Parkinson's disease (update)

Consultation on draft guideline - Stakeholder comments table
4 October 2016 to 15 November 2016

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Please note: because some similar themes were raised by multiple stakeholders, we have provided single responses to these at the foot of this document. References to this shared material are made throughout our responses to individual comments, with hyperlinks to the relevant text.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Abbvie Limited	Appendix F	11	Paragraph 1, section 2.1.6	The guideline mentioned that 3 of the 12 health state utilities in the Lowin et al., 2011 were observed data and the remaining health state utilities were extrapolated. The lack of data were due to the small patient numbers in some health states. A recent analysis was conducted to estimate health state utility from a pooled dataset of EQ-5D data derived from four studies: Adelphi Disease-Specific Programme (N=1410), patient-level data of published clinical study (Fernandez et al., 2015) (N=321), DAPHNE (LCIG in Advanced Parkinson's: Health Outcome & Net Impact, CTgov ref NCT00141518) (N=77) and GLORIA (Global Long-term Registry on efficacy and safety of LCIG in patients with Advanced Parkinson's disease in routine care, Antonini et al., 2015) (N=354). This pooled dataset allowed an increase in the sample size for more severe health state, improving the precision of the estimation of the utility in these state. Regression output indicated a robust relationship between Hoehn & Yahr stage (1 to 5), OFF status (OFF 0 to OFF IV) and EQ-5D. Additional details relating to the utility analysis is available on request (AbbVie data on file). Reference: Antonini A, Yegin A, Preda C, et al.; GLORIA study investigators and coordinators. Global long-term study on motor and non-motor symptoms and safety of levodopa-carbidopa intestinal gel in routine care of advanced Parkinson's disease patients; 12-month interim outcomes. Parkinsonism Relat Disord. 2015 Mar;21(3):231-5	Thank you for your comment. Data and analyses such as these could have been provided in response to the Call for Evidence that was issued during the development of this guideline, and – assuming they were considered relevant and robust – they would have been welcomed. Sadly, no such data were made available.

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				Lowin,J.; Bergman,A.; Chaudhuri,K.R.; Findley,L.J.; Roeder,C.; Schifflers,M.; Wood,E.; Morris,S. A cost-effectiveness analysis of levodopa/carbidopa intestinal gel compared to standard care in late stage Parkinson's disease in the UK. Journal of Medical Economics 2011;14(5):584-93 Fernandez HH, Standaert DG, Hauser RA, et al. Levodopa-carbidopa intestinal gel in advanced Parkinson's disease: final 12-month, open-label results. Mov Disord. 2015 Apr;30(4):500-9.	
Abbvie Limited	Appendix F	12	Paragraph 3, section F3.1.1	The statement is factually incorrect. The combination of Hoehn and Yahr stages and OFF states was first used before Lowin by Palmer et al in 2002 study, hence before the Lowin 2011 study. Reference: Palmer C. Cost-effectiveness of treatment of Parkinson's disease with Entacapone in the United States. Pharmacoeconomics 20[9], 617-628. 2002.	Thank you for this correction. We have updated Appendix F accordingly.
Abbvie Limited	Appendix F	13	Paragraph 1, 2, F3.1.1	While independence is an important function for a patient with Parkinson's Disease, we strongly feel that this definition does not fully account for disease-specific health outcomes which will present a strong proxy for generic outcomes. Use of motor function as a key driver alone does not include Off-time stage and Hoehn and Yahr stage, which are important clinical characteristics of Parkinson's Disease patients. We also believe that a substantial proportion of advanced Parkinson's Disease patients will be under supervision of a family member or a friend, i.e. in informal carer, and will never enter full time care. Adopted model structure, therefore, dismisses these patients almost completely, as only a small proportion is assumed to be in residential care. Combination of these two assumptions leads to the fact that the cohort modelled does not represent population of advanced Parkinson's Disease patients.	Thank you for your comment. The prominence of motor function in estimating patient-relevant outcomes was an empirical finding based on rigorous analysis of rich datasets. For details, please see **theme 5**. The model accurately reflects the fact that a relatively small proportion of people with Parkinson's disease require full-time care. However, it is completely wrong to suggest that the model therefore overlooks the majority of patients, who do not. The benefits, harms and costs of treatment are considered in detail for such people

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Abbvie Limited	Appendix F	13-14	F3.1.1	Residence based economic model structure was only found in one published literature. The validity and robustness of this type of model is uncertain. References: Tomaszewski KJ, Holloway RG. Deep brain stimulation in the treatment of Parkinson's disease: A cost effectiveness analysis. Neurology. 2001; 57(4):663–671	Thank you for your comment. For comments on the structure of the original model, please see **theme 6**. The process by which the structure of the original model was arrived at is discussed in detail in the cited section; the stakeholder's comment does not address any of these arguments. The validity and robustness of the original model were endorsed by the GDG and subject to a wide range of sensitivity analyses that demonstrated that – certainly where the comparison of LCIG and BMT is concerned – no alternative approaches would produce a qualitatively different result. It should also be remembered that alternative model structures – including those advocated by AbbVie – have undemonstrated predictive validity.
Abbvie Limited	Appendix F	14	Paragraph 2, F3.1.1	We consider the absence of data on entering full –time care in trials and lack of publications on this topic to be a major limitation of this analysis. Amount of evidence surrounding the issue is insufficient to support the model structure.	Thank you for your comment. We agree that long-term data on the effect of treatment on patient-relevant outcomes such as time to full-time care would be valuable in refining our estimates. However, such data are unavailable and the kind of long-term randomised trials that would generate them are extremely unlikely. This does not absolve those seeking to simulate the patient pathway of the responsibility to account – in the most robust way possible – for events that are critically important to patients and associated with significant resource impact.

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					The structure adopted for the original analysis allowed for the projection of such endpoints while maximising use of the highest-quality evidence of treatment effects (randomised trials providing mostly moderate- and high-quality evidence). The model structure preferred by AbbVie is dependent on Hoehn and Yahr score, which is also not reported in trials, and necessitates reliance on data of much lower quality than we have based our analysis on (see **theme 6b**).
Abbvie Limited	Appendix F	14	Paragraph 4, F3.1.1	UPDRS-III (motor score) was seen by the committee as a principal measure that was a key clinical outcome in trials and as predictive of institutionalisation. We disagree with the above opinion. Stronger predictors of institutionalization as demonstrated by Aarsland 2000, include UPDRS-II, age and dementia. Regards to baseline characteristics, impairment in UPDRS-II had a higher risk of institutionalization than impairment in UPDRS-III. Across multiple countries, consistently functional impairment and cognitive impairment have been recognized as a strong predictor of nursing home admission in other studies (Wergeland 2015; Luppa 2010; Shih 2016). Recent evidence has predicted the effect of functional status on nursing home admission among patients with advanced Parkinson's disease. These studies showed that limitations to function status, measured by disaggregated limitations of daily living, contribute to the risk of nursing home admission. LCIG improves functional status by improving ability to conduct activities of daily living hence improves function status reducing the overall health care burden and reduce fiscal spending. LCIG thereby creates social value through its alleviation of functional status limitations for advanced Parkinson's diseases.	Thank you for your comment. The prominence of motor function in estimating patient-relevant outcomes was neither an assumption nor an opinion, but an empirical finding based on rigorous analysis of rich datasets. For details, please see **theme 5**. Age is incorporated as a risk factor for entry to full-time care both in terms of baseline age and in terms of increasing hazard over time (as indicated by the positive ln[shape] parameter); see Appendix F.3.1.9. As noted in appendix F.3.1.1, the GDG recognised that factors other than those measured in trials of anti-Parkinsonian interventions may be more predictive of requirement for full-time care, above all dementia and baseline dependence. However, the GDG was content to assume that the interventions under analysis would not have a direct effect on these factors; therefore, the analysis effectively assumed other factors were equal and

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				Reference: Aarsland et al. Predictors of nursing home placement in Parkinson's disease: a population-based, prospective study. J Am Geriatr Soc. 2000 Aug;48(8):938-42 Wergeland et al. Predictors for Nursing Home Admission and Death among Community-Dwelling People 70 Years and Older Who Receive Domiciliary Care. Dement Geriatr Cogn Dis Extra. 2015 Sep 4;5(3):320-9 Luppa et al. Predictors of nursing home admission of individuals without a dementia diagnosis before admission - results from the Leipzig Longitudinal Study of the Aged (LEILA 75+). BMC Health Serv Res. 2010 Jun 29;10:186 Shih T, Sullivan J, Sail K, Jalundhwala Y, van Eijndhoven E, Marshall T, Zadikoff C, Lakdawalla D. The Effect of Functional Status on Nursing Home Admission among Patients with Advanced Parkinson's Disease. 2016 ANN Annual Meeting. Vancouver, BC, Canada, April 15-21. 2016 Sail K, Shih T, Sullivan J, Jalundhwala Y, van Eijndhoven E, Zadikoff C, Marshall T, Lakdawalla D. The social value of improvement in activities of daily living from levodopa-carbidopa intestinal gel use among the Advanced Parkinson's disease population. 20th International Congress of Parkinson's Disease and Movement Disorders, June 19-23, 2016, Berlin, Germany.	sought to quantify the marginal effects of changes in clinical variables on the outcomes of interest.
Abbvie Limited	Appendix F	15	Paragraph 5, F3.1.3	Given that LCIG and DBS are indicated for different cohort of patients, generalisation of evidence is not acceptable. Compared to DBS patients in PDSURG, LCIG patients are • Older • more severe as measured by UPDRS III, % off-time, duration of dyskinesia while awake • have worse quality of life as measured by PDQ-39 Reference:	Thank you for your comment. For comments on the appropriateness of the decision problems addressed in the review questions on treatment for advanced Parkinson's disease, please see **theme 3**. The GDG did not agree that there are substantial differences between the listed characteristics other than age and off-time between the Fernandez et al. (2015) case series and the PDSURG HY≥3 population, and we

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				Fernandez HH, Standaert DG, Hauser RA, et al. Levodopa-carbidopa intestinal gel in advanced Parkinson's disease: final 12-month, open-label results. Mov Disord. 2015 Apr;30(4):500-9.	note that, in at least 1 other important domain (health-related quality of life as measured by EQ-5D), the PDSURG ≥3 participants are the more severely impaired of the 2 populations.
Abbvie Limited	Appendix F	16, 17	Paragraph 6, F3.1.5, Table 6	One year treatment effects of LCIG versus BMT were obtained from the study by Olanow et al., 2014. UPDRS-III was a secondary endpoint in this study and the mean difference in UPDRS-III between LCIG and BMT was not significant. The treatment difference in UPDRS-III for LCIG and DBS was inconsistent to other outcomes (UPDRS-II, off-time, PDQ-39 and EQ-5D) reported in PDSURG and Olanow et al., 2014. AbbVie feels that using treatment effect measured as UPDRS-III from Olanow et al., 2014 is not appropriate. References: Olanow CW, Kieburtz K, Odin P, Espay AJ, Standaert DG, Fernandez HH, et al. Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: a randomised, controlled, double-blind, double-dummy study. Lancet Neurol 2014 Feb;13(2):141-9.	Thank you for your comment. For comments on UPDRS-III results in Olanow et al. (2014), please see **theme 4b**.
Abbvie Limited	Appendix F	17	Table 6	The UPDRS-III change is critical to the economics model because it appears to be the main driver in predicting future admissions to care and in shorter-term utility values. We note from Table 6 that the CG assumed the UPDRS-III score with Dupdopa compared to Best Medical Treatment (BMT) at 1 year was +1.4. UPDRS is scored so that an increase in the score indicates an increasing level of problems, therefore the model assumes LCIG actually makes patients' motor function WORSE than if they had been on BMT alone. We have several comments to make:	Thank you for your comment. The prominence of motor function in estimating patient-relevant outcomes was an empirical finding based on rigorous analysis of rich datasets. For details, please see **theme 5**. (1&2) For comments on UPDRS-III results in Olanow et al. (2014), please see **theme 4b**. (3) potential for imbalance in baseline levels is the reason why mean change values are preferred to absolute

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				(1) This lacks any face validity. We request the CG consult UK specialists who have used LCIG to ask if their experience is that LCIG is less effective than medical treatment alone. (2) Looking at the results of the Olanow RCT, the reduction in UPDRS-III with LCIG was -1.5 at 12 weeks, but the reduction with oral levodopa was -2.9. Therefore LCIG has an effect but this is more than outweighed by the change seen with BMT alone. This simply would not be seen in clinical practice. If BMT were truly this effective there would be no need for any additional treatments for advanced disease. (3) The CG economics model simply takes the difference between the arms of the RCT as being +1.4, being the difference between -1.5 and -2.9. However, this ignores the imbalance in UPDRS-III at baseline, which is helpfully reproduced in Olanow's paper in the table immediately before the results. At baseline, the average UPDRS-III in the LCIG group was 18.1 and in the BMT arm it was 22.5 so despite randomisation, patients in the BMT arm had more motor problems. Therefore, the results may reflect some degree of regression to the mean. It is very disappointing that the draft CG economics model did not adjust for this and does not comment suggesting it was not even noticed. (4) As noted in another comment, the BMT arm also received aggressive titration of their oral levodopa dose that would not happen in UK clinical practice where appointments can be three months apart.	outcomes. If results are reflective of regression to the mean, then that implies that LCIG has no effect. (4) For comments on the standard of care provided in the BMT arm of Olanow et al. (2014), please see **theme 4**. (5) in the scenario painted by AbbVie, the clinician in question would take other domains into account, and note that LCIG is associated with improvements in those areas, which would be ample reason to continue treatment (so long as adverse effects were tolerable and cost were no object). In other words, for a patient following the average course of participants in Olanow et al. (2014), the fact that LCIG appears to have little or no effect on motor symptoms would not be reason to discontinue.

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				(5) To compound this, the draft CG says, "It was considered reasonable to assume that the difference between LCIG and BMT would, on average, be similar at 1 year as observed after 12 weeks …" (Appendix F, page 16) This means that having assumed that LCIG makes the patient's motor function worse than BMT alone, the model then assumes this situation continues for years into the future (page 21, Figure 3, top right panel). To summarise, a doctor is assumed to prescribe LCIG, it improves motor complications but by less than standard care could have done, and the doctor allows this to continue for years. It's actually very surprising that with such a distorted view of UK clinical experience, the economic model produces any QALY gain for LCIG versus BMT whatsoever, which in our opinion lacks face validity.	
Abbvie Limited	Appendix F	17	Table 7	With respect to the LCIG dropout rate after one year AbbVie identified that the following evidence has been omitted. References: Nyholm D, Klangemo K, Johansson A. Levodopa/carbidopa intestinal gel infusion long-term therapy in advanced Parkinson's disease. Eur J Neurol 2012; 19(8):1079-1085. Fernandez et al. Five Years of Levodopa-Carbidopa Intestinal Gel Treatment: Safety and Efficacy from an Open-Label Phase 3 Study in Advanced Parkinson's Disease Patients. 4th World Parkinson Congress, Portland, Oregon, USA, September 20 – 23, 2016 Rodriguez et al. Long-Term, Multi-Year Safety of Levodopa-Carbidopa Intestinal Gel from an Ongoing, Open-Label, Phase 3 Continued-Access-to-Treatment Study in Patients with Advanced Parkinson's Disease. 20th International Congress of Parkinson's Disease and Movement Disorders, Berlin, Germany, June 19-23, 2016	Thank you for highlighting the relevant data in Nyholm et al.'s case series (2012). This provides a time-to-event estimate of discontinuation probability over follow-up of up to 16 years, censoring for death (which is helpful, for our purposes: if death were treated as a discontinuation event, using these data in a model that simulates mortality separately would double-count discontinuations due to death). This publication shows a lower rate of discontinuations than was reported in the case series on which the original model previously relied (Fernandez et al. 2015, Slevin et al. 2015). We have configured our model to perform a scenario analysis making use of these data, by fitting a parametric function to the published Kaplan–Meier curve, and

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					estimating time-dependent probability of discontinuation from this. Using these data, the estimated duration of LCIG rises to an average of 6.4 years (compared with 4.8 years in our base case). Consequently, the estimated costs of LCIG acquisition rise substantially, with over £187,000 (discounted; over £215,000 undiscounted) spent on LCIG over an average patient's lifetime, and the ICER for LCIG -v- BMT rises substantially, too, by over 40% to £581,695 / QALY. The reason for this is that, in the model, discontinuation rates are an important determinant of costs: if people remain on LCIG for longer, their treatment will cost more. However, this parameter has little impact on QALYs, as the duration of treatment effect is specified separately. The conference presentations by Fernandez et al. (2016) and Rodriguez et al. (2016) are not peer-reviewed and not available in full detail, so would not usually be considered an appropriate source of parameters for a health economic model where peer-reviewed alternatives exist.
Abbvie Limited	Appendix F	18	F3.1.7, Table 9	The baseline yearly progression estimates derived from PINE and PDSURG data are significantly different. The higher bound estimates in UPDRS-II, UPDRS-III and PDQ-39 SI from PDSURG are below the lower bound estimates from PINE. There seems a lack of explanation of why significantly different results are predicted by two datasets.	Thank you for your comment. This observation is untrue of PDQ-39 SI, with respect to which any difference between estimates could be ascribed to sampling error with conventional confidence limits. We acknowledge that the outcome of the UPDRS-II analysis appears anomalous in the PINE dataset; as

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					such, it is unsurprising that the alternative dataset does not replicate the finding. We agree that the discrepancy in UPDRS-III trajectories is worthy of comment; we have added a paragraph to this section suggesting that it may reflect differences in underlying populations (in particular, we note that the PINE cohort was older than the PDSURG population and had much more pronounced impairment of motor function at baseline). Importantly, however, it is demonstrated in sensitivity analysis that the choice of progression trajectories has a trivial impact on incremental cost effectiveness, as the difference between strategies (as parameterised using robust, randomised evidence) is much more important than the absolute level of any variable.
Abbvie Limited	Appendix F	18	Table 8	The assumption of using adverse event rates from Slevin et al., 2015 for Year 2+ was not justified. The current inputs for the model assume that adverse event rates at Year 2+ will increase or remain the same compared to Year 1. This assumption is not consistent with findings from the Fernandez et al study and its long-term extension study S187-3-005The study showed the frequency of device complications decreased over the first 12 months of treatment and then remained relatively constant. Fernandez HH, Standaert DG, Hauser RA, et al. Levodopa-carbidopa intestinal gel in advanced Parkinson's disease: final 12-month, open-label results. Mov Disord. 2015 Apr;30(4):500-9.	Thank you for your comment. The publication by Fernandez et al. is limited to 12 months' follow-up, so contains no data on incidence of complications beyond this timepoint. The publication by Rodriguez et al. is not peer-reviewed and not available in full detail, so would not usually be considered an appropriate source of parameters for a health economic model. Lower rates of AEs would not make an important difference to model outputs: removing AEs altogether

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				Rodriguez et al. Long-Term, Multi-Year Safety of Levodopa-Carbidopa Intestinal Gel from an Ongoing, Open-Label, Phase 3 Continued-Access-to-Treatment Study in Patients with Advanced Parkinson's Disease. 20th International Congress of Parkinson's Disease and Movement Disorders, Berlin, Germany, June 19-23, 2016	reduces the ICER for LCIG -v- BMT less than 10%, to £375,371 / QALY.
Abbvie Limited	Appendix F	19	Paragraph 1, F3.1.7	We are concerned with approximation in Off-time estimation, as we deem this to be a clinically significant measure for treatment effect, therefore, the algorithm used might have triggered the overestimation of progression.	Thank you for your comment. We accept that this is a reasonable concern; we would have preferred to have access to off-time recorded as a continuous measure. However, any impact on final cost–utility results is shown to be totally negligible: if we assume average progression is as high as 1 hour per year, the ICER for LCIG -v- BMT goes up less than 0.5%; if we assume it does not progress at all, it goes down by less than £30.
Abbvie Limited	Appendix F	21	Paragraph 1 and Figure 3, F3.1.7	The model assumed that the magnitude of the benefit in off-time of LCIG over BMT observed in the RCTs is constant throughout patient's lifetime. We disagree with this assumption. The LCIG five-year data shows a significant decrease in mean daily hours of off-time from first infusion to the final visit (P<.001), with no significant change from baseline to the final visit. (Fernandez 2016) The parallel lines of LCIG and BMT in Figure 3 (off-time) do not reflect the magnitude of long term treatment benefit of LCIG over BMT. This magnitude should increase over time as BMT patients deteriorate quicker. Reference: Fernandez et al. Five Years of Levodopa-Carbidopa Intestinal Gel Treatment: Safety and Efficacy from an Open-Label Phase 3 Study in Advanced Parkinson's Disease Patients. 4th World Parkinson Congress, Portland, Oregon, USA, September 20 – 23, 2016	Thank you for your comment. For comments on the parameterisation and long-term simulation of off-time effects, please see **theme 7**.

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Abbvie Limited	Appendix F	22	Paragraph 3, F3.1.9	Counterintuitive effect of off-time and EQ-5D variables might be an indication of the fact that model structure is not fit to estimate relationship between clinical variables and the model outcome, which is further supported by wide CI and influenced by imputed data.	Thank you for your comment. As we note, this appearance was only found when the multiply imputed dataset was chosen, and the 2 counterintuitive point estimates were associated with wide confidence intervals such that, at a 95% confidence level, data were comfortably consistent with an effect in the expected direction in all cases. When used in the economic model, this TTE model was subject to appropriate probabilistic handling, through which the uncertainty was propagated to contribute to estimates of decision uncertainty. We do not agree with the implication that, because a model does not find that a particular variable is a significant predictor of a given outcome, the model is flawed.
Abbvie Limited	Appendix F	3	Paragraph 5, section F 1.1	It is our view that LCIG should not be directly compared against DBS. LCIG is an alternative option for patients who have failed on or are unsuitable for CSAI, or are inappropriate candidates for DBS.	Thank you for your comment. For comments on the appropriateness of the decision problems addressed in the review questions on treatment for advanced Parkinson's disease, please see **theme 3**.
Abbvie Limited	Appendix F	30	Paragraph 6, F3.1.11	19.4% of patients using two cassettes a day is a very high number. Conservatively, most of company models, as well as published analyses, use 10% as a point estimate (lowin et al). [redacted][1] We,	Thank you for your comment. This estimate is subject to sensitivity analysis (see Appendix F.4.1.5) and was found to be one of the variables that has, in relative terms, the biggest impact on the value for money provided by LCIG compared with BMT. However, in qualitative terms, this introduces no uncertainty to the decision: even if we

[1] Commercial confidentiality asserted over this portion of the stakeholder comment; text removed

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				therefore, think that base case number should not be higher than numbers stated above and further varied in the sensitivity analysis. AbbVIe is unaware of the data source which was used to support statement that 19.9% of LCIG patients are using 2 cassettes and we could not find a reference in the CG to support this number. We therefore would like to see the source for this information or would like to have it removed Reference: Lowin,J.; Bergman,A.; Chaudhuri,K.R.; Findley,L.J.; Roeder,C.; Schifflers,M.; Wood,E.; Morris,S. A cost-effectiveness analysis of levodopa/carbidopa intestinal gel compared to standard care in late stage Parkinson's disease in the UK. Journal of Medical Economics 2011;14(5):584-93	assume no one requires a second cassette, the ICER for LCIG -v- BMT remains above £320,000 / QALY. The estimate of 19.9% that was attributed to AbbVie was our calculation assuming a lognormal distribution based on the mean and SD reported in the poster submitted by AbbVie in response to the Call for Evidence. However, as we have not relied on such sources in other areas where peer-reviewed literature exists, we agree it is not appropriate to cite, and we have removed it from the Appendix. We have also clarified the wording that made our draft description of the method ambiguous.
Abbvie Limited	Appendix F	33	Table 22	DBS adverse events were not explicitly modelled. The base case analysis was based on the aggregated cost of DBS serious adverse events reported in PDSURG. The Guideline did not specify the component of cost items. We understand adverse event rates for DBS are variable due to various methodologies used for identifying, collecting and reporting. (Burdick 2010) We believe the uncertainty of DBS adverse event costs should be explored. Reference: Burdick et al. Relationship between higher rates of adverse events in deep brain stimulation using standardized prospective recording and patient outcomes. Neurosurg Focus 29 (2):E4, 2010	Thank you for your comment. Because, as noted, individual DBS AEs are not explicitly modelled, it is not possible to perform sensitivity analysis on any individual component rate or cost. However, the global total was varied in sensitivity analysis and found to have a minor impact on results (at the lower 95%CI, the ICER fell to £31,774 / QALY; at the upper 95%CI, the ICER rose to £33,653 / QALY).
Abbvie Limited	Appendix F	34	Paragraph 3, F3.1.12	AbbVie would like to note that list price value is not representative as LCIG is supplied to NHSE with a discount, which cannot be disclosed here owing to the confidentiality of the arrangement,	Thank you for your comment.This is an important reason why the GDG agreed it was useful to perform detailed one-way sensitivity analysis on the price of LCIG.

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Abbvie Limited	Appendix F	36	Paragraph 1, F3.1.14	As LCIG and DBS are indicated for two different cohorts of patients, their baseline quality of life cannot be assumed to be the same. 0.41 is a very low baseline parameter and it is inconsistent with published data and company analyses. For example, Lowin CUA uses a much higher number of 0.643 and Fernandez study 0.6 correspondingly. Reference: Lowin,J.; Bergman,A.; Chaudhuri,K.R.; Findley,L.J.; Roeder,C.; Schifflers,M.; Wood,E.; Morris,S. A cost-effectiveness analysis of levodopa/carbidopa intestinal gel compared to standard care in late stage Parkinson's disease in the UK. Journal of Medical Economics 2011;14(5):584-93. Fernandez HH, Standaert DG, Hauser RA, et al. Levodopa-carbidopa intestinal gel in advanced Parkinson's disease: final 12-month, open-label results. Mov Disord. 2015 Apr;30(4):500-9.	Thank you for your comment. For comments on the appropriateness of the decision problems addressed in the review questions on treatment for advanced Parkinson's disease, please see **theme 3**. We tested the impact of baseline quality of life in sensitivity analysis. Using a starting value of 0.643 raises the ICER for LCIG -v- BMT to £621,733 / QALY.
Abbvie Limited	Appendix F	37	Paragraph 6, F3.1.14	The statement regarding utility decrement associated with DBS surgery and LCIG tube contradicts itself, as it implies that PEG surgery is more uncomfortable and disturbing to the patient than brain surgery. A recent patient preference study shows that a portable infusion pump is preferred to brain stimulator for advanced Parkinson's disease. (Marshall 2016) Reference: Marshall et al. Patient Preferences For Device-Aided Treatments Indicated For Advanced Parkinson's Disease (APD). American Academy of Neurology Annual Meeting, 15–21 April 2016, Vancouver, British Columbia, Canada	Thank you for your comment. We were unable to identify the alleged contradiction. However, the premise of the comment is incorrect: when severity and duration of disutility are combined, a QALY loss of 0.013 is estimated for the cycle in which DBS surgery takes place whereas, for LCIG insertion, the analogous figure is 0.0092. We have included this information in the Appendix.
Abbvie Limited	Appendix F	38	Table 30	It is not clear what the '0.75' is referring to in row 10. The uncertainty of including utility decrements was not assessed in the sensitivity analysis.	Thank you for your comment. The parameters detailed in Table 30 indicate the GDG's assumption that LCIG PEG placement is associated with 7 days at 50% quality of life followed by 7 days at 75% quality of life.

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					All utility decrements were tested in sensitivity analysis. The fact that they are not shown in Figure 14 of Appendix F reflects the fact that none of these parameters were among the 30 most influential tested. From this, it can easily be inferred that these parameters have no material impact on cost-utility results. If all treatment-related utility decrements are omitted from the model, the ICER for LCIG -v- BMT becomes £373,585 / QALY.
Abbvie Limited	Appendix F	40	F4.1.1	In relation to the life extension which was observed in DBS arm, we would like to point out that this is unlikely outcome, which would imply that DBS is life-extending treatment, which is not the nature or the goal of the therapy. This high number is not consistent with previous publications We would also like to reference this particular draft Guideline where on p 62 Appendix F it says with the reference to SMC recommendation for LCIG that:*" the model also structurally assumes that LCIG has a large disease-modifying effect, so it is also very likely that a substantial impact on average life expectancy is predicted (which the GDG for this guideline found implausible)."* [redacted][1], we would like to point out that such a large life extension observed in DBS arm indicates that the model structurally favours DBS and that optimistic assumptions were used for DBS. We found the statement contradicts itself and inevitably implies that DBS does bear disease-modifying effect.	Thank you for your comment. The model predicts around 10% life extension with DBS, which the GDG considered was plausible given its potential to reduce symptomatic burden, bearing in mind that the excess mortality in Parkinson's is invariably related to symptoms. There is observational evidence to support this finding and the GDG's rationale: Ngoga et al. (2014) found that survival was significantly longer in people receiving DBS compared with those who elected to continue with medical management, when a range of potential effect modifiers had been adjusted for. They also found that people who received DBS were significantly less likely to die of respiratory causes. We would not be comfortably directly relying on this evidence in our decision model, as it is subject to potentially serious selection biases that are most likely to exaggerate the effect of DBS, and we believe it is much better to make maximum use of the

[1] Commercial confidentiality asserted over this portion of the stakeholder comment; text removed

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					good-quality randomised evidence that exists. However, we note that it provides a degree of validation to our findings. In contrast, there is no evidence -- even of an observational nature -- on mortality risk in people receiving LCIG. We acknowledge that it is difficult for us to provide conclusive comments on the model submitted to the SMC, as we have not had access to it (although we sought such evidence from all stakeholders in our Call for Evidence), and it is incompletely described in publicly available documentation. However, the Lowin et al. (2011) model on which it was based structurally assumed that treatment affected HY state and mortality risk was a direct function of HY state; therefore, because LCIG was assumed to result in HY benefit compared with standard care (though there is no evidence to substantiate this), a large benefit in life expectancy was (around 17% extension of life). It was this finding that the GDG found implausible. In contrast to Lowin et al. (2011)'s analysis, our model uses an evidence-based approach to capture the extent to which clinical variables may influence (not completely determine) expected survival, and combines that with randomised evidence on the extent to which treatment affects those variables to estimate long-term prognosis

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					for people receiving those treatments. We are confident that this is a superior approach.
Abbvie Limited	Appendix F	40	Paragraph 3	The carer's EQ-5D data were predicted from the patient's characteristics using the PINE study. We disagree with the incorporation of these data to the base case as none of the clinical variables have a statistically significant impact on carer quality of life. The analysis may underestimate the benefit of LCIG on carer quality of life. (Santos-Garcia 2012) Reference: Santos-Garcia et al. Duodenal levodopa/carbidopa infusion therapy in patients with advanced Parkinson's disease leads to improvement in caregivers' stress and burden. European Journal of Neurology 2012, 19: 1261–1265	Thank you for your comment. We acknowledge in our documentation that the carer QoL model was unable to detect any predictors at a 95% confidence level. We agree that it is difficult to draw firm conclusions from these data. However, it does provide potential for carer benefit to be estimated; omitting carer QoL from the model makes ICERs rise, with LCIG -v- BMT rising to £458,714 / QALY.
Abbvie Limited	Appendix F	40	Paragraph 5, F4.1.1	As stated in the comment 19 above, UPDRS-III score was not the primary outcome of the Olanow trial, and, furthermore to this, the treatment difference in UPDRS III between LCIG and BMT was insignificant. Therefore, the use of this value completely undermines results of the analysis. Substantial life extension cannot be expected to be the benefit of either LCIG or DBS, as this would imply life-extending nature of treatments.	Thank you for your comment. For comments on UPDRS-III results in Olanow et al. (2014), please see **theme 4b**.
Abbvie Limited	Appendix F	40	Paragraph 8, F4.1.2	We find that reference to the cost of LCIG is completely inappropriate, as the aim of clinical guideline is to provide recommendations on the appropriate treatment and care pathway for people with Parkinson's Disease; therefore, cost and price considerations are outside of the remit of this document.	Thank you for your comment. The purpose of NICE's clinical guidelines is as set out in The Guidelines Manual (2012). Consideration of the costs of healthcare interventions – and the extent to which they are justified by their associated benefits – is a central component of the programme.
Abbvie Limited	Appendix F	41	Table 34	Incremental cost-utility analysis results for both DBS and LCIG are inconsistent with those published earlier (Lowin et al 2001; SMC 2016; McIntosh et al 2016)	Thank you for your comment. These comparisons are made in detail in section F.5.1.3. We conclude that, 'Having reviewed... similarities and differences, we

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				Reference: Lowin,J.; Bergman,A.; Chaudhuri,K.R.; Findley,L.J.; Roeder,C.; Schifflers,M.; Wood,E.; Morris,S. A cost-effectiveness analysis of levodopa/carbidopa intestinal gel compared to standard care in late stage Parkinson's disease in the UK. Journal of Medical Economics 2011;14(5):584-93 McIntosh, E., Gray, A., Daniels, J., Gill, S., Ives, N., Jenkinson, C., Mitchell, R., Pall, H., Patel, S., Quinn, N., Rick, C., Wheatley, K., Williams, A. and on behalf of The PD SURG Collaborators Group (2016), Cost-utility analysis of deep brain stimulation surgery plus best medical therapy versus best medical therapy in patients with Parkinson's: Economic evaluation alongside the PD SURG trial. Mov. Disord. doi: 10.1002/mds.26423 Scottish Medicines Consortium (SMC). Co-careldopa intestinal gel, 20mg/5mg levodopa/carbidopa per ml for continuous intestinal infusion, (LCIG). No. (316/06). 2016 https://www.scottishmedicines.org.uk/files/advice/DAD_co-careldopa_2nd_Resubmission_FINAL_May_2016_for_website.pdf	believe that most discrepancies between our analysis and those produced by others can be explained. Moreover, where differences in approach appear meaningful in this way, we remain confident that the choices we have made are optimal for the representation of the disease and its treatment.' For comments on apparent discrepancies between NICE's conclusions on LCIG and SMC advice, please see **theme 9c**.
Abbvie Limited	Appendix F	46	F4.1.5	We understand that the price reduction for LCIG cassettes is only mentioned here in the context of sensitivity analysis, but we find the tone of it to be compulsory and restrictive. As mentioned above, price negotiation is out of the remit of the Guideline.	Thank you for your comment. The GDG requested detailed one-way sensitivity analysis on the cost of LCIG, as it was aware that it is provided to the NHS at a confidential discount. Because the GDG did not know the level of this discount, it could not estimate the value for money provided by LCIG, compared with BMT, at its real-world price. Therefore, it agreed it would be useful to show what the implications of a wide range of possible prices would be. We have removed reference to this sensitivity analysis from the full guideline.

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Abbvie Limited	Appendix F	6	Paragraph 9, section F2.1.3	Hoehn and Yahr stage structure and Off-time states are most commonly used measures in clinical practice to describe Parkinson's disease progression. This is the reason why the combination of these two measures have been traditionally used in Parkinson's disease modelling, to enable a demonstration of patient transition through Parkinson's Disease. For example, the combination has been adopted in many published cost-utility analyses for LCIG versus BMT (Lowin et al. 2011), DBS versus BMT (Dams et al. 2013 and Eggington et al. 2014) and multiple comparison (Walter and Odin 2015) We recognize that there might be a room for improvement in estimation of degree of correlation between Hoehn and Yahr and Off-time, but it is not clear and is not explained in this document how this will undermine the analysis. Reference: Lowin,J.; Bergman,A.; Chaudhuri,K.R.; Findley,L.J.; Roeder,C.; Schifflers,M.; Wood,E.; Morris,S. A cost-effectiveness analysis of levodopa/carbidopa intestinal gel compared to standard care in late stage Parkinson's disease in the UK. Journal of Medical Economics 2011;14(5):584-93 Dams,J. et al. Cost-Effectiveness of Subthalamic Deep Brain Stimulation in Patients with Early Complications of Parkinson's Disease (EARLYSTIM-Study). Mov.Disord. 2016 (in print). Eggington,S., Valldeoriola,F., Chaudhuri,K.R., Ashkan,K., Annoni,E. The cost-effectiveness of deep brain stimulation in combination with best medical therapy, versus best medical therapy alone, in advanced Parkinson's disease. J Neurol 2014;261(1):106-16. Walter,E. and Odin,P. Cost-effectiveness of continuous subcutaneous apomorphine in the treatment of Parkinson's disease in the UK and Germany. Journal of Medical Economics 2015;18(2):155-65	Thank you for your comment. For comments on the use of Hoehn and Yahr score to simulate disease progression, please see **theme 6b**. We do not accept that the fact that a model structure has been used by more than 1 author makes it fundamentally more reliable. The GDG had significant objections to the appropriateness of this type of model, and concluded that an alternative structure would be more robust.

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Abbvie Limited	Appendix F	62	Scottish Medicines Consortium 2016 Advice	This section contain a range of factual inaccuracies which are discussed below: 1. The model used for the SMC submission was not based on the model in the Lowin publication. 2. With regards to the treatment effect assumption, we would like to note that initial treatment effect (cycles 1 and 2) was derived from observational study S.187.3.004., 3. In the long term, there was no effect of LCIG in the on Hoehn and Yahr stage, while Off-time was assumed to have 50% risk reduction. Reduction in Off-time was supported by published sources (Nilsson et al 2001; Nyholm et al 2008). 4. [redacted][1] 5. With respect to the conclusions which were drawn in this section, we do not think that GDG had enough information to reach those. This leads to the factually incorrect and misleading interpretation of SMC recommendation. We also question the fact that GDG implies that SMC decision was biased and would like to state that it is out of the remit for GDG to critique SMC. 6. In conclusion, we would also like to note that price negotiation is out of the remit of this Guideline. References: Scottish Medicines Consortium (SMC). Co-careldopa intestinal gel, 20mg/5mg levodopa/carbidopa per ml for continuous intestinal infusion, (LCIG). No. (316/06). 2016.	Thank you for your comments. 1. We believe it is disingenuous to say that AbbVie's SMC model was not based on the Lowin et al. (2011) CUA: it relies on the same basic structure (cross-categorisation of HY and off-time states) and adopts many of the same assumptions (most critically, a permanent 50% benefit in off-time for people taking LCIG). 2. This suggests that our statement that the model 'reli[es] on observational evidence to estimate treatment effects' is factually correct. 3. This suggests that our statement that 'short-term treatment benefit is preserved indefinitely for Hoehn and Yahr state, whereas off-time benefit increases as time goes on' is factually correct. We note that the sources cited here provide no justification whatsoever for the assumption of increasing off-time benefit over time. For comments on the parameterisation and long-term simulation of off-time effects, please see **theme 7**. 4. [redacted][2]

[1] Commercial confidentiality asserted over this portion of the stakeholder comment; text removed
[2] Response removed as it relates to material over which commercial confidentiality is asserted

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				https://www.scottishmedicines.org.uk/files/advice/DAD_co-careldopa_2nd_Resubmission_FINAL_May_2016_for_website.pdf Nilsson D, Nyholm D, Aquilonius S-M. Duodenal levodopa infusion in Parkinson's disease – long-term experience. Acta Neurol Scand 2001: 104: 343–348. Nyholm D, Lewander T, Johansson A, Lewitt PA, Lundqvist C, Aquilonius SM. Enteral levodopa/carbidopa infusion in advanced Parkinson disease: long-term exposure. Clin Neuropharmacol 2008 Mar;31(2):63-73.	5. The GDG provide no critique of the SMC's decision and do not in any way imply that the SMC's decision was biased. We do assert that the SMC's decision was, in part, based on a cost–utility analysis that was biased in favour of LCIG. See **theme 9c**. 6. No price negotiation is mentioned or implied. It is (factually accurately) noted that the SMC's decision took account of a patient access scheme of which we have no knowledge.
Abbvie Limited	Appendix F	General	General	The NICE CG team decided to create a de novo economics model but have not reported any attempt to validate the predictions. For example, the predictions of the model were not compared to any relevant dataset, either for BMT or LCIG outcomes that was not used in building the model. The predictions also do not appear to have been checked for face validity against the expert opinion of clinicians who prescribe LCIG. Given that the CG proposes not recommending LCIG based on the long-term results of the economics model, this seems a very serious deficiency.	Thank you for your comment. Predictions from the original model were validated in several ways. The face validity of the model was endorsed by the GDG, which included clinicians who prescribe LCIG. The convergent validity of the model was assessed by comparing its outputs with other published CUAs of therapies for advanced Parkinson's disease. Where differences were observed between our model and others, these could generally be accounted for by differences in assumptions and/or data (see Appendix F.5.1.3). There are no long-term data on the relative effectiveness of the simulated options, so it was not possible to perform formal analysis of the predictive validity of the model. However, we note that its predictions are consistent with a few long-term observational case series of DBS and LCIG (for example, the duration of time over which observed variables reach a similar level to baseline).

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					There is only 1 exception to this of which we are aware: analysis of the trajectory of activities of daily living (UPDRS-II) in the PINE dataset provided a point estimate suggesting that symptoms improve in this domain over time. We acknowledge in our documentation that this was acounterintuitive finding that lacks face validity. However, we demonstrate in sensitivity analysis (in which alternative progression trajectories – including those estimated from the PDSURG dataset – were explored) that any inaccuracy, here, has a trivial impact on incremental cost effectiveness, as the difference between strategies (as parameterised using robust, randomised evidence) is much more important than the absolute level of any variable. It should also be noted that, as no appropriate data are available, no other economic analyses of advanced Parkinson's disease – including those endorsed by AbbVie – have been subject to validation against external data.
Abbvie Limited	Full	186	4478	The statement 'rechargeable systems with a longer lifespan are now available' with DBS does not seem to be based on published evidence but rather an insight from the DBS experts called into this process. We accept this is speculation on our part. However the inclusion of this statement seems out of touch with the balanced approach that would be expected from an independent national clinical guideline. The developments in the LCIG system have not been acknowledged, while they would be expected to be equally pertinent.	Thank you for your comment. The fact that rechargeable DBS systems with a longer lifespan are now available is not specialist insight; it is a simple reflection of a reality with which anyone working in the field would be familiar. For comments on the role of expert witnesses, please see **theme 2**.

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				We suggest that on that basis, the statement needs to be excluded. This could be a clear demonstration of how a lack of LCIG experts being involved has unbalanced the process of reviewing and assessing the two different advanced treatments.	
Abbvie Limited	Full	187	4496	The limited evidence referred to in this draft guidance is likely to be a function of the difficulty of conducting randomised controlled studies in patients with advanced Parkinson's disease. In view of the limited available evidence base, it would be sensible that the strength of recommendation in the guideline would acknowledge and reflect this in a more measured in tone than has been used in the draft. This would preserve options for expert clinicians based at specialist neurological centres who are the only t clinicians that are able to prescribe LCIG. It should be noted that LCIG is only indicated for those patients who have tried and failed all available medical therapy and it is only available for patients that are ineligible for DBS. It would be a serious concern if based on the limited evidence considered the final guidance limits access to an important treatment for a select but significant group of patient with high clinical need and limited available options.	Thank you for your comment. The GDG acknowledged that there are substantial challenges associated with conducting RCTs of surgical interventions for patients with advanced Parkinson's disease. For example, this knowledge informed the group's decision that it would be inappropriate to downgrade DBS RCTs for a lack of blinding. NICE's Social Value Judgements – and the methods informed by them – are explicit that guidance-making GDGs should view limitations in the evidence available to them as a reason to be less inclined to consider courses of action cost effective, not more so. In the case of LCIG, however, any limitations are of minimal consequence: as our extensive sensitivity analysis shows, there is no level of benefit that could justify the costs incurred by LCIG.
Abbvie Limited	Full	187	4496	It appears the literature review was conducted to match endpoints in the model (for example, rates of people entering full-time care). The review is likely biased that other relevant evidence would be omitted (see Comment 3 above). As the model structure is flawed it follows that the literature search is misdirected.	Thank you for your comment. This inference is incorrect. As with all review protocols, the outcomes of interest were specified by the GDG based on group members' experience of what is important to patients and factors

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					that have prognostic value in managing Parkinson's disease. The review protocol was finalised long before the model structure was agreed. Indeed, as the model structure was devised to reflect the outcomes that the GDG considered of critical importance, it is somewhat more true to say that the review protocol defined the model, not the other way around.
Abbvie Limited	Full	187	4522	Whilst Expert Witnesses (Professor Adrian Williams and Dr Caroline Rick) were called for DBS, AbbVie is concerned that no Expert Witnesses were called for LCIG, which does not allow for fair comparison and may lead to inadvertent bias. We note the statement in the draft guidance that 'the 2 expert witnesses provided insight into the strength and limitations' of a DBS clinical trial.	Thank you for your comment. For comments on the role of expert witnesses, please see **theme 2**.
Abbvie Limited	Full	188	4536	The position used for LCIG in the clinical and health economic analyses for the Guideline does not represent clinical practice in the UK. LCIG and DBS are only used when other options are not satisfactorily controlling symptoms. In advanced Parkinson's Disease patients comprise significantly different cohorts – with DBS being earlier in the treatment paradigm with different demographics (e.g. age) and clinical characteristics (e.g. comorbidities). No prospective, randomised head to head studies have been conducted between LCIG and DBS and the publication by Worth P.F 2013 states, unlike DBS, LCIG can be used in patients over 70 years with comorbidities, depression and dysphagia.	Thank you for your comment. For comments on the appropriateness of the decision problems addressed in the review questions on treatment for advanced Parkinson's disease, please see **theme 3**. We note the conclusion of the AbbVie-funded RCT of LCIG -v- BMT, that 'In the final analysis, the value of LCIG as a treatment for PD patients with motor complications will ultimately be determined by trials that provide a full assessment of its relative safety, efficacy, and cost in comparison to other available therapies such as DBS.' As a matter of principle, we agree with this

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				The assumption that patients would be equally eligible for DBS and Duodopa simply does not reflect the treatment pathway in the UK. References: Worth PF. When the going gets tough: how to select patients with Parkinson's disease for advanced therapies. Practical neurology 2013;13 (3):140-52.	conclusion, though the apparent superiority of DBS over LCIG in people who are eligible for both may make it difficult to recruit to such a trial.
Abbvie Limited	Full	189	4558-4562	AbbVie considers that evidence base for LCIG and DBS has not been appropriately considered and as a result the conclusions drawn are fundamentally flawed. Whilst AbbVie recognises the value of high quality evidence, such as data collected though RCTs, we note that in this case the RCTs included for LCIG and DBS cannot be deemed as of the same quality. Olanow (the RCT for LCIG) is a double-blind active comparator controlled randomised trial with an optimized oral medication arm. In comparison, PDSURG (DBS) was randomised, open-label study (Williams, 2010) which was arguably not controlled. The control aspect of PDSURG should be evaluated objectively. The publication notes that in the best medical therapy arm, 'apart from random treatment allocation, all other aspects of the management of patients were at the discretion of the local clinicians' (page 3, Williams et al. 2010). It would be expected that patients receiving DBS may be subject to a very different follow up at their neurological centre as compared to those that continued on medical management. Therefore, it is clear this study cannot be considered to be 'controlled'.	Thank you for your comment. For comments on the use of Olanow et al. (2014) to estimate effectiveness of LCIG -v- BMT, please see **theme 4**.

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				It is noted that within the PDSURG publication this study is not described as a controlled study (Williams, 2010). This brings into question the categorisation (and consequent grading) of this study as a randomised 'controlled' trial and the emphasis that NICE has placed upon it for model construction and input generation. We, therefore, think that the inclusion of the PDSURG study into the evidence base for the draft guideline should allow for a wider range of studies to be included for LCIG. This would include Nyholm et al. (2005) which was a randomised controlled study. No reason was given in Appendix G for its omission. Other relevant studies include a UK based matched cohort study Reddy et al. 2012, Antonini et al 2015, Fernandez et al 2015. References: Olanow CW, Kieburtz K, Odin P, Espay AJ, Standaert DG, Fernandez HH, et al. Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: a randomised, controlled, double-blind, double-dummy study. Lancet Neurol 2014 Feb;13(2):141-9. Nyholm D, Klangemo K, Johansson A. Levodopa/carbidopa intestinal gel infusion long-term therapy in advanced Parkinson's disease. Eur J Neurol 2012; 19(8):1079-1085. Reddy P, Martinez-Martin P, Rizos A, Martin A, Faye GC, Forgacs I, et al. Intrajejunal levodopa versus conventional therapy in Parkinson disease: motor and nonmotor effects. Clin Neuropharmacol 2012 Sep;35(5):205-7. Antonini A, Yegin A, Preda C; GLORIA study investigators and coordinators. Global long-term study on motor and non-motor symptoms and safety of	

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				levodopa-carbidopa intestinal gel in routine care of advanced Parkinson's disease patients; 12-month interim outcomes. Parkinsonism Relat Disord 2015;21(3):231-Fernandez HH, Standaert DG, Hauser RA et al. Levodopa-carbidopa intestinal gel in advanced Parkinson's disease: final 12-month, open-label results. Mov Disord 2015;30(4):500-9.	
Abbvie Limited	Full	189	4577	AbbVie considers that evidence base for LCIG and DBS has not been appropriately considered and as a result the conclusions drawn are fundamentally flawed. Whilst AbbVie recognises the value of high quality evidence, such as data collected though RCTs, we note that in this case the RCTs included for LCIG and DBS cannot be deemed as of the same quality. Olanow (the RCT for LCIG) is a double-blind active comparator controlled randomised trial with an optimized oral medication arm. In comparison, PDSURG (DBS) was randomised, open-label study (Williams, 2010) which was arguably not controlled. The control aspect of PDSURG should be evaluated objectively. The publication notes that in the best medical therapy arm, 'apart from random treatment allocation, all other aspects of the management of patients were at the discretion of the local clinicians' (page 3, Williams et al. 2010). It would be expected that patients receiving DBS may be subject to a very different follow up at their neurological centre as compared to those that continued on medical management. Therefore, it is clear this study cannot be considered to be 'controlled'.	Thank you for your comment. For comments on the use of Olanow et al. (2014) to estimate effectiveness of LCIG -v- BMT, please see **theme 4**.

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				It is noted that within the PDSURG publication this study is not described as a controlled study (Williams, 2010). This brings into question the categorisation (and consequent grading) of this study as a randomised 'controlled' trial and the emphasis that NICE has placed upon it for model construction and input generation. We, therefore, think that the inclusion of the PDSURG study into the evidence base for the draft guideline should allow for a wider range of studies to be included for LCIG. This would include Nyholm et al. (2005) which was a randomised controlled study. No reason was given in Appendix G for its omission. Other relevant studies include a UK based matched cohort study Reddy et al. 2012, Antonini et al 2015, Fernandez et al 2015. References: Olanow CW, Kieburtz K, Odin P, Espay AJ, Standaert DG, Fernandez HH, et al. Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: a randomised, controlled, double-blind, double-dummy study. Lancet Neurol 2014 Feb;13(2):141-9. Nyholm D, Klangemo K, Johansson A. Levodopa/carbidopa intestinal gel infusion long-term therapy in advanced Parkinson's disease. Eur J Neurol 2012; 19(8):1079-1085. Reddy P, Martinez-Martin P, Rizos A, Martin A, Faye GC, Forgacs I, et al. Intrajejunal levodopa versus conventional therapy in Parkinson disease: motor and nonmotor effects. Clin Neuropharmacol 2012 Sep;35(5):205-7. Antonini A, Yegin A, Preda C; GLORIA study investigators and coordinators. Global long-term study on motor and non-motor symptoms and safety of levodopa-carbidopa intestinal gel in routine care of advanced Parkinson's	

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4 October 2016 to 15 November 2016

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				disease patients; 12-month interim outcomes. Parkinsonism Relat Disord 2015;21(3):231-Fernandez HH, Standaert DG, Hauser RA et al. Levodopa-carbidopa intestinal gel in advanced Parkinson's disease: final 12-month, open-label results. Mov Disord 2015;30(4):500-9.	
Abbvie Limited	Full	190	4597-4601	AbbVie considers that evidence base for LCIG and DBS has not been appropriately considered and as a result the conclusions drawn are fundamentally flawed. Whilst AbbVie recognises the value of high quality evidence, such as data collected though RCTs, we note that in this case the RCTs included for LCIG and DBS cannot be deemed as of the same quality. Olanow (the RCT for LCIG) is a double-blind active comparator controlled randomised trial with an optimized oral medication arm. In comparison, PDSURG (DBS) was randomised, open-label study (Williams, 2010) which was arguably not controlled. The control aspect of PDSURG should be evaluated objectively. The publication notes that in the best medical therapy arm, 'apart from random treatment allocation, all other aspects of the management of patients were at the discretion of the local clinicians' (page 3, Williams et al. 2010). It would be expected that patients receiving DBS may be subject to a very different follow up at their neurological centre as compared to those that continued on medical management. Therefore, it is clear this study cannot be considered to be 'controlled'. It is noted that within the PDSURG publication this study is not described as a controlled study (Williams, 2010).	Thank you for your comment. For comments on the use of Olanow et al. (2014) to estimate effectiveness of LCIG -v- BMT, please see **theme 4**.

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				This brings into question the categorisation (and consequent grading) of this study as a randomised 'controlled' trial and the emphasis that NICE has placed upon it for model construction and input generation. We, therefore, think that the inclusion of the PDSURG study into the evidence base for the draft guideline should allow for a wider range of studies to be included for LCIG. This would include Nyholm et al. (2005) which was a randomised controlled study. No reason was given in Appendix G for its omission. Other relevant studies include a UK based matched cohort study Reddy et al. 2012, Antonini et al 2015, Fernandez et al 2015. References: Olanow CW, Kieburtz K, Odin P, Espay AJ, Standaert DG, Fernandez HH, et al. Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: a randomised, controlled, double-blind, double-dummy study. Lancet Neurol 2014 Feb;13(2):141-9. Nyholm D, Klangemo K, Johansson A. Levodopa/carbidopa intestinal gel infusion long-term therapy in advanced Parkinson's disease. Eur J Neurol 2012; 19(8):1079-1085. Reddy P, Martinez-Martin P, Rizos A, Martin A, Faye GC, Forgacs I, et al. Intrajejunal levodopa versus conventional therapy in Parkinson disease: motor and nonmotor effects. Clin Neuropharmacol 2012 Sep;35(5):205-7. Antonini A, Yegin A, Preda C; GLORIA study investigators and coordinators. Global long-term study on motor and non-motor symptoms and safety of levodopa-carbidopa intestinal gel in routine care of advanced Parkinson's disease patients; 12-month interim outcomes. Parkinsonism Relat Disord 2015;21(3):231-Fernandez HH, Standaert DG, Hauser RA et al. Levodopa-	

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				carbidopa intestinal gel in advanced Parkinson's disease: final 12-month, open-label results. Mov Disord 2015;30(4):500-9.	
Abbvie Limited	Full	190	4602-4604	This is an untested assumption that patients with more severe PD Hoehn and Yahr greater than 3 (HY>3) will have the same adverse event rate as the wider patient group. It is clinically accepted that patient with more severe disease are more likely to experience a greater number of adverse events, which are also likely to be more severe in nature. This underrepresents the likely adverse events that would have been experienced in the DBS group which will have reduced the resulting costs incorrectly. We also point out the different methodologies used for collecting adverse events between a pharmaceutical intervention in a regulatory trial (LCIG is classified as a medicinal product by the MHRA) and a surgical procedure in a non-regulatory trial such as DBS. As a medicinal product any untoward event related to treatment would need to be recorded; even those expected as part of a surgical procedure - pain, redness at the wound, bloating following insufflation of the bowel with air as part of the percutaneous endoscopic gastrostomy (PEG) insertion procedure. It seems clear this discrepancy has not been considered when reviewing the evidence on adverse events. This is the reason for a greater of 90% rate of adverse events in both arms within the LCIG study (Olanow 2014), Therefore the methodology for inclusion of adverse events should be reconsidered, as generalisation in this case has led to a substantial over-estimation of adverse events in LCIG arm and under-estimation in DBS arm.	Thank you for your comment. We accept that it is not possible to provide empirical analysis of adverse event (AE) rates subdivided according HY score, which would have enabled us to explore the stakeholder's unsubstantiated hypothesis that there would more AEs in people with more advanced disease. However, we do not accept that the assumption that AEs similar regardless of HY score is untested, insofar as it bears on the costs in the original health economic analysis. Our one-way sensitivity analysis showed that model results for DBS -v- BMT are not especially sensitive to this parameter: when costs of DBS AEs were set to the upper 95%CI of the observed figure, the ICER rose by 3%, to £33,653 / QALY. This is not explicitly shown in Appendix F.4.1.5, as it is not one of the 30 most influential parameters tested. In the original economic model, AE rates are not drawn from Olanow et al. (2014); in this domain only, the RCT was felt to be an unhelpful source of evidence, as people receiving BMT in practice would not experience complications of device insertion, as the control participants in the trial did. Instead, AE rates come from observational case series (Fernandez et al., 2015; Slevin et al., 2015). For similar reasons, no indirect comparison was attempted between DBS and LCIG in this domain.

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Abbvie Limited	Full	190	4612	The ethical and design issues related to studying an invasive intervention in subjects that have no other treatment option is the reason for the small numbers in Olanow RCT (34 and 37 patients respectfully in the LCIG and active comparator arms respectively). This is the reason for the short follow up of 12 weeks which is not representative of the length of treatment with LCIG in clinical practice. The trial was designed in conjunction with the FDA to test whether there would be a statistically significantly improvement in Off- time versus active comparator to meet FDA criteria for licencing in the US. The RCT showed an improvement in Off-time such that the endpoint has been met and demonstrated significance. The trial was not designed to show improvements in UPDRS, improvement in ON-time without troublesome dyskinesia, CGI, UPDRS II or UPDRS III. Due to the relatively small number of patients a hierarchical cut-off analysis was utilised for secondary measures. The economic evaluation of LCIG thus rests upon a single small, short-term study that was very specifically designed to test a different primary endpoint; this is used in an indirect comparative analysis whilst ignoring the other published clinical data that is available. The lack of evidence from an expert witness with knowledge of LCIG has compounded the issue. It is unreasonable to reach a definitive negative recommendation on LCIG from an approach that has multiple flaws. References: Olanow CW, Kieburtz K, Odin P, Espay AJ, Standaert DG, Fernandez HH, et al. Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: a randomised, controlled, double-blind, double-dummy study. Lancet Neurol 2014 Feb;13(2):141-9.	Thank you for your comment. The GDG acknowledged that there are substantial challenges associated with conducting RCTs of surgical interventions for patients with advanced Parkinson's disease. For example, this knowledge informed the group's decision that it would be inappropriate to downgrade DBS RCTs for a lack of blinding. For comments on the use of Olanow et al. (2014) to estimate effectiveness of LCIG -v- BMT, please see **theme 4**. For comments on the role of expert witnesses, please see **theme 2**. NICE's Social Value Judgements – and the methods informed by them – are explicit that guidance-making GDGs should view limitations in the evidence available to them as a reason to be less inclined to consider courses of action cost effective, not more so. In the case of LCIG, however, any limitations are of minimal consequence: as our extensive sensitivity analysis shows, there is no level of benefit that could justify the costs incurred by LCIG.

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Abbvie Limited	Full	190	4623	The Olanow study is a controlled active comparator study (Olanow, 2014). Patients in the active comparator arm were subjected to gastrointestinal surgery, insertion of an intestinal tube through which dummy LCIG was administered, and the administration of oral immediate release levodopa/carbidopa. The frequent follow up of subjects and use of rescue doses is also out of keeping with standard clinical practice in the UK The Olanow study was designed in conjunction with the FDA specifically to demonstrate the efficacy benefits of LCIG upon off-time in appropriate patients with advanced Parkinson's disease. The comparator arm was not meant to reflect standard clinical practice in any way but to stringently control for all other possible causes of bias. This explains the small size and short duration of this study. Clearly the short duration is unrepresentative of the ongoing long term nature of this treatment in a standard clinical setting (rather than within a clinical study). The use of this active comparator arm against LCIG in a model that is attempting to represent a standard clinical setting is incorrect and introduces considerable bias into the analysis. The omission in calling an expert witness has prevented such errors from being identified earlier within the guideline process. We suggest that comparison versus baseline rather than comparison versus an active control group is more appropriate for the purposes of the indirect treatment comparisons of LCIG against DBS and BMT. There are several well conducted prospective open label studies and registries that provide	Thank you for your comment. For comments on the use of Olanow et al. (2014) to estimate effectiveness of LCIG -v- BMT, please see **theme 4**. For comments on the role of expert witnesses, please see **theme 2**.

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				consistent results that corroborate the results seen in Olanow when LCIG treatment is compared to baseline [Fernandez, 2015; Antonini, 2015; References: Olanow CW, Kieburtz K, Odin P, Espay AJ, Standaert DG, Fernandez HH, et al. Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: a randomised, controlled, double-blind, double-dummy study. Lancet Neurol 2014 Feb;13(2):141-9. Antonini A, Yegin A, Preda C; GLORIA study investigators and coordinators. Global long-term study on motor and non-motor symptoms and safety of levodopa-carbidopa intestinal gel in routine care of advanced Parkinson's disease patients; 12-month interim outcomes. Parkinsonism Relat Disord 2015;21(3):231-Fernandez HH, Standaert DG, Hauser RA et al. Levodopa-carbidopa intestinal gel in advanced Parkinson's disease: final 12-month, open-label results. Mov Disord 2015;30(4):500-9.	
Abbvie Limited	Full	190	4631	The use of a common comparator is questionable when the population that are eligible for LCIG in the UK is completely exclusive of the population that is eligible for DBS. In the indirect comparison between DBS and LCIG, the BMT common comparator is made up of two different sub-populations: one from the LCIG clinical study (Olanow 2014) and one from the DBS clinical study (PDSURG). The sub- population from the DBS clinical studies is not relevant for comparison with LCIG as these patients were all eligible for DBS, and thus lead to differences in the treatment effect by trial interaction that cannot be addressed. These are not the patients that would have been treated with LCIG in UK clinical practice. Therefore, the conclusions from such a comparison are of highly questionable relevance to the UK population. There was no basis to assume that there was a common comparator used in Olanow and PDSURG (general comment 5). Olanow used an active	Thank you for your comments. For comments on the appropriateness of the decision problems addressed in the review questions on treatment for advanced Parkinson's disease, please see **theme 3**. It is, of course, true to state that, if 2 interventions are always fundamentally mutually exclusive, there is no point in performing a comparison – directly or indirectly – between them. It follows that the only question an indirect comparison between DBS and LCIG can usefully answer is, in patients who have no contraindication to either intervention, which should, on average, be preferred?

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				comparator which would never be the case the clinical practice, while PDSURG used BMT. It is not possible to use those studies for indirect comparison, as this contradicts both NICE Methods Guide and GRADE framework.	This is the end to which the GDG considered the indirect comparison undertaken for this guideline. We do not accept that it is accurate to refer to the placebo arm of Olanow et al. (2014) as representing an active comparator. We note that the authors make no such claim (indeed, at multiple junctures, they explicitly differentiate between 'active' [i.e. LCIG] and 'placebo' arms). We note that the populations studied in PDUSRG (HY≥3) and Olanow et al. (2014) were closely comparable; see **theme 3**. For these reasons, the GDG agreed it was reasonable to consider the control arms of PDSURG and Olanow et al. (2014) as being homogeneous (or, at least, acceptably heterogeneous). One exception to this principle was in the domain of adverse events: the GDG agreed that, as the control arm of Olanow et al. (2014) underwent surgical PEG placement from which they could not benefit but might experience harm, it would not be appropriate to assess the safety profile of LCIG with reference to its comparison with placebo intestinal infusion; therefore, these data were not subject to indirect comparison with DBS and alternative AE estimates were used in the original economic model

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Abbvie Limited	Full	192	4697	The use of term "reasonably cost-effective" is not in line with widely accepted definition of cost-effectiveness, where interventions with ICERs above £30,000 are considered to be cost-effective.	Thank you for your comment. We have deleted this comment and included the study to which it refers (Valldeoriola et al. 2007) amongst cost-utility analyses that found 'DBS is cost effective compared with BMT… but generally with ICERs very close to accepted thresholds'.
Abbvie Limited	Full	192	4705	The position used for LCIG in the clinical and health economic analyses for the Guideline does not represent clinical practice in the UK. LCIG and DBS are only used when other options are not satisfactorily controlling symptoms. In advanced Parkinson's Disease patients comprise significantly different cohorts – with DBS being earlier in the treatment paradigm with different demographics (e.g. age) and clinical characteristics (e.g. comorbidities). No prospective, randomised head to head studies have been conducted between LCIG and DBS and the publication by Worth P.F 2013 states, unlike DBS, LCIG can be used in patients over 70 years with comorbidities, depression and dysphagia. The assumption that patients would be equally eligible for DBS and Duodopa simply does not reflect the treatment pathway in the UK. References: Worth PF. When the going gets tough: how to select patients with Parkinson's disease for advanced therapies. Practical neurology 2013;13 (3):140-52.	Thank you for your comment. For comments on the appropriateness of the decision problems addressed in the review questions on treatment for advanced Parkinson's disease, please see **theme 3**. We note the conclusion of the AbbVie-funded RCT of LCIG -v- BMT, that 'In the final analysis, the value of LCIG as a treatment for PD patients with motor complications will ultimately be determined by trials that provide a full assessment of its relative safety, efficacy, and cost in comparison to other available therapies such as DBS.' As a matter of principle, we agree with this conclusion, though the apparent superiority of DBS over LCIG in people who are eligible for both may make it difficult to recruit to such a trial.
Abbvie Limited	Full	192	4709	Residence based economic models are a very crude measure of defining the outcome of advanced Parkinson's disease treatments such as LCIG and DBS. The health states represented in this type of model are not disease specific	Thank you for your comment. For comments on the structure of the original model, please see **theme 6**.

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				and are not captured in clinical trials. This model structure is rarely used in the published literature and no validation exercises have been published or conducted for the model in question. Hoehn & Yahr and off-time based model has more advantages over residence-based model. The entire spectrum of disease can be considered more precisely and progression over time can be modelled in greater detail. Secondly, Hoehn & Yahr stages and improvement in off-time are a standard measures used in many clinical trials. Sufficient data are available to apply such a model to different interventions and settings. Thirdly Hoehn and Yahr and Off-time based health states have been associated with declining QoL. (Sail et al, Jalundhwala et.al) Reference: Sail K, Merikle E, Niecko T, Jackson J, Espay A. Impact of disease severity, motor and non-motor symptom burden on health related quality of life among patients with Parkinson's disease. World Congress of Parkinson's Disease and Related Disorders. December 2013, Geneva, Switzerland. Jalundhwala Y, Kandukuri L, Marshall T, Yucel A, Chatamra K, Sail K. Assessing the impact of PD motor symptom states on quality of life in patients with advanced Parkinson's disease 20th International Congress of Parkinson's Disease and Movement Disorders, June 19-23, 2016, Berlin, Germany	For comments on Hoehn & Yahr score as a measure of disease progression, please see **theme 6b**, where we note that your second point is entirely untrue: few trials of DBS and no trials of LCIG have reported Hoehn and Yahr score as an outcome.
Abbvie Limited	Full	192	4712	The PDSURG dataset (Williams, 2010) was used to estimate transitions however it is of questionable validity to apply this onto a LCIG- treated population. LCIG is only available in the UK for patients that are ineligible for DBS. This is a mutually exclusive group to that within the PDSURG dataset.	Thank you for your comment. For comments on the appropriateness of the decision problems addressed in the review questions on treatment for advanced Parkinson's disease, please see **theme 3**.
Abbvie Limited	Full	192	4715	UPDRS III is identified as being the strongest predictor of time to care and time to death. It is noted that this is based partly on PDSURG datasets [Williams, 2010 and individual patient level data from PDSURG]. We have	Thank you for your comment. For comments on the appropriateness of the decision problems addressed in the review questions on treatment for advanced Parkinson's disease, please see **theme 3**.

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				already commented on our serious concern around the application of PDSURG data to the model It is invalid to apply a PDSURG dataset to a model generalised transitions or within a combined BMT group, as LCIG is only available in the UK to advanced Parkinson's disease patients that are ineligible for treatment with DBS. The PDSURG dataset cannot represent a group to which it is mutually exclusive.	The prominence of motor function in estimating patient-relevant outcomes was neither an empirical finding based on rigorous analysis of rich datasets. For details, please see **theme 5**. Even if it were accepted -- which, per the arguments in **theme 3**, we certainly do not -- that participants in PDSURG are fundamentally different from people who might receive LCIG in practice, a relatively weak generalisability assumption is being made, in this instance, which is limited to relative effects and implies nothing about absolute event rates: the model simply assumes that the extent to which changes in measured variables affects patient-relevant outcomes is transferable between people receiving different interventions. Such approaches are common and uncontroversial in disease modelling of this type.
Abbvie Limited	Full	193	4721-4734	AbbVie consider that the use of the Olanow study in the health economic evaluation to reflect clinical practice in the UK is inappropriate. The Olanow study included an active comparator arm in which patients were subjected to gastrointestinal surgery, insertion of an intestinal tube through which dummy LCIG was administered and administration of oral immediate release levodopa/carbidopa [Olanow, 2014]. The frequent follow up of patients and use of rescue doses is out of keeping with standard clinical practice in the UK.	Thank you for your comment. For comments on the use of Olanow et al. (2014) to estimate effectiveness of LCIG -v- BMT, please see **theme 4**.

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				The Olanow study was designed in conjunction with the Food and Drug Administration (FDA) specifically to demonstrate the efficacy benefits of LCIG upon off-time in appropriate patients with advanced Parkinson's disease. The comparator arm was not meant to reflect standard clinical practice in any way, but to stringently control for all other possible causes of bias. This explains the small size and short duration of this study. Clearly the short duration is unrepresentative of the ongoing long term nature of this treatment in a standard clinical setting. The use of this active comparator arm against LCIG in a model that is attempting to represent a standard clinical setting is not appropriate. We also note, BMT is composed partly of patients from the PDSURG comparator arm (non-DBS treated arm) (Williams, 2010). By definition this group of patients was eligible for DBS (since they were enrolled in PDSURG) and therefore ineligible for LCIG treatment. Due to the serious issues with BMT outlined above, we are concerned about the validity of evidence obtained through the indirect comparison of LCIG and DBS. We suggest use of the comparison versus baseline is more appropriate for the purposes of the indirect treatment comparisons of LCIG against DBS and BMT. There are several well conducted prospective open label studies and registries that provide consistent results that corroborate the results seen in Olanow study when LCIG treatment is compared to baseline [Fernandez, 2015; Antonini, 2015; Fernandez, 2013].	

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				References: Antonini A, Yegin A, Preda C; GLORIA study investigators and coordinators. Global long-term study on motor and non-motor symptoms and safety of levodopa-carbidopa intestinal gel in routine care of advanced Parkinson's disease patients; 12-month interim outcomes. Parkinsonism Relat Disord 2015;21(3):231-5. Fernandez HH, Vanagunas A, Odin P et al. Levodopa-carbidopa intestinal gel in advanced Parkinson's disease open-label study: interim results. Parkinsonism Relat Disord 2013;19(3):339-45. Fernandez HH, Standaert DG, Hauser RA et al. Levodopa-carbidopa intestinal gel in advanced Parkinson's disease: final 12-month, open-label results. Mov Disord 2015;30(4):500-9	
Abbvie Limited	Full	193	4746, 4747	The PDSURG dataset [subset of Williams, 2010] was used to estimate the absolute rates of progression in this model. As has been noted before it is of questionable validity to apply this to the LCIG treated population. LCIG is only available for patients that are ineligible for DBS in the UK. This is a mutually exclusive group to that in the PDSURG dataset.	Thank you for your comment. PINE or PDSURG data may be used to estimate absolute rates of progression. However, we demonstrate in sensitivity analysis that this choice – and, for that matter, any other trajectory assumed – has a trivial impact on incremental cost effectiveness, as the difference between strategies (as parameterised using robust, randomised evidence) is much more important than the absolute level of any variable. For comments on the appropriateness of the decision problems addressed in the review questions on treatment for advanced Parkinson's disease, please see **theme 3**.

