YHEC

York Health Economics Consortium

PRESCRIPTION CHARGES COALITION

Economic evaluation of the benefits of extending free prescriptions to people with long-term conditions

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INVESTORS IN PEOPLE

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Executive Summary

1.   INTRODUCTION

The Prescription Charges Coalition (PCC) has been campaigning to address the impact of prescription charges on the working-age population with long-term conditions in England. Research carried out by the Coalition has found qualitative evidence that prescription charges for working-age people with more than 40 long-term conditions can have a significant impact on medicine adherence, self-management, quality of life and health outcomes. Whilst those over the age of 60 are exempt from prescription charges, since 2010 the prescription charge has risen 26% by £1.60 to £8.80 in 2018 compared to a rise in average earnings over the same period of 16%. The impact of prescription charges on working age people has therefore been increasing.

The PCC commissioned York Health Economics Consortium (YHEC) to carry out economic analysis to try to quantify the impact of prescription charges on working-age people with long-term conditions. The conditions for which working-age patients are not exempt from prescription charges are wide ranging so the analysis was targeted at two conditions: Parkinson's Disease (PD) and Inflammatory Bowel Disease (IBD – the main forms of which are Crohn's disease and ulcerative colitis).

2.   METHODOLOGY

The economic analysis was based on a targeted literature review for both conditions, designed to find evidence of the extent of non-compliance with drug regimes and the potential health and societal impact of non-compliance on health outcomes. Data extracted from the literature review were combined with nationally available data sources and information from research carried out by the PCC to develop a simple economic model to compare the benefits of extending free prescriptions for working-age populations with PD and IBD with the equivalent loss of revenue to the NHS.

There were a number of limitations to the analysis. The literature search and review was pragmatic rather than systematic but the results were discussed with experts advising Parkinson's UK and Crohn's and Colitis UK to ensure validity. There was a lack of quantitative data on the direct link between issues around low incomes, such as the affordability of charges, and a lack of adherence to drug regimes so assumptions were made based on qualitative evidence carried out by the PCC. Sensitivity analysis was used to test the extent to which findings would change if key variables were higher or lower than base case assumptions.

3.   RESULTS

The literature review produced a number of studies for both conditions that demonstrated an impact on the use of healthcare resources associated with non-compliance with drug regimes. There was a lack of data identified on health-related quality of life and societal benefits such as the ability to return to work so the results reported may be understated. We adopted a

conservative approach to analysis using lower estimates of benefit and higher estimates of cost where there was a range available.

For working-age people with PD and IBD who are not exempt from prescription charges, the economic analysis suggests that any loss in prescription revenue from removing charges would be more than offset by savings to the NHS in England. For PD this results from reduced hospital stays and A&E visits resulting from individuals' inadequate adherence to medication due to cost reasons when prescription charges are in place. For IBD, this relates to reduced levels of relapse/flares, and an associated reduction in the incidence of colorectal cancer and number of GP appointments.

The economic model developed suggests that the discounted net cost saving from removal of charges for PD over eight years (at which point the average person with PD not exempt from charges would reach 60) would be £627 per person or £5.4m. This is for the 8,712 people with PD estimated in 2018 in England to have PD and not be exempt from prescription charges. Over a twelve month period the net saving is estimated at £0.8 million.

For IBD the economic model suggests that the discounted net cost saving from removal of charges over 26 years (at which point the average person with IBD not exempt from charges would reach 60) would be £3,061 per person or £340.4m for the 111,200 people with IBD estimated in 2018 in England to have IBD and not be exempt from prescription charges. Over a twelve month period the net saving is estimated at £20.0m.

For PD minimal assumptions had to be made and we can rely on most of the parameters being robust. The main assumption in the modelling is essentially about adherence levels due to cost. Whilst the overall level of savings from removing prescription charges was sensitive to varying assumptions on adherence over sensible ranges, the actual finding that removing charges would be cost saving to the English NHS even after loss of prescription charge revenue remained almost regardless of the adherence levels considered.

For IBD a number of assumptions had to be made to generate the findings. For example, for Crohn's Disease (CD) there were few data on the effects of non-adherence that could be incorporated into the model and the analysis was, therefore, largely reliant on the 2017 PCC survey. However, the results were tested against a wide range of potential parameter values and found to be robust in sensitivity analysis.

4.   DISCUSSION

The conservative approach to economic analysis suggest that the cost to the NHS of providing exemptions to working-age people with PD and IBD would be more than offset by reductions in healthcare resource use. Even if the results had been cost neutral there is an argument that the improvements in patient outcomes, quality of life and the potential societal benefits, none of which were quantified in this analysis, would make this economically justified.

Section 1:   Introduction

1.1   INTRODUCTION

This report describes a study carried out to understand the potential cost benefit of extending prescription charge exemptions to people with long-term conditions who do not currently receive exemptions. The objectives of the project were:

- Carry out a targeted literature search and review to identify evidence of the extent of non-compliance with drug regimes and the potential health and societal impact of non-compliance on health outcomes
- Use nationally available data sources to estimate the extent of the potential benefits among the patient population and also the costs of extending free prescriptions to patients with the particular condition
- Model the costs and benefits of extending free prescriptions to the patient groups in question

The range of long-term conditions that are currently not included on the medical exemption list means that it is not feasible for them all to be examined as part of the research. This is because each condition is unique and lack of adherence to drug regimes will have different effects on patients from condition to condition. In discussion with the PCC two long-term conditions were selected as tracer conditions: Inflammatory Bowel Disease (IBD) and Parkinson's Disease (PD).

1.2   METHODOLOGY

The logic for an evaluation of this nature is that people with long-term conditions who have to pay for their prescriptions, may choose not to do so, particularly if they are in a lower than average income category. This partial or complete lack of adherence to their prescribed medicine can lead to worsening of symptoms and an increase in complications associated with their condition. This could lead to the following economic outcomes:

- Poorer health outcomes
- Increased cost to the National Health Service
- Indirect societal costs such as lost productivity through people being absent from work

The key sources of evidence for the economic evaluation were derived from published medical literature and from data gathered by the PCC on lack of adherence to drug regimes for economic reasons. The literature review sought to find evidence on the impact on the health of patients not taking their medicine optimally, including increased levels of complications and mortality.

Using evidence from the literature review and other available data sources notably on costs, economic models were constructed. A primary source of data for the economic models was the 2017 PCC survey of people with long-term conditions.

In the remainder of this report the methods and findings of the literature review are summarised, with two separate sections describing the economic models and results for PD and IBD separately. The two modelling sections have been written up to be used as stand-alone documents and so have some elements that are repetitive between the sections. For IBD the focus was on people with ulcerative colitis (UC) and Crohn's disease (CD).

Section 2: Literature Review

2.1 LITERATURE SEARCH METHODOLOGY

For ease of work up of the search terminology, the two conditions were split into separate tables. Search terms included generic terminology for the two conditions plus disease specific terms. Animal studies were removed from the MEDLINE strategy using a standard algorithm. The strategy also excluded publication types that are unlikely to yield relevant information; comments, editorial, news, letters and case reports. The MEDLINE search is limited to English language studies only, with no date restriction.

The literature searches were conducted in a range of relevant bibliographic databases containing published literature, including MEDLINE, NHS EED and HTA. In addition to the searches of bibliographic databases some additional activities have been carried out including checking the reference lists of any identified relevant reviews for eligible studies;

The results of the bibliographic database searches were transferred into an EndNote library and de-duplicated using several algorithms. The de-duplicated references are held in a separate EndNote library duplicates database for checking if required.

2.1.1 Inflammatory Bowel Disease

For Inflammatory Bowel Disease, the search concepts used were:

(inflammatory bowel disease) OR (ulcerative colitis) OR (crohn disease)
AND
(medication non-compliance) OR (medication non-adherence) OR (treatment adherence) OR (treatment compliance))) OR (stop* AND (therapy OR treatment)
AND
((outcome OR effect OR symptom))

The results were filtered using an economics filter and return on investment terms. The search terms and strategy are set out in Appendix A.

2.1.2 Parkinson's Disease

For Parkinson's Disease, the search concepts were:

("Parkinson Disease"[Mesh])
AND
(medication non-compliance) OR (medication non-adherence) OR (treatment adherence) OR (treatment compliance))) OR (stop* AND (therapy OR treatment)
AND
((outcome OR effect OR symptom))

The search terms and strategy are set out in Appendix A.

2.2 SEARCH RESULTS

For the Inflammatory Bowel Disease search 215 references were found and for Parkinson's Disease 97 were found. Of these only the papers identified in the economics filter were screened and reviewed (83 and 38 records respectively). These have been screened using the initial title and abstract selection. For IBD we identified 14 records, with eight having full text available for data extraction. We excluded any studies that considered non-adherence in the context of the use of infliximab as we understand that this is an infusion therapy provided in hospital settings so does not incur prescription charges. For Parkinson's Disease we found seven records with full text for data extraction.

2.3 NARRATIVE SYNTHESIS OF ELIGIBLE STUDIES

For the purposes of a rapid review, only those papers with an economic filter applied were screened with the resulting papers being rapidly reviewed. The results are summarised below.

2.3.1 Inflammatory Bowel Disease

Our review found a number of good quality systematic reviews and study reports on the links between non-adherence to medication and relapse or flares in IBD conditions. There is also some evidence that adherence to medication can help to prevent colorectal cancer. Some of the evidence found was from overseas studies, particularly from the USA, so the results will need to be interpreted with caution.

Annahazi et al. (2015) is a review of the impact of therapies on the management of ulcerative colitis (UC) and Crohn's disease (CD). The paper provides references to the impact on relapse rates of withdrawal of the following therapies for both forms of IBD: aminosalicylic compounds; thiopurines; methotrexate; and biological therapies. The review cites a number of different trials but there is no meta-analysis of the results.

Eaden et al. (2000) carried out a case-control study of cases of colorectal cancer in UC in the UK to examine the impact of different therapeutic approaches. They found that regular 5-ASA medication reduced cancer risk by 75%.

