Economic Plan

This document identifies the priorities for economic analysis and the proposed methods for addressing these questions as described in section 7.1.3 of the Guidelines Manual (2009).

1 Guideline

Full title of guideline: Ulcerative colitis: the management of ulcerative colitis

2 Process for agreement

The economic plan was prepared by the guideline economist in consultation with the rest of the NCC technical team and GDG. It was discussed and agreed on 20 January 2012 by the following people[a]:

For the NCC and GDG:

NCC economist:	Lola Adedokun
	Dave Wonderling
NCC representative(s)[b]:	Kate Kelley
GDG representative(s)[c]:	Alan Lobo

For NICE (completed by NICE):

CCP lead:	Sarah Willett
Commissioning manager:	Clifford Middleton
Economic lead:	Jasdeep Hayre
Costing lead:	David Pearson

Proposals for any changes to the agreed priorities will be circulated by email to this group. If substantive revisions are agreed, they will require to be recorded as addenda to this

[a] This may be done by face-to-face meeting, teleconference, or email as convenient.

[b] May be the project manager, a systematic reviewer or research fellow and/or the centre director or manager, as appropriate for the NCC and guideline.

[c] May be GDG chair, clinical lead and/or other members as appropriate.

document (section 7) or as an updated version of the document[d].

[d] In case clinical questions are changed, for example, section 4 requires updating as well as other sections if modelling priorities are affected.

3 Topic priorities identified in the Scope

This section contains all topics covered by the scope. These topics usually reflect selected clinical issues. Please indicate if an area is relevant for economic consideration and if modelling is deemed appropriate to address it.

Area[e]	Relevant?[f]	Appropriate for modelling?[g]
a) Drug therapy, including the following drug categories: • aminosalicylates • corticosteroids • immunomodulators (azathioprine, mercaptopurine, methotrexate, ciclosporin and tacrolimus)	Yes	**Induction of remission** The choice of drug therapy for use in people with ulcerative colitis (UC) is dependent on clinical severity, extent of disease and patient preference. The scope has identified severity at two levels- mild/moderate active UC and severe active UC. In addition, UC can affect any part of the colon and can be defined as proctitis, proctosigmoiditis, left sided ulcerative colitis and extensive ulcerative colitis. *Mild/moderate active UC* People with mild/moderate active UC are often treated with aminosalicylates, corticosteroids or combinations of both. These drugs are available as different preparations such as oral (tablets, capsules, granules, pellets) and rectal (foam enema, liquid enema, suppositories). In addition, various daily doses and dosing regimens are widely prescribed. The choice and sequence of drug therapy has economic implications due to first line drug costs as well as additional costs that would be incurred in the event of failure to induce remission. These additional costs could be due to initiation of further induction treatment and additional resource use (e.g. GP consultations). Relevant studies evaluating the cost effectiveness of some of the drug preparations included in the scope

[e] This corresponds to the "Key clinical issues that will be covered " section in the scope.

[f] Please state if this area is deemed relevant for considering opportunity costs and likely disinvestments. Areas might pose a decision problem directly or implicitly infomr the choice between options. Categories should include information on relevance and if of high or low priority for health economic work (see below).

[g] Health economic work comprises literature reviews, qualitative consideration of expected costs and effects and/or formal decision modelling. Decision modelling is particularly useful where it can reduce uncertainty over cost effectiveness and/or where a recommendation is likely to result in considerable changes in health and/or costs. For further details please see section 7.1 of the Guidelines Manual (2009). It may not be feasible or efficient to address every relevant decision problem by de novo work. There rationale for choosing areas for cost effectiveness modelling should be discussed in detail in Section 5.

were identified and are listed below.

Brereton et al 2010[1] (UK)): oral mesalazine - Mezavant versus Asacol. QALYs reported.

Connolly et al 2009[2] (UK): oral and topical mesalazine versus oral mesalazine. QALYs reported.

Buckland et al 2008[3] (UK): high dose (4.8g/day) versus low dose (2.4g/day) mesalazine. QALYs reported.

Mackowiak et al 2006[4] (USA): oral mesalamine versus balsalazide. QALYs not reported.

The studies have modelled different drug preparations and treatment pathways hence the results cannot be aggregated.

An original economic analysis is therefore necessary to help reduce the uncertainty regarding the relative cost effectiveness of treatment sequences for induction. This area is considered to be a high priority for modelling in this guideline.