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Abbvie Limited	Full	193	4750-4751	EQ-5D is a generic quality of life (QoL) measure, therefore using clinical variables to estimate EQ-5D does not present a robust approach, specifically if this function was not validated before.	Thank you for your comment. EQ-5D is the preferred measure of health-related quality of life in NICE's reference case, as it applies to clinical guidelines (see The Guidelines manual, 2012). As reported in the guideline and Appendix F, the model was configured to estimate EQ-5D in a number of ways, with the impact of these approaches tested in sensitivity analysis. In response to stakeholder comments about the sensitivity of the EQ-5D, we have also undertaken a new scenario analysis in which HRQoL is estimated via a published mapping function from PDQ-39 to EQ-5D; using this approach makes the ICER for LCIG -v- BMT rise somewhat; see **theme 8**.
Abbvie Limited	Full	194	4774	It is noted that the differential in predicted quality-adjusted life years (QALY) between LCIG and DBS when compared to BMT is largely driven by the UPDRS III inputs. The other key model inputs: UPDRS II, off-time improvement, PDQ-39, HY and PDQ-39 are comparable between LCIG and DBS as shown in table 6, Appendix F. There are several considerations which suggest that the UPDRS III benefit for LCIG has been underestimated in this analysis. This are listed as follows: 1. Olanow et al. (2014) was designed with the FDA to demonstrate the improvement in off-time for patients with advanced Parkinson's disease treated with LCIG compared with an active comparator arm. In the active	Thank you for your comment. The premise of this comment is false. Differences in variables other than UPDRS-III are also important in defining QALYs. In particular, DBS is estimated to result in an additional EQ-5D benefit of a little over 0.05, at the 1-year point. In our indirect comparison, we showed that, despite this difference in point estimates, at a 95% confidence level, data are consistent with there being no difference between DBS and LCIG. We assert that we handle this correctly in the model, by configuring the analysis to reflect parameter uncertainty and propagating that through the decision model, rather than by allowing model inputs to be defined by some arbitrary level of significance. However, even if we were to take the view

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				comparator arm gastrointestinal surgery, insertion of an intestinal tube and administration of placebo LCIG gel infusion was undertaken. The primary end-point was met and a significant improvement in off-time versus the active comparator was demonstrated in Olanow 2014. The study was not powered to detect treatment effects in secondary endpoints. In addition UPDRS III was administered during the best 'on' time in the study. It is not expected that there would be a significant difference in the perception of the patient, or physician of the quality of the best 'on' when comparing between oral levodopa, LCIG, or even DBS as a point in time assessment. Therefore the results from UPDRS III must be corroborated with the wider evidence base which documents the efficacy of LCIG treatment. 2. The small study size means that the sample tested cannot be assumed to represent the wider population. This is the rationale for undertaking a concurrent large open-label study which enrolled 354 patients (Fernandez, 2015). This study was also designed with the FDA and had a longer follow-up period of 54 weeks. This study showed a UPDRS III improvement of -6.3 versus baseline. This is Comparable to the -4.93 improvement that was derived for the DBS group within the draft guideline (line 4846). 3. Other published studies that should be considered include a randomised controlled trial (Nyholm, 2005), a UK-based case-control study (Reddy,2012) and a large registry which collected data on over 300 patients (Antonini,2013). These showed improvements in UPDRS III compared to baseline of -14.0 at 3 weeks, -10.7 at 6 months and -3.3 at 52 weeks respectively	that a difference between LCIG and DBS has not been demonstrated, and consequently assume that LCIG confers an identical benefit in EQ-5D as DBS in the model, the ICER for LCIG -v- BMT would remain as high as £196,367 / QALY. 1. For comments on UPDRS-III results in Olanow et al. (2014), please see **theme 4b**. Contrary to the suggestion that motor dysfunction in the 'on' state would not be expected to be affected by therapy, there was a clearly documented benefit in UPDRS-III in the 'on' state for DBS -v- BMT in the RCTs identified as relevant to these review questions. We agree that domains other than UPDRS-III are important, which is why they were incorporated in the original health economic model. In particular, it is critical that the model directly adopts the empirical effect treatments have on HRQoL – which can be assumed to span all relevant domains (assuming it is measured with a sufficiently sensitive instrument and, in the case in hand, we are greatly assisted by the fact that NICE's preferred measure of HRQoL – EQ-5D – was directly measured in the key trials of LCIG -v- BMT and DBS -v-BMT). 2. For comments on the use of Olanow et al. (2014) to estimate effectiveness of LCIG -v- BMT, please see **theme 4**. 3. Nyholm et al. (2005) was excluded from our review because it did not consider PEG-delivered LCIG; rather, it

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				4. As per comment number 5, we have given a rationale for the comparison versus baseline being a more relevant measure of UPDRS III effect rather than comparison with an active comparator arm that has no relevance to clinical practice in the UK. If this measure were used, an improvement in the UPDRS III score by -1.5 would have been demonstrated in Olanow, rather than a deterioration of +1.4 which was shown for the active comparator (Olanow, 2014). 5. There are several reasons given for the unexpected improvement in the active comparator arm of Olanow which should be considered. The active comparator arm had a higher (worse) UPDRS III score at baseline compared to the LCIG treatment arm (22.5 vs 18.1). There is evidence that the placebo effect is magnified by the invasiveness of the intervention which may have played a role. Also the aggressive monitoring and titration of all the patients during this study and use of rescue doses may have a part to play. It is worth noting that in the active comparator arm the total dose of levodopa and size of rescue doses was higher than in the LCIG arm (an increase of 250 mg at 12 weeks vs baseline compared to an increase of 91.7 mg at 12 weeks vs baseline; and 180.6 mg compared to 139.8 mg respectively) 6. There was a difference in baseline measures of UPDRS III for the compiled DBS group (25.1 in the 'off' state) and the LCIG group (18.1 in the best 'on' state). It is conceivable that a group with a higher UPDRS III value at baseline may show a greater improvement once they are started on an advanced treatment.	was a study of nasojejunal delivery, which is neither licensed nor practical for long-term use. We also note that motor dysfunction (UPDRS-III) was the only domain of the UPDRS with respect to which the trial did not show a significant benefit for LCIG. We cannot identify the estimate of -10.7 points' change from baseline in Reddy et al.'s cohort study (2012); however, if we assume that it is accurate – and we set aside our firm belief that observational before–after data are a very poor second to randomised evidence – using this effect gives an ICER of £212,518 / QALY for LCIG -v- BMT. Using Antonini et al.'s uncontrolled before–after change of -3.3 (2015), this figure rises to £287,116 / QALY. 4. As stated elsewhere (see **theme 4**), we find the argument that high-quality randomised evidence should be discarded because it produces an inconvenient result transparently unconvincing. However, if we use the estimated effect of -1.5 points, the ICER for LCIG -v- BMT is £321,738 / QALY. 5–7. For comments on UPDRS-III results in Olanow et al. (2014), please see **theme 4b**. As we note (see also **theme 1e**), the GDG recognised the nontrivial improvements made in some domains by participants randomised to oral therapy in the RCT of LCIG -v- BMT, and took this as evidence that redoubled effort to optimise oral therapy can often provide worthwhile gains. If the NHS is not matching the standard of care seen in Olanow

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				7. We are aware of various methodologies used for UPDRS III measurement and it is clinically difficult to ensure that a patient is 'completely on' at the time of assessment. With regard to DBS we are aware that UPDRS III measurements in the 'off' state can be misleading as the neurostimulator does send stimulation to the brain even when it is switched off. This means a true UPDRS III (off) cannot be assessed and will actually be lower already than baseline. In summary we are concerned that the benefits of DBS compared to LCIG are driven essentially by a single parameter, UPDRS III. This specific input has a weak and inconsistent evidence base and it has been applied incorrectly within the indirect treatment comparison of LCIG vs DBS and LCIG vs BMT. This single inaccuracy has had an enormous impact on the final conclusions of these review questions, and we believe it is inappropriately applied. References: Olanow CW, Kieburtz K, Odin P, Espay AJ, Standaert DG, Fernandez HH, et al. Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: a randomised, controlled, double-blind, double-dummy study. Lancet Neurol 2014 Feb;13(2):141-9. Nyholm D, Klangemo K, Johansson A. Levodopa/carbidopa intestinal gel infusion long-term therapy in advanced Parkinson's disease. Eur J Neurol 2012; 19(8):1079-1085. Reddy P, Martinez-Martin P, Rizos A, Martin A, Faye GC, Forgacs I, et al. Intrajejunal levodopa versus conventional therapy in Parkinson disease: motor and nonmotor effects. Clin Neuropharmacol 2012 Sep;35(5):205-7. Antonini A, Yegin A, Preda C; GLORIA study investigators and coordinators. Global long-term study on motor and non-motor symptoms and safety of	et al.'s control arm, that is an argument for it to pay attention to the processes by which it is failing to provide optimised oral therapy, not a reason to abandon the approach and choose one that will use massively more resources. 6. It is unclear whence the estimate of a UPDRS-III (off) of 25.1 in the 'compiled DBS group' derives, nor to what the 'compiled DBS group' refers. Even presuming the numbers are correct, no inference can be drawn from a comparison between 'off' and 'on' scores. 7. UPDRS-III scores were estimated in the 'on' state in all trials that are used to estimate treatment effects, as well as all evidence that uses the measure as one of the potential surrogate predictors of patient-relevant outcomes. Therefore, this hypothesis is moot. If AbbVie asserts that LCIG should be reserved for cases where DBS is not an option, there is little point in arguing that the indirect comparison of the 2 options is flawed; all that matters is how LCIG fares in comparison with BMT. As we explain in **theme 4b**, shortcomings in the evidence base available to estimate the UPDRS-III effects of LCIG compared with BMT bear on the precision – not the accuracy – of the estimate. Moreover, as demonstrated in extensive sensitivity analysis, any latent inaccuracy certainly does not have an 'enormous impact' of final

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				levodopa-carbidopa intestinal gel in routine care of advanced Parkinson's disease patients; 12-month interim outcomes. Parkinsonism Relat Disord 2015;21(3):231-Fernandez HH, Standaert DG, Hauser RA et al. Levodopa-carbidopa intestinal gel in advanced Parkinson's disease: final 12-month, open-label results. Mov Disord 2015;30(4):500-9.	conclusions; in fact, it can be shown to be qualitatively irrelevant (see **theme 4**). We agree that our analysis could only be strengthened by more powerful data on the UPDRS-III effects of LCIG; however, all such data could do is enable us to arrive at a more precise estimate of the amount of net harm the provision of LCIG at its list price would imply for the NHS. We also note that, despite its shortcomings, evidence on the UPDRS-III effects of LCIG is much superior – in terms of both quantity and quality – than can be found for Hoehn and Yahr score, which AbbVie insists is a superior metric with which to simulate Parkinson's disease.
Abbvie Limited	Full	194	4786	Such a strong statement in relation to the cost of LCIG is overreaching the remint of clinical guideline, which has no means of influencing the price to the NHS or making technology assessment based recommendation.	Thank you for your comment. The purpose of NICE's clinical guidelines is as set out in The Guidelines Manual (2012). Consideration of the costs of healthcare interventions – and the extent to which they are justified by their associated benefits – is a central component of the programme. No price negotiation is mentioned or implied here or elsewhere in the guideline.
Abbvie Limited	Full	194	Figure 2	DBS is contradicted in patients with cognitive decline. The treatment is associated with the development of cognitive deficits such as hallucinations and delusion. (Burdick 2012) The natural progression of Parkinson's disease itself leads to cognitive decline. Cognitive decline, hallucinations followed by functional status (ADL impairment) are the most important predictors of nursing home admission in Parkinson's disease. (Aarsland 2000 and Shih 2016) however, as predicted in	Thank you for your comment. As noted in appendix F.3.1.1, the GDG recognised that factors other than those measured in trials of anti-Parkinsonian interventions may be more predictive of requirement for full-time care, above all dementia and baseline dependence. However, the GDG was content to assume that the interventions under analysis would not have a direct effect on these

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				figure 2, DBS patients seem spend a smaller proportion of their lives in full time care. Therefore, we disagree with the model structure that predicts DBS to delay time to full time care. Reference: Burdick et al. Relationship between higher rates of adverse events in deep brain stimulation using standardized prospective recording and patient outcomes. Neurosurg Focus 29 (2):E4, 2010 Aarsland et al. Predictors of nursing home placement in Parkinson's disease: a population-based, prospective study. J Am Geriatr Soc. 2000 Aug;48(8):938-42 Shih T, Sullivan J, Sail K, Jalundhwala Y, van Eijndhoven E, Marshall T, Zadikoff C, Lakdawalla D. The Effect of Functional Status on Nursing Home Admission among Patients with Advanced Parkinson's Disease. 2016 ANN Annual Meeting. Vancouver, BC, Canada, April 15-21. 2016	factors; therefore, the analysis effectively assumed other factors were equal and sought to quantify the marginal effects of changes in clinical variables on the outcomes of interest. Because DBS is effective in improving domains that are associated with reduced hazard of requirement for full-time care -- above all, motor dysfunction as measured by UPDRS-III -- it is to be expected that the intervention should confer benefit in delaying time to care, and that is what the original model predicts.
Abbvie Limited	Full	195	4802	The reported ICER for LCIG is inconsistent with published evidence and SMC recommendation and is 10 times higher than ICER in SMCs final recommendation. We would like to point out that the ICER published by SMC does not take into account PAS details of which cannot be discussed here, owing to the confidentiality of the discount. Reference: Scottish Medicines Consortium (SMC). Co-careldopa intestinal gel, 20mg/5mg levodopa/carbidopa per ml for continuous intestinal infusion, (LCIG). No. (316/06). 2016 https://www.scottishmedicines.org.uk/files/advice/DAD_co-careldopa_2nd_Resubmission_FINAL_May_2016_for_website.pdf	Thank you for your comment. The reported ICER for LCIG is only inconsistent with the published evidence funded by the manufacturer of LCIG. Two other publications, which do not share this conflict of interest, conclude as we do that LCIG cannot be considered close to being cost effective compared with BMT. See Appendix F.5.1.3. For comments on apparent discrepancies between NICE's conclusions on LCIG and SMC advice, please see **theme 9c**.

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Abbvie Limited	Full	195	4825	A single 12 week RCT with LCIG is highly unlikely to ever demonstrate the rate of falls and this adds to the argument that a wider evidence base should be considered. The Olanow study was a high quality controlled, double-blind randomised clinical trial. The limitations of conducting studies ethically in this group that has no other treatment options with a surgical procedure need to be considered. A short 12 week study is not an appropriate source of the inputs that been sought within the treatment analysis. References: Olanow CW, Kieburtz K, Odin P, Espay AJ, Standaert DG, Fernandez HH, et al. Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: a randomised, controlled, double-blind, double-dummy study. Lancet Neurol 2014 Feb;13(2):141-9.	Thank you for your comment. For comments on the use of Olanow et al. (2014) to estimate effectiveness of LCIG -v- BMT, please see **theme 4**. We certainly agree that estimation of the benefits, harms and costs of LCIG compared with BMT could only be made more precise by high-quality randomised evidence with longer follow-up than 12 weeks. However, the absence of such evidence is not a reason to discard best available evidence and rely, instead, on very low-quality evidence that is subject to a wide range of biases.
Abbvie Limited	Full	195	Table 22	Utility gain of 0.729 for DBS is inconsistent with published data. McIntosh et al (2016) reports QALY gain of 0.02 at 1 year, 0.33 at 5 years and 0.6 at 10 years. References: McIntosh, E., Gray, A., Daniels, J., Gill, S., Ives, N., Jenkinson, C., Mitchell, R., Pall, H., Patel, S., Quinn, N., Rick, C., Wheatley, K., Williams, A. and on behalf of The PD SURG Collaborators Group (2016), Cost-utility analysis of deep brain stimulation surgery plus best medical therapy versus best medical therapy in patients with Parkinson's: Economic evaluation alongside the PD SURG trial. Mov. Disord.	Thank you for your comment. If we constrain the original model to a time horizon of 10 years, it estimates benefits of 0.63 QALYs, compared with BMT. This is very close to McIntosh et al.'s estimate (2016).
Abbvie Limited	Full	196	4853-65	The results from Olanow comparing the LCIG group to the active comparator group should be considered in the context of the active comparator group. In this group gastrointestinal surgery, insertion of an intestinal tube and administration of placebo LCIG gel infusion was undertaken. The comparator arm does not reflect standard clinical practice in any way.	Thank you for your comment. For comments on the use of Olanow et al. (2014) to estimate effectiveness of LCIG -v- BMT, please see **theme 4**.

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				We suggest use of the comparison versus baseline is more appropriate for the purposes of the indirect treatment comparisons of LCIG against DBS and BMT. There are several well conducted prospective open label studies and registries that provide consistent results that corroborate the results seen in Olanow study when LCIG treatment is compared to baseline [Fernandez, 2015; Antonini, 2015; Fernandez, 2013]. References: Antonini A, Yegin A, Preda C; GLORIA study investigators and coordinators. Global long-term study on motor and non-motor symptoms and safety of levodopa-carbidopa intestinal gel in routine care of advanced Parkinson's disease patients; 12-month interim outcomes. Parkinsonism Relat Disord 2015;21(3):231-5. Fernandez HH, Standaert DG, Hauser RA et al. Levodopa-carbidopa intestinal gel in advanced Parkinson's disease: final 12-month, open-label results. Mov Disord 2015;30(4):500-9	
Abbvie Limited	Full	196	4861-4863	See comment regarding line 4774. A study powered to detect that level of difference would have to be quite large. A large open label study with 292 patients on LCIG demonstrated a statistically significant improvement from baseline to last visit,the mean change was -7.4 pointson the UPDRS III Reference: Olanow CW, Kieburtz K, Odin P, Espay AJ, Standaert DG, Fernandez HH, et al. Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: a randomised,	Thank you for your comment. A trial powered to detect difference in UPDRS-III between LCIG and BMT would only have to be 'quite large' if the anticipated benefit is quite small. A trial would have 80% power to demonstrate a true difference of the magnitude suggested from Fernandez et al. (2015) at the 0.05 significance level with a little under 50 participants per arm (assuming an SD of around 13, as indicated in Fernandez et al.'s graph).

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				controlled, double-blind, double-dummy study. Lancet Neurol 2014 Feb;13(2):141-9. Fernandez et al. Levodopa-Carbidopa Intestinal Gel in Advanced Parkinson's Disease: Final 12-Month, Op	
Abbvie Limited	Full	197	4870 – 4872	See comment regarding line 4774	Thank you for your comment. The premise of this comment is false. Differences in variables other than UPDRS-III are also important in defining QALYs. In particular, DBS is estimated to result in an additional EQ-5D benefit of a little over 0.05, at the 1-year point. In our indirect comparison, we showed that, despite this difference in point estimates, at a 95% confidence level, data are consistent with there being no difference between DBS and LCIG. We assert that we handle this correctly in the model, by configuring the analysis to reflect parameter uncertainty and propagating that through the decision model, rather than by allowing model inputs to be defined by some arbitrary level of significance. However, even if we were to take the view that a difference between LCIG and DBS has not been demonstrated, and consequently assume that LCIG confers an identical benefit in EQ-5D as DBS in the model, the ICER for LCIG -v- BMT would remain as high as £196,367 / QALY. 1. For comments on UPDRS-III results in Olanow et al. (2014), please see **theme 4b**. Contrary to the suggestion that motor dysfunction in the 'on' state would not be expected to be affected by therapy, there was a clearly

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					documented benefit in UPDRS-III in the 'on' state for DBS -v- BMT in the RCTs identified as relevant to these review questions. We agree that domains other than UPDRS-III are important, which is why they were incorporated in the original health economic model. In particular, it is critical that the model directly adopts the empirical effect treatments have on HRQoL – which can be assumed to span all relevant domains (assuming it is measured with a sufficiently sensitive instrument and, in the case in hand, we are greatly assisted by the fact that NICE's preferred measure of HRQoL – EQ-5D – was directly measured in the key trials of LCIG -v- BMT and DBS -v-BMT). 2. For comments on the use of Olanow et al. (2014) to estimate effectiveness of LCIG -v- BMT, please see **theme 4**. 3. Nyholm et al. (2005) was excluded from our review because it did not consider PEG-delivered LCIG; rather, it was a study of nasojejunal delivery, which is neither licensed nor practical for long-term use. We also note that motor dysfunction (UPDRS-III) was the only domain of the UPDRS with respect to which the trial did not show a significant benefit for LCIG. We cannot identify the estimate of -10.78 points' change from baseline in Reddy et al.'s cohort study (2012); however, if we assume that it is accurate – and we set aside our firm belief that observational before–after data are a very poor second to randomised evidence – using this effect gives an ICER of

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					£212,518 / QALY for LCIG -v- BMT. Using Antonini et al.'s uncontrolled before–after change of -3.3 (2015), this figure rises to £287,116 / QALY. 4. As stated elsewhere (see **theme 4**), we find the argument that high-quality randomised evidence should be discarded because it produces an inconvenient result transparently unconvincing. However, if we use the estimated effect of -1.5 points, the ICER for LCIG -v- BMT is £321,738 / QALY. 5–7. For comments on UPDRS-III results in Olanow et al. (2014), please see **theme 4b**. As we note (see also **theme 1e**), the GDG recognised the nontrivial improvements made in some domains by participants randomised to oral therapy in the RCT of LCIG -v- BMT, and took this as evidence that redoubled effort to optimise oral therapy can often provide worthwhile gains. If the NHS is not matching the standard of care seen in Olanow et al.'s control arm, that is an argument for it to pay attention to the processes by which it is failing to provide optimised oral therapy, not a reason to abandon the approach and choose one that will use massively more resources. 6. It is unclear whence the estimate of a UPDRS-III (off) of 25.1 in the 'compiled DBS group' derives, nor to what the 'compiled DBS group' refers. Even presuming the

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					numbers are correct, no inference can be drawn from a comparison between 'off' and 'on' scores. 7. UPDRS-III scores were estimated in the 'on' state in all trials that are used to estimate treatment effects, as well as all evidence that uses the measure as one of the potential surrogate predictors of patient-relevant outcomes. Therefore, this hypothesis is moot. If AbbVie asserts that LCIG should be reserved for cases where DBS is not an option, there is little point in arguing that the indirect comparison of the 2 options is flawed; all that matters is how LCIG fares in comparison with BMT. As we explain in **theme 4b**, shortcomings in the evidence base available to estimate the UPDRS-III effects of LCIG compared with BMT bear on the precision – not the accuracy – of the estimate. Moreover, as demonstrated in extensive sensitivity analysis, any latent inaccuracy certainly does not have an 'enormous impact' of final conclusions; in fact, it can be shown to be qualitatively irrelevant (see **theme 4**). We agree that our analysis could only be strengthened by more powerful data on the UPDRS-III effects of LCIG; however, all such data could do is enable us to arrive at a more precise estimate of the amount of net harm the provision of LCIG at its list price would imply for the NHS. We also note that, despite its shortcomings, evidence on the UPDRS-III effects of LCIG is hugely much superior –

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					in terms of both quantity and quality – than can be found for Hoehn and Yahr score, which AbbVie insists is a superior metric with which to simulate Parkinson's disease.
Abbvie Limited	Full	197	4893, 4907	See comment regarding line 4853	Thank you for your comment. For comments on the use of Olanow et al. (2014) to estimate effectiveness of LCIG -v- BMT, please see **theme 4**.
Abbvie Limited	Full	198	4923	0.75 should read as 0.729	Thank you for your comment. This evidence statement states our analysis suggests 'around 0.75' QALYs are gained with DBS compared with BMT, which is a reasonable summary of a base-case of 0.729 QALYs with associated uncertainty.
Abbvie Limited	Full	199	Trade-off between benefits and harms	AbbVie disagrees with the section as the comparison of DBS and LCIG is not valid due to different populations and clinical applications of those treatments (for a detailed explanation please refers to the general comment 2 above). As explained in the comment 17 above, difference in the UPDRS-III outcome as presented in Olanow (2014) cannot deemed to be representative for LCIG. Other studies do show significant large improvement on the UPDRS-III. For example, Reddy et al. (2012) and Fernandez et al (2015). Therefore, to draw a conclusion that benefits of DBS outweigh the benefits of LCIG is not possible if it is based on the secondary outcome of a single RCT where the difference was not statistically significant. In relation to the clinical conclusion, we would once again emphasise that LCIG is indicated for the cohort of patients who are not eligible for DBS. Therefore, LCIG and DBS are not the options of choice in clinical practice.	Thank you for your comment. The point of the indirect comparison was to assess evidence for the relative benefits and harms of DBS and LCIG in a population for which either intervention would be appropriate; for the reasons outlined in **theme 3**, the PDSURG HY≥3 participants and the Olanow et al. (2014) cohort were judged to provide an acceptably homogeneous population to enable this. We repeat the GDG's view that, if DBS and LCIG are not seen as direct comparators in practice, that is only because of a prevailing belief that, even when cost is disregarded, DBS is to be preferred as it is more effective than LCIG, a belief that is validated by this analysis.

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				We note that it is methodologically incorrect for the GDG to infer a 'trend' towards DBS superiority over LCIG in the comparisons which were not statistically significant. This statement implies that DBS would be demonstrated as superior should further data be available. Wood et al (2014) demonstrate how insecure such conclusions are, given probabilistic determination based upon the fiducial distribution. The comment should be reworded with the suggestion of superiority for DBS on the non-significant items removed. Reference: Fernandez HH, Standaert DG, Hauser RA, Lang AE, Fung VS, Klostermann F, Lew MF, Odin P, Steiger M, Yakupov EZ, Chouinard S. Levodopa-carbidopa intestinal gel in advanced Parkinson's disease: Final 12-month, open-label results. Movement Disorders. 2015 Apr 1;30(4):500-9. Reddy P, Martinez-Martin P, Rizos A, Martin A, Faye GC, Forgacs I, et al. Intrajejunal levodopa versus conventional therapy in Parkinson disease: motor and nonmotor effects. Clin Neuropharmacol 2012 Sep;35(5):205-7 Wood J, Freemantle N, King M, Nazareth I. The trap of trends to statistical significance: how likely it really is that a near significant P value becomes more significant with extra data. BMJ 2014; 348: g2215 doi: 10.1136/bmj.g2215 Olanow CW, Kieburtz K, Odin P, Espay AJ, Standaert DG, Fernandez HH, et al. Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: a randomised, controlled, double-blind, double-dummy study. Lancet Neurol 2014 Feb;13(2):141-9.	When it comes to UPDRS-III, we agree that LCIG was unlikely to demonstrate superiority over DBS when it could not demonstrate superiority over BMT in the only randomised experiment to which it has been subject. The superiority of DBS, in this domain, is an inevitable -- rather than an impossible -- conclusion. Wood et al.'s analysis demonstrates that a trend towards some finding is always more likely than not to reflect a true difference in direction of effect (if not in magnitude). Moreover, the GDG's point (which is expressed in appropriately conservative terms) was that DBS appeared superior to LCIG in all domains, a finding that is less likely to be due to chance than any trend in a single outcome, which is what Wood et al. simulate. We do not accept that any rewording is necessary.
Abbvie Limited	Full	204	4949	LCIG delivers benefit to cohort of patients who have exhausted all other available options and/or are not eligible for those options. AbbVie, therefore, disagrees with the statement, as it will have a very negative impact on the choice of therapies for clinicians and will prevent access to LCIG for patients.	Thank you for your comment. For comments on the effectiveness and cost effectiveness of LCIG, please see **theme 1**.

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				AbbVie strongly believe that patients in the later stage of Parkinson's disease whose symptoms are not controlled with BMT and who are not eligible for DBS should be offered LCIG.	For comments on the effectiveness and cost effectiveness of LCIG in subgroups of people with advanced Parkinson's disease, please see **theme 1b**. For comments on the paucity of therapeutic options for people with advanced Parkinson's disease, please see **theme 1e**.
Abbvie Limited	Full	General	General	AbbVie is very concerned by the negative recommendation for Levodopa-carbidopa intestinal gel (LCIG). The recommendation is entirely inconsistent with previously published commissioning recommendations. Most notably the NHS England funding Policy (NHS England, 2015) and the Scottish Medicines Consortium (SMC) recommendation (SMC, 2016). In its current form the draft guideline will introduce a significant degree of confusion for expert Parkinson's Disease clinicians in specialist neurological centres who wish to prescribe LCIG for appropriate patient based upon expert clinical judgement. LCIG is indicated for those patients who have tried and failed all currently available medical interventions. Furthermore in the UK it is available only for patients that are ineligible for deep brain stimulation (DBS); a key criterion for funding as per SMC guidance and NHS England policy. If the negative draft recommendation is not changed, then access will be withdrawn to an important treatment for a select, but significant group of patients with high clinical need and no other treatment options.	Thank you for your comment. For comments on the relationship between NICE's conclusions on LCIG and NHS England's specialised commissioning policy, please see **theme 9a**. For comments on apparent discrepancies between NICE's appraisal of the evidence on LCIG and the view taken by NHS England's specialised commissioning policy, please see **theme 9b**. For comments on apparent discrepancies between NICE's conclusions on LCIG and SMC advice, please see **theme 9c**. For comments on the effectiveness and cost effectiveness of LCIG, please see **theme 1**. For comments on the appropriateness of the decision problems addressed in the review questions on treatment for advanced Parkinson's disease, please see **theme 3**.

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				Reference: Scottish Medicines Consortium (SMC). Co-careldopa intestinal gel, 20mg/5mg levodopa/carbidopa per ml for continuous intestinal infusion, (LCIG). No. (316/06). 2016 https://www.scottishmedicines.org.uk/files/advice/DAD_co-careldopa_2nd_Resubmission_FINAL_May_2016_for_website.pdf	For comments on the paucity of therapeutic options for people with advanced Parkinson's disease, please see **theme 1e**.
Abbvie Limited	Full	General	General	The position used for LCIG in the clinical and health economic analyses for the Guideline does not represent clinical practice in the UK. LCIG and DBS are only used when other options are not satisfactorily controlling symptoms. In advanced Parkinson's Disease patients comprise significantly different cohorts – with DBS being earlier in the treatment paradigm with different demographics (e.g. age) and clinical characteristics (e.g. comorbidities). No prospective, randomised head to head studies have been conducted between LCIG and DBS and the publication by Worth P.F 2013 states, unlike DBS, LCIG can be used in patients over 70 years with comorbidities, depression and dysphagia. The assumption that patients would be equally eligible for DBS and Duodopa simply does not reflect the treatment pathway in the UK and is a significant error, which underpins the GDG's analysis. References: Worth PF. When the going gets tough: how to select patients with Parkinson's disease for advanced therapies. Practical neurology 2013;13 (3):140-52.	Thank you for your comment. For comments on the appropriateness of the decision problems addressed in the review questions on treatment for advanced Parkinson's disease, please see **theme 3**. We note the conclusion of the AbbVie-funded RCT of LCIG -v- BMT, that 'In the final analysis, the value of LCIG as a treatment for PD patients with motor complications will ultimately be determined by trials that provide a full assessment of its relative safety, efficacy, and cost in comparison to other available therapies such as DBS.' As a matter of principle, we agree with this conclusion, though the apparent superiority of DBS over LCIG in people who are eligible for both may make it difficult to recruit to such a trial.
Abbvie Limited	Full	General	General	The model structure used to indirectly compare LCIG, DBS and BMT is overly simplistic and is inconsistent with published literature.	Thank you for your comment. For comments on the structure of the original model, please see **theme 6**.

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				The model comprises three states – home, full-time care and death. We note that admission to full-time care is not an outcome of any of the trials included into the model. Clinicians will typically treat a patient and judge the success by reduced symptoms burden and/or better disease control; admission to long-term care is an important, but rare event and the patient may need treatment for a decade or more before this happens. To cope with this, the economic model has a complicated underlying structure of additional equations to link trial end-points (UPDRS-II, UPDRS-III, EQ-5D, PDQ-39, Off-time) to admission rate to full-time care several years in the future. We question the validity of the model structure as it does not represent natural disease progression and does not reflect the impact of active interventions, such as LCIG and DBS. Therefore, it is not an appropriate tool for a valid comparison of advanced Parkinson's Disease treatments.	
Abbvie Limited	Full	General	General	AbbVie considers that the evidence base for LCIG and DBS has not been appropriately considered and as a result the conclusions drawn are fundamentally flawed. Whilst AbbVie recognises the value of high quality evidence, such as data collected though RCTs, we note that in this case the RCTs included for LCIG and DBS cannot be deemed as of the same quality. Olanow (the RCT for LCIG) is a double-blind active comparator controlled randomised trial with an optimized oral medication arm. In comparison, PDSURG (DBS) was randomised, open-label study (Williams, 2010) which was arguably not controlled.	Thank you for your comment. For comments on the use of Olanow et al. (2014) to estimate effectiveness of LCIG -v- BMT, please see **theme 4**. Our appraisal of included RCT evidence agrees with your suggestion that the 1 trial of LCIG compared with BMT provides higher-quality evidence than the available evidence on DBS -v- LCIG. When the dimensions of GRADE are considered, evidence of LCIG -v- BMT is generally considered of moderate–high quality, whereas DBS -v- BMT generally achieves low–moderate quality.

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				The control aspect of PDSURG should be evaluated objectively. The publication notes that in the best medical therapy arm, 'apart from random treatment allocation, all other aspects of the management of patients were at the discretion of the local clinicians' (page 3, Williams et al. 2010). It would be expected that patients receiving DBS may be subject to a very different follow up at their neurological centre as compared to those that continued on medical management. Therefore, it is clear this study cannot be considered to be 'controlled'. It is noted that within the PDSURG publication this study is not described as a controlled study (Williams, 2010). This brings into question the categorisation (and consequent grading) of this study as a randomised 'controlled' trial and the emphasis that NICE has placed upon it for model construction and input generation. We, therefore, suggest that the inclusion of the PDSURG study into the evidence base for the draft guideline should allow for a wider range of studies to be included for LCIG. This would include Nyholm et al. (2005) which was a randomised controlled study. No reason was given in Appendix G for its omission. Other relevant studies include a UK based matched cohort study Reddy et al. 2012, Antonini et al 2015, Fernandez et al 2015. References: Olanow CW, Kieburtz K, Odin P, Espay AJ, Standaert DG, Fernandez HH, et al. Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: a randomised,	The biases to which the available evidence is subject are discussed in the 'quality of evidence' section of 10.3.6. It is noted that, in the case of DBS RCTs, the absence of blinding may lead to some overestimate of treatment effect; however, the GDG considered it would be unreasonable for a trial of neurosurgical intervention to attempt a sham control arm. The GDG discussed the available evidence in the light of these strengths and weaknesses. However, the fact that some of the included RCTs were at risk of bias cannot be used as justification for considering them on an equal footing with very low quality uncontrolled observational evidence. We apologise for omitting exclusion reasons for these questions; details have now been added to Appendix G. Nyholm et al. (2005) was excluded because it did not consider PEG-delivered LCIG; rather, it was a study of nasojejunal delivery, which is neither licensed nor practical for long-term use.

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				controlled, double-blind, double-dummy study. Lancet Neurol 2014 Feb;13(2):141-9. Nyholm D, Klangemo K, Johansson A. Levodopa/carbidopa intestinal gel infusion long-term therapy in advanced Parkinson's disease. Eur J Neurol 2012; 19(8):1079-1085. Reddy P, Martinez-Martin P, Rizos A, Martin A, Faye GC, Forgacs I, et al. Intrajejunal levodopa versus conventional therapy in Parkinson disease: motor and nonmotor effects. Clin Neuropharmacol 2012 Sep;35(5):205-7. Antonini A, Yegin A, Preda C; GLORIA study investigators and coordinators. Global long-term study on motor and non-motor symptoms and safety of levodopa-carbidopa intestinal gel in routine care of advanced Parkinson's disease patients; 12-month interim outcomes. Parkinsonism Relat Disord 2015;21(3):231-Fernandez HH, Standaert DG, Hauser RA et al. Levodopa-carbidopa intestinal gel in advanced Parkinson's disease: final 12-month, open-label results. Mov Disord 2015;30(4):500-9.	
Abbvie Limited	Full	General	General	AbbVie consider that the use of the Olanow study in the health economic evaluation to reflect clinical practice in the UK is inappropriate. The Olanow study included an active comparator arm in which patients were subjected to gastrointestinal surgery, insertion of an intestinal tube through which dummy LCIG was administered and administration of oral immediate release levodopa/carbidopa [Olanow, 2014]. The frequent follow up of patients and use of rescue doses is out of keeping with standard clinical practice in the UK. The Olanow study was designed in conjunction with the Food and Drug Administration (FDA) specifically to demonstrate the efficacy benefits of LCIG upon off-time in appropriate patients with advanced Parkinson's disease. The	Thank you for your comment. For comments on the use of Olanow et al. (2014) to estimate effectiveness of LCIG -v- BMT, please see **theme 4**. For comments on the appropriateness of the decision problems addressed in the review questions on treatment for advanced Parkinson's disease, please see **theme 3**.

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				comparator arm was not meant to reflect standard clinical practice in any way, but to stringently control for all other possible causes of bias. This explains the small size and short duration of this study. Clearly the short duration is unrepresentative of the ongoing long term nature of this treatment in a standard clinical setting. The use of this active comparator arm against LCIG in a model that is attempting to represent a standard clinical setting is not appropriate. We also note, BMT is composed partly of patients from the PDSURG comparator arm (non-DBS treated arm) (Williams, 2010). By definition this group of patients was eligible for DBS (since they were enrolled in PDSURG) and therefore ineligible for LCIG treatment. Due to the serious issues with BMT outlined above, we are concerned about the validity of evidence obtained through the indirect comparison of LCIG and DBS. We suggest use of the comparison versus baseline is more appropriate for the purposes of the indirect treatment comparisons of LCIG against DBS and BMT. There are several well conducted prospective open label studies and registries that provide consistent results that corroborate the results seen in Olanow study when LCIG treatment is compared to baseline [Fernandez, 2015; Antonini, 2015; Fernandez, 2013]. References: Antonini A, Yegin A, Preda C; GLORIA study investigators and coordinators. Global long-term study on motor and non-motor symptoms and safety of levodopa-carbidopa intestinal gel in routine care of advanced	

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				Parkinson's disease patients; 12-month interim outcomes. Parkinsonism Relat Disord 2015;21(3):231-5. Fernandez HH, Vanagunas A, Odin P et al. Levodopa-carbidopa intestinal gel in advanced Parkinson's disease open-label study: interim results. Parkinsonism Relat Disord 2013;19(3):339-45. Fernandez HH, Standaert DG, Hauser RA et al. Levodopa-carbidopa intestinal gel in advanced Parkinson's disease: final 12-month, open-label results. Mov Disord 2015;30(4):500-9	
Abbvie Limited	Full	General	General	In the absence of direct head to head comparisons, the use of flawed assumptions and comparisons not based upon sound clinical judgement, AbbVie are concerned that there may have been a lack of clinical input in the development of the draft guideline from experts experienced in LCIG. In contrast, expert witnesses were called to support consideration of evidence for DBS.	Thank you for your comment. For comments on the role of expert witnesses, please see **theme 2**.
Abbvie Limited	Model	Parameters worksheet	Cells F77, F78	The values in these cells should read as 18.1 and 22.5 correspondingly as per Olanow publication, table 2. We would like to note that correcting these values brings ICER to £410,945. Reference: Olanow CW, Kieburtz K, Odin P, Espay AJ, Standaert DG, Fernandez HH, et al. Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: a randomised, controlled, double-blind, double-dummy study. Lancet Neurol 2014 Feb;13(2):141-9.	Thank you for drawing our attention to this error. We agree that, when it is corrected, the ICER for LCIG -v- BMT rises slightly; including other minor amendments, the revised ICER is £411,697 / QALY (using the specimen scenario settings adopted for one-way sensitivity analysis; see Appendix F.4.1.5).

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Abbvie Limited	Short	19	5	AbbVie is very concerned by the negative recommendation for Levodopa-carbidopa intestinal gel (LCIG). The recommendation is entirely inconsistent with previously published commissioning recommendations. Most notably the NHS England funding Policy (NHS England, 2015) and the Scottish Medicines Consortium (SMC) recommendation (SMC, 2016). 1. Which areas will have the biggest impact on practice and be challenging to implement? Please say for whom and why. NHS England already makes Duodopa available to patients who have no further treatment options through specialised neuroscience centres. The draft recommendation with respect to Duodopa will have a significant impact on practising clinicians, in the event that NHS England's commissioning process takes its lead from final guidance. Clinicians would be denied a therapeutic option to which they currently have access for a select, but significant group of patients with high clinical need. Practising clinicians would view this guidance as a retrograde step – which will cause further implementation challenges by undermining the clinical credibility of the guidance as a whole. 2. Would implementation of any of the draft recommendations have significant cost implications? The disruption to current clinical practice if NHS England chooses to decommission Duodopa in the light of the NICE guidance would clearly create a deadweight cost which would need to be absorbed by the NHS. In addition, AbbVie provides a number of value-added services to support the use of Duodopa which may need to be re-provided in the future at public expense.	Thank you for your comment. For comments on the effectiveness and cost effectiveness of LCIG, please see **theme 1**. For comments on the relationship between NICE's conclusions on LCIG and NHS England's specialised commissioning policy, please see **theme 9a**. For comments on apparent discrepancies between NICE's appraisal of the evidence on LCIG and the view taken by NHS England's specialised commissioning policy, please see **theme 9b**. For comments on apparent discrepancies between NICE's conclusions on LCIG and SMC advice, please see **theme 9c**.

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				3. What would help users overcome any challenges? (For example, existing practical resources or national initiatives, or examples of good practice.) AbbVie has no comment on this.	
Abertawe Bro Morgannwg University Health Board	Appendix F	Section		Assumptions about treatment while in full-time care and table 41 page – 55 This assumption in real clinical practice is incorrect. Commonest cause of Care home admission in PD is dementia and Neuropsychiatric symptoms. In these situations it is common to consider burden of treatment against benefit and many clinicians will consider against DBS battery change, Apomorphine s/c infusions or LCIG continuation	Thank you for your comment. This assumption was tested in sensitivity analysis (see Appendix F.4.1.7); it was found to have no material impact on results.
Abertawe Bro Morgannwg University Health Board	Appendix F	Section		Scenario analyses for LCIG page – 56 This comparison is not like for like. Patient group receiving DS and LCIG are at different stages of PD and overarching numbers receiving LCIG are the ones refused or can't have DBS and possibly with mild to moderate cognitive impairment too as a result of PD	Thank you for your comment. For comments on the appropriateness of the decision problems addressed in the review questions on treatment for advanced Parkinson's disease, please see **theme 3**.
Abertawe Bro Morgannwg University Health Board	Appendix F	section	DBS IPG life span; Figure 11 & 12	Need to take consideration that life span analysis after DBS is for a very selective group of patients who have good prognosis otherwise they won't be otherwise selected for DBS.	Thank you for your comment. These analyses relate to the lifespan of the device, not the patient.
Abertawe Bro Morgannwg University	Appendix F	section	Table 35 & 36	This Is again based on Patients being compared in BMT / DBS/ LCIG are in clinical practice in similar stages of disease state. In day to day clinical practice any patient having LCIG are in more advanced stage of PD than DBS / BT. £/QUALY will proportionately go up as the disease progresses as	Thank you for your comment. For comments on the effectiveness and cost effectiveness of LCIG, please see **theme 1**.

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Health Board			in terms of Time to death and £/ QUALY	increased death rate due to underlying Neurodegenerative pathology itself will be QUALY limiting.	This comment may be read to imply that health gains experienced by people in the advanced stages of a disease such as Parkinson's should be valued more highly than those achieved in people with less advanced disease (or other conditions). If so, this position is not supported by NICE's Social Value Judgements and research on society's preferences for the distribution of healthcare resources.
Abertawe Bro Morgannwg University Health Board	Appendix F	section	Table 37	Other medications? How calculated Care of treatment? How calculated LCIG will be used in one select group of patiens who had DBS turned down with marked fluctuating PD and dose failures.	Thank you for your comment. Full details of cost calculations are provided in sections F3.1.11-F3.1.13. For comments on the effectiveness and cost effectiveness of LCIG, please see **theme 1**.
Abertawe Bro Morgannwg University Health Board	Appendix F	section	29 Para 2 Apomorphine	This model of Apomorphine initiation and use is not used in clinical practice. Patients initiating Apomorphine doesn't need hospital stay or admission. We in ABMUHB have got enough evidence (Unpublished) on it. Even in selected group it can be initiated at home	Thank you for your comment. The GDG agreed that this comment reflects common practice in many areas, and revised its base-case to assume that only 20% of people starting apomorphine would be admitted to hospital. This had a negligible impact on model results (ICERs for DBS -v- BMT and LCIG -v- BMT rose by less than 0.5%).
Abertawe Bro Morgannwg University Health Board	Appendix F	Section	F.2.1.2 Multiple comparison CUA's	LCIG in clinical practice is used after CSAI and SC and only if later two fails to control symptoms, so direct comparison in routine clinical practice is not practicable.	Thank you for your comment. For comments on the appropriateness of the decision problems addressed in the review questions on treatment for advanced Parkinson's disease, please see **theme 3**.

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Abertawe Bro Morgannwg University Health Board	Appendix F	section	F.2.1.4 DBS vs BMT CUA's	Most patients in routine clinical practice in UK have DBS after BMT fails or not able to control symptoms. DBS cost should also include cost of battery replacement and patient travel to tertiary centers (often >1 hr journey time) being reimbursed by referring Trust or Health Board (Wales). Table 14 Most patients undergoing DBS won't continue with CSAI	Thank you for your comment. For comments on the appropriateness of the decision problems addressed in the review questions on treatment for advanced Parkinson's disease, please see **theme 3**. Most analyses of DBS (including the original one developed for this guideline) account for the costs of battery replacement. We are not aware of any analyses including reimbursed travel costs. NICE guidelines apply to the English NHS and do not take account of any variations in practice in Wales or elsewhere.
Abertawe Bro Morgannwg University Health Board	Appendix F	section	LCIG, 30 paragraph three	In my clinical practice and using LCIG for last 11 years in clinical practice, patient need 48 hr admission Pre PEJ and have a NJ tube inserted radiologically. They stay 48 hr after PEJ insertion and all further adjustment of LCIG in done at home by specialist nurse employed by Pharmaceuticals	Thank you for your comment. The assumptions in the model amount to 2 days' additional inpatient treatment to the resource use proposed in this comment. This was based on GDG advice regarding average consumption in the NHS. The assumption has a trivial impact on cost–utility results: even if no additional inpatient days are accounted for, the ICER for LCIG -v- BMT drops less than 1.5% – from £411,697 to £405,823.
Abertawe Bro Morgannwg University Health Board	Appendix F	Section	Page 14 para 4	In clinical practice decisions to explore Both LCIG, DBS are very much related to Patient's cognition, age, dependency, and of course co morbidities.	Thank you for your comment. For comments on the appropriateness of the decision problems addressed in the review questions on treatment for advanced Parkinson's disease, please see **theme 3**.

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Abertawe Bro Morgannwg University Health Board	Appendix F	section	Table 21	Doesn't take into consideration of Patient travels and reimbursement to their travel cost to tertiary centres by Health Boards in Wales and possibly in England.	Thank you for your comment. We are not aware of any analyses including reimbursed travel costs. NICE guidelines apply to the English NHS and do not take account of any variations in practice in Wales or elsewhere.
Abertawe Bro Morgannwg University Health Board	Appendix F	section	Table 27	Not clear why Local Authority Residential costs are so much higher than Private Nursing costs.	Thank you for your comment. This is an empirical finding in the standard source for unit costs in this area (the PSSRU's Unit Costs of Health and Social Care). Exploration of the PSSRU's findings is beyond the scope of this guideline. Were the local authority to purchase beds from the private sector at standard rates, this would make a negligible difference to the results of the economic model.
Abertawe Bro Morgannwg University Health Board	Appendix F	section	Table 30 LCIG	Naso testing phase Hospital stay 2 days (not 3) PEG / PEJ tube placement & Duodopa initiation Hospital stay 3 days not 7 PEG / PEJ removal due to withdrawal Out patient not admitted into hospital	Thank you for your comment. In this table, 'days' relates to the assumed duration of quality of life impact, not to any resource use parameters such as hospital admissions.
Acadia Pharmaceuticals Inc	Full Appendix D Appendix G	101 169 31	2427	Two randomized controlled trials comparing quetiapine to placebo that reported no statistically significant treatment effect for quetiapine (Rabey 2007 and Ondo 2005) have been excluded from the network meta-analysis. Rabey 2007 was excluded from the systematic literature review (SLR) supporting the draft guideline update due to the narrow population definition used in the SLR; therefore, it was not considered for network meta-analysis.	Thank you for your comment. Rabey 2007 only reported disaggregated results for BPRS total, which was not originally an outcome measure used in the analysis. However, we have now undertaken an analysis on this outcome and therefore this study has now been added to the list of included studies.

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				The randomised controlled trial (RCT) reported in this publication also included patients with dementia who were treated with cholinesterase inhibitors and was excluded from the SLR for that reason. However, results were reported separately for non-demented patients, none of whom received cholinesterase inhibitors; these results were not extracted and did not appear to be considered by the guideline committee. An additional study, Ondo 2005, was excluded from the Brief Psychiatric Rating Scale Hallucination Item (BPRS-H) network meta-analysis and the pooled hallucination scale network meta-analysis because it did not report numerical estimates for a non-significant change in the BPRS-H item. Both Rabey 2007 and Ondo 2005 were included in the European Federation of the Neurological Societies Guidelines (EFNS) (Ferreira 2013) and were identified as the highest quality quetiapine studies available. The exclusion of Rabey 2007 and Ondo 2005 from the BPRS hallucination network and the pooled scale hallucination network biases these analyses in favour of quetiapine, which should be acknowledged in the guideline update.	With regards to Ondo 2005 - unfortunately, without any numerical estimates provided by the study, no meta-analyses could be performed, and the study was therefore excluded from the network meta-analysis. However, the presence of this study was noted by the GDG and considered as a limitation in the evidence base. Following further discussions, the recommendations have been amended to a stronger "offer" level recommendation for clozapine (recognising the stronger evidence behind this choice), within its licensed indication of standard treatment having failed. Quetiapine has been kept at the weaker "consider" level to make clear the weaker evidence base for this option.
Acadia Pharmaceuticals Inc	Full Appendix E	102 150	2480-2488	The conclusion that quetiapine has a high probability of being the optimal treatment for hallucinations is sensitive to the inclusion of Fernandez 2009 in the supporting network meta-analyses. However, this study had several limitations and should have been excluded from network meta-analysis. (1) Fernandez 2009 is the only randomised controlled trial (RCT) of quetiapine that found a statistically significant treatment effect, and only for two of the three secondary endpoints. The study authors characterized the study as not suited for indirect comparison.	Thank you for your comment. The GDG discussed the notable shortcomings of the Fernandez study, and whilst they did not agree it was appropriate to exclude it from the analysis, they did agree its presence lowered the overall quality of the evidence for quetiapine. After further discussion, a number of changes have been made to this section: 1) We have now undertaken an analysis on the total BPRS score and this has been included amongst the

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				(2) The study was designed as a pilot clinical/polysomnography study, only powered to detect REM sleep differences. (3) The sample size was small, with only 16 patients across two study arms. Such a small sample size increases the likelihood that statistically significant findings are due to chance rather than to a true treatment effect and limits the generalizability of the findings. (4) Overall attrition rate was very high (50%) in the quetiapine arm, leading to attrition bias in the study findings. The published findings reflect observed outcomes for only four quetiapine-treated patients who completed the study; outcomes for the remaining four patients who were randomized to quetiapine but dropped out of the study were imputed from baseline characteristics using a linear model. Given the limitations associated with the Fernandez 2009 study for the purposes of evaluating the treatment effect of quetiapine, it is appropriate to consider a network meta-analysis without the Fernandez study. We replicated the results reported for the pooled hallucination scale network meta-analysis and then reran the analysis, excluding the Fernandez 2009 study from the network. The probability that quetiapine is the optimal treatment drops from 95% to 65%, resulting in an equivocal conclusion about quetiapine. In presenting the network meta-analyses regarding optimal treatment for hallucinations in the guideline update, the limitations of the Fernandez 2009 study and the sensitivity of the network meta-analysis findings to its inclusion or exclusion should be described fully.	evidence. 2) The recommendations have been amended to a stronger "offer" level recommendation for clozapine (recognising the stronger evidence behind this choice), within its licensed indication of standard treatment having failed. Quetiapine has been kept at the weaker "consider" level to make clear the weaker evidence base for this option.
Acadia Pharmaceuticals Inc	Full	102	2480-2488	Conclusions based on network meta-analyses are sensitive to the specific endpoints used and studies included in the networks. The most common clinical efficacy endpoint across randomised controlled trials (RCTs) of treatments for hallucinations and delusions in Parkinson's disease patients,	Thank you for your comment. We have now undertaken an analysis on the total BPRS score and this has been included amongst the evidence.

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				the total Brief Psychiatric Rating Scale (BPRS) score, was not considered in the draft guideline update. An evidence network for this endpoint includes a larger number of studies and allows for comparison of both clozapine and quetiapine in a single network. The BPRS scale includes items that capture a range of psychiatric symptoms, beyond the psychotic symptoms that may emerge in Parkinson's disease patients. Although not explicitly discussed in the draft guideline update, a network meta-analysis of total BPRS score may have not been considered due to the narrow focus of the SLR on psychosis-related endpoints. We conducted a network meta-analysis using the total BPRS score as the efficacy endpoint and included three quetiapine RCTs (Fernandez 2009, Rabey 2007, and Shotbolt 2009), two olanzapine RCTs (reported in Breier 2002), one clozapine RCT (Friedman 1999), and one head-to-head RCT of quetiapine and clozapine (Morgante 2004) in the network. The analysis shows clear superiority of clozapine and ranks quetiapine as equivalent to placebo. We recommend that the guideline committee conduct a similar analysis and report the results because the current body of RCT-based evidence does not suggest that clozapine and quetiapine are equally efficacious.	The recommendations have been amended to a stronger "offer" level recommendation for clozapine (recognising the stronger evidence behind this choice), within its licensed indication of standard treatment having failed. Quetiapine has been kept at the weaker "consider" level to make clear the weaker evidence base for this option.
Association for Palliative Medicine of Great Britain and Ireland	Full		5471	The term *advance directives* is obsolete since the introduction of the Mental Capacity Act 2005. A better way to phrase this sentence would be "The aim of this review question was to determine the needs of people with Parkinson's disease for advance care planning and palliative care plans throughout the course of their disease"	Thank you for your comment. The suggested change has been made to the text.

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Association for Palliative Medicine of Great Britain and Ireland	Full		5501	Can you double check if the study referred to does use the term *advance directive* as it is obsolete, as mentioned above	Thank you for your comment - the term advance directive has now been removed from the guideline as it was not used in the study.
Association for Palliative Medicine of Great Britain and Ireland	Full		5513	The term used should be *advance* care planning, not advanced	Thank you for your comment - this has now been changed accordingly.
Association for Palliative Medicine of Great Britain and Ireland	Full		5545	There is no such thing as an *advanced care directive* – do you mean *advance care planning*? The terms used need to be consistent with those used in the Mental Capacity Act 2005	Thank you for your comment. The suggested change has been made to the text.
Association for Palliative Medicine of Great Britain and Ireland	Full		5552	The term is *advance care planning*, not advanced care planning	Thank you - this has now been changed accordingly.
Association for Palliative Medicine of Great Britain and Ireland	Full		5558	It should say *advance* care documents, not advanced care documents	Thank you - this has now been changed accordingly.
Association for Palliative Medicine of	Full		5645	Terminology should stay consistent - both *terminal care* and *end of life care* are used. Would suggest not using the phrase terminal care and just using the phrase end of life care	Thank you - this has now been changed accordingly.

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Great Britain and Ireland					
Association for Palliative Medicine of Great Britain and Ireland	Full		5656	It should say *Advance* Decisions to Refuse Treatment (ADRT) not Advanced	Thank you - this has now been changed accordingly.
Association for Palliative Medicine of Great Britain and Ireland	Full & short	General	General	The APM welcomes this draft guideline, especially the recognition that people with Parkinson's disease should have palliative care discussed with them and that some of these patients may, at some point, benefit from onward referral to specialist palliative care services.	Thank you for your comment
Association for Palliative Medicine of Great Britain and Ireland	Full & short	General	General	Throughout both documents the correct terminology regarding advance care planning, as per the Mental Capacity Act 2005, has not been used. This guideline should be using best current terminology. I have outlined below all the examples I have spotted where this has not been done correctly.	Thank you for your comment. We have now changed this accordingly in line with your specific comments.
Association for Palliative Medicine of Great Britain and Ireland	Short	19	18	Should say *Advance* Decisions to refuse Treatment not Advanced	Thank you for your comment. This has now been changed accordingly.
Association of British Neurologists	Full	106	2539	It is indicated in the guideline that dopaminergic therapy must not be reduced without expert advice, when the patients has hallucinations or delusions. While it is entirely reasonable to seek expert advice in this situation, such advice is not necessarily available at all times quickly enough to address acute and urgent situations. Summarising the expert approach to this in the guidelines would be more useful, namely reduction in dopaminergic therapy	Thank you for your comment. The GDG felt it appropriate to clarify that people should seek advice from specialist care before modifying dopaminergic therapy, because of the known harms that can result if this is done incorrectly. However, they did acknowledge that such advice may not always be available in a timely fashion, and therefore if

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				(in particular drug classes other than L-dopa) but avoiding total cessation of treatment because of the risk of neuroleptic malignant syndrome.	advice has been sought and is not available, a clinician may still feel it appropriate to modify therapy in urgent cases. The guideline does also contain a specific recommendation about modifying dopaminergic therapy, so the GDG did not feel this represented a gap in the guidance provided.
Association of British Neurologists	Full	118	2753	"The evidence showed a clinical harm of glycopyrrolate from side effects, as omdocated by discontinuation of medication" Presumably this should be 'indicated'. It may be more useful to use the main primary name for this drug per BNF, namely Glycopyrronium bromide. It is not made clear which formulation is proposed for this use. The evidence leading to this recommendation, being derived across other disease areas, is, as the GDG states, difficult to apply to Parkinson's because of the cognitive issues. There appears to be no clinical evidence, and not any theoretical basis, why this antimuscarinic/anticholinergic drug is a better choice than any other from the same class. It is stated that "the GDG noted that their experience of these drugs [anticholinergics] is that they do cause serious side effects and may not be well tolerated." In the absence of trial evidence, and any reported comparative experience by the GDG with Glycopyrronium bromide in Parkinson's, versus other agents of this class, it would be better to avoid recommending this drug specifically.	Thank you for your comment. You are correct that should have been indicated, and this has been corrected. The name has also been changed to glycopyrronium bromide as per your suggestion. Whilst it is true that the evidence for this question was derived from a broader patient population, the evidence base does include trials in people with idiopathic Parkinson's disease, and there is a trial of glycopyrrolate in this group. The GDG did agree that glycopyrrolate was likely to cause fewer cognitive side-effects than other, centrally acting, anticholinergics, and therefore it was appropriate that this drug be considered above other anticholinergic options. The trials in the evidence base were all of oral glycopyrrolate, but the GDG felt it appropriate not to be too specific on this point as they were aware of other alternatives that may be more commonly used in certain

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					local areas (e.g. spray) and did not want to preclude the use of these alternatives.
Association of British Neurologists	Full	14	93	It should be clear how the recommendations should be interpreted. We use similar forms of words (for example, 'Do not offer...') when we are confident that an intervention will not be of benefit for most patients. The wording used again tends to imply a degree of recognition that while an intervention will not be of benefit to most patients, there may of course be residual patients who do stand to make substantial benefits. It should be made more abundantly clear when this might be the case including how such circumstances should be addressed through NHS commissioning pathways. The reality is that NICE guidelines which state "do not offer treatment X" will be used literally (or in isolation of the finer point) by many groups and organisations to remove that treatment option from all patients. However, the guidelines are clear that the statement is made for most patients, therefore in a minority group, or subset of patients, the guidelines are acknowledging that the treatment could be beneficial. At each point where a treatment could offer benefit to *some* patients, it is suggested that the statement "do not offer treatment X" should be qualified to make sure that this point is understood. There are circumstances where a treatment is *never* recommended for example Stalevo as the first line of treatment, but there are many circumstances where assessing the individual makes a treatment which would not be appropriate for most patients, appropriate and beneficial for that individual.	Thank you for your comment. NICE follows a standard method when it comes to developing recommendations and the type of wordings used in the Parkinson's guideline is the same wording used in all NICE clinical guidelines and can therefore not be changed. In the full guideline, section 1.3, we do provide guidance on how to interpret our recommendations.

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Association of British Neurologists	Full	173	4136	The recommendation for protein redistribution as described is not evidence based. The downgrading to 'discuss' does not reflect the GDG detailed deliberations of the pros and cons. The evidence summarised was very low quality, except one study that was low quality, and it does not appear that any of those studies were the same approach as the guideline recommends. It is important that the guideline makes evidence based recommendations, rather than simply summarising one possible approach as the best method. This is particularly so given the very limited evidence on improving Parkinson's symptoms. Some of the discussion of the GDG on the topic of diet is entirely hypothetical. "This could help a patient to remain independent for as long as possible and avoid other complications, such as falls, that could result in lengthy inpatient stays and an increased rate of hospital admissions with greater resource use/cost." In the absence of evidence lending support to these idealised aims, it is misleading.	Thank you for your comment. The GDG agrees that there is limited evidence available on the benefits of protein redistribution. Nevertheless, the GDG agreed that, based on their clinical experience, a protein redistribution diet is often helpful to patients, and a discussion should therefore be promoted with patients.
Association of British Neurologists	Full	173	4143	The recommendation to use Vitamin D has insufficient evidence, being based on 1 single 1-year duration study and with changes below minimal clinically important differences. The editorial commentary with this paper reflects a more measured view of whether this treatment should be made available routinely: "If the findings of Suzuki et al are replicated, and if future studies confirm that the treatment of vitamin D deficiency is not associated with unintended adverse outcomes, then there is a case to translate this treatment promptly." In the absence of	Thank you for your comment. The GDG agreed it was unclear whether there were specific extra benefits of vitamin D supplementation in people with PD compared to the general population, but noted that because people with Parkinson's disease are at an increased risk of falls, advising them to take vitamin D supplements is more beneficial than not recommending. The GDG agreed that there may well be individuals who will gain a greater or lesser benefit with supplementation (as indeed there are with most treatments), but there are

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				such information, on both counts, it appears premature to recommend this as a standard treatment for Parkinson's disease. The recommendation appears to omit the possibility of greater or lesser benefit according to the patient's genetic profile (which is a key message in the single study). It would appear that we know too little to make such a treatment recommendation, as some patients may only exhibit adverse effects of such treatment and have no observable benefit.	not currently practical ways to identify these people ahead of recommending treatment.
Association of British Neurologists	Full	173	4150	Research Recommendation 8- How effective is long term creatine supplementation on clinical outcomes in Parkinson's Disease? This recommendation appears to have been made before the publication of the largest interventional trial ever undertaken in PD; the LS1 trial of creatine supplementation which demonstrated no change in BMI using creatine supplementation at a dose of 10g/day. This is so conspicuous that it really ought to be updated.	Thank you for your comment. This study has now been included into the guideline, a negative recommendation made around creatine supplementation, and the corresponding research recommendation removed.
Association of British Neurologists	Full	20	285	It is correctly stated that we need "to be more aware that each patient is an individual." This should be taken account of better throughout the recommendations. We know that people with Parkinson's are a heterogeneous group, in terms of age, rate of progression, range of symptoms and most relevantly response to treatments. Mean effect sizes in randomised trials provide little insight into the range of responses to a specific intervention. While mean effect size is of unarguable importance, there has to be detailed account taken of the range of responses seen in response to an intervention to inform the recommendations, especially when there is a risk that considering group or	Thank you for your comment. It is important to note that NICE clinical guidelines are guidance for providers on the general population with a specific condition. A 'do not offer' recommendation does not mean that the treatment is ineffective for everyone but for most. In section 1.3 of the guideline, guidance on how to interpret NICE's recommendations is provided. NICE's recommendations should be taken into consideration together with the clinician's own personal experience and knowledge in the field as well as the individual patient's health and care needs.

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				'average' responses will lead to recommendation for removal of an already available therapeutic option. In other words, we aspire to be part of an evolving era of personalised/ precision medicine, thus the recommendations should recognise this, and allow treatments that reflect the awareness "that each patient is an individual".	It should be noted, however, that we do not agree that simply because the responses to a treatment may be heterogeneous, that this means that randomised trials do not provide valuable information. If there are identifiable subgroups of people where treatment response would be higher, then it should be possible to conduct trials specifically in these subgroups, and such trials would have been included within the scope of this guideline.
Association of British Neurologists	Full	204	4949	Recommendation 79- Do not offer levodopa–carbidopa intestinal gel…. This recommendation appears to have been based entirely on the modelled cost utility analysis. The GDG earlier commented on page 203, that in advanced PD, it may be more difficult to achieve improvement across the 3 levels of the 5 EQ-5D domains. Nevertheless this metric appears to be the only one determining the subsequent recommendations. The lack of sensitivity of the EQ5D to capture change in QoL in PD is clearly appreciated by the GDG and the authors of the guidance. On page 207, the improvements in QoL with early DBS measured by the PDQ39 are not accompanied by any change in EQ5D. Prior to making a recommendation on the use of LCIG greater consideration should be more evenly distributed to the other metrics eg PDQ39 SI shows a clear advantage of 7 points in favour of LCIG. It is unarguable that the very high cost of LCIG must be a major issue in the recommendations provided. It is not under debate whether this intervention would be of benefit for most patients- clearly not. It is however necessary to	Thank you for your comment. For comments on the ability of EQ-5D to capture HRQoL in advanced Parkinson's disease, please see **theme 8**. For comments on the effectiveness and cost effectiveness of LCIG in subgroups of people with advanced Parkinson's disease, please see **theme 1b**. For comments on self-limiting resource use with LCIG, please see **theme 1c**.

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				have this as an option for carefully selected individuals and the document might be better if rephrased to address this. It should be of some reassurance that after lengthy previous consultations, and the eventual specialist commissioning decision taken to support the use of LCIG, that the number of prescriptions of LCIG has remained low i.e. clinicians are using this expensive therapy in only a small number of individuals in whom BMT and DBS have failed or are otherwise inappropriate. It is also to some extent self-policing, that patients who can achieve adequate symptom control without LCIG prefer not to have PEG-J tubes in place. Those that have PEG-J tubes have frequent problems with the tubes, and those that are not receiving major beneficial effects from the therapy tend to abandon it. This is to some extent reflected by the GDG who noted "the high ongoing cost and impact of LCIG and queried whether treatment and evidence would be better considered on a 'responder' basis". This suggestion does not appear to have been incorporated into the recommendation.	
Association of British Neurologists	Full	222	5450	It is suggested in the guideline that advice should be sought from an expert before modifying dopaminergic therapy, in the context of impulse control disorders. This raises questions about the proposed readership of the guidelines, which are extensive and detailed in many other areas and entirely within the scope of the expert clinician. It would be more useful to summarise the approach to the management of impulse control disorders, so that experts can utilise the guidelines to assist them with these treatment approaches, and those less expert can understand the issues (and take first steps, when circumstances are appropriate). For example, in a patient who suddenly admits a significant gambling addiction (or other significant ICD) and is on a high dose of a dopamine agonist, it is appropriate as an immediate measure to begin lowering the dose. That does not need to wait for expert advice.	Thank you for your comment. The GDG felt it appropriate to clarify that people should seek advice from specialist care before modifying dopaminergic therapy, because of the known harms that can result if this is done incorrectly. However, they GDG did acknowledge that such advice may not always be available in a timely fashion, and therefore if advice has been sought and is not available, a clinician may still feel it appropriate to modify therapy in urgent cases. The guideline does also contain a specific recommendation about modifying dopaminergic therapy,

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					so the GDG did not feel this represented a gap in the guidance provided.
Association of British Neurologists	Full	223	5464	It is suggested that the cognitive behavioural therapy should be used for patients with impulse control disorders. This is not widely available, and has a major resource implications.	Thank you for your comment. The GDG agreed that there are difficulties accessing this service in many areas, but noted that it was shown to be effective where available and hope that the recommendations will lead to the service becoming more available.
Association of British Neurologists	Full	25	415	The priorities of patients based on a Parkinson's UK survey, are also listed in the document. These include; "New treatments that may be available in the future - 90% of patients" "What drugs are available and/or their side effects- 84% of patients" This clearly demonstrates that the majority of patients feel that PD in general, remains suboptimally treated. Any restriction of the existing range of therapies a clinician may offer, even if their effectiveness has thus far been shown to be low for the majority of individuals, runs completely contrary to the message being sent by patients.	Thank you for your comments. The GDG acknowledge that all people would want to have access to all possible treatment options, but there is a responsibility on NICE and the NHS to only recommend effective and cost-effective treatments.
Association of British Neurologists	Full	40	835	The application of diagnostic criteria refers only to the UK criteria, mention of the recent movement disorder society criteria would be appropriate.	Thank you for your comment. Unfortunately, this chapter has not been included as part of the scope for this guideline update, hence it has not been updated and no changes can be made.
Association of British Neurologists	Full	42	922	The suggested time limits for patients to be seen in the specialist clinic is presented only as a footnote here, but in the short version of the guidelines receives a far greater prominence. This recommendation has major resource implications, which do not appear to have been considered.	Thank you for your comment. Unfortunately, this chapter has not been included as part of the scope for this guideline update, hence it has not been updated and no changes can be made.

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Association of British Neurologists	Full	46	1015	The clinical application of FP-CIT SPECT for differentiation of essential tremor from Parkinson's disease represents only one aspect of its usage. There needs to be recognition of the evolution in understanding of essential tremor versus dystonic tremor, as well as inclusion of other situations where clinical differentiation of dopamine deficiency disorders versus normal dopamine levels is usefully addressed by such imaging. Examples include drug induced parkinsonism and vascular parkinsonism.	Thank you for your comment. Unfortunately, this chapter has not been included as part of the scope for this guideline update, hence it has not been updated and no changes can be made.
Association of British Neurologists	Full	55	1258	"Anticholinergics are most commonly used in the earlier stages" This is a potentially misleading statement. It could be misinterpreted to mean that it is a common treatment choice in earlier stages of Parkinson's which it is not. It is noted that Benzhexol is used as the primary name. This is outdated and should be reversed.	Thank you for your comment. This section has now been clarified to make it clear that this only refers to those cases where anti-cholinergics are used, and not that the use of them is common. The wording has now been changed to use trihexyphenidyl as the primary name.
Association of British Neurologists	Full	67	1648	On Dopamine agonists. "It was noted that both are valid treatment options, and clinicians will often try an ergot agonist if a non-ergot one has not proven effective." This is severely outdated. Most Parkinson's experts would no longer consider an ergot agonist as a valid treatment option.	Thank you for your comment. After further discussion, the GDG agreed that this statement was too strongly written and it is appropriate to prefer a non-ergot agonist. Two new recommendations have therefore been added to clarify this point; one that ergot agonists should not be used first-line, and the second that they should only be considered if there has been an inadequate response to a non-ergot agonist.
Association of British Neurologists	Full	67	1650-1655	The recommendation for initial treatment choice of L-dopa versus other drug classes does not appear to reflect either the medical literature, or clinical practice/experience. The primary differentiation of the treatment choice based on motor symptoms that affect, or do not affect quality-of-life, does not appear to ne an evidence-based guideline. The complexity of this decision making process should be recognised, considering quality-of-life, comorbidities	Thank you for your comment. The GDG acknowledges that due to the complex nature of decision making, a discussion should take place between the clinician and patient to discuss the patient's clinical and lifestyle circumstances, goals and preferences before making a decision about the most appropriate treatment.