Goodhand et al. (2013) carried out a trial for young adults to assess the impact of a transition clinic on adherence to medication. 12% of patients were non-adherent and this was associated with escalation in therapy, hospital admission and surgery in the six months of follow-up.

Higgins et al. (2009) carried out a systematic review of literature on the impact of non-adherence with 5-ASA medications and the incidence of flares and the costs of care in UC patients. The review found that the relative risk for flare in non-adherent vs. adherent patients ranged from 3.65 to infinity. None of the RCTs reviewed measured the impact of adherence on disease activity. The comorbidity-adjusted annual costs of care in adherent patients were 12.5% less than in non-adherent patients, despite increased medication expenditures.

Two papers by *Kane et al.* reported the results of studies into lack of adherence to medication and associated costs. A retrospective review (2008) of UC patient data observed a twofold difference in gastroenterology related inpatient cost in non-adherent versus adherent patients (22.8% vs 11.7%, P\0.01). Non-adherence also incurred more costs for outpatient services and office visits. Patients who were persistent with their medications incurred 12.5% lower medical costs (P = 0.03). A report (2008) described UC patients who were non-compliant with medication having a fivefold greater risk of recurrence of relapse compared to compliant patients. Some of the studies reviewed suggested an increased rate of colorectal cancer in non-adherent patients.

Mitra et al. (2012) carried out an observational cohort study to examine the association between adherence to 5-ASAa and all-cause costs and health care utilisation among UC patients. Adherent patients had 31% fewer hospitalisations and 34% fewer ED admissions compared to non-adherent patients. Including pharmacy costs (higher in adherent patients), total all-cause costs were 29% higher in non-adherent patients ($13,465 vs $17,339).

Testa et al. (2017) reviewed the role medication adherence plays in the routine management of UC. They reported the fivefold risk of relapse in non-adherent patients first reported by Kane et al., as well as the reduction in colorectal cancer risk from adherence to 5-ASA medication reported by *Eaden et al*.

2.3.2 Parkinson's Disease

Fewer papers were returned in the searches for Parkinson's Disease (PD) but there are some useful reviews of the impact on health care utilisation and associated costs of non-adherence to medication. As with IBD, most of the studies of interest are from the USA so we will need to use the results with care.

Daley et al. (2012) carried out a systematic review of literature on clinical and demographic factors associated with medication non-adherence in PD. They found one study that positively

correlated low income with non-adherence but the results were not statistically significant and the study was assessed as of moderate quality.

Davis et al. (2010) estimated the association between medication non-adherence and healthcare costs. Unadjusted mean medical costs were significantly higher (P<0.01) among non-adherers ($15,826) compared with adherers ($9,228), although low adherers had lower prescription drug costs ($2,684 vs $3,584; P<0.05). Statistical analysis showed a large positive relationship between non-adherence and both medical and total healthcare costs.

Delea et al. (2011) examined the association between adherence to levodopa/carbidopa/ entacapone therapy and healthcare utilisation and costs. Satisfactory adherence was associated with 39% fewer PD-related hospitalisations, 47% lower all-case inpatient costs and 18% lower all-cause total costs compared with unsatisfactory adherence.

Malek et al. (2015) carried out a literature review on the prevalence of significant medication non-compliance in PD, finding that non-compliance ranged between 10% and 67%. In terms of costs, the paper quoted the work of *Richy and Wei* (2014).

Richy et al. (2013) determined the patient characteristics and healthcare costs associated with compliance and non-compliance among PD patients in the USA. They found that, although total drug mean costs were higher for compliant patients than non-compliant patients (driven mainly by the cost of PD-related medications), the mean costs associated with emergency room and inpatient visits were higher for patients non-compliant with their prescribed medication. Overall, the total all-cause annual healthcare mean cost was lower for compliant ($77,499) than for non-compliant patients ($84,949; p<0.0001).

Wei et al. (2014) examined the associations of adherence to anti-parkinson drugs (APDs) with healthcare utilisation and economic outcomes among patients with PD. They found that increasing adherence to APD therapy was associated with decreased healthcare utilisation and expenditures. Compared with patients with low adherence, those with high adherence had significantly lower rates of hospitalisation (RR = 0.86), emergency room visits (RR = 0.91), skilled nursing facility episodes (RR = 0.67), home health agency episodes (RR = 0.83), physician visits (RR = 0.93), as well as lower total healthcare expenditures (-$2242), measured over 19 months.

Wei et al. (2015) also examined the effect of prior anti-parkinson drug (APD) nonadherence on subsequent APD regimen modifications and the influence of modifications on healthcare utilisation and costs by patients with PD. The study found that initiation of APD modifications in any given month was higher among patients who were non-adherent to APDs in the preceding month (adjusted hazard ratio [HR] = 1.23), compared to their adherent counterparts. Modifications significantly predicted higher risk of all-cause and PD-related hospitalisations (adjusted relative risk [RR] = 1.22 and 1.83, respectively), home health agency utilisation (RR = 1.18 and 1.52), and use of physician services (RR = 1.14 and 1.41), as well as higher total all-cause healthcare expenditures (mean = $1064) in any given 3-month interval.

2.3.3 Suitability of papers identified for economic modelling

Several of the papers found provide information that can be incorporated into economic models, although given the differences between the UK and US healthcare systems only papers that either provided evidence of adherence and risk reductions or changes in resource use (rather than just cost) could be used.

Section 3:   Parkinson's Disease

3.1   APPROACH TO ECONOMIC MODELLING

A cost-consequence approach was taken to economic modelling, based on consideration of the incremental costs of extending free prescriptions to people with Parkinson's Disease (PD) compared with the estimated incremental benefits of greater adherence to drug regimes for a subset of patients whose adherence may be affected by low incomes. A pragmatic approach has been adopted and a number of assumptions have been made to allow a simplified model to be constructed, based on the available evidence.

The model was constructed with a structure incorporating decision trees and a Markov process. The decision trees determined each model cycle, including the following parameters:

- The probability a person with PD would not purchase a prescription prepayment certificate (PPC) if they were not exempt from prescription charges
- The probability a person with PD who did not purchase a PPC would not fully adhere to their medication due to the cost of prescriptions
- The probability a person with PD who purchased a PPC each year would not fully adhere to their medication due to delaying purchase of their PPC at the start of the year due to cost

The Markov process was used to model mortality over time. A schematic of the model is shown in Figure 3.1.

Figure 3.1   Simplified schematic of model
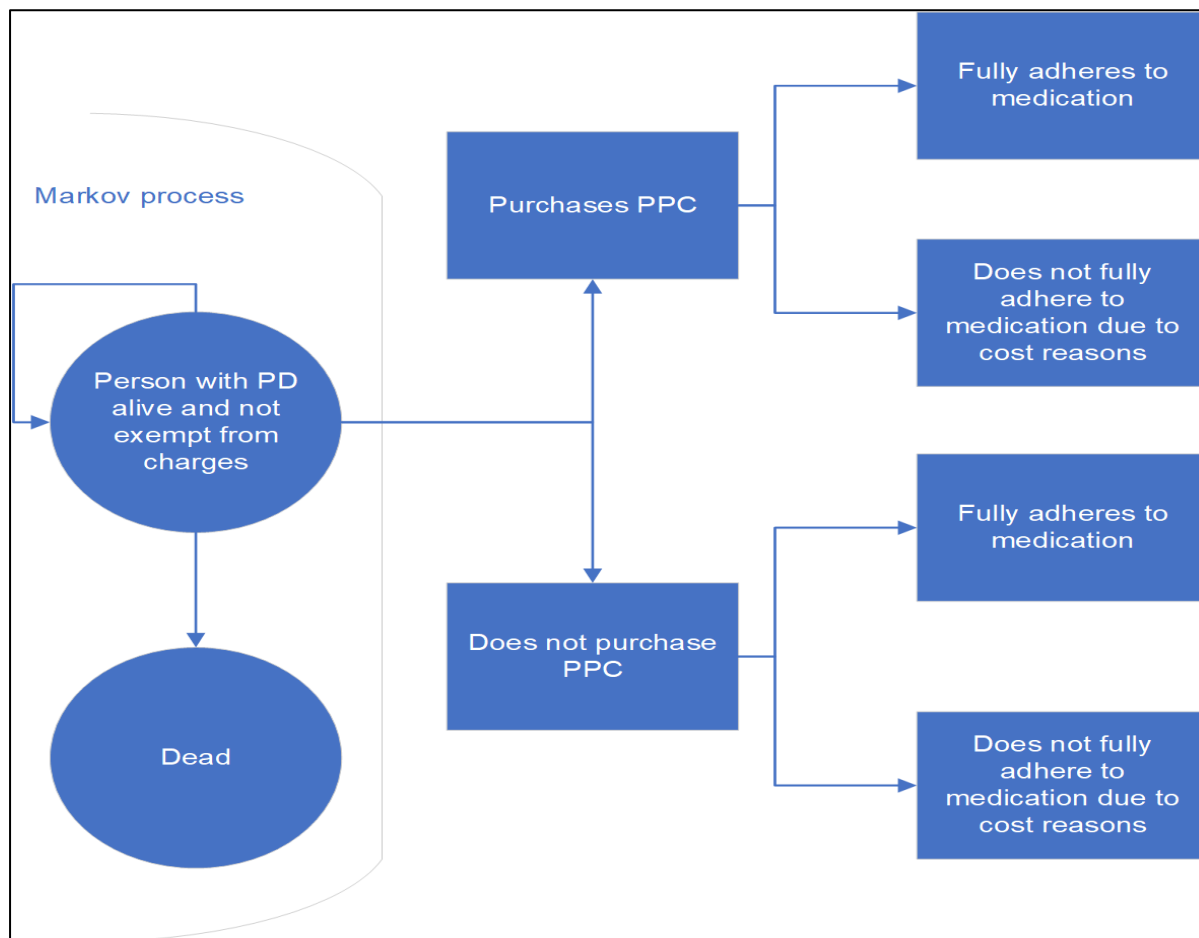
The model explored current rates of adherence with drug regimens compared to adherence rates should prescription charges be removed. While it is recognised that there are many different factors involved in non-adherence, for simplicity in the modelling process only non-adherence due to cost was included with removing prescription charges negating this barrier to adherence.