Severe active UC

There is minimal variation in practice with regards to choice and route of drug administration for induction of remission in this population. The treatment pathway appears to be defined as thus - intravenous corticosteroids escalated to ciclosporin therapy and/or surgery if necessary. The use of infliximab in severe active UC is guided by the NICE health technological appraisal. The wording of the appraisal implies that infliximab cannot be considered as a direct alternative to ciclosporin. Sequencing of treatments for severe UC is therefore considered to be inappropriate for modelling.

Maintenance of remission

Following the induction of disease remission, patients are often placed on drug maintenance therapy. The choice of drug is dependent on factors like previous drug treatment, severity and frequency of exacerbations. This topic area is likely to impact costs as failure to maintain disease remission will result in further acute exacerbations requiring more medical or surgical

			treatment. Following treatment for exacerbations, costs of further maintenance treatment will also be incurred. Relevant economic studies were identified and are listed below. Connolly et al 2008[5] (UK): once daily 2g dosing versus twice daily 1g dosing with mesalazine, QALYs reported. Yen et al 2008[6] (USA): mesalazine versus no maintenance therapy, QALYs reported. Piodi et al 2004[7] (Italy): oral and topical 5-ASA versus oral 5-ASA, QALYs not reported. d'Albasio et al 1997[8] (Italy): oral and topical 5-ASA versus oral 5-ASA, QALYs not reported. The studies do not address all the drug comparators included in this guideline therefore this area is considered a high priority for modelling.
b)	Indications and timing of surgical management, specifically, ileoanal pouch surgery or total colectomy for acute severe colitis, recurrent relapses or continuous uncontrolled symptoms.	Yes	No relevant economic papers were identified for this topic. This area would have an economic impact if recommendations suggest changes to amount of surgery than is currently being carried out in practice. This area has been given medium priority for modelling.
c)	Monitoring of bone health.	Yes	No relevant economic papers were identified for this topic. This is a relevant area for economic analysis as the choice and frequency of monitoring would have cost implications. However, due to time constraints, it has been assigned a medium priority. It may be possible to reference other NICE guidelines.
d)	Monitoring of growth in children.	Yes	No relevant economic papers were identified for this topic. This is an area of clinical importance as some of the drugs indicated for UC can impact on growth if used for prolonged periods e.g. corticosteroids. Due to time

		constraints, this area has been assigned a low priority for modelling.
e) Information, education and support for people with ulcerative colitis and their families and carers.	No	No relevant economic papers were identified for this topic. Although this could have economic implications for the NHS, it is unlikely that there will be sufficient data to conduct a meaningful economic analysis. This area has therefore been assigned a low priority.

4 List of Modelling Questions

Insert a list of the clinical areas which have selected for de Novo modelling in the table below along with a brief description of the model using a 'PICO' format. Please include details of the type of analysis[h]

#	Areas prioritised for health economic modelling
	Area 1: Induction of remission
Population	People with mild to moderate ulcerative colitis as defined by some validated index (or author reported as being used in the clinical review).
Interventions included in analysis	Aminosalicylates, corticosteroids, and immunomodulators. If clinical evidence permits we will assess the treatment sequences in terms of extent of disease i.e. distal and extensive disease.
Type of analysis	Cost utility analysis
	Area 2: Maintenance of remission
Population	People with ulcerative colitis in remission as defined by some validated index (or author reported as being used in the clinical review). Depending on the availability of data, subgroup analysis would be conducted for disease extent and severity.
Interventions included in analysis	Aminosalicylates, corticosteroids, immunomodulators and no treatment.
Type of analysis	Cost utility analysis

[h]This section should give details of the proposed areas economic analysis will be conducted including the type of analysis (CUA, CEA, CMA etc).

5 Planned de novo modelling

This section will specify modelling work prioritised by the GDG. It will provide details on how cost effectiveness will be considered for relevant, prioritised clinical areas/decision problems. Proposed modelling work should be listed in chronological order. For each decision model, please state the proposed analytical methods, relevant references and any comments on, for example, possible diversions from the reference case.

