expected to increase by 23.2%, and the estimated yearly incidence is expected to increase by 23.9%."[4] The long-term plan calls for a 'fundamental shift' in the way that the NHS works, with non-financial gains and improved efficacy, such as moving patients out of the acute sector, all being extremely valuable benefits. When considering the overall Parkinson's treatment pathway, further items that have been excluded from the report that the PKG can positively influence, include: reducing uncontrolled patient numbers (where a significant amount of cost exists), and allowing more new patients to be seen faster, reducing the clinical risk of patients not being followed-up in adequate time, etc. [2]https://committees.parliament.uk/writtenevidence/41401/pdf/#:~:text=Some%20people%20with%20Parkinson's%20are,on%20this%20time%20last%20year.&text=(March%20%E2%80%93%20June%202020)%20to%20the%20same%20period%20in%202019. [3]The NHS Long-Term Plan, 2019 [4] https://cks.nice.org.uk/topics/parkinsons-disease/background-information/prevalence/	
Global Kinetics PTY	18	11	Conclusions	The report states: "it is unclear whether PKG… offer(s) any clinical benefit… (to patients) receiving advanced therapies". PKG has been studied in patients with advanced disease stage and those treated with advanced therapies.	Not a factual inaccuracy. Both these papers were included in our assessment

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

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
				• As referenced in: Horne M, Kotschet K, McGregor S. 2016. The Clinical Validation of Objective Measurement of Movement in Parkinson's Disease. CNS 2016: Jun 2016. 2:(1): o DBS Testing - Rating scores and PKG measures before and six months after DBS in 30 PD patients. o A change in dyskinesia following insertion of Deep Brain Stimulators was observed and was commensurate to the changes obtained by clinical scales. A consistent change in bradykinesia and dyskinesia following levodopa was measured in patients with fluctuating PD. Bradykinesia was measured in 18 newly diagnosed participants and differed from 35 control subjects with a Sensitivity of 100% and Selectivity of 83% (Area under Receiver operator curve of 0.96). Asymmetry was greater than controls in 56% (i.e. difference >5 BKS, which is ~ 4 UPDRS III units), which broadly correlated with differences found with clinical scales. It was found that five days of recording produced a consistent bradykinesia score with a 6% standard error. • As referenced in: Khodakarami H, Farzanehfar P, Horne M. The Use of Data from the Parkinson's KinetiGraph to Identify Potential Candidates for Device Assisted Therapies. Sensors 2019, 19, 2241; doi: 10.3390/s19102241. o This study included MDS clinics and patients referred for DAT, Device Assisted Therapy (e.g., deep brain stimulation implants or duodenal infusion) or to optimize PD treatment. Subjects were randomly assigned to either a construction set (n = 112, to train, develop, cross validate, and then evaluate the classifier's performance) or to a test set (n = 60 to test the fully specified classifier), resulting in a sensitivity and specificity of 89% and 86.6%, respectively. The classifier's performance was then assessed in PwP who underwent deep brain stimulation (n = 31), were managed in a non-specialist clinic (n = 81) or in PwP in the first five years from diagnosis (n = 22). This is the first objective decision tool for managing DAT referral. The classifier identified 87%, 92%, and 100% of the candidates referred for DAT in each of the above clinical settings, respectively. Furthermore, the classifier score changed appropriately when therapeutic intervention resolved troublesome fluctuations or dyskinesia that would otherwise have required DAT. This study suggests that information from objective measurement could improve time to treatment with advanced therapy.	(see Table 4). Our comment refers to the fact that there is a limited evidence base on patients receiving, or eligible for, advanced therapy, as it is primarily these two papers.

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

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
Global Kinetics PTY	19	143	7.1.1	Confirm if this is data from the Woodrow et al, 2020 study. • Per **Table 2** (PKG+; all participants): o Change in UPDRS Total = 8.5 points (p = 0.001) o Change in UPDRS III = 6.4 points (p = 0.01) o Change in UPDRS IV = 1.5 points (p <0.001) • Per **Table 4** (PKG+ arm; only out of target): o Change in UPDRS Total = 11.6 points (p <0.001) o Change in UPDRS III = 7.9 points (p <0.001) o Change in UPDRS IV = 2.3 points (p <0.001)	No data are reported in 7.1.1. The EAG does not understand what is being asked here.
Global Kinetics PTY	20	146	7.3	The report states that "…there is little to no evidence on the possible benefits… in other patient types, such as those… on more advanced therapies". However, the validation study was completed in a patient population of early stage and later stage patients, as referenced in: Horne M, Kotschet K, McGregor S. 2016. The Clinical Validation of Objective Measurement of Movement in Parkinson's Disease. CNS 2016: Jun 2016. 2:(1)	Not a factual inaccuracy. This paper was included in our assessment (see Table 4). Our comment is simply to note that the number of studies/patients where DBS was in use was small.
Parkinson's UK	21	102	5.2	The economic modelling used does not include costs linked to people with Parkinson's whose symptoms are 'uncontrolled'. There is strong evidence to show that for this group, there are high costs to the NHS and their clinical outcomes are worse (Odin, P., Chaudhuri, K.R., Volkmann, J. *et al.* Viewpoint and practical recommendations from a movement disorder specialist panel on objective measurement in the clinical management of Parkinson's disease. *npj Parkinson's Disease* 4, 14 (2018).). Chaudri et al. (2022) demonstrate that when indirect costs are accounted for, the PKG device results in improved patient outcomes and are cost-effective for use in the NHS (Chaudhuri KR, Hand A, Obam F, Belsey J. (2022) 'Cost-effectiveness analysis of the Parkinson's KinetiGraph and clinical assessment in the management of Parkinson's disease'. J Med Econ 2022;25:774-82.). We recommend that the model is amended to include people with Parkinson's whose symptoms are 'uncontrolled'.	The EAG considers the average cost effects (i.e. averaged over 'controlled' and 'uncontrolled' status) from remote monitoring. The EAG did not establish a relationship between disease severity and costs since the EAG could not reliably infer any cost saving to the NHS/PSS that result from the generally modest impacts on patient outcomes for patients in management phase Parkinson's disease associated with remote