3.2   MODEL INPUTS AND ASSUMPTIONS

3.2.1   Number of people with PD not eligible for exemption

Research by *Parkinson's UK* (2018) estimates that there are 8,718 people under the age of 60 living with PD in England who are potentially ineligible for exemption from prescription charges on the grounds of age. Whilst it is possible that some of these people may be exempt for other reasons other than age, this population was included in the model. The results were interpreted as being the maximum costs or cost savings available from the removal of prescription charges.

3.2.2 Model start age

The average age of people in England living with PD, estimated from prevalence rates provided by Parkinson's UK, is approximately 75. However, by this age a patient would automatically be exempt from prescription charges. Using the Parkinson's UK prevalence rates just for those people under the age of 60, the average age of people in England with PD who are potentially eligible for charges is 52. This was used as the model start age in the base case.

3.2.3 Model time horizon

At age 60 people are automatically exempt from prescription charges. The model time horizon was therefore until people reached age 60 (a time horizon of 8 years).

3.2.4 Cycle length

The chosen cycle length was one year. As the only transition in the model was into a 'dead' state and this was considered independent of adherence to medication, a half cycle adjustment was not necessary.

3.2.5 Discount rate

Costs were discounted at 3.5%. A scenario analysis explored the impact on results of not applying a discount rate. This form of presentation is usually used for budget impact analysis where costs are reported at the forecast value in each year (that is not discounted). Sensitivity analysis tested the impact on results of using discount rates of 1.5% and 5.0%.

3.2.6 Model perspective

The model perspective was the NHS in England.

3.3 DECISION TREE AND MARKOV PROBABILITIES

3.3.1 Percentage of people with PD ineligible for exemption who will purchase a PPC

A survey from Parkinson's UK in 2008 (*Parkinson's UK* 2014) found that 76% of those who were ineligible for exemption purchased a PPC. This is more optimistic than the PCC 2017 survey which found that 77% of people under the age of 60 with long-term conditions purchased a PPC. The latter of these values (77%) was used in the base case analysis due to it being a more up to date figure than the Parkinson's UK survey, albeit on a wider population. Due to uncertainty in this value, it was varied by +-25% (ie 61% to 95%) in sensitivity analysis.

3.3.2 Percentage of people who do not purchase a PPC who are not 100% adherent for cost reasons

Whilst there is no direct evidence on the percentage of patients with PD who are not 100% adherent due to cost, evidence from the PCC 2017 survey suggests that 33% of people with long-term conditions paying prescription charges have not picked up a prescription due to cost. In addition, in the same research it was reported that 13% of people with long-term conditions paying prescription charges reported taking their medicines less frequently than required to reduce costs. It is unclear what the overlap between the 33% and 13% exists. With no overlap 46% of people with long-term conditions had not been 100% adherent due to cost. With full overlap, the percentage would be 33%. In the base case the midpoint of these values (39.5%) was used with the range of 33% to 46% used in sensitivity analysis.

3.3.3 Percentage of people who purchase a PPC who are not 100% adherent for cost reasons

Research from the PCC provides qualitative evidence that some people with long-term conditions and purchasing a PPC still are not 100% adherent for cost reasons. This was either due to not being able to afford the PPC at the time it needed renewing or due to fears that overuse of the certificate would result in increases in the cost of the PPC in the future. With no quantitative evidence on the scale of this issue, in the base case it was assumed that 10% of people with a PPC would not be adherent for cost reasons. In sensitivity analysis, values between 0% and 20% were explored.

3.3.4 Mortality

Published studies have reported a higher rate of mortality for people with PD with Hobson et al reporting an estimated Standardised Mortality Ratio (SMR) for people with PD in the UK under the age of 75 at onset (so all people under 60 included in the model) of 2.09. This ratio was applied to age-related background mortality taken from Office of National Statistics (ONS) life tables (ONS, 2017).

3.4 HEALTH OUTCOMES AND RESOURCE USE

Health outcomes and resource use based upon adherence to PD medications were taken from the literature identified in the rapid review. The only paper that provided evidence on outcomes and resource use that could be incorporated into a model was the study in the USA by *Delea et al*. This study estimated that over a 12-month period, people with PD who were satisfactorily adherent (defined as having prescriptions to cover at least 80% of their medication requirement over the previous 12 months) had statistically significantly lower rates of hospital admissions, length of hospital stays (LOS) and emergency room visits.

The relevant data from the study are:

- Hospital admissions: 0.31 (satisfactory adherence) vs 0.52 (unsatisfactory adherence)
- LOS: 2.25 (satisfactory adherence) vs 5.27 (unsatisfactory adherence)
- Emergency room visits: 0.73 (satisfactory adherence) vs 1.11 (unsatisfactory adherence)

Whilst based on the USA health system, the study results were considered to be generalisable to the UK as they are based upon actual patient outcomes resulting from lack of adherence which should not differ between the UK and the USA. Whilst 80% adherence was chosen as the cut-off point in the Delea study, the same study reported results of higher resource use with unsatisfactory adherence, even if the cut-off was 95% prescription coverage (although the actual resource use for a 95% cut-off were not reported). The resource use values based upon 80% adherence were therefore incorporated into the economic model as annual resource use depending on whether a person with PD was adherent or not.

Evidence from the survey by the PCC suggests that skipping medication resulted in high levels of hospitalisation, GP visits and deteriorating health. The Delea study found no impact on GP visits but did find lower rates of hospital admissions and emergency room visits. Other aspects of deteriorating health could not be quantified either from the survey or from published papers found in the rapid review and so were not included in the model. This may, therefore, have resulted in an underestimate in the impact on health outcomes from unsatisfactory adherence.

3.5   COSTS

Costs for resource use were taken from NHS Reference Costs (2016/17). Costing both hospital admissions and LOS is likely to lead to double counting, so only LOS was costed using the cost of excess bed days at £305.85 per day. However, this potentially underestimates the cost of the hospitalisation as it will not include any costs of treatment. The cost of the hospitalisation should therefore be considered an underestimate, thus producing a conservative estimate of the benefits of increasing adherence.

For A&E attendance, the average cost of all admitted and non-admitted types, excluding dentistry and patients dead on arrival, was used (£163 – NHS Reference Costs). It was assumed that half the visits were by ambulance at a cost of £247 (See, Treat and Convey – NHS Reference Costs). In sensitivity analysis, the impact of this assumption was tested by assuming no attendances were by ambulance or all attendances were by ambulance.

Both the severity of reasons for hospital admission and A&E attendance were assumed to be independent of medication adherence.

3.5.1 Lost revenue to the NHS through removing prescription charges

The cost of the PPC was £104 and was considered not to increase over time. The actual cost to the NHS of the drugs prescribed was not considered in the analysis as the NHS has already considered that these are cost-effective and should be funded. It was also assumed that the people not purchasing a PPC were spending no more than £104 a year on prescription charges. The lost revenue to the NHS of making people with PD exempt from charges was therefore assumed to be £104 per person.

3.6 RESULTS

3.6.1 Base case

Under the base case assumptions the model predicts that if all people with PD were made exempt from prescription charges, then for the 8,712 people with PD assumed not to be eligible for exemption from charges:

- Hospital admissions would fall 11.4%
- Total days in hospital would fall 20.4%
- A&E attendances would fall 9.0%

This is over an eight year time horizon before the average age of these patients reaches 60.

This fall in healthcare resource use would result in net discounted cost savings (after the loss of revenue from removing prescription charges) of £627 per person (£703 undiscounted). For all 8,712 people the total net discounted cost saving of removing prescription charges over eight years would be £5.5m (£6.1m undiscounted) after the total discounted loss of revenue from prescription charges of £6.3m (£7.3m undiscounted). The results of the base case are summarised in Tables 3.1 and 3.2

Table 3.1: Healthcare resource use results of base case analysis for 8,712 people with PD not exempt from prescription charges (8 year time horizon)

	Events with prescription charges	Events removal of prescription charges	Reduction with prescription charges removed
Hospital admissions	23,770	21,049	2,721 (11.4%)
Inpatient days	191,911	152,776	39,135 (20.4%)
A&E visits	54,492	49,567	4,924 (9.0%)

Table 3.2: Cost results of base case analysis for 8,712 people with PD not exempt from prescription charges (8 year time horizon)

	Costs with prescription charges		Costs with removal of prescription charges		Cost saving with removal of prescription charges	
	Undiscounted	Discounted	Undiscounted	Discounted	Undiscounted	Discounted
Inpatient days	£58,696,001	£52,278,692	£46,726,417	£41,617,758	£11,969,584 (20.4%)	£10,660,934 (20.4%)
A&E visits	£15,611,822	£13,904,962	£14,201,001	£12,648,388	£1,410,821 (9.0%)	£1,256,574 (9.0%)
Revenue from prescription charges	£7,253,376	£6,450,558	£0	£0	-£7,253,376 (-100.0%)	-£6,450,558 (-100.0%)
Total (net of prescription charges)	£67,054,447	£59,733,096	£60,927,418	£54,266,146	£6,127,029 (9.1%)	£5,466,951 (9.2%)

Reducing the base case time horizon to 12 months, the revenue loss from removing prescription charges for the 8,712 people with PD not exempt was estimated by the model to be £0.9m. However, this would be offset by a reduction in costs of hospital stay and A&E attendance of £1.7m meaning that removal of prescription charges would generate a net saving of £0.8m or £93 per person. Base case results for a 12 month time horizon are shown in Tables 3.3 and 3.4.