Scope area[i] (clinical question(s)[j])	*Outline proposed analysis*
Model 1 - Drug therapy- induction of remission	**Aim**: To determine the most cost effective drug treatment sequence for induction of remission in people with mild/moderate ulcerative colitis. **Population**: People with mild to moderate active ulcerative colitis as defined by some validated index (or author reported as being used in the clinical review). Depending on the availability of data, we may conduct an additional analysis in the paediatric population. **Modelling approach**: A cost utility analysis based on a decision tree structure (example below), where the difference in costs and quality of life between treatment sequences will be driven by the difference in the numbers of patients who achieve clinical remission (outcome of the clinical review). In line with the clinical review protocol, author definitions of remission would be used. We will use different mean utility scores for active disease and remission. QALYS will be calculated by adding up time in remission and time in active disease, each weighted by the relevant utility. If clinical evidence permits we will assess the treatment sequences in terms of extent of disease i.e. distal and extensive disease. The GDG raised the issue regarding the use of different brands and doses of aminosalicylates in clinical practice. We would allow for the use of different brands and doses in the model, depending on the availability of clinical data. We may conduct a network meta-analysis, if necessary. **Perspective**: The analysis will be conducted from an NHS and personal social services perspective. **Time horizon**: A single course of treatment to induce remission in mild/moderate UC is unlikely to last more than 12 weeks. A time horizon of up to 36 weeks is deemed suitable to capture any benefits from initial treatment as well as

[i] This should be the key areas relevant for considering opportunity costs and high priority for de novo modelling, as identified in section 3.

[j] Two or more questions may be addressed by a single analysis if appropriate.

	other lines of treatment in the event of failure with first line therapy. **Interventions**: Aminosalicylates, corticosteroids, and immunomodulators. The inclusion or exclusion of treatment sequences and the number of strategies in the model will be based on the evidence from the clinical review, current clinical practice, GDG opinion and cost implications. The formulations and doses of drugs included in the model will be based on the clinical review, published sources (e.g. BNF) and GDG consent to ensure that it is in line with clinical practice. Immunomodulators (methotrexate, azathioprine and tacrolimus) will be included in the sequences if clinical evidence permits. The terminal treatment for all strategies will be surgery following inpatient admission. Different sequences of drug treatment will be modelled in order to determine the most cost effective treatment pathway. **Data sources**: All inputs for the model will be taken from published sources, unless unavailable. GDG opinion would be sought to inform any assumptions in the model. The probabilities of treatment success (remission), estimates of drug use, resource use and utility will be obtained from the clinical review conducted for this guideline. If utility data is unavailable, a systematic literature search will be conducted. Cost effectiveness models identified in the literature have used the following studies as a source for utility data – Luces et al 2007[9], Bassi et al 2005[10] and Casellas et al 2005[11]. Costs of drug treatment will be calculated from dosages and unit costs reported in the NHS drug tariff and BNF. Costs for other types of resource use such as diagnostic examinations and consultations will be taken from NHS reference costs or other UK specific sources. **Threshold and discounting**: As in the reference case, we will adopt a cost effectiveness threshold of £20,000 per QALY gained in the base case analysis. Discounting is not necessary given the short time horizon. **Sensitivity analysis**: We will conduct both deterministic and probabilistic sensitivity analysis to test the robustness of the results of the model to variations in key parameters.

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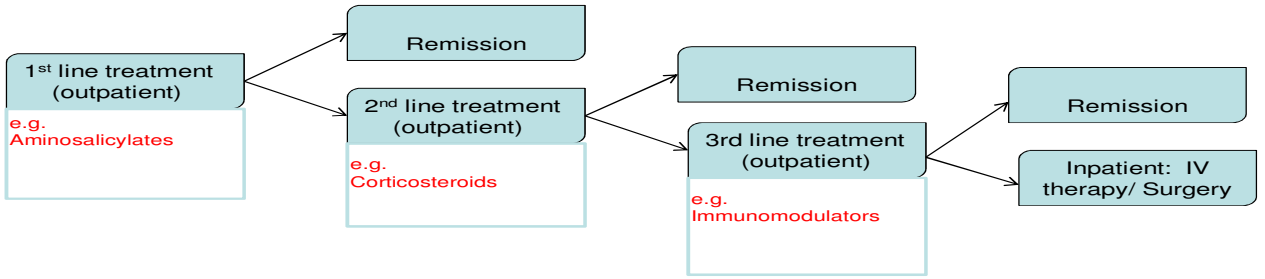
Induction of remission model



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<tr><td>Model 2 - Drug therapy- maintenance of remission</td><td>

Aim: To determine the most cost effective drug treatment for maintenance of remission in people with ulcerative colitis.

