NCGC National Clinical Guideline Centre

Crohn's disease

Appendix C

Clinical Guideline <...>

Review protocols

10 October 2012

NICE's original guidance on Crohn's disease: management in adults, children and young people was published in October 2012; it was partially updated in May 2016 when a new recommendation on inducing remission was added. It has now undergone a further partial update published in May 2019. The full, current recommendations can be found on the NICE website.

This document preserves evidence for areas of the guideline that have not been updated in 2019. Black shading indicates text from 2012 replaced by the 2019 update.

Commissioned by the National Institute for Health and Clinical Excellence

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Review Protocols: clinical and health economic

A.1 Induction of remission

Conventional glucocorticosteroid for induction of remission in Crohn's disease	
Component	Description
Review questions	In individuals diagnosed with Crohn's disease what is the clinical and cost effectiveness of conventional glucocorticosteroid treatment for induction of remission • compared with placebo? • compared with 5-aminosalicylate (5-ASA) treatment? • *plus* 5-ASA treatment compared with placebo? • compared with azathioprine or mercaptopurine (AZA/MP)? • *plus* azathioprine or mercaptopurine (AZA/MP) compared with conventional glucocorticosteroid treatment *plus* placebo? • compared with methotrexate? • *plus* methotrexate compared with conventional glucocorticosteroid treatment *plus* placebo ?
Objectives	Assess the clinical and cost effectiveness of conventional glucocorticosteroid vs. placebo and other active drugs for induction of remission in Crohn's disease and to develop a recommended sequence strategy for drug treatment in induction of remission in Crohn's disease.
Population	Included: Adults and children with Crohn's disease Excluded: Nil
Intervention	Conventional glucocorticosteroid: any formulation of systemically available glucocorticosteroid by any oral or parenteral methods of delivery
Comparison	Placebo 5-aminosalicylates Immunosuppressives: AZA/MP; methotrexate
Outcomes	Remission as defined by: • Absence of clinical symptoms (determined by investigator) • Crohn's Disease Activity Index (CDAI) ≤ 150 at weeks 4-6 (early), weeks 10 -12 (middle) and weeks 15 or later (late) following initiation of therapy +/- fall of > 70 points in CDAI • Harvey Bradshaw Index (HBI) < 3 • Endoscopic healing • Fistula healing Adverse events Withdrawal rate/premature termination IBDQ scores Glucocorticosteroid-sparing (immunosuppressive studies)

Conventional glucocorticosteroid for induction of remission in Crohn's disease	
	In paediatric studies the main outcomes include: Remission as defined by: • Absence of clinical symptoms (determined by investigator) • Paediatric Crohn's Disease Activity Index (PCDAI) < 10 at weeks 4 - 6 (early), weeks 10 -12 (middle) and weeks 15 or later (late) following initiation of therapy • Endoscopic healing Adverse events Withdrawal rate/premature termination Growth as measured by height velocity Glucocorticosteroid-sparing (immunosuppressive studies)
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library and CINAHL. Randomised controlled trials (RCTs) will be considered. If no RCTs are found for certain outcomes such as adverse events, well-conducted cohort studies and observational studies may also be considered. Studies will be restricted to English language only. No date restriction will be applied. Databases will be searched from their date of origin.

The review strategy	Cochrane Reviews will be quality assessed and presented.
	Further meta-analyses will be conducted as appropriate.
	If there is heterogeneity the following subgroups will be analysed separately:
	• Disease severity
	  ○ Mild-moderate active disease
	  ○ Moderate-severe active disease
	  ○ Severe-fulminating active disease OR
	• Active/quiescent
	• Concurrent medications
	• Age
	• Disease location
	  ○ Small bowel
	  ○ Colon
	  ○ Small bowel and colon