Table 3.3: Healthcare resource use results of base case analysis for 8,712 people with PD not exempt from prescription charges (12 month time horizon)

	Events with prescription charges	Events removal of prescription charges	Cost saving with removal of prescription charges
Hospital admissions	3,052	2,703	349 (11.4%)
Inpatient days	24,640	19,616	5,025 (20.4%)
A&E visits	6,996	6,364	632 (9.0%)

Table 3.4: Cost results of base case analysis for 8,712 people with PD not exempt from prescription charges (12 month time horizon)

	Events with prescription charges	Events removal of prescription charges	Cost saving with removal of prescription charges
Inpatient days	£7,536,226	£5,999,401	£1,536,825 (20.4%)
A&E visits	£2,004,467	£1,823,326	£181,141 (9.0%)
Revenue from prescription charges	£906,672	£0	-£906,672 (-100.0%)
Net cost	£8,634,021	£7,822,727	£811,294 (9.4%)

3.6.2   Scenario and sensitivity analysis

Scenario and sensitivity analysis was performed using the parameter values described in section 3.3 and 3.4. The results in terms of the impact on the net discounted cost saving should prescription charges be removed compared to the base case cost saving are shown in Table 3.5. The analysis shows that the parameters where uncertainty had the largest potential impact on the level of saving were:

- The percentage people with a PPC but who were still not-adherent for cost reasons
- The percentage of people ineligible for exemption who do not purchase a PPC

However, the finding of a cost saving to the NHS from the removal of prescription charges held across all values for all parameters considered apart from the analysis whereby all patients with an exemption certificate were never fully adherent due to cost reasons. Provided at least 1.4% of people with a PPC did not have 100% adherence due to the cost of the PPC then removing prescription charges would remain cost saving. This implies that, given the assumptions used, the removal of prescription charges for the eligible population would be cost-saving under almost the full range of plausible parameter values.

Removing prescription charges would cease to be cost saving if 99.2% of people with PD ineligible for exemption purchased a PPC. It is plausible that more people with PD might be adherent to medication than the PCC 2017 survey of all people with long-term conditions may suggest due to the impact of non-full adherence on PD symptoms. However, removing prescription charges continues to be cost saving so long as at least 1.4% of people without a PPC are not fully adherent for cost reasons – well below the 33%-46% suggested by the survey.

Table 3.5: Results of scenario and sensitivity analysis

Parameter	Value in base case analysis	Value in sensitivity/scenario analysis	Net discounted cost saving with prescription charges removed (percentage difference from base case saving)
Discount rate	3.5%	1.5%	£5,827,686 (+6.6%)
		5.0%	£5,221,927 (-4.5%)
Percentage of people ineligible for exemption who will purchase a PPC	77%	59%	£9,906,745 (+81.2%)
		95%	£1,027,156 (-81.2%)
Percentage of people with PPC not adherent for cost reasons	10%	0%	-£777,487 (-114.2%)
		20%	£11,711,388 (+114.2%)
Percentage of people not purchasing a PPC who are not adherent for cost reasons	39.5%	33%	£4,533,407 (-17.1%)
		46%	£6,400,494 (+17.1%)
Percentage of people conveyed to A&E by ambulance	50%	0%	£4,925,285 (-9.9%)
		100%	£6,008,615 (+9,9%)

3.7   DISCUSSION

For people with PD who are not exempt from prescription charges, the economic analysis suggests that any loss in prescription revenue from removing charges would be more than offset by savings to the NHS in England from reduced hospital stays and A&E visits resulting from individuals' inadequate adherence to medication due to cost reasons when prescription charges are in place. The economic model developed suggests that the discounted net cost saving from removal of charges over eight years (at which point the average person with PD not exempt from charges would reach 60) would be £627 per person or £5.5 million. This is for the 8,712 people with PD estimated in 2018 in England to have PD and not be exempt from prescription charges.

One of the strengths of the findings is that minimal assumptions had to be made and we can rely on most of the parameters being robust. The main assumption in the modelling is essentially about adherence levels due to cost. Whilst the overall level of savings from removing prescription charges was sensitive to varying assumptions on adherence over sensible ranges, the actual finding that removing charges would be cost saving to the English NHS even after loss of prescription charge revenue remained for almost all values of adherence levels considered.

An additional strength of the analysis is that several of the assumptions or parameter values chosen in the model can be considered conservative and likely to lead to an underestimate of the potential cost saving from removing charges. For example, no cost was considered for any treatment related to a hospital admission with only the costs of the length of hospital stay being included in the analysis and mortality and severity of reason for admission or A&E visit were considered independent of adherence levels.

Section 4: Inflammatory Bowel Disease

4.1 APPROACH

A similar pragmatic cost-consequence approach was taken to economic modelling for IBD, considering the incremental costs of extending free prescriptions to people with IBD compared with the estimated incremental benefits of greater adherence to drug regimes for a subset of patients whose adherence may be affected by low incomes.

The model was constructed with a structure incorporating decision trees and a Markov process. The decision trees determined each model cycle, including the following parameters:

- The probability a person with IBD would not purchase a prescription prepayment certificate (PPC) if they were not exempt from prescription charges
- The probability a person with IBD who did not purchase a PPC would not fully adhere to their medication due to the cost of prescriptions
- The probability a person with IBD who purchased a PPC each year would not fully adhere to their medication due to delaying purchase of their PPC at the start of the year due to cost

The Markov process was used to model mortality over time. A schematic of the model is shown in Figure 3.1.

Figure 4.1:   Simplified schematic of model
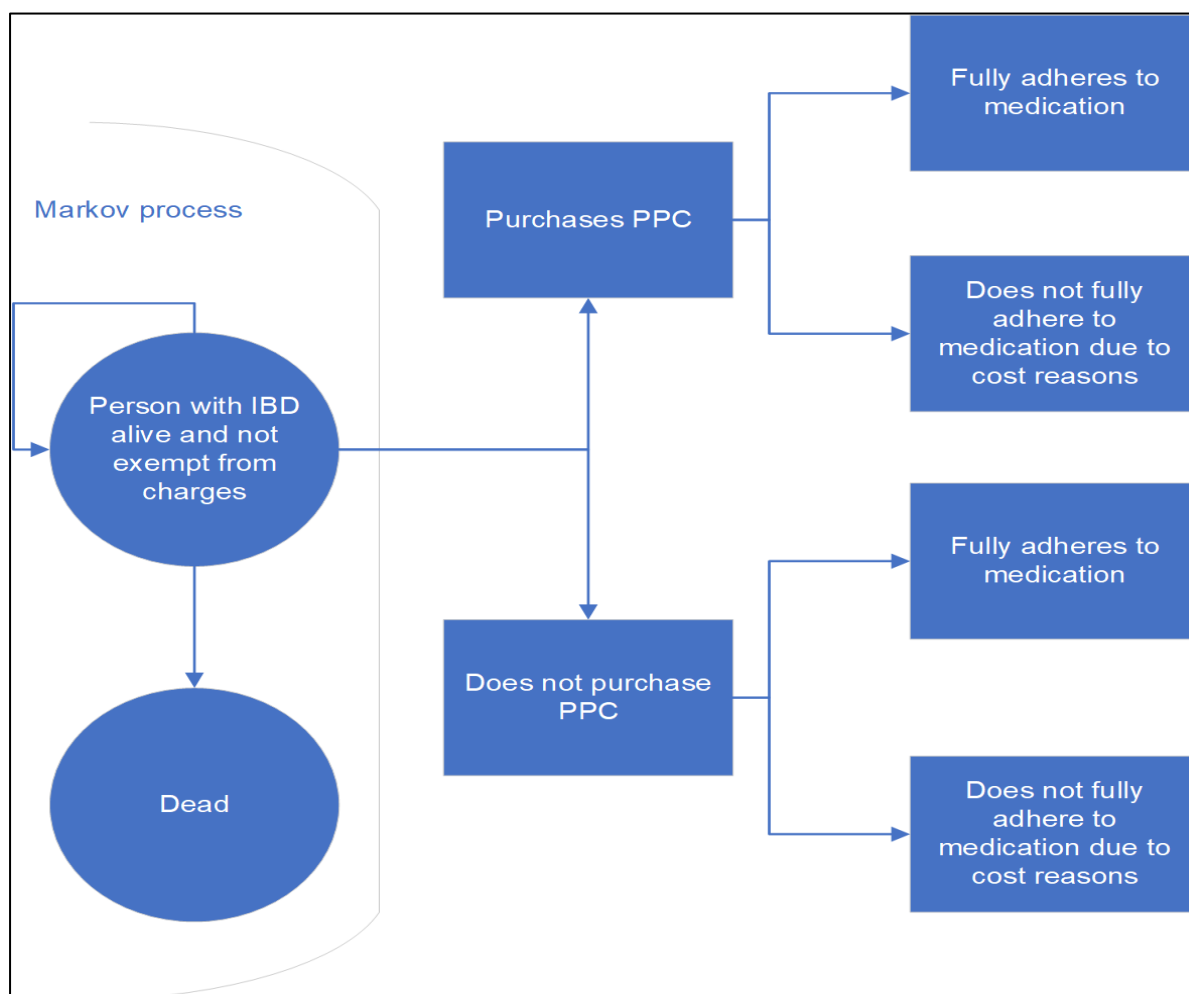
Whilst the overarching model structure is for all people with IBD, the transition parameters and costs associated with adherence and non-adherence could potentially vary by whether people had ulcerative colitis (UC) or Crohn's disease (CD). As such, the model generates results for these conditions separately which are then combined to provide overall results for the IBD population.

The model explored current rates of adherence to drug regimes compared to adherence rates should prescription charges be removed. While it is recognised that there are many different factors involved in non-adherence, for simplicity in the modelling process only non-adherence due to cost was included with removing prescription charges negating this barrier to adherence.

4.2 MODEL INPUTS AND ASSUMPTIONS

4.2.1 Number of people with IBD and not eligible for exemption

No published statistics could be found on the actual number of people living in England with IBD who are not eligible for exemption.

It is estimated (*NICE*, 2014) that there are 261,000 people living in the UK with a diagnosis of IBD (115,000 CD and 146,000 UC). If the geographical and age distribution of people with IBD is the same as the UK as a whole (84.1% in England and 55.5% aged 18-59), this would suggest that there are 121,800 people in England with IBD who are not exempt from prescriptions on the grounds of age (53,700 with CD and 68,100 with UC).