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

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
					monitoring therapies (PKG: approximately UPDRSIII 2.82 and UPDRS IV 0.73 reductions). Note the EAG have conducted a thorough critique of Chaudhuri et al (2022) and have concerns regarding the key structural assumptions of the model (Section 4.2.4, p85)
Parkinson's UK	22	104	5.4	The devices being evaluated here are being measured against UPDRS scales. It is our understanding that these scales are not used remotely. If the model does not include the cost of using these scales for Standard of Care (SoC) (as the scales are being used in clinic and therefore at no cost), it is not comparing like for like. We recommend that the model be revised to take account of this discrepancy because it will likely affect the Incremental Cost Effectiveness Ratios (ICERs) of the remote monitoring devices being evaluated.	The UPDRS scores estimated in the model are simply a measure of disease severity exogeneous to observation/recording. There is no cost per se of measuring underlying disease severity according to UPDRS (whether that be for SoC or that using a remote monitoring therapy.
Parkinson's UK	23	142	6.8	We also note that the model includes costs for a nurse-led rather than a consultant-led service which could lead to the Standard of Care costs being underestimated. This will likely adversely affect the ICERs of the PKG and other devices being evaluated. We recommend revising the model to account for the cost of a consultant-led service and a nurses-led service.	See Section B comment issue 4.
Parkinson's UK	24	general	general	We also believe consideration should be given to the positive feedback PKG has received from people with Parkinson's. From a multicentre service evaluation of the implementation of PKG devices, 78% reported a positive experience, 20% a neutral experience and only 2% a negative experience (Thomas, C., Mohamed, B., Abdeldagir, E., Silverdale, M.A., Kobylecki, C., Osborne, L., Smith, M., Hulejczuk, A., Saha, A.R., Bain, P.G., Caroll, C. (Can Implementation of Technology Transform the Management of Parkinson's: Lessons	The report contains discussion of patient opinions on PKG and other devices. See Section 3.3.5.

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

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
				learnt from the Parkinson's KinetiGraph (PKG) service evaluation project.Poster Presented at Parkinson's Study Group MDS Vancouver in 2017). They also reported enhanced discussions with their clinicians and greater confidence in the therapies applied. From another service evaluation, 92.5% of people with Parkinson's either agreed 27.5% or strongly agreed 65% with the statement, "I would be willing to use the PKG again to assist in the management of my Parkinson's Disease in the future" (Price, J., Martin, H., Ebenezer, L., Cotton, P., Shuri, J., Martin, A., Sauerbi,er (2016) 'A service evaluation by Parkinson's Disease Nurse Specialists of Parkinson's Kinetigraph (PKG) movement recording system-use in routine clinical care of patients with Parkinson's Disease' Poster presented at World Parkinson Congress (2016)).	
Parkinson's UK	25	11	n/a	The report authors question the quality of the available evidence of the cost effectiveness of these devices, for example "Concerns about potential bias, together with the other limitations in the available evidence, means that cost-effectiveness estimates are highly uncertain." Yet make a firm conclusion in "The results of the economic analysis are largely unfavourable, with ICERs in excess of thresholds typically adopted by NICE." We recommend that wherever the report sets out its conclusions on cost effectiveness, these are qualified with the limitations of the available evidence on cost-effectiveness	Not a factual inaccuracy. Uncertainties raised throughout the report by the EAG. Readers can refer to Section 7.3, a section dedicated entirely to the uncertainties in the EAG's analysis.
PD Neurotechnology	26	6	Scientific Summary	We appreciate the time and effort it takes to evaluate novel Health Technologies, touching upon digital health, Artificial Intelligence, Big Data Analysis, Data security, management and privacy, Software as a Medical Device, mHealth and Internet of Medical Things, Wearables, digital transformation and chronic disease management. Furthermore, we appreciate the fact that Parkinson's Disease is a very complex disease, where the patient's phenotype and corresponding treatment needs change with time in varying speed by patient. After a while, literally every time the patient visits the physician, he/she is a different patient, with different needs on all aspects of his/ her management. Accordingly, the patient management is considered optimal in a Multi-Disciplinary expert Team context, on the basis of understanding the fine elements of the patient's symptomatology, grading them and reacting to those grades and on the basis of adjusting medication regimes with a very big number of doses daily. (Oftentimes more than 10 per day). Unfortunately, so far, this entails a very high degree of subjectivity and is prone to errors in fine tuning the doses and in their adherence by the patient.	This comment does not identify any factual inaccuracies, but see EAG comments below. See also our response to comment 49

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

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
				Overall, we fully understand the methodology used and would like to comment on the following overarching themes: (Most of the rest of the comments 27 -64 *[2 – 39 when submitted as standalone document])* detail the points raised here. They also include the Appendix* references) A) Regulatory aspects are briefly touched upon, considering CE marking as the main point of consideration. One of the devices does not have a CE mark. Data management, privacy and security are not analysed. PD Neurotechnology is certified among other with ISOs 27001 for Data management and data security and ISO 27701 for data privacy and GDPR aspects. B) There is a matter of definition of Continuous Objective monitoring with regard to the frequency and duration of monitoring in combination to the follow-up and treatment protocol by the clinicians. The following, in our view, are missing from the analysis: a. The minimum time needed in order to have a result is only mentioned for one of the devices (six days). PDMonitor can offer a complete evaluation in as little as half an hour of use (30'), for that half hour. It is recommended to use it for 2-5 days, in order to draw representative results from a behavioural standpoint, as patients' activities, diet or adherence to medication may differ day by day. b. All devices can be used as a Holter, i.e. for ad-hoc monitoring sessions, but with the exception of PDmonitor, as far as we can tell, all other have logistical difficulties being used for Long Term continuous monitoring sessions, as they all need to be taken to a base at the hospital or physician practice, to download the results. PDMonitor's architecture allows it to remain at the patient's home and transmit results as soon as the session is over through the internet. This means that it stays with the patient for as long as needed, allowing intermittent monitoring, without logistical issues. These issues are briefly mentioned in the DAR, but not analysed. In a scenario of frequent monitoring, more often than every 2-3 months, which is referenced in the DAR as necessary for certain patients, PDMonitor, as far as what we can tell, is the only one without these logistical issues. c. In the use case scenarios, the repeat use after a monitoring session, within the same month, is not referenced at all. This type of use allows for a treatment change and then a monitoring session, the week after, to evaluate the impact of this change and possibly adjust the treatment	