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				particularly cerebrovascular disease and mental health problems, including cognitive state.	Thank you for your comment. We did identify evidence for levodopa being, on average, the best treatment for motor symptoms, whilst the same pattern was not consistently found for non-motor symptoms, and it was these findings that led the GDG to make the distinction between those two groups of individuals. The GDG has therefore made a recommendation to offer levodopa to people in the early stages of PD whose motor symptoms impact on their quality of life. However, this recommendation does mean in an individual case a person and their clinician might not decide that an alternative treatment is more appropriate, given particular individual characteristics.
Association of British Neurologists	Full	80	2019	Recommendation 30 – Do not offer anticholinergics…. There is no doubt that anticholinergic prescription can lead to intolerable side effects in many people. This however overlooks the fact that many people particularly with young onset PD use trihexyphenidyl for painful off-period dystonia with good effect, with good tolerability over long terms periods. This should be added to the guidelines. Off Period dystonia can be very disabling and falls under the umbrella of "motor fluctuations". A few people also gain benefit for tremor.	Thank you for your comment. The GDG acknowledged that there may be specific circumstances where anticholinergics are a useful option, but this does not apply to the average person with PD. In addition, because no evidence was identified for anticholinergics, together with the known adverse effects, the GDG agreed that a "do not" recommendation was justified. The GDG also noted that the particular cases identified where anticholinergics may be useful (e.g. very young people with dystonia) were highly likely to be already under the care of experienced clinicians, who would be aware of this as a treatment option.
Association of British Neurologists	Full	80	2021	Recommendation 31- Do not offer Amantadine…..	Thank you for your comments. After discussion of the consultation responses the GDG agreed that, whilst there was no evidence for the routine use of amantadine as an

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				Amantadine has great benefits in well selected individuals and with appropriate supervision can be used safely. It is not expensive. The paucity of evidence supporting its use should therefore mean that the anecdotal observations of the GDG should be used to make a recommendation. The GDG felt that in the absence of any evidence of benefits, it was appropriate to recommend that amantadine not be routinely used as an adjunctive therapy, when options with clear evidence of benefit exist. However, because of the specific uses amantadine may have in certain people (e.g. to treat dyskinesia), they did not feel it appropriate to make a stronger "do not use" recommendation. On this occasion the advice of the GDG appears to not be adequately represented in the recommendation.	adjuvant treatment, it did have a role as a specific option for the treatment of dyskinesia. Therefore, a new recommendation has been added to this section to support the use of amantadine in this context.
Association of British Neurologists	Full	83	2106	It is stated that the Epworth sleep scale is used routinely in clinical practice. This is incorrect. It may well be used in a few specialised centres, but it is not a routine component of clinical practice in the majority of clinics. The management of daytime sleepiness by adjusting baseline therapy appears rather as an afterthought, thereby giving undue prominence to modafinil.	Thank you for your comment. The GDG has agreed to change it to "the Epworth sleep scale is commonly understood in clinical practice". The GDG agreed it was sensible to reorder these recommendations so the modification of medicines came before the recommendation for modafinil.
Association of British Neurologists	Full	91	2215-2226	The recommendations for the management of nocturnal akinesia are over stated, in the absence of sufficient evidence. The paper quoted regarding a modified release dopamine agonist is compared to placebo, so there is no evidence comparing this modified release dopamine agonist to other treatment modalities. There does not appear to be evidence on timing of the intake of modified release dopamine agonists, despite the recommendation that such treatment may be taken at night. In the absence of trial evidence, the pharmacokinetic characteristics of standard release and modified release	Thank you for your comment. After further discussion, the GDG agreed that these recommendations had been too strongly worded based on the underlying evidence. Accordingly, the words modified release have been removed from the recommendations, and the final recommendation about when dopamine agonists should be taken has been entirely removed. This leads to a simpler set of recommendations which the GDG believes

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				dopamine agonists might be considered, and these would not lend support to these recommendations about timing or choice of medication. The evidence summarised for controlled-release L-dopa appears to show no difference (from standard release), but the guideline recommends it as a treatment option.	are supported both by the evidence and clinical judgement.
Association of British Neurologists	Full	97	2354	The text states that "The GDG were not confident that it [midodrine] clearly represents the optimal choice for people with OH and Parkinson's disease." Accordingly, the conclusion that midodrine is the first line choice in the recommendation is not justified. The label status appears to be used in one way here (to support on-label midodrine use), but in the opposite way for quetiapine versus clozapine (to support off-label quetiapine use). It is fully recognised that these issues are difficult to balance, but the question is whether the guidelines are useful when they make one decision or another (and why they make this balanced decision in a particular direction). On a different day, or with a different group of experts, it could equally be decided that, on balance, a different course of action may be best. It is suggested that the balancing evidence and facts are provided, and where there is no definitely better course of action, the option to use one treatment or another should be left open.	Thank you for your comments. According to the NICE guidelines manual, off-label use may only be recommended if the clinical need cannot be met by a licensed product and there is sufficient evidence and/or experience of using the medicine to demonstrate its safety and efficacy to support this. In the absence of good evidence, the GDG therefore decided to recommend the licensed drug (midodrine) ahead of an unlicensed one (fludrocortisone), but felt it important that a caveat be added that in people in whom midodrine is contraindicated, fludrocortisone is an appropriate first-line treatment. The noted contradiction between this recommendation and those for treatment of psychosis has hopefully been addressed by changes to the psychosis recommendations to ensure that the recommendation for clozapine (within its licensed indication of having failed standard treatment) is stronger than that for quetiapine (they are now an "offer" and "consider" recommendation respectively.

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Barts Health NHS Trust	long	80		Anticholinergics are mentioned only in relation to avoiding them in people with dyskinesia and/or motor fluctuation (pg 80). Would it not be appropriate to also avoid them in elderly or with cognitive impairment? There has been a lot in the pharmaceutical press recently about the adverse effects of anticholinergics in the elderly.	Thank you for your comment. The GDG agreed in general that it would be appropriate to avoid the use of anticholinergic medicines wherever possible. However, there are certain circumstances (e.g. topical atropine drops for sialorrhoea) where clinicians may believe the risk of harm to be low, or other problems requiring treatment where all the available options have anticholinergic properties. The specific recommendation made here came from the fact that an evidence search was conducted looking for a benefit from anticholinergic treatment, and none could be found. Therefore, in the absence of any benefit, a specific recommendation was made that they should be avoided in this area.
Barts Health NHS Trust	short	10	17	Change to include examples of dopaminergic therapies (including COMT and MAO-B inhibitors)	Thank you for your comment. The GDG agreed that the term "dopaminergic therapies" is well understood by clinicians (the primary target for this recommendation) and hence did not feel examples needed to be provided.
Barts Health NHS Trust	short	11	15	We think Patients starting modafinil should initially be reviewed after 3 months and 6 months and then at least every 12 months. [note modafinil can exacerbate dyskinesias and other movement discorders).	Thank you for your comment. However, as we did not identify any evidence to support when and how frequent patients should be reviewed when receiving modafinil, the GDG feel that recommending "at least every 12 months" is sufficient, with this not of cause precluding more frequent monitoring if this was felt appropriate for an individual.
Barts Health NHS Trust	short	19	5	Please give advice on what should happen to patients stable on duodopa (we have two patients who have been on duodopa for at least 5 years each)	Thank you for your comment. Our revised recommendation emphasises that NHS England's specialised commissioning policy remains in place. It will

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					be for NHS England to consider transition arrangements in the event of any future revision to that policy.
Barts Health NHS Trust	short	92 and 114		Autonomic dysfunction. includes only management of orthostatic hypotension (pg 92), thermoregulatory dysfunction and sialorrhoea (pg 114). Is there no evidence available for the management of urinary dysfunction, erectile dysfunction or constipation, or do they expect us to follow existing local guidelines?	Thank you for your comment. Unfortunately these issues were not included within the scope of this guideline update, and therefore no specific recommendations could be made.
Barts Health NHS Trust	short	Whole document	Whole document	Considering that drug therapy is the mainstay of treatment for patients with Parkinson's Disease, it is astonishing that no reference is made to the qualified healthcare professional who is an expert on drugs and their use. There should be a statement that patients should have access to a Clinical Pharmacist with experience in neurological conditions. Also, patients seeking information and advice about their drug therapy should be encouraged to discuss this with their pharmacist working in primary care (eg pharmacist working in GP surgery or their community pharmacist). We note that reference is made to: Physiotherapy Speech and language therapy Occupational therapy Nurses Dieticians The only mention of pharmacists is in the "Non-Pharmacological " section !!!! This is regarding seeking advice on over-the-counter dietary supplements (not even other medications!).	Thank you for your comment. The GDG agreed that the role of clinical pharmacists was a key one in the management of Parkinson's disease. However, the scope of the guideline did not include any questions about the role of the clinical pharmacist, and therefore it was not possible to make specific recommendations around this area. The GDG stressed that this should not be taken as implying they do not form an important part of the pathway.

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Belfast Health & Social Care Trust (BHSCT)			4949	We have experience in managing Young Onset Parkinson's Disease with patients who have age at onset as young as mid 20s, recognising the significant burden of neuropsychiatric comorbidity (such as affective disorders and impulse control disorders [ICDs]) within this cohort such that a significant number of these patients are unsuitable in the longer term for CSAI due to disabling ICDs (exacerbated by dopamine agonists) and also unsuitable for DBS due to significant depression. We have experience of using LCIG in this cohort and whilst the absolute numbers of patients requiring LCIG in these circumstances is expected to be low this very effective therapy provides patients with young onset Parkinson's Disease with real hope of effective long-term therapy. Parkinson's disease is a heterogeneous disorder and we recognise the challenge in developing guidance applicable to all patients but would ask that consideration be given to the small but not insignificant number of patients with young onset or monogenetic disease who may require LCIG given the increased burden of neuropsychiatric comorbidity and very long disease duration which could exceed six decades.	Thank you for your comment. For comments on the effectiveness and cost effectiveness of LCIG in subgroups of people with advanced Parkinson's disease, please see **theme 1b**.
Belfast Health & Social Care Trust (BHSCT)	Full		4943, 4947, 4949	We agree that best medical therapy may include continuous subcutaneous apomorphine infusion (CSAI) and that deep brain stimulation (DBS) should be considered in patients whose symptoms are not controlled on best medical therapy. However, a small proportion of patients who have failed to adequately respond to or tolerate CSAI (or who are not suitable for CSAI) are also deemed not suitable for DBS. We are concerned about the impact recommendation 79 (Do not offer levodopa-carbidopa intestinal gel at any stage of Parkinson's disease) could have on this patient group. These	Thank you for your comments. For comments on the effectiveness and cost effectiveness of LCIG, please see **theme 1**. For comments on the effectiveness and cost effectiveness of LCIG in subgroups of people with advanced Parkinson's disease, please see **theme 1b**.

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				patients are deemed not suitable for DBS for a variety of reasons including age, co-morbidity, surgical risk, speech difficulty/risk of decline following STN DBS, postural instability on the 'On' phase and cognitive deficits or depression identified on neuropsychological evaluation. Such patients are not in the terminal stages of Parkinson's disease and can continue to be functionally independent while in the 'On' phase. However, they are challenging to manage, generally having disabling motor fluctuations despite being on complex drug regimens that expose them to the neuropsychiatric complications of dopaminergic medications. In our experience, Levodopa-carbidopa intestinal gel (LCIG) has been an invaluable treatment option in such patients, providing superior control of motor fluctuations compared to best medical treatment and allowing rationalisation of their medication regimens often to levodopa monotherapy, reducing the risk of neuropsychiatric complications of drug treatment. We feel it would be helpful if there were more specific recommendations regarding what treatment should be offered to patient that do not achieve satisfactory control with/do not tolerate CSAI and who are not suitable for DBS.	For comments on the paucity of therapeutic options for people with advanced Parkinson's disease, please see **theme 1e**.
Belfast Health & Social Care Trust (BHSCT)	Full		General	The movement disorder clinic at the BHSCT is a regional service and receives referrals from throughout Northern Ireland for further management of people with Parkinson's disease experiencing disabling motor fluctuations despite best medical therapy. In addition to caring for persons with sporadic Parkinson's disease the service provides expertise in the diagnosis and on going management of monogenetic forms of Parkinson's disease and young onset Parkinson's disease of all aetiologies (age at onset <45 years).	Thank you for taking the time to comment on this guideline.

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Bial	Full	69	1697	Table 6: Opicapone should be included in the list of available COMT inhibitors	Thank you for your comment. The guideline did not look for evidence on opicapone, as it was not licensed at the time the scoping was undertaken. Whilst we did not specifically look for evidence, the fact that opicapone is classed as a COMT inhibitor means it is covered as part of our recommendations for adjuvant treatment, and could be considered as an option under those class level recommendations (within the licensed indication). The GDG did not feel it was appropriate to make recommendations about which specific choices within those classes should be preferred for adjuvant treatment. In addition, NICE has recently published an evidence summary on opicapone in March 2017, though this will not be formally included as part of the guideline. Table 6 reports only those treatments which were looked for as part of the clinical literature searches, and it is for this reason that opicapone is not on the list.
Bial	Full	70	1705	The systematic search carried out on the 2 February 2016 (Appendix I – page 23 -25) did not include opicapone as a search term. It appears the search did not identify the BIPARK I study published in the Lancet Neurology. If this is the case it could be regarded as a significant omission that impacts upon the integrity of chapter 6.2.2 Ferreira, JJ, Lees, A, Rocha, J-F, Poewe, W, Rascol, O, Soares-da-Silva, P, and for the Bi-Park 1 investigators. Opicapone as an adjunct to levodopa in patients with Parkinson's disease and end-of-dose motor fluctuations: a	Thank you for your comment. The guideline did not look for evidence on opicapone, as it was not licensed at the time the scoping was undertaken. Whilst we did not specifically look for evidence, the fact that opicapone is classed as a COMT inhibitor means it is covered as part of our recommendations for adjuvant treatment, and could be considered as an option under those class level recommendations (within the licensed indication). The GDG did not feel it was appropriate to make

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				randomised, double-blind, placebo-controlled and active-controlled parallel-group trial. Lancet Neurol. 2016; 15: 154-65	recommendations about which specific choices within those classes should be preferred for adjuvant treatment. In addition, NICE has recently published an evidence summary on opicapone in March 2017, though this will not be formally included as part of the guideline.
Bial	Full	71	1764	Omission of BIPARK I?	Thank you for your comment. The guideline did not look for evidence on opicapone, as it was not licensed at the time the scoping was undertaken. Whilst we did not specifically look for evidence, the fact that opicapone is classed as a COMT inhibitor means it is covered as part of our recommendations for adjuvant treatment, and could be considered as an option under those class level recommendations (within the licensed indication). The GDG did not feel it was appropriate to make recommendations about which specific choices within those classes should be preferred for adjuvant treatment. In addition, NICE has recently published an evidence summary on opicapone in March 2017, though this will not be formally included as part of the guideline.
Bial	Full	71	1783	Omission of BIPARK I – Opicapone versus entacapone	Thank you for your comment. The guideline did not look for evidence on opicapone, as it was not licensed at the time the scoping was undertaken. Whilst we did not specifically look for evidence, the fact that opicapone is classed as a COMT inhibitor means it is covered as part of our recommendations for adjuvant treatment, and could be considered as an option under those class level

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					recommendations (within the licensed indication). The GDG did not feel it was appropriate to make recommendations about which specific choices within those classes should be preferred for adjuvant treatment. In addition, NICE has recently published an evidence summary on opicapone in March 2017, though this will not be formally included as part of the guideline.
Bial	Full	74	1875	Opicapone has demonstrated the minimal clinically important difference (MCID) of at least an additional 60 minute reduction in OFF time compared to placebo. This is high quality evidence from a double blind, randomized, placebo controlled, phase III trial. This should be included. Hauser RA, Gordon MF, Mizuno Y, et al. minimal clinically important difference in Parkinson's disease as assessed in pivotal trials of pramipexole extended release. Parkinsons Dis 2014; 2014: 467131	Thank you for your comment. The guideline did not look for evidence on opicapone, as it was not licensed at the time the scoping was undertaken. Whilst we did not specifically look for evidence, the fact that opicapone is classed as a COMT inhibitor means it is covered as part of our recommendations for adjuvant treatment, and could be considered as an option under those class level recommendations (within the licensed indication). The GDG did not feel it was appropriate to make recommendations about which specific choices within those classes should be preferred for adjuvant treatment. In addition, NICE has recently published an evidence summary on opicapone in March 2017, though this will not be formally included as part of the guideline.
Bial	Full	75	1939	BIPARK I - Opicapone demonstrated statistically significant improvement in the patient's condition (Global Assessment of Change - GAC) versus entacapone. This should be included.	Thanks you for your comments. The guideline did not look for evidence on opicapone, as it was not licensed at the time the scoping was undertaken. Whilst we did not specifically look for evidence, the fact that opicapone is classed as a COMT inhibitor means it is covered as part

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				Opicapone offers patients less OFF time and more ON without troublesome dyskinesia, with the advantage of a once daily dose that allows optimal titration of existing l-dopa regimens.	of our recommendations for adjuvant treatment, and could be considered as an option under those class level recommendations (within the licensed indication). The GDG did not feel it was appropriate to make recommendations about which specific choices within those classes should be preferred for adjuvant treatment. In addition, NICE has recently published an evidence summary on opicapone in March 2017, though this will not be formally included as part of the guideline.
Bial	Full	75	1950	Absolute reduction in OFF time of 2 hours achieved with 50mg opicapone once daily in the BIPARK I study. This should be included.	Thanks you for your comments. The guideline did not look for evidence on opicapone, as it was not licensed at the time the scoping was undertaken. Whilst we did not specifically look for evidence, the fact that opicapone is classed as a COMT inhibitor means it is covered as part of our recommendations for adjuvant treatment, and could be considered as an option under those class level recommendations (within the licensed indication). The GDG did not feel it was appropriate to make recommendations about which specific choices within those classes should be preferred for adjuvant treatment. In addition, NICE has recently published an evidence summary on opicapone in March 2017, though this will not be formally included as part of the guideline.
Bial	Full	76	General	We request the addition of Global Assessment of Change scale and inclusion of the opicapone vs. entacapone data from the BIPARK I study.	Thanks you for your comments. The guideline did not look for evidence on opicapone, as it was not licensed at the time the scoping was undertaken. Whilst we did not

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				I.e. Opicapone demonstrated statistically significant improvements in the patient's condition (GAC) versus entacapone. Global Assessment/Improvement Scales are acknowledged as valuable evidence in Table 15, 16 and section 8.1.5.3.	specifically look for evidence, the fact that opicapone is classed as a COMT inhibitor means it is covered as part of our recommendations for adjuvant treatment, and could be considered as an option under those class level recommendations (within the licensed indication). The GDG did not feel it was appropriate to make recommendations about which specific choices within those classes should be preferred for adjuvant treatment. In addition, NICE has recently published an evidence summary on opicapone in March 2017, though this will not be formally included as part of the guideline.
Bial	Full	79	2018	Table 7: BIPARK I supports the inclusion of improvements in overall condition (GAC) as a benefit of the COMT inhibitors	Thank you for your comment. The guideline did not look for evidence on opicapone, as it was not licensed at the time the scoping was undertaken. Whilst we did not specifically look for evidence, the fact that opicapone is classed as a COMT inhibitor means it is covered as part of our recommendations for adjuvant treatment, and could be considered as an option under those class level recommendations (within the licensed indication). The GDG did not feel it was appropriate to make recommendations about which specific choices within those classes should be preferred for adjuvant treatment. In addition, NICE has recently published an evidence summary on opicapone in March 2017, though this will not be formally included as part of the guideline.

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Boston Scientific	Appendix F	25	Section F.3.1.11	We would like to note that Boston Scientific is also a supplier of non-rechargeable DBS systems and would request that this is reflected in the final documents. Boston Scientific's non-rechargeable systems incorporate a 20% larger battery capacity than the current market leading devices, enabling a longer interval between replacements. We would also like to highlight that both Boston Scientific's rechargeable and non-rechargeable DBS systems are the first purpose-built DBS systems available worldwide, incorporating technology designed specifically for neurological applications rather than designed from a pre-existing cardiac device.	Thank you for this information. The text has been revised as follows: *The NHS has 2 primary suppliers of replaceable systems – Medtronic and St Jude Medical. The committee was aware that, alongside its rechargeable IPG (see below), Boston Scientific also manufacture a replaceable device. However, it advised that it is not commonly used in NHS practice; moreover, unlike the other devices featured here, it does not appear in the NHS Supply Chain Catalogue, which would make it difficult to cost in a comparable way. For these reasons, the analysis assumed that all replaceable devices were those manufactured by either Medtronic or St Jude Medical.*
Boston Scientific	Appendix F	25	Section F.3.1.11	We disagree with the committee's assumption that the rechargeable DBS market in the UK represents only 10% of the market and believe rechargeable technology is a larger (and growing) part of the DBS market.	Thank you for your comment. We are unaware of data that would provide an authoritative answer to this question. However, regardless of the true market share of rechargeable technology, it was felt to be important to configure the model to provide an estimate for DBS using non-rechargeable batteries (for which reliable lifespan data are available) and restrict consideration of rechargeable batteries to a more exploratory scenario analysis.
Boston Scientific	Appendix F	32	Section F.3.1.12	We are concerned that the economic modelling may not reflect the true resource implication for Trusts due to incorrect reference costs being cited. For example, HRG AA53 is not the most representative HRG for a DBS implantation. For Parkinson's Disease patients, the most relevant HRG is	Thank you for your comment. The GDG had no doubt that the HRG cost cited here is much too low to reflect the full costs of DBS implantation. Indeed, the cost of available

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				AA60 "Insertion of Neurostimulator for Treatment of Neurological Conditions". The 2014/15 reference costs for this HRG are £14,378.97 for elective inpatient admissions (inclusive of device costs). Similarly, we are at a loss as to why the resources for a replacement DBS procedure would be recorded under a thoracic procedure HRG rather than a nervous system HRG. We would recommend NICE review these cost inputs and revise the analysis accordingly to ensure it is correct.	IPGs, electrodes and extensions alone exceed this amount. Replacement of DBS batteries is a thoracic procedure, which is why it has been estimated using a thoracic HRG.
Boston Scientific	Appendix F	56	Table 43	We are disappointed that the economic evaluation did not find rechargeable DBS systems at least as cost-effective as non-rechargeable systems. We note that the effects (QALYs) for both rechargeable and non-rechargeable DBS systems are almost identical. This conflicts with the generally accepted principal that an invasive surgery such as a replacement should result in a reduction in QALYs. From what we can see, the economic model (which was kindly shared with us) appears to include a 3-day loss of QALYs as a result of the replacement procedure. Please could you confirm if this is correct, and what evidence base was used to justify a 3-day effect for a replacement surgery versus a 7+18 (i.e., 25 day) effect for the initial implant procedure? Furthermore, from what we can see in the economic modelling, there has been no QALY impact from severe adverse events or subsequent surgical events associated with a replacement procedure. Please could you confirm if this is the case, and as above, clarify what evidence base was used to assume no QALY effect for these events post-replacement procedures versus the QALY effect assumed for the initial implant procedure?	Thank you for your comment. You are correct that the economic model assumes a 3-day loss of QALYs as a result of the replacement procedure. This is because, in contrast to the neurosurgical procedure required to implant the device, battery replacement is a simple thoracic procedure. It is also correct that, because the GDG's experience is that AEs of battery replacement are rare and minor, no disutility was assumed. Therefore, the GDG agreed it was valid that, once averaged out over a simulated patient's lifetime, the impact of any battery replacement procedures would be very small. It is a much bolder assumption to take it for granted that rechargeable batteries are subject to no replacement costs and disutilities at all, as we do in our speculative scenario analysis. Therefore, rather than underestimating the cost effectiveness of rechargeable IPGs, we assert that this analysis provides an estimate of the greatest

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					value that a rechargeable system could provide. The true value for money is likely to be less favourable.
Boston Scientific	Appendix F	General	General	We are disappointed to note the use of commercial brand names such as "Stimlock" in the Appendix document and are concerned that such references may unintentionally suggest a commercial preference. We would request that beyond company names, that NICE reference no brand names from companies so as to be impartial in this regard.	Thank you for bringing this issue to our attention. We have reviewed the document and replaced brand names with generic descriptions wherever possible.
Boston Scientific	Economic model	Sheet "QALYs"	Cell G8	We note that the economic model that was kindly shared with us includes, in cell G8 of sheet "QALYs", a formula which includes the following function: "…IF(MOD(D8*cycleLength,CHOOSE(swtchDBSreplacementMedMean, IPG_median, IPG_mean))<cycleLength…" We would like NICE to clarify if this condition will be true for the first cycle (i.e., cycle 0), and if so, whether this will result in a loss of utility due to replacement will be taken into account (i.e., double counting of the operative impact in addition to the operative loss of QALY ("uDBS_operative_loss") already counted)?	Thank you for drawing our attention to this error, which we have corrected, making a negligible difference to model outputs.
Boston Scientific	Economic model	Sheet "QALYs"	Cell G8	We note that the economic model that was kindly shared with us includes, in cell G8 of sheet "QALYs", a formula which includes the following function: "…+uDBS_battery_replacement*CHOOSE(swtchDBSreplacementMode, INDEX(BatteryLifeSim!$AC$6:$AC$205, $D8), IF(MOD(D8*cycleLength,CHOOSE(swtchDBSreplacementMedMean, IPG_median, IPG_mean))<cycleLength, uDBS_battery_replacement, 1)))" We are unclear as to why the calculation has been constructed so as to use the square of QALY loss for cycle of battery replacement (i.e., "uDBS_battery_replacement" x "uDBS_battery_replacement" if the IF function is found to be true). Please could you clarify what the	Thank you for drawing our attention to this error, which we have corrected, making a negligible difference to model outputs.

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				"uDBS_battery_replacement" x "uDBS_battery_replacement" calculation is meant to reflect?	
Boston Scientific	Full	195	4797-4798	We are pleased to see the benefits of a longer lasting non-rechargeable (primary cell) DBS device have been highlighted in this draft guideline and acknowledged as a driver of improved cost-effectiveness. This aligns with Boston Scientific's product development where we have introduced a non-rechargeable DBS device to the market incorporating a 20% larger battery capacity than the current market leading devices in order to extend the duration between replacement surgeries. Similarly, our new directional lead allows for more targeted therapy, thereby reducing both the drain on the battery as well as reducing unwanted side effects through reduced brain volume stimulation and limited current leakage.	Thank you for your comments.
Boston Scientific	Full	203	4947-4948	We support the provisional recommendation that DBS therapy be offered to patients in the later stages of Parkinson's disease and are pleased that NICE have acknowledged that this therapy should be available to patients due to the improved quality and duration of life it can offer to them.	Thank you for taking the time to comment on this guideline.
Boston Scientific	Full	203	4947-4948	We are disappointed that despite NICE's analysis confirming that DBS offers clinical benefits over medical management for patients with early PD, this treatment option has not been recommended in the draft guideline for this group of patients. We feel strongly that this therapy should be available to all PD patients, regardless of the stage of their disease and are concerned that under the current proposals, patient access to this therapy would be much more restrictive than in other countries).	Thank you for your comment. The GDG's consideration of DBS for the early Parkinson's disease population is set out in detail in 10.4.7. The group agreed that, as the magnitude of benefit in this population was smaller than in the advanced Parkinson's disease group (both in the identified evidence and in group member's experience), and DBS was on the borderline of cost effectiveness compared with BMT in the latter group, it could not recommend DBS when medical avenues remained open.

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Boston Scientific	Full	208	5110	We disagree with the committee's conclusion that the EARLYSTIM data is not representative of UK patients and would like to ask NICE to clarify the evidence base used to come to this conclusion.	Thank you for your comment. We have added the following detail: 'In particular, the group noted that the mean age of the group was 52, and their mean disease duration was 7 years, suggesting an average age at onset of 45, which is much younger than observed in UK practice.'
Boston Scientific	Full	General	General	Thank you for the opportunity to comment on the draft for the above clinical guideline. We welcome the update of these guidelines to reflect current best clinical practice. Going forwards, we hope that new data collected on PD patients, such as that collected by the British Society for Stereotactic and Functional Neurosurgery registry (led by Mr James Fitzgerald in Oxford) can contribute to keeping these guidelines updated in a more timely manner to ensure the interval to the next update is significantly less than the current 10 year interval.	Thank you for your comment. All active NICE guidelines are formally reviewed every 2 years to identify if sufficient new evidence has been published to justify an update, and therefore if relevant data become available early then such an additional update is entirely possible.
Britannia Pharmaceuticals Ltd	Short version Short	30 8	1.5.7.1 1.3.5	The following quotes and references are from various parts of the draft guideline, which we would like to comment on within this first comment: *"Intermittent apomorphine injections may be used to reduce off time in people with PD with severe motor complications" (Deleted Recommendation)* "*Offer a choice of dopamine agonists, MAO-B inhibitors or COMT inhibitors as an adjunct to levodopa to people who have developed dyskinesia and/or motor fluctuations despite optimal levodopa therapy"* *What is the comparative effectiveness of pharmacological interventions as adjuvants to oral levodopa preparations?*	Thank you for your comment. The recommendations for advanced Parkinson's disease have now been updated to include the options to offer intermittent injections and/or subcutaneous infusions, so both the possible routes of apomorphine delivery are now included within the guideline. The text of section 6.2 has now been updated to make clear that apomorphine was considered as an option within this question as shown in the relevant PICO table. However, the question specifically related to the choice of first-line adjuvant, and the GDG agreed that apomorphine was unlikely to be used as a first-line adjuvant to

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	version Appendix C Full version	31 69	Q19 1697	*PICO table for adjuvant treatment of motor symptoms (no mention of apomorphine intermittent injection).* Within the guideline (Short & Full) no reference is made to the specific role of apomorphine intermittent injection. We would suggest it appears under 6.2 Adjuvant treatment of motor symptoms > Interventions > Dopamine agonists Apomorphine is available in two subcutaneous formulations – APO-go® PEN (subcutaneous intermittent injection) and APO-go® PUMP (subcutaneous continuous infusion). The role of APO-go® PEN in the treatment pathway is not mentioned in the current draft guideline and the distinction between these two formulations and the different types of patients they are each suitable for is not explained. In summary, the choice of treatment with PEN or PUMP will depend on the patient's symptoms and stage of disease; they are not just different options for the same type of patient. • APO-go® PEN (10mg/ml Solution for Injection) is a ready-to-use injection that can be administered intermittently whenever patients need it throughout the day in order to rapidly achieve an ON state. It is therefore an adjunct therapy suited to PD patients who have started to experience motor complications and OFF periods despite taking standard effective doses of oral therapy. For example, those patients who experience episodes of delayed ON following a dose of oral medication, early-morning OFF periods [4], predictable or unpredictable OFF periods, or who have impaired levodopa absorption due to gastric emptying problems can benefit from the APO-go® PEN as it	levodopa monotherapy. In addition, no randomised controlled trial evidence for apomorphine was identified in the specific population specified for this question (levodopa monotherapy versus levodopa plus apomorphine). The GDG therefore agreed that the appropriate place to include intermittent apomorphine injections was in the section on advanced Parkinson's disease, and as above this has now been included.

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				has been shown in clinical studies to provide rapid and reliable restoration of mobility and motor function. • APO-go® PUMP (5mg/ml Solution for Infusion in Pre-filled Syringe) is intended for PD patients who require continuous dopaminergic stimulation and is therefore suited to patients with later stage Parkinson's disease experiencing frequent or longer OFF periods and dyskinesias that cannot be controlled with optimised oral medication, or those who feel APO-go® PEN injections are needed too frequently. The efficacy of APO-go® PEN has been proven in a series of pivotal, randomised, controlled clinical trials [1-3]. It has a rapid and reliable onset of effect with improvements in motor function observed within 4–12 minutes in 95% of patients [5]. The duration of clinical effect ranges from approximately 40–90 minutes [5]. References: 1. Dewey RB, Jr., Hutton JT, LeWitt PA, Factor SA. A randomized, double-blind, placebo-controlled trial of subcutaneously injected apomorphine for parkinsonian off-state events. *Archives of neurology* 2001; 58(9): 1385-1392. 2. Pfeiffer RF, Gutmann L, Hull KL, Jr., Bottini PB, Sherry JH. Continued efficacy and safety of subcutaneous apomorphine in patients with advanced Parkinson's disease. *Parkinsonism & related disorders* 2007; 13(2): 93-100. doi: 10.1016/j.parkreldis.2006.06.012 3. Pahwa R, Koller WC, Trosch RM, Sherry JH. Subcutaneous apomorphine in patients with advanced Parkinson's disease: a dose-escalation study with randomized, double-blind, placebo-controlled	

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				crossover evaluation of a single dose. *J Neurol Sci* 2007; 258(1-2): 137-143. doi: 10.1016/j.jns.2007.03.013 4. Isaacson SH, et al. Apomorphine subcutaneous injections for the management of morning akinesia in Parkinson's disease. Mov Disord Clin Pract. 2016. doi: 10.1002/mdc3.12350 5. APO-go PEN 10mg/ml Solution for Injection. EU Summary of Product Characteristics In, 2014.	
Britannia Pharmaceuticals Ltd	Full version	218	5370	Impulse control disorders (ICDs) are recognised as unwanted complications of dopaminergic therapy in patients with PD. However, the risk of developing ICDs is not the same for all Dopamine Agonists (DA) and seems to be related to the dopamine receptor profile of each particular DA [1]. Dopamine Agonists with a high affinity for the D3 receptor are associated with a higher risk of developing ICDs compared with those with a specific D2 affinity, such as apomorphine [1]. In addition, the mode of administration of levodopa and DAs appears to be an important contributing factor to ICD development. One study concluded that the oral route of administration had a greater association with ICD development that the non-oral route [2]. It has also been suggested in recent studies that stable, continuous administration of levodopa and DAs using infusion-based therapies might decrease the risk of ICDs [3, 4]. <u>References:</u>	Thank you for your comment. The GDG agree that it is plausible that there may be differences in ICD rates between different DA formulations, but did not feel the currently available evidence was sufficiently robust in order for them to make recommendations. In addition, thank you for the references. In the agreed protocol for this particular topic, only evidence from multivariate analysis from retrospective or prospective cohort studies and case-control studies were of interest. Unfortunately, the Seeman study does not meet this predefined inclusion criteria within our protocol for this topic and was therefore not included.

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				1. Seeman P. Parkinson's disease treatment may cause impulse-control disorder via dopamine D3 receptors. *Synapse* 2015; 69(4): 183-189. doi: 10.1002/syn.21805 2. Garcia-Ruiz PJ, Martinez Castrillo JC, Alonso-Canovas A, Herranz Barcenas A, Vela L, Sanchez Alonso P *et al.* Impulse control disorder in patients with Parkinson's disease under dopamine agonist therapy: a multicentre study. *Journal of neurology, neurosurgery, and psychiatry* 2014; 85(8): 840-844. doi: 10.1136/jnnp-2013-306787 3. Todorova A, Samuel M, Brown RG, Chaudhuri KR. Infusion Therapies and Development of Impulse Control Disorders in Advanced Parkinson Disease: Clinical Experience After 3 Years' Follow-up. *Clinical neuropharmacology* 2015; 38(4): 132-134. doi: 10.1097/WNF.0000000000000091 Barbosa P, Lees AJ, Magee C, Djamshidian A, Warner TT. A Retrospective Evaluation of the Frequency of Impulsive Compulsive Behaviors in Parkinson's Disease Patients Treated with Continuous Waking Day Apomorphine Pumps. 2016 International Parkinson and Movement Disorder Society. DOI:10.1002/mdc3.12416.	
British Geriatrics Society				We welcome the production of a new clinical guideline on the diagnosis and management of Parkinson's disease. It is 10 years since the first guideline was released and there have been significant advances in the understanding of the condition over that time.	Thank you for your comment. Responses to the specific comments raised are given below: On further consideration, the GDG agrees that the evidence base was not strong enough to justify the

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				While there are some changes that will undoubtedly improve the care of people with Parkinson's disease there are other changes that will limit choice and, in some cases, remove access to potentially life-changing treatment. We welcome the recognition of additional of Midodrine as treatment for orthostatic hypotension. The addition of domperidone for the same purpose is cautiously welcomed but we are mindful of the MHRA recommendations on caution in the use of this drug. We are pleased that the treatment of dementia in Parkinson's disease has been broadened to include all cholinesterase inhibitors and consideration of memantine as a second line therapy. We feel that considering treatment of mild to severe dementia in Parkinson's disease will enable more people to receive beneficial therapy for cognitive impairment. There are some areas of concern within the guideline. We note the recommendation of removal of proton pump inhibitors for orthostatic hypotension and question whether there is a strong enough evidence base to justify that. We believe that the advice that only levodopa should be offered to patients with early Parkinson's disease whose motor symptoms impact on their quality of life is unnecessarily limiting. While we recognise that levodopa is highly potent in terms of its effect on motor symptoms, there are many patients for whom the increased risk of motor fluctuations or the need to take a once daily treatment to allow work to continue would outweigh that potency. Much of the evidence for this recommendation appears to have come from the PD MED	recommendation to remove proton pump inhibitors for orthostatic hypotension, and the recommendation has now been removed. The GDG discussed again the evidence base used to recommend offering levodopa to patients with early PD whose motor symptoms impact on their quality of life and agreed that supporting evidence was not just based on the PD MED trial. However, the GDG agreed that the way the recommendation was phrased was unnecessarily limiting. The recommendations have now been restructured to make it clear that a discussion of all relevant treatment options should take place with everyone before initiating therapy, regardless of whether they have motor symptoms or not. However they agreed to retain the recommendation that, for most people with motor symptoms, levodopa would represent the most effective first-line choice, given its greater impact on those symptoms. The GDG also agreed that it would be useful to retain the recommendation to prefer non-ergot dopamine agonists from the old guideline. This recommendation clarifies that ergot agonists should not be used first-line, and that they should only be considered if there has been an inadequate response to a non-ergot agonist. Thank you for your comment on cognitive assessment

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				trial. We feel that the trial had methodological issues that make the drawing of such strong conclusions from it difficult to justify. We are surprised that the recommendation to use non-ergot dopamine agonists is no longer in the guideline. Although practicing movement disorder specialists are well aware of this, to lose this recommendation from the print guidance may be confusing to new specialists. As guidelines such as this are a driver for service development we are disappointed that there is no specific recommendation to encourage cognitive assessment of people with Parkinson's disease or in whom symptoms that suggest a high risk of cognitive impairment have developed. We would welcome inclusion of advice on the consideration of cognitive assessments. We would have been pleased to see guidance on the management of restless legs syndrome in the context of Parkinson's disease, particular as taking care to identify and mange this problem is specified. The advice not to offer amantadine to people with dyskinesia does not fit with current practice. Patients with dyskinesia often have significantly reduced quality of life and may progress to more expensive advanced therapies. Amantadine offers the opportunity to improve the symptoms of dyskinesia and can help to delay progression to the alternative treatments. The removal of levodopa-carbidopa intestinal gel (LCIG) is of great concern to us. It is a treatment that is only considered in people with advanced Parkinson's disease. To date, use of the drug has been in relatively small numbers so the overall cost impact is relatively low. Due to the nature of the testing process for LCIG it is only continued in patients in whom benefit has	and restless leg syndrome. However this was not included in the scope of this guideline update, and therefore evidence on these could not be considered. The GDG acknowledge that amantadine may be an effective treatment option for people with dyskinesia, which cannot be adequately managed by modification of existing therapy and have therefore agreed to change the current recommendation to reflect this. For comments on the effectiveness and cost effectiveness of LCIG, please see **theme 1**. For comments on the number of people receiving (or likely to receive) LCIG, please see **theme 1d**. For comments on the relationship between NICE's conclusions on LCIG and NHS England's specialised commissioning policy, please see **theme 9a**. For comments on apparent discrepancies between NICE's appraisal of the evidence on LCIG and the view taken by NHS England's specialised commissioning policy, please see **theme 9b**.

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				been shown. Therefore we feel that the economic calculations use for this recommendation do not take account of the real world use of the drug. We also note that LCIG was very recently assessed by NHS England (including economic analysis) and was approved for use as long as assessments took place in specialist centres. We would ask strongly for this recommendation to be reconsidered.	
British Society for Stereotactic and Functional Neurosurgery	Full	200		We would like to thank the guidance committee for taking into account the relative contribution of non-motor symptoms of PD when extrapolating 1-year treatment DBS effects to the lifetime horizon of the model. The assumption that was adopted was that while the motor effect of DBS did not diminish, its contribution to overall quality of life was gradually reduced by the development of non-motor symptoms over time. Data on the impact of advanced therapies on non-motor symptoms of PD is only now beginning to emerge and we would therefore like to highlight the new evidence which actually shows a positive impact (around 30%) of DBS on these symptoms[1,2]. This knowledge may further underpin the contribution of DBS to overall quality of life of patients with the corresponding socio-economic benefits to both patients and their care givers. 1, Dafsari HS, Reddy P, Herchenbach C, Wawro S, Petry-Schmelzer JN, Visser-Vandewalle V, Rizos A, Silverdale M, Ashkan K, Samuel M, Evans J, Huber CA, Fink GR, Antonini A, Chaudhuri KR, Martinez-Martin P, Timmermann L. Beneficial Effects of Bilateral Subthalamic Stimulation on Non-Motor Symptoms in Parkinson's Disease. Brain Stimul. 2016 Jan-Feb;9(1):78-85. 2, Reich M, Chaudhuri KR, Ashkan K, Hulse N, Costello A, Moriarty J, Samuel M. Changes in the non-motor symptom scale in Parkinson's disease after deep brain stimulation. Basal Ganglia. 2011;1(3):131-133.	Thank you for your comment. Non-motor symptoms were specified as relevant outcomes in the protocols for all review questions relating to advanced Parkinson's disease, and evidence was identified. In particular, measured effects in disease-related and health-related quality of life were directly incorporated into the original health economic model, and the GDG was confident that this provided an empirical reflection of the impact of symptoms – and the benefits associated with alleviation of symptoms – across all relevant domains. Although "socio-economic" benefits are outside NICE's reference case for economic evaluation, carer QoL was examined in this model. The cited evidence does not meet the eligibility criteria for the relevant review questions, due to its observational design.

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British Society for Stereotactic and Functional Neurosurgery	Full	200-201		We appreciate the vigilance of the guidance committee in taking into consideration the technological advances in DBS manufacturing and optimisation since the PDSURG data. The relevance of the rechargeable batteries has been discussed comprehensively in this document, especially with respect to their contribution in lowering the ICER for DBS versus best medical therapy. Here we would also like to highlight other advances which we believe will contribute to cost effectiveness of DBS: new electrode designs are likely to improve the efficacy of the therapy whilst reducing the side effects thus decreasing the frequency and intensity of the follow up care; advanced programming platforms will reduce programming time and the number of follow up programming visits; whilst improved imaging techniques will make targeting easier and more accurate, cutting down the operative time and thus post-operative recovery period and length of hospital stay. As the efficacy and efficiency of DBS as a therapy improves, its cost effectiveness is also likely to follow.	Thank you for your comment. As detailed in 10.3.6, the GDG agreed that there are some respects in which DBS may have become more effective and less expensive than observed in trials such as PDSURG, and this was one reason for the GDG's preference to estimate current costs in detail rather than rely on the global totals observed in PDSURG. It is also true to say that some of the advances mentioned have been accompanied by nontrivial increases in cost. For example, rechargeable batteries may make IPG replacement less frequently needed, but the acquisition cost of the units is also higher. Our exploratory analysis suggested that, at current list prices, rechargeable IPGs would have to last indefinitely before they would have a similar balance of costs, benefits and harms as units with conventional batteries. While we are sure that surgical candidates welcome any reduction in adverse effects that might be expected by advances in technology, they would make a small difference to the overall cost effectiveness of DBS (as indicated in our sensitivity analyses showing that adverse event rates were not a major driver of outcomes).
British Society for Stereotactic and Functional	Full	209	5114-5128	We are deeply grateful to the guidance committee for recommending the need for a randomised trial to study the timing of DBS in PD: "earlier" versus "standard practice". We believe such a trial is deliverable in the UK based on the experience of running the PDSURG study (largest trial of its kind to date in the world) and will further promote collaboration between DBS centres in the	Thank you for your comment. Such research would be very welcome, and would add considerable value to future updates of this guidance.

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Neurosurgery				UK to answer a very worthwhile clinically relevant research question. BSSFN will be keen to work towards such a trial moving forward.	
British Society for Stereotactic and Functional Neurosurgery	Full	General	General	The British Society for Stereotactic and Functional Neurosurgery (BSSFN) is the national body representing clinicians interested in functional neurosurgery including deep brain stimulation (DBS). We would like to thank the NICE Parkinson's Disease (PD) guidance committee for their efforts in producing this document.	Thank you for your comments.
British Society for Stereotactic and Functional Neurosurgery	Full	General	General	Although based on the evidence from the modern literature, DBS remains the mainstay of surgery for those patients with PD in whom best medical therapy has failed to control the symptoms, there remains a small group of patients in whom DBS is not possible (eg due to recurrent infections). In such a group, traditional stereotactic lesional surgery has a role to play and we recommend acknowledging this in the document.	Thank you for your comment. Lesioning was not considered as part of the review question on surgical management of advanced Parkinson's disease. This was because the GDG considered that it is currently used in very few cases. Hence, it was not prioritised.
British Society for Stereotactic and Functional Neurosurgery	Full	General and 203	General and 4947/8	In the UK, the standard practice is to provide DBS within a multi-disciplinary team (MDT). One of the essential functions of the MDT is to ensure patients have tried best medical therapy before proceeding to DBS. The recommendations in the current document are therefore very much in keeping with today's UK practice. In lines 4947/8 the document mentions "Consider deep brain stimulation for people in later stages of Parkinson's disease whose symptoms are not controlled by best medical therapy." We suggest removing the term "later" as the sentence is already clear in that the best medical therapy should precede DBS. The term "later" here therefore may give the false impression that DBS is the last resort to be used at the end stages of PD when no response to	Thank you for your comment. The GDG discussed this wording, and agreed that "later stages" should be replaced by "advanced Parkinson's disease".

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				medical therapy remains (a scenario which is actually a contraindication to DBS).	
College of Occupational Therapists	Full	140	3293	The College fully supports this statement	Thank you for your comment.
College of Occupational Therapists	Full	156	3808	This highlights evidence in *'carer quality of life in the carers of those who received occupational therapy'*. Suggest further examination of this and inclusion in recommendation.	Thank you for your comment. This evidence was included as part of the GDG's discussions around occupational therapy, and formed part of the reasoning why two positive recommendations were made for occupational therapy.
College of Occupational Therapists	Full	159	3820	We generally support the statement but the, *'who are in'* should be replaced with 'from'. The statement should read: *63. Consider referring people <u>from</u> the early stages of Parkinson's disease to an occupational therapist with experience of Parkinson's disease for assessment, education and advice on motor and non-motor symptoms. [new 2017]*	Thank you for your comment. The recommendations around occupational therapy were specifically split into two components; a strong "offer" recommendation for people with Activities of Daily Living (ADL) problems where good evidence was available, and a weaker "consider" recommendation for earlier stages where there same strength evidence was not available. The GDG did not wish to lose this distinction, and felt that people in the later stages of Parkinson's disease, who would all at that stage experience difficulties with activities of daily living, would be adequately captured by the second and stronger recommendation.
College of Occupational Therapists	Full	159	3823-3824	*'…daily living activities.'* This could be seen as reductionist. It suggests activities that are only completed on a daily basis, i.e. self-care, cooking etc, and could exclude activities completed on a less than daily basis. We would suggest therefore amending the statement and replace with *'personally meaningful activities'.* Would read as follows:	Thank you for your comment. The GDG discussed this point and agreed that whilst there was logic behind the alternative wording suggested, "daily living activities" was the terminology used in the trial which provided evidence for this recommendation, and therefore they felt the original meaning of this recommendation should be

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				Offer Parkinson's disease-specific occupational therapy for people who are having difficulties with personally meaningful activities. [new 2017]	maintained, to ensure it linked directly to this evidence base. A slight edit has been made to this recommendation, so it now says "activities of daily living, to be consistent with other pieces of NICE guidance"
College of Occupational Therapists	Full	General	General	Occupational therapists are a major contributor to home hazard assessment and addressing falls risk in people homes. There is little detail of falls in the document and no mention of the important part occupational therapist play in this. This is a major omission and needs to be rectified. Reference: College of Occupational Therapists (2015) *Occupational therapy in the prevention and management of falls in adults.* London: COT. Available at: https://www.cot.co.uk/sites/default/files/general/public/Falls-guidelines.pdf	Thank you for your comment. Unfortunately, we did not identify any RCT evidence in this area as part of our review on occupational therapy, and hence the GDG agreed that no specific recommendations could be made. NICE does however, have a generic guideline on "Falls in older people" (https://www.nice.org.uk/guidance/cg161), which is referenced as part of this guideline.
Complementary and Natural Healthcare Council	Appendix E	General	General	The Stallibrass et al RCT(1) has not been included in the GRADE profiles. This again results from the mis-categorisation of the Alexander Technique as physiotherapy, as outlined in comments 1 and 2 above. Reference 1. Stallibrass C, et al. Randomized, controlled trial of the Alexander Technique for idiopathic Parkinson's disease. Clin Rehabil 2002;16:695–708.	Thank you for your comment. You are correct that this RCT was incorrectly excluded from the draft version of the guideline. This error has now been corrected, and the GDG agreed that it was appropriate to add in a consider recommendation for the Alexander technique in people with Parkinson's disease who are experiencing balance or motor function problems.
Complementary and Natural Healthcare Council	Appendix G	46	Table G5.1	The Stallibrass et al RCT1 is listed as an excluded study. The rationale given is that it is 'already included within the Tomlinson 2013 Cochrane review'. However the Cochrane review is of physiotherapy as the intervention. As stated above, the Alexander Technique is unrelated to physiotherapy and so the study should not have been included in the review (see comment 1).	Thank you for your comment. You are correct that this RCT was incorrectly excluded from the draft version of the guideline. This error has now been corrected, and the GDG agreed it was appropriate to add in a consider recommendation for the Alexander technique in people

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				We therefore strongly recommend that the Stallibrass et al RCT therefore needs to be considered in the current update as it evaluates an entirely distinctive intervention that will otherwise be omitted and so will mean that patients do not have access to an intervention which could provide benefit. Reference Stallibrass C, et al. Randomized, controlled trial of the Alexander Technique for idiopathic Parkinson's disease. Clin Rehabil 2002;16:695–708.	with Parkinson's disease who are experiencing balance or motor function problems.
Complementary and Natural Healthcare Council	Appendix N	6	Table N6	We welcome mention of the Alexander Technique in the Research recommendations but once again refer to the fact that it is incorrectly categorised as 'Physiotherapy and physical activity'. (see comment 1).	Thank you for your comment. The Alexander Technique has now been separated out to a specific category on self-management methods.
Complementary and Natural Healthcare Council	Full	144	3453	Under Table 17, the Alexander Technique has been included under the heading '*Physiotherapy including (but not restricted to) the following:…. Alexander Technique*…' The Alexander Technique is not a strand of physiotherapy. It is one of the disciplines included on CNHC's Accredited Register. As such it has been recognised by the Professional Standards Authority for Health and Social Care under Standard 1 of its Accredited Registers Programme, as a discipline that meets the definition of health care under the Health and Social Care Act 2012 as follows: 'Standard 1 The Professional Standards Authority will decide whether an occupation is 'health or social care' having regard to the definition of health care set out in the National Health Service Reform and Health Care Professions Act 2002, section 25E (8) as inserted by the Health and Social Care Act 2012, section 228.'	Thank you for pointing this out, and this error has been corrected throughout the guideline. Specifically: 1) An additional recommendation about the Alexander technique has been added to the guideline. 2) The research recommendation made separates out physiotherapy and the Alexander technique as separate headings. 3) This has also been adjusted in Table 17 as you have pointed out.

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Complementary and Natural Healthcare Council	Full	144	3453	In addition to comment 1 above, there are published National Occupational Standards (NOS) for the Alexander Technique which have been developed and funded by government. The definition of the Alexander Technique provided in the Overview is as follows: 'The Alexander Technique (AT) is a taught practical discipline with significant healthcare implications. AT lessons help people to free themselves from unhelpful postural and movement habits and develop a more intelligent and skilled control of the manner in which they engage in activity.' This definition and the relevant NOS has no connection whatsoever with physiotherapy. The relevant NOS can be found here: https://tools.skillsforhealth.org.uk/competence/show/html/id/2800/	Thank you for your comment. The references to the Alexander Technique as a form of physiotherapy have now been corrected in the guideline.
Complementary and Natural Healthcare Council	General	General	General	Given that government has set out its Accredited Registers programme precisely to enable healthcare professionals to be able to refer to non-regulated practitioners, (the GMC has updated its guidance to doctors accordingly) we see no reason why the Alexander Technique needs to be incorrectly collapsed into a category with physiotherapy. Removal of the Alexander Technique from the physiotherapy category will enable it to be visible as the distinct discipline that it actually is both in the research and the referral pathways. This would be in the best interests of patients by providing clear choice and patient-centred care.	Thank you for your comment. The Alexander Technique was included in a single section alongside physiotherapy as part of the scope for this guideline, and it would not be appropriate to make alterations to that now. However, RCT evidence related to the Alexander Technique has now been included separately, a specific recommendation around the Alexander Technique made, and references to it changed from physiotherapy to self-management. We hope these changes address the concerns raised.
Complementary and Natural Healthcare Council	Short	35	Table	We are very concerned that the following recommendation (79 in original guideline) has been removed from the draft guideline: *'The Alexander Technique may be offered to benefit people with PD by helping them to make lifestyle adjustments that affect both the physical nature of the condition and the person's attitudes to having PD*. (1.9.2.2). The reason	Thank you for your comment. After further discussion, the GDG agreed it was appropriate to add in a consider recommendation for the Alexander technique in people with Parkinson's disease who are experiencing balance or motor function problems.

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				provided for removing the Alexander Technique again relate to referral to a physiotherapist. (*'This recommendation has been replaced by recommendations from the guideline update....which are included in section 1.7.'*) However, as stated in our comments 1 and 2 above, the Alexander Technique is not a strand of physiotherapy and physiotherapists are not trained to offer the Alexander Technique lessons unless they have undertaken training that meets the National Occupational Standards set out at comment 2 above. In which case they could refer to themselves as Alexander Technique teachers, in addition to being physiotherapists.	
Complementary and Natural Healthcare Council	Short	35	Table	In addition to our comment 3, we consider the removal of the Alexander Technique from this guidance as a retrograde step in light of the evidence provided in a RCT (N=93) in which it was reported that one-to-one Alexander lessons with a registered teacher led to an increased ability of people with Parkinson's to carry out everyday activities.[1] We would also refer you to a number of other pieces of research which support the results from this RCT, namely the preceding pilot study, as well as case studies and research (N=22) that reported improved postural alignment and balance, and reduced rigidity in people with Parkinson's following an AT-based intervention.[2,3,4] In addition, we refer you to an analysis demonstrating that people with Parkinson's retained and continued to implement the skills learnt in the AT lessons over the longer term (6 months follow-up).[5] References 1. Stallibrass C, et al. Randomized, controlled trial of the Alexander Technique for idiopathic Parkinson's disease. Clin Rehabil 2002;16:695–708.	Thank you for your comment. After further discussion, the GDG agreed it was appropriate to add in a consider recommendation for the Alexander technique in people with Parkinson's disease who are experiencing balance or motor function problems.

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				2. Stallibrass C. An evaluation of the Alexander Technique for the management of disability in Parkinson's disease – a preliminary study. Clin Rehabil 1997;11:8–12. 3. Marcus RL, et al. Long-term effectiveness of Alexander Technique classes for managing symptoms of Parkinson's disease: case studies. 4th World Parkinson Congress, Portland, OR, USA 2016; Poster 40:20. 4. Cohen RG, et al. Lighten up: Specific postural instructions affect axial rigidity and step initiation in patients with Parkinson's Disease. Neurorehabil Neural Repair 2015;29:878−88. 5. Stallibrass C, et al. Retention of skills learnt in Alexander Technique lessons: 28 people with idiopathic Parkinson's disease. J Bodyw Mov Ther 2005;9:150–7.	
Department of Health				I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation.	Thank you.
Essex Centre for Neurological Sciences	Full	204	2949	Strongly disagree with advice not to use Duodopa in any patients. There are a number of centres with expertise in Duodopa who I do not believe were consulted to provide further evidence of how this medication can be invaluable in carefully selected patients, especially those not suitable for DBS, as per NHS England guidance.	Thank you for your comment. For comments on the effectiveness and cost effectiveness of LCIG, please see **theme 1**.
Essex Centre for Neurological Sciences	Full	80	2021	It is suggested that Amantidine is not offered in dyskinesia. This old drug can be a useful option to trial in some circumstances of dyskinesia by people with experience in treating PD.	Thank you for your comment. After discussion of the consultation responses the GDG agreed that, whilst there was no evidence for the routine use of amantadine as an adjuvant treatment, it did have a role as a specific option for the treatment of dyskinesia. Therefore, a new recommendation has been added to this section to support the use of amantadine in this context.

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Essex Centre for Neurological Sciences	Full	91	2220	Many patients prefer a transdermal medication and so Rotigotine should be considered first line as well as oral agonists given other benefits of agonists are similar, despite the lack of trial data	Thank you for your comment. The GDG did not feel it appropriate to recommend rotigotine as first line treatment due to it being a more expensive drug, and because we found no evidence to suggest that rotigotine is better than levodopa, the GDG found it difficult to justify why rotigotine should be recommended over levodopa. However, there is nothing in the recommendations to prevent clinicians using their judgement in individual cases where they believe rotigotine to be the appropriate first-line option.
Essex Centre for Neurological Sciences	Full	97	2357	Although Fludrocortisone may be off label there is a wealth of practical experience with it and is an easy once daily medication	Thank you for your comment. According to the NICE guidelines manual, off-label use may only be recommended if the clinical need cannot be met by a licensed product and there is sufficient evidence and/or experience of using the medicine to demonstrate its safety and efficacy to support this. In the absence of good evidence, the GDG therefore decided to recommend the licensed drug (midodrine) ahead of an unlicensed one (fludrocortisone), but felt it important that a caveat be added that in people in whom midodrine is contraindicated, fludrocortisone is an appropriate first-line treatment.
Ever Pharma	Appendix B	5		Scope mentions "intermittent apomorphine injections *and* continuous infusion", however *only* apomorphine continuous infusion is mentioned in the draft guideline	Thank you for your comment. After further discussion, the recommendation on best medical therapy for advanced Parkinson's disease has now been updated to specify intermittent apomorphine injection and/or subcutaneous apomorphine infusion.

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Ever Pharma	Full Version	186	4468	Apomorphine, both *intermittent injection* and *continuous sc infusion* should be included in the title of this section alongside DBS and LCIG as advanced therapies	Thank you for your comment. The primary comparison of interest in this section was DBS versus levodopa, rather than apomorphine, and hence the title is appropriate to the decision problem. However, recommendations around both intermittent and continuous apomorphine are now included as part of this section.
Ever Pharma	Full Version	186	4475	Apomorphine *intermittent injection* should also be included	Thank you for your comment. The primary comparison of interest in this section was DBS versus levodopa, rather than apomorphine, and hence the wording is appropriate to the decision problem. However, recommendations around both intermittent and continuous apomorphine are now included as part of this section.
Ever Pharma	Full Version	186	4487	Apomorphine *intermittent injection* should also be included	Thank you for your comment. The primary comparison of interest in this section was DBS versus levodopa, rather than apomorphine, and hence the wording is appropriate to the decision problem. However, recommendations around both intermittent and continuous apomorphine are now included as part of this section.
Ever Pharma	Full Version	189	4563	Suggest to add Apomorphine *intermittent* subcutaneous injection therapy: Evidence: A summary of 29 clinical trials that evaluated the safety and efficacy of the use of intermittent *s.c.* injections of APO for treatment of Parkinson's Disease (PD) is provided (Cotzias, 1970 (n=15);Merello Piekelny, 1997(n=12); Dewey (APO 202), 2001(n=20); APO 301(n=17); Ostergaard, 1995(n=22); Van Laar 1993(n=5); Pfeiffer/Sherry(APO 302) 2007(n=35); Pahwa (APO 303); 2007(n=51); Hardie 1984(n=8);Kempster 1990(n=14);	Thank you for your comment. Apomorphine was among the interventions considered in section 6.2 (adjuvant therapy) in this guideline; however, no trials meeting the inclusion criteria were found (levodopa monotherapy versus levodopa plus apomorphine). The details of this have now been included within the full guideline at this point. In addition, thank you for the references. In the agreed protocol for this particular topic only systematic review

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				Poewe 1988(n=7); Hughes 1991(n=15); Hughes/Bishop 1991(n=7); Defond 1993(n=7); Trosch 2008(n=51); Gervason 1993(n=10); Harder 1998(n=10)-ef; Le Witt 2009(n=546); Ondo 2012(n=20); Hellman 2007(n=18); Stibe 1988(n=8); Pollak 1989(n=6); Frankel 1990(n=32); Hughes 1993(n=77); Pietz 1998(n=24); Tyne 2004(n=27); Poewe/Kleedorfer 1989(n=17); Pollak 1990(n=5); Ellis 1997 (n=12)) A total of 1070 subjects participated in studies of subcutaneous injections, in studies that were randomized, placebo- or active-controlled, and double-blind or open-label In the randomized, placebo-controlled (and one active-controlled) studies involving a total of 185 PD patients, APO was evaluated for treatment durations ranging from a single administration to repeated administration for up to four weeks. In four parallel treatment studies (van Laar, 1993; Østergaard 1995; Pahwa, 2007, Hardie 1984), 86 subjects received APO and 48 received placebo. In two cross-over studies (Dewey 2001; Pfeiffer, 2007), 55 subjects received APO. All randomized studies enrolled subjects with PD that were being treated with oral medications including levodopa, but who were suffering from "off" periods in spite of optimized oral medication. Measurements of efficacy included reversal of an "off" state to an "on" state, daily time spent in "off" state, and determinations of motor scores using UPDRS and Columbia rating systems or improvements on Pegboard test. All but one (Hardie, 1984; this study did not assess a statistical significance of results) studies showed statistically significant improvement in efficacy measures for APO compared to placebo. The results of the six randomized, placebo-controlled studies showed unequivocal evidence that *s.c.* injections of APO are efficacious in reversing the "off" state in PD, reducing the daily time in the "off" state, and improving the motor score.	and/or RCT evidence reporting long-term treatment effects were of interest. Unfortunately, studies by Antonini (2011), Drapier (2012), Elia (2012), Garcia Ruiz (2008), Gunzler (2008), Gunzler (2009), Hellmann (2008), Kanovsky (2001), Katzenschlager (2005), LeWitt (2009), Ondo (2012), Ostergaard (1995), Pahwa (2007), Trosch (2008), van Laar (2010) were not RCTs or their trial duration was only 3 days. Moreover, the Nyholm study is a post-hoc analysis study and the studies by Peron (2010 and Pfeiffer (2007) did not include a control arm that met the inclusion criteria for this particular review (levodopa monotherapy or levodopa + an intervention drug of interest). For the remaining suggested references (published before 2006), these were all considered in the previous full guideline but unfortunately, none of these met the inclusion criteria and were therefore excluded. These will therefore not be considered in this current guideline update as the criteria for inclusion have not become expanded.

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				Bowron (2004) has provided practical advice for the use of APO injections. Domperidone or trimethobenzamide should be started 72 hours before the start of APO and should be continued until nausea wanes. To determine the optimum dose of APO, anti-parkinson medications should be withheld for a minimum of 4 to 6 hours to provoke an "off" state. Increasing doses starting at 1 mg APO and going to no more than 10 mg, should be administered at 30 minute intervals, and the response monitored by a motor score. If there is no response at 7 mg, the patient should be considered a non-responder. Further, training of patients and caregivers in the use of the injection pen or infusion pump and dosing schedule was highly recommended. It was noted that initial consultations could be time-consuming, but are necessary to ensure the success of the treatment. Follow-up consultations are also necessary. Intermittent *s.c.* bolus/injections (ITT) In total, there were 29 clinical studies identified, with contributing information to the efficacy results in *s.c.* intermittent bolus/injection administration. This represents in total 1070 patients exposed to intermittent APO injections in these studies. Most frequently used primary efficacy assessments: UPDR-III; APO injection effect latency; APO injection effect duration; Time spent in OFF; Frequency of OFF episodes in day; Change of levodopa dose or levodopa Equivalent Dose. In the following text we will present the results of clinical trials for each of the primary/main efficacy results/measurements. For population in double-blind randomized studies, the average bolus/injection dose was 4.462 mg (0.25 – 5.8 mg) APO (calculated from table 67; when only range reported, highest value taken into calculation).	

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				In ITT population of open-label controlled and non-controlled studies, the mean bolus dose was 3.48 mg (1.9-6.07 mg) (calculated from table 66; when only range reported, highest value was taken into calculation). When combined dose exposure both for randomized, double-blind studies and open label studies were calculated, the mean bolus dose was 3.68 mg/bolus injection and mean dose range was 1.74 – 6.939mg. For reports of total daily dose in ITT population, open-label and some randomized double-blind studies had reported this dosages. From available data we calculated the final mean of daily dose on ITT treatment to be 15.749 mg per day, with range (4-127mg/day)(range by Gervason, 1993 study). UPDRS and UPDRS-III Studies contributing to information on UPDRS-III: Dewey (2001), APO 301, Østergaard (1995), Pfeiffer (2007), Pahwa (2007), Hellmann (2007), and Trosch (2008); In the study of Dewey (2001), there was a statistically significant change of UPDRS-III score when OFF state and ON state UPDRS-III was compared, which was -23.9 ± 1.9 score change (-62% ± 4.4% ; p<0.01). In APO 301 study, UPDRS-III change when compared pre-APO dose score with score measured 20 min. after APO was significantly changed from 41.3 ± 2.49 to 20.0 ± 3.6 (-47.4%; p<0.0001) Østergaard (1995) demonstrated a slight reduction in bradykinesia mainly. The UPDRS-III screening score 9.8 was reduced to 7.9 at maintenance week 4 measurements and 6.7 when maintenance week 8 was measured. Pfeiffer (2007) performed a comparison of APO against placebo and assessed UPDRS-III score at 10, 20 and 90 min. He found that there was a significantly superior improvement seen in pooled APO group compared to placebo. Group	

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				of APO improved -24.2, compared to -7.4 on placebo; p<0.0001. At 90 min. the difference did not reach statistical significance (p=0.85) Pahwa (2007) found that APO group mean reduction of UPDRS total score at 20 min after administration improved significantly better that that on placebo. APO group on 4mg/bolus showed at 20 min improvement of -11.2 vs. placebo -2.8, with p=0.0002. There was a significant difference found also at 40 min but not at 90 min after study drug administration in benefit to APO (-13.5 vs. -3.0; p<0.0001 and -5.1 vs. -1.6; p=0.229 for 45 and 90 min respectively) Hellmann (2007) administered 1, 2, 4 mg of APO as a *s.c.* bolus injections to a patients with idiopathic PD with severe motor fluctuations. After administration of study drug the peak improvement was seen at 30 min, with UPDRS-III improvement from 31.5±9 to 20.0±6.4 (reduction 38%). The report did not state p value for UPDRS-III change. Trosch (2008) found out that at intervals 20, 40, 90 min after APO administration there was statistically significant improvement when compared to pre-dose (p<0.01). The mean reduction at 20 min. post-dose was -10.5 and mean reduction after 40 min. post-dose was -15.3. In summary: Studies of ITT APO showed significant improvements of UPDRS-III, or UPDRS total scores compared to placebo. Range of improvement on UPDRS-III was (38 – 75%). Statistical significance for improvements was reported: Dewey (2001), p<0.001; Pfeiffer (2007), p<0.0001; and Pahwa (2008), p=0.0002. APO effect latency Studies contributing to this investigation: Merello (1997), APO 301, Pfeiffer (2007), Kampster (1990), Frankel (1990), Poewe (1989), Pietz (1998), Hughes/Lees (1991), Hughes/Bishop (1991), Gervason (1993), Hardie (1984), Van Laar (1993), Stibe (1988), Cotzias (1970), and Dewey (2001).	

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				Merello (1997) investigated the effect of APO vs. Madopar in double-blind study. It was shown that the APO effect latency was 8.08±13.6min, whilst Madopar latency was 26.8 ± 12.7min. This difference was shorter for APO and statistically significant, p<0.0003. APO 301 demonstrated a initial beneficial effect of APO at 10 min after drug administration. Difference between APO when compared to placebo at 10 min. was 15.4 ± 3.65 (35.9% improvement) vs. 2.7 ± 1.98 (6.7% improvement) and statistically significant p=0.0086. Pfeiffer (2007) observed that the APO effect to start at 7.26 min in group of APO and 11.44 min. in placebo. The specific examination for this study was also Webster step second test. In this test, the first improvement indicating effect was seen at 7.5 min. Improvements in this scale were in favor of APO (improvement -269.5 vs. placebo -58.0; p=0.0230). (see also table 55) Van Laar (1993) showed that the mean latency of APO effect onset was 7.3min (range 1.5 -15 min) Kampster (1990) studied in this open-label study the effect of APO on motor functions as well as duration of the effect. It was observed that "time to effect onset" was 3-14 min (mean 7.9 min) compared to peroral Levodopa 19-75min (mean 35.4). The "best on" walking time was 12.1 min for APO compared to 11.1 min in oral Levodopa patients (r=0.80; p<0.001). Frankel (1990) reported the APO effect latency mean 7.5 min (range 3.5-12.5 min). Poewe (1988) treated 7 patients with APO. The effect latency was reported as a range between 5 to 15 minutes. Pietz (1998) observe effect latency 10.0 min (range 3-30min). Hughes/Lees 1991) observed the effect latency between 5 to 25 minutes. Gervason (1993) found that the mean latency of APO effect was on the first day of treatment for the first APO administration mean 13.7±4.08 (range 8-19)	

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				and the latency time decreased for the second APO administration followed at 10min from the first bolus. Latency of the second APO dose after 10 min was 11.6min (range 6-22). The mean latency time was 12.9 ± 5.88 (range 7-23) on the second day of treatment for the first injection. For the injection following after 80 min. from the first APO injection, the latency time was 11.2 min (range 7-16) Hardie (1984) reported observed APO effect latency 12 min. (mean 6 min). Stibe (1988) reported effect latency as a range (5-15 min). Cotzias (1970) reported 30-60 min delay in APO effect. Dewey (2001) reported onset of effect latency to be 22 minutes. When calculated from the table 66 and 67, the mean effect onset latency was 17.28 minutes (range 3-60min). In summary: Studies of APO ITT showed that APO had shorter effect latency as Levodopa or Placebo in randomized controlled studies. There was a tendency for shortening of mean latency time when APO was administered repeatedly (Gervason (1993)). Approximate mean latency time was 9.659 min (range 1.5 -30 min.). Studies of Kempster (1990), Pfeiffer (2007), Merello (1997) and APO301 were statistically significant in favor of shorted effect latency in APO treated population ($p<0.001$; $p=0.023$; $p<0.0003$; $p=0.0086$, respectively) APO effect duration The following studies contributed to the assessments done for this measurements: Kampster (1990), Poewe (1989), Hughes/Lees (1991), Hughes/Bishop (1991), Gervason (1993), Merello (1997), Harder (1998), Frankel (1990), Stibe (1988), Pietz (1998), Van Laar (1993), and Cotzias (1970). Cotzias (1970) reported the duration of APO effect 120 minutes.	

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				Kampster (1990) observed the mean duration of motoric response following APO administration to be 56 minutes (range 30-80 min). Poewe (1988) observed the duration of APO effect ranging from 1.5hr to 2.5 hrs. Hughes/Lees (1991), reported APO duration of motoric effect to range from 10 to 107 minutes. Hughes/Bishop (1991) observed that there was no change of the effect duration with repeated injections and the duration of motoric response to APO was mean 36 min (range 5-65 min). Gervason (1993) found that duration of effect changed from treatment day 1 to treatment day 2. On the first day of the treatment the mean duration of effect was 62.4 ± 16.99 min (range 28-84 min) and on the second day of treatment 63.80 ± 2.94 min (range 51-80 min). When repeated dosages were administered on the first (10 min after first APO dose) and the second day (80 min after first APO dose), there were some differences observed on the day 2 of treatment 57.3 min (range 42-68 min) for the second bolus 80 min after first APO dose. Merello (1997) observed the APO effect duration to be 56.6 ± 13.6 min. The difference was longer in favor of the control, Madopar (97 ± 35.8 min, $p<0.001$) Harder (1998) reported different effect durations for different APO dosages. For APO doses of 1, 2 and 3 mg the effects durations were 0.25 hrs, 0.58 hrs, and 0.74 hrs, respectively. Frankel (1990) observed duration of effect 60min (ranged 20-120min). In this study 33% of patients complained on some reduction in the duration of APO effects. 13% patients complained on the loss of effect.	