Budesonide for induction of remission in Crohn's disease	
Component	Description
Review question	In individuals diagnosed with Crohn's disease what is the clinical and cost effectiveness of low dose and high dose budesonide for induction of remission compared with • placebo? • conventional glucocorticosteroid treatment? • 5-aminosalicylate (5-ASA) treatment? • azathioprine or mercaptopurine (AZA/MP)? • methotrexate?
Objectives	Evaluate the efficacy and safety of oral budesonide for the induction of remission in Crohn's disease.
Population	Included: Patients of all ages with active Crohn's disease Excluded: Nil
Intervention	Oral budesonide
Comparison	Placebo Immunosuppressives 5-ASAs Conventional glucocorticosteroid
Outcomes	Remission as defined by: • Absence of clinical symptoms (determined by investigator) • Crohn's Disease Activity Index (CDAI) ≤ 150 +/- fall of > 70 at weeks 4-6 (early), weeks 10-12 (middle) and weeks 15 or later (late) following initiation of therapy • Harvey Bradshaw Index (HBI) < 3 Adverse events
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library and CINAHL. Randomised controlled trials (RCTs) will be considered. If no RCTs are found for certain outcomes such as adverse events, well conducted cohort studies and observational studies may also be considered. Studies will be restricted to English language only. No date restriction will be applied. Databases will be searched from their date of origin.
The review strategy	Meta-analyses will be conducted where possible. If there is heterogeneity the following subgroups will be analysed separately: • Disease severity o Mild-moderate active disease o Moderate-severe active disease o Severe-fulminating active disease OR • Active/quiescent • Concurrent medications • Age • Disease location o Small bowel

Budesonide for induction of remission in Crohn's disease	
	o Colon o Small bowel and colon

5-ASA for induction of remission in Crohn's disease	
Component	Description
Review questions	In individuals diagnosed with Crohn's disease what is the clinical and cost effectiveness of 5-aminosalicylate (5-ASA) treatment for induction of remission compared with • placebo? • azathioprine or mercaptopurine (AZA/MP)? • methotrexate?
Objectives	Assess the clinical and cost effectiveness of 5-ASA, for induction of remission in Crohn's disease and to develop a recommended sequence strategy for drug treatment in induction of remission in Crohn's disease.
Population	Included: Adults and children with Crohn's disease Excluded: Nil
Intervention	5-aminosalicylates Azathioprine/mercaptopurine Methotrexate
Comparison	Placebo 5-aminosalicylates Azathioprine/mercaptopurine Methotrexate
Outcomes	Remission as defined by: • Absence of clinical symptoms (determined by investigator) • Crohn's Disease Activity Index (CDAI) ≤ 150 at weeks 4-6 (early), weeks 10-12 (middle) and weeks 15 or later (late) following initiation of therapy +/- fall of > 70 points in CDAI • Harvey Bradshaw Index (HBI) < 3 • Endoscopic healing • Fistula healing Adverse events Withdrawal rate/premature termination IBDQ scores Glucocorticosteroid-sparing (immunosuppressive studies) In paediatric studies the main outcomes include: Remission as defined by: • Absence of clinical symptoms (determined by investigator) • Paediatric Crohn's Disease Activity Index (PCDAI) ≤ 150 at weeks 4-6 (early), weeks 10-12 (middle) and weeks 15 or later (late) following initiation of therapy • Endoscopic healing Adverse events Withdrawal rate/premature termination Growth as measured by height velocity Glucocorticosteroid sparing (immunosuppressive studies)
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library and CINAHL. Randomised controlled trials (RCTs) will be considered. If no RCTs are found

5-ASA for induction of remission in Crohn's disease	
	for certain outcomes such as adverse events, well conducted cohort studies and observational studies may also be considered. Studies will be restricted to English language only No date restriction will be applied. Databases will be searched from their date of origin.
The review strategy	Cochrane Reviews will be quality assessed and presented. Further meta-analyses will be conducted as appropriate. If there is heterogeneity the following subgroups will be analysed separately: • Disease severity o Mild-moderate active disease o Moderate-severe active disease o Severe-fulminating active disease OR • Active/quiescent • Concurrent medications • Age • Disease location o Small bowel o Colon o Small bowel and colon