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

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
				further. This type of fine tuning, based on our understanding, can only be achieved with the architecture of the PDMonitor system, as mentioned above. C) There is a new paradigm in using devices like the ones under evaluation. However, this new paradigm, in the DAR, is only discussed through the specific device driven publications. There is extensive literature on the matter of continuous objective monitoring in Parkinson's Disease and what that should look like, in a real life setting and also there is extensive coverage of this aspect by the NHS, with regard to its digital transformation goals. These are briefly referenced in the Appendix to this document and also in the PDMonitor Business case, included in the Appendix as part of a relevant link. D) The devices also have other key differences which are not covered in the evaluation. PDMonitor, apart from its advantage mentioned above, pertaining to its architecture as a system, monitors all motor symptoms across limbs and in an aggregated manner, keeps patient data for 10 years allowing for ease of comparison with the past and also for establishing trends of patient's symptomatology. It also allows for comparison among the symptoms and for an active communication between the patient and the physician, based on facts. To this end, the mobile app plays a significant role. Please refer to a detailed assessment of the technical differences between the devices, listed in the Appendix. E) Data about PDMonitor's performance was only taken from 2 papers. There are more than 15 publications about the performance of the PDMonitor's algorithms, included in the relevant brochure submitted to NICE and mentioned in the Appendix as part of a link, for easy reference. PDMonitor's performance with regard to various symptoms is included in our brochures with a clear reference to the study population and characteristics, and officially included in the PDMonitor Instructions For Use, which officially reflect the Technical File submitted to the Notified Body. (DQD MED) Furthermore, it is included in other publications as per our publications brochure, submitted to NICE and other publications listed in the Appendix, as part of the respective link. Finally, pls see a reference in the Appendix of latest submitted or published papers which further describe PDMonitor performance and other abstracts in submission process. F) Furthermore, on PDMonitor monitoring performance, it is important to note that PDMonitor shows symptom monitoring results on clinically relevant scales, UPDRS, which make results easily actionable. Validation as shown in our	All references listed in company-supplied documentation were reviewed by the EAG for eligibility. It was our view that most papers were not eligible for inclusion: many were conference abstracts with insufficient reporting or were not of PDMonitor explicitly.

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

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
				publications and mentioned in the DAR was based on comparison with expert physician ratings. G) Clinical effectiveness data about PDMonitor is not publicised as of yet, nonetheless you can see attached in progress abstracts. Respective articles are expected to go public in the next months. Furthermore, clinical effectiveness data was also submitted to NICE in February and re-submitted in an updated presentation, today. A relevant link is included in the Appendix. H) Cost effectiveness data about PDMonitor is included in the NHS business case document submitted to NICE in February, also refenced in the Appendix. A provisional 9% cost saving on direct healthcare hospitalisation cost, without taking into account other direct healthcare costs, such as medication or visits costs or indirect cost benefits or quality of life improvement. I) In the coming months, as our studies and real-life evidence mature, we will publish more papers and conference abstracts about PDMonitor clinical effectiveness and cost effectiveness. It must be noted that we have Real World Data from PDmonitor's use in the last 24 months (despite the pandemic, which actually coincided with PDMonitor's launch) with more than 500 patients, in Sales or in Studies, with more than 7000 days of monitoring in 10 European countries, with more than 150 trained physicians in PDMonitor use, out of which more than 20 expert physicians. J) We will stratify this data and produce more publications, while in parallel we will deepen our work in the UK, which so far relates to 4 centers, namely: King's College, St. George's, Belfast and Dementech. Accordingly, we would welcome the opportunity to work with NICE in further using PDMonitor for Continuous Objective monitoring to prove Cost effectiveness in the NHS context, as decried in our Business Case, but also in other use cases.	These data were not, to our knowledge, supplied to the EAG. Material mentioned by the company here (supplied by the company after DAR submission) may contain some relevant diagnostic accuracy data, but the EAG has not been able to assess this in the limited time available

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

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
PD Neurotechnology	27	25	1.2.2	Daytime Lying in bed is also important to be monitored and is one of the behavioural aspects monitored with PDMonitor, together with activity levels and Lack of Movement. Please also refer to the User Manual, included in the material submitted to NICE and in the Appendix as a link to that material.	Not a factual inaccuracy.
PD Neurotechnology	28	25	1.2.2	Stratifying patients for Advanced therapies is very important in the patient journey. Publications of some of the devices under evaluation attest to that, as mentioned in the DAR. PDMonitor's Real World Evidence include numerous cases and will soon be published accordingly.	Not a factual inaccuracy.
PD Neurotechnology	29	26	1.3.1	"People with Parkinson's disease (PwP) experience a range of motor symptoms, which can fluctuate in severity during the day and between days." => Furthermore, their status possibly changes month by month, especially after a certain stage in the disease, possibly before the next visit to the physician and even so these changes may go undetected, due to the white coat effect, hence the need for LT monitoring to understand promptly status changes and act upon them through optimization.	Not a factual inaccuracy. Section 1.3.1 concerns PKG, not PDMonitor
PD Neurotechnology	30	26	1.3.1	"to assess motor symptoms (bradykinesia and dyskinesia)" => motor symptoms also include tremor, gait impairment, postural instability and FOG. Also upper limbs vs lower limbs tremor, dyskinesia or bradykinesia are equally important, as well as differences between left and right. They help personalize treatment and assess status change from unilateral to bilateral symptomatology. Among other, see also the Opinion letters included in our brochures list, part of the Appendix with submitted material to NICE, in February.	Not a factual inaccuracy.
PD Neurotechnology	31	26	1.3.1	"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." => Diaries could actually be replaced, as PDMonitor intel is far more encompassing and precise compared to diaries. System is user friendly. Please refer to presentation with unpublished material and to relevant abstract, all included in the Appendix as part of the respective links with data submitted in February and new data submitted today.	Not a factual inaccuracy. This was the view of NICE/clinical experts
PD Neurotechnology	32	26	1.3.1	"Results from the monitoring devices may also have more general benefits" => Additional benefits of PDMonitor relate to the fundamentals of participatory patient, taking control of their own fate, by looking at reports, understanding progress, and eventually turning into a self-managed patient in an equitable manner. Please also refer to the Appendix and to submitted brochures.	Not a factual inaccuracy.
PD Neurotechnology	33	26	1.3.1	"This assessment considers only wearable remote monitoring devices that produce results with no input, or limited input, from the user." => PDMonitor is an entire ecosystem around the patient, allowing for not only the patient's objective monitoring, but also the patient's nutrition and medication and non-motor input through the use of a user friendly mobile	Not a factual inaccuracy.