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				Stibe (1988) reported the duration of motoric improvement as a range from 40 to 90 min. Pietz (1998) observed a mean duration of effect 47.5 (ranged 25-90min) Van Laar (1993) observed the mean duration of response after APO administration to be 96 min (range 20-120 min). When calculated from available data in tables 64 and 65, the mean effect duration was 67.66 minutes (ranges 10 – 120min). In summary: Selected studies, that monitored duration of APO effect showed, that the mean duration of effect was 67.66 minutes (ranges 10-120 min). Time spent in "Off" and reduction of "Off" time The following studies contributed to the assessments of time spent "Off" and/or changes in "Off" time: Poewe (1988), Poewe (1989), Defond (1993), Pollak (1989), Pollak (1990), Frankel (1990), Pietz (1998), Dewey (2001), Ellis (1997), Østergaard (1995), Stibe (1988), and Hughes (1993). Poewe (1988) observed reduction of time spent in "Off" from 4.9 hrs before APO to 1.8 hrs on APO. The decrease in the duration of time spent in "Off" was also found in the study of Poewe (1989) who found pre-APO time spent in "Off" 4.7 hrs (range 2-7 hrs) to 1.7 hrs (range 0.5-4 hrs) in a day. Defond (1993) observed that the patients spent mean of 40% of waking hours per day in "Off". When APO was administered mean time % spent in "off" dropped to 18%, which was reduction of 55%, $p<0.02$. Pollak (1989) reported a decrease of 63% when compared time spent in "Off" during a waking day (from 4.7 hrs to 1.7 hrs) when on APO. Pollak (1990) observed 64% improvement in time spent "Off". Pietz (1998) showed that total time spent in "Off" during day was reduced when APO was administered. Reduction was from 50% of time without APO	

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				to 29.5% spent in "Off" when on APO. 20.5% reduction was statistically significant (p<0.001). Dewey (2001) reported 5.9 hours in a waking day that patients spent in "Off" at baseline, with decrease to 3.9 hrs after last follow-up. Change was 33.9% and statistically significant p=0.02. Ellis (1997) reported a significant improvement in duration of "Off" periods (>60% reduction of "Off" time in all patients (p-value not specified in the original report by Ellis) Østergaard (1995) reported significant reduction of mean daily duration of "Off" periods. The reduction was 43.24% from the time in "Off" before APO was introduced (7.4 hrs at baseline; 4.2 hrs at follow-up; p<0.001). Stibe (1988) reported mean reduction of "Off" time during day to be 3.3 hrs, as observed in patients exposed to APO (fell from 6.0 to 2.7 hrs, *i.e.* 50% improvement). Hughes (1993) reported the drop in a total time "Off" spent during waking hours. Before administration of APO, mean duration of time spent in "Off" was 6.2 hrs daily. Upon stabilization of APO therapy this time reduced to 2.6 hrs daily. After one year of treatment, the mean duration of time spent in "Off" was 3.1. In summary: In selected APO ITT studies the mean time spent in "Off" was reported pre-dose 6.9hrs/day. After administration of APO, mean time was reduced by 51.1% (range 20.5 – 63%). Study of Frankel (1990) reported 57.9% improvement with p<0.02. Study of Dewey (2001) reported reduction of 55%, with p<0.02.	

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				Change of per oral Levodopa dose and Levodopa Equivalent dosages when on ITT APO The following studies contributed to the knowledge of oral antiparkinsonian treatment changes in patients exposed to APO: Poewe (1989), Defond (1993), Pollak (1989), Pietz (1998), Ellis (1997), Pollak (1990), Frankel (1990), and Hughes (1993). Poewe (1989) reported decrease of L-DOPA from 1013 mg (500-2250 mg) to 936 mg (500-2250 mg) when on APO. Defond (1993) found out only non-statistically significant changes in L-DOPA therapy (numeric results not reported in original article). Pollak (1989) reported 15% reduction of Levodopa in patients exposed to a mean single dosage of 2.25 mg of APO (daily mean APO dose 9 mg). Pollak (1990) reported decrease in Levodopa dose 14% when on ITT APO. Frankel (1990) observed that there was decrease of 4.57% in Levodopa dosage when on ITT APO. Hughes (1993) observed that dose of Levodopa changed of 61% when on ITT APO. Pietz (1998) reported that out of 24 patients, 6 experienced decrease in Levodopa (values not reported). They found that dosing of APO 2.0 mg (range 0.5-5 mg) resulted in a total increase in Levodopa daily dosage from 825 mg pre-APO to 1050 mg when on APO. There was also significant increase (p=0.027) of number of Levodopa dosages per day from 7 to 10. Ellis (1997) reported reduction of mean Levodopa by 20% of previous daily dose (pre-APO dose 704.2 ± 497 mg) to (566.7 ± 392 mg) when on APO. In summary: All selected studies, but Pietz (1998) showed decrease in Levodopa or Levodopa equivalent dose of other per oral dopaminergic therapy to be approximately 74.45mg/day, which is 10.7% (ranges 4.56 – 20%). In the study of Pietz (1998) increase of daily dose was reported 225mg/day and increase of frequency of dosing from 7 to 10/day (p=0.027)	

Dyskinesia (AIMS, and other measures of dyskinesia)
The following studies contributed to the information on dyskinesia in Parkinson´s disease treated with *s.c.* APO as bolus/intermittent injections.
Studies contributing to information about dyskinesia: Dewey (2001), APO 301, Pfeiffer (2007), Pahwa (2007), Kempster (1990), Defond (1993), Trosch (2008), and Pietz (1998).
Dewey (2001) reported comparison of dyskinesia score in "Off" and "On" states. There was no difference in dyskinesia score following levodopa challenge ($p<0.001$), but in the group receiving APO, dyskinesia similar to those on levodopa were seen ($p=0.001$).
In study APO 301, Dyskinesia rating scale was measured over 60 minutes (intervals 10, 20, 60 min. from APO administration). In this clinical study day 1 and day 2 observations were assessed. When only day 1 of treatment was assessed there was statistically significant increase on Dyskinesia rating scale after APO injections at any time (10, 20, 60min).

Dyskinesia Rating Scale Results [Study APO301]

Min after injection	APO	Placebo	p-value 1	p-value 2
10	0(0,2)	0(-3,0)	0.0156	0.0383
20	1(-3,3)	0,(0,0)	0.0507	0.0066
60	0(-3,3)	0(-3,0)	0.1093	0.0159
p-value 1: From Wilcoxon Signed Rank Test p-value 2: From Wilcoxon Rank Sum test, Day-1 data only				

Preiffer (2007) found out that APO significantly increased dyskinesia, compared to placebo at 10 and 20 minutes post-dose ($p=0.0021$, $p<0.0001$ respectively), but not at 90 min ($p=0.2536$).

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Pahwa (2007) reported that there was the increase in dyskinesia in the cross-over population exposed to APO at all time points (p<0.033). Increase of dyskinesia was also reported with increasing in APO doses (p<0.001).
Kempster (1990) did not find dyskinesias during "Off" periods.
Defond (1993) reported that no aggravation on AIMS scale occurred (p not reported).
Trosch (2008) observed that changes in distribution of dyskinesia scores at 20 minutes and 40 minutes post-dose APO in visits in 1, 2 weeks and 1 month was statistically significant (p<0.01). However, at all time-points the median change of dyskinesia was zero, indicating that most patients did not experience changes (see table below).
Median (minimum, maximum) Change from Pre-dose in Dyskinesia Rating[a] at 20, 40, 90 Minutes Post Dose at the Week 1 and 2 and the Month 1, 4 and 6 Evaluation Visits[b] (Trosch et al. 2008)
<table>
<tr><th>Time from dose administration [min]</th><th>Week 1 (n=49)</th><th>Week 2(n=48)</th><th>Month 1(n=45)</th><th>Month 4 (n=36)</th><th>Month 6 (n=31)</th></tr>
<tr><td>20 min</td><td>0(-1, 2)*</td><td>0(0, 2)*</td><td>0(-1, 1)*</td><td>0(-1, 2)</td><td>0(-1, 2)</td></tr>
<tr><td>40 min</td><td>0(-1, 2)**</td><td>0(-1, 2)*</td><td>0(-2, 2)*</td><td>0(-1, 2)</td><td>0(-1, 2)</td></tr>
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</td><td></td></tr>
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90 min	0(-1, 2)	0(-1, 1)	0(-1, 1)	0(-1, 2)	0(-1, 1)

a- Dyskinesia rating scale =0, none; 1, mild; 2, moderate; 3, severe
b- Only patients with both pre- and post-dose values are included
*p<0.01, **p<0.001 (Wilcoxon Signed Rank test)

Pietz (1998) reported changes of dyskinesia score in patients exposed to APO and those not. In patients administered APO there was a dyskinesia score when in "On" 1.6(range 0-4). In "On" without APO the dyskinesia score was 1.7 (range 0-4). Dyskinesia duration score was in the group of patients on APO 1.4 (range 0-3) and in patients without APO 1.3(range 0-3). In OBESO score, there was pre-dose intensity 2.2 (0-4) and duration 1.7(0-3). These values changed minimally post-APO-dose to 1.9 (0-4) in intensity and 1.5 (0-3) in duration.
In summary: There was a neutral effect of APO in ITT modus of administration reported in studies of Pietz 1998), Trosch (2008), Defond (1993), Kempster (1990). Dewey *et al.* (2001) found equivalent neutral effect on dyskinesia in the group of APO and Levodopa treatment (p=0.001). In study of Pfeiffer (2007) there was significant increase in Dyskinesia at 10 and 20 minutes post-dose (p=0.0021 and p<0.0001 respectively). In the study APO 301 and increase in Dyskinesia post-dose 10, 20, 60 minutes was observed. Pahwa (2007) reported increase of dyskinesia at all time in patients on APO (p<0.033) as well as increase of dyskinesia with the increased APO dose (p<0.033).

Additional measurements of efficacy, secondarily reported
OFF episodes numbers per day
Ostergaard (1995) observed significant increase in mean daily numbers of "Off" periods (-34%; 95%CI; range 5-70%; p<0.02). Pietz (1998) observed that number of "Off" periods per day increased from 4 to 5 (p<0.001).

Columbia scale
Van Laar (1993) reported the mean difference scores of sum on Columbia items showed p-values (<0.00 to 0.03). Combined Mann-Whitney statistic showed the result of all patients that yielded Z-value 4.76, p=0.001, which confirmed statistically significant positive effect of APO.

Websters steps second test
Dewey (2001) reported an improvement of -402 (median Q3-Q1: 9701), -65%, p<0.01.
Pfeiffer (2007) observed significant improvement of pooled APO exposed subjects, when pre-dose and APO dose results were assessed (see table below)
Median change from pre-dose WSST at 7.5 min was -269.5 (APO) vs. -58.0 (placebo), p=0.0230. Results at 10 minutes since exposure were -400.5 (APO) vs. -78.0 (Placebo), p=0.005.

Websters Step Second Test APO vs. Placebo (Pfeiffer et al. 2007)

Time-after exposure to IMP	Difference reduction WSST APO	Difference – reduction WSST Placebo	P values
7.5 min	-269.5	-58.0	0.023
10 min	-400.5	-78.0	0.005
15 min	-426.5	-66.0	0.0005

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<table>
<tr><td>20 min</td><td>-426.5</td><td>-39.9</td><td><0.0001</td></tr>
<tr><td>40 min</td><td>-445</td><td>-62.5</td><td>0.0004</td></tr>
</table>

Time-walking distance (12-25m)
Kempster (1990) observed mean walking time response amplitude 12.5s in APO group and 12.3s in Levodopa group (r=0.81; p<0.001).

Tremor and rigidity
Hellmann (2007) reported improvements of tremor, rigidity and bradykinesia. Tremor dropped in all patients exposed to APO from 7.7 ± 4.6 to 3.3 ± 2.5 (UPDRS items 20 and 21, Drop 57.1%). Rigidity assessed as item 22 of UPDRS fell from pre-APO 7.5 ± 2.8 to 4.2 ± 2.3(Drop 41.25%). Bradykinesia dropped from 11.2 ± 2.9 to 8.1 ± 3.3 (UPDRS items 23-26, Drop 27.6%)).

UPDRS-time course
APO 301 study (see also table below) – the repeated ANCOVA analysis showed a statistically significant difference in 10, 20 and 60 minutes UPDRS-III scores between treatment of APO vs. Placebo. Analysis of Day 1 data in parallel groups supported a statistically significant greater reduction (p=0.0059) in UPDRS scores following APO to placebo injection only at the 60 min. time-points.

APO 301: Effect of Treatment on Time Course of Change in UPDRS –III Score from Pre-dosing for ITT Population(APO 301)
</td><td></td></tr>
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<tr><td></td><td></td><td></td><td></td><td>
<table>
<tr><td>Time Relative to dosing mean</td><td>APO N=17 [Std error] (% change from baseline)</td><td>Placebo N=17 [Std error] (% change from baseline)</td><td>p-value (1)</td><td>p-value (2)</td><td>p-value (3)</td></tr>
<tr><td>Pre-dose UPDRS score</td><td>41.3 (2.49)</td><td>40.1 (2.23)</td><td></td><td></td><td></td></tr>
<tr><td>10 min after injection</td><td>15.4 (3.65) (-35.9%)</td><td>-2.7 (1.98) (-6.7%)</td><td>0.0086</td><td>0.2429</td><td>0.2678</td></tr>
<tr><td>20 min after injection</td><td>-20.0 (3.60) (-47.4%)</td><td>-3.0 (2.24) (-5.9%)</td><td><0.0001</td><td>0.2752</td><td>0.0736</td></tr>
<tr><td>60 min after injection</td><td>-12.6 (2.87) (-30.2%)</td><td>-0.4 (1.3) (-0.1%)</td><td>0.0009</td><td>0.8452</td><td>0.0018</td></tr>
</table>
</td><td></td></tr>
</table>

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<table>
<tr><td>Area Under the Curve</td><td>1572 (160)</td><td>2298 (132)</td><td><0.0001</td><td>…</td><td>0.0219</td></tr>
<tr><td colspan="6">(1) Repeated measures ANCOVA with sequence, subject within sequence, pre-dose score, treatment, and period
(2) P-value for sequence effect using subject within sequence MS as error term
(3) ANCOVA with terms pre-dose and treatment – Day 1 data only</td></tr>
</table>

Tapping hand test
Dewey (2001) reported a change on APO +109 (±23), +88% change, p<0.001.
Kempster (1990) reported the mean amplitude of hand-tapping to be 18 on APO and 20 on Levodopa (r=0.92; p<0.001). Mean peak "on" phase tapping scores were 47 for APO and 48 for Levodopa group (r=0.89; p<0.001).

CGI
Østergaard (1995) reported that 12 of 14 patients that completed maintenance phase of this study reported "much" or "very much" improvement on CGI scale.
Pietz (1998) reported CGI scores in patients. 10 patients of 24 ITT population reported clear improvement. 8 of 24 reported slight improvement. 5 of 24 patients reported no change and 1 patient reported worsening of status. Items "much worse" were not reported.

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<tr><td></td><td></td><td></td><td></td><td>In summary: In additional measurement of efficacy, 7 studies observed improvements of motoric functions or global clinical status to be significantly due to APO (see table below)
Additional Efficacy Parameters in ITT Clinical Studies of APO
<table>
<tr><td>Study</td><td>Disability score</td><td>Columbia scale</td><td>Webster´s step second test</td><td>Time walking distance</td><td>Tapping hand test</td><td>CGI-I</td></tr>
<tr><td>Cotzias, 1970</td><td>>20 % improve-ment on APO</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Van Laar, 1993</td><td></td><td>Improve-ment p=0.001</td><td></td><td></td><td></td><td></td></tr>
</table></td><td></td></tr>
</table>

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				Dewey, 2001 | | | Improvement 65%, p<0.01 | | +109±23. Difference 88%; p<0.001 | | Pfeiffer, 2007 | | | Significant improvement | | | | Kempster, 1990 | | | | 12.5; p<0.001 | Amplitude 18 on APO vs 20 on LEV;p<0.001) Peak "On" 47-Apo, 48 LEV;p<0.001 | | Østergaard, 1995 | | | | | | 12 pts score 1 or 2	

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				Pietz, 1998 | | | | | | Score 2: 10pts; Score 3: 8 pts; Score 4: 5 pts; Score 5: 1 pt	
Ever Pharma	Full Version	189	4563	Suggest to add Apomorphine *continuous* subcutaneous infusions: Evidence: There are nine publications describing parallel-group studies of the use of both intermittent APO injections and continuous APO infusions for the treatment of PD.(Stibe 1988(n=8); Pollak 1989(n=6); Frankel 1990(n=32); Hughes 1993(n=77); Pietz 1998(n=24); Tyne 2004(n=27); Poewe/Kleedorfer 1989(n=17); Pollak 1990(n=5); Ellis 1997 (n=12)) In these studies, there were 172 patients on intermittent injections and 122 on continuous infusions, with a few of the ones on continuous infusion receiving booster injections, as needed (Tyne 2004). Both modes of administration were effective in reducing "off" time. Because of different safety profiles with	Thank you for your comment. Apomorphine was among the interventions considered in section 6.2 (adjuvant therapy) in this guideline; however, no trials meeting the inclusion criteria were found (levodopa monotherapy versus levodopa plus apomorphine). The details of this have now been included within the full guideline at this point. In addition, thank you for the references. In the agreed protocol for this particular topic only systematic review and/or RCT evidence reporting long-term treatment effects were of interest. Unfortunately, studies by Drapier (2012), Elia (2012), Garcia Ruiz (2008), Gunzler (2008), Gunzler (2009), Hellmann (2008), Kanovsky (2001),

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				regard to cutaneous nodules and dyskinesia, some patients preferred or tolerated one mode of administration over the other. 23 additional clinical studies that examined the efficacy of continuous *s.c.* infusions of APO (Gunzler 2008(n=14); Gunzler 2009(n=14); Stocchi 1993(n=10); Morgante 2004(n=12); Nyholm 2009(n=4); Elia 2012(n=10); De Gaspari 2006(n=13); Antonini 2011(n=12); Peron 2010 (20); Poewe 1993(n=18); Gancher 1995(n=7); Colzi 1998(n=19); Stocchi 2001(n=30); Kanovsky 2001(n=12); Manson 2002(n=64); Katzenschlager 2005(n=12); Garcia-Ruiz 2008(n=82); Di Rosa 2003(n=12); Drapier 2012(n=23); Kreczy-Kleedorfer 1993(n=14); Reuter 1999(n=6); Stocchi 2003(n=7); Van Laar 2010(n=10). In all these studies, 640 patients received APO, and the duration of follow-up was up to 9 years after the start of treatment. Besides studies of Gunzler, (2008 and 2009), due to the necessity of using a pump to continuously deliver APO, all studies were open-label studies. One study had blinded raters to evaluate the effects of 100 mg/day APO versus continued oral therapy that included levodopa (Morgante (2004)). One study of Reuter, 1999 had 3 of total 8 patients on blinded-placebo treatment and 5 on open-label treatment. This study is reported under open-label controlled trials of APO infusions because 62.5%% of population was on open-label APO medication. All studies evaluated the changes from baseline with APO treatment. The primary measures of efficacy were reduction in daily "off" hours, reduction in levodopa dosage, and improvement in motor function. For the 10 studies that measured daily "off" hours, all reported a significant decrease with continuous infusion APO. Open-Label, controlled trials (Nyholm 2009, Elia 2012, De Gaspari 2006, Antonini 2011 and Peron 2010) compared continuous *s.c.* APO infusions with other treatments for advanced PD (STN-DBS, Jejunal Levodopa).	Katzenschlager (2005), LeWitt (2009), Ondo (2012), Ostergaard (1995), Pahwa (2007), Trosch (2008), van Laar (2010) were not RCTs or their trial duration was only 3 days. Moreover, the Nyholm study is a post-hoc analysis study and the studies by Peron (2010 and Pfeiffer (2007) did not include a control arm that met the inclusion criteria for this particular review (levodopa monotherapy or levodopa + an intervention drug of interest). For the remaining suggested references (published before 2006), these were all considered in the previous full guideline but unfortunately, none of these met the inclusion criteria and were therefore excluded. These will therefore not be considered in this current guideline update as the criteria for inclusion remains the same.

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				Studies with 12-month and 5-year follow-ups (De Gaspari, 2006; Antonini, 2011) compared APO infusions with STN-DBS. Both treatments reduced daily "off" time and levodopa usage. For the APO-treated group, there was no change reported in motor scores (AIMS, UDPRS), but there were improvements for the STN-DBS group. On the other hand, there was a decline in category fluency and worsening of a neuropsychiatric inventory with STN-DBS, but not with APO. Two studies from Gunzler (2008, 2009) were randomized, double-blind, placebo controlled studies in efficacy of s.c. infusions of APO. Gunzler 2008 exposed 14 patients to APO infusion in randomized, double-blind placebo-controlled conditions. Gunzler 2009 had two sub-studies: Outpatient study - which was a single-blind randomized study with 50 newly recruited subjects focusing on UPDRS-III score change, finger tapping alternate and repetitive foot-tapping rates and gait measures. Inpatient double-blind, placebo-controlled, cross-over subanalysis of patients from Gunzler 2008 study - in which variance and reliability of the finger and foot-tapping techniques during placebo day, compared the validity of these outcome measures to detect improvement in parkinsonism during high-dose APO infusion. In these studies it was confirmed that high-dose APO significantly increased foot tapping and tended toward increasing finger tapping compared with placebo. There was no decline in finger or foot tapping rates during low-dose APO infusions. One study comparing APO infusions with intraduodenal levodopa infusions concluded that intraduodenal levodopa improved motor fluctuations substantially (Nyholm, 2009). However, the publication was based on a subset of four patients from a larger study, and these four advanced PD	

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				patients had been treated with APO infusions and oral levodopa prior to study start and had motor fluctuations in spite of APO treatment. The results of the comparative studies illustrate the trade-offs in advantages and disadvantages for the three main treatments for advanced PD. Not all PD patients are good candidates for DBS: advanced age, existing significant co-morbidity, and existing active mental health problems limit suitability. However, DBS is effective in treating tremor that is resistant to pharmacological agents. For infusions of APO and levodopa, the restrictions on age and mental illness, particularly depression, are not as stringent (Antonini, 2009; Grimes, 2012). The profile of expected adverse effects may also be a factor in the choice. Development of inflammatory nodules or panniculitis during use of APO infusions has caused patients to stop using APO. Verbal fluency can decline with DBS. Deleu (2004) did a thorough review of the safety and efficacy information in published clinical studies of APO use in PD. The authors recommended that *s.c.* APO, either as intermittent injections or continuous infusions should be offered to any suitable PD patient who has difficulties with his/her management with conventional therapy. Further, they concluded that low-dose levodopa therapy in combination with waking-day hours *s.c.* APO infusion probably be the most efficient treatment, and that continuous APO infusions should be evaluated before more invasive measures or neurosurgical interventions. In addition to the physiological or pharmacological considerations, other factors can be important in the choice of treatment. The need for day-to-day support for infusions of APO or levodopa is greater than the need for STN-DBS, after it has been established. APO infusions can be started or stopped easily. It is a little more difficult with levodopa infusions, and DBS requires surgical facilities and staff that may not be available in rural areas. If the	

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				patient is uncertain about treatment and is not determined, APO may be preferable to the other treatments (Antonini, 2009). APO drug dose exposures In the CSAI treatment (calculation from available data in table 68), there was a mean infusion rate of 4.425 mg/hr, with ranges (2.9 – 8 mg/hr). Total daily dose for CSAI treatment was a mean of 81.637 mg (range 12.2-160 mg). UPDRS and UPDRS-III Studies contributing to this efficacy measures: Gunzler (2009), Nyholm (2009), De Gaspari (2006), Antonini (2011), Garcia-Ruiz (2008), Drapier (2012), Kreczy-Kleedorfer (1993), Stocchi (2003), Kanovsky (2002), Elia (2012), Peron (2010), and Katzenschlager (2005). Gunzler (2009) showed correlation between improvement on Alternate Foot Tapping score (AFT), and Repetitive Foot Tapping score (RFT) and UPDRS - (23, 24, 25, 26, 31). For AFT the R^2 in UPDRS was 0.09, p=0.039). For RFT, the R^2 for UPDRS was 0.08, p=0.0483. Nyholm (2009) found that total UPDRS score was equal between Continuous *S.c.* APO Infusions (CSAI) and monotherapy with Levodopa in 3 out of 4 patients. UPDRS score for bradykinesia was equal in 2 patients and higher for CSAI group than in Levodopa group in 2 patients. De Gaspari (2006) observed no change in UPDRS-III score when baseline results were compared with the results at follow-up (90 min after therapy start) in patients on CSAI (19.5 ± 15.6 at baseline; 19.25 ± 14.5 in CSAI after therapy start) Antonini (2011) reported no difference on UPDRS-III between CSAI and Deep Brain Stimulation at baseline, 1-year follow-up and patient´s last follow-up visit (5 years). Garcia-Ruiz (2008) reported statistically significant changes in total UPDRS and motor UPDRS-III scores from baseline to the last follow-up visit (mean FU	

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<tr><td></td><td></td><td></td><td></td><td>19.93 ± 16.3 MTH). Total UPDRS change (68.12 ± 21.14 at baseline; 44.70 ± 24.63 at last follow-up; p<0.0001). For motor UPDRS-III this difference was (42.28 ± 14.05 at baseline, vs. 28.62 ± 15.84; p<0.0001).
Drapier (2012) reported changes in UPDRS-III between values from baseline and 12-months follow-up. The difference was not statistically significant (mean 18.3 ± 8.3 vs. 21.8 ± 11.1; p=0.08)
Kreczy-Kleedorfer (1993) monitored changes in UPDRS-III score from baseline to follow-up (mean FU 25.6 months) visit, but found only non-statistically significant differences.Stocchi (2003) measured total mean UPDRS both in “On” and in “Off” states in patients exposed to CSAI. Mean UPDRS score in “On” was 9.06 ± 4.6 and was similar for day 1 and day 2 of CSAI treatment. Mean total UPDRS in “Off” was 56.3 ± 14.8 and was similar for day 1 and day 2 of the CSAI treatment.
Kanovsky (2002) reported the results of open-label prospective study with patients treated with CSAI with motor fluctuations. CSAI was titrated and stabilized for mean 8 weeks. Results of measurements were reported for onset of therapy, follow-up at 6 month, 12 and 24 months. Difference between mean and total UPDRS scores at 6, 12, 24 month was significant p>0.005 (see table below).
Table: Results of repeated assessments UPDRS-total and UPDRS-III (Kanovsky et al. 2002)
<table>
<tr><td>Score</td><td>Onset</td><td>6 months</td><td>12 months</td><td>24 months</td></tr>
<tr><td>UPDRS total</td><td>68.3±12.4</td><td>39.5±9.3</td><td>37.9±8.2</td><td>38.1±9.1</td></tr>
<tr><td>UPDRS-III</td><td>29.7±6.2</td><td>16.3±6.8</td><td>15.6±6.5</td><td>16.5±7.1</td></tr>
</table>
</td><td></td></tr>
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				Elia (2012) reported that CSAI produced worst UPDRS score, that was significantly different than that observed in group exposed to STN-DBS and jejunally administered Levodopa ($p<0.001$). Katzenschlager (2005) observed no significant differences between pre-APO and post-APO as well as pre-Levodopa and post-Levodopa effect on UPDRS-III. Mean pre-dose "On" UPDRS-III was 19.7 in group receiving Levodopa and 19.9 in group on APO. Mean "Off" UPDRS-III in Levodopa group were pre-dose 52.4 and in APO group pre-dose 55.5. When measured at month 6 of exposure, mean "On" UPDRS-III in Levodopa group was 18.9 and in APO group 20.9. Peron (2010) reported open-label study of STN-DBS and APO treatment of PD. There was not significant change in UPDRS-III from mean 14.7 ± 9.5 at baseline to 16.0 ± 11.0 for follow-up after 6 months ($p=0.2$). In summary: From the listed studies of CSAI and effect on total UPDRS, or UPDRS-III, the study of Garcia-Ruiz (2008) had 82 patients exposed to APO. There was a 34.3% improvement on total UPDRS score ($p<0.0001$) and 32.31% improvement on UPDRS-III ($p<0.0001$). Study of Kanovsky (2002) reported 12 patients exposed to APO. They showed significant improvements on UPDRS-total and UPDRS-III (44%; 44%; $p>0.005$). However, Peron (2010) reported that no statistically significant changes in UPDRS-III changes were measured in 20 patients exposed to APO. Studies from Nyholm (2009), Gaspari (2006), Antonini (2011), Drapier (2012), Kreczy-Kleedorfer (1993), and Katzenschlager (2005) showed that changes of UPDRS and/or UPDRS-III but these changes were not statistically significant and they reported no difference at follow-up visits when compared to the baseline results.	

				APO effect latency Studies contributing to this efficacy measures: Elia (2012), Stocchi (2003), and Pietz (1998). Elia (2012) compared the time to best "On" between Deep Brain Stimulation of Subthalamic nucleus (STN-DBS), jejunal Levodopa and CSAI. For STN-DBS the mean time to best "On" was 186±53.2 min when Levodopa was not administered. When STN-DBS was combined with per oral Levodopa, time to best "On" decreased to the mean 159 ± 17.9 min. Jejunal levodopa administration resulted in time to best motor "On" mean 492 ± 59.7 min. When combined with addition of per oral Levodopa mean best time "On" dropped to 203.3 ± 22.2min.($p<0.001$). In the group of CSAI, mean time to best motor "On" was 199.5 ± 65.7 minutes. After an addition of oral Levodopa this time has not changed (196.7 ± 32.5). Author concluded that difference in mean time to best "On" was significantly longer for jejunal Levodopa compared to STN-DBS ($p<0.01$) and significantly longer when compared to CSAI ($p<0.01$). NO difference was found between CSAI and STN-DBS. Stocchi (2003) reported mean time to reach "On" in patients on CSAI to be 42.9 min (range 30-60 min). Pietz (1998) reported latency to onset of APO infusion effect to be 10.0 min (ranges 5-30min). In summary: Three studies reported results for CSAI APO effect latency. Values between these studies differ substantially. We may hypothesize this to be the effect of different assessment procedures between teams of these studies. APO effect duration Studies contributing to this efficacy measures: Gancher (1995) and Stocchi (2003). Gancher (1995) reported that the duration of antiparkinson effect was significantly correlated with the APO dose ($p<0.001$).	

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				Stocchi (2003) reported results of open-label study with CSAI monotherapy and combination therapy with oral Levodopa. When CSAI was ceased, all patients turned to "Off" state within mean 87.1 ± 27.5 minutes. Time spent in "Off" during day Studies contributing to this efficacy measures: Stocchi (1993), Morgante (2004), De Gaspari (2006), Antonini (2011), Poewe (1993), Kanovsky (2002), Colzi (1998), Katzenschlager (2005), Garcia-Ruiz (2008), Di Rosa (2003), Drapier (2012), Kreczy-Kleedorfer (1993), Poewe (1989), Reuter (1999), Frankel (1990), Hughes (1993), Stibe (1988), Pollak (1989), and Pietz (1998). In summary: The mean (calculated from results) improvement on the parameter "Time spent in OFF per day" showed approximately 62.33% improvement with the range (10-100%). Majority of listed studies reported this difference as statistically significant (13 studies of 19). Change of per oral Levodopa dose and Levodopa Equivalent dosages when on APO Studies contributing to this efficacy measures: *Morgante (2004), *De Gaspari (2006), Poewe (1993), *Gancher (1995), *Colzi (1998), *Stocchi (2001), Manson (2002),*Katzenschlager (2005), *Kanovsky (2002), *Garcia-Ruiz (2008), *Di Rosa (2003), *Frankel (1990), *Drapier (2012), Kreczy-Kleedorfer (1993), Tyne (2004), Hughes (1993), Stibe (1988), Pollak (1989), *Pietz (1998), Poewe (1989), and *Peron (2010). *result statistically significant In summary: 20 of 21 studies that reported changes in dosing of Levodopa or Levodopa Equivalent doses of other dopaminergic therapy showed mean decrease of Levodopa or other dopaminergic therapy by approximately 45%.	

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				Majority of studies presented the results of Levodopa or Levodopa Equivalent dose decrease as a statistically significant. Dyskinesia (AIMS, UPDRS dyskinesia measurements and other assessments of dyskinesia) AIMS studies (Stocchi (1993), Morgante (2004), De Gaspari (2006), Stocchi (2001), and Di Rosa (2003)): Stocchi (1993) reported a significant improvement of peak-dose-dyskinesia on AIMS (numeric result not stated in original publication). Morgante (2004) reported a significant improvement of dyskinesia on AIMS, from pre-dose by 48%, $p<0.001$. Stocchi (2001) reported a reduction of dyskinesias on AIMS. With APO use for up to 5 years, there was a tendency for dyskinesias to return after 5-years exposure, but never to the pre-infusion levels (numeric data not part of original publication). Di Rosa (2003), observed a 37% improvement of AIMS (Baseline 7.7 ± 1.2, Endpoint 4 ± 0.6, $p<0.01$). AIMS in patients exposed to Levodopa did not change. Katzenschlager (2005) reported a change in AIMS from 9.7 ± 4.9 at baseline to 5.9 ± 2.9 at a 6-month follow-up visit (change -39%, $p<0.01$). Ellia (2012) reported increase in AIMS ($p=0.021$) with plateau between 90 min and 130 min of APO exposure. UPDRS dyskinesia assessments (Antonini (2011), Colzi (1998), Katzenschlager (2005), and Drapier (2012)):	

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				Antonini (2011) reported improvement of duration and disability of dyskinesia on UPDRS items 32, 33. This improvement when exposed to APO was not significant. Colzi (1998) reported improvement of inter-dose dyskinesia disability of 65% ($p<0.001$). Duration of waking dyskinesia was reduced by 85% (p-value not reported). Katzenschlager (2005) reported changes in dyskinesia items on UPDRS (32-duration, 33-severity). UPDRS-32 changed from 2.1 ± 0.8 to 1.7 ± 0.7 (change -40%, $p<0.01$). On UPDRS-33 there was improvement from 2.4 ± 1.1 to 1.7 ± 0.8 (change -31%, $p<0.05$). Drapier (2012), reported dyskinesia scores from UPDRS items (reported as sum of 32, 33, 34, 35 items). This score has changed from baseline 3.7 ± 3.4 to 3.2 ± 1.6 ($p=0.58$). UPDRS-dyskinesia items were significantly reduced in study of Colzi (1998) and Katzenschlager (2005), $p<0.001$ and $p<0.01$, respectively. The study of Drapier (2012) showed improvements on UPDRS-dyskinesia items, which were not significant ($p=0.58$). Other dyskinesia assessments were reported in Nyholm (2009), Poewe (1993), Colzi (1998), Kanovsky (2002), Kreczy-Kleedorfer (1993), Stibe (1988), Frankel (1990), Pietz (1998), Manson (2002), Drapier (2012), Katzenschlager (2005), and Garcia-Ruiz (2005). In summary: Studies of Morgante (2004), Di Rosa (2003) and Katzenschlager (2005) showed statistically significant improvements on AIMS score when on CSAI ($p<0.001$; $p<0.01$; $p<0.01$). Elia (2012) showed a worsening of AIMS score between 90-130 min, $p=0.021$.	

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				Other dyskinesia measurements showed statistically significant improvements on dyskinesia scales: – Colzi (1998) showing inter-dose dyskinesia disability reduced by 65% (p<0.001); – Kanovsky (2002) showing improvement in dyskinetic time from baseline to final follow-up, with p≤0.01; – Manson (2002) dyskinesia severity reduction by 64% on monotherapy and 30% on polytherapy, p<0.005; – Drapier (2012) reported self scoring diaries improvement from baseline to follow-up, p=0.0001; – Katzenschlager (2005) reported an improvement of 36% on Goetz scale, p<0.01; Diskinesia severity and duration on Visual Analogue scales, p<0.05; Significant correlation (p<0.01) between APO dose at 6-month follow-up and 1. Change in dyskinesia rates in Levodopa challenges (AIMS p=0.769; Goetz p=0.727) and 2. APO challenges (AIMS p=0.68); Garcia-Ruiz (2005) reported significant change in dyskinesia severity by 31.14% (p<0.0006). <u>References:</u>	

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				Antonini, A., I. U. Isaias, et al. (2011). "A 5-year prospective assessment of advanced Parkinson disease patients treated with subcutaneous apomorphine infusion or deep brain stimulation." J Neurol 258(4): 579-585. Colzi, A., K. Turner, et al. (1998). "Continuous subcutaneous waking day apomorphine in the long term treatment of levodopa induced interdose dyskinesias in Parkinson's disease." J Neurol Neurosurg Psychiatry 64(5): 573-576. Cotzias, G. C., P. S. Papavasiliou, et al. (1970). "Similarities between neurologic effects of L-dipa and of apomorphine." N Engl J Med 282(1): 31-33. Deffond, D., F. Durif, et al. (1993). "Apomorphine in treatment of Parkinson's disease: comparison between subcutaneous and sublingual routes." Journal of neurology, neurosurgery, and psychiatry 56(1): 101-103. De Gaspari, D., C. Siri, et al. (2006). "Clinical and neuropsychological follow up at 12 months in patients with complicated Parkinson's disease treated with subcutaneous apomorphine infusion or deep brain stimulation of the subthalamic nucleus." J Neurol Neurosurg Psychiatry 77(4): 450-453. Dewey, R. B., Jr., J. T. Hutton, et al. (2001). "A randomized, double-blind, placebo-controlled trial of subcutaneously injected apomorphine for parkinsonian off-state events." Arch Neurol 58(9): 1385-1392.	

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				Di Rosa, A. E., A. Epifanio, et al. (2003). "Continuous apomorphine infusion and neuropsychiatric disorders: a controlled study in patients with advanced Parkinson's disease." Neurol Sci 24(3): 174-175. Drapier, S., A. S. Gillioz, et al. (2012). "Apomorphine infusion in advanced Parkinson's patients with subthalamic stimulation contraindications." Parkinsonism & related disorders 18(1): 40-44. Elia, A. E., C. Dollenz, et al. (2012). "Motor features and response to oral levodopa in patients with Parkinson's disease under continuous dopaminergic infusion or deep brain stimulation." Eur J Neurol 19(1): 76-83. Ellis, C., G. Lemmens, et al. (1997). "Use of apomorphine in parkinsonian patients with neuropsychiatric complications to oral treatment." Parkinsonism Relat Disord 3(2): 103-107. Frankel, J. P., A. J. Lees, et al. (1990). "Subcutaneous apomorphine in the treatment of Parkinson's disease." J Neurol Neurosurg Psychiatry 53(2): 96-101. Gancher, S. (1995). "Pharmacokinetics of apomorphine in Parkinson's disease." J Neural Transm Suppl 45: 137-141. Gancher, S. T., J. G. Nutt, et al. (1995). "Apomorphine infusional therapy in Parkinson's disease: clinical utility and lack of tolerance." Mov Disord 10(1): 37-43. Garcia Ruiz, P. J., A. Sesar Ignacio, et al. (2008). "Efficacy of long-term continuous subcutaneous apomorphine infusion in advanced Parkinson's disease with motor fluctuations: a multicenter study." Mov Disord 23(8): 1130-1136.	

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				Gervason, C. L., P. R. Pollak, et al. (1993). "Reproducibility of motor effects induced by successive subcutaneous apomorphine injections in Parkinson's disease." Clin Neuropharmacol 16(2): 113-119. Gunzler, S. A., C. Koudelka, et al. (2008). "Effect of low concentrations of apomorphine on parkinsonism in a randomized, placebo-controlled, crossover study." Arch Neurol 65(2): 193-198. Gunzler, S. A., M. Pavel, et al. (2009). "Foot-tapping rate as an objective outcome measure for Parkinson disease clinical trials." Clinical neuropharmacology 32(2): 97-102. Harder, S., H. Baas, et al. (1998). "Dose response and concentration response relationship of apomorphine in patients with Parkinson's disease and end-of-dose akinesia." Int J Clin Pharmacology and Therapeutics 36(7): 355-361 Hardie, R. J., A. J. Lees, et al. (1984). "On-off fluctuations in Parkinson's disease. A clinical and neuropharmacological study." Brain : a journal of neurology 107: 487-506. Hellmann, M. A., T. Sabach, et al. (2008). "Effect of subcutaneous apomorphine on tremor in idiopathic Parkinson's disease." Biomed Pharmacother 62(4): 250-252. Hughes, A. J., S. Bishop, et al. (1993). "Subcutaneous apomorphine in Parkinson's disease: response to chronic administration for up to five years." Mov Disord 8(2): 165-170. Hughes, A. J., A. J. Lees, et al. (1991). "The motor response to sequential apomorphine in parkinsonian fluctuations." Journal of neurology, neurosurgery, and psychiatry 54(4): 358-360.	

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				Hughes, A. J., S. Bishop, et al. (1991). "The motor response to repeated apomorphine administration in Parkinson's disease." Clinical neuropharmacology 14(3): 209-213. Kanovský, P., D. Kubová, et al. (2001). "Levodopa-induced dyskinesias and continuous subcutaneous infusions of apomorphine: results of a two-year, prospective follow-up." Mov Disord. 17(1): 188-191. Katzenschlager, R., A. Hughes, et al. (2005). "Continuous subcutaneous apomorphine therapy improves dyskinesias in Parkinson's disease: a prospective study using single-dose challenges." Mov Disord 20(2): 151-157. Kempster, P. A., J. P. Frankel, et al. (1990). "Comparison of motor response to apomorphine and levodopa in Parkinson's disease." Journal of neurology, neurosurgery, and psychiatry 53(11): 1004-1007. Kreczy-Kleedorfer, B., M. Wagner. et al. (1993, in German). "Long-term results of continuous s.c. apomorphine therapy in patients with advanced Parkinson's disease." Der Nervenarzt 64: 221-225 LeWitt, P. A., W. G. Ondo, et al. (2009). "Open-label study assessment of safety and adverse effects of subcutaneous apomorphine injections in treating "off" episodes in advanced Parkinson disease." Clin Neuropharmacol 32(2): 89-93. Manson, A. J., K. Turner, et al. (2002). "Apomorphine monotherapy in the treatment of refractory motor complications of Parkinson's disease: long-term follow-up study of 64 patients." Mov Disord 17(6): 1235-1241.	

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				Merello, M., R. Pikielny, et al. (1997). "Comparison of subcutaneous apomorphine versus dispersible madopar latency and effect duration in Parkinson's disease patients: a double-blind single-dose study." Clinical neuropharmacology 20(2): 165-167. Morgante, L., G. Basile, et al. (2004). "Continuous apomorphine infusion (CAI) and neuropsychiatric disorders in patients with advanced Parkinson's disease: a follow-up of two years." Arch Gerontol Geriatr Suppl(9): 291-296. Nyholm, D., R. Constantinescu, et al. (2009). "Comparison of apomorphine and levodopa infusions in four patients with Parkinson's disease with symptom fluctuations." Acta Neurol Scand 119(5): 345-348. Ondo, W. G., C. Hunter, et al. (2012). "Apomorphine injections: predictors of initial common adverse events and long term tolerability." Parkinsonism & related disorders 18(5): 619-622. Ostergaard, L., L. Werdelin, et al. (1995). "Pen injected apomorphine against off phenomena in late Parkinson's disease: a double blind, placebo controlled study." J Neurol Neurosurg Psychiatry 58(6): 681-687. Pahwa, R., W. C. Koller, et al. (2007). "Subcutaneous apomorphine in patients with advanced Parkinson's disease: a dose-escalation study with randomized, double-blind, placebo-controlled crossover evaluation of a single dose." J Neurol Sci 258(1-2): 137-143.	

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				Péron, J., I. Biseul, et al. (2010). "Subthalamic Nucleus Stimulation Affects Fear and Sadness. Recognition in Parkinson's Disease." Neuropsychology 24(1): 1–8 Pfeiffer, R. F., L. Gutmann, et al. (2007). "Continued efficacy and safety of subcutaneous apomorphine in patients with advanced Parkinson's disease." Parkinsonism & Relat Disord 13(2): 93-100. Pietz, K., P. Hagell, et al. (1998). "Subcutaneous apomorphine in late stage Parkinson's disease: a long term follow up." J Neurol Neurosurg Psychiatry 65(5): 709-716. Poewe, W., B. Kleedorfer, et al. (1993). "Continuous subcutaneous apomorphine infusions for fluctuating Parkinson's disease. Long-term follow-up in 18 patients." Adv Neurol 60: 656-659. Poewe, W., B. Kleedorfer, et al. (1989). "Side-effects of subcutaneous apomorphine in Parkinson's disease." Lancet 1(8646): 1084-1085. Pollak, P., A. S. Champay, et al. (1990). "Subcutaneous administration of apomorphine in motor fluctuations in Parkinson's disease." Rev Neurol (Paris) 146(2): 116-122. Pollak, P., A. S. Champay, et al. (1989). "Subcutaneous apomorphine in Parkinson's disease." Journal of neurology, neurosurgery, and psychiatry 52(4): 544. Reuter, I., C. M. Ellis, K. R. Chaudhuri (1999). "Nocturnal subcutaneous apomorphine infusion in Parkinson's disease and restless legs syndrome." Acta Neurol Scand 100: 163-167	

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				Stibe CM, Kempster PA, Lees AJ, et al. Subcutaneous apomorphine in parkinsonian on-off oscillations. *Lancet* 1988;331:403-6. Stocchi, F., L. Bramante, et al. (1993). "Apomorphine and lisuride infusion. A comparative chronic study." Advances in neurology 60: 653-655. Stocchi, F., A. Berardelli, et al. (2003): "Apomorphine Infusion and the Long-Duration Response to Levodopa in Advanced Parkinson's Disease." Clinical Neuropharmacology 26(3): 151–155 Stocchi, F., L. Vacca, et al. (2001). "Subcutaneous continuous apomorphine infusion in fluctuating patients with Parkinson's disease: long-term results." Neurol Sci 22(1): 93-94. Trosch, R. M., D. Silver, et al. (2008). "Intermittent subcutaneous apomorphine therapy for 'off' episodes in Parkinson's disease: a 6-month open-label study." CNS Drugs 22(6): 519-527. Tyne, H., J. Parsons, et al. (2004). "A 10 year retrospective audit of long-term apomorphine use in Parkinson's disease." J Neurol 251: 1370–1374 van Laar, T., A. G. Postma, et al. (2010). "Continuous subcutaneous infusion of apomorphine can be used safely in patients with Parkinson's disease and pre-existing visual hallucinations." Parkinsonism & related disorders 16(1): 71-72. van Laar, T., E. N. Jansen, et al. (1993). "A double-blind study of the efficacy of apomorphine and its assessment in 'off'-	

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				periods in Parkinson's disease." Clin Neurol Neurosurg 95(3): 231-235.	
Ever Pharma	Full Version	203	4944	Apomorphine *intermittent injection* should also be included	Thank you for your comment. Intermittent apomorphine injections have now been included as part of this section.
Ever Pharma	Full Version	50	1146	Suggest to change from Apomorphine Challenge to Apomorphine Response Test.	Thank you for your comment. Unfortunately, this statement is taken from a part of the guideline which was not included as part of this update, and therefore no substantive changes can be made.
Ever Pharma	Full Version	69	1697	We feel that Apomorphine *intermittent injections* should be included in this section. Even though the objective would be to reduce the L-Dopa dose, intermittent injections of Apomorphine should still be considered as an adjuvant treatment.	Thank you for your comment. Our evidence review did not identify any evidence matching the review protocol for this question (apomorphine-levodopa versus levodopa monotherapy), and the GDG did not feel it appropriate to make consensus based recommendations that apomorphine should be used as a first-line adjuvant. However, as mentioned in response to a previous comment intermittent apomorphine has now been added to the recommendations for advanced PD. The relevant evidence around apomorphine as an adjunct has now been clarified within the guideline
Ever Pharma	Full Version	79	2006-2016	Suggest to add Apomorphine therapy for wearing-off, and motor fluctuations in late stage PD should be given in this paragraph. This is either as intermittent bolus s.c. injections, or subcutaneous infusions.	Thank you for your comment**.** Our evidence review did not identify any evidence matching the review protocol for this question (apomorphine-levodopa versus levodopa monotherapy), and the GDG did not feel it appropriate to make consensus based recommendations that apomorphine should be used as a first-line adjuvant. However, as mentioned in response to a previous

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					comment intermittent apomorphine has now been added to the recommendations for advanced PD. The relevant evidence around apomorphine as an adjunct has now been clarified within the guideline.
Ever Pharma	Full Version	General	General	In the original scope for the PD Guidelines Update, it was specified to consider Apomorphine in *both* Intermittent injection *and* continuous sc infusion. The draft guideline seems only to mention continuous infusion, hence we recommend that intermittent injection is specified and also some clarity given on patient suitability and stage of disease etc.	Thank you for your comment. The recommendation around apomorphine use has now been updated to refer to both injections and infusions. Unfortunately, in the absence of robust evidence, the GDG did not feel it possible to make specific recommendations about patient suitability.
Ever Pharma	Short Version	18	19	Suggest to retitle as Advanced therapies including DBS, LCIG and Apomorphine, both *intermittent injection* and *continuous sc infusion*	Thank you for your comment. A reference to intermittent apomorphine injections has now been added to this section, in line with the suggestion made.
Ever Pharma	Short Version	18	23	Apomorphine *intermittent injection* should also be included	Thank you for your comment. A reference to intermittent apomorphine injections has now been added to this section, in line with the suggestion made.
Ever Pharma	Short Version	3	11	Suggest to retitle as Advanced therapies including DBS, LCIG and Apomorphine, both *intermittent injection* and *continuous sc infusion*	Thank you for your comment. A reference to intermittent apomorphine injections has now been added to this section, in line with the suggestion made. However, the primary focus of the modelling work undertaken in this question was on the cost-effectiveness of DBS and duodopa, and therefore this title for the section has been retained.
Ever Pharma	Short	8	15	We feel that Apomorphine *intermittent injections* should be included in this section. Even though the objective would be to reduce the L-Dopa dose,	Thank you for your comment. The GDG discussed this issue, but agreed that apomorphine was unlikely to be used as a first-line adjuvant to levodopa for people with

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	Version			intermittent injections of Apomorphine should still be considered as an adjuvant treatment.	Parkinson's disease, and therefore the appropriate place to refer to it was in the section on advanced therapies.
Ever Pharma	Short Version	General	General	In the original scope for the PD Guidelines Update, it was specified to consider Apomorphine in *both* Intermittent injection *and* continuous sc infusion. The draft guideline seems only to mention continuous infusion, hence we recommend that intermittent injection is specified and also some clarity given on patient suitability and stage of disease etc.	Thank you for your comment. A reference to intermittent apomorphine injections has now been added to this section, in line with the suggestion made.
Global Kinetics Corporation	General	General	General	Dear Sir I write regarding the draft Parkinson's disease in adults: diagnosis and management, NICE guideline methods, evidence and recommendations. Our organisation broadly agrees with the comprehensive guidelines presented. However, our company feels that the guidelines regrettably do not recognise continuous objective measurement in Parkinson's disease management. Thousands of people with Parkinson's have experienced the PKG, clinicians need guidance on how and when continuous objective measurement should be used and the demonstrated benefits of adding continuous objective measurement to routine clinical care. Previously, it had been demonstrated that there is a significant unmet need for objective measures of dyskinesia and bradykinesia of Parkinson's disease that are continuous throughout the day and related to levodopa dosing . Other monitoring methods, such as patient diaries and histories are not always valid and reliable , clinical rating scales and clinical assessment do not allow for continuous, quantitative assessments over a period and thus are not truly reflective of a patient's functional status. We note that patient recorded diaries can be useful in determining the change in motor symptoms, particularly that which occurs after dosing with medication. However, each of these clinical ratings has limitations regarding inter-rater variability and continuous monitoring. The use of self-administered	Thank you for your comment. Unfortunately, the issues raised fall outside the scope of the guideline update that was undertaken, and therefore it was not possible to make recommendations on these issues. However, this does not in any way preclude them from being included in future updates of the guidance if there is evidence showing they improve patient outcomes.

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				scales such as a home diary heavily relies on the accuracy of completion and is therefore associated with a large recall bias and diary fatigue, this is particularly applicable in patients with cognitive dysfunction or depression , . These subjective measurement methods do not accurately correlate with medication timing, or bradykinesia and dyskinesia, they provide a limited aid for clinicians to use to educate their patients about motor symptoms and the control of these through their medication. Therefore, there is a need for a monitoring method which is, objective (with good inter-reliability between clinicians), quantitative, technically reliable, non-intrusive and therefore reflective of the patient's typical status/condition, able to actively involve the patient and easy for the patient to be compliant with. This would provide a continuous measure over several days of the frequency and severity of a patient's motor symptoms and motor complications, the effect of therapeutic intervention and treatment compliance. There is a clear need for continuous objective measures of dyskinesia and bradykinesia while patients go about their normal daily activities. A good objective measurement would allow the clinician to treat patients knowing the frequency and severity of a patient's motor symptoms and complications and the effect of therapeutic intervention and treatment compliance8. Indeed, we believe that it is important the revised guidelines reflect what Maetzler et al (2013) describes as a rapidly growing interest in the quantitative assessment of Parkinson's disease associated signs and disability using wearable technology. Maetzler et al state that both persons with Parkinson's disease and their clinicians see advantages in such developments. Specifically, quantitative assessments using wearable technology that may allow for continuous, unobtrusive, objective, and ecologically valid data collection. Also, this approach may improve patient-doctor interaction, influence therapeutic decisions, and ultimately ameliorate	

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				patients' global health status. In addition, such measures have the potential to be used as outcome parameters in clinical trials, allowing for frequent assessments; e.g., in the home setting. One continuous objective measurement device, the Parkinson's KinetiGraph data logger (PKG), is currently being used successfully in routine clinical care, thousands of people with Parkinson's have experienced the PKG. It is designed to monitor the frequency and severity of motor symptoms and correlate these with the timing of levodopa medication. The Parkinson's KinetiGraph is a means of objectively measuring motor symptoms of Parkinson's patients in their own home. It consists of a report derived from data recorded by a data logger. The data logger is worn on the wrist (like a watch) continuously over 10 days during the activities of daily living. For most patients, the PKG Data Logger is mailed to the patient and the recording is managed remotely by the clinician. The data collected is analysed by GKC and converted into bradykinesia and dyskinesia scores to provide a report detailing an objective assessment of their frequency and severity. The Parkinson's KinetiGraph provides a valuable method of objective monitoring of motor complications and can be utilised to optimise the treatment of patients with Parkinson's or to identify patients with more advanced disease who are potential candidates for more invasive therapies. Validation studies performed with PKG have concluded that PKG algorithms can be used as objective, continuous, quantitative measures of severity and proportion of time spent in bradykinesia or dyskinesia and the temporal correlation of the motor fluctuations with timing of medications1, . The research conducted by Griffiths et al (2012) concluded that the PKG algorithm provides objective, continuous and automated assessment of the clinical features of bradykinesia and dyskinesia in Parkinson's disease1.	

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				Moreover, it was proven that PKG can be useful tool in identifying and measuring daytime sleep and impulsive-compulsive behaviour . Optimisation of the treatment regimen through effective monitoring with objective measurement can be beneficial for both the healthcare system and patients, their families and carers. Optimised treatment leads to improved motor control, thus potentially reducing the utilisation of healthcare resources (e.g. number of hospital admissions) and improved health-related quality of life for patients. Early clinical utility evidence has shown that adding the PKG to routine clinical care changes Parkinson's clinician's clinical decision making and can improve patient outcomes based on those modified decisions , , , . Two studies have noted that clinician's treatment decisions were changed by the PKG up to 50% of the time when using the PKG in routine clinical care13,14,15. Also, one study showed clinically and statistically significant changes in UPDRS III and UPDRS total scores13,14. Lower UPDRS scores are associated with less overall patient costs. From the view point of hospital budget and optimising workload on the medical staff, the Parkinson's KinetiGraph possesses several important advantages. It impacts the routine clinical practice of management of Parkinson's disease patients by reducing length of their hospital stay and annual number of hospitalisations, shortening duration of out-patient visits, transmitting the workload from highly paid physicians to less costly nurses, as such leading to substantial budget savings. Additionally, Parkinson's KinetiGraph can be a supportive tool while deciding on eligibility of a patient for a high-cost advanced treatment and provide extra justification of this decision for the payers. As Ossig et al (2016) conclude there is an interest to collect objective and ecologically relevant data to evaluate therapeutic effects and to rate disease	

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				severity. Wearable technical devices can provide potentially relevant, factual, accurate and continuous health data that are less open to subjective interpretation. Ultimately, such techniques will help to overcome the drawbacks that are inherent to single or multiple "snapshot" assessments in current clinical practice and clinically oriented research. We are disappointed that NICE have chosen not to include continuous objective measurement or indeed the Parkinson's Kinetigraph as part of the draft guidelines. We would welcome the opportunity for you to include objective measurement in future iterations of the guidelines for Parkinson's disease in adults.	
Hillingdon Hospital NHS Trust	Full	204	4949-4950	If class 1 evidence is important in deciding what treatment to recommend as the panel has been exhorting, why is apomorphine, which lacks such evidence, recommended instead of Duodopa? I acknowledge that Duodopa cost per QALY is high, but every PD specialists will recognise a cohort of advanced PD patients where DBS is not suitable and apomorphine is not tolerated, but where Duodopa can significantly improve their motor fluctuations. To impose a blanket ban on its use will set back management of advanced PD by a decade, and deprive patients with severe motor fluctuations a very useful avenue of treatment. With its relatively high costs, some sort of restrictions may be required but a blanket ban is completely unhelpful.	Thank you for your comment. The recommendation that apomorphine should be considered as part of BMT was a result of its inclusion in the BMT (and DBS) arm of the PDSURG trial. The GDG acknowledged that this was not ideal, but had no way of unpicking the contribution that apomorphine infusions made to the effects observed in the trial; the group's consideration of the issue is discussed in detail in 10.3.7. For comments on the effectiveness and cost effectiveness of LCIG, please see **theme 1**. For comments on the effectiveness and cost effectiveness of LCIG in subgroups of people with advanced Parkinson's disease, please see **theme 1b**.
Hillingdon Hospital NHS Trust	Full	80	2021	Lack of randomised controlled trial evidence of efficacy does not necessarily mean lack of efficacy. There are several uncontrolled studies supporting the effectiveness of Amantadine as adjunctive treatment in PD. The vast majority	Thank you for your comment. After discussion of the consultation responses the GDG agreed that, whilst there was no evidence for the routine use of amantadine as an

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				of PD specialists will recognise a role of the medication in treating dyskinesias in PD. To completely exclude its use deprives PD patients of a useful drug to treat dyskinesias. ADS-5102 (albeit is an extended release preparation of Amantadine) does improve dyskinesia in PD in a randomised controlled study [Mov Disord. 2015; 30(6): 789-95]. There is no reason why standard release will not do so. One analogy I can see is with Tetrabenazine. European neurologists have long recognised its role in treating chorea in Huntington's disease, but it is not used in the US because of lack of class 1 evidence. The recently completed class 1 trial in US merely confirms what everyone has known for years.	adjuvant treatment, it did have a role as a specific option for the treatment of dyskinesia. Therefore, a new recommendation has been added to this section to support the use of amantadine in this context.
Hillingdon Hospital NHS Trust	Full	97	2354-2356	Following on from my previous comment, if Amantadine has insufficient evidence of its efficacy in PD, how is Midodrine which has next to zero evidence in treating orthostatic hypotension in PD, be recommended as the first line treatment? It is hard to obtain a supply for most patients and poorly tolerated, unlike Fludrocortisone. How is it recommended ahead of Fludrocortisone if there is absence of evidence for both? There is much greater experience for most clinicians in using Fludrocortisone. This recommendation, along with the other ones I am commenting here, seems to ignore some real-life practice and patient experiences.	Thank you for your comment. We hope that this seeming contradiction has been addressed by the fact that a recommendation has now been added to support the use of amantadine to treat dyskinesia. We agree that there is no PD specific RCT evidence for midodrine, but note that the evidence for fludrocortisone is also limited (one RCT of 17 people not showing a difference between it and domperidone). According to the NICE guidelines manual, off-label use may only be recommended if the clinical need cannot be met by a licensed product and there is sufficient evidence and/or experience of using the medicine to demonstrate its safety and efficacy to support this.In the absence of good evidence, the GDG therefore decided to recommend the licensed drug (midodrine) ahead of an unlicensed one (fludrocortisone), but felt it important that a caveat be added that in people in whom midodrine is contraindicated, fludrocortisone is an appropriate first-line treatment.

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Imperial College Healthcare NHS Trust	Full	204	4949	Recommendation 79- Do not offer levodopa–carbidopa intestinal gel…. We have grave concerns about the wording of this &the potential complete withdrawal of this option of therapy for advanced PD. Yes, it is costly but so are multiple hospitalisations and care packages for this vulnerable group – which is the main alternative. This patient group is broadly different to those offered surgery in PD. It is a small group who may benefit hugely from this treatment option in enabling them to remain independent & physically able despite a long PD disease duration. Again the wording here used here is destructive and it appears a backward step in world health care to be withdrawing a viable alternative way of administering what remains the gold standard treatment for PD, levodopa. • If however , this statement remains, then some clear guidance would be needed on how to manage 1. patients already on duodopa treatment – ie a statement that allows continued access, & 2 . patients who fail apomorphine & are not suitable for DBS	Thank you for your comment. For comments on the effectiveness and cost effectiveness of LCIG, please see **theme 1**. For comments on the effectiveness and cost effectiveness of LCIG in subgroups of people with advanced Parkinson's disease, please see **theme 1b**. For comments on the paucity of therapeutic options for people with advanced Parkinson's disease, please see **theme 1e**.
Imperial College Healthcare NHS Trust	Full	118	2753	In the absence of trial evidence, and any reported comparative experience by the GDG with Glycopyrronium bromide in Parkinson's, versus other agents of this class, it would be better to avoid recommending this drug specifically. In addition, this is again an off licence recommendation and so will no doubt require a hospital prescription, therefore having practical implications on patient accessibility to this agent and hospital drug budgets. The literature suggests that Glycopyrrolate is only effective for a short period (a week or so) and in our experience (and in the literature)	Thank you for your comment. Whilst it is true that the evidence for this question was derived from a broader patient population, the evidence base does include trials in people with idiopathic Parkinson's disease, and there is a trial of glycopyrrolate in this group. The GDG acknowledged that there are issues of cost and access with both of these treatment options. However, they felt that since they represented the two alternatives with proven efficacy in RCTs, it was appropriate they be recommended as treatment options for this population,

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				Botulinum Toxin injections help only 50-60% of patients, with the potential for facial paralysis and swallowing impairment. There is a limited resource capacity of clinicians undertaking injections for sialorrhoea and if Botulinum Tox. becomes a mainstay for treatment of sialorrhoea , these patients will need to come back every 3-5 months. The cost of the drug is approx. £250 per vial. Mov Disord. 2011 Oct; 26(0 3): S42–S80.	with botulinum toxin restricted to a second-line setting (in part, because of the cost considerations highlighted in this comment). Both recommendations were kept at the "consider" level to acknowledge that the evidence base behind them is not overwhelmingly strong.
Imperial College Healthcare NHS Trust	Full	138	3248	56. Offer a cholinesterase inhibitorg for people with mild or moderate Parkinson's disease dementia. [new 2017] 57. Consider a cholinesterase inhibitorh for people with severe Parkinson's disease dementia. [new 2017] 58. Consider memantinei for people with Parkinson's disease dementia, only if cholinesterase in hibitors are not tolerated or are contraindicated All now available as generics – so prices are brand specific- but cheapest of the generic brands is currently donepezil. Can be prescribed on FP10 & by GP but only when written in line with eg NICE guidance on Alzheimers . This is obviously a challenge both for hospitals, in terms of managing the prescriptions & for patients in terms of travelling to collect the drug. Not licensed specifically in PD so again a statement needed that GPs can prescribe if NICE are recommending in this group	Thank you for your comments. NICE has specific footnotes which are appended to all recommendations for the use of medicines outside of their licensed indications, which set out the specifics of how they should be used. The GDG were not aware of any reasons why these particular recommendations would be more complex to implement than others relating to the using of medicines outside of their licensed indications.

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Imperial College Healthcare NHS Trust	Full	223	5464	It is suggested that the cognitive behavioural therapy should be used for patients with impulse control disorders. It is not practical to state this due to lack of availability and expertise. We are unaware of anyone who does CBT with ICD (or even PD) experience outside of the London team who conducted the study. A more sensible recommendation would be to have 'supportive talk therapy' (which people can interpret themselves about what and how to offer and PDNS are very able to do this) to address issues of insight, behaviour change and non-pharmacological strategies to manage the condition.	Thank you for your comment. The GDG agreed that there are difficulties accessing this service in many areas, but noted that it was shown to be effective where available and hope that the recommendations will lead to the service becoming more available. They did not feel it appropriate to recommend an alternative intervention were evidence of effectiveness has not been shown.
Imperial College Healthcare NHS Trust	Full	230	5651	87. Give people with Parkinson's disease and their family members and carers oral and written information about the following, and record that the discussion has taken place: The use of the word 'Give' is not ideal. People need to choose the time when they want to receive all this kind of information. The wording for 86 is better – 'Offer'. Our (palliative care specialists) job is to make them aware that this sort of information is available and that we are open to discussing advance care planning, when the time is right. Sometimes though, with the patient's permission, it is the family/carer that needs this discussion the most. The long term side effects of the PD medications, I would have thought should come under discussion of treatment options anyway. Doesn't seem to fit well in to this part of the guidance. Again, 'available support services' could come in at a different part of the guidance, perhaps, as they are not inevitably linked to dying discussions. As you know, the AHPs tend to get involved far earlier that we do.	Thank you for your comment. The GDG agree with your comment (changing the word "give" to "offer") and have therefore made the suggested change to the recommendation. The GDG believes that discussing the long-term side effects of PD medications at the end of life is part of palliative care. Patients need to made aware of what the consequences are of withdrawing PD medication at the end of life and also when and if this may happen. The recommendation has been altered to make clear this was the focus of the comment around medicines.

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Imperial College Healthcare NHS Trust	Full	80	2019	Recommendation 30 – Do not offer anticholinergics…. This wording is dogmatic and misleading. Written in this way may lead to confusion with patients, commissioners & and prescribers. There is good evidence that Anticholinergics have a role in PD management (*Movement Disorders* Vol. 17, Suppl. 4, 2002, p. S7-S12)	Thank you for your comment. The GDG acknowledged that there may be specific circumstances where anticholinergics are a useful option, but this does not apply to the average person with PD (the target of guideline recommendations). In addition, because no evidence (from RCTs) was identified for anticholinergics, together with the known adverse effects, the GDG agreed that a "do not" recommendation was justified. The GDG also noted that the particular cases identified where anticholinergics may be useful (e.g. very young people with dystonia) were highly likely to be already under the care of experienced clinicians, who would be aware of this as a treatment option. In addition, thank you for highlighting the reference by the Movement Disorder Society. In the agreed protocol for this particular topic, only systematic review and/or RCT evidence were of interest. Unfortunately, the Movement Disorder Society's paper is an editorial, it does therefore not meet the inclusion criteria for this particular review as set out in the review protocol.
Imperial College Healthcare NHS Trust	Full	80	2021	Recommendation 31- Do not offer Amantadine….. This wording is dogmatic and misleading. Written in this way may lead to confusion with patients, commissioners & and prescribers.	Thank you for your comment. After discussion of the consultation responses the GDG agreed that, whilst there was no evidence for the routine use of amantadine as an adjuvant treatment, it did have a role as a specific option for the treatment of dyskinesia. Therefore, a new

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				There is good evidence that Amantadine has a role in PD management, particularly in the management of dyskinesias where little else is currently on offer as treatment. *(Movement Disorders* Vol. 17, Suppl. 4, 2002, p. S13-S22)	recommendation has been added to this section to support the use of amantadine in this context.
Imperial College Healthcare NHS Trust	Full	97	2354	The text states that "The GDG were not confident that it [midodrine] clearly represents the optimal choice for people with OH and Parkinson's disease." Accordingly, the conclusion that midodrine is the first line choice in the recommendation is not justified. In addition, this recommendation has practical implications on patient accessibility and hospital prescribing budgets. As it is off-licence it is predominantly a hospital based prescription – which is costly & makes it awkward for patients to renew. Mov Disord. 2011 Oct; 26(0 3): S42–S80.	Thank you for your comment. According to the NICE guidelines manual, off-label use may only be recommended if the clinical need cannot be met by a licensed product and there is sufficient evidence and/or experience of using the medicine to demonstrate its safety and efficacy to support this. In the absence of good evidence, the GDG therefore decided to recommend the licensed drug (midodrine) ahead of an unlicensed one (fludrocortisone), but felt it important that a caveat be added that in people in whom midodrine is contraindicated, fludrocortisone is an appropriate first-line treatment.
Kings College Hospital NHS Foundation Trust	Full Health Economic Report	F2.1.3		At Kings, we have been using Intrajejunal levodopa infusion (IJLI) since 2007 and have the largest cohort in the UK and we are deeply concerned at some of the analytical approaches used not to recommend this treatment which benefits a large number of people with Parkinson's. 1. The GDG recommends using UK based cohorts whenever possible. Yet they ignore 2 major comparative although UK based patient studies which were independently performed and not Industry funded. They rely on a small study from Sweden by Nyholm et al of 8 patients with considerable flaws in design and administration of IJLI, Also they	Thank you for your comment. The cost–utility analysis mentioned in F2.1.3 that relies on Nyholm et al.'s small study was not the original model developed for this guideline; rather it was the model funded by the manufacturer of LCIG (Lowin et al. 2011), which includes a clinician from Kings College Hospital among its authorship. We criticise the authors of this paper for choosing to rely on this low-quality evidence.

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	Appendix F			use the Slevin study for data capture yet do not use data from an international registry (GLORIA) with 2 years FU data published by Antonini et al (2015) These are discussed below: Reddy et al. Clin Neuropharm 2012;35: 205-207. 17 patients in London were started on IJLY based on clinical decision and compared to a matched group on "best medical therapy" followed up at 6 months. Effect size of intervention was carried out using the methods of : Deyo RA, Centor RM. J Chronic Dis 1986;39:897-906 and Wyrwich KW, Bullinger, M, Aaronson N, et al. Qual Life Res 2005;14:285Y295. IJLI showed a large effect size (>0.8) on motor UPDRS 3 (1.13), motor complications (1.52), and importantly quality of life (1.12) and non-motor symptoms, a key determinant of quality of life (0.82). Martinez-Martin et al. Movement Disorders 2015; 30: 510-516. This was an UK led multicentre European study of open label comparison of a matched group of PD patients with IJLI (n=43), and apomorphine infusion (n=43). At 6 months follow up IJLI showed a similar large effect size on UPDRS 3 (1), UPDRS 4 (1.69), Quality of life (1.14) and non motor scale total score (0.83). We also calculated the (NNT) for obtaining 1 patient improving the threshold or more for each outcome variable of interest. The selected threshold was 1/2SDBaseline, and is one of the most widely used benchmarks for interpretation of change, related to the minimal important difference and the effect size. This was1.52 for quality of life as judged by PDQ 8 scores.	For the reasons stated in **theme 4**, the GDG believed that, in estimating the effectiveness of LCIG compared with BMT, primary reliance should be placed on the high-quality RCT reported by Olanow et al. (2014). Therefore, little benefit could be drawn from the observational studies cited here (and, in the case of Reddy et al., 2012, few of the outcome measures of interest for our original model are reported) It is unclear which source of evidence the stakeholder has in mind in suggesting that the GDG relied on study with a sample size of 24. It is possible this is a reference to Nyholm et al.'s crossover RCT (2005). As detailed in Appendix G, this was excluded from consideration for this guideline because it did not consider PEG-delivered LCIG; rather, it was a study of nasojejunal delivery, which is neither licensed nor practical for long-term use. One included cost–utlity analysis relied on this source for its effect estimates (Kristiansen et al., 2009); again, we criticise the authors for this choice. The GLORIA case series has not, to our knowledge, reported 24-month results yet (Antonini et al.'s 2015 publication is limited to 12 months' follow-up).

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				In spite the data is excluded on the basis of "Considered against data requirements of original health economic model, but EXCLUDED as more robust sources of health-related quality of life data, with longer follow-up were available " (appendix M) However, the authors accept Nyhom data and other 6 months FU data even from studies with a sample size of 8 or 24. Finally "real life" data incuding UK patients have been published in the GLORIA , Levodopa-Carbidopa Intestinal Gel in Routine Care of Advanced Parkinson's Disease Patients, had 375 patients with 258 completed (Antonini et al. Park Rel Disord 2015). A consistent and significant improvement in Quality of life ($p<0.001$) as well as off hours per day were seen at 24 months . As authors in these peer reviewed papers in high quality journals, we are at a loss to understand the rationale behind the analysis provided by the GDG which seems selective, biased and prone to neglect UK based data as well as large scale 24 months real life follow up data. PDQ 8 and quality of life data is shown in all these studies ranging from 6 months to 24 months follow up.	
Kings College Hospital NHS Foundation Trust	Full Health Economic Report	F2.1.3		The GDG ignores the favourable report of the SMC which took into account the dataset from the Reddy et al, Paper quoted above.	Thank you for your comment. For comments on apparent discrepancies between NICE's conclusions on LCIG and SMC advice, please see **theme 9c**.