Population: People with ulcerative colitis in remission as defined by some validated index (or author reported as being used in the clinical review). Depending on the availability of data, we may conduct an additional analysis in the paediatric population.

Modelling approach: A cost utility analysis based on a Markov model structure (example below) with health states that reflect remission or active disease. Patients who have a relapse (active disease) will enter the induction of remission model (specific pathway to be determined). They will be assumed to undergo diagnostic examinations such as sigmoidoscopy and microbiological tests, the costs of which would be captured in the model.

The GDG raised the issue regarding the use of different brands and doses of aminosalicylates in clinical practice. We would allow for the use of different brands and doses in the model, depending on the availability of clinical data. The difference in costs and quality of life between treatments will be driven by the difference in the numbers of patients in either active or remission states at different periods of the model. Depending on the availability of data, subgroup analysis would be conducted for disease extent and severity. We may conduct a network meta-analysis, if

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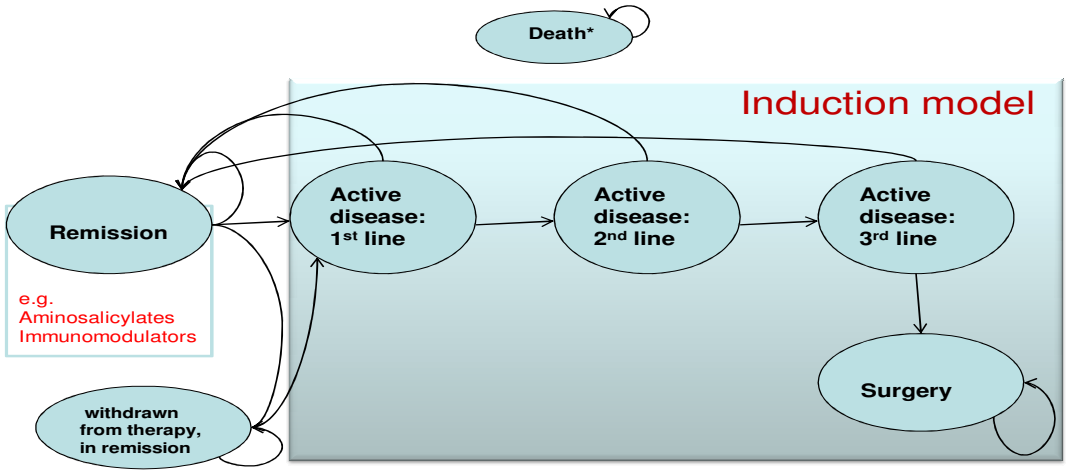
	necessary. **Perspective**: The analysis will be conducted from an NHS and personal social services perspective. **Time horizon**: Ulcerative colitis is a chronic condition with patients remaining on maintenance therapy for years. A long-term time horizon would be used so as to capture the benefits and costs associated with different treatments. In the base case, the longest follow-up period from the reviewed trials will be used, assuming there are no effects on mortality. A lifetime horizon will be assessed by sensitivity analysis. **Cycle length:** A cycle length of 3 months will be considered. This will allow the effects of disease recurrence and resulting acute treatment to be modelled. **Interventions**: Aminosalicylates, corticosteroids, immunomodulators and no treatment. We would assess oral and topical preparations of the drugs in line with the clinical evidence, current clinical practice and GDG opinion. The induction of remission treatment sequence will be fixed for all patients who go into relapse. **Data sources**: All inputs for the model will be taken from published sources, unless unavailable. GDG opinion will be sought to inform any assumptions in the model. The probabilities of relapse, estimates of drug use, resource use and utility data will be obtained from the clinical review conducted for this guideline. If utility data is unavailable, a systematic literature search will be conducted. Cost effectiveness models identified in the literature have used a study by Arseneau et al 2006[12] as a source for utility data. Costs of drug treatment will be calculated from dosages and unit costs reported in the NHS drug tariff and BNF. Costs for other types of resource use such as hospitalisations and consultations will be taken from NHS reference costs or other UK specific sources. A literature search would be conducted for long term relapse probabilities. **Threshold and discounting**: As in the reference case, we will adopt a cost effectiveness threshold of £20,000 per QALY gained in the base case analysis and all future costs and outcomes will be discounted at 3.5% per annum. **Sensitivity analysis**: We will conduct both deterministic and probabilistic sensitivity analysis to test the robustness of the results of the model to variations in key parameters.