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

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
				app, or alternatively the same input by the caregiver at home, through the caregiver's mobile app. We have provisional evidence, included in today's and February's submissions to attest to that and publications in progress.	
PD Neurotechnology	34	27	1.3.1	"event markers for medication reminders" => Since monitoring is done for 6 days a year or every 3 months, having a reminder skews the results as adherence monitoring is biased. Also, getting used to taking pills on time, based on reminders, and then not getting alerts, immediately after, when the device is not in use could confuse patients. That is why pill alerts during monitoring is possibly not a good practice.	Not a factual inaccuracy.
PD Neurotechnology	35	27	1.3.1	"It is also intended to be used to monitor activity associated with movement during sleep." => Activity during sleep is more complex and includes among other capturing the RBD and RLS, or patient turns while asleep, which are the main Sleep related symptoms. Hence, this functionality is far from optimal, while single sensor watch like technologies have limitations capturing the right Sleep symptoms in exactly the same way as they cannot capture all daytime symptoms, as needed. (see comment above). PD Neurotechnology is expected to capture these Sleep symptoms with the next version of PDMonitor. It is the only device which can do that, because of the 5 wearable monitoring devices.	Not a factual inaccuracy.
PD Neurotechnology	36	27	1.3.1	"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." => This comes as a contradiction to the latest study by PKG, recently publicized, whereby they test the use of their device while performing Long Term continuous monitoring, for 6 days every month. PD Neurotechnology considers this as the best practice, for patients in advanced fluctuations or troublesome dyskinesias, based on the advice by the company's medical advisory board, with evidence about this soon to be published in a delphi forum paper. Opinion letters are included in the Appendix as a link of the material already submitted. This is also provisionally validated with Real Life Evidence, from the Greek LT continuous monitoring real life registry. Building on this point, PDMonitor is the only medical device that allows for user friendly LT continuous objective monitoring, due to its cloud based architecture, which allows for the device to stay with the patient for as long as needed, days, weeks, months or even years. (not just a holter). Please see more about this in the Appendix.	Not a factual inaccuracy. This was the view of NICE/clinical experts
PD Neurotechnology	37	27	1.3.1	"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." => This is not needed in the case of PDMonitor, as home internet allows for prompt monitoring of even same day, or for less than a day.	Not a factual inaccuracy. Section 1.3.1 concerns PKG, not PDMonitor

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

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
PD Neurotechnology	38	27	1.3.1	"The PKG measures bradykinesia, dyskinesia, tremors, motor fluctuations, immobility and when the watch is not being worn." => This is a small subset of symptoms captured by PDMonitor, where on top of the ones mentioned here, the following symptoms are also captured: gait impairment, postural instability, Freezing of Gait, together with a number of gait parameters such as stride length, number of steps, etc. Also, bradykinesia, tremor, dyskinesia are captured left vs right, which helps ascertain whether the disease has progressed from unilateral to bilateral. Symptoms are displayed in the UPDRS scale, in 30' intervals, helping the physician understand the patient's status in the same way as they have been used to, so far. Finally and most importantly, there is a global OFF score, integrating symptoms and giving a clear holistic view of the patient's status. In the same global graph, the physician can look and compare OFF score and fluctuations, Dyskinesia score fluctuations, UPDRS score and fluctuations, accompanied by activity measures and a heat map. Medication and Nutrition types and timing are also evidently shown, both together with the above universal bio markers and with each symptom measured, making treatment optimization easy to manage. Please refer to the Appendix for evidence to the above.	Not a factual inaccuracy. Section 1.3.1 concerns PKG, not PDMonitor
PD Neurotechnology	39	28	1.3.2	"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." => PDMonitor can record up to 3 days of motion data before the monitoring devices need to be recharged.	Section 1.3.1 concerns Kinesa 360, not PDMonitor
PD Neurotechnology	40	29	1.3.4	"The PDMonitor system consists of the SmartBox, 5 monitoring devices and a PDMonitor mobile application." => It also consists of the cloud module, where all info is uploaded and securely kept for 10 years. Furthermore, there is a cloud-based management tool, called the Physician Tool, which offers a user friendly depiction of all symptoms (except rigidity), the OFF score and other aggregate symptoms, helps group patients based on the change in their OFF score, or Dyskinesia score or UPDRS score, helps compare symptoms to each other and reports across time. This means that this not just a reporting tool, but also an active management tool per patient, but also for the entire practice. (for patients using PDMonitor) It is also an Electronic Patient Record, where data is kept for 10 years, easily retractable and compared through time with summary scores and bio markers. Apart from accessing the data through the portal, concise reports are also available in pdf format. Please refer to the Appendix for further info.	Not a factual inaccuracy.
PD Neurotechnology	41	29	1.3.4	"and symptoms related to Parkinson's disease" => including self-reported non motor symptoms	Not a factual inaccuracy.
PD Neurotechnology	42	29	1.3.4	"1.3.4 PDMonitor (PD Neurotechnology" => Please refer to comments on other devices about PDMonitor characteristics and functionalities which are referenced in the Appendix. Please also refer to PDMonitor brochures for detailing of PDMonitor advantages and	Not a factual inaccuracy.

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

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
				usage in daily practice, as well as publications so far. They were all submitted to NICE in February for this Diagnostic Assessment Program. In summary, PDMonitor works for any kind of continuous objective monitoring, in line with the physician's request. With regards to Long Term continuous objective monitoring it is also ideally suited, given the overall architecture, cloud based, which allows for the device to stay at patient's home, without the unnecessary back and forth to the hospital. (not just a holter, but much more than that) It also captures all motor symptoms, (except rigidity) top to bottom, left to right, including gait impairment, postural instability and freezing of gait. As mentioned above aggregate bio markers are also derived for OFF and UPDRS. They are all needed for a proper assessment of the patient. Furthermore, PDMonitor offers a holistic view to the physician through the use of the mobile app, which allows for the timing and type of medication to be captured, together with the timing and type of nutrition and the non-motor symptoms, and feedback to the patient. Finally, data is kept for 10 years, abiding by GDPR, hence offer an electronic patient record with the entire patient history. Finally, the Physician Tool is a management tool that offers user friendly, validated, easily actionable, continuous intel, using known scales in PD management to the physician, in order to take prompt and precise decisions. Furthermore, the company's certifications are such that prove data security and management and GDPR compliance.	We note that the EAG report can only give a summary of the properties of the technology, not an exhaustive description.
PD Neurotechnology	43	31	1.4	"PD Monitor is available in the UK and is currently in demo use at King's College, St George's and Belfast Trusts." => It is also used with patients paying out of pocket at Dementech and as part of a clinical study at Dementech/ King's college.	Not a factual inaccuracy, but we accept this clarification.
PD Neurotechnology	44	31	1.4	"The maintenance stage is when symptoms are controlled, perhaps by medication." => As mentioned also later in the DAR, symptom fluctuations in line with treatment and its side effects are a decisive factor of the patient's quality of life. They may also lead to falls, traumas, adhoc outpatient visits, etc. Hence, there is an unmet need, evidenced through numerous publications and white papers, some of them listed in the Appendix, for continuous objective monitoring at home, in order to promptly capture changes in the patient's status and accordingly optimize treatment.	Not a factual inaccuracy.
PD Neurotechnology	45	32	1.6	"between review appointments (to allow for more frequent monitoring of symptoms, or where there is substantial time between appointments)" => In this case and especially for patients with advanced fluctuations and/ or troublesome dyskinesias, patients that based on same paragraph could be seen every 2-3 months, you may end up using continuous objective monitoring once per month for a few days, which is what we call LT continuous objective monitoring. This will support identifying promptly patient status changes and accordingly offer treatment optimization even with additional monitoring sessions within the same month of treatment change.	Not a factual inaccuracy.