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Kings College Hospital NHS Foundation Trust	Full Health Economic Report Appendix F	P15	F3.1.3 Table 5 Line 1	The authors use the PINE data with a mean age of 75.6 years. They ignore other cohorts such as DeNoPa, Parkwest, Icicle. The mean age of subjects in the Reddy study(quoted above) was 57.82 ±7.71 while in the Euroinf study (Martinez-Martin et al, quoted above) was 62.7±9.1. The PINE data therefore is likely to be biased towards increased attrition in modelling when IJLI is normally used in a substantially younger population as in the UK . WE also have concerns in extrapolating DBS data to a population suitable for IJLI as this is not the case.	Thank you for your comment. We did not have access to patient-level data from the other cohorts mentioned. Age was controlled for in all relevant analyses. In the particular case of expected survival, the model's base-case function was drawn from PDSURG data (mean age 59); see Appendix F.3.1.10. Alternative approaches to modelling survival were tested in sensitivity analysis, and showed no material impact on results. For comments on the appropriateness of the decision problems addressed in the review questions on treatment for advanced Parkinson's disease, please see **theme 3**.
Kings College Hospital NHS Foundation Trust	P 34 Full Health Economic Report	P34	Table 26 Line 1	The GDG cost " LCIG resource use covered the naso-testing phase" and cost this at Weighted average unit cost of £858.76 However, many centres, such as here at Kings Parkinson's centre of excellence, naso testing or nasoduodenal test is NOT performed A presentation from clinicians involved in IJLI therapy delivery (such as we believe was obtained for DBS therapy) could have explained the current IJLI pathway clearly to the GDG.	Thank you for your comment. As described in Appendix F.3.1.11, nasoduodenal testing was assumed to take place in 25% of cases, reflecting the GDG's knowledge that many centres omit this step. If we assume that nasoduodenal testing is performed in 0% of cases, the ICER for LCIG -v- BMT becomes £399,895 / QALY. For comments on the role of expert witnesses, please see **theme 2**.

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Kings College Hospital NHS Foundation Trust	Short version of draft guideline	1.8.4 P 19	4	The advise " Do not offer levodopa–carbidopa intestinal gel at any stage of Parkinson's 5 disease. " is damaging and challenging to many of us in the frontline delivering this therapy for the following reasons: 1. It deprives patients of a levodopa based therapeutic option when DBS is not suitable and apomorphine is not tolerated or there is needlephobia. What are we supposed to do with these patients in whom clearly "best medical therapy" is not appropriate and no longer effective?. 2. At Kings, we have a duodopa cohort with some patients coming up to 8 years of successful treatment. One such patient is still working while another was still able to perform and European concert tour while on duodopa while being housebound before. We have seen no neuropathy or no major side effects in a cohort of currently existing 20 patients when supported by a dedicated multi speciality service. 3. It takes away any major role of tertiary services, if even these services are unable to provide a therapy commonly available across Europe. We would be happy to submit our long term experience and data (most of which has been published in peer reviewed journals) in the NICE shared learning database including personal testimonies from caregivers who have been able to return to work after IJLI has been initiated in some of our cases.	Thank you for your comment. For comments on the effectiveness and cost effectiveness of LCIG, please see **theme 1**. For comments on the paucity of therapeutic options for people with advanced Parkinson's disease, please see **theme 1e**. We note the evidence submitted by King's in response to our call for evidence, which included some of the data referred to in this comment. Unfortunately, as detailed in Appendix M, none of these data met our stated inclusion criteria. As described in Appendix F.3.1.11, nasoduodenal testing was assumed to take place in 25% of cases, reflecting the GDG's knowledge that many centres omit this step. If we assume that nasoduodenal testing is performed in 0% of cases, the ICER for LCIG -v- BMT becomes £399,895 / QALY.

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				4. We would also like to point out that nasoduodenal testing is not routinely performed and in fact not at all at our centre thus reducing costs. We would recommend that the committee reconsiders this recommendation and considers IJLI to be available for use at suitably equipped and specialist centres with obligatory motor, non motor and quality life outcome data as well as validated patient related outcome data to be provided every year .	
Max Appeal	Short		22 -6	Context - 22q1.2 Deletion Syndrome (DS) is a frequent genetic condition, now estimated as (1:500) and vastly underdiagnosed. Although as yet there are few studies of neurodegenerative disorders in 22q11.2 DS, it is recognised there is evidence of early onset Parkinson Disease. Reference; Practical guidelines for managing adults with 22q11.2 deletion syndrome. http://www.maxappeal.org.uk/downloads/22q_adults.pdf	Thank you for providing us with this information.
Medicines and Technologies programme	short	10	21	Rec 1.4.6 suggests that a specialist should be consulted for advice on managing problematic impulse control disorder, is rec 1.4.8 for prescribers managing 'non-problematic' impulse control disorder? This needs to be clear as it comes across that advice needs to be sought from the specialist (rec1.4.6) but then there is a rec on how to manage it (rec1.4.8).	Thank you for your comment. Recommendation 1.4.8 is aimed at both specialists managing ICDs and non-specialists doing the same (either if they are not seen as problematic or if advice from a specialist professional is not available in the time frame needed). The GDG therefore agreed the recommendation needed to be left non-specific so it was able to cover these different situations.
Medicines and Technologie	short	11	4	Rec 1.4.8 Would this rec apply if the person with PD was only on monotherapy with a dopamine agonist with no levodopa therapy? Does this need to be made clearer in the rec?	Thank you for your comment. Yes the recommendation would apply to people who are on DA monotherapy as well and we have amended the recommendation to reflect this. It now reads "(1.4.8) When managing impulse control

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s programme					disorders, modify dopaminergic therapy by first gradually reducing any dopamine agonist. Monitor whether the impulse control disorder improves and whether the person has any symptoms of dopamine agonist withdrawal".
Medicines and Technologies programme	short	24	15	Research rec on psychotic symptoms looks at the use of rivastigmine which is currently unlicensed for this indication and this needs to be highlighted in the text with a footnote, similar to what you have done with other off-label/unlicensed use of medicines in the guideline recs.	Thank you for your comment, this footnote has now been added.
Medicines and Technologies programme	short	24	2-4	Research rec on orthostatic hypotension includes looking into the medicines pyridostigmine, ephedrine and pseudoephedrine. All 3 medicines are currently unlicensed for this indication and this needs to be highlighted in the text with a footnote, similar to what you have done with other off-label/unlicensed use of medicines in the guideline recs.	Thank you for your comment, this footnote has now been added.
Medicines and Technologies programme	short	30/31	Rec 1.6.1.3	I could find no replacement for this recommendation in the guideline update. This is an important part of managing PD as the medicines are time sensitive and need to be given at the right time in order to manage symptoms of the condition and to continue on with daily activities. A national patient safety alert was issued in 2010 'Reducing harm from omitted and delayed medicines in hospital' and this report included medicines for PD as being critical medicines where timeliness of administration is crucial. This is embedded in practice now, however it is still important to highlight this as part of the medicines optimisation agenda to ensure optimal use of medicines for PD.	Thank you for your comment. After consideration, the GDG has agreed to carry forward recommendations 1.6.1.1-1.6.1.3 around drug administration forward to the new guideline. Recommendation 1.6.1.4 has not been brought forward as this has been updated in the section on impulse control disorders.
Medicines and Technologie	short	9 and 10	11 and 17	Recs 1.4.1 and 1.4.5	Thank you for your comment. The GDG agreed these two recommendations were making the same point and accordingly one of them has been deleted from the guideline.

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s programme				Rec 1.4.1 already informs the user about impulse control disorders developing in people with PD on dopaminergic therapy, is rec 1.4.5 also needed as its saying the same thing and has the same impact?	
Medicines and Technologies programme	short	general		There are many terms in the guideline recs such as impulse control disorders, wearing off, dopaminergic therapy, problematic impulse control disorders, REM sleep behaviour disorder, nocturnal akinesia, etc – it would be helpful to have a glossary to briefly outline what these mean. Specialists in PD will of course be familiar with these terms however for specialists in other areas, general prescribers, or health and social care practitioners, having terms defined would help with understanding the rec so that it can partly help with implementation of them in practice.	Thank you for your comment. The GDG discussed whether a glossary for the guideline would be useful, but agreed that there were sufficient sources of information available to define these terms that it would be unlikely to add anything substantive. Where terms have been used in a non-standard way in the guideline, these have been defined in the relevant place within the guideline.
Medtronic Limited	Appendix G	63		Appendix G does not list the excluded studies from the evidence review of DBS, LCIG and BMT. For transparency of this document we would ask that these excluded studies be listed here.	Thank you for your comment. This excluded studies table was mistakenly omitted and has now been added to the relevant appendix.
Medtronic Limited	Full	186	4487-91	We note that the GDG acknowledges that the clinical and cost-effectiveness of apomorphine is not established (page 201), and understand that the GDG defined BMT as potentially including apomorphine on the basis of the PD SURG trial. However, the statements on apomorphine effectiveness and cost in the introduction to the section on "advanced therapies" (see below) indicate to the reader that these were in fact established, without providing any references. Line 4487: "Apomorphine is also an effective treatment for Parkinson's Disease". Line 4490-91: "The cost of subcutaneous apomorphine is considerably less than the other two advanced therapies."	Thank you for your comment. This section of the guideline is part of a clinical introduction, setting out the a priori views of the GDG/clinical community, rather than specifically making evidence based statements/recommendations. However, we agree that the first statement referenced was overly strongly phrased, and this has therefore been amended to clarify that it is a clinical view, rather than an evidence based statement. With regards to the second point, justification can be obtained either from the list prices of the treatments (where available), or the data collected as part of the

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				We would ask the GDG to adequately reflect the evidence available when making statements on its effectiveness and cost, with provision of references and rewording to reflect the uncertainty in these parameters.	economic model and summarised in Appendix F, and therefore the GDG believe it is appropriate that this comment should remain.
Medtronic Limited	Full	203	4943-44	In line with proposed wording change above for recommendation 78, we propose the consistent reflection of this proposed change to replace "later stages" with "advanced disease" also for recommendation 76, as follows: Proposed Wording 76. Offer people with advanced Parkinson's disease best medical therapy, which may include continuous subcutaneous apomorphine infusion. [new 2017]	Thank you for your comment. This recommendation has been edited in line with the suggestion made.
Medtronic Limited	Full	203	4945-46	In line with proposed wording change above for recommendation 78, we propose the consistent reflection of this proposed change to add "adequately" to "controlled by best medical therapy" also for recommendation 77, as follows: Proposed wording: 77. Do not offer deep brain stimulation to people whose Parkinson's disease is adequately controlled by best medical therapy. [new 2017]	Thank you for your comment. This recommendation has been edited in line with the suggestion made.
Medtronic Limited	Full	203	4947-48	We respectfully propose the following 3 changes to the wording of recommendation 78 (underlined in the rephrased recommendations below): Proposed Wording 78. Consider deep brain stimulation for people with advanced Parkinson's disease whose motor complications are not adequately controlled by best medical therapy.	Thank you for your comments. After further consideration, the GDG has decided to amend the recommendation to read: "Consider deep brain stimulation for people with advanced Parkinson's disease whose symptoms are not adequately controlled by best medical therapy"

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				1. We suggest to replace the phrase "later stages of PD" with "advanced PD", consistent with wording in heading 10 "advanced therapies" and the evidence review section 10.3. based on the following rationale: "Advanced PD" is the terminology commonly used to describe the eligible DBS population within the four DBS RCTs informing these recommendations (Deuschl 2006, Weaver 2009, Williams 2010, Okun 2012), whereas "later stages of PD" is not used. We believe "advanced PD" may more adequately reflect the complexity of PD, with increasing duration of disease, worsening of motor (and non-motor) symptoms and the occurrence of motor complications associated with medical therapy. "Later stages" of PD suggests emphasis mainly on time/duration with PD which is generally insufficient as an indicator for DBS. In addition, the emphasis of "later stages" under the heading of "advanced PD" may potentially be misunderstood as referring to "later in advanced PD", ie end stage PD. However, patients in the later stages in advanced PD are more likely to not be eligible for DBS given the increasing likelihood of moderate to severe cognitive impairment or dementia which is a contraindication for treatment with DBS. 2. Furthermore we would suggest including wording that more clearly indicates when to consider DBS. We propose to expand on "symptoms" in recommendation 78 to reflect symptoms that indicate when DBS should be considered, namely when motor complications (such as dyskinesias and/or motor fluctuations) are present.	We hope this addresses the concerns raised under point 1 and point 3. Concerning point 2, the GDG agreed that DBS was likely to be made available only through specialist commissioning policies, and that these policies would specify the appropriate groups of people for surgery, and therefore it was not necessary to include this as part of the guideline.

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				The rationale for this proposal is reflected in the patient inclusion criteria of the DBS RCTs informing the guidelines, which may provide a basis for our proposed rewording the recommendation. Three of the 4 RCTs included in the systematic evidence review (Deuschl 2006, Weaver 2009, Okun 2012), include selection criteria on the presence of motor complications - most frequently motor fluctuations, dyskinesia – in spite of best medical therapy. Williams (2010) had broader selection criteria; however a large majority (at least 77% of patients) was selected on the basis of presence of at least one type of motor complication at study entry (Williams 2010, table 1). The importance of presence of motor complications as key DBS eligibility criteria is further highlighted by the fact that the pilot study by Charles 2014 (included in section 10.4), the only DBS RCT study with explicit inclusion of patients <u>without</u> motor complications, did not lead to significant improvements for DBS in UPDRS motor outcomes and quality of life – in contrast with all the other DBS RCTs. 3. Additionally, we propose to add the word "adequately" for recommendation 78 to read "<u>adequately</u> controlled by best medical therapy" to reflect the fact that disease control by medical therapy is not binary, i.e there is a gradual decrease in symptom control with medical therapy. As disease advances, medical therapy may still aid in control of symptoms, however, complications of therapy such as dyskinesias and motor fluctuations may already impact patient's quality of life, indicating medical therapy does not provide adequate symptom control anymore and DBS may become a treatment option.	

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				In summary, we suggest these changes to the recommendations as terminology that may better reflect the fact that selection of patients for DBS is based on patients who have advanced to a disease stage where the presence of motor complications (ie, dyskinesias and/or motor fluctuations) significantly impacts the patient's quality of life despite best medical therapy.	
Medtronic Limited	Full	204	5043-5048	We respectfully propose NICE reword this section to reflect clarity of the assumptions in the cost-effectiveness model by Fundament et al (2016) (proposed change underlined). "The model projected 2-year data from the RCT to a 15-year time horizon, assuming that DBS benefits over BMT would remain constant in all domains except motor complications (UPDRS-IV), for which it was assumed that the gap between DBS and BMT would widen over an 8-year period due to worsening UPDRS IV scores in the BMT arm.	Thank you for these suggestions, which we have partially adopted. The relevant sentence now reads: 'The model projected 2-year data from the RCT to a 15-year time horizon, assuming that the benefits of DBS over BMT would remain constant in all domains except motor complications (UPDRS-IV), for which it was assumed that the gap between DBS and BMT would widen over an 8-year period, during which time people on BMT would continue to decline, whereas people who had undergone DBS would experience no motor complications they had not experienced in the 2 years following insertion.'
Medtronic Limited	Full	204-209		We are pleased to see that the GDG has recognized the potential benefit of DBS surgery earlier in the course of PD and has included in the updated PD guidelines the question of whether "there is a benefit in receiving DBS earlier in the course of PD". However, we believe that the systematic evidence review addressing this question may have misinterpreted the definition of 'early DBS'. As developers of DBS therapy, we would like to clarify that the efficacy of DBS therapy in PD has been primarily demonstrated in patients with presence of motor complications.	Thank you for your comment. The definition of 'early DBS' agreed by the GDG for the purposes of this question was was 'Patients with a confirmed diagnosis of Parkinson's disease who are **either** within 5 years of developing motor complications, **or** Hoehn & Yahr stage <3'. It is not strictly correct to say that Charles et al. (2014) excluded participants with motor complications; rather, they excluded people with a history of motor fluctuations. In fact, baseline motor dysfunction was very similar in this

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				This is clearly reflected in 5 of the 6 DBS RCTs selected to inform the draft NICE guidelines. The presence of motor complications is a key patient characteristic in these RCTs, and all show that DBS leads to statistically and clinically significant improvement in motor outcomes and disease-specific quality of life. While the majority of the RCTs are in advanced PD, 2 of these RCTs include patients with earlier PD (EARLYSTIM (Schüpbach 2014), PD SURG subgroup of patients with H&Y<3 (Williams 2010)). In contrast, the pilot RCT by Charles et al (2014) included in the evidence review includes patients with early PD without motor complications, with DBS resulting in non-significant improvements in motor outcomes and disease-specific quality of life. Consequently, our view is that the definition of "earlier DBS" in the systematic evidence review should reflect DBS in "PD with early motor complications", which can be achieved by jointly combining both aspects of the current PICO *population* criteria for systematic review (in table 23 line 4969). This would mean that the results of Charles et al (2014) are not relevant to the systematic review question on "early DBS" and should not be included. Without a revised systematic review omitting Charles et al (2014), the key question of "early DBS" in PD with early motor complications remains unanswered within the clinical guidelines. Such an assessment is pertinent and separate from the question of DBS in early PD (irrespective of the presence of motor complications), and may subsequently impact the considerations for further research within the research recommendations (Section 10.4.9, page 209).	trial to that seen in other included RCTs (UPDRS-III [on] = 11.7 compared with 12.3 in Schuepbach et al. 2013). Moreover, the inclusion of Charles et al. (2014) in the evidence synthesis for this question has very little impact on pooled effect estimates. This is because the RCT was very small (n=30) and because its results were broadly consistent with those observed in other included RCTs. While it is true to say that the trial reported non-significant improvements in motor outcomes and disease-specific quality of life, in each case, results are consistent with those reported in the larger 24-month RCT (Schuepbach et al. 2013), as evidenced by I^2 values of 33% or less in the relevant stratum. For all these reasons, we do not believe it is necessary to revise the analysis, nor do we believe that materially different results would be derived if we did.

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Medtronic Limited	Full	208	5110	In section 10.4.7 "Trade-off between benefit and harms, we would appreciate further expansion and clarification by the GDG on the 3rd sentence of the 1st paragraph which states "the EARLYSTIM cohort was very specific and unlike people with PD that are commonly seen in UK practice" and "… BMT in the EARLYSTIM trial was thought likely to be considerably different to that in the UK" as these statements indicate the GDG judges that the EARLYSTIM RCT is not applicable to the UK. Medtronic disagree with the above statement, however acknowledging that we do not have the full insights, we ask NICE for greater clarity as to how the CDG arrived at this judgement. In so doing we would like to highlight to the GDG that BMT in the EARLYSTIM trial was implemented according to a specific protocol, developed based on evidence-based European treatment guidelines that included apomorphine as a BMT option.	Thank you for your comment. We have added the following detail: 'In particular, the group noted that the mean age of the group was 52, and their mean disease duration was 7 years, suggesting an average age at onset of 45, which is much younger than observed in UK practice.' We have revised the second statement to explain that '… the GDG was uncertain about whether BMT in the EARLYSTIM trial was thought likely to be considerably different to would be representative of that provided in the UK, as it was aware that there are substantial differences between countries in availability of – and preferences for – medical therapies.'
Medtronic Limited	Full	208	5110	In section 10.4.7 "Trade-off between benefit and harms , we observe that the statement in the last sentence which states "The point at which early DBS should be offered was felt to be when people would currently offer adjuvant therapy to initial levodopa", may reflect "early DBS" in a population irrespective of presence of motor complications as per the systematic evidence review informing the guidelines. We ask the GDG to reconsider this statement based on the evidence presented above (comment 7) and to rephrase it to state as follows: "….Early DBS should be offered when patients have motor complications impacting their quality of life. " These considerations should also be reflected in the definitions of research recommendations.	Thank you for your comment. We have amended this sentence to clarify that it refers to the research recommendation proposed by the GDG.

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Medtronic Limited	Full	209	5110	For consistency, please also consider the proposed revision on Fundament et al (2016) (comment 8) – in the paragraph interpreting the study in the section "Trade-off between net health benefit and resource use".	Thank you for your comment. We do not believe this is necessary; this text is already clear that a relative benefit of DBS over BMT is benefit referred to, and the assumed profile of growing benefit need not be restated.
Medtronic Limited	Full	209	5110	In section 10.4.7 "Trade-off between net health benefits and resource use (3rd paragraph) discussing the UK-focused CUA by Fundament et al (2016), it appears that the GDG interpreted the assumption on the length of DBS effect on motor complications to be overly optimistic, and argue that "it was also true that these symptoms normally respond well to the kind of optimised second-line pharmacological management to which early DBS should be compared". We would like to highlight to the GDG that medical therapy in EARLYSTIM (the BMT treatment arm) was optimised throughout the trial, and that response to UPDRS IV (complications of therapy) in the BMT significantly decreased in the 2 years of the trial.	Thank you for your comment. The GDG were aware that DBS had shown benefits in this domain in the trial. However, it took the view that it is one thing to note that a treatment has a benefit over another in a randomised trial, but it is quite another to assume that the difference between the 2 will continue to grow at the same rate over a time period 4 times longer than that observed. The group agreed that this was an optimistic and un-evidenced assumption, noted that it was critical to cost–utility outputs, and agreed that it would have preferred a much more conservative approach.
Medtronic Limited	Full	42,43, 140		We have noted that other sections of the guideline also use the terminology "later disease" without specific definition of what is meant by the term. It may be appropriate to replace these with "advanced disease", for consistency, as per our recommendation above.	Thank you for your comment. Unfortunately, the terminology "later disease" has been used in sections that are not part of this guideline update, and hence no changes can be made. We have attempted to use the term "advanced" consistently throughout those parts of the guideline which have been updated.
Medtronic Limited	Full	general	general	The NICE guideline scope (Appendix 2) in section 4.5.5. has specified a review question to address the definition of appropriate referral criteria for DBS. However, in the guideline document, we observe that such referral criteria are not defined and would kindly ask if an explanation for this omission is available?	Thank you for your comment. As detailed below, the GDG agreed with some of your proposed amendments to its recommendations on provision of DBS, and this goes some way to clarifying the expected indicated population.

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				It is acknowledged that clearer guidance on criteria for referral of patients to a DBS specialist centre, to further assess eligibility, would be helpful for neurologists and other health care professionals. In the absence of referral criteria, we consider that our proposed changes to recommendation 78 – which is the specification of the types of symptoms indicating use of DBS, i.e. motor complications (such as dyskinesias and/or motor fluctuations) - may be considered a reasonable amendment towards slightly addressing this need (comment 1 above). As noted above, motor complications as key indicators for DBS are consistent with the characteristics of included advanced PD patient populations in the major DBS RCTs (Deuschl 2006, Weaver 2009, Williams 2010, Okun 2012), and are relatively consistent with wording within the patient criteria specified in the UK national commissioning policy for DBS in Movement Disorders (April 2013; Reference: NHSCB/D03/P/b).	In general, however, the GDG took the view that DBS was likely to be made available only through specialist commissioning policies, and that these policies would specify the appropriate groups of people for surgery, and therefore it was not necessary to include this as part of the guideline. While the scope of a guideline is not subject to change once development begins, draft review questions may be amended, added or removed, as highlighted in that document.
Medtronic Limited	Short	18,19	21-26 (p18); 1-3 (p19)	'In line with our comments on the full guidance we respectfully request that NICE consider the proposed wording changes to recommendations as per comments 1-3 also in the short version of the guidelines, as follows (proposed change underlined): Proposed wording: 1.8.1 Offer people with advanced Parkinson's disease best medical therapy, which may include continuous subcutaneous apomorphine infusion. [new 2017] 1.8.2 Do not offer deep brain stimulation to people whose Parkinson's disease is adequately controlled by best medical therapy. [new 2017]	Thank you for your comment. The recommendations have been redrafted along the lines suggested, but the GDG agreed that the phrase "whose symptoms are not adequately controlled by best medical therapy" was the most appropriate choice of words.

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				1.8.3 Consider deep brain stimulation for people with advanced Parkinson's disease whose motor complications are not adequately controlled by best medical therapy. [new 2017]	
Oxford Neurological Society	Full	80	2019, 2021	The Society would like to welcome and encourage the change in pharmacological recommendations proposed. Question 1: The recommendation limiting the use of anticholinergics and amantadine could prove particularly challenging due to the established role of these drugs in the scientific literature over the years. It is currently entrenched in the medical school curriculum and could be hard to overcome for clinicians who do not stay on top of current developments in PD (Parkinson's Disease) treatment. Question 3: We understand why the committee decided against a categorical "do not offer" recommendation for all purposes of amantadine use. However, we believe that a stronger and clearer message is needed for these drug recommendations; e.g. many textbooks or drug reviews still feature amantadine as a "promising drug" or as simply less effective for a first line treatment, as if it were equally proven to work. We believe that it should be made clear that there is no clinical evidence to justify the use of amantadine or anticholinergics, and that there is substantive evidence of adverse effects associated with those drugs.	Thank you for your comment. During the post-consultation meeting, the GDG discussed and acknowledged that the Amantadine recommendation needed to be rephrased on the basis that it may be an effective treatment option for people with dyskinesia, which cannot be adequately managed by modification of existing therapy. The GDG has therefore agreed to change the current recommendation to reflect this. The GDG did agree that a strong "do not offer" recommendation for anticholinergics was justified, and the LETR table was been updated to make this reasoning clearer.
Parkinson's Disease Nurse	Short	10	1	We note addition of high alcohol consumption and smoking, but wonder if vaping should also be added	Thank you for your comment. No evidence with regards to the risk of ICD and vaping was identified, and hence it was not felt possible to include this in the recommendations. However, this may well be an issue for

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Specialist Association					consideration in future updates of the guideline, when enough time has passed for evidence on this issue to emerge.
Parkinson's Disease Nurse Specialist Association	Short	11	8	We welcome Cognitive behaviour therapy as a treatment strategy but there is limited access across the country.	Thank you for your comment. The GDG agreed that there are difficulties accessing this service in many areas, and hope that the recommendations will lead to the service becoming more available.
Parkinson's Disease Nurse Specialist Association	Short	12	1-3	We welcome the addition of melatonin as treatment option for REM sleep behaviour disorder especially because of concerns using Clonazepam on longer term basis	Thank you for your comment.
Parkinson's Disease Nurse Specialist Association	Short	12	9	We are concerned about the lack of evidence to support the recommendation for use of controlled release levodopa for nocturnal hypokinesia. There is evidence for use of rotigotine patch to help with nocturnal problems which undoubtedly impact on quality of life. Rotigotine is better tolerated in some patients and there is concern that it would not be in the patients best interests to try one medication which it was suspected they would not tolerate, just so that another could then be used.	Thank you for your comment. After further discussion, the GDG agreed that these recommendations had been too strongly worded based on the underlying evidence. Accordingly, the words modified release have been removed from the recommendations, and the final recommendation about when dopamine agonists should be taken has been entirely removed. This leads to a simpler set of recommendations which the GDG believes are supported both by the evidence and clinical judgement.
Parkinson's Disease Nurse Specialist Association	Short	13	4-7	We were surprised to see Midodrine as first line choice and are concerned there will be problems around prescribing this drug which in many areas remains Consultant only prescription. There are also concerns that the need for initial and ongoing monitoring will influence it's use.	Thank you for your comment. The GDG agreed that the evidence behind the use of midodrine was not particular strong, but in view of it being the only medicine with a license in this area felt it was appropriate to make a "consider" level recommendation. The GDG agreed there

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					may be many reasons why midodrine is not the optimal choice for individual people, and in this situation fludrocortisone is a logical and commonly used alternative.
Parkinson's Disease Nurse Specialist Association	Short	13	9	We anticipated a more detailed section relating to the specific issues that people with depression and / or anxiety and Parkinson's will experience.	Thank you for your comment. The scope for this guideline update, which was publically consulted on, specified that evidence on interventions for depression and/or anxiety will not be included as part of this update, and the guideline will cross-refer to the NICE guideline on depression in people with a chronic physical health problem. At this stage it is not possible to alter this decision and hence this recommendation cannot be changed. Evidence from people with Parkinson's disease will have been included as part of the development of this other guideline. The NICE guideline on depression does contain recommendations on managing comorbid anxiety and depression, and NICE has also produced a number of pieces of guidance looking at specific types of anxiety (https://www.nice.org.uk/guidance/conditions-and-diseases/mental-health-and-behavioural-conditions/anxiety)
Parkinson's Disease Nurse Specialist Association	Short	14	11	We were surprised that Clozapine was identified as one of the first line options when there remains limited accessibility to registered services and issues around monitoring.	Thank you for your comment. After further discussion, the GDG amended this recommendation so that the use of clozapine is recommended when standard treatments have failed, as per the license for clozapine.

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Parkinson's Disease Nurse Specialist Association	Short	14	5-7	Regarding hallucinations and psychosis, Advice should be sought from health professional with knowledge and expertise in medication management	Thank you for your comment. The GDG felt that it would be generally understood who "a healthcare professional with specialist expertise in PD" is when discussing modifications to medicines. Therefore, they agreed that no changes need to be made to the current recommendation.
Parkinson's Disease Nurse Specialist Association	Short	15	15	We welcome that cholinesterase inhibitors can be considered across the cognitive deficit spectrum	Thank you for your comment.
Parkinson's Disease Nurse Specialist Association	Short	15	3-9	We welcome the addition of glycopyrrolate, but are concerned that if it is not tolerated for reasons given such as cognitive decline or hallucinations etc, an anticholinergic can be considered and we would suggest that under these circumstances, this too would be unlikely to be tolerated.	Thank you for your comment. The GDG agreed that the majority of anticholinergics would be inappropriate in this situation. However, they felt that the topical administration of atropine might prove an acceptable alternative in these circumstances, and felt this option should be left open.
Parkinson's Disease Nurse Specialist Association	Short	18	12-15	We welcome the addition of vitamin d supplement guidance recognising the specific bone health issues for people with Parkinson's	Thank you for your comment.
Parkinson's Disease Nurse Specialist Association	Short	18	22-24	Suggest adding intermittent subcutaneous Apomorphine injections which may also be used at this stage	Thank you for your comment. A reference to intermittent apomorphine injections has now been added to this section, in line with the suggestion made.
Parkinson's Disease	Short	18	5-7	In relation to protein redistribution diet to address motor fluctuations, we wonder if fat content in diet, should also be addressed as this too can affect	Thank you for your comment. Unfortunately, we did not identify any evidence on the issues mentioned, and

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Nurse Specialist Association				gastric emptying and influence medication absorption. We support need for input from dietician with close monitoring of dietary changes to ensure that these do not compromise the patients nutritional status. We also wonder about addition of monitoring for other factors such as small intestinal bacterial overgrowth which could be affecting absorption of medication and therefore also be impacting on efficacy of medication.	therefore the GDG did not feel it was appropriate for them to make recommendations on these topics.
Parkinson's Disease Nurse Specialist Association	Short	19	1-3	Would suggest that any patient who's symptoms are not controlled by best medical therapy should be considered for DBS regardless of disease stage such as early disease tremor dominant with severe impact on quality of life. We would welcome clarification on what constitutes Later stages of Parkinson's disease.	Thank you for your comment. The wording of this recommendation has now been altered in two ways. First, it has been made clear that DBS referral may be appropriate whenever symptoms are not adequately controlled, and the reference to "later stages" has been changed to "advanced Parkinson's disease", which the GDG agreed was a more commonly used and better understood term.
Parkinson's Disease Nurse Specialist Association	short	19	4-6	We are extremely concerned that this treatment option could be removed, when for some patients there may be no alternative and for a select few it is a valuable treatment option. There are also concerns that where DBS and LCIG are being compared, the patients that would be suitable for either treatment would be different and with clearly different selection criteria and have different needs. It states that this is an effective long term treatment for PD, but that treatment costs are high at present. We are therefore concerned that consideration of economic factors have outweighed efficacy and quality of life for patients. While we acknowledge that there can be PEJ complications and other adverse events, we wonder if the 19 specialist centres that have been set up, would help to streamline the process and improve patient selection and tolerability.	Thank you for your comment. For comments on the effectiveness and cost effectiveness of LCIG, please see **theme 1**. For comments on the appropriateness of the decision problems addressed in the review questions on treatment for advanced Parkinson's disease, please see **theme 3**.
Parkinson's Disease	Short	19	9-26	We welcome the recognition of discussing palliation in Parkinson's and Advanced care planning.	Thank you for your comment.

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Nurse Specialist Association					
Parkinson's Disease Nurse Specialist Association	Short	7	7	We welcome the recognition that some patients in early stage will require levodopa for their motor symptoms and anticipate this will help to reduce anxiety around the situation	Thank you for your comment.
Parkinson's Disease Nurse Specialist Association	Short	8	11-14	Would suggest that the health care professional should be one who is knowledgable and expert in the management of medications used in Parkinson disease. This refers to other health care professionals who will have specialist expertise in Parkinson's for their specialist therapy area, but may not have specialist knowledge around medication management.	Thank you for your comment. The GDG felt that it would be generally understood who "a healthcare professional with specialist expertise in PD" is when discussing modifications to medicines. Therefore, they agreed that no changes need to be made to the current recommendation.
Parkinson's Disease Nurse Specialist Association	Short	8	1-9	We welcome the recognition of the importance for both oral and written information around the risks relating to impulse control disorder, excessive sleepiness etc. but would suggest that information about dopamine agonist withdrawal syndrome should also be included here.	Thank you for your comment. The GDG discussed this point and agreed that discussions around dopamine agonist withdrawal syndrome would form part of the initial conversation with people when therapy choices were being made, and therefore felt these issues were suitably covered in recommendations 1.3.1 and 1.3.7
Parkinson's Disease Nurse Specialist Association	Short	9	11-13	We welcome the recognition of impulse control disorders at any stage of the disease trajectory and on any of the treatments used, not just dopamine agonists.	Thank you for your comment.
Parkinson's Disease Nurse	Short	9	6	We are concerned about the removal of amantadine as a treatment option for those patients who experience dyskinesias but are unable to tolerate any reduction in dopaminergic therapy. While there is limited evidence in the	Thank you for your comment. After discussion, the GDG agreed that amantadine may be a useful treatment option for managing dyskinesia in people with Parkinson's

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Specialist Association				literature, some patients do benefit and for those there may be no alternative to manage their symptoms and would welcome option to use under these circumstances.	disease, where this cannot be adequately managed by modification of existing therapy. The recommendation has therefore been changed from a "do not" to a "consider" recommendation to reflect this.
Parkinson's UK	Full	119	2763 - 3274	Parkinson's UK welcome the section on pharmacological management of dementia associated with Parkinson's disease. More information is given in 'Treatment of Psychosis and Dementia in Parkinson's Disease Jennifer G. Goldman, MD, including: '*Parkinson's disease has been increasingly recognised as having a multitude of non-motor symptoms including psychosis, cognitive impairment and dementia, mood disturbances, fatigue, apathy, and sleep disorders. Psychosis and dementia, in particular, greatly affect quality of life for both patients and caregivers and are associated with poor outcomes. Safe and effective treatment options for psychosis and dementia in PD are much needed. Antipsychotics with dopamine-blocking properties can worsen parkinsonian motor features and have been associated with increased morbidity and mortality in elderly, dementia patients. For treating PD psychosis, a first step would be eliminating confounding variables, such as delirium, infections, or toxic-metabolic imbalances, followed by simplifying parkinsonian medications as tolerated.*' There is more evidence in Cognitive Impairment and Dementia in Parkinson's Disease: Practical Issues and Management Murat Emre, MD,1* Paul J. Ford, PhD,2 Bas¸ar Bilgic¸, MD,1 and Ergun Y. Uc¸, MD3,4.	Thank you for your comment. Unfortunately, the scope of this guideline only covers the use of cholinesterase inhibitors and memantine for Parkinson's disease dementia, and all other aspects of the identification and management of dementia in people with Parkinson's disease will be covered by the NICE guideline on dementia. This guideline is currently being updated and will specifically look at evidence in people with both Parkinson's disease dementia and dementia with Lewy bodies.

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				Parkinson's UK have also created an information sheet on this topic which can be found online at https://www.parkinsons.org.uk/content/parkinsons-dementia-information-sheet Dementia affects a large proportion of people with Parkinson's and we recommend that this guideline should cover treatment and support for this in more detail.	
Parkinson's UK	Full	12	1	We recommend that this section includes background information that includes advice on facilitators and barriers to use of the guideline, and on available tools and resources that could help implementation.	Thank you for your comment which has been passed on to NICE's implementation team for consideration.
Parkinson's UK	Full	12	1	We recommend that a section describing key messages, and audit criteria is included here (as in the previous guideline). Also it is unclear whether audit criteria have been updated.	Thank you for your comment which has been passed on to NICE's implementation team for consideration.
Parkinson's UK	Full	12	2 - 75	The precise roles of Technical Analysts and Technical Advisers were not given. The methodological expertise in the group is therefore unclear.	Thank you for your comment. Technical analysts undertake the evidence reviews during development of guidelines. This involves identifying the relevant evidence, extracting the data, conducting analyses, presenting the evidence to the GDG for their consideration and writing the guideline. The work of the technical analysts is overseen and supported by a Technical Advisor.
Parkinson's UK	Full	142	3389-3398	9.1.3 The presentation of p values is not meaningful here. We presume it is to indicate statistical significance, but without details of the statistical tests and the null hypotheses that are being tested, the p values cannot be interpreted. Parkinson's UK believes it would be more useful to show the effect size with 95% confidence intervals.	Thank you for your comment. Unfortunately, this chapter was not included as part of the scope for this guideline update, hence it has not been updated and no changes can be made.
Parkinson's UK	Full	144	3442 - 3459	We welcome the fact that the draft guideline looks at the various causes of falls including gait, functional mobility and balance etc.	Thank you for your comment. The GDG believe that the recommendation "Offer Parkinson's disease-specific

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				Many people with Parkinson's share their experience of regular falls with us, with statements such as "*freezing is the cause of many a fall for me. The problem is my body goes faster than my feet, so I often leave them on the pavement."* Falls are a significant problem both in the later stages of Parkinson's and in optimally medicated early-stage Parkinson's (Bloem, Bastiaan R., et al. "Prospective assessment of falls in Parkinson's disease." *Journal of neurology* 248.11 (2001): 950-958.). Research has shown that a combination of both disease-specific and balance- and mobility-related measures can accurately predict falls in individuals with PD (Kerr, G. K., et al. "Predictors of future falls in Parkinson disease." *Neurology*75.2 (2010): 116-124.). There are a number of recent publications that build on these findings developing risk falls assessment and screening: • Research article '*Three Simple Clinical Tests to Accurately Predict Falls in People with Parkinson's Disease*' by Serene S. Paul, BAppSc (Phty)(Hons), Colleen G. Canning, PhD, Catherine Sherrington, PhD, Stephen R. Lord, PhD, DSc, Jacqueline C. T. Close, MD, Victor S. C. Fung, PhD, FRACP Research article: '*Prediction of Falls and/or Near Falls in People with Mild Parkinson's Disease*' by Beata Lindholm, Peter Hagell, Oskar Hansson, Maria H. Nilsson Department of Neurology, Skåne University Hospital, Malmö, Sweden, Published Jan 30th 2015	physiotherapy for people who are experiencing balance or motor function problems" should cover the needs of people who fall or at risk of falls as a result of their Parkinson's disease, as these are related to balance problems.

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Parkinson's UK	Full	144	3445	9.2.1 Parkinson's UK fully accepts why randomised controlled trials (RCT) are considered the highest quality evidence. However, for physiotherapy, where it is not possible to use a double-blind approach (which is the primary benefit of an RCT), a well-designed cohort study could provide useful evidence. This may be particularly important for the occupational therapy and speech and language reviews where so few RCTs were suitable for the review.	Thank you for your comment. Whilst blinding is a useful feature of a well-designed RCT, we do not believe this is the primary benefit of an RCT. The primary benefit is randomisation, and the avoidance of selection bias which even the best designed cohort study is likely to suffer from. The GDG felt the evidence available from RCTs was sufficient for them to be able to make recommendations on the non-pharmacological topics considered in the guideline, and therefore it was not appropriate to move to the lower standards of evidence available from cohort studies.
Parkinson's UK	Full	15	105	The methods section does not describe how stakeholders' views were sought. It is noted that a large number of stakeholders were represented, including many whose interest might be commercial. Parkinson's UK wonders whether the views of some stakeholders were 'drowned out' among so many voices. There was no evidence that the views and preferences of the target population were sought for this update, beyond the inclusion of patient/carer representatives within the Guideline Development Group (GDG). No clear process was described for gathering such views and preferences. It was unclear how decisions were made regarding which sections of the guideline to update. Also relevant to the methods section, it is expected that the final version will include details about the search strategy. It is noted from the separate appendices that the review question search strategies did not include Cumulative Index to Nursing and Allied Health (CINAHL). Relevant articles from nursing and allied health journals may have been missed as a result. Also the methods for formulating recommendations are not included. A good description was provided in the 2006 guideline. We hope this procedure	Thank you for your comments. The methods used for this guideline update are described in detail in the NICE guideline manual: "https://www.nice.org.uk/media/default/about/what-we-do/our-programmes/developing-nice-guidelines-the-manual.pdf" CINAHL is not searched as standard for guidelines anymore due to the considerable overlap with Medline. This decision was made after a project that was carried out by the NICE Information Services team was shown to not retrieve anything unique which was of sufficiently high quality to meet the GRADE inclusion criteria. Specifically, the study found that only 0.33% (95% CI: 0.01-0.64%) of references per guideline were unique to CINAHL. No

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				was replicated, and we would recommend this is outlined in detail in the update.	significant relationship was found between question type and unique CINAHL yield for drug-related questions. Beckles Z, Glover S, Ashe J, Stockton S, Boynton J, Lai R, Alderson P. Searching CINAHL did not add value to clinical questions posed in NICE guidelines. Journal of clinical epidemiology. 2013 Sep 30;66(9):1051-7.
Parkinson's UK	Full	153	3680	9.3.1 Parkinson's UK fully accepts why RCTs are considered the highest quality evidence. However, for occupational therapy, where it is not possible to use a double-blind approach (which is the primary benefit of an RCT), a well-designed cohort study could provide useful evidence. This may be particularly important for the occupational therapy reviews where so few RCTs were suitable for the review.	Thank you for your comment. Whilst blinding is a useful feature of a well-designed RCT, we do not believe this is the primary benefit of an RCT. The primary benefit is randomisation, and the avoidance of selection bias which even the best designed cohort study is likely to suffer from. The GDG felt the evidence available from RCTs was sufficient for them to be able to make recommendations on the non-pharmacological topics considered in the guideline, and therefore it was not appropriate to move to the lower standards of evidence available from cohort studies.
Parkinson's UK	Full	156	3794 - 3813	The guideline investigates what kind of activities an occupational therapist (OT) could support. The 'Systematic Review of the Effectiveness of Occupational Therapy–Related Interventions for People With Parkinson's Disease' by Erin R. Foster, Mayuri Bedekar, Linda Tickle-Degnen gives some good evidence about the important interventions that can be made by an OT.	Thank you for this information. The GDG did not feel sufficient evidence was available to make specific recommendations about what occupational therapy interventions should involve. However, they felt that because the recommendations specify "Parkinson's disease specific occupational therapy" and an "occupational therapist with experience of Parkinson's disease", that this should ensure the interventions given are appropriately tailored to the needs of individuals with Parkinson's disease.

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				'Moderate to strong evidence exists for task-specific benefits of targeted physical activity training on motor performance, postural stability, and balance. Low to moderate evidence indicates that more complex, multimodal activity training supports improvement in functional movement activities. The evidence is moderate that the use of external supports during functional mobility or other movement activities has positive effects on motor control. In addition, moderate evidence is available that individualized interventions focused on promoting participant wellness initiatives and personal control by means of cognitive–behavioural strategies can improve targeted areas of quality of life.' Though the guideline draft provides little evidence for this section, it is important that this guideline notes that an occupational therapist positively contributes when part of a multidisciplinary team.	
Parkinson's UK	Full	160	3826	9.4.1 Parkinson's UK fully accepts why RCTs are considered the highest quality evidence. However, for speech and language therapy, where it is not possible to use a double-blind approach (which is the primary benefit of an RCT), a well-designed cohort study could provide useful evidence. This may be particularly important for the speech and language reviews where so few RCTs were suitable for the review.	Thank you for your comment. Whilst blinding is a useful feature of a well-designed RCT, we do not believe this is the primary benefit of an RCT. The primary benefit is randomisation, and the avoidance of selection bias which even the best designed cohort study is likely to suffer from. The GDG felt the evidence available from RCTs was sufficient for them to be able to make recommendations on the non-pharmacological topics considered in the guideline, and therefore it was not appropriate to move to the lower standards of evidence available from cohort studies.
Parkinson's UK	Full	167	4014	We appreciate these guidelines have to be evidence based but in this area it is acknowledged there is little evidence, so nothing is stated which doesn't help show what areas can be addressed with dietetic intervention. It makes it	Thank you for your comment. Unfortunately, in the absence of any evidence the GDG did not feel it appropriate to make any specific recommendations about

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				challenging to be able to convey how the work of a nutritionist can benefit a person with Parkinson's. We believe a recommendation should be added around dietetic intervention.	dietetic interventions. However, in the absence of this evidence, the GDG have agreed this is an important area for future research and have therefore added a research recommendation around dietetic interventions. We hope that if such research is carried out, then recommendations will be possible in future updates of this guidance.
Parkinson's UK	Full	173	4149	We are disappointed that no recommendations have been made to research any nutritional areas to rectify the current lack of evidence. We feel many clinicians are not clear about the role of a dietitian in the care of people with Parkinson's and this is a good opportunity to address this. We recommend that end of life nutritional management is added to the research questions in this section of the guideline.	Thank you for your comment. In the absence of evidence for dietetic interventions, the GDG have agreed this is an important area for future research and have therefore added a research recommendation around dietetic interventions. They agreed that a general research recommendation about dietetic interventions would both be of more value and more likely to be undertaken that one specifically in end of life care.
Parkinson's UK	Full	173	4150 – 4151	Research recommendation 8 asks- How effective is long term creatine supplementation on clinical outcomes in Parkinson's Disease? However it has not accounted for the publication of the largest interventional trial ever undertaken in Parkinson's; the LS1 trial of creatine supplementation which demonstrated no change in BMI using creatine supplementation at a dose of 10g/day. This recommendation should be updated to reflect this.	Thank you for your comment. This study has now been included into the guideline, a negative recommendation made around creatine supplementation, and the corresponding research recommendation removed.
Parkinson's UK	Full	186	4479	UK centres currently have access to rechargeable implantable pulse generators (IPG), and via the multidisciplinary team, consider the use of these in comparison to primary cells. This is presently standard practice.	Thank you for your comment. As detailed in 10.3.6, the GDG agreed that there are some respects in which DBS may have become more effective and less expensive than observed in trials such as PDSURG, and this was one reason for the GDG's preference to estimate current

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				The UK Deep Brain Stimulation (DBS) network of neurologists, neurosurgeons and DBS specialist nurses is gathering comprehensive national views of battery longevity. There are also new technologies which are being developed, e.g. visual guidance software and directional leads. The emergence of new technologies makes current DBS practice significantly improved compared with when PDSURG and other trials were performed. So, from this point of view, the cost effectiveness of DBS may well have improved, with the emergence of more efficient programming, less stimulation-induced side effects, and less frequent IPG replacements. We therefore recommend that the GDG reanalyses the cost effectiveness of DBS.	costs in detail rather than rely on the global totals observed in PDSURG. It is also true to say that some of the advances mentioned have been accompanied by nontrivial increases in cost. For example, rechargeable batteries may make IPG replacement less frequently needed, but the acquisition cost of the units is also higher. Our exploratory analysis suggested that, at current list prices, rechargeable IPGs would have to last indefinitely before they would have a similar balance of costs, benefits and harms as units with conventional batteries.
Parkinson's UK	Full	187	4522 - 4531	We are disappointed to see that in section 10.2 that there were no expert witnesses for Levodopa Carbidopa Intestinal Gel (LCIG) also known as Duodopa. We strongly recommend NICE seeks this expert testimony before this guideline is finalised.	Thank you for your comment. For comments on the role of expert witnesses, please see **theme 2**.
Parkinson's UK	Full	189 - 198	4563-4940	We recognise the GDG has looked for published evidence. It therefore evaluates LCIG in relation to its licensed indication, which does not restrict it to those not eligible for DBS. Information about this is only available in confidential information submitted by the manufacturer. However when making the case in Scotland a detailed advice document (DAD) was created for the Scottish Medicines Consortium (SMC). Scotland has assessed the DAD and acknowledged that the review of published information does not show how it would be used in clinical practice. Furthermore, the SMC got a Patient Access Scheme (PAS) for LCIG and we would encourage NICE to obtain a similar PAS.	Thank you for your comment. For comments on the appropriateness of the decision problems addressed in the review questions on treatment for advanced Parkinson's disease, please see **theme 3**. It is not in NICE's remit or power to 'obtain' a PAS, though it will incorporate appropriate confidential discounts offered by a manufacturer in its analyses. Accordingly, the GDG would have been very happy to consider the cost effectiveness of LCIG as modified by a PAS;

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					however, no such approach was made by the manufacturer.
Parkinson's UK	Full	192	4702	We agree that the question of health economics is difficult to answer, and the extensive efforts of the committee are recognised. We have spoken to the UK DBS national network, who are not aware of the costs of potentially using continuous subcutaneous apomorphine infusion + best medical (oral / transdermal) therapy for a 5-6 year cycle, for example. This would be in cases where DBS and other therapies are not appropriate, and would be a comparable cost of 1 "cycle" of a primary cell IPG. It should be noted too that multidisciplinary teams do presently give consideration to the use of stereotaxic lesional surgery in highly selected patients, as a legitimate but second best surgical option to DBS when there are reasons when DBS cannot be offered. In modern practice, this is rare and the number of neurosurgeons with experience of lesional surgery is low.	We acknowledge that the absence of empirical data on the effectiveness and cost effectiveness of apomorphine (infusion and injections) is a limitation of the analyses undertaken for this guideline; however, CSAI was included in the BMT to which DBS was compared in PDSURG and, based on this evidence, one of the cost savings captured in our analysis of DBS is its capacity to reduce requirement for apomorphine. Lesioning was not considered as part of the review question on surgical management of advanced Parkinson's disease. This was because the GDG considered that it is currently used in very few cases. As evidence of this, it was noted that, in the protocol for PDSURG, clinicians treating people who had been randomised to surgery could theoretically choose to provide lesional surgery or DBS and, in 100% of cases, DBS was chosen.
Parkinson's UK	Full	204	4949 - 4950	Question 1: Which areas will have the biggest impact on practice and be challenging to implement? Please say for whom and why. Parkinson's UK believe that by removing the option for clinicians to offer LCIG will have a severe negative impact on people with Parkinson's, and their carers.	Thank you for your comment. For comments on the effectiveness and cost effectiveness of LCIG, please see **theme 1**.

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Parkinson's UK	Full	209	5117	Having consulted with the UK DBS national network of neurologists, neurosurgeons and DBS specialist nurses , we agree with the committee that a trial addressing the optimal timing of DBS would be very valuable in determining at which stage and under which clinical situations to offer DBS.	Thank you for your comment. Such research would be very welcome, and would add considerable value to future updates of this guidance.
Parkinson's UK	Full	21	334	In section 3.1.3 it is disappointing to see the emphasis on p values in the review of evidence. It is now widely accepted among medical statisticians that only using p values is misleading and even disingenuous (see for example Sterne JA, Smith GD (2001) "Sifting the evidence–what's wrong with significance tests?" BMJ. 322 (7280): 226–231) as they are dependent on the nature of the null hypothesis being tested and are highly influenced by sample size (so that with a large sample size even tiny treatment effects can be deemed 'statistically significant'). A proper review of evidence should show estimates of effect size with 90% or 95% confidence intervals which enables the magnitude of the effect to be seen as well as the relative uncertainty associated with the estimate. In other parts of the guidelines this has generally been done but Section 3.1.3 is notably different. We therefore recommend that p values are not the only evidence relied upon to inform this recommendation.	Thank you for your comment. Unfortunately, this chapter has not been included as part of the scope for this guideline update, hence it has not been updated and no changes can be made.
Parkinson's UK	Full	22	387	We are pleased to see the inclusion of information about people with Parkinson's having symptoms which affect their ability to express emotions through their facial expressions, as well as behavior traits which can come across as aggressive or short tempered. It is vital that professionals across the health system are aware of these symptoms.	Thank you for your comment.
Parkinson's UK	Full	228	5639 - 5640	We are disappointed not to see any references to enteral feeding in the section on nutrition. The guideline states there is no evidence on end of life nutritional management, but it is nevertheless a topic that should be addressed as part of advanced care planning.	Thank you for your comment. Unfortunately, no evidence was identified on this topic, so the GDG did not feel a recommendation could be made. NICE does have a specific guideline on enteral feeding, but this did not

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					identify any evidence specific to people with Parkinson's disease.
Parkinson's UK	Full	23	409	We do not believe there is any value in showing regression coefficients in Table 4.2 as we do not think these can be meaningfully interpreted.	Thank you for your comment. Unfortunately, this chapter has not been included as part of the scope for this guideline update, hence it has not been updated and no changes can be made.
Parkinson's UK	Full	25	415	In table 4.3 in the draft guideline documenting findings from the PDS survey in 1999 it can be seen that information patients prioritise includes; "*New treatments that may be available in the future - 90% of patients*" "*What drugs are available and/or their side effects- 84% of patients*" This demonstrates that many people with Parkinson's feel that there are fewer treatments and drugs to make use of. With this in mind, we advise that recommendations in this guideline should be removed that restrict treatments that work effectively for people with Parkinson's.	Thank you for your comment. The GDG acknowledge that all people would want to have access to all possible treatment options, but there is a responsibility on NICE and the NHS to only recommend effective and cost-effective treatments.
Parkinson's UK	Full	25	425 - 431	We are pleased to see in the draft guideline the inclusion that many people with Parkinson's will need information about the condition and their treatment options at various stages of their condition. We also welcome that sometimes this information will need to be repeated. They will also need that information provided in numerous ways such as online, paper based and verbally. We know from speaking to people with Parkinson's, conducting regular surveys and completing routine audits, that people with Parkinson's are often left without the information they so desperately need. Parkinson's UK has free resources (which are Information Standard accredited) to help support people with Parkinson's to learn more about the	Thank you for your comment. Alongside each NICE guideline which is produced, NICE also produces information specifically for patients which often contains links to appropriate resources and services. We will bring this information to the attention of the team responsible for that guidance.

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				condition and could be signposted to at this stage. We therefore recommend that this guideline encourages health and care professionals to signpost to Parkinson's UK as a source of information for patients and carers.	
Parkinson's UK	Full	39	801	*How does the accuracy of UK PDS Brain Bank Clinical Criteria compare with the accuracy of pathological diagnosis?* Recent, potentially important evidence was found: Jellinger, Kurt A., et al. "Accuracy of clinical diagnosis of Parkinson disease: A systematic review and meta-analysis." *Neurology* 87.2 (2016): 237-238. This evidence has not been included in the draft guideline update and we recommend that it is included in the final guideline.	Thank you for your comment. Unfortunately, this chapter has not been included as part of the scope for this guideline update, hence it has not been updated and no changes can be made.
Parkinson's UK	Full	42	922	A timeline is suggested for patients to be seen in the specialist clinic – "*suspected Parkinson's disease should be seen within 6 weeks, and new referrals in later disease with more complex problems require an appointment within 2 weeks*". This appears as a footnote in the full guideline. Yet this instruction will have a serious impact on resources, and strategic planning needs to be done in advance to ensure this can be met.	Thank you for your comment. Unfortunately, this chapter has not been included as part of the scope for this guideline update, hence it has not been updated and no changes can be made.
Parkinson's UK	Full	43	923	Parkinson's UK welcome the requirement for people with Parkinson's receiving treatment, to be monitored every 2-3 months for new treatment follow up.	Thank you for your comment. Unfortunately, this chapter has not been included as part of the scope for this guideline update, hence it has not been updated and no changes can be made.
Parkinson's UK	Full	43	941	We are concerned that the two studies noted below were not included in the evidence for the draft guideline update. *How useful is SPECT in discriminating PD from alternative conditions?* Recent systematic review evidence was found: Suwijn, Sven R., et al. "The diagnostic accuracy of dopamine transporter SPECT imaging to detect nigrostriatal cell loss in patients with Parkinson's disease or clinically uncertain parkinsonism: a systematic review." *EJNMMI research* 5.1 (2015): 1, and Brigo, F., et al. "[123I] FP-CIT SPECT (DaTSCAN) may be a useful tool to differentiate	Thank you for your comment. Unfortunately, this chapter has not been included as part of the scope for this guideline update, hence it has not been updated and no changes can be made.

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				between Parkinson's disease and vascular or drug-induced parkinsonisms: a meta-analysis.' *European Journal of Neurology* 21.11(2014):1369-e90. We would recommend these two studies are included in the final guideline and analysed.	
Parkinson's UK	Full	46	1015	The clinical application of FP-CIT SPECT for differentiation of essential tremor from Parkinson's disease represents only one aspect of its usage. There needs to be recognition of the evolution in understanding of essential tremor versus dystonic tremor, as well as inclusion of other situations where clinical differentiation of dopamine deficiency disorders versus normal dopamine levels is usefully addressed by such imaging. Examples include drug induced parkinsonism and vascular parkinsonism.	Thank you for your comment. Unfortunately, this chapter has not been included as part of the scope for this guideline update, hence it has not been updated and no changes can be made.
Parkinson's UK	Full	55	1258 - 1259	We believe the statement "a*nticholinergics are most commonly used in the earlier stages*" could be misleading. It could be interpreted to mean that it is a common treatment choice in earlier stages of Parkinson's which it is not. Therefore we recommend the final guideline removes this comment.	Thank you for your comment. This section has now been clarified to make it clear that this only refers to those cases where anti-cholinergics are used, and not that the use of them is common.
Parkinson's UK	Full	67	1648	The following information on Dopamine agonists. "*It was noted that both are valid treatment options, and clinicians will often try an ergot agonist if a non-ergot one has not proven effective*" is very out of date. Most Parkinson's experts would no longer consider an ergot agonist as a valid treatment option, therefore we recommend the final guideline states removed from the guideline. We are surprised that the recommendation to use non-ergot dopamine agonists is no longer in the guideline. Although practicing movement disorder specialists are well aware of this, to lose this recommendation from the print guidance may be confusing to new specialists.	Thank you for your comment. After further discussion, the GDG agreed that this statement was too strongly written and it is appropriate to prefer a non-ergot agonist. Two new recommendations have therefore been added to clarify this point; one that ergot agonists should not be used first-line, and the second that they should only be considered if there has been an inadequate response to a non-ergot agonist.

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Parkinson's UK	Full	69	1698	Benzhexol is used as the primary name in the guideline. This name is out of date and should be amended to Trihexyphenidyl as the primary name. Benzhexol should be referenced as the secondary or alternative name.	Thank you for your comment - this has now been changed accordingly.
Parkinson's UK	Full	81	2027	We welcome the information given on non-motor symptoms and the effect they can have on people with Parkinson's.	Thank you for your comment.
Parkinson's UK	Full	83	2106	After consulting with representatives from the Association of British Neurologists (ABN) it is not correct to say that the Epworth sleep scale is used routinely in clinical practice. It is used in a few specialised centres, but it is not currently a routine component of clinical practice in the majority of clinics. Therefore we recommend that the final guideline removes the word 'routinely'.	Thank you for your comment. The GDG has agreed to change it to "the Epworth sleep scale is commonly understood in clinical practice".
Parkinson's UK	Full	87	2173 - 2177	The paper quoted tested a modified release dopamine agonist compared to a placebo. There is no evidence comparing this modified release dopamine agonist to other treatment modalities. There does not appear to be evidence on timing of the intake of modified release dopamine agonists, despite the recommendation that such treatment may be taken at night. In the absence of trial evidence, the pharmacokinetic characteristics of standard release and modified release dopamine agonists might be considered, and these would not lend support to recommendations 1.5.6, 1.5.7 and 1.5.8 (recommendations 35, 36 and 37 in the full guideline) about timing or choice of medication. Parkinson's UK recommends that the guideline is updated to reflect this.	Thank you for your comment. After further discussion, the GDG agreed that these recommendations had been too strongly worded based on the underlying evidence. Accordingly, the words modified release have been removed from the recommendations, and the final recommendation about when dopamine agonists should be taken has been entirely removed. This leads to a simpler set of recommendations which the GDG believes are supported both by the evidence and clinical judgement.
Parkinson's UK	Full	general	general	The Parkinson's Disease Society (PDS) is referenced throughout the guideline, however the organisation is now called Parkinson's UK and should	Thank you for your comment. The parts of the guideline where PDS has been referenced have all been carried forward from the 2006 guideline (thus representing

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				be referred to as such, unless it is in a piece of research which was produced when we were known as the Parkinson's Disease Society (up to March 2010).	evidence from before March 2010, making the 'old' name appropriate). In a few instances, the organisation is referred to more generically, and we have updated the name as requested.
Parkinson's UK	Full Short	General General	General general	The statement '*We have not updated recommendations shaded in grey, and cannot accept comments on them*' severely constricts the remit for comment. This appears to represent a very reductive interpretation of the guidance given in the guideline development manual, which does not preclude seeking comments on unchanged portions of the guideline. It is unclear whether evidence searches relating to recommendations in those unchanged portions have been refreshed. To test whether they remain current, quick searches were carried out for two unchanged questions selected at random: (1) Full draft guideline, line 801: *How does the accuracy of UK PDS Brain Bank Clinical Criteria compare with the accuracy of pathological diagnosis?* Recent, potentially important evidence was found: Jellinger, Kurt A., et al. "Accuracy of clinical diagnosis of Parkinson disease: A systematic review and meta-analysis." *Neurology* 87.2 (2016): 237-238. This evidence has not been included in the draft guideline update. (2) Full draft guideline, line 941: *How useful is SPECT in discriminating PD from alternative conditions?* Recent systematic review evidence was found: Suwijn, Sven R., et al. "The diagnostic accuracy of dopamine transporter SPECT imaging to detect nigrostriatal cell loss in patients with Parkinson's disease or clinically uncertain parkinsonism: a systematic review." *EJNMMI*	Thank you for your comment. Your interpretation of this is correct. As these parts of the guideline were not included as part of the scope of this update, no additional evidence searches were undertaken for these questions, and hence the recommendations cannot be substantively changed. These searches would not be updated unless these sections of the guideline were included as part of a future update.

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				research 5.1 (2015): 1, and Brigo, F., et al. "[123I] FP-CIT SPECT (DaTSCAN) may be a useful tool to differentiate between Parkinson's disease and vascular or drug-induced parkinsonisms: a meta-analysis.' *European Journal of Neurology* 21.11(2014):1369-e90. Neither of these two studies were included in the draft guideline update. These examples suggest that evidence searches relating to recommendations in those unchanged portions have not been refreshed.	
Parkinson's UK	Full	general	general	We are concerned that references throughout the draft guideline about stopping medicines abruptly do not appear to be as prominent as they were in the previous guideline. The draft guideline should emphasise the importance of people taking their medication as prescribed. As well as ensuring professionals understand the importance of people with Parkinson's taking their medication at the right time.	Thank you for your comment. After further discussion with the GDG, it has now been agreed to carry forward the recommendations on drug administration from the old guideline.
Parkinson's UK	Full	general	general	When a NICE guidelines states "do not offer treatment X", professionals will interpret this literally and remove that treatment option from all patients. However, the guidelines are clear that the statement is made for most patients, therefore the guideline acknowledges it could be beneficial for a smaller group of people. At each point where a treatment could offer benefit to *some* patients, we recommend that the statement "do not offer treatment X" in the guideline is qualified to make sure that this point is understood.	Thank you for your comment. In section 1.3 in the guideline, advice is provided on how one should interpret the recommendations and it does mention that when a "do not offer" recommendation is made, it may not apply to all patients but for most. The way recommendations are made is standardised across all NICE guidelines. It is important to note that NICE guidelines are guidance for providers and are therefore not mandatory. The ultimate decision about a patient's care will also depend on the clinician's own experience and knowledge of the patient's condition and health needs.
Parkinson's UK	Full	general	general	Being aware that each patient is an individual should be heeded throughout this guideline and the recommendations.	Thank you for your comment. It is important to note that NICE clinical guidelines are guidance for providers on the

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				The fact that people with Parkinson's are a varied group mean that effect sizes in randomised trials do not give much insight into the range of impact there could be to a specific intervention. Detailed attention should be given to the range of reactions people have after receiving an intervention. And these results should inform the recommendations. We are concerned that some recommendations in this guideline, which will remove available therapeutic options only consider 'average' responses without acknowledging that everyone with Parkinson's has different symptoms.	general population with a specific condition. A 'do not offer' recommendation does not mean that the treatment is ineffective for everyone but for most. In section 1.3 of the guideline, guidance on how to interpret NICE's recommendations is provided. NICE's recommendations should be taken into consideration together with the clinician's own personal experience and knowledge in the field as well as the individual patient's health and care needs, which may of course be considerably different between individuals. However, we do not accept that variability in response to a treatment means that the results from RCTs do not have value. If there is an a priori identifiable group of people who will benefit from a treatment more than others, then it should be possible to conduct studies specifically in that subgroup and demonstrate this larger effect. If it is not possible to identify those people who will benefit more, then the "average" response in an RCT is the correct data to use for decision making purposes.
Parkinson's UK	Full	general	general	We are disappointed that there is no specific recommendation to encourage cognitive assessment of people with Parkinson's disease. Or in people whose symptoms suggest a high risk of cognitive impairment. Parkinson's UK believes advice on the consideration of cognitive assessments should be included.	Thank you for your comment. Unfortunately, this topic is not within the scope of this guideline update so the GDG have not looked at any evidence in this area to formulate any recommendations. Recommendations on the diagnosis of Parkinson's disease dementia are within the scope of the NICE guideline on dementia, which is currently being updated and is expected to publish in 2018.

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Parkinson's UK	Full and short	general	general	Anxiety is not mentioned in the full version or short version of this guideline. Yet clinicians have told Parkinson's UK that anxiety has a high impact on people with Parkinson's and their carers. Anxiety disorder occurs in 25-43% of people with Parkinson's, and significant symptoms in up to 58% (*Dissanayaka N, et al. (2014) The clinical spectrum of anxiety in Parkinson's disease. Mov Disord 29(8):967–975.*). In the PROMS-PD study (*Brown RG, et al. (2011) Depression and anxiety related subtypes in Parkinson's disease. J Neurol Neurosurg Psychiatry 82(7):803–9*) out of 513 people with Parkinson's, 31% had a psychiatric symptom profile with prominent anxiety. Parkinson's UK recommends that information on identifying, treating and managing anxiety when living with Parkinson's is added into this guideline.	Thank you for your comment. The areas to be covered as part of this guideline update were detailed in the published scope, which went through a period of public consultation before this update began. Unfortunately, it is not now possible to include areas outside of that agreed remit.
Parkinson's UK	Short	10	14 - 16	We believe a recommendation should be added that when considering the need to switch or modify medication, advice should always be sought from a healthcare professional with specialist expertise in Parkinson's disease before modifying therapy.	Thank you for your comment. The GDG agreed with the general sentiment expressed here, and variously through the guideline have made recommendations to this effect. However, the GDG acknowledged that such advice may not always be available in a timely fashion, and therefore there are circumstances where it may not be possible to obtain such advice in advance of modifying therapy.
Parkinson's UK	Short	10	21 - 24	Recommendation 1.4.6 (recommendation 82 in the full guideline) suggests that advice should be sought from an expert before modifying dopaminergic therapy, in the context of impulse control disorders. This will not be as useful as possible for the intended reader.	Thank you for your comment. The GDG agreed that it is important to provide such a summary, and therefore recommendations 1.4.7 to 1.4.9 specify the steps to managing impulse control disorders for which evidence was available.