The PCC 2017 survey provides evidence that 8.7% of people with IBD who are not exempt from prescription charges due to age will be exempt from charges for other reasons. It can therefore be estimated that approximately 111,200 people live in England with a diagnosis of IBD and are not eligible for prescription charge exemption (49,000 with CD and 62,200 with UC).

4.2.2 Model start age

Using data for IBD patients only from the PCC 2017 survey, the average age of respondents 18 or over and under 60 suggests that the average age of people with IBD and not exempt from prescriptions on grounds of age is 34. A scenario analysis explored model findings if the start age was 18 (ie the point at which a person would become eligible for prescription charges).

4.2.3 Model time horizon

At age 60 people automatically are exempt from prescription charges. The model time horizon was therefore until people reached age 60 (a time horizon of 26 years).

4.2.4 Cycle length

The chosen cycle length was one year. As the only transition in the model was into a 'dead' state and this was considered independent of adherence to medication a half cycle adjustment was not necessary.

4.2.5 Discount rate

Costs were discounted at 3.5%. A scenario analysis explored the impact on results of not applying a discount rate. This form of presentation is usually used for budget impact analysis where costs are reported at the forecast value in each year (that is not discounted). Sensitivity analysis tested the impact on results of using discount rates of 1.5% and 5.0%.

4.2.6 Model perspective

The model perspective was the NHS in England.

4.3 DECISION TREE AND MARKOV PROBABILITIES

4.3.1 Percentage of people with IBD ineligible for exemption who will purchase a PPC

The PCC 2017 survey reported that 53.0% of people with IBD who are not exempt from charges purchased a PPC. This value was used in the base case of the model with a value +-25% used in sensitivity analysis (39.8% to 66.3%).

4.3.2 Percentage of people who do not purchase a PPC who are not 100% adherent for cost reasons

Whilst there is no published evidence on the percentage of patients with IBD who are not 100% adherent due to cost, evidence from the PCC 2017 survey suggests that 33.6% of people with IBD paying prescription charges have not picked up a prescription due to cost. In addition, in the same research it was reported that 14.8% of people with IBD paying prescription charges reported taking their medicines less frequently than required to reduce costs. It is unclear what the overlap between the 33.6% and 14.8% exists. With no overlap 48.4% of people with long-term conditions had not been 100% adherent due to cost. With full overlap, the percentage would be 33.6%. In the base case the midpoint of these values (41.0%) was used with the range of 33.6% to 48.4% used in sensitivity analysis.

4.3.3 Percentage of people who purchase a PPC who are not 100% adherent for cost reasons

Research from the PCC 2017 survey provides qualitative evidence that some people with long-term conditions (including IBD) and purchasing a PPC still are not 100% adherent for cost reasons. This was either due to not being able to afford the PPC or due to unpredictability i the need for medication. With no quantitative evidence on the scale of this issue, it was assumed that 10% of people with a PPC would not be adherent for cost reasons. In sensitivity analysis, values between 0% and 20% were explored.

4.3.4 Mortality

A systematic review and meta-analysis reported a higher rate of mortality for people with IBD (*Bewtra et al.* 2013) with an estimated Standardised Mortality Ratio (SMR) for people with UC of 1.19 and for people with CD of 1.38. These ratios were applied to age-related background mortality taken from Office of National Statistics (ONS) life tables (ONS, 2017).

4.4 HEALTH OUTCOMES AND RESOURCE USE

4.4.1 Ulcerative colitis

Evidence from the literature review linked poor adherence to medication in UC to both an increase in flare ups and in the development of colorectal cancer.

The *Kane and Shaya* 2008 study identified in the literature review provided evidence that patients with UC who adhered to 5-ASA medication had an 11.1% annual risk of flare up compared to a 40.6% risk in non-adherent patients. ('adherent' defined as picking up 80% of the prescriptions required for full medication coverage). These values were used in the model base case. The study did not provide 95% confidence intervals but could be calculated from the information in the paper and were 2.7% to 19.5% for adherent patients and 23.6% to 57.6% for non-adherent patients. These ranges were explored in sensitivity analysis.

The literature review identified that 100% adherence to medication in people with UC (notably ASAs) resulted in a reduction in colorectal cancer risk (adjusted for other factors), which was estimated to be 53% (95% CI: 0%-78%) in the *Eaden* 2000 study. The baseline colorectal cancer risk for people with UC was identified from a systematic review and meta-analysis (*Castano-Milla et al*, 2014) and was estimated to be 1.58 (95% CI: 1.39-1.76) per 1,000 patient years. The mean values reported for baseline cancer risk and risk reduction from the identified studies was used in the base case, with sensitivity analysis exploring the impact on base case results from using the upper and lower bounds of the confidence intervals reported in the studies. The lower bound of risk reduction of 0%, essentially provides an estimate of results if adherence had no impact on the development of colorectal cancer.

Cases of colorectal cancer were assumed to be independent of mortality. Given colorectal cancer will in some cases result in mortality and greater adherence to medication leads to reductions in colorectal cancer rates, this assumption will result in a conservative estimate of health benefits from removing prescription charges.

4.4.2 Crohn's disease

There was an absence of evidence from the literature review that could be incorporated into the model on the impact of less than full adherence on health outcomes and resource use for people with CD.

In the absence of published evidence, the model used evidence from the PCC 2017 survey. Focusing on people with IBD only, of those that responded to say they had missed medication in the past, 27.1% had stated they went to a doctor whereas 12.4% had been hospitalised. Hospitalised patients were assumed to have experienced relapse. Although the survey included people with UC, it was assumed that these values applied on an annual basis in the base case to those people with CD who were not fully adherent due to cost reasons. In a sensitivity analysis, the impact on base case results of changing the percentage of people non-adherent who required GP care or had relapse by +-25% was explored.

4.5 COSTS

4.5.1 Ulcerative colitis

The cost of flare up and colorectal cancer was taken from a UK cost of illness study for IBD (*Ghosh*, 2015). This study estimated the additional cost of a person with UC in a year that they relapsed instead of being entirely in remission to be £1,210 with mild/moderate disease or £9,067 with acute disease. The study estimated that 80% of people with relapse have mild/moderate disease which provides an estimated weighted average cost of relapse of £2,781 compared to if the person had been in remission or £2,868 after adjusting for inflation since the study publication date (*PSSRU*, 2017). The same study estimated the cost of treating colorectal cancer to be £10,514 or £10,844 after inflation adjustment.

In the absence of distributions around these estimates, sensitivity analysis explored the impact of costs being 25% higher and lower on the base case results.

Ultimately continued flare up of UC can lead to surgery which has further potential costs but also potentially long-term savings if reliance on medication and number of flare ups is reduced. However, given the assumptions that would have to be made over which point surgery would be an option, its success and complication rates and ongoing resource use post-surgery, surgery has not been included in the model. Another consequence would be treatment with biologic drugs, which would be a similar cost per year to treating colorectal cancer.

4.5.2 Crohn's disease

For those people with CD who saw a doctor as a result of not fully adhering to medication, whilst the doctor could have been a specialist consultant or nurse or a GP for simplicity it was assumed that they would require one GP appointment at a cost of £38 (REF PSSRU). This would likely be an underestimate for a specialist consultant or nurse. Using values from the same UK cost of illness study on IBD as used for UC, the additional cost of a person with CD in a year that they relapsed instead of being entirely in remission would be £8,713 or £8,986 after adjusting for healthcare inflation (*PSSRU,* 2017).

Again, in the absence of distributions around these estimates and to reflect the uncertainty on the nature of the 'doctor' visited in non-hospitalised patients, sensitivity analysis explored the impact of cost of relapse being 25% higher and lower on the base case results.

4.5.3 Lost revenue to the NHS through removing prescription charges

The cost of the PPC was £104 and was considered not to increase over time. The actual cost to the NHS of the drugs prescribed was not considered in the analysis as the NHS has already considered that these are cost-effective and should be funded. It was also assumed that the people not purchasing a PPC were spending no more than £104 a year on prescription charges. The lost revenue to the NHS of making people with IBD exempt from charges was therefore assumed to be £104 per person.

4.6 RESULTS

4.6.1 Base case

Under the base case assumptions the model predicts that if all people with IBD were made exempt from prescription charges, then for the 111,200 people with IBD assumed not to be eligible for exemption from charges:

- Relapses for UC would fall 135,541 with 45,053 fewer relapses in people with CD
- There would be 344 fewer cases of colorectal cancer
- People with CD would have 98,463 fewer visits to GPs

This is over a 26 year time horizon at the end of which the average age of these patients reaches 60.

This improvement in health outcomes would result in net discounted cost savings of £3,061 per person (£4,517 undiscounted), which includes a loss in discounted prescription charge revenue of £1,818 per person (£2,704 undiscounted). For all 111,200 people, the total net discounted cost saving of removing prescription charges over 26 years would be £340.4m (£502.3 undiscounted), which includes a total discounted loss of revenue over 26 years from prescription charges of £202.1m (£300.7m undiscounted). The results of the base case are summarised in Tables 4.1 and 4.2.

Table 4.1: Health outcomes of base case analysis for 111,200 people with IBD not exempt from prescription charges (62,200 UC and 49,000 CD - 26 year time horizon)

	Events with prescription charges	Events removal of prescription charges	Reduction with prescription charges removed
UC			
Relapses	312,068	175,527	136,541 (43.8%)
Colorectal cancer	1,668	1,324	344 (20.6%)
CD			
Relapses	-	-	45,053
Additional GP visits	-	-	98,463

Table 4.2: Cost results of base case analysis for 111,200 people with IBD not exempt from prescription charges (62,200 UC and 49,000 CD - 26 year time horizon)

	Costs with prescription charges		Costs with removal of prescription charges		Reduction with removal of prescription charges	
	Undiscounted	Discounted	Undiscounted	Discounted	Undiscounted	Discounted
UC						
Relapses	£895,012,328	£604,522,574	£503,410,845	£340,021,261	£381,601,483 (43.8%)	£264,501,313 (43.8%)
Colorectal cancer	£18,086,861	£12,216,497	£14,359,619	£9,698,988	£3,727,242 (20.6%)	£2,517,510 (20.6%)
Revenue from prescription charges	£168,188,800	£113,084,422	£0	£0	-£168,188,800 (-100%)	-£113,084,422 (-100%)
Total (net of revenue from prescription charges)	£744,910,389	£503,654,649	£517,770,464	£349,720,248	£227,139,925 (30.5%)	£153,934,401 (30.6%)
CD						
Relapses	-	-	-	-	£403,948,738	£273,038,454
Additional GP visits	-	-	-	-	£3,741,612	£2,529,043
Revenue from prescription charges	-	-	-	-	-£132,496,000	-£89,085,798
Total (net of revenue from prescription charges)	-	-	-	-	£275,194,350	£186,481,699
TOTAL IBD (net of revenue from prescription charges)	-	-	-	-	£502,334,275	£340,416,100

Reducing the base case time horizon to 12 months, the revenue loss from removing prescription charges for the 111,200 people with IBD not exempt was estimated by the model to be £11.5m. However, this would be offset by a reduction in costs of relapse and treating colorectal cancer of £31.5m meaning that removal of prescription charges would generate a net saving of £20.0m in 12 months for the NHS in England, or £180 per person. Base case results for a 12 month time horizon are shown in Tables 4.3 and 4.4.