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

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
PD Neurotechnology	46	32	1.7	"the association between monitoring results and clinical measures (such as bradykinesia and dyskinesia)" => As mentioned above monitoring of all motor symptoms (except rigidity) and OFF score and UPDRS is also possible, with PDMonitor, and needed as these symptoms and aggregate scores are all used in today's clinical practice.	Not a factual inaccuracy.
PD Neurotechnology	47	33	1.7	"• Rating scales such as the UPDRS, MBRS and the Hoehn and Yahr scales • Other measures of bradykinesia and dyskinesia, sleep disturbance or tremor" => PDMonitor also captures OFF time and relevant fluctuations. As mentioned above, PDMonitor captures all other motor symptoms, except rigidity. Finally, scales used and validation are very important. To this end, PDMonitor uses UPDRS scales, validated against expert physician monitoring.	Not a factual inaccuracy.
PD Neurotechnology	48	33	1.7	"Clinical outcomes" => all other motor symptoms, as mentioned above	Not a factual inaccuracy.
PD Neurotechnology	49	34	1.7	"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." => We understand that this assessment is made based on published evidence, accordingly >17 additional publications, as per our brochures submitted to NICE in February should be possibly taken into account. Furthermore, in the Appendix, you can read a performance related publication, under submission. Finally, in February we submitted a plethora of unpublished evidence on outcomes improvement, on the pipeline to be expanded and publicized in the coming months. Finally, pls note that PDMonitor Instructions For Use clearly state its Performance results, submitted to DQS MED for CE marking class IIa certification.	The EAG assessed all published and unpublished evidence as reported by all manufacturers for eligibility. The EAG received an RFI document and "Instructions for use" document from PD Neurotechnology via NICE, along with some other material online. In our view, none of this documentation either contained, nor referred to, any eligible studies. The EAG notes that if it is to consider unpublished data, this must be provided in an unambiguous format, such as a draft paper, or trial report document.

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

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
					Therefore, our view was that the evidence the company provide din February was not eligible for inclusion. We note that some evidence supplied with this documentation (and after report submission) may contain relevant diagnostic accuracy data, but we have not been able to fully assess it in the limited time available.
PD Neurotechnology	50	34	1.7	"Costs" => Our view on costs is included in our business case, submitted to NICE in February. Accordingly, there is a possible net saving of ca. 9% on direct hospitalisation cost for the advanced patient population without significant cognitive impairment, without taking into account other direct cost, indirect cost and possible quality of life improvement.	Not a factual inaccuracy. The EAG's economic analysis uses a direct evidence-based approach for the technologies. There is no clinical evidence to support the net savings reported here.
PD Neurotechnology	51	36	2.1.1	"The searches were carried out on 1st February 2022" => We were asked to submit published and unpublished evidence, post that date, to NICE, therefore we kindly ask that this evidence is taken into account. Please refer to the Appendix.	Not a factual inaccuracy.
PD Neurotechnology	52	40	3.1	"the study of PDMonitor was conducted in Greece and Italy." => the study of PDMonitor that proves performance and was used for CE marking class IIa technical file was conducted also in Germany. Among other ongoing studies, there is one in the UK.	Not a factual inaccuracy (in our understanding of the relevant publication)
PD Neurotechnology	53	44	3.2	Tables 1 and 2 do not take into account a number of publications and conference proceedings, submitted to NICE in February. Furthermore, additional intel can be found in the Appendix.	See response to comment 49
PD Neurotechnology	54	44	3.2	"Evidence on the intermediate impact of the devices, such as whether their use led to changes in treatment, was generally only available for PKG." => Please also refer to unpublished evidence submitted to NICE in February.	See response to comment 49

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

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
PD Neurotechnology	55	44	3.2	"There was limited evidence on patient, carer or clinical opinions, mostly for PKG." => Please also refer to unpublished evidence submitted to NICE in February.	See response to comment 49
PD Neurotechnology	56	76	3.6	"One paper95 and one conference abstract93 discussing the PDMonitor technology were identified." => Pls refer to comments, as per above, about existing publications, one under submission and pipeline of publications, based on data submission to NICE in February.	See response to comment 49
PD Neurotechnology	57	90	4.3	"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." => We suggest that a similar approach is taken towards the PDMonitor business case, submitted to NICE along with other non-published evidence in February 2022.	Not a factual inaccuracy
PD Neurotechnology	58	102	5.3	"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" => In the case of PDMonitor, there are two aggregate scales: OFF and UPDRS score which are expressed as a function of time, as are the symptoms based on UPDRS scales, and as a total % of time above a certain threshold. Accordingly, it has been evident to physicians using this technology what they need to optimize and how it fares before and after. Unpublished evidence, included in the Appendix attest to that.	Not a factual inaccuracy.
PD Neurotechnology	59	106	5.4	"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-	Not a factual inaccuracy. The time horizon statement is in reference to the internal consistency of the EAG economic analysis. By using a 5-year time horizon our analysis keeps within the observation period of the studies used to inform the key relationships established and used within the model. The rationale is not related to treatment plan optimisation. For further details see Section 5.4 of the EAG report.