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				We believe this recommendation should be changed to summarise the correct approach to management of impulse control disorders, so that experts can utilise the guidelines to assist them with these treatment approaches, and those less expert can understand the issues (and take first steps, when circumstances are appropriate).	
Parkinson's UK	Short	10	3 - 18	We welcome enhanced information and recommendations around impulse control disorders.	Thank you for your comment.
Parkinson's UK	Short	11	8-9	Recommendation 1.4.9 (recommendation 85 in the full guideline) suggests that the cognitive behavioural therapy (CBT) should be used for patients with impulse control disorders. We agree that this form of treatment could help people with Parkinson's, however work must be done to increase access to CBT across the country as it is often not available, and people with Parkinson's who do meet the criteria may have to wait a long time for treatment.	Thank you for your comment. The GDG agreed that there are difficulties accessing this service in many areas, and hope that the recommendations will lead to the service becoming more available.
Parkinson's UK	Short	12	17 - 24	We support the British Geriatrics Society's view that there is not strong enough evidence to justify recommendation 1.5.9 (recommendation 38 in the full guideline) to remove the proton pump inhibitors for orthostatic hypotension. We recommend that the guideline development group review this evidence again.	Thank you for your comment. After further discussion, the GDG has agreed that proton pump inhibitors should be removed from the list of medicines specified here.
Parkinson's UK	Short	12	5 - 15	Recommendations 1.5.6, 1.5.7 and 1.5.8 (recommendations 35, 36 and 37 in the full guideline) do not have sufficient evidence. The evidence summarised for controlled-release levodopa appears to show no difference (from standard release), yet the guideline recommends it as a treatment option.	Thank you for your comment. After further discussion, the GDG agreed that these recommendations had been too strongly worded based on the underlying evidence. Accordingly, the words modified release have been removed from the recommendations, and the final recommendation about when dopamine agonists should

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					be taken has been entirely removed. This leads to a simpler set of recommendations which the GDG believes are supported both by the evidence and clinical judgement.
Parkinson's UK	Short	12	5 - 15	We believe a recommendation should be added that when considering the need to switch or modify medication, advice should always be sought from a healthcare professional with specialist expertise in Parkinson's disease before modifying therapy.	Thank you for your comment. The GDG agreed with the general sentiment expressed here, and variously through the guideline have made recommendations to this effect. However, the GDG acknowledged that such advice may not always be available in a timely fashion, and therefore there are circumstances where it may not be possible to obtain such advice in advance of modifying therapy.
Parkinson's UK	Short	13	1 - 7	We believe a recommendation should be added that when considering the need to switch or modify medication, advice should always be sought from a healthcare professional with specialist expertise in Parkinson's disease before modifying therapy.	Thank you for your comment. The GDG agreed with the general sentiment expressed here, and variously through the guideline have made recommendations to this effect. However, the GDG acknowledged that such advice may not always be available in a timely fashion, and therefore there are circumstances where it may not be possible to obtain such advice in advance of modifying therapy.
Parkinson's UK	Short	13	1 -3	We welcome recommendation 1.5.10 (recommendation 39 in the full guideline) to consider midodrine as treatment for orthostatic hypotension.	Thank you for your comment.
Parkinson's UK	Short	13	1-3	Recommendation 1.5.10 (recommendation 39 in the full guideline) says to "*consider midodrine*". However in the evidence it says "*The GDG were not confident that it [midodrine] clearly represents the optimal choice for people with OH and Parkinson's disease*." With that in mind the recommendation that midodrine is the first choice cannot be justified.	Thank you for your comment. The GDG agreed that the evidence behind the use of midodrine was not particular strong, but in view of it being the only medicine with a license in this area felt it was appropriate to make a "consider" level recommendation. The GDG agreed there may be many reasons why midodrine is not the optimal choice for individual people, and in this situation fludrocortisone is a logical and commonly used

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				The label status appears to be used in one way here (to support on-label midodrine use), but in the opposite way for quetiapine versus clozapine (to support off-label quetiapine use). In situations like this, where opinions conflict and there is no definite answer, we recommend that the option to use one treatment or another should be left open.	alternative. The recommendations for quetiapine and clozapine have now been altered so a stronger "offer" level recommendation is made for clozapine versus a "consider" recommendation for quetiapine.
Parkinson's UK	Short	13	4-7	We cautiously welcome recommendation 1.5.11 (recommendation 40 in the full guideline) to consider domperidone as treatment for orthostatic hypotension but we have sought advice from the British Geriatrics Society and are mindful of the Medicines and Healthcare products Regulatory Agency (MHRA) recommendations on caution in the use of this drug.	Thank you for your comment. After receiving consultation feedback on this recommendation, the GDG has agreed that the evidence base for the use of domperidone was not sufficiently strong, and therefore this recommendation has been removed from the final version of the guideline.
Parkinson's UK	Short	13	9 - 11	Parkinson's UK strongly believes that recommendation 1.5.12 (recommendation 41 in the full guideline) is not adequate. Referring to a general guideline on '*depression in adults with a chronic physical health problem*' does not equip professionals with enough information about people with Parkinson's who experience depression. Depression is a really key area that must be covered coherently in this guideline. '*The non-motor symptoms of Parkinson's disease (PD) can be as disabling for an individual as their motor symptoms, if not more so.*' (Hinnell, C., Hurt, C. S., Landau, S., Brown, R. G., Samuel, M., & on behalf of the, P.P. D. S. G. (2012). Non-motor versus motor symptoms: How much do they matter to health status in Parkinson's disease? Movement Disorders, 27(2): p. 236-241).	Thank you for your comment. The scope for this guideline update, which was publically consulted on, specified that evidence on interventions for depression will not be included as part of this update, and the guideline will cross-refer to the NICE guideline on depression in people with a chronic physical health problem. At this stage it is not possible to alter this decision and hence this recommendation cannot be changed. It is important to stress that, as you correctly point out, evidence from people with Parkinson's disease will have been included as part of the development of this other guideline. The NICE guideline on depression does contain recommendations on managing comorbid anxiety and

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				'*Non-motor symptoms dominate the clinical picture of PD and contribute to severe disability, impaired quality of life, and shortened life expectancy*' (Chaudhuri, K.R., Healy, D.G., Schapira, A.H. (2006). Non-motor symptoms of Parkinson's disease: diagnosis and management. Lancet Neurol. 5(3): p. 235-45). Anxiety and depression are the most prevalent non-motor symptoms in PD. Depending on criteria used depression affects up to 50% of people affected by PD (Burn, D.J. (2002). Beyond the iron mask: towards better recognition and treatment of depression associated with Parkinson's disease. Mov Disord, 17(3): p. 445-54) and up to 31% of people with PD report some level of anxiety (Brown, R.G., et al. (2011). Depression and anxiety related subtypes in Parkinson's disease. Journal of Neurology, Neurosurgery & Psychiatry, 82(7): p. 803-809). The NICE guideline on *depression in adults with a chronic physical health problem* does not include specific advice about managing depression in Parkinson's. Though we recognise that some of the research included studies that were about people with Parkinson's. This guideline must make clear that depression in Parkinson's is caused by an actual mechanism of the illness, it is not only a reaction to living with the condition (Chaudhuri KR, Schapira AH (2009) Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment. Lancet Neurol 8(5):464–474.), although this is also a factor for some people.	depression, and NICE has also produced a number of pieces of guidance looking at specific types of anxiety (https://www.nice.org.uk/guidance/conditions-and-diseases/mental-health-and-behavioural-conditions/anxiety)

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				Additionally some general treatments for people with depression aren't effective for people with Parkinson's because of their biochemistry. Some of the other symptoms of Parkinson's, in particular facial masking, slowness of speech and other communication issues can both mask depression, and be mistaken for symptoms of depression, which makes accurate screening for depression a very important aspect of managing the condition. Parkinson's UK believe that more comprehensive guidance should be added to this section to give professionals the knowledge and information they need to deal with the specific causes and impact of depression for people with Parkinson's.	
Parkinson's UK	Short	14	3-7	Recommendation 1.5.16 (recommendation 45 in the full guideline) indicates that dopaminergic therapy must not be reduced without expert advice, when the patient has hallucinations or delusions. We agree that this is what should take place in an ideal situation, but it is important to acknowledge that sometimes expert advice is not available quickly enough when needing to address urgent and acute situations. The recommendation should be changed to reflect this, stating that "*people should seek advice from a professional with specialist expertise in Parkinson's disease where possible, before modifying therapy."* The guideline should also include information on the expert approach to this. Specifically a reduction in dopaminergic therapy (in particular drug classes	Thank you for your comment. The GDG felt it appropriate to clarify that people should seek advice from specialist care before modifying dopaminergic therapy, because of the known harms that can result if this is done incorrectly. However, they GDG did acknowledge that such advice may not always be available in a timely fashion, and therefore if advice has been sought and is not available, a clinician may still feel it appropriate to modify therapy in urgent cases. The guideline does also contain a specific recommendation about modifying dopaminergic therapy, so the GDG did not feel this represented a gap in the guidance provided.

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				other than levodopa) while avoiding total cessation of treatment due to the risk of neuroleptic malignant syndrome.	
Parkinson's UK	Short	15	3-5	Concerning recommendation 1.5.22 (recommendation 53 in the full guideline) it is stated that "t*he evidence showed a clinical harm of glycopyrrolate from side effects, as omdocated by discontinuation of medication" Presumably this should be 'indicated'. It may be more useful to use the main primary name for this drug per BNF, namely Glycopyrronium bromide. It is not made clear which formulation is proposed for this use*." As the evidence leading to this recommendation is derived from across other disease areas, it is difficult to apply to Parkinson's because of the cognitive issues. There appears to be no clinical evidence why this antimuscarinic/anticholinergic drug is a better choice than any other from the same class. Alongside this, the "*GDG noted that their experience of these drugs [anticholinergics] is that they do cause serious side effects and may not be well tolerated.*" In the absence of trial evidence, and any reported comparative experience by the GDG with Glycopyrronium bromide in Parkinson's, versus other agents of this class, Parkinson's UK believe it would be better to avoid recommending this drug specifically and leave treatment options open.	Thank you for your comment. You are correct that should have been indicated, and this has been corrected. The name has also been changed to glycopyrronium bromide as per your suggestion. Whilst it is true that the evidence for this question was derived from a broader patient population, the evidence base does include trials in people with idiopathic Parkinson's disease, and there is a trial of glycopyrrolate in this group. The GDG did agree that glycopyrrolate was likely to cause fewer cognitive side-effects than other, centrally acting, anticholinergics, and therefore it was appropriate that this drug be considered above other anticholinergic options. The trials in the evidence base were al of oral glycopyrrolate, but the GDG felt it appropriate not to be too specific on this point as they were aware of other alternatives that may be more commonly used in certain local areas (e.g. spray) and did not want to preclude the use of these alternatives.
Parkinson's UK	Short	16	1 - 3	We are pleased that recommendation 1.5.27 (recommendation 58 in the full guideline) has been broadened to include all cholinesterase inhibitors and consideration of memantine as a second line therapy for people with Parkinson's disease dementia.	Thank you for your comment.

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				We support the British Geriatrics Society's view that considering treatment of mild to severe dementia in Parkinson's disease will enable more people to receive beneficial therapy for cognitive impairment.	
Parkinson's UK	Short	16 17	22-23 1 - 6	Parkinson's UK hears from people with Parkinson's across the country that they find their Parkinson's disease nurse specialists invaluable. There is a need for stronger evidence in this important area of Parkinson's care. Parkinson's nurses are also vital in the delivery of specialised local services for people living with the condition throughout the UK. In addition, these nurses can save the NHS millions of pounds by driving down demand for consultant appointments, decreasing unexpected hospital admissions and shortened hospital stays. Parkinson's nurses can help to save £147,000 in days spent in hospital. £80,000 in unplanned admissions, and £43,812 in avoided consultant admissions (Parkinson's nurses – affordable, local, accessible and expert care A guide for commissioners in England which can be found online at (https://www.parkinsons.org.uk/sites/default/files/publications/download/english/englandnursereport.pdf We also speak to people daily who benefit from the support and expertise provided by Parkinson's nurses. "*The expertise makes such an enormous difference to our lives. While you see a consultant once every six months, if you're lucky, our nurse was always there to turn to if we thought something might be wrong. Last year I was getting worried about my husband when he started putting clothes on back to*	Thank you for your comment. Unfortunately, the recommendations on Parkinson's disease nurse specialists were not included within the scope of this guideline update, and therefore no substantive changes to these recommendations could be made.

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				front, and doing other little things out of the ordinary. I mentioned it to our Parkinson's nurse and after asking him some questions she immediately decided he needed to see a dementia specialist. We got a diagnosis of mild dementia within a matter of weeks which meant we could start him on medication quickly – which would never have happened without our nurse. Parkinson's is so complex and affects everyone differently so you absolutely need to have specialist knowledge to deal with it. Without a Parkinson's nurse, life could become extremely difficult." We believe the final line of recommendation 1.7.1 (recommendation 60 in full guideline) should be changed to state that where available people with Parkinson's are allocated a Parkinson's nurse. We also believe a recommendation should be added to seek advice from a healthcare professional with specialist expertise in Parkinson's disease before modifying any therapies.	
Parkinson's UK	Short	17	12 - 13	Recommendation 1.7.3 (recommendation 62 in the full guideline) should include that people who fall, or are at risk of falls, because of their Parkinson's symptoms should be referred to a physiotherapist with experience of Parkinson's.	Thank you for your comment. The GDG believe that the recommendation "Offer Parkinson's disease-specific physiotherapy for people who are experiencing balance or motor function problems" should cover the needs of people who fall or at risk of falls as a result of their Parkinson's disease, as these are related to balance problems.
Parkinson's UK	Short	17	14-20	The guideline should recommend that occupational therapists form part of the multidisciplinary teams assessing and supporting people living with Parkinson's.	Thank you for your comment. Unfortunately, the GDG were not able to make recommendations on how multidisciplinary teams should be formed, as this did not fall within the scope of this guideline update. However,

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					the GDG did express their agreement with the sentiment behind this comment.
Parkinson's UK	Short	17	15-20	We support recommendation 1.7.4 (recommendation 63 the full guideline) in the short guideline that states people who are in the early stages of Parkinson's should be referred to an OT, we would add that the OT should have experience with Parkinson's and that referral to an OT should not just be in the early stages of the condition. Services provided by an occupational therapist can benefit people at varying stages of Parkinson's, and this recommendation should be amended to reflect this, so it is not only those who are in the early stages of Parkinson's.	Thank you for your comment. The recommendation that follows rec 1.7.4 recommend OT for people who have difficulties with daily living activities. The GDG agreed that this second recommendation therefore covers people with Parkinson's disease who are not in the early stages of the condition.
Parkinson's UK	Short	17	19-20	In recommendation 1.7.5 (recommendation 64 in the full guideline) the guideline states people with Parkinson's should be offered disease specific occupational therapy to help with difficulties around daily living activities. The definition of 'daily living activities' is core basic functions like eating, but does not include acquiring the food or preparing it. In this instance daily living would equate to a person being able to raise their hand to their mouth, chewing and swallowing. These are basic core functions. We are concerned that using the term 'daily living activities' would preclude things like leisure, recreation and social interaction. Though a lot of evidence has been excluded from this section, we believe the Sturkenboom et al (2014) assessor-blind randomised controlled trial ('Efficacy of occupational therapy for patients with Parkinson's disease: a randomised controlled trial' by Ingrid H W M Sturkenboom, Maud J L Graff, Jan C M Hendriks, Yvonne Veenhuizen, Marten Munneke, Bastiaan R Bloem, Maria W Nijhuis-van der Sanden, for the OTiP study group) is crucial to focus on. The trial talks about purposefully meaningful daily living activities. We believe it is essential that occupational therapists look at people's satisfaction with their	Thank you for your comment. The GDG discussed this point and agreed that whilst there was logic behind the alternative wording suggested, "daily living activities" is a standard terminology used in the field which is well understood, as well as being the terminology used in the trial which provided evidence for this recommendation, and therefore they felt the original wording of this recommendation should be maintained. A slight edit has been made to this recommendation, so it now says "activities of daily living, to be consistent with other pieces of NICE guidance." We can confirm that when developing recommendations on occupational therapy, the GDG did take the evidence from the Sturkenboom et al., 2014 study into consideration, and it formed the key evidence behind this specific recommendation.

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				performance of meaningful daily living activities including things like going to church if that is their preference, and social activities. The recommendation must make it clear that purposefully meaningful daily activities should be considered and supported through occupational therapists' interventions.	
Parkinson's UK	Short	17	19-20	Recommendation 1.7.5 (recommendation 64 in the full guideline) should include that people who fall, or are at risk of falls, because of their Parkinson's symptoms should be referred to a physiotherapist with experience of Parkinson's disease.	Thank you for your comment. The GDG believe that the recommendation "Offer Parkinson's disease-specific physiotherapy for people who are experiencing balance or motor function problems" should cover the needs of people who fall or at risk of falls as a result of their Parkinson's disease, as these are related to balance problems.
Parkinson's UK	Short	17	22- 29	Parkinson's UK believe a recommendation should be added to ensure that speech and language therapists are included in multidisciplinary teams who work with and support people with Parkinson's.	Thank you for your comment. Unfortunately, the GDG were not able to make recommendations on how multidisciplinary teams should be formed, as this did not fall within the scope of this guideline update. However, the GDG did express their agreement with the sentiment behind this comment.
Parkinson's UK	Short	17	8 - 13	We welcome recommendations 1.7.2 and 1.7.3 (recommendations 61 and 62 in the full guideline) that people with Parkinson's should be referred to Parkinson's specific physiotherapy.	Thank you for your comment.
Parkinson's UK	Short	17	8 - 13	We believe a recommendation should be added that physiotherapists should work closely with occupational therapists as part of a multidisciplinary team to address the reason and cause for falls and help prevent these.	Thank you for your comment. Unfortunately, the GDG were not able to make recommendations on how multidisciplinary teams should be formed, as this did not fall within the scope of this guideline update. However, the GDG did express their agreement with the sentiment behind this comment.

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Parkinson's UK	Short	18	1- 3	We welcome recommendation 1.7.7 (recommendation 66 in the full guideline) to consider referring people with Parkinson's for alternative and augmentative communication and equipment.	Thank you for your comment.
Parkinson's UK	Short	18	10-11	Recommendation 1.7.10 (recommendation 69 in the full guideline) refers to considering referral to a specialist dietitian. However we are concerned this is not clear. Does the recommendation mean someone should be referred in general or just for the protein redistribution information? In the early stages of the condition people can have many general questions regarding healthy eating and maintaining a healthy weight, dietitians are ideally positioned to assist and can ensure people get up to date and appropriate guidance. As the disease progresses anybody who is unintentionally losing weight or has any degree of dysphagia should be referred to ensure they do not become malnourished and to allow timely and appropriate discussions regarding PEG feeding so appropriate advance planning can be made. We strongly believe that the guideline should clarify this recommendation, stating that people with Parkinson's should have access to a specialist dietitian.	Thank you for your comment. In the absence of evidence about what interventions and advice this dietician should give, the GDG did not feel they were able to be more specific than this recommendation. However, this recommendation has now been moved to the first one in this section, to make clear these referrals are not just concerned with protein redistribution.
Parkinson's UK	Short	18	12 - 15	Recommendation 1.7.11 must highlight Parkinson's specific causes of falls and give more information on Parkinson's specific guidance around falls. It is not good enough to signpost to a generic falls document – that is generally for older people. People with Parkinson's fall for unique and specific reasons including postural hypertension, start hesitation, freezing, inability to control their speed, difficulty negotiating change in surfaces (carpet to lino) difficulty with mobility in visually	Thank you for your comment. Specific evidence on falls was sought as part of the evidence review on physiotherapy, and unfortunately no strong evidence was found on this issue. The reference to falls as part of recommendation 1.7.11 is specifically related to the advice on vitamin D supplementation included in that recommendation.

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				complex areas, instability turning and changing direction, reduced saving reactions, involuntary movements, tremor, reduced use of hand function and unsuitability of a lot of walking aids. If someone with Parkinson's is sent to a clinic where professionals know little about their condition, and the reason for their falls, they could be given inappropriate aids and interventions. The recommendation must be changed to state that people with Parkinson's who are falling regularly, or at risk of falling, must be referred to physiotherapy and occupational therapy services with expertise in Parkinson's to look at their motor function and balance, as well as environmental factors.	The GDG believe that the recommendation "Offer Parkinson's disease-specific physiotherapy for people who are experiencing balance or motor function problems" should cover the needs of people who fall or at risk of falls as a result of their Parkinson's disease, as these are related to balance problems.
Parkinson's UK	Short	18	4 - 18	We are disappointed not to see any references to enteral feeding in the section on nutrition. The 'Best practice guideline for dietitians on the management of Parkinson's' written by the British Dietetic Association in partnership with Parkinson's UK says 'Swallowing difficulties need to be addressed promptly to prevent weight loss and malnutrition. About 95% of Parkinson's patients experience swallowing difficulties at some stage of the condition. Dysphagia occurs in the later stages of Parkinson's. Significant problems with swallowing require expert assessment from a speech and language therapist and guidance regarding appropriate food texture modification. Since texture modified diets e.g. puree, may be nutritionally dilute and not energy dense enough to prevent weight loss, additional use of supplementary enteral nutrition support may be indicated. Active nutritional support via the enteral route e.g. naso-gastric tube for short-term feeding or if indicated, a Percutaneous Endoscopic Gastrostomy (PEG) could be considered for long-term feeding. PEGs are	Thank you for your comment. Unfortunately, end of life nutritional management is not within the scope of the current guideline update, and it was therefore not possible for the GDG to make a research recommendation on this topic. However, NICE does have a specific guideline on end of life nutrition, which did consider evidence from people with Parkinson's disease.

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				being used increasingly in the treatment of patients with neurogenic dysphagia to prevent or reverse nutritional deficits, and this can improve fitness and quality of life for those patients unable to take sufficient supplements orally.' This can be found online at https://www.parkinsons.org.uk/sites/default/files/publications/download/english/dietitians_bestpracticeguideline.pdf The guideline states there is no evidence on end of life nutritional management, but it is nevertheless a topic that should be addressed as part of advanced care planning. We recommend that this topic be added to the research questions in this section of the guideline.	
Parkinson's UK	Short	18	5-7	Recommendation 1.7.8 (recommendation 67 in the full guideline) stipulates their diet should be discussed where most of the protein is eaten in the last meal of the day. However this recommendation should also include that if this issue is raised and the patient is interested, a referral should be made to a specialist dietitian to ensure it's done correctly, and the overall nutritional status is not compromised. It should also state that if the change is not a success, it must be stopped after 1 month. It should also be stopped if there is increased dyskinesia or marked weight loss. To enable this, the patient should have their weight checked at the start of the process.	Thank you for your comment. A recommendation on referring people with Parkinson's disease to a dietitian for specialist advice has been made by the GDG. Please see recommendation 1.7.10 (short guideline). In the absence of evidence about what interventions and advice this dietician should give, the GDG did not feel they were able to be more specific than this recommendation.
Parkinson's UK	Short	19	4-6	We are incredibly concerned by recommendation 1.8.4 (recommendation 79 in the full guideline) stating clinicians should not offer LCIG at any stage of Parkinson's disease. We strongly believe that LCIG should remain an option to be prescribed for people with advanced Parkinson's.	Thank you for your comment. The GDG was grateful to receive the eloquent testimony of people living with Parkinson's disease, and did not disagree that it would be to the benefit of people with advanced Parkinson's disease if LCIG could remain available at a cost that

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				For most people, conventional medical treatments can help to manage their symptoms throughout their journey with Parkinson's, and they have no need for advanced treatments. However, people with symptoms that are not well managed by conventional medication will need access to advanced treatments. There is a very small minority of people with advanced Parkinson's who have very severe and extreme symptoms, despite Best Medical Treatment (BMT), including apomorphine. Some people also experience severe neuropsychiatric side effects from apomorphine and cannot tolerate it. The impact on quality of life for people in this position is severe, and it has a knock-on effect on carers and families. Deep Brain Stimulation (DBS) surgery can be life-changing for some. However, people with mental health symptoms, cognitive impairment and speech dysfunction caused by their Parkinson's are not clinically suitable for DBS, so this treatment is not an option for them. These symptoms are common in Parkinson's. In clinical practice, LCIG is only used when all other interventions, including BMT and DBS have been considered and have been shown to be ineffective for the person, or they are clinically unsuitable options. This impact of this recommendation in the draft guideline could be catastrophic as it leaves people with Parkinson's no treatment options once all other oral treatments BMT and DBS have failed. LCIG was classified by the EU as an Orphan treatment, because the number of people for whom it is a suitable treatment was less than 5 in 10,000. There	would not result in unacceptable harm being caused elsewhere in the NHS. For comments on the effectiveness and cost effectiveness of LCIG, please see **theme 1**. For comments on the effectiveness and cost effectiveness of LCIG in subgroups of people with advanced Parkinson's disease, please see **theme 1b**. For comments on the paucity of therapeutic options for people with advanced Parkinson's disease, please see **theme 1e**. For comments on the small population for whom LCIG is currently used, please see **theme 1d**. For comments on the ability of EQ-5D to capture HRQoL in advanced Parkinson's disease, please see **theme 8**. For comments on the relationship between NICE's conclusions on LCIG and NHS England's specialised commissioning policy, please see **theme 9a**. For comments on apparent discrepancies between NICE's appraisal of the evidence on LCIG and the view taken by NHS England's specialised commissioning policy, please see **theme 9b**.

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				are known issues with using standard health technology assessment methodology to evaluate the efficacy of orphan medications, which are thought to place orphan medicines at a disadvantage compared with treatments in more widespread use. References for this include: http://rarejournal.org/rarejournal/article/view/60/95) Sussex, J., Rollet, P., Garau, M., Schmitt, C., Kent, A. and Hutchings, A., 2013. A pilot study of multi-criteria decision analysis for valuing orphan medicines. *Value in Health*, 16(8), pp.1163-1169 Online at https://www.clinicalkey.com/#!/content/playContent/1-s2.0-S1098301513043568?returnurl=null&referrer=null Iskrov, G., Miteva-Katrandzhieva, T., and Stefanov R, 2016. Multi-Criteria Decision Analysis for Assessment and Appraisal of Orphan Drugs. *Frontiers in Public Health* 4: 214. Online at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5042964/ Dr Neil Archibald, a Consultant Neurologist told us '*I believe it is reasonable to say there isn't enough evidence to say LCIG is cost effective. But this guideline goes further than that and states it should not be used, which is fundamentally different. LCIG is also not a comparative treatment, because you can't get it unless you have taken apomorphine and it's been ineffective, and are not suitable for DBS. For example DBS is not suitable for many people over 70, anyone with cognitive impairment, people with certain types of falls, and speech and swallowing problems. You can't secure NHS England funding unless you prove these steps have been taken and other treatment options are not suitable. This treatment is used for a tiny number of patients,*	For comments on apparent discrepancies between NICE's conclusions on LCIG and SMC advice, please see **theme 9c**.

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				and is an incredibly important treatment for these people. In 12 months, out of 1500 patients we have 3 who were successfully prescribed LCIG.' Dr Richard Genever, Chair of British Geriatrics Society Movement Disorders Section confirms "*the removal of LCIG is of great concern to us. It is a treatment that is only considered in people with advanced Parkinson's disease. To date, use of the drug has been in relatively small numbers so the overall cost impact is relatively low. Due to the nature of the testing process for LCIG it is only continued in patients in whom benefit has been shown. Therefore we feel that the economic calculations used for this recommendation do not take account of the real world use of the drug. We also note that LCIG was very recently assessed by NHS England (including economic analysis) and was approved for use as long as assessments took place in specialist centres. We would ask strongly for this recommendation to be reconsidered*." As well as benefitting the person with Parkinson's, it is important to acknowledge the benefit to the carer of the person with Parkinson's using LCIG. People with Parkinson's can have very disruptive nights, which put a lot of strain on them and the people caring for them. Carers often get little sleep, and are disrupted regularly. When using LCIG, people with Parkinson's can cope for hours at a time, particularly through the night. Parkinson's UK strongly believes the health economics around this should be considered and this should be added to the research questions for the development of future guidelines. "On/off" responses to medication cause fluctuations from hour to hour and day to day. Someone is "on" when their medication is working. But when someone	

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				is "off", they can barely move and may become acutely anxious. Some people cycle between painful cramps (dystonia) when "off" and involuntary movements (dyskinesia) that can cause injury to themselves or others when they are "on". "On/off" fluctuations can be unpredictable. Some people become reluctant to leave familiar surroundings in case they "switch off" and are unable to move or communicate, which could leave them in a vulnerable or even dangerous situation. Others are "off" for hours at a time, and become confined to their bed or chair. We have examples from people with Parkinson's and their carers, about the benefits that LCIG has had on their life. Some of these include: "*My husband has had Parkinson's for 11 years and has tried various medications without any improvement at all, and now as time advances he is getting much worse. He can't walk without falling, which he does at least twice a day. I'm his carer and I have a lot of trouble trying to get him up – I'm not young myself anymore. So when he was given the option to try something called Duodopa, we felt we had nothing to lose. He spent a few days in hospital, so the consultant could trial this new drug. It worked like a treat, it was unbelievable as my husband, who had been falling so often, got up and walked right across the room. We were both delighted as he just kept walking around*." "*I'm at the stage where no other treatment really works for me and one medication I tried caused me other serious health problems. I'm on tablets now, around 16 a day, but they can take a long time to kick in, I often freeze to the spot and once I get walking I can only go in a straight line, corners are impossible. I have carers twice a day because I struggle so much to get*	

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				dressed or undressed, it's not ideal because I'm in my pyjamas by 5pm every evening. I know Duodopa is expensive but how can you put a price on someone's quality of life? Surely it would also lighten the load on carers as well if more people were able to access Duodopa." "*My husband's condition has deteriorated so much that he is now bed-bound 99% of the time. He is exhausted, in pain, his tremor is so violent that he has to have something in his mouth as his teeth chatter so much and he sweats badly. Tablets do not work for him anymore and do nothing to ease these symptoms. In the past he's been put on an apomorphine pump but this caused major problems with psychosis so we were reluctant to try that again. He became a completely different person, he would hallucinate and think people were trying to poison him – this was not the shy, gentle man that I know. Without duodopa, we have two options. He can stay on tablets which do nothing to stop his violent tremor or the pain and leave him bed-bound, or he can go on apomorphine which results in a dangerous mental state. It's like banging our heads against a brick wall. As his carer and wife, it is so hard and distressing to watch him go through all this, something that I wouldn't even put an animal through. It's frustrating, annoying, upsetting and very difficult – the house is a horrible place to be at times. Both our Parkinson's nurse and neurologist have agreed that Duodopa is the only option left to us. It really frightens me that at just 59 we're being told nothing more can be done for my husband.*" "*Before being placed on Duopoda, I didn't have much quality of life at all. I was really struggling. I couldn't go out on my own, and couldn't be left alone as I used to fall a lot. I couldn't eat because the more I ate the less effective my drugs were so I got really thin and ended up weighing just over six stone.*	

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				(I'm 5 feet 4 inches tall). I was diagnosed with Parkinson's in 1996 and my problems have become fairly complex over the years. Prior to Duodopa, I had very limited mobility. Most of the time I couldn't walk, but when I could I would often freeze. Sometimes this happened in traffic in the middle of the road. This was extremely embarrassing and meant I couldn't go out alone for my own safety. My speech was very faint and indistinct- people couldn't understand me. I had problems choking. I had all sorts of muscle and joint pains and was very dyskineti. I also had real difficulty sleeping, partly because I couldn't change my position without help, for example to turn over. These symptoms made me feel very low and were incredibly demoralising. Not being able to predict how I was going to be from one minute to the next made planning anything extremely difficult. As my condition progressed I had tried all the drugs really; Dopamine agonists, Tolcapone and Entacapone, Apomorphine, they really were scraping the barrel by the end. I would get hopeful when I started something new, then I would get unmanageable side-effects and have to come off it. It was back to square one and was really disappointing. I felt depressed and hopeless when I thought there weren't any more options. Everything I had tried had failed and I thought I had reached the end of the road. I ended up asking one of the specialist nurses if there were any other options I'd missed. She mentioned Duodopa. I'd never heard of it. Taking Duodopa has had an effect on most of my symptoms. It made the on-off fluctuations more predictable. It's now easier for me to get out of an 'off period'. My speech is a lot better than it was and people usually understand me, which makes me significantly less frustrated. I have less pain, less choking problems and I sleep better. I realise that one drug will not help everyone, but this option has benefited me. My quality of life has markedly improved, I'm happier because I am more predictably able to do things."	

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				Though we understand LCIG is more expensive than some other therapies, it is not offered to everyone, and we believe some of the economic modelling does not take into account the discounts the manufacturer offers to NHS England. In Scotland. Duodopa was considered by the SMC and approved on the basis of its processes for evaluating orphan treatments. Here is the link to the decision on Duodopa with a link to the detailed advice https://www.scottishmedicines.org.uk/SMC_Advice/Advice/316_06_co_careldopa_Duodopa/co_careldopa_levodopa_Duodopa_2nd_Resubmission This recommendation appears to have been based entirely on the modelled cost utility analysis. The GDG said (page 203 in the full guideline) that in advanced Parkinson's, it may be more difficult to achieve improvement across the 3 levels of the 5 EQ-5D domains. Nevertheless this metric appears to be the only one determining the subsequent recommendations in the guideline not to prescribe the treatment. The lack of sensitivity of the EQ5D to capture change in quality of life (QoL) in Parkinson's is clearly appreciated by the GDG and the authors of the guidance. On page 207 of the full guideline, the improvements in QoL with early DBS measured by the PDQ39 are not accompanied by any change in EQ5D. Prior to making a recommendation on the use of LCIG greater consideration should be more evenly distributed to the other metrics e.g. PDQ39 SI shows a clear advantage of 7 points in favour of LCIG. The evidence used focused on one RCT which had a low number of participants. If the results of the evidence are to make a strong	

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				recommendation, NICE should ensure that the results from the qualifying RCT are in line with the general evidence. That is not the case here. Yet, when analysing DBS, the guideline does consider 4 different studies, none of which are double blinded. By analysing 4 of these, an average is able to be worked out. This was not done with LCIG. With NHS England having a policy in place to commission LCIG, the recommendation in the draft NICE guideline conflicts with this and could be confusing for clinicians and people with Parkinson's. We recommend that the NICE guideline stays in line with the NHS England policy on this and recommends this treatment where appropriate. After lengthy previous consultations, and the eventual specialist commissioning decision taken to support the use of LCIG, the number of prescriptions for it have remained low i.e. clinicians are using this expensive therapy in only a small number of individuals in whom BMT and DBS have failed or are otherwise inappropriate. We have heard anecdotally from clinicians that people who have started setting up a service that provides levodopa-carbidopa intestinal gel, have halted this in light of the draft guideline recommendation and will not move forward until they know the outcome. Another centre has said that no other patients are going to be considered to start LCIG until the final NICE guidance comes out. This will be seriously impacting people with Parkinson's who need this treatment, now. Parkinson's UK believe this recommendation 1.8.4 must be changed to ensure that LCIG can still be offered as an option by clinicians for the small	

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				number of patients whose severe symptoms cannot be adequately managed using either BMT or DBS.	
Parkinson's UK	Short	19 and 20	7-29 1- 5	We strongly support recommendations 1.9.1, 1.9.2, 1.9.3 and 1.9.4 (recommendations 86, 87, 88 and 89 in the full guideline) given on the importance of palliative care and advanced care planning decisions.	Thank you for your comment.
Parkinson's UK	Short	19 and 20	7-29 1- 5	As Parkinson's progresses someone may lose the ability to make or communicate these wishes, so it's vital that professionals, friends and family know what they want. A recommendation should be added to encourage discussions around wishes for end of life care. Also, advanced care planning should be encouraged to happen as early as possible, without making the person with Parkinson's or their carer uncomfortable.	Thank you for your comment. The GDG agreed that the key issue was to provide appropriate information about these issues, and that this should lead on to a conversation if this is something the person wishes.
Parkinson's UK	Short	31	3 - 18	A recommendation should be added to inform carers that people with Parkinson's may hide the fact they are suffering from an impulse control disorder. They should be advised to talk to the person with Parkinson's about these risks, and speak to medical professionals if they think impulse control disorder might be a problem for the person they care for. They should also be advised them to seek advice from relevant organisations including Parkinson's UK.	Thank you for your comment. The recommendation has been amended to make it clearer that people with PD may conceal that they are suffering from ICDs (see recommendation 1.4.3). The recommendation also recommend to advise the person who to contact if ICD develop, which would be their local healthcare provider.
Parkinson's UK	Short	4	16- 18	We strongly support recommendation 1.1.4 (recommendation 4 in the full guideline) that information should be given to carers. This is particularly important when people with Parkinson's disease have cognitive impairment, dementia or depression.	Thank you for your comment, and we entirely agree with the sentiments behind it.
Parkinson's UK	Short	4	19 - 21	Recommendation 1.1.5 (recommendation 5 in the full guideline) should include that people with Parkinson's must be given access to a multidisciplinary team as soon as possible after diagnosis. For example this should include speech and language therapists, occupational therapists,	Thank you for your comment. Unfortunately, this recommendation is from a part of the guideline that was not included as part of this update, and therefore no

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				physiotherapists, mental health professionals, dietetics and Parkinson's nurses.	substantive changes to this recommendation can be made.
Parkinson's UK	Short	4	2 - 21	People with Parkinson's should be encouraged to discuss advanced care planning, and preferences for palliative care. The UK Parkinson's audit found that less than 1/3 of people with markers of advanced Parkinson's had documented discussions about end of life care/Lasting Power of Attorney with their clinicians (239 clinical services took part): REF Parkinson's 2015 audit https://www.parkinsons.org.uk/sites/default/files/audit2015_summaryreport.pdf . Loss of capacity to communicate end of life wishes is a high risk for people with Parkinson's, as up to eight out of 10 people who have Parkinson's for more than 10 years develop dementia (Perez et al, Risk of dementia in an elderly population of Parkinson's disease patients: A 15-year population-based study, 2012). Research also shows that half of Parkinson's patients are unable to make or communicate decisions in the last month of life - 68% had difficulty communicating and 47% were confused. (Fleming, A., Cook, K. F., Nelson, N. D., & Lai, E. C. (2005). A 2008-2011 UK study also showed that 90 per cent of patients with Parkinson's had not discussed their wishes with a health or legal professional or written them down. (Walker RW, End Stage Disease in Parkinson's, Presentation to Autumn 2013 British Geriatrics Society meeting).	Thank you for your comment. Unfortunately, the communication section is not within the scope of this guideline update, and therefore no substantive changes to this section can be made. However, information needs around palliative care for patients and carers are covered in the palliative care chapter (1.9 in the full guideline).

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				We believe a recommendation should be added to this section around providing information about palliative care and instigating end of life care discussions.	
Parkinson's UK	Short	4	2 - 21	At the beginning of 2016 Parkinson's UK completed some work on "outcomes" of self management. This looked at information gathered from feedback forms completed by 675 participants who attended groups, telephone interviews and a focus group. Comments made by people with Parkinson's who have attended our self management programme include: "*I would recommend this course to everyone, even if they are shy or uncomfortable with public speaking, because with encouragement they will settle down and thoroughly enjoy the laughter and meeting brave people – and be inspired to carry on enjoying life."* "*Beginning at a very negative point, after three weeks I am totally changed. My attitude is one of motivation now rather than lacklustre acceptance. Thank you, I wish we had three more weeks."* "*The course is brilliant. I have got out of it things I had never considered. I have plans now which I believe will improve my husband's life and my life*." Outside of Parkinson's UK there is research into the benefits of self-management for long term conditions. The recent NHS England funded "Realising the Value" programme created a guide on supporting self management based on the findings of the research projects http://www.nesta.org.uk/self-management-education	Thank you for your comment. Unfortunately, this topic is not included in the guideline scope for this guideline update, and hence no substantive changes to the recommendations can be made.

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				Parkinson's UK believe a recommendation should be added to this section that people with Parkinson's should be signposted towards courses on self-management to enable them to live with the condition in the best way possible.	
Parkinson's UK	Short	5	17-18	Recommendation 1.2.3 (recommendation 12 in the full guideline) the diagnostic criteria refer only to the UK criteria. It would be useful to include the recent Movement Disorder Society criteria which can be seen at https://www.ncbi.nlm.nih.gov/pubmed/26474316	Thank you for your comment. Unfortunately, this recommendation is from a part of the guideline that was not included as part of this update, and therefore no substantive changes to this recommendation can be made.
Parkinson's UK	Short	5	19 - 21	We are pleased to see, and strongly support, recommendation 1.2.4 so that as much tissue as possible is donated to the brain bank for research.	Thank you for your comment.
Parkinson's UK	Short	7	18	A recommendation should be added to the information and support section to alert people with Parkinson's who are of working age, and their friends and family, about the pre-payment certificate option to help with the cost of prescriptions.	Thank you for your comment. Whilst a pre-payment certificate option to help with the cost of prescriptions is a relevant issue, the GDG did not believe they represented a specifically Parkinson's disease related point, and therefore they did not feel a recommendation within this guideline would be appropriate.
Parkinson's UK	Short	7	7 - 15	We believe a recommendation should be added that when considering the need to switch or modify medication, advice should always be sought from a healthcare professional with specialist expertise in Parkinson's disease before modifying therapy.	Thank you for your comment. The GDG agreed with the general sentiment expressed here, and variously through the guideline have made recommendations to this effect. However, the GDG acknowledged that such advice may not always be available in a timely fashion, and therefore there are circumstances where it may not be possible to obtain such advice in advance of modifying therapy.
Parkinson's UK	Short	7	7- 15	Recommendations 1.3.1 and 1.3.2 (recommendations 25 and 26 in the full guideline) for initial treatment choice of levodopa as opposed to other drug options is not supported by medical literature, or clinical practice/experience.	Thank you for your comment. The GDG acknowledges that due to the complex nature of decision making, a discussion should take place between the clinician and

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				The guideline must accept and convey the complicated nature of these decisions, including considering quality-of-life, comorbidities particularly cerebrovascular disease and mental health problems, including cognitive state. Parkinson's UK are concerned that this recommendation does not acknowledge the treatment options based on motor symptoms that affect, or do not affect quality-of-life. This recommendation should be changed to make it clear that different treatment options are suitable for different people depending on the symptoms of their Parkinson's disease.	patient to discuss the patient's clinical and lifestyle circumstances, goals and preferences before making a decision about the most appropriate treatment. We did identify evidence for levodopa being the most effective treatment for motor symptoms. The GDG has therefore made a recommendation to offer levodopa to people in the early stages of PD whose motor symptoms impact on their quality of life. However, this only represents an average effect for the majority of people, and therefore this recommendation does mean that levodopa must be used if there are good reasons to believe that an alternative treatment is more suitable for a particular individual.
Parkinson's UK	Short	9	4 - 5	Recommendation 1.3.6 (recommendation 30 in the full guideline) instructs not to offer anticholinergics. Though we acknowledge that anticholinergic medication can lead to serious negative side effects for many people, this recommendation doesn't factor in that many people, particularly younger people with Parkinson's, use trihexyphenidyl to treat painful off-period dystonia with good effect. Off Period dystonia can be very disabling and falls under the umbrella of "motor fluctuations". A few people also gain benefit for tremor. People report that they are also able to tolerate the side effects well over long terms periods. We recommend that this information is added to the final guideline.	Thank you for your comment. The GDG agreed that there may be circumstances where anticholinergics are effective but this does not apply to the average person with PD, who are the target of these guidelines. In addition, because no evidence of benefit was identified for anticholinergics, the GDG agreed that a "do not" recommendation is justified, but this does not of course preclude clinicians from using them in specific people who they feel may benefit.
Parkinson's UK	Short	9	6-7	Recommendation 1.3.7 (recommendation 31 in the full guideline)	Thank you for your comment. After discussion, the GDG agreed that amantadine may be a useful treatment option for managing dyskinesia in people with Parkinson's'

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				Amantadine has great benefits when given to specific individuals, alongside appropriate supervision. With a lack of evidence supporting its use, we believe that anecdotal observations made by the GDG should be used to impact the recommendation. The GDG felt that without any qualifying evidence of the benefits, it was right to recommend that amantadine is not routinely used as an adjunctive therapy. Especially when alternative options, with clear evidence of benefit, exist. However, because of the specific uses amantadine may have in certain people (e.g. to treat dyskinesia), they did not feel it appropriate to make a stronger "do not use" recommendation. Other evidence includes: Amantadine's role in the treatment of levodopa-induced dyskinesia. By Robert L. Rodnitzky, MD and Nandakumar S. Narayanan, MD, PhD. Can be found online at http://www.neurology.org/content/82/4/288 Amantadine extended release for levodopa-induced dyskinesia in Parkinson's disease (EASED Study). Authors Rajesh Pahwa MD, Caroline M. Tanner MD, PhD, Robert A. Hauser MD, Kapil Sethi MD, Stuart Isaacson MD, Daniel Truong MD, Lynn Struck MD, April E. Ruby, Natalie L. McClure PhD, Gregory T. Went PhD, Mary Jean Stempien MD. Can be found online at http://onlinelibrary.wiley.com/doi/10.1002/mds.26159/full	disease, where this cannot be adequately managed by modification of existing therapy. The recommendation has therefore been changed from a "do not" to a "consider" recommendation to reflect this.

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				Susan Ashley, Parkinson's nurse (RGN, M.Sc. (Advanced Practice), B. Sc. (Hons.), B.A.) told us '*I fully appreciate that the evidence for amantadine in levodopa induced dyskinesia isn't robust, but for many people (30% or more), as long as they do not have side effects, it can work very well to ameliorate debilitating dyskinesia. The only other option is to reduce levodopa which will then compromise motor function, increase risk of falls, dysphagia etc. I believe Amantadine, despite being an 'old' drug and one that has to be used with caution and careful supervision, can really help some people.*' The British Geriatrics Society agrees with this view and commented "*the advice not to offer amantadine to people with dyskinesia does not fit with current practice. Patients with dyskinesia often have significantly reduced quality of life and may progress to more expensive advanced therapies. Amantadine offers the opportunity to improve the symptoms of dyskinesia and can help to delay progression to the alternative treatments*." Parkinson's UK believes the final recommendation in this section does not reflect the testimony of the GDG, and should be amended to reflect this.	
Pennine Acute NHS Trust	Full	186	4468	Section on advanced therapies doesn't mention apomorphine pen injection device, only discussing the pump usage	Thank you for your comment. This section has now been updated to reference both injections and infusions of apomorphine
Pennine Acute NHS Trust	Full	69	1688	Question 1. We have noticed that the section 6.2 contains no mention of Apomorphine in the form of pen injection device as treatment for wearing off and significant prolonged off periods. The drug has good evidence for its use in prolonged off periods. It is not mentioned at all, and is used frequently. For many on the apomorphine pump device for continuous infusion of the drug they need injections from the pen device before pump is set up and running and after pump is taken down and overnight. Can this please be looked at. I	Thank you for your comments. The recommendations for advanced Parkinson's disease have now been updated to include the options to offer intermittent injections and/or subcutaneous infusions, so both the possible routes of apomorphine delivery are now mentioned within the guideline.

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				would add that patients in UK often 'graduate' from using the pen occasionally for off periods to needing the pump over longer term, and it gets people used to the drug and needles effectively.	The text of section 6.2 has now been updated to make clear that apomorphine was considered as an option within this question (PICO table etc.) However, this question specifically related to the choice of first-line adjuvant, and the GDG agreed that apomorphine was unlikely to be used as a first-line adjuvant to levodopa monotherapy. In addition, no randomised controlled trial evidence for apomorphine was identified in the specific population specified for this question (levodopa monotherapy versus levodopa plus apomorphine). The GDG therefore agreed that the appropriate place to include intermittent apomorphine injections was in the section on advanced Parkinson's disease, and as above this has now been included.
Pennine Acute NHS Trust	Full	General	General	There is no mention of Safinamide, a newly licenced and approved drug in our Uk and our region (Greater Manchester Medicines Management Group) which has MAOB and antidyskinesia properties. There should be sufficient time for this to be included in the guidance.	Thank you for your comment. The guideline did not look for evidence on safinamide, as it was not licensed at the time the scoping exercise was undertaken. Whilst we did not specifically look for evidence, the fact that safinamide is classed as an MAO-B means they are covered as part of our recommendations for adjuvant treatment, and could be considered as options under those class level recommendations (within the licensed indication). In addition, NICE has recently published an evidence summary on safinamide in February 2017, though this will not be formally included as part of the guideline.

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Pennine Acute NHS Trust	short	30	table	Suggests new recommendations due on use of intermittent apomorphine injections and yet does not refer to them at all in the sections 1.3 and 1.8 referenced in the table	Thank you for this comment. A reference to intermittent apomorphine injections has now been included in recommendation 1.8.1
Pennine Acute NHS Trust	short	9	6	Question 1. We are concerned this recommendation will be challenging as amantadine has been used for decades in NHS to treat dyskinesias alone. The guidance, full or short, discusses only the use amantadine to treat motor fluctuations, including dyskinesias. Amantadine is an extremely useful drug as a standalone for dyskinesia suppression and certainly works. For a single drug with no rival it is quite well tolerated also. Please consider allowing amantadine for standalone dyskinesia suppression as only other option is levodopa reduction, or reduction of other medications and patients don't tolerate treatment reductions physically very well. Those who are over 70-75 and unsuitable for deep brain stimulation for dyskinesia could be left OFF and disabled without the use of amantadine as an option.	Thank you for your comment. After discussion, the GDG agreed that amantadine may be a useful treatment option for managing dyskinesia in people with Parkinson's disease, where this cannot be adequately managed by modification of existing therapy. The recommendation has therefore been changed from a "do not" to a "consider" recommendation to reflect this.
Profile Pharma	Full	69	1697	We appreciate the guideline scoping exercise was concluded in December 2014 but in February 2015 another Monoamine Oxidase B inhibitor (with additional effects on glutamate pathways) was licenced by the EMA through the centralised procedure. Xadago (safinamide) has been available in the UK since May 2016. It is licenced as an adjuvant therapy to levodopa in mid to late stage PD. Whilst it has not been included within the scope of this guideline due to timing it is currently undergoing a review by NICE in the form of an Evidence summary: new medicine. For the sake of completeness and listing all the available MOAB-inhibitors, is it possible to state it is available but not reviewed in the guideline but cross reference to the ESNM as it should be published before the final guideline?	Thank you for your comment. As you correctly state, the guideline did not look for evidence on safinamide as it was not licensed at the time the scoping was undertaken. Whilst we did not specifically look for evidence, the fact that safinamide is classed as an MAO-B means they are covered as part of our recommendations for adjuvant treatment, and could be considered as options under those class level recommendations (within the licensed indication). In addition, NICE has recently published an evidence summary on safinamide in February 2017, though this will not be formally included as part of the guideline.

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Profile Pharma	Full	79	2016	Should this read table 7 rather than table 5?	Thank you. This has now been amended accordingly.
Profile Pharma	Full	80	2018	At the end of the table it would be helpful to list the adverse events as was done in table 4 on page 68	Thank you for your comment. Unfortunately, the information available to spell out specific adverse event risks was not as good for adjuvant therapy compared to that for first line therapy. The fact that the majority of people are taking multiple medicines means it is not obvious in many cases which drug is the cause of the adverse event. However, where specific evidence of differences was found (e.g. hallucinations) then this has been specifically included as part of the table.
Profile Pharma	short	9	2	At the end of the table it would be helpful to list the adverse events as was done in table 1 on page 7	Thank you for your comment. Unfortunately the information available to spell out specific adverse event risks not as good for adjuvant therapy compared to that for first line therapy. The fact the majority of people are taking multiple medicines means it is not obvious in many cases which drug is the cause of the adverse event. However, where specific evidence of differences was found (e.g. hallucinations) then this has been specifically included as part of the table.
Quality Standards	Short	General		No comments	Thank you
Queens Medical Centre Nottingham University	Full	79	General	The statement that levodopa-carbidopa intestinal gel (LCIG) should not be offered at any stage of Parkinson's disease (PD) we believe is a major fault in the draft guidance, and a regressive step in the management of patients with advanced, fluctuating and difficult to manage PD. The existing guidance on LCIG use, published by NHS England, allows for its use in specialist centres in accordance with published inclusion, exclusion and stopping criteria. Whilst	Thank you for your comment. For comments on the effectiveness and cost effectiveness of LCIG, please see **theme 1**.

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Hospitals NHS Trust				some of these criteria are ambiguous, and could be tightened (for example, the assertion that a patient must have "50% Off periods" without specifying the time frame, or the method by which this is to be established.) applied correctly they support the rational use of what is clearly a very effective therapy for a small sub-cohort of patients whose disabling PD symptoms simply cannot be managed with conventional Best Medical therapy (BMT). As a large PD centre offering LCIG, we have helped a handful of patients of exactly this type: For example, a patient of 71 with gastric dysmotility and advanced fluctuating PD, turned down for Deep Brain Stimulation because of age and comorbidities, and who, anti-coagulated on account of an artificial heart valve, had experienced frequent and severe subcutaneous haematomas with an apomorphine infusion, has had her life transformed by LCIG. The fear of sudden and unpredictable Offs, with the associated risks of falls and fractures, has gone. She is able to leave the house independently, can go out for meals and day-trips, none of which had been possible before LCIG. Whilst one could argue that such cases are exceptional, the counter argument runs stronger: such patients DO exist. Furthermore, in our experience getting funding on a IFR basis for exceptionality meant in reality no patients were funded as all were felt (probably correctly) to be a 'subgroup'. By adopting blanket restrictions and prohibitions we deprive capable and responsible clinicians of a therapy which when utilised correctly and in line with existing guidance, can deliver such benefits to this very small and selected cohort of patients. Our suggestion to the Clinical Guidance (CG) development group, is that statement 79 is revised. Acknowledging that LCIG is an expensive therapy, we firmly believe that there must be an allowance for it to be used by responsible and experienced clinicians, in line with clear and transparent criteria, within the final recommendations. The evidence reviewed by the	For comments on the effectiveness and cost effectiveness of LCIG in subgroups of people with advanced Parkinson's disease, please see **theme 1b**. For comments on the paucity of therapeutic options for people with advanced Parkinson's disease, please see **theme 1e**. For comments on the relationship between NICE's conclusions on LCIG and NHS England's specialised commissioning policy, please see **theme 9a**.

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				committee draws attention to the benefits LCIG can deliver in improving daily On-time, and reducing disabling dyskinesias, and consideration must be given to the committee about how these improvements, shown in high quality studies, map on to the lives and treatment experiences of our PD patients . We would instead endorse a statement supporting the use of LCIG in specialist centres according to agreed and published criteria. Thus we would like to see the existing position of LCIG therapy, which we believe supports the rational use of this therapy, broadly continue. We acknowledge that current NHS England inclusion criteria can and indeed should be tightened. We would like to see more specific guidance upon how suitable patients should be assessed. We firmly believe that the CG recommendation should be to support the use of LCIG restricted to specialist centres and in line with clear and transparent criteria.	
Royal College of General Practitioners	Short	10	21	The comment below applies to this statement too. (LS)	Thank you for your comment. The GDG agreed that there are difficulties accessing this service in many areas, and hope that the recommendations will lead to the service becoming more available.
Royal College of General Practitioners	Short	11	8	There are concerns that the specialist CBT mentioned is not widely available and will be a challenge to access. (LS)	Thank you for your comment. The GDG agreed that there are difficulties accessing this service in many areas, and hope that the recommendations will lead to the service becoming more available.
Royal College of General Practitioners	Short	20 and 26	General	The long list of alterations made since the last edition is evidence both of how much additional work has gone into this, and of how quickly the field can change. We also note that several of the interventions recommended in section 1.5 are off licence. The combination suggests that the evidence of efficacy in several of these recommendations may not be very strong. While it is clearly appropriate to list suggestions for difficult areas of symptom control,	Thank you for your comment. Within this update, recommendations were only made either if there was robust evidence to support them or the GDG were confident from their clinical experience they were appropriate. The text referenced is a standard inclusion in all NICE guidelines, and we still believe is appropriate

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				there is a mismatch between what can be taken to be the evidence base, and the rather heavy-handed statement in lines 18-22 of p20. Also where the recommendations are made for particular drugs to control certain symptoms are made in section 1.5, is it possible to give at least estimates of NNT? (DJ)	here. NNT was not a metric used as part of the analysis in this guideline and we are therefore unfortunately not able to provide this information.
Royal College of General Practitioners	Short	5	23	Review the diagnosis of Parkinson's disease regularly, and reconsider it if atypical clinical features develop.' Of course this is reasonable. '(People diagnosed with Parkinson's disease should be seen at regular intervals of 6–12 months to review their diagnosis.)' Why? If no atypical features have developed it seems a waste of everyone's time. The document has already correctly stated that the diagnosis is clinical and the typical features become more marked in time. Why not leave it up to GPs to decide when review is appropriate? (DJ)	Thank you for your comment. Unfortunately, this recommendation is from a part of the guideline that was not included as part of this update, and therefore no substantive changes to this recommendation can be made.
Royal College of General Practitioners	Short	6	2	This does say '*consider*' when it cannot be distinguished from essential tremor. The risk here is that specialists will order the investigation when they are fairly sure of the diagnosis, just to make sure they have done everything. This could result in unnecessary & expensive investigation, and we wonder if it would sense to express the same recommendation slightly differently, for instance '*Do not consider [this investigation] unless there are major doubts ….'* (DJ)	Thank you for your comment. Unfortunately, this recommendation is from a part of the guideline that was not included as part of this update, and therefore no substantive changes to this recommendation can be made.
Royal College of	Short	8	11	Locally there is a shortage of neurologists / Parkinson's Disease specialists and Parkinson's Disease nurse specialists so it will be challenging to seek	Thank you for your comment. The GDG noted this problem, and agreed therefore that the recommendation should be phrased as to "seek" advice before modifying

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General Practitioners				advise before modifying therapy, there might be a significant delay in treating the patient whilst waiting for specialist advice. (LS)	treatment. If there is an urgent need to modify treatment and such advice has been sought but is not available, then the GDG agreed it may sometimes be necessary to modify therapy without first consulting such a specialist.
Royal College of General Practitioners	Short	General	General	We feel that this is a very specialised area. However, in such an area where GPs would consider to have a strong responsibility for the long term care of their patients with this condition, we note that neither the words 'general practitioner' nor 'primary care' appear anywhere in this guideline. That includes para 1.7, and it is particularly odd that 1.7.1 includes the kind of help that GPs would expect to be providing. Also omitted from 1.1.5. (DJ) From a GP point of view, it is striking how much of this guideline is concerned with control of symptoms, and how little is about function. The word does appear once or twice, it is noted that it's been taken out (under '*Recommendations to be deleted*') more than it's been put in. Even where a recommendation for research into physiotherapy appears (p25, line 9), the aim is stated to be about reducing or delaying symptoms, not about maintaining function. It is worth to pay much attention to function when developing a guideline. (DJ)	Thank you for your comments. In general, unless there are specific reasons for doing so, NICE guidance does not specify who should be carrying out particular interventions/tasks, but rather what those interventions should be. The GDG do however agree that the points you raise and others through the guideline would indeed often be undertaken by GPs. Whilst it is true that the word function does not appear often in the short version of the guideline, evidence on this outcome was included as part of many review questions, was considered as part of the GDG's decision making ,and would be something that would be expected to improve with appropriate care.
Royal College of General Practitioners	Short	General	General	On a positive note, it is encouraging to see a guideline specifically advising against a number of investigations & interventions. (DJ)	Thank you for your comment.

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Royal College of General Practitioners	Short	P7	6	There may be advantages in holding off treatment as long as possible. It is not clear what the advantage is of earlier treatment when symptoms are not affecting quality of life. More important, these two sections once again fall into the trap of implying that shared decision making should take place when symptoms are mild (1.3.2) but not when they are more severe (1.3.1). The addition ('*after a discussion …*', with the two bullet points) should be included in 1.3.1, where it applies just as strongly. (DJ)	Thank you for your comment. The recommendations have now been amended to reflect the need for a discussion to take place between the patient and clinician when considering starting pharmacological treatment for people with PD, whatever the person's symptoms at the time. No evidence was identified to suggest that holding off treatment provides benefits to the individual, and therefore the GDG agreed that such a recommendation would not be appropriate.
Royal College of Nursing	Appendix N			There is no mention of the need for more PDNS research in terms of varied roles and economics.	Thank you for your comment. Unfortunately, the chapter and topic on PDNS have not been included as part of the scope for this guideline update, and therefore substantive changes to this section cannot be made.
Royal College of Nursing	Full	106	2535	This is welcomed. The cost of a general medical review every time person is reviewed by PD expert should be taken into consideration. PDNSs may not be able to undertake this review.	Thank you for your comment. The general medical review is recommended but it is not mandatory, but we hope that over time services would be configured to enable this to be possible as a matter of routine.
Royal College of Nursing	Full	140	3294	Cholinesterase inhibitors this could be picked up by PDNS if they are prescribers and have training.	Thank you for your comment. We agree that this is certainly a potential way these treatments could be prescribed.
Royal College of Nursing	Full	141	3330	Would 2004 really be referred to as recent, although we appreciate this may be the only study but it is not recent.	Thank you for your comment. Unfortunately, this chapter was not included as part of the scope for this guideline update, hence it has not been updated and no changes can be made.
Royal College of Nursing	Full	141	3343	*"What is the effectiveness of Parkinson Disease Nurse Specialist care versus standard medical care in the management of people with Parkinson's disease?"*	Thank you for your comment. Unfortunately, this chapter has not been included as part of the scope for this guideline update, hence it has not been updated and no changes can be made.

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				We welcome that the guideline developers considered the effectiveness of Parkinson Disease Nurse Specialist (PDNS). We, however, note the comparator and sample size varied between studies limiting the ability to draw general conclusions. The challenge is that nurses do not always measure their worth in the way NICE evidence requires. Perhaps further thought needs to be given to the evidence base NICE uses and / or call for further research in this area.	
Royal College of Nursing	Full	141	3433 - 3440	Recommendation 9.1.6 - access to a Parkinson's disease specialist nurse is to be celebrated. Given the increasing reduction in specialist nurse roles. It is worth mentioning that there are currently not enough PDNS and if every Parkinson's Disease patient is to have access to a PDNS there will need to be some investment in getting more PDNS to provide this service.	Thank you for your comment. Unfortunately, this chapter was not included as part of the scope for this guideline update, hence it has not been updated and no changes can be made.
Royal College of Nursing	Full	143	3422	We note that the statement on PDNS is unchanged from 2004, there is no mention of the role in acute setting or deep brain stimulation nurses? - This should be noted as roles are expanding.	Thank you for your comment. Unfortunately, this chapter was not included as part of the scope for this guideline update, hence it has not been updated and no changes can be made.
Royal College of Nursing	Full	143	3440	As per earlier comment, more research is needed in to PDNSs and we suggest that this should be stated in this guidance document.	Thank you for your comment. Unfortunately, this chapter was not included as part of the scope for this guideline update, hence it has not been updated and no changes can be made.
Royal College of Nursing	Full	159	3823	Specific occupational therapy – The recommendation is welcome. However, in practice nationally we are not sure there is currently expertise for this?	Thank you for your comment. The GDG acknowledged that this service may not be currently available everywhere. However, the good evidence that PD-specific occupational therapy works, combined with the evidence that generic occupational therapy may be

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					considerably less effective, meant the GDG felt it was appropriate to encourage the development of these services in areas where they may not exist.
Royal College of Nursing	Full	164	3939	Communication aids: This is welcomed. It has significant cost implications on the types / possible communication equipment, for example when considering/suggesting use of I-pads/tablets etc.	Thank you for your comment. The GDG acknowledge that it has significant cost implications and therefore should not be offered to everyone, but should only be considered as needed by the individual.
Royal College of Nursing	Full	173	4136	Distribution of protein for people on levodopa – It is good to have this confirmed.	Thank you for your comment.
Royal College of Nursing	Full	203	4943	*Offer patients in late stage best medical treatment including apomorphine infusion:* We are concerned with this recommendation as nationally there may not be resources for response test, reviews and prescribing.	Thank you for your comment. The recommendation specifies only that best medical therapy may include apomorphine, and therefore it is not expected this would be appropriate for all individuals. This recommendation has also now been edited to include apomorphine injections, and therefore a greater amount of choice is available at the local level.
Royal College of Nursing	Full	204	4949	*Do not offer any patient Dudopa*: This will be a significant change to practice as this treatment is currently being offered and is reflected in NHS England's funding plan.	Thank you for your comments. For comments on the relationship between NICE's conclusions on LCIG and NHS England's specialised commissioning policy, please see **theme 9a**.
Royal College of Nursing	Full	223	5464	*Offer CBT for ICDs*: there is no current resource for this. PDNSs could do this but we would need more PDNSs in place to implement the recommendation effectively.	Thank you for your comment. The GDG agreed that there are difficulties accessing this service in many areas, but noted that it was shown to be effective where available and hope that the recommendations will lead to the service becoming more available. The GDG did note that one potential way this could be achieved is through

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					training of PDNSs, but that doing so would involve extra resources being put into PDNS services to replace those taking on these new responsibilities
Royal College of Nursing	Full	230	5647	This recommendation is welcomed. The need for discussion with patient /carers may need additional PDNS resource.	Thank you for your comment. The GDG hopes that the recommendation would lead to more resources becoming available to provide this service.
Royal College of Nursing	Full	230	5667	*Palliative care referrals*: This recommendation is welcomed. It may need increase in resources to enable effective implementation.	Thank you for your comment. The GDG hopes that the recommendation would lead to more resources becoming available to provide this service.
Royal College of Nursing	Full	26	472	Should this also include primary care?	Thank you for your comment. Unfortunately, this chapter has not been included as part of the scope for this guideline update, hence it has not been updated and no changes can be made.
Royal College of Nursing	Full	79	2006	Potential to utilise Parkinson Disease Nurse Specialists (PDNS) for monitoring and treatment of dykiensia.	Thank you for your comment. Unfortunately, the chapter and topic on PDNS have not been included as part of the scope for this guideline update, and therefore substantive changes to this section cannot be made.
Royal College of Nursing	Full	85	2111	This is welcomed. There is a cost implication of Modafanil monitoring as this will take additional time at clinics.	Thank you for your comment.
Royal College of Nursing	General	General	General	The Royal College of Nursing welcomes the draft guidelines update for diagnosis and management of Parkinson's Disease in adults. The RCN invited members who care for people with Parkinson Disease to review and comment on its behalf. The comments below include the views of our reviewers.	Thank you for taking the time to comment on the guideline. We have responded to your individual comments accordingly.

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Royal College of Nursing	General	General	General	The draft guidelines seem comprehensive and clearly set out.	Thank you for your comment.
Royal College of Psychiatrists	Full	100-105	2385-2529	'The GDG discussed the evidence base for quetiapine and clozapine and recognised that both drugs appear effective at improving psychosis in people with Parkinson's disease without worsening motor function, and there is little evidence that either is superior to the other'. We think this conclusion is incorrect. A. In the evidence provided in the RCTs assessed by the panel, there are 3 studies comparing quetiapine with placebo. Shotbolt et al (2009) (13 placebo versus 11 quetiapine) found no improvement in psychotic symptoms using the BPRS and specifically no improvement in hallucinations using the Baylor PD hallucinations scale. Ondo et al (2005) (21 quetiapine versus 10 placebo) also found no changes in the Baylor hallucinations scale. Fernandez et al (2009) (8 placebo versus 8 quetiapine) did find a difference in the BPRS hallucinations item. Thus the two larger of the three trials found that quetiapine was ineffective for the treatment of hallucinations. There are two larger trials of clozapine versus placebo. Friedman et al (1999) (30 placebo versus 30 clozapine) found significant improvement in the clozapine group in SAPS, BPRS and specifically the BPRS hallucinations item (p=0.002). Pollak et al (2004) (32 clozapine versus 28 placebo) found a significant improvement in PANSS positive symptoms and specifically stated that all items except grandiosity improved i.e. hallucinations improved significantly; they stated that 25/27 clozapine	Thank you for your comment. The GDG has reconsidered this question in light of the responses received during consultation, and the following changes have been made. 1) A new outcome of the BPRS total score has been added to the list of NMAs included in the guideline. 2) To take account of the greater efficacy demonstrated with clozapine compared with quetiapine, these two recommendations have been separated, with quetiapine listed as a consider recommendation, and clozapine a stronger offer recommendation, within its license of people who have failed on standard treatment. The GDG emphasised that this standard treatment which fails before the use of clozapine may include quetiapine. We believe that these changes address the concerns that have been raised.

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				patients, who completed the study, had no hallucinations and delusions at the end of the study. There is one study which compares head-to-head clozapine and quetiapine (Margante et al, 2004) (20 clozapine versus 20 quetiapine). This found no difference in the general psychopathology measured by BPRS but did not discuss hallucinations. In your summary this is regarded as a low quality study. Therefore, only one of 3 studies specifically measuring hallucinations shows that quetiapine is effective in PD whereas two larger studies show superiority for clozapine on hallucinations with bigger effect sizes. This, and substantial clinical experience with both drugs, favours clozapine. Please also see table in review by Borek and Friedman 2014 Expert Opinion in Pharmacother. Aug;15(11):1553-64. http://dx.doi.org/10.1517/14656566.2014.918955 B. Having looked at the levels of evidence listed: Hallucinations – 1) 'A network meta-analysis pooling 5 RCTs using different measures of hallucination suggested that quetiapine has a medium-sized effect in reducing symptoms of hallucinations and has a high probability of being the optimal option.' Which are these RCTs as I could only see 3 and 2 were negative? There were none included for clozapine - why was the Friedman data not included? 2) 'A network meta-analysis pooling 3 RCTs reporting hallucinations using the BPRS scale suggested that quetiapine has a high probability of being the optimum option.' Thus 2 negative out of 3 studies suggests that quetiapine is optimum for treating hallucinations? No data on clozapine were included.	

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				Positive symptoms – 'A network meta-analysis pooling 4 RCTs using different measures of 'positive' symptoms of psychosis suggested that clozapine has a large effect in reducing symptoms, and appears certain to be the optimal option. No data on quetiapine were available.' We suggest that the distinction between positive symptoms and hallucinations to distinguish the effects of quetiapine and clozapine is spurious as it suggest that clozapine should be used for positive symptoms and quetiapine for hallucinations when hallucinations are a positive symptoms. Clozapine clearly has the largest effect size for the important psychotic symptoms seen in PD; in most studies the positive symptoms have been disaggregated into hallucinations and delusions and this effect holds. Motor symptoms – 'A network meta-analysis pooling 8 RCTs using UPDRS III (motor) subscale suggested that both quetiapine and clozapine may be effective in improving motor function of Parkinson's disease, with quetiapine having the highest probability of being the optimum option, although the confidence intervals of the mean difference crossed the line of minimal clinically important difference as defined by Schrag et al., 2006 and Horvath et al., 2015.' Adverse events – 'A network meta-analysis pooling 8 RCTs suggested no meaningful difference between quetiapine, clozapine and placebo in reducing the risk of treatment discontinuation due to adverse events, although quetiapine had the highest probability of being the optimum option.'	

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				For both of the above statements the effect of quetiapine over clozapine seems marginal. I could not find anything in the quetiapine studies to suggest this drug actually improves motor function whereas in the clozapine studies it measurably improved tremor. In open label studies and clinical experiences clozapine also improves dyskinesia. In conclusion the evidence suggests that clozapine has better efficacy quetiapine. Providing clozapine treatment is much more difficult than quetiapine because of a) the need to admit patients for initiation of therapy in order to monitor possible adverse effects and b) to monitor white cell counts in the community on a regular basis. However, this should not obscure the fact that it is better. A statement as to the efficacy of clozapine could be used to encourage services throughout the UK to provide this treatment. As it is, the recommendations provide a way for services not to grapple with providing clozapine treatment as they will invariably choose quetiapine and may avoid clozapine because it is stated as being equivalent in efficacy. Psychiatrists have a great deal of experience in using clozapine and mental health trusts have systems to monitor white counts and other effects. It is advisable that clozapine initiation and monitoring should be undertaken by psychiatrists.	
Royal College of Psychiatrists	Full	106	2547	The recommendation on the use of Clozapine does not specify that there are other suppliers to register with not just the CPMS. In addition, although the risks of agranulocytosis were highlighted, it's not highlighted that Clozapine on the whole has more side effects and more risk issues than all other antipsychotics including higher than usual incidences of hypersalivation,	Thank you for your comment. The recommendation has been corrected to account for the fact there are now other suppliers than the CPMS. After a discussion post-consultation, the GDG has

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				excessive sedation and unusual side effects including myocarditis and neuroleptic malignant syndrome. Rather than simply recommend Clozapine as a first line drug in this instance, it's unusual to note that the Psychiatrists who have expertise in the use of Clozapine use it as a tertiary medication. It would make more sense to suggest joint working/review with an old age psychiatrist who would already be registered with an appropriate monitoring service and who would have more experience in monitoring and using Clozapine.	decided to modify these recommendations. Clozapine is now no longer recommended as a first-line option, but rather as the option to use after standard treatment has failed. This is in line with the license for clozapine and hopefully aligns more closely with the way it is used in clinical practice.
Royal College of Psychiatrists	Full	107	2553-2557	Recommendations 48: 'Do not offer olanzapine to treat hallucinations and delusions in people with Parkinson's disease; and 49. Recognise that other antipsychotic medicines (such as phenothiazines and butyrophenones) exacerbate the motor features of Parkinson's disease. Statement 49 is a carry-over from previous recommendations and has not been updated. Statement 48 is stronger because there is RCT evidence for olanzapine. These two statements put together have the wrong emphasis. It could be taken as saying that olanzapine is not be used under any circumstances and therefore it may be better to use other first and second generation antipsychotic as long as they are monitored. On face value this is misleading and both statements should be given the same weight. If you are saying do not use olanzapine you should also say do not use other first and second generation antipsychotics.	Thank you for your comment. The GDG agreed that on face value these two recommendations do not appear fully coherent, but felt that in context they were not likely to lead to any misinterpretation. Specifically, they felt that people were well aware in general of the harms of first and second generation antipsychotics, but there had been some specific hopes that olanzapine would prove to be a useful treatment in this group, which it was appropriate to specifically comment on. Combined with the fact that, as you correctly noted, there are proven harms of olanzapine from RCTs, the GDG felt it appropriate to keep these two recommendations separate.
Royal College of Speech & Language Therapists	Full		3847-3851	The RCSLT believe that the Ramig et al 2001 *(Intensive voice treatment for patients with Parkinson's disease: a 2 year follow-up. Journal of Neurology, Neurosurgery and Psychiatry 71 (4): 493 – 498)* reference should perhaps be included in the analysis.	Thank you for your comment. Unfortunately, according to the study protocol, only studies looking at SLT compared to usual care is relevant and because RET is not classified as usual care for people with speech and communication or swallowing complications, this study was excluded from this guideline update.

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				This reference provides two year follow-up data, and although it compares two treatments, the other treatment given as a comparator, ('respiratory therapy (RET)'), was used as a placebo to ensure that there was not a bias towards general treatment effects and interactions with a therapist. If the GDG will consider this the study should be included in the analysis to provide more patient treatment numbers, and long-term follow-up, which is not provided by the other papers analysed.	
Royal College of Speech & Language Therapists	Full	117/118	2750	We are pleased that the speech and language therapist's (SLTs) role in the management of saliva difficulties in people with Parkinson's is recognized in this guideline. It carries a significant burden to people with Parkinson's and their carers. However, SLTs are not provided with guidance on what their specific role is with saliva management in the speech and language therapy section of the guideline. The RCSLT suggest more training is needed for SLTs to fulfil this role appropriately.	Thank you for your comment. Unfortunately, the GDG were not able to identify any evidence on saliva difficulties as part of the review on speech and language therapy, and therefore they did not feel it possible to make any more specific recommendations. Issues of staff training were unfortunately outside the scope of this guideline and therefore potential training needs of staff were not considered.
Royal College of Speech & Language Therapists	Full	118	2753	(Rec 53). 'Consider glycopyrrolate to manage drooling of saliva in people with Parkinson's disease'. The RCSLT believe that this may prove challenging for two reasons: 1. Glycopyrrolate is unlicensed for saliva management and therefore NICE needs to be clear that this can only be continued in the community when it has been initiated in an outpatient clinic setting 2. Many prescribers feel that glycopyrrolate may interfere with the absorption of dopamine and therefore it should not be used alongside dopamine medication in people with Parkinson's. Whilst the risk of anticholinergic side effects is discussed in the guideline the concerns over drug interaction is not so clearly outlined. Stockleys database of	Thank you for your comment. All recommendations for the use of medicines outside of their licensed indications are footnoted in NICE guidance to make their status clear and set out the additional obligations this places on clinicians. The GDG discussed potential drug interactions and agreed that these should form part of the normal considerations clinicians should always have when prescribing medicines, and did not merit specific comment within the guideline.