Table 4.3: Health outcomes of base case analysis for 111,200 people with IBD not exempt from prescription charges (62,200 UC and 49,000 CD - 12 month time horizon)

	Events with prescription charges	Events removal of prescription charges	Reduction with prescription charges removed
UC			
Relapses	12,275	6,904	5,371 (43.8%)
Colorectal cancer	66	52	14 (20.6%)
CD			
Relapses	-	-	1,778
Doctor visits due to non-adherence for cost reasons	-	-	3,887

Table 4.4: Cost results of base case analysis for 8,712 people with PD not exempt from prescription charges (12 month time horizon)

	Costs with prescription charges	Costs with removal of prescription charges	Reduction with removal of prescription charges
UC			
Relapses	£35,204,563	£19,801,246	£15,403,318 (43.8%)
Colorectal cancer	£711,432	£564,824	£146,608 (20.6%)
Revenue from prescription charges	£6,468,800	£0	-£6,468,800 (-100%)
Total (net of revenue from prescription charges)	£29,447,195	£20,366,069	£9,081,126 (30.8%)
CD			
Relapses	-	-	£15,945,540
Additional GP visits	-	-	£147,697
Revenue from prescription charges	-	-	-£5,096,000
Total (net of revenue from prescription charges)	-	-	£10,997,237
TOTAL IBD (net of revenue from prescription charges)	-	-	£20,015,363

4.6.2   Scenario and sensitivity analysis

Scenario and sensitivity analysis was performed using the parameter values described in section 4.3 and 4.4. The results in terms of the impact on the net discounted cost saving should prescription charges be removed compared to the base case cost saving are shown in Table 4.5. The analysis shows that the parameters where uncertainty had the largest potential impact on the level of saving were:

- The percentage people with a PPC but who were still not-adherent for cost reasons
- The percentage of people ineligible for exemption who do not purchase a PPC
- The annual relapse rates for adherent and non-adherent patients

However, the finding of a cost saving to the NHS from the removal of prescription charges held across all values of all parameters considered.

The sensitivity analysis showed that although reductions in colorectal cancer and in the number of overall GP visits from increased adherence due to removal of prescription charges may be important at a patient and system management level, they are not important factors in the potential cost savings generated from removal of charges. The cost savings are essentially driven by a reduction in relapse rates.

Table 4.5: Results of scenario and sensitivity analysis

Parameter	Value in base case analysis	Value in sensitivity/scenario analysis	Net discounted cost reduction with prescription charges removed (percentage difference from base case for people with UC or CD only)
UC			
Discount rate	3.5%	1.5%	£190,416,534 (+23.7%)
		5.0%	£133,311,401 (-13.4%)
Percentage of people ineligible for exemption who will purchase a PPC	53%	39.8%	£203,305,971 (+32.1%)
		66.3%	£104,188,804 (-32.3%)
Percentage of people with PPC not adherent for cost reasons	10%	0%	£52,708,292 (-59.3%)
		20%	£245,160,511 (+59.3%)
Percentage of people not purchasing a PPC who are not adherent for cost reasons	41%	33.6%	£122,205,960 (-20.6%)
		48.4%	£185,662,842 (+20.6%)
Annual relapse adherent	11.1%	2.7%	£229,250,029 (+48.9%)
		19.5%	£78,618,773 (-48.9%)

Annual relapse non-adherent	40.6%	23.6%	£1,509,916 (-99.0%)
		57.6%	£309,048,731 (+100.8%)
Colorectal cancer risk (1,000 patient years	1.58	1.39	£153,615,729 (-0.2%)
		1.76	£154,221,206 (+0.2%)
Colorectal cancer risk reduction with medication adherence	53%	0%	£151,416,892 (-1.6%)
		78%	£155,594,886 (+1.1%)
Cost of colorectal cancer treatment	£10,844	£8,675	£153,430,853 (-0.3%)
		£13,555	£154,563,779 (+0.4%)
Cost of relapse	£2,868	£2,294	£100,957,249 (-34.4%)
		£3,585	£220,059,730 (+43.0%)
CD			
Discount rate	3.5%	1.5%	£230,690,777 (+23.7%)
		5.0%	£161,491,955 (-13.4%)
Percentage of people ineligible for exemption who will purchase a PPC	53%	39.8%	£237,433,913 (+27.3%)
		66.3%	£96,543,322 (-48.2%)
Percentage of people with PPC not adherent for cost reasons	10%	0%	£92,334,963 (-50.5%)
		20%	£280,628,436 (+50.5%)
Percentage of people not purchasing a PPC who are not adherent for cost reasons	41%	33.6%	£153,737,464 (-17.6%)
		48.4%	£219,225,934 (+17.6%)
Annual relapse in people non-adherent for cost reasons	12.4%	9.9%	£131,433,624 (-29.3%)
		15.5%	£254,741,313 (+36.6%)
Annual additional GP visit due to non-adherence for cost reasons	27.1%	21.7%	£185,977,757 (-0.3%)
		33.9%	£187,116,293 (+0.3%)
Cost of GP visit	£38	£28.50	£185,849,438 (-0.3%)
		£47.50	£187,113,960 (+0.3%)
Cost of relapse	£8,986	£7,189	£132,367,341 (-29.0%)
		£11,233	£255,517,855 (-37.0%)

4.7   DISCUSSION

For people with IBD (UC and CD) who are not exempt from prescription charges, the economic analysis suggests that any loss in prescription revenue from removing charges would be more than offset by savings to the NHS in England from reduced relapse and colorectal cancer rates resulting from avoidance of inadequate adherence to medication due to cost reasons when prescription charges are in place. The economic model developed suggests that the discounted net cost saving from removal of charges over 26 years (at which point the average person with IBD not exempt from charges would reach 60) would be £3,061 per person or £340.4 for the 111,200 people with IBD estimated in 2018 in England to have IBD and not be exempt from prescription charges.

A number of assumptions had to be made to generate the findings. For example, for CD there were few data on the effects of non-adherence that could be incorporated into the model and the analysis was, therefore, largely reliant on the 2017 PCC survey. However, the results were tested against a wide range of potential parameter values and found to be robust in sensitivity analysis.

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References

APPENDIX A

Search terms for Inflammatory Bowel Disease

	Eligible studies	Ineligible studies
Population Patients of any age with Inflammatory Bowel Disease	Inflammatory Bowel Disease IBD Crohn's Disease Ulcerative Colitis. Proctitis Pouchitis Crohn's Colitis Indeterminate Colitis Unspecified colitis MeSH terms: Crohn disease "Colitis, Ulcerative"[Mesh] "Inflammatory Bowel Diseases"[Mesh] "Proctitis"[Mesh]) "Pouchitis"[Mesh]	People without Inflammatory Bowel Disease. People with forms of colitis other than Ulcerative Colitis or Crohn's Colitis. People with Irritable Bowel Syndrome.
Interventions Patients requiring drug treatment for Inflammatory Bowel Disease.	Corticosteroids prednisolone budesonide aminosalicylates balsalazide aminosalicylic acid mesalamine mesalazine olsalazine sulfasalazine immunomodulators azathioprine 6-mercaptopurine methotrexate Ciclosporin Tacrolimus Antibiotics: ciprofloxacin metronidazole MESH "Adrenal Cortex Hormones"[Mesh] "Prednisolone"[Mesh] "Budesonide"[Mesh] "Aminosalicylic Acids"[Mesh] "Mesalamine"[Mesh] Sulfasalazine"[Mesh] "Methotrexate"[Mesh] Cyclosporine"[Mesh] "Tacrolimus"[Mesh] Ciprofloxacin"[Mesh] "Metronidazole"[Mesh]	Patients not requiring drug treatment for Inflammatory Bowel Disease.

Comparators Non-compliance effects	Non adherence to therapy Non compliance Stopping/ceasing therapy Abandon treatment Medication compliance Discontinue therapy Non-Compliance, Medication Non-Adherence, Medication Therapeutic Adherence and Compliance Treatment Adherence therapeutic adherence MeSH terms: "patient compliance"[MeSH] "Treatment Adherence and Compliance"[Mesh] "Medication Adherence"[Mesh]	Studies not reporting the effect of non-adherence to drug regimes for Inflammatory Bowel Disease.
Outcomes Lack of compliance with drug regimes. Cost-effectiveness outcomes	Cost-effectiveness outcomes cost per condition prevented total cost savings return on investment, cost per QALY, health-related quality of life HRQOL productivity gains. Health outcomes e.g. number of complications: strictures, bowel perforation, number of hospitalisations Emergency admissions Inpatient bed days Escalating treatment/dose escalation Emergency surgery Colectomy Increased risk of cancer anaemia Disease control, disease management Disease activity Improvement/relief of symptoms Recurrence or deterioration of symptoms or disease Relapse symptom control "daily living" daily living/activities (incontinence, psychological impact) gastrointestinal symptoms: stomach pain, constipation, or diarrhoea	Studies not reporting compliance with drug regimes, cost-effectiveness or health outcomes.