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

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
				up)." => This rationale is not taking into account the treatment plan to optimize existing regimens with time. (dosage, number of doses in specific times through the day)	
PD Neurotechnology	60	106	5.4	"The economic analysis also implicitly assumes that remote monitoring will not continue beyond the maintenance disease stage reflecting the available clinical evidence" => This is based on some of the studies assessed. Nonetheless, based on Real Life Evidence, ongoing studies, opinion letters and other submitted material, included in the Appendix, a time in the life of a patient where LT continuous objective monitoring is needed is among other when advanced fluctuations or troublesome dyskinesias appear.	Not a factual inaccuracy. See comment 59 for further details.
PD Neurotechnology	61	106	5.4	"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" => This is not our understanding based on literature review, establishing the clinical unmet need and also based on Real World Evidence. Please also refer to third party publications as per the Appendix.	Not a factual inaccuracy. See comment 59 for further details.
PD Neurotechnology	62	117	5.11.1	"Table 29 Remote continuous monitoring device costs" => If the total cost of PDMonitor is 12,000, how can the yearly cost be the same?! PDMonitor's useful life is officially 7 years (could be more), ie. cost is 12,000/7 = 1714.3 GBP per year. If LT continuous objective monitoring is applied, then 1714.3/12 = 142.9 GBP per month, which together with Staton is the second cheapest of the five, after KinesiaU. Therefore, for the population where more frequent monitoring than every 2-3 months is needed (benchmark given in the beginning of the assessment report) the cost rankings changes as per above. Based on our analysis, explained in the Business Case document submitted to NICE in February, about 17% of population are eligible, ie. the ones in advanced fluctuations, with no cognitive impairment.	This is a factual inaccuracy, erratum makes the following change: Original £12,000† †assumes one patient per subscription/device Revised £2,400 (routine-use) †assume one patient per subscription/device with routine use over a 5-year time horizon This was a typo in the EAG report.
PD Neurotechnology	63	117	5.11.1	"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." => As mentioned in the answers to	Not a factual inaccuracy.

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

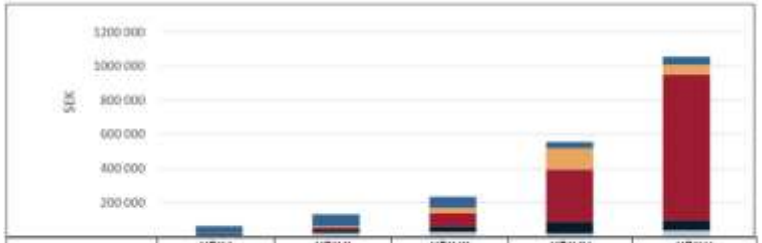
Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG response
				relevant question by NICE, in the information submitted in February, PDMonitor usage scenario and price may vary for earlier patients, used as a one-off optimization tool (e.g. 2-3 monitorings within one month and then off to another patient)	
PD Neurotechnology	64	117-136	5.11.1 – 6.6	All tables used contain the above bias	Not a factual inaccuracy.

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

Section B: Comments on the economic model

Stakeholder	Issue	Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)	EAG response
Great Lakes NeuroTechnologies Inc.	1	As described above, the cost model of KinesiaU was misunderstood. The EAG is correct that KinesiaU comprises patient-level costs for access to the company's smartphone/smartwatch app (£5 per month) and clinician-specific costs for access to the KinesiaU portal (£59 per month). However, the £59 per month for clinician access to the portal is only for months that the clinician accesses the portal to download patient data, which according to the model would be only three times per year per patient, on average. If we assume that the patient uses the device all year (£5/month x 12 months) but the clinician only access patient data three times per year (£59/month x 3 months) total costs for KinesiaU would be only £237 per patient per year. Likewise, as described above, KinesiaU continuous monitoring includes nearly identical data processing to the Kinesia 360 for its continuous passive monitoring as described in (Pulliam et al., 2018). Kinesia 360 was designed for the clinical trial market (all hardware included) while the KinesiaU was designed to allow patients to use their own compatible smartphone and smartwatch instead of our proprietary sensor hardware. Therefore, the same economic analysis applied to Kinesia 360 should be applied to KinesiaU but reflecting the lower costs of KinesiaU.	The economic analysis applied to Kinesia 360 should be applied to KinesiaU but reflecting the clarified lower costs of KinesiaU described herein.	This will significantly improve the cost-effectiveness of KinesiaU.	See comment 5.
Global Kinetics PTY	2	When assessing health state costs for the model, the EAG report considers the costs of initiating and administering the technology under review, combined with an assessment of outpatient attendance and drug treatment costs. These estimates were independent of the clinical state of the patient – ie *they did not reflect changes in costs associated with evolving disability.* This assumption undermines the validity of the model, as it fails to take into account the fact that costs of care change substantially as the clinical condition deteriorates. Given that the primary benefit of the PKG system, as demonstrated by Woodrow et al[1], is to allow optimisation of treatment with consequent maintenance of patients in a better	We propose that the basis of costing in the economic model, insofar as it affects PKG, should be amended by the EAG in order to reflect the health state-specific values cited in our comment. Given the fundamental importance of this aspect of the model, we would suggest	We would anticipate that this modification will increase the incremental health-state related cost difference between PKG and SoC, with a consequent reduction in the ICER	See comment 21.

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

Stakeholder	Issue	Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)	EAG response
		controlled clinical state. Whilst the impact on other costs should not be ignored, omitting health state-specific costing means that the model, as presented, fails to capture the health economic impact of using the device. The most recently published study to assess the cost of care associated with PD is based on an analysis of 960 patients treated over a 7-year period in Sweden[2]. Costs of care were analysed by Hoehn & Yahr stage, a scale which is widely used to capture the degree of disability experience by patients with PD. The figure below (figure 1) is taken from the paper – all costs are in 2019 Swedish Krona (approximate exchange rate: 12SEK = £1). Each advance in Hoehn & Yahr stage is associated with a doubling in overall expenditure, while the distribution of individual cost components also changes substantially (table 1) These findings qualitatively mimic the results described by Findlay et al in an earlier UK analysis assessing patterns in change in costs as OFF-time increases[3] Figure 1 – extract from Hjalte et al[2]  H&Y I (n=410) / H&Y II (n=493) / H&Y III (n=334) / H&Y IV (n=73) / H&Y V (n=14) Productivity loss: 36 974 (138 760) / 67 383 (186 770) / 63 351 (189 042) / 37 266 (156 303) / 47 535 (177 858) Informal care costs: 1 771 (21 700) / 7 497 (38 903) / 30 840 (94 830) / 122 829 (259 001) / 55 421 (139 705) Transport costs: 447 (844) / 1 218 (5 254) / 1 147 (3 292) / 2 061 (5 107) / 1 075 (2 056) Formal care costs: 1 186 (12 783) / 13 183 (120 159) / 79 259 (279 433) / 306 465 (372 060) / 855 038 (606 877) Drug costs: 10 783 (19 237) / 18 296 (45 897) / 31 307 (74 725) / 69 283 (137 407) / 60 221 (119 896) Inpatient and outpatient costs: 11 245 (22 974) / 22 865 (55 696) / 28 492 (50 114) / 18 765 (19 923) / 37 035 (94 172)	that the base-case should be modified to reflect this change, rather than simply carry out a scenario analysis		