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				drug interactions *states 'it would be prudent to be alert for any evidence of reduced levodopa response if antimuscarinics are added'. We suggest including* this type of statement in this guideline as well as the concerns over side effects.	
Royal College of Speech & Language Therapists	Full	164	3932	The RCSLT note that within the recommendations for 9.2.7 and 9.3.7., it promotes early referral for physiotherapy and occupational therapy, but this wording is not replicated for speech and language therapy in 9.4.7. If it were, this would reflect SLT wisdom that preventive and early work is important to forestall decline/ later complications. We recommend early referral to speech and language therapy and therefore not waiting until frank complications/decline is apparent.	Thank you for your comment. The GDG recognise the importance of early referral and have therefore added the following recommendation to the guideline: "Consider referring people who are in the early stages of Parkinson's disease to a speech and language therapist with experience of Parkinson's disease for assessment, education and advice". We hope this is sufficient to address your concern.
Royal College of Speech & Language Therapists	Full	164	3935/3936	The RCSLT observe that this recommendation (65) has been reworded and with new research appraised and added i.e. EMST. 'New 2017' should therefore be added at the end in brackets to alert readers, familiar with the old guideline, to this amendment.	Thank you - "2017" at the end of the second bullet point refer to this recommendation (65) as a whole.
Royal College of Speech & Language Therapists	Full	164	general	The most challenging issue for speech and language therapy is providing continuity of care for people with a long term condition such as Parkinson's and we feel that no guidance is provided on whether it is necessary to keep patients on an SLT caseload for regular 6 or 12 monthly review, and if so, how this may be achieved with current staffing levels.	Thank you for your comment. The GDG recognise the challenge and lack of guidance for speech and language therapist in providing continuity of care for people with Parkinson's disease and have noted this challenge in the Linking Evidence to Recommendation (LETR) table. In brief, they felt the ideal situation would be periodic SLT reviews, but were not convinced services in many areas were set up in such a way that this could be provided. However, as we did not identify any evidence on this matter, no specific recommendation could be made.

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Royal College of Speech & Language Therapists	Short	19	5	We feel that the statement *'Do not offer levodopa – carbidopa intestinal gel at any stage of Parkinson's disease'* is detrimental to those patients requiring complex disease management who have speech problems and is therefore discriminating against those with communication difficulties. Statement 1.8.3 allows the use of DBS for this group of patients*: 'Consider deep brain stimulation for people in the later stages of Parkinson's disease whose symptoms are not controlled by best medical therapy'*, but does not allow treatment with levodopa–carbidopa intestinal gel. It is important to note that DBS is not optimal treatment for those with speech difficulties due to the high risk of speech deterioration with this surgical intervention. The reference: Mov Disord. 2014 Apr; 29(4):532-8. doi: 10.1002/mds.25816. Epub 2014 Feb 14. predictive factors of speech intelligibility following subthalamic nucleus stimulation in consecutive patients with Parkinson's disease. Tripoliti E[1], Limousin P, Foltynie T, Candelario J, Aviles-Olmos I, Hariz MI, Zrinzo L., states that the majority of patients undergoing DBS experience speech deterioration over time. We therefore believe that clinically, it is considered unwise to proceed with DBS for those patients who already have significant speech difficulties at this stage. This group of complex patients with speech deterioration should therefore be offered the option of levodopa –carbidopa intestinal gel which has not been shown to cause additional speech defects, unlike DBS. Levodopa – carbidopa intestinal gel should be considered alongside DBS for complex patients so that the most appropriate intervention is selected, not just for those with speech difficulties but others with cognitive impairment, psychiatric disturbance and other comorbidities which would exclude deep	Thank you for your comment. For comments on the effectiveness and cost effectiveness of LCIG in subgroups of people with advanced Parkinson's disease, please see **theme 1b**.

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				brain stimulation. We believe this also limits patient choice at this stage of the disease.	
Salford Royal NHS Foundation Trust	Full	188	4544	There is increasing evidence for non-motor symptoms as determinants of health-related quality of life in PD, and open-label UK-based study evidence for the effects of LCIG on non-motor symptoms versus both best medical treatment and apomorphine (e.g. Martinez-Martin *et al. Mov Disord* 2015;30:510-16). These data show clear effect sizes on quality of life measures and non-motor symptoms. They have not been considered in the assessment of the GDG. While we accept they fall outwith the search strategy used for evidence, they provide evidence which is otherwise unavailable of the non-motor efficacy of infusion-based therapies.	Thank you for your comment. Non-motor symptoms were specified as relevant outcomes in the protocols for all review questions relating to advanced Parkinson's disease, and evidence was identified. In particular, measured effects in disease-related and health-related quality of life were directly incorporated into the original health economic model, and the GDG was confident that this provided an empirical reflection of the impact of symptoms – and the benefits associated with alleviation of symptoms – across all relevant domains.
Salford Royal NHS Foundation Trust	Full	189	4555	Table 21 states that Hoehn and Yahr was used as a measure of progression, although this does not encompass all aspects of PD disease progression and is potentially inappropriate.	Thank you for your comment. The GDG acknowledged that Hoehn and Yahr score is a blunt measure of disease progression; this was one reason why it was reticent to adopt an economic model structure based on this measure. However, the group advised that, when reviewing published RCTs for global measures of disease progression, this was the only such outcome that was likely to be reported.
Salford Royal NHS Foundation Trust	Full	189	4576	The GDG acknowledge that they did not include studies that focused on a population in whom deep brain stimulation (DBS) or LCIG was contraindicated. In the practice of our advanced therapies MDT, DBS is usually the preferred option with LCIG being offered where significant contraindications to DBS, such as cognitive or speech impairment, exist. The GDG stated in section 10.3.7 that "if DBS and LCIG were both options, then DBS should be preferred to LCIG". This does reflect the current practice of our	Thank you for your comment. The reviews sought to identify studies that focused on a population in whom DBS or LCIG was contraindicated; however, no such evidence was identified. Nevertheless, the GDG felt confident in extrapolating from evidence assembled from patients who may have been eligible for either option, as it did not consider it plausible that effects would be

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				advanced therapies MDT in which DBS significantly predominates over LCIG in terms of cases performed over the last year. However, the small but significant numbers of patients for whom DBS is not suitable will effectively be left without effective treatment and we consider this to be inequitable.	substantially different in such people (and that any differences that exist would be much more likely to reflect a smaller effect in people with contraindications than in the RCTs; see **theme 3**). For comments on the paucity of therapeutic options for people with advanced Parkinson's disease, please see **theme 1e**.
Salford Royal NHS Foundation Trust	Full	204	4949	We are concerned about the recommendation "do not offer levodopa-carbidopa intestinal gel (LCIG) at any stage of PD". This recommendation will be a challenging change in practice because it will limit the scope of advanced therapies we are able to offer to patients with motor complications of PD. As part of the NHS England funding criteria all centres in the UK are required to record outcomes on patients receiving LCIG which should be able to support its use in a small but significant proportion of patients.	Thank you for your comment. For comments on the effectiveness and cost effectiveness of LCIG, please see **theme 1**. For comments on the effectiveness and cost effectiveness of LCIG in subgroups of people with advanced Parkinson's disease, please see **theme 1b**.
Salford Royal NHS Foundation Trust	Full	80	2021	We are concerned that the GDG recommend that amantadine should not be offered to people with Parkinson's disease (PD) who have developed dyskinesia. The literature search seems to have been focused on amantadine as an adjuvant treatment for motor fluctuations in PD, and excluded studies explicitly examining anti-dyskinetic effects such as Wolf et al (Mov Disord 2010;25:1357-63) whilst not even apparently considering other evidence (e.g. Ory-Magne et al, Neurology 2014;82(4):300-7). Both of these studies were double-blind randomised placebo-controlled trials. The Movement Disorder Society's most recent evidence-based medicine guidance also recommends amantadine as a treatment for dyskinesia. Given the paucity of pharmacological treatment options for dyskinesia, we are concerned that NICE recommendation "do not offer amantadine….for dyskinesia" will limit further our ability to treat this disabling complication. We note that when	Thank you for your comment. After discussion of the consultation responses the GDG agreed that, whilst there was no evidence for the routine use of amantadine as an adjuvant treatment, it did have a role as a specific option for the treatment of dyskinesia. Therefore, a new recommendation has been added to this section to support the use of amantadine in this context.

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				amantadine was temporarily unavailable due to manufacturing problem several years ago we received many complaints from patients unable to access this medication about worsening of their dyskinesias, in line with the evidence presented above.	
Salford Royal NHS Foundation Trust	Short version	30	n/a	We noted that there is no explicit mention of the use of intermittent apomorphine injection to manage "off" periods in PD. This was contained in the 2006 guideline as per the table listing changes to the guidance. However, the evidence for intermittent apomorphine injection is not considered, and no guidance is given for the use of intermittent apomorphine. This is despite several placebo-controlled studies, referenced in the 2006 guidelines, supporting the use of intermittent apomorphine injection. (e.g. Dewey *et al. Arch Neurol* 2001;58:1385-92). We are concerned that this treatment, which is very effective for patients with refractory "off" periods, delayed "on" and nocturnal and early morning akinesia, may be denied to patients if it is not explicitly recommended in the current guidelines, and are not clear why it has been removed from the current guidelines.	Thank you for your comment. A recommendation for the use of intermittent apomorphine injections has now been added the section on advanced therapies.
Sheffield Teaching Hospitals		General		The recommendations have overlooked some important aspects of therapy for parkinson's disease. Firstly the use of lesional surgery eg. Pallidotomy which has a long history of being an effective and cost effective therapy for PD, particularly when DBS is not appropriate.	Thank you for your comment. Pallidotomy was not considered as part of the review question on surgical management of advanced Parkinson's disease. This was because the GDG considered that it is currently used in very few cases; hence, it was not prioritised.
Sheffield Teaching Hospitals		General		The recommendations have not included comment on the surgical treatments of tremor in PD ie. Thalamic DBS or thalamotomy. This is often intractable to medical therapy and not addressed adequately by STN DBS.	Thank you for your comment. Thalamotomy was not considered as part of the review question on surgical management of advanced Parkinson's disease. This was because the GDG considered that it is currently used in very few cases; hence, it was not prioritised.

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					The target of DBS was also excluded from consideration. However, the review was not limited to STN stimulation; the review only appears to concentrate on this approach because the majority of relevant literature describes this target.
Sheffield Teaching Hospitals		General		In the section on impulse control disorders, it appears that the use of DBS has not been considered. STN DBS enabled an approximately 40-50% reduction in medication which typically addresses the problem of medication induced pathology in PD	Thank you for your comment. The effects of DBS on medication reduction has been captured in the DBS chapter, and is included as part of the health economic model. We did not specifically consider the use of DBS for ICD because it was discussed and agreed that in clinical practice, providing DBS solely for the purpose of managing an ICD is highly unlikely.
Social Care	Short	General		Accepting that the Guideline is about diagnosis and management of the diseases, with the exception of a reference to a possible Carer's assessment the guideline seems to make no reference to the possibility of a person with Parkinson's disease having any social care needs or possibly benefitting from the support of social care services. This seems surprising given both the emotional and physical impact Parkinson's can have on a person's life. Whether it is involvement in terms of helping a person to come to terms with their condition, or ensuring that practical care needs are met (through the provision of, for example, equipment and adaptations, support in the home, respite care or residential care) social care has a large part to play in the lives of many people with Parkinson's diseases and this is not reflected in the guideline	Thank you for your comment. The GDG fully agree that people with Parkinson's disease are likely to have social care needs, particularly as the disease progresses. However, the scope for this update did not include any topics with a social care focus, and therefore it was not possible to make any recommendations in this area.
Social Care	Short	Information &	Page 4 onwards	The guideline seems to say very little about interacting with the patient and their family. It may be worth considering this in the context of the Motor	Thank you for this comment. Unfortunately, issues of communication and general information provision were not within the scope of this guideline update, and

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		Support		Neurone Diseases guidance that contains the following (although not all of it may be appropriate to Parkinson's): *'Information about the diagnosis, prognosis and management of MND should be given by a consultant neurologist with up‑to‑date knowledge and experience of treating people with MND unless it is clinically necessary to give the diagnosis in an urgent situation. The neurologist should have knowledge and expertise in the following:* *•Symptoms of MND.* *•Types and possible causes of MND.* *•Treatment options.* *•How MND may progress (including cognitive and behavioural changes) and how progression may affect the treatments offered.* *•Crisis prevention (for example, if there is an acute hospital admission or a breakdown in care arrangements).* *•Opportunities for people with MND to be involved in research.* *•Likely needs and concerns of people with MND and their family members and/or carers (as appropriate).* *•Advance care planning. [new 2016]*	therefore recommendations on this topic could not be made. The only specific issues of information provision included were on impulse control disorders and pregnancy, neither of which lend themselves to the sort of broad recommendations suggested here.

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				1.2.2 Ask people about how much information they wish to receive about MND, and about their preferences for involving their family members and/or carers (as appropriate). [new 2016] *1.2.3 Ensure people are provided with information about MND and support at diagnosis or when they ask for it. If the person agrees, share the information with their family members and/or carers (as appropriate). Information should be oral and written, and may include the following:* *•What MND is.* *•Types and possible causes.* *•Likely symptoms and how they can be managed.* *•How MND may progress.* *•Treatment options.* *•Where the person's appointments will take place.* *•Which healthcare professionals and social care practitioners will undertake the person's care.* *•Expected waiting times for consultations, investigations and treatments.* *•Local services (including social care and specialist palliative care services) and how to get in touch with them.*	

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				•Local support groups, online forums and national charities, and how to get in touch with them. *•Legal rights, including social care support, employment rights and benefits.* *•Requirements for disclosure, such as notifying the Driver and Vehicle Licensing Agency (DVLA).* *•Opportunities for advance care planning. [new 2016]* *1.2.4 When MND is diagnosed, provide people with a single point of contact for the specialist MND multidisciplinary team (see section 1.5). Provide information about what to do if there are any concerns between assessments or appointments, during 'out‑of‑hours' or in an emergency, or if there is a problem with equipment. [new 2016]* *1.2.5 Offer the person with MND a face‑to‑face, follow‑up appointment with a healthcare professional from the multidisciplinary team, to take place within 4 weeks of diagnosis. [new 2016]* *1.2.6 When MND is suspected or confirmed, inform the person's GP without delay and provide information about the likely prognosis. [new 2016]* *1.2.7 Set aside enough time to discuss the person's concerns and questions, which may include the following:* *•What will happen to me?*	

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				•Are there any treatments available? *•Is there a cure?* *•How long will I live?* *•What will the impact on my day‑to‑day life be?* *•What will happen next with my healthcare?* *•Will my children get MND?* *•How do I tell my family and friends?* *•How will I die? [new 2016]* *1.2.8 If the person has any social care needs, refer them to social services for an assessment. Be aware that some people with MND may not have informal care available, and may live alone or care for someone else. [new 2016]* *1.2.9 Advise carers that they have a legal right to have a Carer's Assessment of their needs; support them with requesting this from their local authority. [new 2016]* *1.3 Cognitive assessments* *Please also refer to the recommendations in NICE's guideline on patient experience in adult NHS services.*	

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				1.3.1 Be aware that people with MND and frontotemporal dementia may lack mental capacity. Care should be provided in line with the Mental Capacity Act 2005. [new 2016] *1.3.2 At diagnosis, and if there is concern about cognition and behaviour, explore any cognitive or behavioural changes with the person and their family members and/or carers as appropriate. If needed, refer the person for a formal assessment in line with the NICE guideline on dementia. [new 2016]* *1.3.3 Tailor all discussions to the person's needs, taking into account their communication ability, cognitive status and mental capacity. [new 2016]*	
The Association of Family Therapy and Systemic Practice in the UK	Short	10	3 to 13	Re Impulsive Control Disorders, Information and Support. The potential impact of impulse control disorders on relationships could helpfully be mentioned here	Thank you for your comment. The GDG agreed the impact on relationships would be a sensible thing to mention in these discussions. However, no direct evidence was identified for this theme and therefore the GDG did not feel it appropriate to make a recommendation.
The Association of Family Therapy and Systemic Practice in the UK	short	Introduction 1 & 2		The document's target audience includes people with PD, their families and carers. Its medical/pharmacolgical emphasis makes it very difficult for a lay person to read	Thank you for your comment. As far as possible, the terms of the guideline have been written in a way accessible to as wide an audience as possible. However, in certain cases there is a need for precise terminology to avoid potential misunderstandings, and in such circumstances it has not been possible to avoid the use of technical terms.
The Association of Family Therapy and	short	Section 1.7		Advocates a "comprehensive care plan". The absence of any consideration of attending to the emotional and psychological needs of patients and their families is inconsistent with this statement. PD is a life-changing diagnosis with major implications for relationships, and for personal and professional	Thank you for your comment. Unfortunately, this recommendation is from a part of the guideline that was not included as part of this update, and therefore changes to this recommendation cannot be made

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Systemic Practice in the UK		16 to 20		lives. The emotional health of people with PD has a huge impact on their physical symptoms. This aspect of management is almost totally ignored.	
The Association of Family Therapy and Systemic Practice in the UK	short	Section 1.1.5 p.4	19-21	Advocates a "comprehensive care plan". The absence of any consideration of attending to the emotional and psychological needs of patients and their families is inconsistent with this statement. PD is a life-changing diagnosis with major implications for relationships, and for personal and professional lives. The emotional health of people with PD has a huge impact on their physical symptoms. This aspect of management is almost totally ignored.	Thank you for your comment. Unfortunately, this recommendation is from a part of the guideline that was not included as part of this update, and therefore changes to this recommendation cannot be made.
The Association of Family Therapy and Systemic Practice in the UK	Short and Full	23 to 25 (Full) Guideline Appendix N		Re: Recommendations for Research There is a gap in knowledge about the impact of impulse control disorders associated with Parkinson's Disease on relationships, and approaches which could help to mitigate these, including psychological / systemic therapies. Clinical experience would suggest these are significant issues for people with Parkinson's and their carers / relatives, and that systemic therapy can be helpful here.	Thank you for your comment. The GDG discussed this issue, but agreed there was already considerable research ongoing on this topic, and therefore did not feel it was a high priority for additional research compared to the other topics identified.
The Cure Parkinson's Trust			476	This needs further clarification i.e. as to when it might become a problem and how it is currently handled (do patients get approval from their consultant etc.) otherwise most patients will think they cannot drive the moment they are diagnosed and may avoid that situation and or telling DVLA and their insurers.	Thank you for your comment. Unfortunately, this recommendation is from a part of the guideline that was not included as part of the scope of this update, and therefore substantive changes to this recommendation cannot be made
The Cure Parkinson's Trust		173		Note the recommendation to test Creatine supplementation	Thank you for your comment. We have now identified and included the large, recently published US creatine supplementation RCT in the evidence base (Kieburtz et al, 2015). This research recommendation has therefore been removed from the guideline.

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The Cure Parkinson's Trust		40 Section 5.1.7		Explain to patients the difficulties of diagnosis and the need for vigilance, self-awareness and reporting to ensure correct diagnosis as condition progresses. Some drugs are counter indicated in conditions that have PD like symptoms.	Thank you for your comment. Unfortunately, this recommendation is from a part of the guideline that was not included as part of the scope of this update, and therefore substantive changes to this recommendation cannot be made.
The Cure Parkinson's Trust		42 Section 5.2.4 43 Section 5.2.9.		Need specifics here i.e referral to consultant to be made within X weeks of from primary care visit and patient to be seen by Y weeks. Needs specifics i.e. review with consultant to be offered at least every 6 months. In the case of evidence of development of atypical changes, significant problems reported by patient or observed by consultant follow up appointment to be available within 2-4mths and at that interval thereafter until stability resumed/achieved.	Thank you for your comments. Unfortunately, this recommendation is from a part of the guideline that was not included as part of the scope of this update, and therefore substantive changes to this recommendation cannot be made. After further discussion, the GDG agreed that the recommendations around specific timing for referral were not evidence based, and the key things to emphasise were that people should be referred quickly, and that treatment should not be started before specialist diagnosis.
The Cure Parkinson's Trust		72 Section 6.2.3.5		There is now a large amount of information about the use of anti-cholinergics in falls prevention – maybe this is dealt with elsewhere?	Thank you for your comment. Unfortunately, this topic is not within the scope of this guideline update, so we have not been able to include evidence on the use of anticholinergics in falls prevention.
The Cure Parkinson's Trust		Section 4	490	This section could be clearer about the fact that ICD's are ENTIRELY the result of treatment NOT the condition of PD itself although this is made clear later on.	Thank you for your comment. A modification has been made to the first sentence of this introduction to clarify this point.
The Cure Parkinson's Trust		Section 4.1.6 & 4.1.7	599	Note the requirement that prescribers obtain written informed consent when DA agonists are offered… this has huge implications for the liability of prescribers and I would expect them to comment.	Thank you for your comment. The recommendation does not ask for prescribers to obtain written informed consent when offering dopamine agonists; it recommends giving people and their family members and carers (as

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				Also note that patients and carers are to be made aware of whom they can contact should they be concerned about ICDs – so who should they contact and again what is the liability here?	appropriate) oral and written information about the risks of developing ICD when receiving dopaminergic therapy and that it is recorded that the discussion has taken place. Should patients and carers have any concerns about ICDs, they should be advised to contact their local healthcare service. The GDG did not believe that either of these recommendations introduced any liability on behalf of individual medical professionals.
The Cure Parkinson's Trust		Section 4.2.7		It is not clear to me whether genetic counselling is recommended as it is mentioned above but it certainly should be especially for those with young onset PD which is the very group that are likely to be involved in decisions of pregnancy	Thank you for your comment. Unfortunately sufficient evidence was not obtained on the issue of genetic counselling for the GDG to be able to make a recommendation, but they agree that it was an important issue which should be referred to as part of their discussions.
The Cure Parkinson's Trust	Full	176 Section 9.6.1	Table 6.1	I would argue that Clinical Rating Scales such as the UPDRS provide only a snapshot of the condition. Patients plan their medication around clinical appointments to be able to physically attend, and this can provide a skewed picture. Patients often report anecdotally that in their clinical appointments they want to appear at their best, so denying the reality of disease progression. Although the full spectrum of UPDRS assessments should cover many areas including patient recorded outcomes. Arguably primary outcome measures in clinical trials should be confined to measurements of symptoms such as the UPDRS motor tests SOLEY in the "off" medication" state. Research should focus on the validation of more subtle and continuous measurement systems and the validation of biomarkers.	Thank you for your comment. Unfortunately, this is a reference to a part of the guideline which has not been included as part of this update, and therefore no changes can be made. However, the GDG do acknowledge and agree with the general sentiment, and agree that future work is necessary on how to assess people with PD.

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The Cure Parkinson's Trust	Full	178 Section 9.6.4	Table 6.2	There are considerably more agents being considered as potentially neuroprotective agents than this list. Numerous research groups, companies and Parkinson's research charities are investing in finding new treatments to slow, stop and reverse Parkinson's. Please see https://www.cureparkinsons.org.uk/Pages/Category/clinical-trials	Thank you for your comment. Unfortunately, this chapter is part of the guideline that has not been considered in this guideline update. No changes can therefore be made.
The Cure Parkinson's Trust	Full	180 Section 10	4468	On the advice of people living with Parkinson's, we refer to this stage of Parkinson's as complex rather than advanced.	Thank you for your comment. The GDG were of the view that advanced is currently still the most commonly used term, and therefore for ease of comprehension that term should be maintained. However, if there is a significant shift in terminology this will be recognised in future updates of the guideline.
The Cure Parkinson's Trust	Full	204 Section 10.3.8	4949	The Cure Parkinson's Trust is extremely concerned about this recommendation and the strength of the language used ("at no stage"). The Cure Parkinson's Trust was set up and is run by people living with Parkinson's. Its primary aim is to identify new treatments to slow, stop and reverse Parkinson's, providing disease modifying treatment options and choices for everyone matched to their own type and stage of Parkinson's. As is well documented, each person with Parkinson's experiences their own complex series of symptoms and side-effects, making it difficult to treat as not all treatments suit all people, and an individual's needs can change very rapidly, particularly as the disease progresses. This unpredictability has a significant impact on quality of life and that of their carers and families and with time becomes magnified.	Thank you for your comment. The GDG was grateful to receive the eloquent testimony of people living with Parkinson's disease, and did not disagree that it would be to the benefit of people with advanced Parkinson's disease if LCIG could remain available at a cost that would not result in unacceptable harm being caused elsewhere in the NHS. For comments on the effectiveness and cost effectiveness of LCIG, please see **theme 1**. For comments on the effectiveness and cost effectiveness of LCIG in subgroups of people with advanced Parkinson's disease, please see **theme 1b**.

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				The gold standard treatment remains Levodopa, which is ingested orally, a number of times a day and the medication is effective for a period of time, creating fluctuations described as "on/off" times. Daily "on" time is reduced the longer the person lives with the condition, each dose taking longer to become effective. With reduced and unreliable efficacy, the individual with Parkinson's loses control over their lives. In addition, people with Parkinson's too frequently experience gut complications in the form of upset stomach or constipation, and this significantly impacts how medication is absorbed and therefore time to be effective. Those living with advanced/complex Parkinson's will have reduced time during the day when their medication is effective, when they can move, communicate and experience any quality of life. With time the side effects of the medication also become much more pronounced, severe cramping and dystonia, dyskinesia, chronic sleep disturbance, fatigue, balance issues (and increased risk of falls). As Parkinson's advocate Annie says: "It's the tyranny of the drugs". For the right candidate, Duodopa removes this complicated timetable by providing continuous release of dopamine, providing reliability and reducing the impact of gut related issues. This restores control over medication and with that comes a significant improvement in quality of life for the individual their families and the carers of that individual. A caregiver of one candidate said "Duodopa provided hope for a degree of restoration of quality of life at a stage in Parkinson's where there is no hope."	For comments on the paucity of therapeutic options for people with advanced Parkinson's disease, please see **theme 1e**. For comments on apparent discrepancies between NICE's appraisal of the evidence on LCIG and the view taken by NHS England's specialised commissioning policy, please see **theme 9b**. For comments on apparent discrepancies between NICE's conclusions on LCIG and SMC advice, please see **theme 9c**.

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				Those living with this complex, chronic, progressive disease have very few treatment choices available to them, particularly as the disease advances, and not everyone is suitable for DBS. Protecting the treatment options and choices available becomes vitally important, which means ensuring that Duodopa is readily offered and available as a treatment choice for the right candidate. We believe decision making needs to be a joint process: people living with Parkinson's should make health and care choices in partnership with their healthcare teams deciding together which treatments might be relevant for them. We want to see all approved treatments for Parkinson's being made available UK-wide to enable successful shared decision making and people living with Parkinson's can exercise choice over their medication and treatment options. We have considerable concerns with this draft guidance as it is inconsistent with the advice offered by other UK assessors (NHS England and SMC) who see the value in offering the choice of Duodopa in cases where there are no other treatment options available, and oral medication is no longer efficacious. This guidance gives no appropriate guidance as to how to assess those that would best benefit from DBS, Apomorphine or Duodopa. These treatments should not be compared as they each provide unique symptomatic relief, and each of these treatments should be made available in order to ensure the optimum choice is a possibility for the individual patient.	

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The Cure Parkinson's Trust	Full	25 Section 3.1.4	439 431	Involvement of carers – please can you add family members here too. Family members may not have full care responsibilities but are often involved in supporting decision-making Add reference to CPT as source of reliable information (and others such as MJFF if external from UK sources permitted)	Thank you for your comment. Unfortunately, this chapter has not been included as part of the scope for this guideline update, hence it has not been updated and no changes can be made.
The Cure Parkinson's Trust	Full	31 Section 4.1.7		Recommendations when starting dopamine agonist therapy: Please can these recommendations reflect the need to reinforce the information given. The same information needs to be provided repeatedly and reinforced via the GP and pharmacist, particularly when there is a change in dose. This information needs to be shared with care givers and family members too.	Thank you for your comment. The GDG felt that the need for information to be repeated was appropriately covered by recommendation 9 in this section, about discussing ICDs at review appointments. The recommendation applies to any healthcare provider (including GPs and Pharmacists) responsible for reviewing medical therapy. The GDG did not want to be too specific here as different areas may have different models of care and there was no evidence to suggest one model is better than another.
The Cure Parkinson's Trust	Full	79 Section 6.2.9	2014	Please can you rephrase this - perhaps it should read: Lifestyle, circumstances and hopes, as to how this informs clinical practice. (Hope is important as it reflects what a person would like to be able to achieve which can be impacted by clinical decisions) The way it reads currently it implies clinical circumstances affect the doctor, not the person with Parkinson's. However, pg21 line 349 does refer to feelings of optimism being related to means of communication and the possible impact on quality of life and is also reinforced on line 396 in relation to the receipt of educational information.	Thank you for your comment. The GDG agrees that the recommendation should include people's aspirations and goals in life and have therefore agreed to amend the recommendation to include "goals" to reflect this.

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The Cure Parkinson's Trust	Full	80 Section 6.2.9; 31	2021	I query the evidence around amantadine and dyskinesia The review does not seem to encompass recent publications and clinical trial with slow release formulation.	Thank you for your comment. Our evidence review did not identify any relevant randomised controlled trials of this new formulation. However, after discussion of the consultation responses the GDG agreed that, whilst there was no evidence for the routine use of amantadine as an adjuvant treatment, it did have a role as a specific option for the treatment of dyskinesia. Therefore, a new recommendation has been added to this section to support the use of amantadine in this context.
The Society of Teachers of the Alexander Technique	Appendix E	General	General	The Stallibrass et al RCT[1] is missing from the GRADE profiles. This results from the erroneous categorisation of the Alexander Technique as physiotherapy, and the exclusion of the RCT on the basis that it appears in a Cochrane review of physiotherapy (see comments 1 and 4). Reference Stallibrass C, et al. Randomized, controlled trial of the Alexander Technique for idiopathic Parkinson's disease. Clin Rehabil 2002;16:695–708.	Thank you for your comment. You are correct that this RCT was incorrectly excluded from the draft version of the guideline. This error has now been corrected, and the GDG agreed it was appropriate to add in a recommendation for the Alexander technique in people with Parkinson's disease who are experiencing balance or motor function problems.
The Society of Teachers of the Alexander Technique	Appendix G	46	Table G5.1	The Stallibrass et al RCT[1] is listed as an excluded study. The rationale given is that it is *'already included within the Tomlinson 2013 Cochrane review*'. However the Cochrane review is of physiotherapy as the intervention − since the Alexander Technique is unrelated to physiotherapy, the study should not have been included in the review (see comment 1). The Stallibrass et al RCT therefore does need to be considered in the current update as it evaluates an entirely distinctive intervention that will otherwise be omitted. Reference Stallibrass C, et al. Randomized, controlled trial of the Alexander Technique for idiopathic Parkinson's disease. Clin Rehabil 2002;16:695–708.	Thank you for your comment. You are correct that this RCT was incorrectly excluded from the draft version of the guideline. This error has now been corrected, and the GDG agreed it was appropriate to add in a consider recommendation for the Alexander technique in people with Parkinson's disease who are experiencing balance or motor function problems.

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The Society of Teachers of the Alexander Technique	Appendix N	6	Table N6	We welcome mention of the Alexander Technique in the Research recommendations but point out that it is incorrectly categorised as 'Physiotherapy and physical activity'. The Alexander Technique is a taught self-management method unrelated to physiotherapy and 'physical activity' (see comment 1). Note that there is existing evidence for the effect of Alexander Technique training on some of the outcomes of interest listed in Table N6. This evidence covers posture, gait, and health-related quality of life in non-Parkinson's populations as well as depression in a Parkinson's population (see comment 2).	Thank you for your comment. The Alexander Technique has now been separated out to a specific category on self-management methods.
The Society of Teachers of the Alexander Technique	Full	144	3453	The draft guidelines state *'Physiotherapy including (but not restricted to) the following:.....The Alexander technique.'* Here and elsewhere (see comments below), the Alexander Technique has been erroneously categorised as 'physiotherapy' or 'physiotherapy and physical activity'. It is wholly inaccurate to describe the Alexander Technique as physiotherapy or as physical activity. As a direct consequence of this misclassification, the existing Parkinson's guidelines recommendation for Alexander lessons has been removed (see comment 2). Firstly, the Alexander Technique is a taught practical educational approach for improving awareness and coordination of postural support, movement and balance, brought about through enabling greater choice and control of response. Alexander lessons involve integrated cognitive and experiential learning that can lead to therapeutic and self-development-related benefits. For reference, we give a comprehensive description of the Alexander Technique and how it is taught at the end of this comment.	Thank you for your comment. Various changes to the guideline have now been made to address this miscategorisation. Specifically: 1) The RCT of the Alexander technique has now been added to the guideline, and a recommendation about its use made based on this evidence 2) In other places where it is mentioned, it has now been separated out into another category distinct from physiotherapy interventions. We hope that these adjustments have addressed the concerns raised.

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				Secondly, Alexander Technique instruction is delivered by qualified teachers who have undergone a 3-year Alexander Technique teacher training course, or equivalent, and are registered with a professional association such as STAT. The minimum level of qualification required is equivalent to 5 (England and Wales); 6 (Northern Ireland); 8 (Scotland) on the UK Qualification Comparison Chart. Unless a physiotherapist has undertaken this specialised education and training, they would be unqualified to incorporate Alexander Technique teaching in the intervention they deliver. Furthermore, since in the whole of the UK there are currently fewer than 10 healthcare professionals with dual physiotherapy and Alexander Technique training, categorising the Alexander Technique under the umbrella of physiotherapy will effectively deny the vast majority of patients an opportunity to access this intervention and unjustifiably discourage General Practitioners from considering referral to it. As a general principle, we consider that any intervention should be defined by the profession in question, this being the only body with the required professional knowledge and experience. We therefore request that Alexander Technique lessons and the Alexander Technique itself are not described as 'physiotherapy or physical activity', and are not subsumed under this category. The effectiveness of Alexander Technique lessons should be considered in a separate section for self-management strategies (see comment 6). We have raised this issue of inappropriate categorisation of the Alexander Technique previously in our submission to the ongoing NICE low back pain guideline update, so we are disappointed that these draft guidelines perpetuate the problem. Description of the Alexander Technique provided by STAT for reference	

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				The Alexander Technique is a taught practical method and an embodied, contemplative practice. Alexander lessons enable people to free themselves from unhelpful movement and postural habits and develop a more intelligent and skilled control of the manner in which they respond to stimuli and engage in activity.[1] Alexander Technique teachers think in terms of encouraging clients to develop greater all-round awareness, freedom of head poise, and expansion rather than contraction when initiating any action. The resultant lessening of unnecessary tension leads to more freedom of balance and movement. People are enabled to explore the working of their postural supporting mechanisms through experiential learning aided by hands-on guidance and support from the teacher, integrated with spoken advice to encourage changes in an individual's own thinking and attitude. We teach intentional inhibition[2] of maladaptive habitual responses, enhancement of spatial perception and awareness, and clarity in framing purposeful intent. We help people attend to postural sensory feedback and make use of this information; show them how to allow the neuromuscular mechanisms to determine appropriate postural support and the pathways of skilled movement without habitual interference in the underlying non-conscious processes; and how to initiate movement through clarity of intention in a way that is compatible with current theories of skilled motor control.[3] Further description of the Alexander Technique and the aims and content of Alexander lessons are provided in the published appendix to the ATLAS RCT.[4] References	

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				1. Skills for Health. Competencies / National Occupational Standards; CNH3 Deliver Alexander Technique teaching June 2010. Available at: https://tools.skillsforhealth.org.uk/competence/show/pdf/id/2800/ 2. Filevich E, et al. Intentional inhibition in human action: the power of "no". Neurosci Biobehav Rev 2012;36:1107–18. 3. Ballard K. Ideomotor principle – was Alexander correct? In: Connected Perspectives – The Alexander Technique in context. Editors: Rennie C, Shoop T, Thapen K. Hite Books and Publishing 2015. 4. MacPherson H, et al. Alexander Technique lessons or acupuncture sessions for persons with chronic neck pain: A randomized trial. Ann Intern Med 2015;163:653−62.	
The Society of Teachers of the Alexander Technique	Full and Short	General	General	Overall, the draft guidelines appear to place little emphasis on self-management. This seems surprising and at odds with accepted management strategies in general for long-term conditions. There is widespread acknowledgement that self-management methods are helpful for people with chronic conditions. Of note, self-efficacy appears to be a significant predictor for people developing better self-management of their Parkinson's symptoms.[1, 2] Relatedly, evidence from the ATLAS RCT suggests that attending AT lessons improves self-efficacy. [3] References 1. Chenoweth L, et al. Factors supporting self-management in Parkinson's disease: implications for nursing practice. Int J Older People Nurs 2008;3:187−93.	Thank you for your comment. The areas to be covered as part of this guideline update were detailed in the published scope, which went through a period of public consultation before this update began. Unfortunately, it is not now possible to include areas outside of that agreed remit. However, as described in responses to other comments raised, evidence related to the Alexander technique has now been included in the guideline and a recommendation about it made, and we hope this goes at least some way to addressing your concerns.

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				2. Lee J, et al. Regular exercise and related factors in patients with Parkinson's disease: Applying zero-inflated negative binomial modeling of exercise count data. Appl Nurs Res 2016;30:164−169. 3. MacPherson H, et al. Alexander Technique lessons or acupuncture sessions for persons with chronic neck pain: A randomized trial. Ann Intern Med 2015;163:653-62.	
The Society of Teachers of the Alexander Technique	Short	35	Table	We are very concerned at the removal of recommendation number 79 in the current guidelines, namely *'The Alexander Technique may be offered to benefit people with PD by helping them to make lifestyle adjustments that affect both the physical nature of the condition and the person's attitudes to having PD.'* (page 142 of existing guidelines) The rationale for the removal is given as *'This recommendation has been replaced by recommendations from the guideline update....which are included in section 1.7.'* However, section 1.7 relates to referral to a physiotherapist − yet the only healthcare professionals who are qualified to deliver Alexander Technique teaching are those who have undertaken the 3-year specialised education and training (see comment 1). In our view, removing the recommendation for Alexander Technique lessons as an option for people with Parkinson's is retrograde, particularly in light of existing evidence. A RCT (N=93) reported that one-to-one Alexander lessons with a registered teacher led to an increased ability of people with Parkinson's to carry out everyday activities.[1] Compared with usual care, significant improvement was observed following 24 Alexander lessons in the primary outcome of self-assessment Parkinson's disease disability scale (regardless of whether measured at best or worst time). The difference between groups was maintained at the 6 month follow-up (p≤0.04). In addition, the secondary	Thank you for your comment. After further discussion, the GDG agreed it was appropriate to add in a consider recommendation for the Alexander technique in people with Parkinson's disease who are experiencing balance or motor function problems.

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				measure of Beck's depression inventory showed short-term improvement that was significantly greater than for usual care (p=0.03). Qualitative self-report measures revealed an overall greater degree of change for the Alexander group versus comparators, with improvements in balance, posture and walking cited frequently, as well as increased coping ability and reduced stress. A further (preliminary) finding was a significantly lower rate of increase of Parkinson's disease medication during the study in the Alexander group than for either the usual care or massage comparators (p=0.001). This RCT is supported by the preceding pilot study, as well as by case studies and by research (N=22) that reported improved postural alignment and balance, and reduced rigidity in people with Parkinson's following an AT-based intervention.[2,3,4] The distinctive educational and self-management nature of the Alexander Technique is illustrated by an analysis demonstrating that people with Parkinson's retained and continued to implement over the longer term, the skills learnt in the lessons (6 months follow-up).[5] Large RCTs in non-Parkinson's populations have demonstrated the long-term (1 year) benefits of attending one-to-one lessons with registered Alexander Technique teachers in improving health-related quality of life, as well as reducing chronic musculoskeletal pain.[6,7] Bio-mechanical studies have shown that healthy people with extensive training in the Alexander Technique demonstrate improved movement coordination and balance, including more stable gait patterns compared with	

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				non-trained, age-matched controls.[8–12] These findings are of great relevance to people with Parkinson's and merit further study in this population. Currently, Alexander Technique lessons are usually paid for privately and a relatively small proportion of people with Parkinson's are therefore able to make use of this intervention.[13] Alexander Technique lessons represent an important intervention option for people with Parkinson's to help them better manage their condition. References 1. Stallibrass C, et al. Randomized, controlled trial of the Alexander Technique for idiopathic Parkinson's disease. Clin Rehabil 2002;16:695–708. 2. Stallibrass C. An evaluation of the Alexander Technique for the management of disability in Parkinson's disease – a preliminary study. Clin Rehabil 1997;11:8–12. 3. Marcus RL, et al. Long-term effectiveness of Alexander Technique classes for managing symptoms of Parkinson's disease: case studies. 4th World Parkinson Congress, Portland, OR, USA 2016; Poster 40:20. 4. Cohen RG, et al. Lighten up: Specific postural instructions affect axial rigidity and step initiation in patients with Parkinson's Disease. Neurorehabil Neural Repair 2015;29:878−88. 5. Stallibrass C, et al. Retention of skills learnt in Alexander Technique lessons: 28 people with idiopathic Parkinson's disease. J Bodyw Mov Ther 2005;9:150–7.	

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				6. Little P, et al. Randomised controlled trial of Alexander Technique lessons; exercise and massage (ATEAM) for chronic and recurrent back pain. BMJ 2008;337:a884. 7. MacPherson H, et al. Alexander Technique lessons or acupuncture sessions for persons with chronic neck pain: A randomized trial. Ann Intern Med 2015;163:653-62. 8. Cacciatore TW, et al. Increased dynamic regulation of postural tone through Alexander Technique training. Hum Mov Sci 2011;30:74–89. 9. Cacciatore TW, et al. Prolonged weight-shift and altered spinal coordination during sit-to-stand in practitioners of the Alexander Technique. Gait Posture 2011;34:496–501. 10. Cacciatore TW, et al. Neuromechanical interference of posture on movement: evidence from Alexander Technique teachers rising from a chair. J Neurophysiol 2014;112:719–29. 11. O'Neill MM, et al. Effects of Alexander Technique training experience on gait behavior in older adults. J Bodyw Mov Ther 2015;19:473–81. 12. Hamel KA, et al. Older adult Alexander Technique practitioners walk differently than healthy age-matched controls. J Bodyw Mov Ther 2016; In Press. Eldred J, et al. Teachers of the Alexander Technique in the UK and the people who take their lessons: A national cross-sectional survey. Comp Ther Med 2015;23:451−61.	
The Walton Centre NHS Trust				Finally, can we congratulate the panel for tackling such a difficult guideline and coming up overall with a guideline that seems largely very sensible and reflects mainstream practice. We have some generic comments to make that we hope can be considered.	Thank you for your comments. 1. The GDG and the developers are grateful for all stakeholders' scrutiny of the draft guideline, and approach

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				1. We hope our comments will be seen as constructive suggestions. Some of this is to do not so much about what is said but the way it comes across. In places we do think there is the potential for quite significant misunderstanding especially by health care practitioners who are not experts in PD and patient organisations. These guidelines might also slightly confuse patients. 2. We recognise that there is a mixture of evidence based recommendation (which we understand is the basis of NICE guidelines) but there are also recommendations based on opinion or anecdote; to provide pragmatic guidance in areas with less evidence base, we would note that the panel (to the best of our knowledge) does not have input from parkinsons disease experts who regularly provide therapy specifically to the most advanced and often young patients, and in this regard the panel may not have insight into therapies such as duodopa as based direct on personal experience. 3. We also note that paradoxically in other parts of the guidelines certain interventions are not advised because there is no firm evidence. In some ways we recognise that the authors of these guidelines are possibly trying to have it both ways, a difficult thing to achieve if these guidelines are to provide a comprehensive and current guide to best practice. 4. As the panel is aware, we make the point that 'absence of evidence of benefit' is not the same thing as 'evidence of absence of benefit'. The authors do acknowledge that here and there in the text but seem to lose track of this particularly with regard to things like Atropine for dribbling, Amantadine and Fludrocortisone. They also argue that cost cannot be an argument in some	all feedback as a constructive means to optimising guidance. 2. & 3. Where robust evidence was lacking, the GDG followed section 9.1.6 of The Guidelines Manual 2012 (to which this guideline was developed), drawing on the expertise of GDG members and extrapolating from other evidence of which group members were aware. This process is detailed in the relevant 'Evidence to recommendations' section of each chapter. The GDG comprised a broad range of clinical and patient experts, with extensive experience of all stages of Parkinson's disease, including LCIG and other therapies for advanced disease. 4. As explained in the guideline, there are particular legal considerations surrounding the prescription of an off-label medicine over a licensed option on the grounds of cost alone. This is why the GDG were not able to favour fludrocortisone over midrodine. This is quite a different situation from considering the balance of benefits, harms and costs presented by a series of options (as in the case of treatments for advanced Parkinson's disease including LCIG), which is a fundamental component of NICE's remit. 5. All NICE guidelines, including this one, emphasise that 'Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their

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				circumstances (Midodrine versus Fludrocortisone) but then use cost as an argument for effectively banning Duodopa. 5. We consider that there are shortcomings in the guidelines. If one were to be rigid in their application then one does not allow individual disease management. This is the hallmark of best practice in PD. Each patient's personal care of their PD may not be applicable to trial data as after all many studies in PD use patients without any other significant co-morbidities; excludes those with dementia (particularly the studies on medication affecting motor control); and are of the relatively younger PD patient. With the relatively older agents (e.g. amantadine) there is insufficient trial data but a vast experience of personal care information. 6. The PD patient has in particular been a vulnerable group of patients where drug therapy has advanced slowly, and the therapies have been difficult to use because of adverse events such as delusions/hallucinations and other non-motor symptoms. Furthermore, the postcode lottery of prescribing of certain therapies has never been raised by NICE. For example why is apomorphine not an option in many areas of the country? 7. The authors of the NICE document have not reflected on the individual patient who has trialled conventional therapy but either due to side-effects (often unpredictable), or lack of efficacy has few options available in trying to preserve mobility. There must be a common sense approach to advanced therapies in order to allow the experienced clinician to offer therapy if the options are limited. An example is Carbidopa-levodopa gel (Duodopa). As stated above, we have personal experience of PD patients and their	clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.' 6. By providing guidelines on best practice to the NHS, NICE guidance aims to reduce inappropriate variation in practice. The guideline recommends that apomorphine should be considered as part of best medical therapy for people with advanced Parkinson's disease. 7. For comments on the effectiveness and cost effectiveness of LCIG, please see **theme 1**. For comments on the paucity of therapeutic options for people with advanced Parkinson's disease, please see **theme 1e**. 8. No evidence was found for this intervention that met the criteria of the relevant review questions. 9. & 10. Unfortunately, these recommendations are from a part of the guideline that was not included as part of the scope of this update, and therefore substantive changes cannot be made

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				family/carers lives being transformed by this therapy, whose monitoring data is published but in a non-RCT trial. 8. No mention is made of the use of apomorphine by s/c injection for morning awakening "off" immobility, or for overnight akinesia (single injection or via infusion), despite published evidence. 9. With regards to the use of DAT scans in diagnosis, we are of the opinion that the guidelines could potentially reduce the number of inappropriate scans – we often see DAT scans used where clinical judgement should suffice and we would consider that inappropriate use of such scans could be reduced if there were clear clinical indicators for such scans, eg distinguishing between a true degenerative parkinsonian disorder vs a drug-induced one (to aid management regarding use of dopamine when patients are mentally stable), distinguishing parkinsons from other unusual tremor conditions, distinguishing the cause of severe bradykinesia between PD, depression, frontal abulia, …a scenario familiar to those of us who provide a lot of tertiary centre opinions. 10. We would consider that imaging with CT or MRI is sometimes indicated in some cases of atypical PD (eg to assist diagnosis in MSA, in cases of strictly unilateral progressive parkinsonism etc) – we would not consider such scans to be useful in a majority of routine cases though.	
The Walton Centre NHS Trust	Short	11	3	Re 1.4.8 In practice, it is often necessary to reduce dopamine agonists and then actually increase L dopa if the ICD has settled. The guidance makes it look as if an L Dopa reduction will occur, but clearly this is typically only necessary in	Thank you for your comment. The GDG agrees there was the potential for this recommendation to be misinterpreted and have amended the recommendation to reflect this. It now reads "(1.4.8) When managing impulse control disorders, modify dopaminergic therapy by first gradually

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				a very small number of patients who find their ICD has not fully settled on full discontinuation of the dopamine agonist.	reducing any dopamine agonist. Monitor whether the impulse control disorder improves and whether the person has any symptoms of dopamine agonist withdrawal".
The Walton Centre NHS Trust	Short	12	16	Re 1.5.9: In addition to reviewing the patients existing medications to look for causes of postural hypotension, we consider it important to review the diagnosis of Parkinson's disease as well and ensure that an alternative cause of parkinsonism is not the potential diagnosis (eg MSA, Lewy Body disease). In addition, the guidance does not include the potential to reduce orthostatic hypotension with additional cautious use of domperidone where it has been caused or exacerbated by L-dopa (with ECG check of QT interval and discussion re rare side cardiac side effects related to arrhythmia). The guidance does not comment on the frequent postural hypotension that occurs temporarily (temporary for most patients) with introduction of L-dopa and the potential for this to settle or be effectively managed with a brief course of domperidone for 2-3 months in many patients. The guidance goes straight to pharmacological therapies for postural hypotension without addressing other non-pharmacological methods that can be employed usefully in some patients who are mildly affected (eg addition of salt to diet, head-up incline to bed, compression stockings).	Thank you for your comment. Whilst the guideline does not contain a recommendation specifically to review the diagnosis of Parkinson's disease if postural hypotension develops, recommendation 1.2.5 is to reconsider the diagnosis if atypical clinical features develop, of which postural hypotension could be one such. The version of the guideline which went out for consultation did contain a reference to the use of domperidone for orthostatic hypotension. However, following the consultation responses received the GDG agreed the evidence behind this was not sufficiently strong, and hence this recommendation was removed. Unfortunately, non-pharmacological methods for postural hypotension are not included in the guideline scope for this guideline update, and hence no recommendations on this topic could be made.
The Walton Centre NHS Trust	Short	12	9	Re 1.5.7: Re Rotigotine – we think there needs to be some clarification about whether this would replace an oral agonist or be an addition to it (we assume the latter but think this would be faintly unconventional practice).	Thank you for your comment. The GDG agreed that both options are plausible and therefore no restriction was made to the recommendation specifying one alternative over the other.

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The Walton Centre NHS Trust	Short	13	1	Re 1.5.10: Re recommendations regarding midodrine, we fear this is going to be an unworkable recommendation. Although there may be better research evidence for Midodrine over Fludrocortisone, there is extensive long term clinical experience using Fludrocortisone for orthostatic hypotension and despite what might or might not exist in terms of published trials it is usually an effective intervention. Midodrine is far more complex with a great deal more potential difficulty concerning side effects. It is often contra-indicated in older patients. In our experience, GPs will almost never prescribe it. Logistical consequences of all patients with Parkinson's disease who have orthostatic hypotension being treated with Midodrine and their prescriptions being written out by hospital neurologists are almost unimaginable. We do not think this is workable. We consider that Midodrine should be a second line drug after Fludrocortisone and in our opinion will continue to be so.	Thank you for your comment. The GDG agreed that the evidence behind the use of midodrine was not particular strong, but in view of it being the only medicine with a license in this area felt it was appropriate to make a "consider" level recommendation. The GDG agreed there may be many reasons why midodrine is not the optimal choice for individual people, and in this situation fludrocortisone is a logical and commonly used alternative.
The Walton Centre NHS Trust	Short	13	8	Re 1.5.12 While we understand the simplicity of referring to a different guideline on managing depression in adults where patients with PD are recognised to have depression, we believe it is good practice to ensure adequate dopaminergic therapy and also to distinguish fluctuating low mood and anxiety as a result of under-treatment / off effect as opposed to true depression.	Thank you for your comment. The scope for this guideline update, which was publically consulted on, specified that evidence on interventions for depression will not be included as part of this update, and the guideline will cross-refer to the NICE guideline on depression in people with a chronic physical health problem. At this stage it is not possible to alter this decision and hence this recommendation cannot be changed. However, the GDG did agree with the sentiments expressed, and stressed it is important to distinguish the underlying cause of anxiety/depression in people with Parkinson's disease before attempting to treat it.

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The Walton Centre NHS Trust	Short	14	3	Re reduction of dopaminergic medications causing hallucinations, is it worth mentioning that hallucinations and illusionary phenomena are more commonly seen at night and if medications are tailored to reduce side effects, a good history will often allow the most appropriate doses in the day or evening to be targeted (eg reduction of evening L dopa medication).	Thank you for your comment. Unfortunately, no evidence for this approach was identified as part of the review and therefore, despite agreeing that it represented sensible advice, the GDG did not feel it was appropriate to make a recommendation on this topic.
The Walton Centre NHS Trust	Short	15	15	Re 1.5.25 We agree about Rivastigmine or possibly Memantine but we think it should be made clear that these drugs should not be prescribed by neurologists in neurology clinics. This would be poor practice because patients require a package of care for dementia in addition to cholinesterase inhibitor prescriptions. The NICE guidelines for the use of these drugs and for dementia would also indicate that these drugs should be given under the auspices of appropriate mental health services so that patients can access the full range of pharmacological, non-pharmacological and community support interventions. We have, many times, seen the situation of a demented patient receiving care comprising only a repeat prescription for Rivastigmine every three months. We stopped people doing this here years ago and think patients have had a better service as a result.	Thank you for your comment. The GDG agree with this sentiment, and they would expect people with Parkinson's disease dementia to receive all the other support specified in the NICE guideline for dementia.
The Walton Centre NHS Trust	Short	15	3	Re: 1.5.22 We do not agree that sublingual Atropine eye drops can be dismissed like this on the basis of opinion and anecdote. We have treated hundreds of patients in this centre (where we have one of the largest movement disorder services in the UK) and we have not seen cases where cognitive side effects have occured. Glycopyrrolate on the other hand is almost always ineffective in practice. We consider that the statement about sublingual Atropine is too strong and not justified by our clinical experience. This is a safe and simple intervention it will be a great disservice to patients if it is thrown out on the basis of no real evidence at all.	Thank you for your comment. After further discussion, the GDG agreed this had been too strongly phrased, and modification have been made to this section, Indeed, the primary reason for allowing consideration of other anticholinergics was to allow people to use topical atropine if it was felt appropriate, and this has now been clarified as part of the recommendation.

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The Walton Centre NHS Trust	Short	16	16	Re 1.6.4 We agree there is no conclusive evidence that monoamine oxidase inhibitors are neuroprotective but do think one can argue that it is reasonable to advise patients that Rasagiline may possibly offer partial neuroprotection and that the data from clinical trials are controversial and conflicting. This allows patients to make an informed choice about whether they wish to try taking a monoamine oxidase inhibitor for that purpose. There can be an open and honest discussion with patients about this.	Thank you for your comment. Unfortunately, these recommendations were not included within the scope of this guideline update, and therefore no substantive changes to these recommendations could be made.
The Walton Centre NHS Trust	Short	17	5	Re 1.7.7 When considering protein intake and food, we consider that there should be some potential recommendations as to considering L dopa therapy at times separate to eating to ensure the most reliable drug absorption.	Thank you for your comment. The GDG discussed this comment, but did not feel in the absence of any evidence it was appropriate to make specific recommendations on this topic.
The Walton Centre NHS Trust	Short	17	8 15	Re 1.7.2 We accept there is now increasing strong scientific evidence on the effectiveness of exercise and physio in early PD. From a practical aspect, we hope the guidelines do not mean referrals have to come from secondary and tertiary centres. i.e patients can presumably be referred by their Gps or self refer for exercise programmes. We are also concerned that in the current financial climate, Physiotherapy and OT services would literally be overwhelmed if all patients with early PD were referred to their services. It is hard to imagine a scenario in which wholesale referral of all patients would be appropriate or necessary, eg in those patients with good functional capacity and mobility with institution of appropriate medical drug therapies. We also comment that Parkinsons UK offers excellent sources of information including DVD's about exercise, mobility and motor / non-motor symptoms and one can argue that the remit of a physiotherapist and OT might be better	Thank you for your comments. The GDG agreed that referrals from primary care would be appropriate, and therefore did not specify they needed to come from any specific service. The GDG agreed that referral would not be appropriate for all individuals in the early stages, and therefore this recommendation was kept at the weaker "consider" level. The GDG also agreed that the appropriate action at this stage was not for people to be provided with physiotherapy, but rather with education and advice about physical activity, which may well include references to the sources of information you describe.

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				utilised to providing more specific targeted clinical input to those most in need as opposed to a generic advice service.	
The Walton Centre NHS Trust	Short	18	22	Re 1.8.1 The guidelines mention Apomorphine via S/C infusion but make no mention of intermittent injections that may be very useful.	Thank you for your comment. A reference to intermittent apomorphine injections has now been added to this section, in line with the suggestion made.
The Walton Centre NHS Trust	Short	18	5	Re 1.8.4 This is potentially one of the most disputed sections of this new draft guideline amongst the whole movement disorder department at our institution, one of the largest movement disorder services in the UK, where advanced therapies are necessary in highly refractory and poorly controlled patients. We can not see that the guidelines have had input from a parkinsons specialist with significant experience in offering an advanced PD service that includes therapy with Duodopa. We consider that this decision not to recommend Duodopa will be very controversial where the argument against using Duodopa seems to be entirely on the basis of cost rather than efficacy. We are strongly of the opinion that there has to be a place for Duodopa because not all patients are suitable to have deep brain stimulation (they may be unwilling or it may be contraindicated) and Apomorphine is not likely to fix dyskinesia nor can dyskinesia be dealt with by optimising drugs; in addition, the panel appear to have removed Amantadine as an alternative option. There will always be patients for whom Duodopa will be the *only* viable option. We are strongly of the opinion that this should be left as an available option in *highly selected cases* in *exceptional situations* and only on the advice and under the care of movement disorders experts with subspecialist experience in managing all aspects of advanced PD.	Thank you for your comment. For comments on the effectiveness and cost effectiveness of LCIG, please see **theme 1**. For comments on the role of expert witnesses, please see **theme 2**. For comments on the effectiveness and cost effectiveness of LCIG in subgroups of people with advanced Parkinson's disease, please see **theme 1b**. For comments on the paucity of therapeutic options for people with advanced Parkinson's disease, please see **theme 1e**.

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The Walton Centre NHS Trust	Short	25	18	Re 1.8.2 In recommending Apomorphine, we think that saying later disease is misleading and rather it should specify when patients are experiencing unpredictable or unmanageable off symptoms/freezing episodes.	Thank you for your comment. The GDG discussed this wording, and agreed that "later stages" should be replaced by "advanced Parkinson's disease"
The Walton Centre NHS Trust	short	4	19	Re 1.1.5, We comment that it is not clear in real everyday clinical practice exactly what a 'care plan' actually constitutes. We would ask that it be explicitly clarified whether this has to represent a separate distinct document as opposed to the traditional clinic letter. We raise concerns that plans for care should reflect changing health care needs that need to be continually updated as different health care professionals become involved in the patient's care. In practice, we argue that separate care plans lead to duplication of work in potentially already stretched services, and may lead to clinical governance issues if they do not state the exact same recommendations for care as the specialist clinic letters. We ask how a care plan can practically respond flexibly to change in clinical problems (as is almost inevitable in something like PD). In this regard, in the real world it is more useful to see the continuing dialogue between primary care, secondary care and other medical services as a record of the actions and recommended direction of the current care plan. We would hope that this statement could be more explicit in explaining that a specialist a clinic letter (a) recording a consultation, and (b) describing a management plan agreed with the patient (and if appropriate with carers or relatives) that has been (c) copied to the patient, GP and any other interested parties would certainly amount to a care plan. We believe that the concept of 'care plan' is often rather ill-defined and therefore think this should be spelled out because it is something that neurologists are sometimes criticised about (unreasonably in our view).	Thank you for your comment. Unfortunately, this recommendation is from a part of the guideline that was not included as part of this update, and therefore no substantive changes to this recommendation can be made.

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The Walton Centre NHS Trust	Short	5	11	We can not see on what basis the guidelines that newly referred patients have to be seen within six weeks and follow ups with complex problems within two weeks. This appears arbitrary and will potentially be difficult to deliver. The guidelines also raise patient expectations and increase their stress where the services have not had either appropriate funding to deliver to this target or, of more concern, have difficulty recruiting specialists because of lack of reasonable applicants. For example, for neurology, there remain a significant number of unfilled consultant posts in the UK. We recognise that guidelines may be *interpreted* as either (a) *aspirational* (to drive forward care and improve appropriate service management and funding) or (b) that which is actually and *realistically expected as a basic standard of care* within the current real world of the NHS. We accept that guidelines may be very useful in driving forward service management and appropriate funding. However, we raise concerns that for every condition that has a guideline recommending such provision of service, other areas of significant need (eg related to rare neurological conditions where such detailed national guidelines do not exist) may potentially suffer, especially where services are already stretched to deliver to current referral targets. We consider that the currently agreed national guidelines for referral to treatment are perfectly reasonable and it may be considered divisive to have conflict between agreed national guidelines and this NICE guideline We consider as one of the largest specialist providers of parkinsons care in the UK, that the idea that any patient with Parkinson's disease with a complex problem (nearly all patients eventually) have to be seen within two weeks of those problems occurring is quite impossible to imagine. This	Thank you for your comment. Unfortunately, this recommendation is from a part of the guideline that was not included as part of this update, and therefore no substantive changes to this recommendation can be made.

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				recommendation must be based on no evidence other than an opinion or anecdote – or even just expectation.	
The Walton Centre NHS Trust	Short	7	14	While we agree that impulse control disorders can occur with any dopaminergic therapy, the way this is written is not clear and makes it look like Levodopa can be as bad as dopamine agonists for this very important and troublesome complication. This is not the case. Dopamine agonists are far more likely to cause impulse control disorders than Levodopa. There are reports of patients developing impulse control disorders on Levodopa but nearly all of these concern patients who are *also* taking Dopamine agonists. We agree that it is worth pointing out that an impulse control disorder can occur in a Levodopa treated patient (without an agonist) but that this is rare, whereas the guidelines as they are currently written give the (wrong) impression that there is not much difference between dopaminergic drugs (Levodopa or agonists) in this regard whereas in fact agonists are a far far bigger problem. In addition, we would consider it imperative to screen for the presence of impulse control disorder prior to initiation since the risk is greater for patients who have previously elicited such behaviour. Impulse control disorder (ICD) is such an important issue that is often poorly recognised in patients unless specifically monitored and screened and we think that there should be explicit guidance in the short guidance to specifically	Thank you for your comment. The GDG agreed that it was important to stress that the risk of ICDs is considerably higher with dopamine agonists, and therefore recommendations 1.3.5, 1.4.2 and 1.4.5 have been written to stress this point. The GDG did not feel there was sufficient evidence to recommend specifically screening for ICDs before starting treatment, but agreed that this history would form an important part of the discussion around the benefits and harms of different drug classes specified in recommendations 1.3.1 and 1.3.7

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				consider screening for impulse control disorder and associated behaviour prior to initiating dopamine agonists and the guidance should make continued active monitoring for ICD obligatory for patients who remain on this treatment, particularly as doses are increased.	
The Walton Centre NHS Trust	short	7	7	We agree that Levodopa should be offered to patients who have symptoms that are significantly impairing quality of like or activities of daily living. We completely agree that trying to use dopamine agonist monotherapy in badly affected newly presenting patients is inappropriate and unlikely to work. However the terminology used 'affecting quality of life' is a bit woolly. Some patients with minor impact on quality of life will elect to try a dopamine agonist especially if younger. We recommend that this should be changed to 'severely affecting quality of life' or where symptoms are causing 'significant and severe impairment of function'. We consider that this terminology may be too loose as it stands because it might lead to the assumption that everybody has to have Levodopa unless their symptoms are absolutely minimal.	Thank you for your comment. The GDG agreed that the decision between initial monotherapy options is often complex, but did not feel they had good evidence to support any specific criteria for deciding between options. However, the recommendations have been restructured to make it clear there should always be a discussion with the individual about treatment options before any therapy is started, and that the choice of therapy should always be based on the person's self-report as to how their quality of life is affected.
The Walton Centre NHS Trust	Short	9	14	Re 1.4.2 It is crucial that the guidance emphasises the increased risk of impulsivity as the doses of dopamine agonists are increased. (They do advice reduction of dose later on once the impulsivity has developed). We consider that it is imperative to screen for the presence of ICD prior to initiation since the risk is greater in patients who have previously elicited such behaviour.	Thank you for your comment. The GDG agrees that there may be an increased risk of impulsivity as the doses of DAs are increased, but also agreed that this is one of many other risk factors for ICDs, and did not feel it appropriate that this factor be specified as more important than other potential factors The GDG did not feel there was sufficient evidence to recommend specifically screening for ICDs before starting treatment, but agreed that this history would form an important part of the discussion around the benefits and harms of different drug classes specified in recommendations 1.3.1 and 1.3.7

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The Walton Centre NHS Trust	Short	9	6	Re 1.3.7: The guidance states that there is no evidence for Improvement of motor symptoms on amantadine. It is not fully clear and we assume this to mean there is no evidence of amantadine improving PD symptoms of bradykinesia, tremor and rigidity as an initial therapy. The guidance does not however explicitly say whether the evidence of amantadine on reducing dyskinesia is available and reviewed. Clearly this is a far more important question when it comes to amantadine as an effective therapy. We consider that this statement about Amantadine is far too strong. We accept there are no randomised trials supporting the use of Amantadine but this is because it is a very old drug and the pharmaceutical industry are clearly not financially motivated to do any such trial. Amantadine is widely used and effective in patients with dyskinesia. Any doctor with an expertise in Parkinson's disease will know this. It can very often prevent or delay the need for something like deep brain stimulation which is about the only other option available to these patients once they have their existing oral medications optimised. We recommend that this option has to be left open and we would continue to use Amantadine despite these guidelines – as would most other experts. We think this is the trap that NICE potentially falls into from time to time, equating lack of clinical trials with proof of a drug being of no benefit. This is not philosophically logical. We would strongly urge that this section is reviewed.	Thank you for your comment. After discussion, the GDG agreed that amantadine may be a useful treatment option for managing dyskinesia in people with Parkinson's disease, where this cannot be adequately managed by modification of existing therapy. The recommendation has therefore been changed from a "do not" to a "consider" recommendation to reflect this.
The Walton Centre NHS Trust	short	9	8	Re 1.4 While we agree that impulse control disorders can occur with any dopaminergic therapy, the way this is written, it looks like Levodopa is as bad as dopamine agonists. This is not the case. Dopamine agonists are far more likely to cause impulse control disorders than Levodopa. There are reports of patients developing impulse control disorders on Levodopa but nearly all of these concern patients who are also taking Dopamine agonists. We agree that it is	Thank you for your comment. The GDG agreed that it was important to stress that the risk of ICDs is considerably higher with dopamine agonists, and therefore recommendations 1.3.5, 1.4.2 and 1.4.5 have been written to stress this point.

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				worth pointing out that an impulse control disorder can occur in a Levodopa treated patient (without an agonist) but this is very rare. The guidelines as they are give the impression that there is not much difference between dopaminergic drugs (Levodopa or agonists) in this regard whereas in fact agonists are a far bigger problem.	
UCB Pharma Limited	Full	108	2572	Please refer to comment number 3	Thank you for your comment. Unfortunately, the management of gastro-intestinal problems was not part of the scope for this guideline update. In addition, outcomes of gastro-intestinal problems were neither prioritised in the outcomes of interest by the GDG. It was therefore not possible to make recommendations on this topic.
UCB Pharma Limited	Full	111	2631	Evidence accounting for a higher prevalence of RLS in patients suffering of PD is available in literature (Bhalsing K et al. 2014). Therefore we strongly recommend that appropriate guidance should be provided in this section. Reference: - Bhalsing K., Suresh K., Muthane U. B., Pal P. K. Prevalence and profile of Restless Legs Syndrome in Parkinson's disease and other neurodegenerative disorders: A case-control study Parkinsonism Relat Disord 2013; 19(4):426-430 - Rijsman R. M., Schoolderman L. F., Rundervoort R. S., Louter M.Restless legs syndrome in Parkinson's disease Parkinsonism Relat Disord 2014 20(Suppl1):S5-9	Thank you for your comment. Unfortunately, this topic was not included within the scope of this guideline update, and therefore no evidence was looked for and hence no recommendations could be made.

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UCB Pharma Limited	Full	213	5262	We would like to note that there is inconsistency of the level of which evidence has been rated throughout the document.	Thank you for your comment. We have responded to this comment where individual examples have been cited.
UCB Pharma Limited	Full	216		Quality of evidence: "*The GDG agreed that the majority of evidence was low quality. The GDG also discussed the retrospective compared with prospective evidence. It was agreed that there exists a need for more evidence from prospective studies with a clear account of dopaminergic medication for patients, and using well-validated scales for the recognition of ICD*. " We believe that this perspective is unclear due to the previous referencing of Trenkwalder et al evidence as high quality evidence. We request that this evidence be taken into consideration and reflected into the guidance. <u>Reference:</u> - Claudia Trenkwalder, MD, Bryan Kies, FCNeurol (SA), Monika Rudzinska, MD, Jennifer Fine, FCP (SA) Neurology, Janos Nikl, MD, Krystyna Honczarenko, MD, Peter Dioszeghy, MD, Dennis Hill, MD, Tim Anderson, FRACP, Vilho Myllyla, MD, Jan Kassubek, MD, Malcolm Steiger, FRCP, Marco Zucconi, MD, Eduardo Tolosa, MD, Werner Poewe, MD, Erwin Surmann, MSc, John Whitesides, PhD, Babak Boroojerdi, MD, and Kallol Ray Chaudhuri, DSc. Rotigotine Effects on Early Morning Motor Function and Sleep in Parkinson's Disease: A Double-Blind, Randomized, placebo-controlled Study (RECOVER) Mov Disord. 2011 Jan; 26(1): 90–99.	Thank you for your comment. The Trenkwalder study is indeed included as part of the evidence here, but this did not change the GDG's conclusion that the majority of the evidence was of low quality, and that additional research in this area would be valuable.

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UCB Pharma Limited	Full	216	5320	'Moderate' quality evidence suggest that Pramipexole PR and Rotigotine are associated with reduced rates of ICD's. This evidence should be clearly indicated in the full and short guidance. Reference: - Rizos A, Sauerbier A, Antonini A, Weintraub D, Martinez-Martin P, Kessel B, Henriksen T, Falup-Pecurariu C, Silverdale M, Durner G, Røkenes Karlsen K, Grilo M, Odin P, Chaudhuri KR; A European multicentre survey of impulse control behaviours in Parkinson's disease patients treated with short- and long-acting dopamine agonists. EUROPAR and the IPMDS Non-Motor-PD-Study Group. Eur J Neurol. 2016 Aug;23(8):1255-61)	Thank you for your comment. This evidence, as you correctly note, is included as part of the full guideline. The GDG discussed whether they felt the evidence was sufficiently robust to merit specific recommendations around ICD rates for individual medicines, but ultimately decided they did not feel confident enough to make such recommendations. The rationale behind the GDG's decision has been discussed in the evidence to recommendations section.
UCB Pharma Limited	Full	25	435	We would like to note that the clinical guideline should indicate that signs and symptoms of ICDs should be considered when communicating with patients with Parkinson's Disease. Reference: - Macphee GJ, Chaudhuri KR, David AS, Worth P, Wood B. Managing impulse control behaviours in Parkinson's disease: practical guidelines. Br J Hosp Med (Lond). 2013 Mar;74(3):160-6.	Thank you for your comment. Unfortunately, this chapter has not been included as part of the scope for this guideline update, hence it has not been updated and no changes can be made.
UCB Pharma Limited	Full	26	446	The clinical guideline should indicate that an appropriate level of communication should be ensured at all stages of the disease, given that the needs/fears/anxieties of patients can vary at different stages of the disease.	Thank you for your comment. Unfortunately, this chapter has not been included as part of the scope for this

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				Reference: https://www.nice.org.uk/guidance/cg35/chapter/1-guidance?unlid=13108985420155301110 26#communication-with-people-with-parkinsons-disease-and-their-carers	guideline update, hence it has not been updated and no changes can be made.
UCB Pharma Limited	Full	30	596	The draft guideline inaccurately implies that there is no evidence reporting the experience of carers for people with ICDs. We would like to note that such evidence has been published by Leroi et al (2012). Reference: Leroi I, Harbishettar V, Andrews M, McDonald K, Byrne EJ, Burns A. Carer burden in apathy and impulse control disorders in Parkinson's disease. Int J Geriatr Psychiatry. 2012 Feb;27(2):160-6. doi: 10.1002/gps.2704. Epub 2011	Thank you for your comment. In the agreed protocol for this particular topic, only qualitative evidence was of interest. Unfortunately, the Leroi study used quantitative methods to measure the carer burden and was therefore not within our protocol for this question. The text of the guideline has been altered to calrify this point.
UCB Pharma Limited	Full	31	615	We feel that this statement fails to explicitly highlight the differences in ICD rates between different DA formulations, an important consideration when starting dopamine agonist therapy. As acknowledged in section 11.1.4, the Rizos, et al. (2016) study provided moderate-quality evidence of the significantly lower rates of ICD for rotigotine compared with other DA formulations which should be highlighted at the point of treatment initiation. Furthermore, Antonini, et al. (2016) highlighted overall ICD behaviours reported as AE's of 9.0% in a post-hoc analysis of over 750 rotigotine patients treated for between 6 months and 6 years, with none of the ICD AEs considered serious, and only 3 were reported to be severe in intensity. What we would request is that the differing instances of ICD's between the DA treatment options (both oral and transdermal) is highlighted in this section.	Thank you for your comment. The GDG agrees that it is plausible that there may be differences in ICD rates between different DA formulations but they do not feel that the current available evidence provided by Rizos et al. and Antonini et al. is sufficiently robust (non-RCTs) in order for them to make a recommendation. The study from Rizos was included in the guideline for the review question on predictors for the development of ICD, and the data on incidence by drug and route of administration are presented in the evidence table for that study (appendix D).