Immunosuppressives for induction of remission in Crohn's disease	
Component	Description
Review questions	In individuals diagnosed with Crohn's disease what is the clinical and cost effectiveness of azathioprine or mercaptopurine (AZA/MP) for induction of remission compared with • placebo? • methotrexate? In individuals diagnosed with Crohn's disease what is the incidence of serious adverse events for the following subgroups: • individuals with normal blood TPMT activity, on a standard dose of azathioprine • individuals with low blood TPMT activity, on a low dose of azathioprine • individuals whose blood TPMT is unknown, on a standard dose of azathioprine? In individuals diagnosed with Crohn's disease what is the clinical and cost effectiveness of methotrexate for induction of remission • compared with placebo? • *plus* conventional glucocorticosteroid treatment compared with placebo *plus* conventional glucocorticosteroid treatment?
Objectives	Assess the clinical and cost effectiveness of Azathioprine/mercaptopurine and methotrexate for induction of remission in Crohn's disease and to develop a recommended sequence strategy for drug treatment in induction of remission in Crohn's disease.
Population	Included: Adults and children with Crohn's disease Excluded: Nil
Intervention	Azathioprine/mercaptopurine Methotrexate
Comparison	• Placebo • *plus* conventional glucocorticosteroid treatment compared with placebo *plus* conventional glucocorticosteroid treatment?
Outcomes	Remission as defined by: • Absence of clinical symptoms (determined by investigator) • Crohn's Disease Activity Index (CDAI) ≤ 150 at weeks 4-6 (early), weeks 10-12 (middle) and weeks 15 or later (late) following initiation of therapy +/- fall of > 70 points in CDAI • Harvey Bradshaw Index (HBI) < 3 • Endoscopic healing • Fistula healing Adverse events Withdrawal rate/premature termination IBDQ scores Glucocorticosteroid-sparing (immunosuppressive studies) In paediatric studies the main outcomes include:

Immunosuppressives for induction of remission in Crohn's disease	
	Remission as defined by: • Absence of clinical symptoms (determined by investigator) • Paediatric Crohn's Disease Activity Index (PCDAI) ≤ 150 at weeks 4-6 (early), weeks 10-12 (middle) and weeks 15 or later (late) following initiation of therapy • Endoscopic healing Adverse events Withdrawal rate/premature termination Growth as measured by height velocity Glucocorticosteroid sparing (immunosuppressive studies) Serious adverse events associated with normal TPMT, low TPMT and unknown TPMT activity.
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library and CINAHL. Randomised controlled trials (RCTs) will be considered. If no RCTs are found for certain outcomes such as adverse events, well conducted cohort studies and observational studies may also be considered. Studies will be restricted to English language only No date restriction will be applied. Databases will be searched from their date of origin.
The review strategy	Cochrane Reviews will be quality assessed and presented. Further meta-analyses will be conducted as appropriate. If there is heterogeneity the following subgroups will be analysed separately: • Disease severity o Mild-moderate active disease o Moderate-severe active disease o Severe-fulminating active disease OR • Active/quiescent • Concurrent medications • Age • Disease location o Small bowel o Colon o Small bowel and colon

A.2 Maintenance of remission

Conventional glucocorticosteroid for maintenance of remission in Crohn's disease	
Component	Description
Review question	In individuals diagnosed with Crohn's disease what is the clinical and cost effectiveness of conventional glucocorticosteroid treatment for maintenance of remission for 12 months or longer • compared with placebo? • compared with 5-aminosalicylate (5-ASA) treatment? • *plus* 5-ASA treatment with conventional glucocorticosteroid *plus* placebo ? • compared with azathioprine or mercaptopurine (AZA/MP)? • *plus* azathioprine or mercaptopurine compared with conventional glucocorticosteroid treatment *plus* placebo? • methotrexate?
Objectives	Evaluate the safety and efficacy of conventional glucocorticosteroid for maintenance of remission in Crohn's disease
Population	Included: Adults and children with Crohn's disease Excluded: No exclusions
Intervention	Conventional glucocorticosteroid: any formulation of systemically available glucocorticosteroid by any oral method of delivery
Comparison	Placebo 5-aminosalicylates Azathioprine Mercaptopurine Methotrexate
Outcomes	Maintenance of remission as defined by: • Crohn's Disease Activity Index (CDAI) ≤ 150 after 12 months • Paediatric Crohn's Disease Activity Index (PCDAI) < 10 • Harvey Bradshaw Index (HBI) < 3 • Other validated index • Mucosal healing Relapse of disease as defined by: • Crohn's Disease Activity Index (CDAI) > 150 • Paediatric Crohn's Disease Activity Index (PCDAI) ≥ 10 • Harvey Bradshaw Index (HBI) ≥ 3 • Other validated index • Mucosal healing • Symptomatic recurrence Adverse events Cancer of the colon Withdrawal due to adverse events
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library and CINAHL. Randomised controlled trials (RCTs) will be considered. If no RCTs are found for certain outcomes such as adverse events, well conducted cohort studies and