	Flare Clinical remission Mucosal healing MeSH terms: Cost-Benefit Analysis* Treatment outcome	
Study design	Economic evaluations (cost-effectiveness studies, cost-utility studies, cost-benefit analyses); Costing reports; Systematic reviews of economic evaluations; Health technology assessments Clinical trials = Randomized controlled trials	Studies with no evidence of cost-effectiveness evaluations being undertaken.
Limits	Evidence in English Evidence available as full text e.g. journal articles, reports, theses	Evidence in languages other than English Evidence in abstract form only e.g. abstracts of conference presentations

Search strategy for Inflammatory Bowel Disease in Ovid MEDLINE

1. exp Inflammatory Bowel Diseases/
2. crohn disease.mp. or exp Crohn Disease/
3. ulcerative colitis.mp. or exp Colitis, Ulcerative/
4. (IBD and inflammat*).mp. or "inflammatory bowel disease".ab,ti. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
5. proctitis.mp. or exp PROCTITIS/
6. pouchitis.mp. or exp POUCHITIS/
7. "crohns colitis".ab,ti.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. "indeterminate colitis".ab,ti.
10. "unspecified colitis".ab,ti.
11. 9 or 10
12. 8 or 11
13. medication adherence.mp. or exp Medication Adherence/
14. exp Patient Compliance/
15. ("medication compliance" or "treatment compliance" or "therapy compliance").ab,ti.
16. ("therap* adherence" or "treat* adherence" or "drug* adherence").ab,ti.
17. ("non adherence" or "non complian*").mp. and (drug* or medicat* or therap*).ab,ti. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
18. (stop* or cease or discontinu* or abandon*).mp. and (drug* or medicat* or therap*).ab,ti. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
19. ((discontinu* or abstention or abstain* or stop* or abandon*) adj4 treat*).ab,ti.
20. ((discontinu* or abstention or abstain* or stop* or abandon*) adj4 medic*).ab,ti.
21. ((discontinu* or abstention or abstain* or stop* or abandon*) adj4 therap*).ab,ti.

22. (adhere* or non adhere* or complian* or non complian* or dropout* or refus* or concordance or persistence or acceptance or cooperat* or co operat* or conform*).ab,ti.
23. exp Patient Dropouts/
24. exp Treatment Refusal/
25. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 23 or 24
26. exp Adrenal Cortex Hormones/ or corticosteroid*.mp.
27. exp Anti-Inflammatory Agents/
28. ("anti inflammatory drug" or "anti inflammatory therapy" or "anti inflammatory agent").ab,ti.
29. exp Sulfasalazine/ or exp Aminosalicylic Acids/ or aminosalicylate.mp. or exp Mesalamine/
30. (mesalamine or mesalazine or olsalazine or balsalazide).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
31. exp Aminosalicylic Acid/
32. exp Immunologic Factors/
33. "immunomodulator*".ab,ti.
34. (azathioprine or "6-mercaptopurine" or methotrexate).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
35. ciclosporin.mp. or exp Cyclosporine/
36. cyclosporin.mp.
37. tacrolimus.mp. or exp Tacrolimus/
38. prednisolone.mp. or exp PREDNISOLONE/
39. budesonide.mp. or exp BUDESONIDE/
40. methotrexate.mp. or exp METHOTREXATE/
41. ciprofloxacin.mp. or exp CIPROFLOXACIN/
42. metronidazole.mp. or exp METRONIDAZOLE/
43. 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42
44. exp "Outcome Assessment (Health Care)"/
45. outcome*.mp. or exp Treatment Outcome/
46. exp Cost-Benefit Analysis/ or cost effective*.mp.
47. cost saving.mp. or exp "Cost Savings"/
48. "return on investment".mp. or exp "Costs and Cost Analysis"/
49. exp Quality-Adjusted Life Years/ or exp "Quality of Life"/
50. ("QALY" or "HRQOL" or "health related quality of life" or "quality of life").ab,ti.
51. exp Efficiency/
52. (economic* or work*).mp. and (productiv* or efficiency or efficient*).ab,ti. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
53. healthcare cost.mp. or exp Health Care Costs/
54. "quality of life".mp. or exp "Quality of Life"/
55. (health adj2 outcome).ab,ti.
56. 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55
57. ((disease or symptom*) adj2 (control* or improv* or relief* or manage* or relaps*)).ab,ti.
58. "relief of symptoms".ab,ti.
59. exp Disease Management/
60. exp RECURRENCE/ or recurrence.mp.
61. exp CLINICAL DETERIORATION/
62. ((disease or condition) adj2 (deteriorat* or declin*)).ab,ti.
63. exp "Activities of Daily Living"/
64. ("daily living" or "daily life" or "self care" or "daily activit*").ab,ti.
65. depression.mp. or exp DEPRESSION/
66. exp URINARY INCONTINENCE/ or incontinence.mp. or exp FECAL INCONTINENCE/
67. (psycho* adj2 (impact or effect)).ab,ti.
68. 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67
69. (bowel adj2 stricture*).ab,ti.
70. exp Constriction, Pathologic/
71. exp Inflammatory Bowel Diseases/
72. 70 and 71
73. 69 or 72
74. exp Intestinal Perforation/

75. (bowel adj2 perforat*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
76. 74 or 75
77. (hospitali$ation* or hospital* or "emergency" or inpatient*).ab,ti.
78. (admit* or admission*).ab,ti.
79. 77 and 78
80. exp Patient Admission/ or exp Hospitalization/
81. exp EMERGENCIES/
82. 80 or 81
83. (increase* or rising or escalate*).mp. and (treatment* or therap* or drug*).ab,ti. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
84. ("inpatient bed day*" or "inpatient day*").ab,ti.
85. (emergenc* and (surger* or surgical or operation*)).ab,ti.
86. ("gastrointestinal symptom*" or "stomach pain*" or constipation or diarrh$ea).ab,ti.
87. flare.mp. or exp SYMPTOM FLARE UP/
88. "clinical remission".ab,ti.
89. mucosal healing.ab,ti.
90. exp WOUND HEALING/ and exp Intestinal Mucosa/
91. 73 or 76 or 79 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90
92. colectomy.mp. or exp COLECTOMY/
93. colorectal cancer.mp. or exp Colorectal Neoplasms/
94. exp Anemia/ or anaemia.mp.
95. 91 or 92 or 93 or 94
96. 25 and 43
97. 56 or 68 or 95
98. 12 and 96 and 97
99. Economics/
100. exp "Costs and Cost Analysis"/
101. Economics, Nursing/ or Economics, Dental/ or exp Economics, Hospital/ or Economics, Pharmaceutical/ or Economics, Medical/
102. (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ab,kf,ti.
103. (expenditure$ not energy).ab,kf,ti.
104. value for money.ab,kf,ti.
105. budget$.ab,kf,ti.
106. 99 or 100 or 101 or 102 or 103 or 104 or 105
107. ((energy or oxygen) adj cost).ab,kf,ti.
108. (metabolic adj cost).ab,kf,ti.
109. ((energy or oxygen) adj expenditure).ab,kf,ti.
110. 107 or 108 or 109
111. ((Economics or "Costs and Cost Analysis" or (Economics, Nursing or Economics, Dental or Economics, Hospital or Economics, Pharmaceutical or Economics, Medical) or (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$) or (expenditure$ not energy) or value for money or budget$) not (((energy or oxygen) adj cost) or (metabolic adj cost) or ((energy or oxygen) adj expenditure))).ab,kf,ti.
112. exp Budgets/
113. exp models, economic/
114. ec.fs.
115. Income/
116. Remuneration/
117. "Salaries and Fringe Benefits"/
118. exp "Fees and Charges"/
119. (expens$ or earning$ or salar$ or wage$1 or pay or pays or paid or paying or payment$1 or income$1 or renumerat$ or financ$ or money or monetary or fee or fees or charg$).ab,kf,ti.
120. 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119
121. exp Cost-Benefit Analysis/
122. ("return on investment" or ROI or (cost adj effective*)).ab,ti.
123. randomized controlled trial.pt.
124. 121 or 122
125. 120 or 124

126. 98 and 125
127. 98 and 123
128. 126 or 127
129. 126
130. limit 129 to english language
131. 127
132. limit 131 to english language

Key to Ovid symbols and commands

$	Unlimited right-hand truncation symbol
*	Unlimited right-hand truncation symbol
$N	Limited right-hand truncation - restricts the number of characters following the word to N
?	Wildcard symbol wild card character stands for zero or one characters within a word or at the end of a word
ti,ab,kf.	Searches are restricted to the Title, Abstract, or Keyword Heading Word fields
adjN	Retrieves records that contain terms (in any order) within a specified number (N) of words of each other
/	Searches are restricted to the Subject Heading field
exp	The subject heading is exploded
pt.	Search is restricted to the publication type field
or/1-21	Combines sets 1 to 21 using OR

APPENDIX B

Search terms for Parkinson's Disease

	Eligible studies	Ineligible studies
Population: Patients of any age with Parkinson's	Parkinson* Disease MeSH terms: Parkinson Disease	People without Parkinson Disease People with other forms of tremor
Interventions Patients requiring drug treatment for Parkinson Disease	antiparkinsonian drugs levodopa carbidopa (co-careldopa) benserazide (co-beneldopa) entacapone dopamine-receptor agonists (pramipexole, ropinirole or rotigotine) Ropinirole Rotigotine Apomorphine Bromocriptine Cabergoline Pergolide Pramipexole monoamine-oxidase-B inhibitors monoamine oxidase type B inhibitor Rasagiline Selegiline COMT inhibitor (AND levodopa) Tolcapone Glutumate antagonists Amantadine anticholinergics Orphenadrine Procyclidine Trihexyphenidyl Benzhexol MeSH terms: "Levodopa"[Mesh] "Dopamine Agonists" "Monoamine Oxidase Inhibitors" "Carbidopa"[Mesh]	Patients not requiring drug treatment for Parkinson Disease
Comparators Non-compliance effects	Non adherence to therapy Non compliance Stopping/ceasing therapy Abandon treatment Medication compliance Discontinue therapy Non-Compliance, Medication Non-Adherence, Medication Therapeutic Adherence and Compliance Treatment Adherence therapeutic adherence MeSH terms: "patient compliance"[MeSH] "Treatment Adherence and Compliance"[Mesh] "Medication Adherence"[Mesh]	Studies not reporting the effect of non-adherence to drug regimes for Parkinson Disease
Outcomes Lack of compliance	Cost-effectiveness outcomes cost per condition prevented, total cost savings, return on investment, cost per QALY,	Studies not reporting compliance with drug regimes, cost-effectiveness or health outcomes.