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				References: - Rizos A, Sauerbier A, Antonini A, Weintraub D, Martinez-Martin P, Kessel B, Henriksen T, Falup-Pecurariu C, Silverdale M, Durner G, Røkenes Karlsen K, Grilo M, Odin P, Chaudhuri KR; A European multicentre survey of impulse control behaviours in Parkinson's disease patients treated with short- and long-acting dopamine agonists. EUROPAR and the IPMDS Non-Motor-PD-Study Group. Eur J Neurol. 2016 Aug;23(8):1255-61) - Antonini A, Chaudhuri KR, Boroojerdi B, Asgharnejad M, Bauer L, Grieger, F, Weintraub D. Impulse control disorder related behaviours during long-term rotigotine treatment: a post hoc analysis. Eur J Neurol 2016; 0:1-10	The study by Antonini et al only contains people taking rotigotine, and therefore it is not possible to calculate relative rates of ICDs compared to alternative medicines.
UCB Pharma Limited	Full	62	1525	To ensure accurate reflection of the published evidence, please do add "compared to placebo" at the end of line 1526, so that the text reads (revision underlined): "….*could not distinguish rates of serious adverse events <u>compared to placebo</u>*"	Thank you for your comment. This text has now been changed as per this suggestion.
UCB Pharma Limited	Full	67	1654	The level of GI function should be assessed in patients when making a diagnosis and eventually non-oral options should be offered if a significant level of GI dysfunction is diagnosed. We believe that this consideration reflected in the guidance due to the issues highlighted by (Barone et al, 2009)	Thank you for your comment. Unfortunately, diagnosis is a part of the guideline that was not included as part of this update, and therefore substantive changes to this recommendation cannot be made.

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				Reference: - Barone P, Antonini A, Colosimo C, Marconi R, Morgante L, Avarello TP, Bottacchi E, Cannas A, Ceravolo G, Ceravolo R, Cicarelli G, Gaglio RM, Giglia RM, Iemolo F, Manfredi M, Meco G, Nicoletti A, Pederzoli M, Petrone A, Pisani A, Pontieri FE, Quatrale R, Ramat S, Scala R, Volpe G, Zappulla S, Bentivoglio AR, Stocchi F, Trianni G, Dotto PD; PRIAMO study group.The PRIAMO study: A multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. Mov Disord. 2009 Aug 15;24(11):1641-9. doi: 10.1002/mds.22643.	
UCB Pharma Limited	Full	68	1667	Since not all DAs are the same in terms of ICDs, prescribing specialists should evaluate which DA to use in light of patients' potential to develop ICD based on available evidence. We are concerned that this recommendation fails to explicitly highlight the differences in ICD rates between different DA formulations, an important consideration when starting dopamine agonist therapy. As acknowledged in section 11.1.4, the Rizos, et al. (2016) study provided moderate-quality evidence of the significantly lower rates of ICD for rotigotine compared with other DA formulations which should be highlighted at the point of treatment initiation. Antonini, et al. (2016) highlighted overall ICD behaviours reported as AE's of 9.0% in a post-hoc analysis of over 750 rotigotine patients treated for between 6 months and 6 years, with none of the ICD AEs considered serious, and only 3 were reported to be severe in intensity. This instance was lower than the insyances of ICD's reported in the DOMINION study.	Thank you for your comment. The GDG agrees that it is plausible that there may be differences in ICD rates between different DA formulations but they do not feel that the current available evidence provided by Rizos et al., Antonini et al., and Weintraub et al is sufficiently robust (non-RCTs) in order for them to make a specific recommendation around this issue. The studies from Rizos and Weintraub were included in the guideline for the review question on predictors for the development of ICD, and the data on incidence by drug and route of administration are presented in the evidence table for that study (appendix D). The study by Antonini et al only contains people taking rotigotine, and therefore it is not possible to calculate relative rates of ICDs compared to alternative medicines.

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				We would request that the guidance acknowledges the level of risk of ICD linked to differing DA formulations. References: - Rizos A, Sauerbier A, Antonini A, Weintraub D, Martinez-Martin P, Kessel B, Henriksen T, Falup-Pecurariu C, Silverdale M, Durner G, Røkenes Karlsen K, Grilo M, Odin P, Chaudhuri KR; EUROPAR and the IPMDS Non-Motor-PD-Study Group. A European multicentre survey of impulse control behaviours in Parkinson's disease patients treated with short- and long-acting dopamine agonists. Eur J Neurol. 2016 Aug 23 (8):1255-61) - Antonini A, Chaudhuri KR, Boroojerdi B, Asgharnejad M, Bauer L, Grieger, F, Weintraub D. Impulse control disorder related behaviours during long-term rotigotine treatment: a post hoc analysis Eur J Neurol 2016; 0:1-10 - Weintraub D, Koester J, Potenza MN, Siderowf AD, Stacy M, Voon V, Whetteckey, J, Wunderlich GR, Lang AE. Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. Arch Neurol. 2010 May;67(5):589-95.	
UCB Pharma Limited	Full	73	1851	The evidence on the impact on quality of life for rotigotine, from the Trenkwalder, et al. study, has been omitted from the draft guideline. The evidence indicated that significantly greater improvements were seen for rotigotine compared with placebo on the PDQ-8 (-5.74 (mean change) [95%	Thank you for your comment. This study has not been included because the review protocol for this question was that levodopa monotherapy was the only dopaminergic therapy that people in the trial were taking

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				CI -8.74, -2.75], p=0.0002). Significantly greater improvements with rotigotine compared to placebo were also seen in the BDI-II (LS mean treatment difference -2.01, p=0.011), Likert pain scale (-0.77 mean change) p=0.004, and UPDRS part II (-1.49) p=0.0005. The mean NMSS total score showed significantly greater improvement with rotigotine compared to placebo. Non-motor symptoms, as a whole, have been identified as having a greater impact on quality of life than motor symptoms (Martinez-Martin, et al. 2011). The Trenkwalder study (2011) demonstrated significant treatment benefits with rotigotine for several motor and non-motor symptom outcomes, including: sleep disturbance, nocturnal limb restlessness, cramps, pain, and immobility and impairment of early morning motor function, mood, and health-related quality of life. These are common and important nocturnal, early-morning, and daytime problems for PD patients. We would request that non-motor symptoms and their impact on patients is highlighted in this section. <u>References:</u> - Claudia Trenkwalder, MD, Bryan Kies, FCNeurol (SA), Monika Rudzinska, MD, Jennifer Fine, FCP (SA) Neurology, Janos Nikl, MD, Krystyna Honczarenko, MD, Peter Dioszeghy, MD, Dennis Hill, MD, Tim Anderson, FRACP, Vilho Myllyla, MD, Jan Kassubek, MD, Malcolm Steiger, FRCP, Marco Zucconi, MD, Eduardo Tolosa, MD, Werner Poewe, MD, Erwin Surmann, MSc, John Whitesides, PhD, Babak Boroojerdi, MD, and Kallol Ray Chaudhuri, DSc. Rotigotine Effects on Early Morning Motor Function and Sleep in Parkinson's	at baseline, in addition to having motor fluctuations. A significant proportion of people in the Trenkwalder study (around 20%) were not using levodopa at baseline, and therefore the study was not included as part of this question.

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				Disease: A Double-Blind, Randomized, placebo-controlled Study (RECOVER) Mov Disord. 2011 Jan; 26(1): 90–99. Martinez-Martin P1, Rodriguez-Blazquez C, Kurtis MM, Chaudhuri KR; NMSS Validation Group. The impact of non-motor symptoms on health-related quality of life of patients with Parkinson's disease. Mov Disord. 2011 Feb 15;26(3):399-406. doi: 10.1002/mds.23462. Epub 2011 Jan 24	
UCB Pharma Limited	Full	73	1853	We would like to note that the statement relating to hallucinations do not reflect the Trenkwalder, et al. high quality evidence, in which no distressing hallucinations or distressing dreams were recorded as individual items of the PDSS-2. Reference: - Claudia Trenkwalder, MD, Bryan Kies, FCNeurol (SA), Monika Rudzinska, MD, Jennifer Fine, FCP (SA) Neurology, Janos Nikl, MD, Krystyna Honczarenko, MD, Peter Dioszeghy, MD, Dennis Hill, MD, Tim Anderson, FRACP, Vilho Myllyla, MD, Jan Kassubek, MD, Malcolm Steiger, FRCP, Marco Zucconi, MD, Eduardo Tolosa, MD, Werner Poewe, MD, Erwin Surmann, MSc, John Whitesides, PhD, Babak Boroojerdi, MD, and Kallol Ray Chaudhuri, DSc. Rotigotine Effects on Early Morning Motor Function and Sleep in Parkinson's Disease: A Double-Blind, Randomized, placebo-controlled Study (RECOVER) Mov Disord. 2011 Jan; 26(1): 90–99.	Thank you for your comment. This study has not been included because the review protocol for this question was that levodopa monotherapy was the only dopaminergic therapy that people in the trial were taking at baseline, in addition to having motor fluctuations. A significant proportion of people in the Trenkwalder study (around 20%) were not using levodopa at baseline, and therefore the study was not included as part of this question.
UCB Pharma Limited	Full	86	2127	Please note that rotigotine is not a standard release dopamine agonist, as implied in Table 9.	Thank you for your comment. This has now been amended accordingly.

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UCB Pharma Limited	Full	87	2174	There is an inconsistency with which the quality of the data is referred to. The Trenkwalder et. al 2011 study is generally accepted as class 1 evidence but not referred to consistently as high level data in the draft guidance and in some cases it is referred to at a similar level to open label/audits of practice. We thus request the Trenkwalder et. al 2011 study be referred to consistently as high quality evidence throughout this guidance. Reference: - Claudia Trenkwalder, MD, Bryan Kies, FCNeurol (SA), Monika Rudzinska, MD, Jennifer Fine, FCP (SA) Neurology, Janos Nikl, MD, Krystyna Honczarenko, MD, Peter Dioszeghy, MD, Dennis Hill, MD, Tim Anderson, FRACP, Vilho Myllyla, MD, Jan Kassubek, MD, Malcolm Steiger, FRCP, Marco Zucconi, MD, Eduardo Tolosa, MD, Werner Poewe, MD, Erwin Surmann, MSc, John Whitesides, PhD, Babak Boroojerdi, MD, and Kallol Ray Chaudhuri, DSc. Rotigotine Effects on Early Morning Motor Function and Sleep in Parkinson's Disease: A Double-Blind, Randomized, placebo-controlled Study (RECOVER) Mov Disord. 2011 Jan; 26(1): 90–99.	Thank you for your comment. The Trenkwalder study itself has been rated as high quality (see Appendix D). However, when we graded the individual outcomes, some of them have been downgraded from high to moderate quality due to imprecision (insignificant results or results falling below our defined minimal important difference). This is not a comment on the overall quality of the study, but simply a comment on the fact that it does not provide definitive answers as to the potential benefits on all outcome measures considered.
UCB Pharma Limited	Full	91	2223	There is a contradiction stated on the evidence of the benefits of the transdermal patch to deliver dopamine through the night. The high quality evidence available (Trenkwalder C et al. Mov Dis 2011) demonstrates the significant benefit for the management of nocturnal akinesia as well as the impact for patient QoL and this can be attributed in no small part, to the unique transdermal delivery system of rotigotine. For patients who are experiencing significant sleep disturbance the recommendation to try long	Thank you for your comment. The GDG did not feel it appropriate to recommend rotigotine as first line treatment due to it being a more expensive drug, and because we found no evidence to suggest that rotigotine is better than levodopa, the GDG found it difficult to justify why rotigotine should be recommended over levodopa. However, there is nothing in the recommendations to prevent clinicians using their judgement in individual

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				acting oral DAs late at night without the evidence to demonstrate the value appears not to be evidence based, but rather cost driven, and could potentially lead to patients having insufficient cover during the day. This issue could have particularly detrimental effects with younger patients coping with Parkinson's. For patients who are experiencing significant nocturnal akinesia symptoms rotigotine should be considered as a first line treatment option based on the evidence available as referenced above and thus should be reflected into the guidance. <u>Reference:</u> - Claudia Trenkwalder, MD, Bryan Kies, FCNeurol (SA), Monika Rudzinska, MD, Jennifer Fine, FCP (SA) Neurology, Janos Nikl, MD, Krystyna Honczarenko, MD, Peter Dioszeghy, MD, Dennis Hill, MD, Tim Anderson, FRACP, Vilho Myllyla, MD, Jan Kassubek, MD, Malcolm Steiger, FRCP, Marco Zucconi, MD, Eduardo Tolosa, MD, Werner Poewe, MD, Erwin Surmann, MSc, John Whitesides, PhD, Babak Boroojerdi, MD, and Kallol Ray Chaudhuri, DSc. Rotigotine Effects on Early Morning Motor Function and Sleep in Parkinson's Disease: A Double-Blind, Randomized, placebo-controlled Study (RECOVER) Mov Disord. 2011 Jan; 26(1): 90–99.	cases where they believe rotigotine to be the appropriate first-line option. On the specific point of when oral dopamine agonists should be taken, the GDG agreed there was insufficient evidence to support this recommendation and it has thus been removed from the updated version of the guideline.
UCB Pharma Limited	Short	11	10	It is important to note that Gastro-intestinal (GI) aspects need to be recognised as part of the non-motor symptoms manifestations of Parkinson's, given the prevalence of the GI manifestations associated with Parkinson's disease (Barone et al. Mov Dis, 2009), as well as the subsequent potential	Thank you for your comment. Unfortunately, the management of gastro-intestinal problems was not part of the scope for this guideline update. In addition, outcomes of gastro-intestinal problems were not prioritised in the

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				impacts from GI disturbance (e.g. dysphagia, gastroparesis) on drug absorption (Kalf et al.Parkinsonism Relat Disord, 2012; Goetze et al. Neurogastroenterol Motil, 2006) and on patient quality of life (Barone et al. Mov Dis, 2009). We would thus suggest that guidance for patients experiencing significant GI disturbance should be included in the clinical guideline. References: - Barone P, Antonini A, Colosimo C, Marconi R, Morgante L, Avarello TP, Bottacchi E, Cannas A, Ceravolo G, Ceravolo R, Cicarelli G, Gaglio RM, Giglia RM, Iemolo F, Manfredi M, Meco G, Nicoletti A, Pederzoli M, Petrone A, Pisani A, Pontieri FE, Quatrale R, Ramat S, Scala R, Volpe G, Zappulla S, Bentivoglio AR, Stocchi F, Trianni G, Dotto PD; PRIAMO study group.The PRIAMO study: A multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. Mov Disord. 2009 Aug 15;24(11):1641-9. doi: 10.1002/mds.22643. - J.G. Kalfa, B.J.M. de Swarta, B.R. Bloemb, M. Munneke. Prevalence of oropharyngeal dysphagia in Parkinson's disease: A meta-analysis. Parkinsonism Relat Disord. 2012 May;18(4):311-5. doi: 10.1016/j.parkreldis.2011.11.006. Epub 2011 Dec 3.	outcomes of interest by the GDG when developing protocols for pharmacotherapeutic review questions. It is therefore not possible to make recommendations on this topic.

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				- O. Goetze, A. B. Nikodem, J. Wiezcorek, M. Banasch, H. Przuntek, T. Mueller, W. E. Schmidt, D. Woitalla Predictors of gastric emptying in Parkinson's disease. Neurogastroenterol Motil. 2006 May;18(5):369-75	
UCB Pharma Limited	Short	11	26	The prevalence of the GI manifestations associated with Parkinson's disease has been highlighted in published literature (Barone et al. Mov Dis, 2009) and the subsequent potential impacts from GI disturbance (eg dysphagia, gastroparesis) on drug absorption (Kalf et al. Parkinsonism Relat Disord, 2012; Goetze et al., Neurogastroenterol Motil 2006) and patient quality of life (Barone et al. Mov Dis, 2009) we feel guidance for patients identified to be experiencing significant GI disturbance would be appropriate here. Since GI issues are another non-motor manifestation of Parkinson's we feel this point should be acknowledged in this section also. References: - O. Goetze, A. B. Nikodem, J. Wiezcorek, M. Banasch, H. Przuntek, T. Mueller, W. E. Schmidt, D. Woitalla Predictors of gastric emptying in Parkinson's disease. Neurogastroenterol Motil. 2006 May;18(5):369-75. - Kalf JG, de Swart BJ, Bloem BR, Munneke M. Prevalence of oropharyngeal dysphagia in Parkinson's disease: a meta-analysis. Parkinsonism Relat Disord. 2012 May;18(4):311-5. doi: 10.1016/j.parkreldis.2011.11.006. Epub 2011 Dec 3. - Barone P, Antonini A, Colosimo C, Marconi R, Morgante L, Avarello TP, Bottacchi E, Cannas A, Ceravolo G, Ceravolo R, Cicarelli G, Gaglio RM,	Thank you for your comment. Unfortunately, the management of gastro-intestinal problems was not part of the scope for this guideline update. In addition, outcomes of gastro-intestinal problems were prioritised in the outcomes of interest by the GDG when developing protocols for pharmacotherapeutic review questions. It is therefore not possible to make recommendations on this topic.

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				Giglia RM, Iemolo F, Manfredi M, Meco G, Nicoletti A, Pederzoli M, Petrone A, Pisani A, Pontieri FE, Quatrale R, Ramat S, Scala R, Volpe G, Zappulla S, Bentivoglio AR, Stocchi F, Trianni G, Dotto PD; PRIAMO study group. The PRIAMO study: A multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. Mov Disord. 2009 Aug 15;24(11):1641-9. doi: 10.1002/mds.22643.	
UCB Pharma Limited	Short	11	3	We would like to note that before considering switching to other drug classes, transdermal rotigotine should be considered as an option for patients experiencing ICDs while being treated with oral DAs. Evidence from an EU multicentre survey of ICDs in patients treated with short and long-acting DAs (Rizos et al.. 2016) indicated that transdermal rotigotine had a lower incidence of ICDs compared to pramipexole and ropinirole. Furthermore, data from a post-hoc analysis of six long-term extension studies of rotigotine in PD patients (Antonini et al. 2016) concluded that the incidence of ICDs AEs in clinical trials with rotigotine was 9.0%, which was lower than the incidence of ICDs reported to occur with other DAs in the DOMINION study (17.1% , Weintraub et al. 2010) <u>References:</u> - Rizos A, Sauerbier A, Antonini A, Weintraub D, Martinez-Martin P, Kessel B, Henriksen T, Falup-Pecurariu C, Silverdale M, Durner G, Røkenes Karlsen K, Grilo M, Odin P, Chaudhuri KR; A European multicentre survey of impulse control behaviours in Parkinson's disease patients treated with short- and long-acting	Thank you for your comment. The GDG agree that it is plausible that there may be differences in ICD rates between different DA formulations (including from the Rizos paper), but they did not feel that the current available studies provide sufficiently robust evidence in order for them to make a specific recommendations on this point.

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				dopamine agonists. EUROPAR and the IPMDS Non-Motor-PD-Study Group. Eur J Neurol. 2016 Aug;23(8):1255-61) - Antonini A, Chaudhuri KR, Boroojerdi B, Asgharnejad M, Bauer L, Grieger, F, Weintraub D.Impulse control disorder related behaviours during long-term rotigotine treatment: a post hoc analysis. Eur J Neurol 2016; 0:1-10 - Weintraub D1, Koester J, Potenza MN, Siderowf AD, Stacy M, Voon V, Whetteckey, J, Wunderlich GR, Lang AE. Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. Arch Neurol. 2010 May;67(5):589-95.	
UCB Pharma Limited	Short	9	16	The draft guideline states that there is an increased risk of developing Impulse Control Disorder (ICD) with Dopamine Agonists (DAs), however there is some evidence indicating reduced risks with certain DAs. We would suggest this to be acknowledged in both the full and the short guideline. <u>Reference:</u> - Rizos A, Sauerbier A, Antonini A, Weintraub D, Martinez-Martin P, Kessel B, Henriksen T, Falup-Pecurariu C, Silverdale M, Durner G, Røkenes Karlsen K, Grilo M, Odin P, Chaudhuri KR; A European multicentre survey of impulse control behaviours in Parkinson's disease patients treated with short- and long-acting	Thank you for your comment. The GDG agree that it is plausible that there may be differences in ICD rates between different DA formulations (including from the Rizos paper), but they did not feel that the current available studies provide sufficiently robust evidence in order for them to make a specific recommendations on this point.

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				dopamine agonists. EUROPAR and the IPMDS Non-Motor-PD-Study Group. Eur J Neurol. 2016 Aug;23(8):1255-61)	
UCB Pharma Limited	Short	General		Adherence to medication is an important consideration in the disease management. Evidence has indicated that if people with Parkinson's don't get their medication on time, their ability to manage their symptoms may be lost. For example they may suddenly not be able to move, get out of bed or walk down a corridor. Adherence to medication needs to be considered as a broader issue for patients with Parkinson's and should be clearly emphasized in the guideline. Reference: https://www.parkinsons.org.uk/content/get-it-time	Thank you for your comment. Unfortunately, adherence to medicines was not a topic that was included within the scope of this guideline update, and therefore no recommendations could be made on this topic.
UK Clinical Pharmacy Association	Full		general	Duodopa recommendation – doesn't seem to have taken in all of the quality of life data that was taken into consideration in the NHSE policy and in the recent SMC guideline It is not clear if the cost-effectiveness analysis takes into consideration the pricing used in the NHSE and SMC assessments or the real life experience studies of QoL that have been published? There is no doubt that strict criteria and careful patient selection is necessary in the successful use of Duodopa, however, there is clear evidence of a significant increase in QoL and reduction in care burden in the correctly assessed complex patients.	Thank you for your comment. For comments on apparent discrepancies between NICE's appraisal of the evidence on LCIG and the view taken by NHS England's specialised commissioning policy, please see **theme 9b**. For comments on apparent discrepancies between NICE's conclusions on LCIG and SMC advice, please see **theme 9c**. For comments on the effectiveness and cost effectiveness of LCIG in subgroups of people with advanced Parkinson's disease, please see **theme 1b**.

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				It is also not clear why it was assessed alongside apomorphine. The UK experience and current commissioning guidelines (which we would support) are such that Duodopa would not generally be used where apomorphine was an option and had not been tried. We would therefore question the validity in a like for like cost effectiveness comparison as they are used at different stages of the pathway. https://www.scottishmedicines.org.uk/SMC_Advice/Advice/316_06_co_careldopa_Duodopa/co_careldopa_levodopa_Duodopa_2nd_Resubmission.	For comments on the inclusion of apomorphine in simulated BMT, please see **theme 3b**.
UK Clinical Pharmacy Association	Full	118	l2753	A few off-label/unlicensed symptom management recommendations (midodrine, fluodrocortisone , glycopyrrolate) – are these going to be supported in the long term by GP prescribing e.g. glycopyrrolate	Thank you for your comments. Unfortunately, this is a topic that falls outside of the remit of the GDG, and therefore we are not able to comment on the way these medicines are going to be prescribed in the future.
UK Clinical Pharmacy Association	Full	173	4143	– Is there something special about vitamin D in PD – or should this just be a reference to the general guidance	Thank you for your comment. The GDG agreed it was unclear whether there were specific extra benefits of vitamin D supplementation in people with PD compared to the general population, but noted that because people with Parkinson's disease are at an increased risk of falls, advising them to take vitamin D supplements is more beneficial than not recommending.
UK Clinical Pharmacy Association	Full	173	4146	– Is the only mention of a pharmacist in the guideline, despite the introductory section highlighting the issue stating: 84% wanted information on drugs available and their side effects 45/100 patients had no access/didn't use a pharmacist Full Increased pharmacy involvement could provide this information and bridge this care gap	Thank you for your comment. Unfortunately the pharmacists' role in PD has not been included in scope of this guideline update. This has resulted in limited recommendations being made around this topic.

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UK Clinical Pharmacy Association	Full	212	2353	–we are interested in the evidence for PPIs causing orthostatic hypotension	Thank you for your comment. After further discussion, the GDG has agreed to remove the reference to PPIs from this recommendation
UK Clinical Pharmacy Association	Full	212	5222	- It talks about an LEDD – is NICE now advocating a particular way of calculating this and if so would it be possible for this evidence based calculation to be included.	Thank you for your comment and in response no, NICE has not expressed any preference as to how this should be calculated. Results in this section are presented according to the way they were calculated as part of the included study.
UK Clinical Pharmacy Association	Full	55	1249	– Talks about levodopa effectiveness decreasing with time. Should this not be more clearly something about narrowing of therapeutic window with long term use causing increasing motor complications which limit its titration and use?	Thank you for your comment. This has now been redrafted to include a reference to increasing long-term complications
UK Clinical Pharmacy Association	short	11	1.5.2	We think Patients starting modafinil should initially be reviewed after 3 months and 6 months and then at least every 12 months. [note modafinil can exacerbate dyskinesias and other movement discorders	Thank you for your comment. However, as we did not identify any evidence to support when and how frequent patients should be reviewed when receiving modafinil, the GDG feel that recommending "at least every 12 months" is sufficient, with this not of cause precluding more frequent monitoring if this was felt appropriate for an individual.
UK Clinical Pharmacy Association	short	6	1.2.13	might be out-of date, but confirm apomorphine should not be used as a challenge test in the diagnosis of PD	Thank you for your comment.
United Lincolnshire Hospitals NHS Trust	Full	67	1650	Dose of levodopa should be adjusted according to the body weight identifying the phenotype of Olfaction-weight-Dyskinesia. Lower body weight or weight loss increases the risk of dyskinesia. LD should not be withheld but the4 dose should depend on body weight. Ref:	Thank you for these references. In the agreed protocol for this particular topic, only systematic review and/or RCT evidence was of interest. Unfortunately, Sharma 2014 study is a non-systematic review and Sharma 2012 is a non-RCT study. These two studies do therefore not meet

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
				1 Prognostic significance of weight changes in Parkinson's disease: the Park-weight phenotype. Sharma JC, Vassallo M. Neurodegener Dis Manag. 2014;4(4):309-16. doi: 10.2217/nmt.14.25. 2 Olfaction, dyskinesia and profile of weight change in Parkinson's disease: identifying neurodegenerative phenotypes. Sharma JC, Turton J. Parkinsonism Relat Disord. 2012 Sep;18(8):964-70. doi: 10.1016/j.parkreldis.2012.05.004.	the predefined inclusion criteria within our protocol for this topic. In addition, the GDG did not feel it appropriate to make recommendations about specific levodopa doses, but felt these decisions were best left to individual clinicians.
United Lincolnshire Hospitals NHS Trust	Full	79	2010	In patients with dyskinesia adjust the dose of levodopa according to the patients' body weight; lower weight requires a lower dose of levodopa Ref: Sharma JC – 2006, 2008, and as avove Olanow W – STRIFDE PD	Thank you for your comment. The GDG agreed that this suggestion would represent good practice, but as this was not a question that was specifically addressed as part of the guideline, no recommendations could be made on this topic.
United Lincolnshire Hospitals NHS Trust	Full version Draft	54	1223	My concern is the embargo on the use of olfaction testing in the diagnosis of Parkinson's disease. The evidence is that in NON-demented patients, the absence of loss of olfaction at five years after the initial diagnosis of a PD syndrome, the diagnosis of idipoathic PD is highly unlikely. There may be an alternative explanation for the PD syndrome such as drugs induced tremor, essential tremor.	Thank you for your comment. Unfortunately, this statement is taken from a part of the guideline which was not included as part of this update, and therefore no substantive changes can be made.

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				Movement disorders society has now amended the diagnostic criteria and have included Olfaction loss as a supportive feature for the diagnosis of Parkinson's disease. Olfactory loss (in the anosmic or clearly hyposmic range, adjusted for age and sex) Reference 1 : Mov Disorders October 2015MDS clinical diagnostic criteria for Parkinson's disease Ronald B. Postuma MD, MSc, et al. Reference 2: Olfactory loss as a supporting feature in the diagnosisof Parkinson's disease: a pragmatic approach Katie Hoyles • Jagdish C. Sharma J Neurol (2013) 260:2951–2958	
University College London Hospital NHS	Full	20 & General	285 & General	A patient is quoted as requesting that we are reminded "to be more aware that each patient is an individual." There are ranges of responses to many Parkinson's therapies that in some instances are predictable; while on other occasions are idiosyncratic. This variability is not captured in the mean effect size seen in randomised trials.	Thank you for your comment. It is important to note that NICE clinical guidelines are guidance for providers on the general population with a specific condition. A 'do not offer' recommendation does not mean that the treatment is ineffective for everyone but for most. In section 1.3 of the guideline, guidance on how to interpret NICE's

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Foundation Trust				The development of personalised/ precision medicine, requires increasing awareness "that each patient is an individual". This philosophy is not adequately reflected in the subsequent recommendations. The recommendations should therefore consider PD heterogeneity of treatment response, especially when there is a risk that considering group or 'average' responses will lead to recommendation for removal of an already available therapeutic option, which may be hugely effective, and/or the only available option to a subgroup of individuals.	recommendations is provided. NICE's recommendations should be taken into consideration together with the clinician's own personal experience and knowledge in the field as well as the individual patient's health and care needs. It should be noted, however, that we do not agree that simply because the responses to a treatment may be heterogeneous, that this means that randomised trials do not provide valuable information. If there are identifiable subgroups of people where treatment response would be higher, then it should be possible to conduct trials specifically in these subgroups, and such trials would have been included within the scope of this guideline.
University College London Hospital NHS Foundation Trust	Full	204	4949	Recommendation 79- Do not offer levodopa–carbidopa intestinal gel…. This recommendation should be modified to allow appropriate use of LCIG under specific circumstances. LCIG is an essential option for a small number of individuals who are not appropriate DBS candidates. Whilst LCIG as a therapy can be complex and has a significant complication rate, in successful cases it can transform people's lives. As the largest Deep Brain stimulation implanting service in the UK, we see a small but significant proportion of patients who are not appropriate for DBS because of clinical contraindications, and yet have exhausted conventional best medical treatment including Apomorphine.	Thank you for your comment. For comments on the effectiveness and cost effectiveness of LCIG, please see **theme 1**. For comments on the effectiveness and cost effectiveness of LCIG in subgroups of people with advanced Parkinson's disease, please see **theme 1b**. For comments on the paucity of therapeutic options for people with advanced Parkinson's disease, please see **theme 1e**.

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				The recommendation must be rephrased to allow access to LCIG in these or similar specific circumstances. In the absence of LCIG, the concern would be that; A small subgroup of patients will experience avoidable/unnecessary suffering as a result of poor symptom control, Clinical teams may be persuaded to offer DBS to patients where the risks of complications/side effects are higher, therefore risking an increase in adverse events.	
University College London Hospital NHS Foundation Trust	Full	80	2019	Recommendation 30 – Do not offer anticholinergics…. This recommendation should be completely removed. Many people particularly with young onset PD use trihexyphenidyl for painful off-period dystonia or tremor with good effect, with good tolerability over long term periods. If necessary, a warning regarding the common side effects of anticholinergics especially in more elderly patients could instead be included. Anticholinergics for symptomatic management of Parkinson's disease. Katzenschlager R et al. Cochrane Database Syst Rev. 2003	Thank you for your comments. The GDG acknowledged that there may be specific circumstances where anticholinergics are a useful option, but this does not apply to the average person with PD (the target of guideline recommendations). In addition, because no evidence was identified for anticholinergics, together with the known adverse effects, the GDG agreed that a "do not" recommendation was justified. The GDG also noted that the particular cases identified where anticholinergics may be useful (e.g. very young people with dystonia) were highly likely to be already under the care of experienced clinicians, who would be aware of this as a treatment option.

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University College London Hospital NHS Foundation Trust	Full	80	2021	Recommendation 31- Do not offer Amantadine….. This recommendation should be completely removed. Amantadine has great benefits for patients with dyskinesia, particularly those in whom there is a narrow therapeutic window between "OFF" and "ON with Dyskinesia". The removal of Amantadine as an option would restrict our ability to treat this group of individuals, and necessitate the use of Advanced therapies at an earlier stage. Amantadine for levodopa-induced dyskinesias: a 1-year follow-up study. Metman LV1, Del Dotto P, LePoole K, Konitsiotis S, Fang J, Chase TN. Arch Neurol. 1999 Nov;56(11):1383-6. The effect of amantadine on levodopa-induced dyskinesias in Parkinson's disease: a double-blind, placebo-controlled study. Snow BJ1, Macdonald L, Mcauley D, Wallis W. Clin Neuropharmacol. 2000 Mar-Apr;23(2):82-5.	Thank you for your comment. After discussion of the consultation responses the GDG agreed that, whilst there was no evidence for the routine use of amantadine as an adjuvant treatment, it did have a role as a specific option for the treatment of dyskinesia. Therefore, a new recommendation has been added to this section to support the use of amantadine in this context.
University College London Hospital NHS Foundation Trust	Full	97	2357	Recommendation 40. If Midodrine is contraindicated… This recommendation should be amended/ reconsidered based on additional information. In a trial conducted in the 1980s, it was concluded that postural hypotension due to levodopa and agonists was centrally mediated so one would not expect Domperidone to influence it. J Neurol Neurosurg Psychiatry. 1981 May;44(5):426-9. Bromocriptine in Parkinson's disease: a study of cardiovascular effects.	Thank you for your comment. After further consideration, the GDG has decided to remove domperidone as an option from this recommendation.

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				Quinn N, Illas A, Lhermitte F, Agid Y. Abstract Blood pressure and pulse rate were studied in 20 Parkinsonian patients on no treatment, and during treatment with bromocriptine (mean dosage 148 mg/day) as the sole anti-Parkinsonian therapy. The drug was shown to reduce erect systolic and diastolic and supine systolic blood pressure and to increase erect pulse rate, in a predictable dose-dependent manner. The occurrence of episodes of significant postural hypotension was less predictable and was a transitory phenomenon in all patients. Peripheral dopamine receptor blockade with domperidone did not alter the findings, suggesting that the principal mechanism for these cardiovascular effects is a central dopaminergic one.	
University College London Hospital NHS Foundation Trust	Full	General	General	Two additional agents for the symptomatic treatment of Parkinson's disease have recently been launched in the UK- Opicapone & Safinamide, the first new agents in a large number of years. It would be helpful if NICE had the opportunity to make a recommendation on the use of these agents rather than deferring until the next round of guidance.	Thank you for your comment. The guideline did not look for evidence on safinamide or opicapone, as they were not licensed at the time the scoping was undertaken. Whilst we did not specifically look for evidence, the fact that safinamide is classed as an MAO-B and opicapone a COMT inhibitor means they are covered as part of our recommendations for adjuvant treatment, and could be considered as options under those class level recommendations (within the licensed indication). In addition, NICE has recently published evidence summaries on safinamide (February 2017) and opicapone (March 2017), though these will not be formally included as part of the guideline.
University Hospitals Coventry &	Full	106	2548	The recommendation for clozapine is welcomed but access to registered services is very restricted.	Thank you for your comment. The GDG agreed that there are difficulties accessing this service in many areas, and

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Warwickshire NHS Trust					hope that the recommendations will lead to the service becoming more available.
University Hospitals Coventry & Warwickshire NHS Trust	Full	111	2634	The recommendation to consider melatonin for treatment of RBD is welcomed especially in the light of concerns over long term clonazepam use.	Thank you for taking the time to comment on the guideline
University Hospitals Coventry & Warwickshire NHS Trust	Full	118	2760	We feel that the risk of anticholinergic medication causing neuropsychiatric effects in Parkinson's is never 'minimal' and feel that most centres and specialists would not advocate their use at all.	Thank you for your comment which was discussed by the GDG. In the GDG's experience there are many centres where topical atropine drops may be used for managing sialorrhoea, and they agreed that where these were used it was because it was felt the risks of cognitive harm was much lower than with other anticholinergic alternatives. It was in order to leave open the possibility of these options that this recommendation was made.
University Hospitals Coventry & Warwickshire NHS Trust	Full	138	3249	We welcome the recommendation of using cholinesterase inhibitors in people with Parkinson's with mild – moderate PD dementia.	Thank you for your comment.
University Hospitals Coventry & Warwickshire NHS Trust	Full	144	3443	'Usual care' is not defined for any of the therapies (physio, OT, SLT) in the full guideline. We note it is partially defined in appendix C but it is still not clear exactly what 'usual care' is.	Thank you for your comment. The GDG did not feel it appropriate to define usual care too specifically, as it was noted that this may vary considerably both between areas and over time. Broadly, trials were considered eligible if the control arm did not also include an active intervention, and this has been clarified in the full guideline.

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University Hospitals Coventry & Warwickshire NHS Trust	Full	187	4522	We note that no expert witnesses or clinicians experienced in the use of LCIG were called to provide assistance.	Thank you for your comment. For comments on the role of expert witnesses, please see **theme 2**.
University Hospitals Coventry & Warwickshire NHS Trust	Full	204	4949	We feel very strongly that this recommendation removes an important treatment modality from the small group of people who are suitable for and who would benefit from LCIG treatment at odds with the NHS England policy released in 2015. This group of patients have no other options to consider as they will have already tried 'Best Medical Therapy' and DBS will have been considered or performed. The small number of patients we have started on this treatment have had life changing results and it would be unethical in our view to completely remove this option for other patients in similar circumstances. We appreciate the cost of the treatment but feel that the number of patients likely to benefit would be small.	Thank you for your comment. For comments on the effectiveness and cost effectiveness of LCIG, please see **theme 1**. For comments on the small population for whom LCIG is currently used, please see **theme 1d**.
University Hospitals Coventry & Warwickshire NHS Trust	Full	28	515	The new section on information needs is welcomed.	Thank you for your comment.
University Hospitals Coventry & Warwickshire NHS Trust	Full	83	2106	We contest the statement that the Epworth Sleepiness scale is routinely used in clinical practice and it is highly subjective.	Thank you for your comment. The GDG has agreed to change it to "the Epworth sleep scale is commonly understood in clinical practice".
University Hospitals Coventry &	Full	91	2216	We are surprised at the recommendation that controlled release levodopa be used for nocturnal hypokinesia in the absence of any evidence and would contest this recommendation	Thank you for your comment. After further discussion, the GDG agreed that these recommendations had been too strongly worded based on the underlying evidence.

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Warwickshire NHS Trust					Accordingly, the words modified release have been removed from the recommendations, and the final recommendation about when dopamine agonists should be taken has been entirely removed. This leads to a simpler set of recommendations which the GDG believes are supported both by the evidence and clinical judgement.
University Hospitals Coventry & Warwickshire NHS Trust	Full	99	2378	We note with disappointment that the specific issues in treatment of depression in Parkinson's are not addressed in this guideline. We highlight the fact that depression rates in Parkinson's are higher than in other long term conditions such as rheumatoid arthritis and diabetes and there is a body of evidence showing abnormal neurotransmitter levels in people with Parkinsons with depression. We feel that the treatment of depression specific to those with Parkinsons merits attention from the GDG. We note also that management of anxiety (a major clinical problem with a massive impact on quality of life) is not addressed at all.	Thank you for your comment. At the scoping stage of this guideline, it was decided that questions around depression would be handled by a cross-referral to the NICE guideline on depression; therefore no evidence search was conducted; and therefore it was not possible to make depression specific recommendations. The NICE guideline on depression does contain recommendations on managing comorbid anxiety and depression, and NICE has also produced a number of pieces of guidance looking at specific types of anxiety (https://www.nice.org.uk/guidance/conditions-and-diseases/mental-health-and-behavioural-conditions/anxiety)
University Hospitals Coventry & Warwickshire NHS Trust	Short	11	8	Whilst the inclusion of CBT into the guideline for management of impulsive behaviours is welcomed, it is almost impossible to access this therapy.	Thank you for your comment. The GDG agreed that there are difficulties accessing this service in many areas, and hope that the recommendations will lead to the service becoming more available.

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University Hospitals Coventry & Warwickshire NHS Trust	Short	8	3	We welcome the guidance highlighting the importance of ensuring people with Parkinsons are aware of the risk of impulse control disorders and excessive sleepiness if taking a dopamine agonist.	Thank you for your comment.
University Hospitals Coventry & Warwickshire NHS Trust	Short	9	6	Whilst we have experienced tolerance issues using amantadine and appreciate that the evidence base for its use in dyskinesia is limited, we are concerned that advising against its use leaves no alternative strategy for managing patients with dyskinesia who are unable to reduce their dopaminergic medications. We suggest the guidance is less prohibitive.	Thank you for your comment. After discussion, the GDG agreed that amantadine may be a useful treatment option for managing dyskinesia in people with Parkinson's disease, where this cannot be adequately managed by modification of existing therapy. The recommendation has therefore been changed from a "do not" to a "consider" recommendation to reflect this.
Worcestershire Health and Care Trust				In clinical terms, it seems entirely inappropriate to exclude Duodopa as a delivery method for a small number of patients, and for it to be offered in a Regional Speciality Centre As with many apparently esoteric treatments, those using the treatment, and patient experiencing a benefits, are entirely convinced of efficacy. Because numbers are small, data to statistically confirm value is scanty. The understanding of PD as an entirety which has subtle or significant nuances which may necessitate a novel of different delivery method, has to be appreciated in the context of specialty neurology.	Thank you for your comment. For comments on the effectiveness and cost effectiveness of LCIG, please see **theme 1**.

**None of the stakeholders who comments on this clinical guideline have declared any links to the tobacco industry.*

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Themes arising from consultation comments on interventions for advanced Parkinson's disease

Several common themes emerge from stakeholders' comments on deep brain stimulation (DBS) and levodopa–carbidopa intestinal gel (LCIG) for advanced Parkinson's disease. We have provided detailed responses to these below.

In some instances, new analyses based on the original economic model developed for this guideline are described. In all such cases, the model was configured to use the same settings adopted for our primary one-way sensitivity analyses (that is, PINE LOCF models for time to full-time care and time to death; PINE extrapolation trajectories; PINE multiply imputed model for EQ-5D; see Appendix F.4.1.5).

Theme 1 – LCIG as an effective treatment for people with advance Parkinson's disease

On reviewing available evidence, the GDG agreed that LCIG is likely to provide substantial symptomatic relief for many people with advanced Parkinson's disease. However, in line with its duty to consider the balance of benefits and costs associated with possible courses of action, the GDG was required to reach conclusions on whether LCIG represents an effective use of NHS resources for people with advanced Parkinson's disease. All plausible evidence available to the GDG demonstrated that the costs associated with LCIG are substantially too high to justify its expected benefits.

Therefore, while the GDG recognised that it is to the benefit of people with advanced Parkinson's disease that LCIG is currently made available to them via NHS England's specialised commissioning policy, the GDG concluded that, at LCIG's list price, its provision comes at a cost that would be considered unacceptably high, according to NICE's principles (that is, it would result in harm being caused elsewhere in the NHS, because the necessary funds have to be provided at the expense of other activity that provides substantially more benefit, relative to its cost).

Theme 1b – subgroups of people for whom LCIG may provide a cost effective option

The GDG gave detailed consideration to whether there may be identifiable subgroups of people with advanced Parkinson's disease for whom treatment with LCIG would provide benefits commensurate with the costs of treatment. It concluded that there was no evidence that such groups exist. Moreover, it agreed that there was no plausible level of benefit that would be sufficient to outweigh the very high costs of the intervention – even if people could be identified who would be expected to achieve gains at the upper 99.9% confidence limit of the observed effect in every single domain of treatment, treating such people would cost £103,395 per QALY gained compared with BMT.

Theme 1c – self-limiting resource use with LCIG

It is suggested that resources devoted to LCIG are limited, because people 'that have PEG-J tubes have frequent problems with the tubes, and those that are not receiving major beneficial effects from the therapy tend to abandon it.' If this is accepted then, in practice, it

might be assumed that the people who remain on LCIG for any length of time are achieving a more cost-effective result than simulated in a RCT-based population. However, it is not possible to posit any level of benefit at which LCIG, at its list price, represents a use of NHS resources that could be considered reasonable, according to NICE criteria. Moreover, any kind of responder analysis – whether self-perpetuating as indicated here or imposed externally – could only be less cost effective than the care of the responders alone, as it would also have to account for the costs of the proportion of people who commence and discontinue therapy having achieved little benefit.

Theme 1d – small population for whom LCIG is currently used

That comparatively few people currently receive LCIG (and no great expansion is anticipated) is suggested by some stakeholders to be a justification for preserving access to the option. This does not withstand careful consideration: if small absolute cost burdens could be used to overlook poor relative value for money, then substantial inequity would be introduced between people in a comparatively limited indication and those with common conditions.

It is further suggested that LCIG should be considered as an 'orphan' intervention. The GDG did not necessarily agree with this, as any narrow indication for its use is at least partially economically and not clinically motivated. However, whether or not LCIG qualifies under this heading, NICE's Social Value Judgements state that 'NICE considers that it should evaluate drugs to treat rare conditions, known as ‘orphan drugs’, in the same way as any other treatment.'

Theme 1e – paucity of alternative therapeutic options for people with advanced Parkinson's disease

The GDG was mindful of the significant symptomatic burden experienced by people with advanced Parkinson's disease, and recognised that few treatments are available to diminish the challenges they face. For this reason, the GDG would have been very glad to recommend the use of LCIG. However, a relative paucity of alternative options cannot, in itself, be a reason to overlook the opportunity costs a course of action imposes on the NHS and, in this case, the GDG found it clear that these were unacceptable. It should also be remembered that the benefits, harms and costs of LCIG were assessed in comparison with best medical therapy, so estimates of the incremental benefits and costs – from the original health economic model and other sources of evidence – already reflected the relatively poor prognosis of people receiving BMT.

Nevertheless, the GDG noted the nontrivial improvements made in some domains by participants randomised to oral therapy in the RCT of LCIG -v- BMT, and took this as evidence that redoubled effort to optimise oral therapy can often provide worthwhile gains.

Theme 2 – expert witnesses for DBS but not for LCIG

The GDG did not seek testimony from experts in DBS; GDG members have this expertise themselves (and also have experience of LCIG in clinical practice). Rather, the GDG sought

testimony from experts who could enrich its knowledge of the PDSURG RCT, which was a critical component of the available evidence. This request was made following the full and helpful response PDSURG investigators made to our Call for Evidence. Unfortunately, the response received from AbbVie to our call for evidence did not provide any information on randomised evidence of LCIG, and we received no response from the investigators of the key trial of LCIG (Olanow et al., 2014, whom we specifically contacted to make aware of this).

Theme 3 – 3-way comparison of DBS, LCIG and BMT

At the outset of guideline development, the GDG held extensive discussions about the appropriate decision problem(s) for the advanced PD population. Group members reported that current practice in the NHS tends to reserve LCIG for people who are unsuitable for DBS. However, the group agreed that there is no clinical rationale for this practice: it is not believed that LCIG is fundamentally more suited to people with contraindications to DBS. Rather, the preference for DBS over LCIG is a practice that has evolved because DBS is generally believed to be both more effective and less costly than LCIG; therefore, the prevailing belief is that LCIG should be reserved for instances where DBS is not an option.

Therefore, the GDG agreed that it would be useful to test these assumptions in an analysis that used best available evidence to compare the benefits, harms and costs of DBS, LCIG and BMT. It is possible that this approach would have identified that current practice is unjustified, and led to recommendations that could optimise the pathway. The analysis demonstrated that the current preference for DBS over LCIG is rational: DBS is both more effective and less costly than LCIG, so it is clearly good practice to choose DBS for anyone who is clinically suitable for either.

The validity of this approach was further justified by the relatively close comparability of the baseline populations in the key RCTs used to inform treatment effects in the HE model (PDSURG HY≥3 and Olanow et al., 2014). Participants in the LCIG trial were somewhat older (mean 64) than those in PDSURG (mean 59) and had greater off-time (6.6 compared with 5.0 hrs/day); however, they were also less severely impaired in activities of daily living (UPDRS-II: 11.7 -v- 14.1), motor function (UPDRS-III: 20.2 -v- 27.2) and PD-related quality of life (PDQ-39: 36.8 -v- 41.5), and had shorter disease duration (10.9 -v- 12.1 yrs). The GDG acknowledged that estimation of off-time in PDSURG is approximate; however, it was agreed that any inaccuracy inherent in the approach is likely to underestimate the true mean. Consequently, it is plausible that differences in off-time, between PDSURG HY≥3 and Olanow et al. participants, were smaller than we can quantify with the data available.

When all the evidence was considered together, the GDG agreed that any discrepancies did not reflect fundamentally different populations, and felt that, on balance, the 2 groups in the key RCTs were well matched. As a result, the group was confident that the 3-way analysis between DBS, LCIG and BMT provided a robust basis for comparing the benefits, harms and costs of the 3 approaches in a homogeneous population.

However, the GDG recognised, from the outset, that there are populations of people for whom either DBS or LCIG would be deemed clinically unsuitable, but who may be good

candidates for the other option. To reflect this, separate review questions were specified that sought to identify and assess evidence for DBS for people who could not have LCIG and vice versa. No evidence was found that would enable the calculation of different effects for people with characteristics that make them ineligible for the other treatment. Therefore, GDG discussion was informed by evidence assembled for the 3-way comparison, but with the contraindicated option excluded from consideration. In the case of LCIG, this meant excluding DBS from the decision-space and assessing how LCIG compared with BMT (indeed, it is only in a decision-space excluding DBS that this is a valid thing to do).

This was believed likely to be a slightly anticonservative approach, which would bias results somewhat in favour of the active interventions, because the GDG agreed that, in real-world practice, people who are considered ineligible for one of the interventions would have more severe impairment than observed on average in trial participants, and felt it was unlikely that a greater relative effect would be seen in such people than in the RCTs.

AbbVie suggests that a more realistic profile of the population expected to receive LCIG in practice can be found in an AbbVie-funded multicentre case-series of people receiving LCIG (Fernandez et al., 2015). When the baseline characteristics of this population are compared with PDSURG HY≥3 participants, higher age and off-time are observed (64 -v- 59 and 6.75 -v- 5.0 hrs/day, respectively), as with Olanow et al. (2014). However, most other variables match relatively well (UPDRS-II 17.4 -v- 14.1; UPDRS-III 28.8 -v- 27.2; PDQ-39 42.8 -v- 41.5; duration of disease 12.6 -v- 12.1 yrs), and LCIG candidates reported conspicuously better health-related quality of life than PDSURG HY≥3 participants (0.59 -v- 0.41). Again, the GDG is not persuaded that differences of this type indicate essentially heterogeneous populations.

Using the baseline parameters from Fernandez et al. (2015) increases the ICER for LCIG -v- BMT by 30% to £537,940 / QALY (mostly because of the large difference in EQ-5D; if that parameter alone is held at the base-case value, the ICER still rises, but only by 3%, to £424,812 / QALY). This reinforces our belief that, if assuming a homogeneous patient population has any impact on the apparent cost effectiveness of LCIG, that effect is to bias the analysis in favour of LCIG.

Theme 3b – inclusion of apomorphine in BMT

Several stakeholders suggest that the analysis of LCIG compared with BMT is flawed because modelled BMT – being predominantly based on evidence from the control arm of PDSURG – may include apomorphine, whereas, in practice, LCIG tends to be reserved for cases where apomorphine is inappropriate or has proven ineffective. The GDG took the view that current practice is influenced by an informal view of the likely benefits and costs of different approaches and, as a matter of theory, it would be helpful to address this in a more formal way; however, the absence of evidence on the benefits, harms and costs of apomorphine in isolation makes that impossible.

Nevertheless, it should also be understood that including apomorphine in the simulated BMT with which LCIG is compared is, from a cost-effectiveness standpoint, a favourable assumption for LCIG. This is because, while the costs of apomorphine for a proportion of

people are included in estimating BMT costs, apomorphine was explicitly excluded as a cointervention in the RCT from which the effect of LCIG compared with BMT is drawn (Olanow et al., 2014). Therefore, the costs but not the benefits of apomorphine are included in the BMT arm of the model.

If it is believed that apomorphine should be excluded from the BMT with which LCIG should be compared, then the costs of apomorphine should be excluded from our estimate of BMT (doing so makes the ICER for LCIG -v- BMT rise 19% to £490,611 / QALY). Alternatively, if it is believed that LCIG should be compared with BMT that may include apomorphine, then the effectiveness of LCIG -v- BMT would be expected to be attenuated (to a degree that it is not possible to quantify without evidence; however, it could only result in worse cost effectiveness for LCIG compared with BMT).

Theme 4 – use of Olanow et al. (2014) to estimate effectiveness of LCIG -v- BMT

Olanow et al. (2014) is the only randomised trial of LCIG compared with BMT; it was judged to provide high-quality evidence per GRADE criteria.

AbbVie's suggestion that uncontrolled comparison versus baseline is a superior method to estimate treatment effects to a well conducted RCT is unsupportable. Randomised controlled evidence is considered to be the most appropriate design for estimating relative treatment effects and is recognised as such in NICE's reference case. Moreover, we note that AbbVie provides no substantiation of their assertion that observational before–after effect estimates should be preferred to experimental evidence.

Similarly, the suggestion that PDSURG – the RCT providing the most applicable source of evidence on DBS -v- BMT – was 'arguably not controlled' lacks credibility, as does its extension that NICE should rely on case series instead. PDSURG was designed as a 'real life' trial that sought to compare the benefits, harms and costs of surgery (with the necessary follow-up it entails) with medical management (which, in a world without surgery, might be assumed to require less intensive follow-up). Such a design is reflective of the true counterfactual to surgical intervention; this is the opposite of an uncontrolled trial.

The implication of AbbVie's argument is that medical therapy at clinician discretion in PDSURG led to less effective care in the BMT arm of PDSURG than in placebo-treated participants in Olanow et al. (2014), thereby exaggerating the benefit of DBS -v- BMT compared with that of LCIG -v- BMT. However, crucially, PDSURG allowed apomorphine injections and infusions in its control arm (indeed, it explicitly detailed appropriate regimens in its protocol) whereas Olanow et al. (2014) specifically prohibited the use of this agent. Therefore, for a population for which apomorphine is a possible component of BMT, Olanow et al.'s findings overestimate the relative benefit that could be expected with LCIG and, for a population for which apomorphine is contraindicated, PDSURG understates the benefit DBS confers.

In the base case of the NICE original model, it is assumed that apomorphine is available for people receiving BMT (under which circumstance, the difference between LCIG and BMT demonstrated by Olanow et al. probably overestimates true benefit). If the assumption were preferred that LCIG can only be made available to people for whom apomorphine is not a

viable option, the estimate from Olanow et al. would be more accurate, but LCIG would be less cost effective, as it would have no benefit in limiting apomorphine resource use (see theme 3b).

AbbVie's suggestion that Olanow et al.'s BMT arm represents a standard of care that cannot be achieved in practice would be, were it true, a poor reflection on the ability of NHS clinicians to prioritise resources. It is invidious to argue that a system that allegedly lacks the resources to deliver optimised oral therapy should expend massively more resource on LCIG.

AbbVie hypothesises that 'the placebo effect is magnified by the invasiveness of the intervention', though it does not adduce any evidence to substantiate this assertion. The opposite may also be the case: 100% of participants in the placebo arm of Olanow et al. (2014) experienced adverse events, and 20% experience serious adverse events. It is very likely that such complications would have negatively influenced patient-reported outcomes, certainly in the domain of health-related quality of life, and plausibly for other endpoints, as well. Therefore, there is no compelling evidence that the control-arm participants of Olanow et al.'s trial achieved any greater benefit than could be expected with assiduous optimisation of oral pharmacotherapy in real-world practice, and they almost certainly experienced greater harm.

Theme 4b – UPDRS-III results in Olanow et al. (2014)

It is noted that Olanow et al.'s results provide an especially unfavourable estimate of LCIG's ability to ameliorate motor symptoms, as measured by UPDRS-III.

Whether UPDRS-III was designated the primary outcome of the Olanow et al.'s RCT has no bearing on the validity of evidence provided by that trial. While it may have been underpowered to detect a difference meeting some prespecified definition of significance, this makes the magnitude of difference observed less precise, not less accurate, and the precision of the estimate is fully accounted for in our probabilistic model.

The GDG broadly accepted AbbVie's suggestion that, to some unknown degree, LCIG is likely to be beneficial compared with BMT in this domain, and that the results from Olanow et al.'s trial are somewhat surprising, and probably reflective of the simple random error inherent in any sampling process. However, this is not a reason to throw away the results of a well conducted RCT and replace them with poorly evidenced parameters that somehow feel more appropriate. Rather, the approach taken is the correct one: we parameterised our probabilistic model to sample from the full distribution of plausible results from the trial and we also conducted extensive one-way sensitivity analysis on all parameters (including this one). These analyses show that there is no probability that LCIG represents good value for money compared with BMT. Even if the model is configured to assume that the true effect, in this domain, is at the upper 95%CI of the sample effect, the ICER for LCIG -v- BMT is £288,396 / QALY. There is effectively no level of UPDRS-III improvement that would be sufficient to justify the costs associated with LCIG treatment.

For these reasons, the GDG remain of the view that Olanow et al.'s RCT is the highest-quality evidence available with which to estimate the effectiveness of LCIG compared with

BMT. However, even if the GDG were to abandon this principle, and the model was configured to rely instead on the before–after data from Fernandez et al. (2015), the ICER for LCIG -v- BMT would only drop 42% to £238,134 / QALY.

Theme 5 – UPDRS-III as the most influential predictor of time to care and time to death

It is important to emphasise that the centrality of UPDRS-III to prediction of model transitions (time to care and time to death) is an empirical finding based on rigorous analysis of rich datasets (and, in the case of time to death, it is a finding repeated in 2 independent datasets).

Multiple clinical variables that were measured in the relevant RCTs were entered into the time-to-event models, including estimates of activities of daily living (UPDRS-II) and quality of life (PDQ-39; EQ-5D). Motor function, as measured by UPDRS-III, was the most consistent predictor of the outcomes of interest.

To the best of our knowledge, ours is the first analysis to examine clinical variables such as these as time-varying covariates of outcome – thereby enabling us to estimate the influence that changes in these variables has on the hazards of interest. This is a more powerful and informative form of analysis than can be obtained when relying on baseline variables alone (see Collett 2015).

AbbVie suggests that activities of daily living provide a more plausible predictor of time to care than motor dysfunction. Per the argument above, the GDG did not accept this. However, even if, in both of the time-to-event models, the coefficient for UPDRS-III is set to 1 (indicating no effect) and the coefficient for UPDRS-II to an implausible value of 2 (indicating hazard of entry to care and death doubles for every point the measure goes up – so LCIG, which reduces UPDRS-II by 3 points in our base case, is associated with hazards of entry to care and death that are 6 times lower than those faced by people receiving BMT), the ICER for LCIG -v- BMT only drops to £349,014 / QALY.

As noted in appendix F.3.1.1, the GDG recognised that factors other than those measured in trials of anti-Parkinsonian interventions may be more predictive of requirement for full-time care, above all dementia and baseline dependence. However, the GDG was content to assume that the interventions under analysis would not have a direct effect on these factors; therefore, the analysis effectively assumed other factors were equal and sought to quantify the marginal effects of changes in clinical variables on the outcomes of interest.

Theme 6 – structure of original health economic model

As detailed in Appendix F.3.1.1, preliminary GDG discussion on model structure included consideration of many potential approaches, ultimately concluding that the best approach was one that combined simple, patient-relevant outcomes – time to full-time care and death – with a relatively broad range of well researched treatment effects that could be associated with the likelihood of those outcomes and patient and carer quality of life.

The basic home–care–dead structure has been used before in simulating Parkinson's disease (Tomaszewski and Holloway, 2001), and such models are common in modelling of

other neurodegenerative diseases (e.g. Alzheimer's disease [see Green et al., 2011, for a review] and dementia with Lewy bodies [Gustavsson et al., 2009]).

It is suggested by some stakeholders that this structure is too simplistic, and fails to represent disease progression. This would be true if the 'home' and 'care' states comprised homogeneous populations with shared costs, quality of life and prognoses. However, several measures of the disease and its symptoms are tracked throughout the model, with the result that relatively subtle differences in treatment effect can be simulated over time, in terms of costs, utility and transition to patient-relevant outcomes. Therefore, the GDG agreed that the original model provided a good simulation of disease progression and its implications.

Theme 6b – Hoehn & Yahr score as a superior measure of disease progression

As detailed in Appendix F.3.1.1, the potential model structures considered by the GDG included one based predominantly on Hoehn & Yahr states, as advocated by AbbVie. This was considered suboptimal, for a number of reasons:

1. The measure is too blunt to reflect the range of responses expected from treatment – GDG members reported that, in their experience, people seldom see an improvement in HY score, and expressed the related view that effective interventions that provide significant symptomatic relief would not necessarily be expected to result in changes in HY state.

2. Probably because investigators agree with (1), data on the effect of treatments on HY score are extremely sparse. In particular, RCTs of the interventions in question seldom report this outcome – it was not reported in publications from PDSURG (although it was subsequently possible for us to calculate the effect using patient-level data made available to us by the investigators) and Olanow et al. (2014) make no mention of this outcome. We contend that the economic analyses funded by the manufacturer of LCIG (including, as far as we can tell, the recent submission to the SMC) are significantly weakened by their failure to consider randomised data. Part of the reason for this is the insistence on a HY-based structure, which renders the models unable to use the most robust source of evidence on the differences between LCIG and BMT. Even if one is willing to accept lower-quality evidence on the HY effects of LCIG such as the case series on which AbbVie places emphasis in its stakeholder comments (e.g. Antonini et al., Fernandez et al.), none reports HY score as an outcome. Consequently, in Lowin et al.'s model, the fundamental treatment effect of LCIG – which is extrapolated to persist for simulated patients' lifetimes – is based on 30 people in 2 trial-arms (effectively case series) measured after 3 weeks' treatment with nasoduodenal – not percutaneous – LCIG (even then, the transitions used appear somewhat more optimistic than the data in the cited analysis).

3. Data are at least as sparse when it comes to associating HY score with costs and quality of life, especially in more severe HY states. This makes any attempt to model these states reliant on demonstrably invalid extrapolations of observed data. For example, Lowin et al. (2011) observed no one in HY5 in their dataset, so were forced to make substantial, untested assumptions that people in HY5 experience an identical degree of impairment

relative to those in HY4 to that which people in HY4 experience compared with those in HY3, and that that the quality of life of people in HY4 and HY5 is mediated by off-time to exactly the same degree as (partially) observed in HY3. In practice, this method is plainly inaccurate, as, by extension, it implies that some people in HY1 would have utility values greater than 1 (there are no such people in Lowin et al.'s model, but this shows that the extrapolation method cannot be wholly valid).

For all these reasons, the GDG advised the model developers that HY score should not be used to define disease progression in the model.

Nevertheless, in order to explore how things might change if we set aside these weighty objections, we have performed a new set of scenario analyses in which we configured our model to approximate the estimation of costs and health-related quality of life described by Lowin et al. (2011); these are now detailed in section F.4.1.7 of appendix F. One assumption of Lowin et al.'s that it is difficult for us to replicate is the assumption that off-time benefit increases over time; however, they provide a sensitivity analysis in which this assumption is removed, which provides a point of comparison for this exercise. Our model, configured to imitate Lowin et al.'s assumptions, estimated that, compared with BMT, LCIG generates an extra 0.98 QALYs at an additional cost of £48,949, leading to an ICER of £49,987 / QALY. This is strikingly similar to Lowin et al.'s sensitivity analysis (1.00 incremental QALYs; £48,283 incremental costs; ICER £48,233).

We emphasise that **we do not believe that this is a valid estimate of the balance of costs and benefits provided by LCIG**: for all the reasons discussed here and elsewhere, we strongly believe that these assumptions substantially and inappropriately bias analyses in favour of intervention (we note that, under the same conditions, DBS becomes hugely dominant) and necessitate reliance on very low-quality data that are also likely to exaggerate treatment effects. Nevertheless, this exercise makes it clear that the substantial differences between Lowin et al.'s analysis and ours arise from the more realistic assumptions and more robust data we have relied on, and not because our model is structurally incapable of arriving at estimates that appear somewhat more favourable for LCIG.

Theme 7 – long-term off-time effects

AbbVie claims that, in the domain of off-time, our model does not reflect the long-term benefit of LCIG over BMT, and that '[t]his magnitude should increase over time as BMT patients deteriorate quicker' [443]. This contention is in line with the critical assumption, common to Lowin et al.'s model and other AbbVie-sponsored CUAs, that LCIG confers a permanent 50% reduction in likelihood of increase in off-time state that should continue to be applied cycle-on-cycle throughout simulated disease course.

A transparent justification is not provided by Lowin et al. (2011) for this assumption, and we have still less information on AbbVie's SMC model that inherited the approach. As far as we can tell, the logic appears to be that, because a small, uncontrolled case-series suggests that the proportion of people who remain on LCIG after a few years still show benefits in off-time, compared with their baseline measurement, it should be assumed that ever-increasing effectiveness is being experienced throughout this period.

What readers are being asked to believe, in the AbbVie-funded CUAs, is that the effects of LCIG are not only maintained, but get greater and greater over time. This is an extremely strong assumption that we believe could only be justified by long-term randomised evidence demonstrating its plausibility.

The NICE model shows that it is not necessary to make such bold assumptions in order to provide a realistic simulation of long-term disease course. Our model simply assumes that, in this domain, the immediate relative benefit observed in the RCT for LCIG -v- BMT is preserved over time. In our base case, it can be seen that, following the initial 1.9-hour reduction in off-time from the RCT, it takes 11.5 years of therapy with LCIG before off-time – following the gradual increase shared by all modelled arms in the extrapolation phase of the model – exceeds its baseline value for the average simulated individual (see Figure 3 in appendix F). If the somewhat shallower estimate of year-on-year progression from PDSURG is preferred, this takes even longer. Therefore, our model is not in conflict with the observational evidence AbbVie cite, despite the inherent biases of evidence of that type: we, too, would expect people receiving LCIG to have measurable benefit in off-time, compared with baseline, for several years after initiation of therapy.

In fact, the GDG agreed that the assumption of 100% preservation of initial treatment effect is somewhat generous to LCIG and DBS: the indefinite persistence of effect is an unusual profile to observe in any long-term randomised evidence of any continuous outcome measure; the gradual attenuation of benefit over time is a more common finding.

Theme 8 – ability of EQ-5D to capture HRQoL in advanced PD

Several stakeholders highlight the GDG's suggestion, in its evidence-to-recommendations discussion, that NICE's preferred generic instrument for estimating quality of life – the EQ-5D – may be problematic for people with advanced Parkinson's disease, because 'it may be more difficult to achieve improvement across the 3 levels of the 5 EQ-5D domains'. While, at an individual level, this may be true, it is not clear that this would translate into insensitivity of the instrument at aggregate level (for example, a mean change of 0.1 levels would be achieved if 1 person in 10 reported a change in category).

One way to explore this issue is to make use of mapping algorithms that can predict EQ-5D from other measures. These have been predominantly estimated in people earlier in the disease course, in whom the EQ-5D has been shown to be a sensitive instrument (Schrag et al., 2000). Therefore, if the observed relationship holds true in advanced disease, changes in EQ-5D can be predicted from a more finely grained instrument.

For example, we can configure the original model to use Young et al.'s simple linear model to predict EQ-5D from PDQ-39 single index. Doing so results in ICERs for DBS and LCIG compared with BMT rising to £47,965 / QALY and £502,131 / QALY, respectively. Part of the reason ICERs go up in this scenario is that quality of life is wholly dependent on PDQ-39, for which we assume observed benefit gradually attenuates over a period of 7 years. However, if we remove this assumption, and allow observed PDQ-39 benefit to persist indefinitely and estimate EQ-5D directly from that, the ICER for DBS comes down to £26,270 / QALY, but LCIG is still associated with an ICER of £210,483 / QALY compared with BMT.

Theme 9a – relationship between NICE's conclusions on LCIG and NHS England's specialised commissioning policy

We have revised our recommendation to emphasise that the commissioning of LCIG is the responsibility of NHS England's specialised services process, that it is currently available through this process, and that we recommend that the commissioning policy is reviewed in the light of our findings.

NHS England's specialised commissioning methods state that it is not obliged to follow any NICE guidance without an associated statutory directive (clinical guidelines such as the Parkinson's disease update do not have this status).

Theme 10b – apparent discrepancies between NICE's appraisal of the evidence on LCIG and the view taken by NHS England's specialised commissioning policy

Multiple stakeholders note that NICE's conclusions on the cost effectiveness of LCIG are at odds with the conclusions reached by NHS England, when reviewing a similar evidence-base to inform its specialised commissioning policy.

NHS England's assessment of the cost effectiveness of LCIG appears to have been substantially based on the cost–utility analysis published by Lowin et al. (2011), which was funded by the manufacturer of LCIG. We provide numerous criticisms of that analysis in Appendix F.2.1.3 and Appendix F.5.1.3 (see also Theme 6b and Theme 7, above).

It is potentially important that NHS England had access to confidential information that has not been made available to NICE. In particular, the manufacturer of LCIG agreed to make it available at a reduced price, though we do not know what price was agreed.

We also recognise that NHS England may choose to place emphasis on considerations outside of NICE's Social Value Judgements and guideline development processes.

Theme 11c – apparent discrepancies between NICE's conclusions on LCIG and SMC advice

Multiple stakeholders note that NICE's conclusions on the cost effectiveness of LCIG are at odds with the advice published by the Scottish Medicines Consortium (SMC), recommending LCIG as an option in Scotland.

The SMC's decision to recommend LCIG in select cases was substantially based on consideration of a submission by the manufacturer of LCIG including an original health economic model. We have not had access to the model itself or to a full description of its methods and results, though we sought access to any new economic models in our call for evidence (see full guideline section 10.1). Our inference from such details as are available is that the economic evidence presented to the SMC was substantially biased in favour of the intervention – the model shares many common features with the published analysis of Lowin et al. (2011); we itemise our substantial criticisms of that analysis in Appendix F.2.1.3 and Appendix F.5.1.3 (see also Theme 6b and Theme 7, above). Even then, the base-case ICER that was submitted to the SMC – £58,250 / QALY versus standard care alone, when LCIG is

assessed at its list price – is 2–3 times higher than the threshold below which, according to NICE's reference case, interventions are generally deemed to provide reasonable value for money in the NHS. It is potentially important that the SMC had access to additional, confidential information that has not been made available to NICE. In particular, the manufacturer of LCIG agreed to make it available at a reduced price, though we do not know what price was agreed.

In addition, it should be understood that there are multiple differences between the SMC's principles and procedures and those followed by NICE, including that the SMC may consider additional factors when it judges that a technology qualifies for 'orphan' status (as in the case of LCIG). For all these reasons, one would not necessarily expect NICE and the SMC to arrive at an identical view of the available evidence.