Conventional glucocorticosteroid for maintenance of remission in Crohn's disease	
	observational studies may also be considered. Studies will be restricted to English language only. No date restriction will be applied. Databases will be searched from their date of origin.
The review strategy	Meta-analyses will be conducted where possible. If there is heterogeneity the following subgroups will be analysed separately: • Disease severity o Mild-moderate active disease o Moderate-severe active disease o Severe-fulminating active disease OR • Active/quiescent • Concurrent medications • Age • Disease location o Small bowel o Colon o Small bowel and colon As this is an unstable condition, cross-over studies will be excluded.

5-Aminosalycilates for maintenance of remission in Crohn's disease	
Component	Description
Review question	In individuals diagnosed with Crohn's disease what is the clinical and cost effectiveness of 5-aminosalicylate (5-ASA) treatment for maintenance of remission compared with • placebo? • azathioprine or mercaptopurine (AZA/MP)? • methotrexate?
Objectives	Evaluate the efficacy and safety of oral 5-aminosalicylates for the maintenance of remission in Crohn's disease.
Population	Included: Patients of all ages with active Crohn's disease
Intervention	Oral 5-aminosalicylates
Comparison	Placebo Azathioprine Mercaptopurine Methotrexate
Outcomes	Maintenance of remission as defined by: • Crohn's Disease Activity Index (CDAI) ≤ 150 after 12 months • Paediatric Crohn's Disease Activity Index (PCDAI) < 10 • Harvey Bradshaw Index (HBI) < 3 • Other validated index • Mucosal healing Relapse of disease as defined by: • Crohn's Disease Activity Index (CDAI) > 150 • Paediatric Crohn's Disease Activity Index (PCDAI) ≥ 10 • Harvey Bradshaw Index (HBI) ≥ 3 • Other validated index • Mucosal healing • Symptomatic recurrence Adverse events Cancer of the colon Withdrawal due to adverse events
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library and CINAHL. Randomised controlled trials (RCTs) will be considered. If no RCTs are found for certain outcomes such as adverse events, well conducted cohort studies and observational studies may also be considered. Studies will be restricted to English language only. No date restriction will be applied. Databases will be searched from their date of origin.

The review strategy	Meta-analyses will be conducted where possible.
	If there is heterogeneity the following subgroups will be analysed separately:
	• Disease severity
	  ○ Mild-moderate active disease
	  ○ Moderate-severe active disease
	  ○ Severe-fulminating active disease OR
	• Active/quiescent
	• Concurrent medications

5-Aminosalycilates for maintenance of remission in Crohn's disease	

	• Age
	• Disease location
	  ○ Small bowel
	  ○ Colon
	  ○ Small bowel and colon
	
	As this is an unstable condition, cross-over studies will be excluded.