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

<table>
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<tr><td></td><td></td><td>
Table 1 – analysis of data presented in figure 1[2]
<table>
<tr><th>Hoehn & Yahr stage</th><th>Total cost (SEK)</th><th>% due to drugs and hospital attendance</th><th>% due to formal care (PSS)</th><th>% due to informal and societal costs</th></tr>
<tr><td>I</td><td>62,406</td><td>35.3%</td><td>1.9%</td><td>62.8%</td></tr>
<tr><td>II</td><td>130,442</td><td>31.6%</td><td>10.1%</td><td>58.3%</td></tr>
<tr><td>III</td><td>234,396</td><td>25.5%</td><td>33.8%</td><td>40.7%</td></tr>
<tr><td>IV</td><td>556,669</td><td>15.8%</td><td>55.1%</td><td>29.1%</td></tr>
<tr><td>V</td><td>1,056,325</td><td>9.2%</td><td>80.9%</td><td>9.9%</td></tr>
</table>
The distribution of Hoehn & Yahr states in the post assessment population, as described by Woodrow et al are presented in Chaudhuri et al[4], broken down by PKG/control arm (table 2). These H&Y estimates were calculated based on a bootstrapped analysis of aggregated results provided to the authors by the investigators of the study reported by Woodrow et al. Although the absolute magnitude of difference within each category is not great, the exponential relationship between costs and Hoehn & Yahr stage means that this difference can have a substantial effect on overall cost of care.

Table 2 – extract of data from Chaudhuri et al[3]
<table>
<tr><th>Hoehn & Yahr stage</th><th>% in PKG arm</th><th>% in control arm</th></tr>
<tr><td>I</td><td>13.9%</td><td>11.7%</td></tr>
<tr><td>II</td><td>49.3%</td><td>40.4%</td></tr>
<tr><td>III</td><td>33.6%</td><td>38.9%</td></tr>
<tr><td>IV</td><td>3.3%</td><td>8.9%</td></tr>
<tr><td>V</td><td>0%</td><td>0.3%</td></tr>
</table>
References:
</td><td></td><td></td><td></td></tr>
</table>

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

Stakeholder	Issue	Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)	EAG response
		1. Woodrow H, Horne M, Fernando C, et al. A blinded controlled trial of objective measurement in Parkinson's disease. *npj Parkinson's Disease* 2020;6:35 2. Hjalte F, Norlin J, Kellerborg K, Odlin P. Parkinson's disease in Sweden – resource use and costs by severity. *Acta Neurolologica Scandinavica* 2021;144:592-9 3. Findley L, Wood E, Lowin J, et al. The economic burden of advanced Parkinson's disease: an analysis of a UK patient dataset, Journal of Medical Economics, 2011;14:130-139 4. Chaudhuri K, Hand A, Obam F, Belsey J. Cost-effectiveness analysis of the Parkinson's KintetiGraph and clinical assessment in the management of Parkinson's disease. *Journal of Medical Economics* 2022;1:774-82			
Global Kinetics PTY	3	As outlined in [our first] comment above, the contribution of drugs and outpatient attendances to the total costs of care in PD is relatively small, ranging from 35% in the most mildly affected patients, down to 9% at the most severe end of the spectrum. Social care costs – both formal and informal – are a far more important determinant of the overall cost of care. It is clearly documented in the NICE Reference Case for cost effectiveness evaluation of diagnostic products that both direct NHS costs and PSS costs should be accounted for in the model, where possible[5]. Given that the components of cost of care[2] and the relevant population distribution in Woodrow et al[1,4] are both available, it would seem reasonable that the reference case should be followed and that PSS costs should be incorporated in the model. This approach was adopted in the 2017 NICE guidelines for PD in adults, with the methodology adopted to apportion care costs to public vs private funding sources being fully documented in paragraph F.3.1.13, appendix F of the documentation supporting the guidance[6].	As part of the revision to the costing approach described in [our first] comment we would propose that the inclusion of PSS components in the base-case model should be undertaken.	We would anticipate that this modification will further increase the incremental cost difference between PKG and SoC, with a consequent additional reduction in the ICER	The EAG's economic analysis relates to management phase Parkinson's disease. The approach adopted in the 2017 NICE guidelines for PD in adults was in relation to advanced disease, where social care costs are relevant. Note Chaudhuri et al (2022) (an economic evaluation of PKG funded by Global Kinetics Pty Ltd.) did not make any direct reference to social care costs.

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

Stakeholder	Issue	Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)	EAG response
		References. 5. National Institute for Health and Care Excellence. Diagnostics Assessment Programme manual. Available at: https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-diagnostics-guidance/Diagnostics-assessment-programme-manual.pdf 6. National Institute for Health and Care Excellence. Parkinson's disease in Adults (NG71). Guidelines appendix F. Full health economics report. Available at: https://www.nice.org.uk/guidance/ng71/documents/guideline-appendix-6			
Global Kinetics PTY	4	The model assumes that all outpatient care contacts are provided by specialist nurses and assigns costs accordingly (£81.41 for face-to-face consultation and £56.41 for a remote appointment). We believe this is not representative of the care delivery process within the NHS. Whilst specialist nursing services are central to the monitoring of PD, they do not operate in isolation. The authors use service codes N22AF and N22AN to arrive at their costing. This code relates to specialist nursing liaison services for dementia and PD. In 2019-20, there were 45 NHS trusts that used one or both of these codes. In every case the Department Code assigned was CHS (Community Health Services)[7]. These codes do not, therefore, relate to hospital-based neurology outpatient services. The more appropriate codes and prices to use would relate specifically to outpatient services, as outlined in table 3 below. This error has potentially important consequences, as one of the benefits of PKG is a reduction in the requirement for face-to-face attendance, as it permits remote objective assessment of PD symptoms, which can normally only be carried out in a face-to-face setting. The model reflects this by assuming an increase in remote consultation rate from 45% in SoC to 79% in PKG-managed patients.	We propose that the base case of the model should be altered to reflect the correct use of outpatient rather than community costs. We would value the input of the committee to estimate the proportions of costs within the model that should be attributable to consultant-led vs non-consultant-led services.	We would anticipate that this modification will increase the incremental cost difference between PKG and SoC, with a consequent reduction in the ICER	As referenced in Section 6.8 of the EAG report (p141), consultation costs associated with SoC and remote monitoring in the model may be underestimated. UK survey evidence suggests PwP consult with a wide variety of health care professionals[1] (distribution detailed below, note participants in the survey were not constrained to only management phase Parkinson's disease). Note that, on average,