Maintenance of remission model



* **Death state can be entered from any other health state.**

6 Clinical Guidelines technical support unit[k]

Please indicate if any of the analyses or areas suggested in section 3 require or would benefit from the Clinical Guidelines Technical Support Unit support or validation.

7 References

1 Brereton N, Bodger K, Kamm MA, et al. A cost-effectiveness analysis of MMX mesalazine compared with mesalazine in the treatment of mild-to-moderate ulcerative colitis from a UK perspective. Journal of Medical Economics 2010 Mar;13:148-61.

2 Connolly MP, Nielsen SK, Currie CJ, et al. An economic evaluation comparing concomitant oral and topical mesalazine versus oral mesalazine alone in mild-to-moderately active ulcerative colitis based on results from randomised controlled trial. Journal of Crohn's and colitis 2009;3(3):168-74.

3 Buckland A, Bodger K. The cost-utility of high dose oral mesalazine for moderately active ulcerative colitis. Aliment Pharmacol Ther 2008;28(11-12):1287-96.

4 Mackowiak J, I. A two-stage decision analysis to assess the cost of 5-aminosalicylic acid failure and the economics of balsalazide versus mesalamine in the treatment of ulcerative colitis. Manag Care Interface 2006;19(10):39-46, 56.

5 Connolly MP, Nielsen SK, Currie CJ, et al. An economic evaluation comparing once daily with twice daily mesalazine for maintaining remission based on results from a randomised controlled clinical trial. Journal of Crohn's and colitis 2009;3(1):32-7.

6 Yen EF, Kane SV, Ladabaum U. Cost-effectiveness of 5-aminosalicylic acid therapy for maintenance of remission in ulcerative colitis. Am J Gastroenterol 2008;103:3094-105.

7 Piodi LP, Ulivieri FM, Cermesoni L, et al. Long-term intermittent treatment with low-dose 5-Aminosalicylic enemas for remission maintenance in ulcerative colitis. Scand J Gastroenterol 2004;39(2):154-7.

8 d'Albasio G, Pacini F, Camarri E, et al. Combined therapy with 5-aminosalicylic acid tablets and enemas for maintaining remission in ulcerative colitis: a randomized double-blind study. Am J Gastroenterol 1997;92(7):1143-7.

[k] The Clinical guidelines technical support unit provides academic support to guidelive developers at any point in guideline development: Conduct, or support the NCC/ICG team in the development of, advanced evidence synthesis, Support complex economic analyses, conduct validation of or amendments to, existing evidence syntheses used in guideline models and address concerns from stakeholder (via consultation). Please contact the Senior technical adviser for further details

9 Luces C, Brown E, Bodger K. Satisfaction with healthcare in inflammatory bowel disease: influence of patient characteristics. Gut 2007 Apr 1;56:A145.

10 Bassi A, Bodger K. Health state utilities & willingness-to-pay in inflammatory bowel disease (IBD) - a study of feasibility & validity. Alimentary Pharmacology & Therapeutics 2005;21:197.

11 Casellas F, Arenas JI, Baudet JS, et al. Impairment of health-related quality of life in patients with inflammatory bowel disease: A Spanish multicenter study. Inflamm Bowel Dis 2005;11:488-96.

12 Arseneau KO, Sultan S, Provenzale DT, et al. Do patient preferences influence decisions on treatment for patients with steroid-refractory ulcerative colitis? Clinical Gastroenterology and Hepatology 2006 Sep;4:1135-42.

8 Addenda to economic plan

Please state any changes that have been made to the above agreed plan, together with date. If clinical questions have changed since the economic plan was signed off, include a new list with all clinical questions as part of the addenda, together with a comment where questions were inserted, deleted or altered and an explanation.

Scope area[l] (clinical question(s) [m])	*Proposed changes*	*Date agreed*

[l] This should be the key areas relevant for considering opportunity costs and high priority for de novo modelling, as identified in section 3.

[m] Two or more questions may be addressed by a single analysis if appropriate.