Budesonide for maintenance of remission in Crohn's disease	
Component	Description
Review question	In individuals diagnosed with Crohn's disease what is the clinical and cost effectiveness of low dose and high dose budesonide for maintenance of remission for 12 months or longer compared with • placebo? • conventional glucocorticosteroid treatment? • 5-aminosalicylate (5-ASA) treatment? • azathioprine or mercaptopurine (AZA/MP)? • methotrexate?
Objectives	Evaluate the safety and efficacy of budesonide for maintenance of remission in Crohn's disease.
Population	Included: Adults and children with Crohn's disease Excluded: No exclusions
Intervention	Oral budesonide
Comparison	Placebo Conventional glucocorticosteroid 5-aminosalicylate Azathioprine Mercaptopurine Methotrexate
Outcomes	Maintenance of remission as defined by: • Crohn's Disease Activity Index (CDAI) ≤ 150 after twelve months • Paediatric Crohn's Disease Activity Index (PCDAI) < 10 • Harvey Bradshaw Index (HBI) < 3 • Other validated index • Mucosal healing Relapse of disease as defined by: • Crohn's Disease Activity Index (CDAI) > 150 • Paediatric Crohn's Disease Activity Index (PCDAI) ≥ 10 • Harvey Bradshaw Index (HBI) ≥ 3 • Other validated index • Mucosal healing • Symptomatic recurrence Adverse events Cancer of the colon Withdrawal due to adverse events
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library and CINAHL. Randomised controlled trials (RCTs) will be considered. If no RCTs are found for certain outcomes such as adverse events, well conducted cohort studies and observational studies may also be considered. Studies will be restricted to English language only. No date restriction will be applied. Databases will be searched from their date of origin.
The review strategy	Meta-analyses will be conducted where possible.

Budesonide for maintenance of remission in Crohn's disease	

	If there is heterogeneity the following subgroups will be analysed separately:
	• Disease severity
	  ○ Mild-moderate active disease
	  ○ Moderate-severe active disease
	  ○ Severe-fulminating active disease OR
	• Active/quiescent
	• Concurrent medications
	• Age
	• Disease location
	  ○ Small bowel
	  ○ Colon
	  ○ Small bowel and colon
	
	As this is an unstable condition, cross-over studies will be excluded.

Azathioprine/mercaptopurine for maintenance of remission in Crohn's disease	
Component	Description
Review question	In individuals diagnosed with Crohn's disease what is the clinical and cost effectiveness of azathioprine or mercaptopurine (AZA/MP) for maintenance of remission for 12 months or longer • compared with placebo? • compared with methotrexate? • *plus* conventional glucocorticosteroid or 5-ASA treatment compared with placebo *plus* conventional glucocorticosteroid or 5-ASA treatment?
Objectives	Evaluate the efficacy and safety of oral azathioprine/mercaptopurine for the maintenance of remission in Crohn's disease.
Population	Included: Patients of all ages with active Crohn's disease Excluded: Nil
Intervention	Oral azathioprine/mercaptopurine
Comparison	Placebo Methotrexate
Outcomes	Maintenance of remission as defined by: • Crohn's Disease Activity Index (CDAI) ≤ 150 after twelve months • Paediatric Crohn's Disease Activity Index (PCDAI) < 10 • Harvey Bradshaw Index (HBI) < 3 • Other validated index • Mucosal healing Relapse of disease as defined by: • Crohn's Disease Activity Index (CDAI) > 150 • Paediatric Crohn's Disease Activity Index (PCDAI) ≥ 10 • Harvey Bradshaw Index (HBI) ≥ 3 • Other validated index • Mucosal healing • Symptomatic recurrence Adverse events Cancer of the colon Withdrawal due to adverse events
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library and CINAHL. Randomised controlled trials (RCTs) will be considered. If no RCTs are found for certain outcomes such as adverse events, well conducted cohort studies and observational studies may also be considered. Studies will be restricted to English language only. No date restriction will be applied. Databases will be searched from their date of origin.

The review strategy	Meta-analyses will be conducted where possible.
	If there is heterogeneity the following subgroups will be analysed separately:
	• Disease severity
	  ○ Mild-moderate active disease
	  ○ Moderate-severe active disease
	  ○ Severe-fulminating active disease OR

Azathioprine/mercaptopurine for maintenance of remission in Crohn's disease	

	• Active/quiescent
	• Concurrent medications
	• Age
	• Disease location
	  ○ Small bowel
	  ○ Colon
	  ○ Small bowel and colon
	As this is an unstable condition, cross-over studies will be excluded.