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

<table>
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<tr><td></td><td></td><td>The net cost-consequences of this will depend on the incremental cost of face-to-face vs remote consultations. Using the CHS codes, this increment is £25, while using the outpatient codes increases the difference to £82 for a consultant-led service and £49 for non-consultant led. This will clearly impact on the overall incremental cost of the technologies under appraisal and consequently requires correction.

Table 3 – NHS costs Neurology Outpatients 2019/20[8]
<table>
<tr><th>Service code</th><th>Description</th><th>Cost (consultant led)</th><th>Cost (non-consultant led)</th></tr>
<tr><td>WF01A</td><td>Non-admitted face-to-face attendance (follow-up)</td><td>£187.17</td><td>£147.08</td></tr>
<tr><td>WF01C</td><td>Non-admitted non-face-to-face attendance (follow-up)</td><td>£104.85</td><td>£98.50</td></tr>
</table>
References
7. NHS England. 2019/20 National Cost Collection Data Publication. Organisation level source data. Available at: https://www.england.nhs.uk/wp-content/uploads/2021/06/NCC_Schedule_1920_Org_level_Data_1-v2.zip
8. NHS England. 2019/20 National Cost Collection Data Publication. National Schedule of NHS Costs. Available at: https://www.england.nhs.uk/wp-content/uploads/2021/06/National_Schedule_of_NHS_Costs_FY1920.xlsx</td><td></td><td></td><td>participants were more likely to have consulted with a GP, Practice Nurse or Parkinson's nurse over the last year than a neurologist (i.e. those costs recommended in issue 4). Note the cost-effectiveness of remote monitoring strategies are contingent on cost-savings achieved between face-to-face and remote consultations, rather than the absolute cost of monitoring.

A scenario analysis considering the maximum unit costs provided by the company are provided in an appendix (as a demonstration of the likely maximum possible monitoring costs)..

Table 5.1.1 from Gruber et al (2017)[1]</td></tr>
</table>

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

Stakeholder	Issue	Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)	EAG response
					 Reference: [1]Gumber A, Ramaswamy B, Ibbotson R, Ismail M, Thongchundee O, Harrop D, et al. Economic, social and financial cost of Parkinson's on individuals, carers and their families in the UK. Project report. Sheffield: Centre for Health and Social Care Research, Sheffield Hallam University; 2017. Available from: http://shura.shu.ac.uk/15930/12/Gumber%20Economic%20Social%20and%20Financial%20Cost%20of%20Parkinsons%20.pdf
Global Kinetics PTY	5	The report does not present any deterministic sensitivity analyses and only a limited range of scenarios, so it is difficult to ascertain to which parameters the model results are most sensitive. Typically in a cost-	We propose that an additional scenario analysis should be run,	Unknown effect	Not a factual inaccuracy. The EAG considered a number

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

Stakeholder	Issue	Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)	EAG response
		effectiveness model, the generation of utility estimates is one of the most important drivers of outcome, and we would therefore anticipate the same situation here. Given that the utility estimates in the EAG model are based on the results of an analysis of data from a US study (albeit standardised to UK index valuation)[9], we believe that exploring the impact of using an alternative source of QoL data would be worthwhile. This would either provide reassurance that the current results are robust to the QoL source or, alternatively, highlight an important area of uncertainty for the committee to consider. References. 9. Chandler C, Folse H, Gal P, et al. Modeling long-term health and economic implications of the new treatment strategies for Parkinson's disease: an individual patient simulation study. *Journal of Market Access & Health Policy* 2021;9:1 10. Dams J, Klotsche J, Bornschein B, et al. Mapping the EQ-5D index by UPDRS and PDQ-8 in patients with Parkinson's disease. *Health and Quality of Life Outcomes* 2013;11:35	either using the algorithm derived by Dams et al[9], or the approach adopted by NICE in the PD management guidelines model[6].		of utility values (including those referenced in this issue) but deemed those by Chandler et al (2020) as the source most appropriate for estimating HRQoL within the UK decision-making context for management-phase Parkinson's disease. Note the EAG report considers two key deterministic sensitivity analyses (surrounding monitoring settings and treatment waning effects) and we discuss the key determinants of cost-effectiveness.
PD Neurotechnology	6	Please refer to above mentioned comments 57-64 *[32-39 when submitted as standalone comments*] for suggested problems and possible changes to the model.			Responses given.

*Appendix - An Appendix was submitted and it is not reproduced here, it contained the company's narrative summary on the differences between the devices included in the assessment. Other materials were also attached to the appendix including manuals, a business case, an unpublished study and references to both published and unpublished studies.

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

Appendix in response to issue 4 from Global Kinetics PTY

Scenario analysis considering the maximum unit costs suggested by Global Kinetics for face-to-face (£187.17) and remote (£104.85) consultations (n.b. EAG base case £81.41 and £56.41, respectively).

Table 1 PKG routine remote monitoring strategy scenario cost-effectiveness results

Routine remote monitoring strategy				Incremental		ICER
		Costs	QALY	Costs	QALYs	(£/QALY)
Deterministic analysis	*Restricted analysis*					
	Standard of care	£22,864	2.788			
	PKG	£25,377	2.834	£2,514	0.04562	£55,097
	Unrestricted analysis					
	Standard of care	£22,864	2.788			
	PKG	£25,377	2.804	£2,514	0.01530	£164,311

Table 2 Kinesia 360 routine remote monitoring strategy scenario cost-effectiveness results

Routine remote monitoring strategy			Incremental		ICER
	Costs	QALY	Costs	QALYs	(£/QALY)
Deterministic					
Standard of care	£22,864	2.788			
Kinesia 360	£34,862	2.969	£11,998	0.18042	£66,500