with drug regimes. Cost-effectiveness outcomes	health-related quality of life HRQOL productivity gains. Health outcomes e.g. number of complications, number of hospitalisations Disease control, disease management Disease activity Improvement/relief of symptoms Recurrence/deterioration of symptoms or disease Consequences Relapse symptom control daily living/activities "daily living" motor complications/motor experiences dyskinesia and/or motor fluctuations movement tremor stiffness balance mental health depression psychosis cognitive impairment autonomic dysfunction sleep disturbance Scales: Assessment scales and tools Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Modified Bradykinesia Ratings Scale (MBRS) Lindop Parkinson's Assessment Scale (LPAS) Hospital anxiety and depression scale Parkinson's non-motor symptoms questionnaire Parkinson's Disease Questionnaire (PDQ-39) MeSH terms: Cost-Benefit Analysis* Treatment outcome	
Study design	Economic evaluations (cost-effectiveness studies, cost-utility studies, cost-benefit analyses); Costing reports; Systematic reviews of economic evaluations; Health technology assessments	Studies with no evidence of cost-effectiveness evaluations being undertaken.
Limits	Evidence in English Evidence available as full text e.g. journal articles, reports, theses	Evidence in languages other than English Evidence in abstract form only e.g. abstracts of conference presentations

Search strategy for Parkinson's Disease in Ovid MEDLINE

1. exp Parkinson Disease/ or parkinson* disease.mp.
2. medication adherence.mp. or exp Medication Adherence/
3. exp Patient Compliance/
4. ("medication compliance" or "treatment compliance" or "therapy compliance").ab,ti.
5. ("therap* adherence" or "treat* adherence" or "drug* adherence").ab,ti.
6. ("non adherence" or "non complian*").mp. and (drug* or medicat* or therap*).ab,ti. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
7. (stop* or cease or discontinu* or abandon*).mp. and (drug* or medicat* or therap*).ab,ti. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
8. ((discontinu* or abstention or abstain* or stop* or abandon*) adj4 treat*).ab,ti.
9. ((discontinu* or abstention or abstain* or stop* or abandon*) adj4 medic*).ab,ti.
10. ((discontinu* or abstention or abstain* or stop* or abandon*) adj4 therap*).ab,ti.
11. (adhere* or non adhere* or complian* or non complian* or dropout* or refus* or concordance or persistence or acceptance or cooperat* or co operat* or conform*).ab,ti.
12. exp Patient Dropouts/
13. exp Treatment Refusal/
14. 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 12 or 13
15. exp Antiparkinson Agents/ or antiparkinsonian drugs.mp.
16. exp Levodopa/
17. exp CARBIDOPA/
18. levodopa carbidopa.ab,ti.
19. co-careldopa.ab,ti.
20. (benserazide or co-beneldopa).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
21. exp BENSERAZIDE/
22. entacapone.mp.
23. exp Dopamine Agonists/
24. "dopamine agonist*".ab,ti.
25. "dopamine receptor agonist* ".ab,ti.
26. ropinirole.mp.
27. rotigotine.mp.
28. apomorphine.mp. or exp APOMORPHINE/
29. bromocriptine.mp. or exp BROMOCRIPTINE/
30. exp Ergolines/
31. cabergoline.mp.
32. exp PERGOLIDE/ or pergolide.mp.
33. pramipexole.mp.
34. exp Monoamine Oxidase Inhibitors/ or monoamine-oxidase-B inhibitors.mp.
35. rasagiline.mp.
36. selegiline.mp. or exp SELEGILINE/
37. exp Catechol O-Methyltransferase Inhibitors/ or COMT inhibitor.mp.
38. tolcapone.mp.
39. glutamate antagonists.mp. or Excitatory Amino Acid Antagonists/
40. amantadine.mp. or exp AMANTADINE/
41. anticholinergic*.mp. or exp Cholinergic Antagonists/
42. orphenadrine.mp. or exp ORPHENADRINE/
43. procyclidine.mp. or exp PROCYCLIDINE/
44. trihexyphenidyl.mp. or exp TRIHEXYPHENIDYL/
45. benhexol.mp.
46. 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45
47. exp "Outcome Assessment (Health Care)"/
48. outcome*.mp. or exp Treatment Outcome/
49. exp Cost-Benefit Analysis/ or cost effective*.mp.

50. cost saving.mp. or exp "Cost Savings"/
51. "return on investment".mp. or exp "Costs and Cost Analysis"/
52. exp Quality-Adjusted Life Years/ or exp "Quality of Life"/
53. ("QALY" or "HRQOL" or "health related quality of life" or "quality of life").ab,ti.
54. exp Efficiency/
55. (economic* or work*).mp. and (productiv* or efficiency or efficient*).ab,ti. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
56. healthcare cost.mp. or exp Health Care Costs/
57. "quality of life".mp. or exp "Quality of Life"/
58. (health adj2 outcome).ab,ti.
59. 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58
60. ((disease or symptom*) adj2 (control* or improv* or relief* or manage* or relaps*)).ab,ti.
61. "relief of symptoms".ab,ti.
62. exp Disease Management/
63. exp RECURRENCE/ or recurrence.mp.
64. exp CLINICAL DETERIORATION/
65. ((disease or condition) adj2 (deteriorat* or declin*)).ab,ti.
66. exp "Activities of Daily Living"/
67. ("daily living" or "daily life" or "self care" or "daily activit*").ab,ti.
68. depression.mp. or exp DEPRESSION/
69. exp URINARY INCONTINENCE/ or incontinence.mp. or exp FECAL INCONTINENCE/
70. (psycho* adj2 (impact or effect)).ab,ti.
71. 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70
72. Dyskinesias/
73. dyskinesia.ab,ti.
74. "motor complication* ".ab,ti.
75. ("motor movement*" or "motor fluctuation*").ab,ti.
76. exp TREMOR/ or tremor.mp.
77. ((muscular or muscle or joint or skeletal) adj1 stiff*).ab,ti.
78. "muscular stiffness* ".ab,ti.
79. Postural Balance/
80. "postur* balance".ab,ti.
81. mental health.mp. or exp Mental Health/
82. depression.mp. or exp DEPRESSION/
83. psychosis.mp. or exp Psychotic Disorders/
84. cognitive impairment.mp. or exp Cognitive Dysfunction/
85. autonomic dysfunction.mp.
86. exp Sleep Wake Disorders/ or sleep disturbance.mp.
87. (Unified Parkinson's Disease Rating Scale or MDS-UPDRS).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
88. (Unified Parkinson's Disease Rating Scale or MDS-UPDRS).ab,ti.
89. (Modified Bradykinesia Ratings Scale or MBRS).ab,ti.
90. (Lindop Parkinson's Assessment Scale or LPAS).ab,ti.
91. (Hospital anxiety and depression scale).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
92. (Hospital anxiety and depression scale).ab,ti.
93. Parkinson's non-motor symptoms questionnaire.ab,ti.
94. (Parkinson* Disease Questionnaire or PDQ-39).ab,ti.
95. (survey or questionnaire).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
96. exp "Surveys and Questionnaires"/
97. 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86
98. 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96
99. 97 or 98
100. (hospitali$ation* or hospital* or "emergency" or inpatient*).ab,ti.
101. (admit* or admission*).ab,ti.
102. 100 and 101
103. exp Patient Admission/ or exp Hospitalization/

104. exp EMERGENCIES/
105. 103 or 104
106. (increase* or rising or escalate*).mp. and (treatment* or therap* or drug*).ab,ti. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
107. ("inpatient bed day*" or "inpatient day*").ab,ti.
108. 102 or 105 or 106 or 107
109. 14 and 46
110. 99 or 108
111. 59 or 71 or 110
112. 1 and 109 and 111
113. Economics/
114. exp "Costs and Cost Analysis"/
115. Economics, Nursing/ or Economics, Dental/ or exp Economics, Hospital/ or Economics, Pharmaceutical/ or Economics, Medical/
116. (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ab,kf,ti.
117. (expenditure$ not energy).ab,kf,ti.
118. value for money.ab,kf,ti.
119. budget$.ab,kf,ti.
120. 113 or 114 or 115 or 116 or 117 or 118 or 119
121. ((energy or oxygen) adj cost).ab,kf,ti.
122. (metabolic adj cost).ab,kf,ti.
123. ((energy or oxygen) adj expenditure).ab,kf,ti.
124. 121 or 122 or 123
125. ((Economics or "Costs and Cost Analysis" or (Economics, Nursing or Economics, Dental or Economics, Hospital or Economics, Pharmaceutical or Economics, Medical) or (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$) or (expenditure$ not energy) or value for money or budget$) not (((energy or oxygen) adj cost) or (metabolic adj cost) or ((energy or oxygen) adj expenditure))).ab,kf,ti.
126. exp Budgets/
127. exp models, economic/
128. ec.fs.
129. Income/
130. Remuneration/
131. "Salaries and Fringe Benefits"/
132. exp "Fees and Charges"/
133. (expens$ or earning$ or salar$ or wage$1 or pay or pays or paid or paying or payment$1 or income$1 or renumerat$ or financ$ or money or monetary or fee or fees or charg$).ab,kf,ti.
134. 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133
135. Cost-Benefit Analysis/
136. ("return on investment" or ROI or (cost adj effective*)).af.
137. 134 or 135 or 136
138. 112 and 137
139. randomized controlled trial.pt.
140. 112 and 139
141. 138
142. limit 141 to english language
143. 140
144. limit 143 to english language