Methotrexate for maintenance of remission in Crohn's disease	
Component	Description
Review question	In individuals diagnosed with Crohn's disease what is the clinical and cost effectiveness of methotrexate for maintenance of remission for 12 months or longer • compared with placebo? • *plus* conventional glucocorticosteroid treatment compared with placebo plus conventional glucocorticosteroid treatment?
Objectives	Evaluate the efficacy and safety of oral methotrexate for the maintenance of remission in Crohn's disease.
Population	Included: Patients of all ages with active Crohn's disease Excluded: Nil
Intervention	Oral methotrexate
Comparison	Placebo
Outcomes	Maintenance of remission as defined by: • Crohn's Disease Activity Index (CDAI) ≤ 150 after 12 months • Paediatric Crohn's Disease Activity Index (PCDAI) < 10 • Harvey Bradshaw Index (HBI) < 3 • Other validated index • Mucosal healing Relapse of disease as defined by: • Crohn's Disease Activity Index (CDAI) > 150 • Paediatric Crohn's Disease Activity Index (PCDAI) ≥ 10 • Harvey Bradshaw Index (HBI) ≥ 3 • Other validated index • Mucosal healing • Symptomatic recurrence Adverse events Cancer of the colon Withdrawal due to adverse events
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, and CINAHL. Randomised controlled trials (RCTs) will be considered. If no RCTs are found for certain outcomes such as adverse events, well conducted cohort studies and observational studies may also be considered. Studies will be restricted to English language only. No date restriction will be applied. Databases will be searched from their date of origin.

The review strategy	Meta-analyses will be conducted where possible.
	If there is heterogeneity the following subgroups will be analysed separately:
	• Disease severity
	  ○ Mild-moderate active disease
	  ○ Moderate-severe active disease
	  ○ Severe-fulminating active disease OR
	• Active/quiescent
	• Concurrent medications

Methotrexate for maintenance of remission in Crohn's disease	

	• Age
	• Disease location
	  ○ Small bowel
	  ○ Colon
	  ○ Small bowel and colon
	
	As this is an unstable condition, cross-over studies will be excluded.

A.2.1 Health economic review protocol

Review question	All induction and maintenance questions – health economic evidence
Objectives	To identify economic studies relevant to the review questions set out above.
Criteria	Populations, interventions and comparators as specified in the individual review protocols above. Must be a relevant economic study design (cost-utility analysis, cost-benefit analysis, cost-effectiveness analysis, cost-consequence analysis, comparative cost analysis).
Search strategy	An economic study search was undertaken using population specific terms and an economic study filter – see Appendix D.
Review strategy	Each study is assessed using the NICE economic evaluation checklist – NICE (2009) Guidelines Manual, Appendix H. **Inclusion/exclusion criteria** • If a study is rated as both 'Directly applicable' and 'Minor limitations' (using the NICE economic evaluation checklist) then it should be included in the guideline. An evidence table should be completed and it should be included in the economic profile. • If a study is rated as either 'Not applicable' or 'Very serious limitations' then it should be excluded from the guideline. It should not be included in the economic profile and there is no need to include an evidence table. • If a study is rated as 'Partially applicable' and/or 'Potentially serious limitations' then there is discretion over whether it should be included. The health economist should make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the GDG if required. The ultimate aim being to include studies that are helpful for decision making in the context of the guideline and current NHS setting. Where exclusions occur on this basis, this should be noted in the relevant section of the guideline with references. Also exclude: • unpublished reports unless submitted as part of a call for evidence • abstract-only studies • letters • editorials • reviews of economic evaluations • foreign language articles **Where there is discretion** The health economist should be guided by the following hierarchies. *Setting:* • UK NHS • OECD countries with predominantly public health insurance systems (e.g. France, Germany, Sweden) • OECD countries with predominantly private health insurance systems (e.g. USA, Switzerland) • Non-OECD settings (always 'Not applicable') *Economic study type:* • Cost-utility analysis • Other type of full economic evaluation (cost-benefit analysis, cost-effectiveness analysis, cost-consequence analysis) • Comparative cost analysis • Non-comparative cost analyses including cost of illness studies (always 'Not applicable') *Year of analysis:* • The more recent the study, the more applicable it is *Quality and relevance of effectiveness data used in the economic analysis:*

Review question	All induction and maintenance questions – health economic evidence
	• The more closely the effectiveness data used in the economic analysis matches with the studies included for the clinical review the more useful the analysis will be to decision making for the guideline.

A.3 Post-surgical maintenance

Post-surgical maintenance of remission in Crohn's disease	
	Please note that evidence on treatments for post-surgical maintenance of remission in Crohn's disease was reviewed in 2019. The updated evidence review and full current recommendations can be found on the NICE website.
	• budesonide • 5-aminosalicylate treatment • azathioprine • mercaptopurine • methotrexate • metronidazole or • combinations thereof • or nutritional treatment compared with • placebo • no treatment?
Objectives	Evaluate the efficacy and safety of post-surgical treatment for maintenance of remission of Crohn's disease for 12 months or longer.
Population	Included: Patients of all ages with active Crohn's disease.
Intervention	Post-surgical medical and/or nutritional treatment: Conventional glucocorticosteroid treatment Budesonide 5-aminosalicylates Azathioprine/mercaptopurine Methotrexate Metronidazole Enteral nutrition
Comparison	No treatment Other active agent
Outcomes	Maintenance of remission as defined by: • Absence of clinical symptoms (determined by investigator) • Crohn's Disease Activity Index (CDAI) ≤ 150 at weeks 4-6 (early), weeks 10-12 (middle) and weeks 15 or later (late) following initiation of therapy • Harvey Bradshaw Index (HBI) < 3 • Endoscopic evaluation (Rutgeerts score) Relapse Relapse + withdrawals Serious adverse events Withdrawal due to adverse events Quality of life
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library and CINAHL. Randomised controlled trials (RCTs) will be considered. If no RCTs are found for certain outcomes such as adverse events, well conducted cohort studies and observational studies may also be considered.

Post-surgical maintenance of remission in Crohn's disease	
	Studies will be restricted to English language only. No date restriction will be applied. Databases will be searched from their date of origin.
The review strategy	Meta-analyses will be conducted where possible. If there is heterogeneity the following subgroups will be analysed separately: • Disease severity o Mild-moderate active disease o Moderate-severe active disease o Severe-fulminating active disease OR • Active/quiescent • Concurrent medications • Age • Disease location o Small bowel o Colon o Small bowel and colon

A.4 Enteral nutrition

Enteral nutritional for induction of remission in Crohn's disease	
Component	Description
Review question	In adults and children diagnosed with Crohn's disease what is the clinical and cost effectiveness of enteral nutrition (elemental, semi-elemental and polymeric) as a sole source of nutrition for induction of remission compared with • usual diet • conventional glucocorticosteroid treatment • budesonide • a combination of conventional glucocorticosteroid treatment plus 5-ASA treatment • a combination of conventional glucocorticosteroid treatment plus azathioprine or mercaptopurine • a combination of conventional glucocorticosteroid treatment plus methotrexate In adults and children diagnosed with Crohn's disease what is the clinical and cost effectiveness for induction of remission of enteral nutrition (elemental, semi-elemental and polymeric) *plus* medical therapy versus usual diet.
Objectives	Evaluate the efficacy and safety of enteral nutritional therapy for the induction of remission in Crohn's disease.
Population	Included: Patients of all ages with active Crohn's disease Excluded: Nil
Intervention	Enteral nutritional therapy including elemental (amino-acid based), semi-elemental (oligopeptide) and polymeric (whole protein) diets alone or in addition to a glucocorticosteroid.
Comparison	Placebo Other active agent
Outcomes	Remission as defined by: • Absence of clinical symptoms (determined by investigator) • Crohn's Disease Activity Index (CDAI) ≤ 150 at weeks 4 - 6 (early), weeks 10 -12 (middle) and weeks 15 or later (late) following initiation of therapy +/- fall of > 70 CDAI • Paediatric Crohn's Disease Activity Index (PCDAI < 10) Fistula healing • Harvey Bradshaw Index (HBI) < 3 • Adverse events
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library and CINAHL. Randomised controlled trials (RCTs) will be considered. If no RCTs are found for certain outcomes such as adverse events, well conducted cohort studies and observational studies may also be considered. Studies will be restricted to English language only. No date restriction will be applied. Databases will be searched from their date of origin.
The review strategy	Meta-analyses will be conducted where possible. If there is heterogeneity the following subgroups will be analysed separately:

Enteral nutritional for induction of remission in Crohn's disease	
	• Disease severity o Mild-moderate active disease o Moderate-severe active disease o Severe-fulminating active disease OR • Active/quiescent • Concurrent medications • Age • Disease location o Small bowel o Colon o Small bowel and colon

Enteral nutritional for maintenance of remission in Crohn's disease	
Component	Description
Review question	1. What is the clinical and cost effectiveness of enteral nutrition (elemental, semi-elemental and polymeric) for maintenance of remission compared with • usual diet • medical treatment • conventional glucocorticosteroid treatment • budesonide • 5-ASA treatment • azathioprine or mercaptopurine • methotrexate. 2. What is the clinical and cost effectiveness of enteral nutrition (elemental, semi-elemental and polymeric) for maintenance of remission in combination with • conventional glucocorticosteroid treatment • budesonide • 5-ASA treatment • azathioprine or mercaptopurine • methotrexate? compared with any of the above?
Objectives	Evaluate the efficacy and safety of enteral nutritional therapy for the maintenance of remission in Crohn's disease.
Population	Included: Patients of all ages with active Crohn's disease Excluded: Nil
Intervention	Enteral nutritional therapy including elemental (amino-acid based), semi-elemental (oligopeptide) and polymeric (whole protein) diets alone or as an adjunct to other active agent.
Comparison	Placebo Other active agent (including glucocorticosteroid, 5-ASA or immunosuppressives) In combination with other active agent (including glucocorticosteroid, 5-ASA or immunosuppressives)
Outcomes	Maintenance of remission as defined by: • Crohn's Disease Activity Index (CDAI) ≤ 150 after 12 months • Paediatric Crohn's Disease Activity Index (PCDAI) < 10 • Harvey Bradshaw Index (HBI) < 3 • Other validated index • Mucosal healing • Symptomatic recurrence Adverse events Withdrawal due to adverse events
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library and CINAHL. Randomised controlled trials (RCTs) will be considered. If no RCTs are found for certain outcomes such as adverse events, well conducted cohort studies

Enteral nutritional for maintenance of remission in Crohn's disease	
	and observational studies may also be considered. Studies will be restricted to English language only. No date restriction will be applied. Databases will be searched from their date of origin.

The review strategy	Meta-analyses will be conducted where possible.
	If there is heterogeneity the following subgroups will be analysed separately:
	• Disease severity
	  ○ Mild-moderate active disease
	  ○ Moderate-severe active disease
	  ○ Severe-fulminating active disease OR
	• Active/quiescent
	• Concurrent medications
	• Age
	• Disease location
	  ○ Small bowel
	  ○ Colon
	  ○ Small bowel and colon

A.5 Surgery

Surgical resection limited to the distal ileum in Crohn's disease	
Component	Description
Review question	In individuals diagnosed with Crohn's disease limited to the distal ileum, what is the clinical and cost-effectiveness of surgical resection for induction and maintenance of remission compared with medical or nutritional treatment?
Objectives	Evaluate the efficacy and safety of surgical resection of the distal ileum compared with medical and nutritional treatment
Population	Included: Patients of all ages with active Crohn's disease
Intervention	Surgical resection of the distal ileum
Comparison	Medical treatment for Crohn's disease Nutritional treatment for Crohn's disease
Outcomes	Adults Remission as defined by: • CDAI ≤ 150 +/- fall of > 70 • HBI < 3 • Endoscopic healing • Fistula healing • Any valid index IBDQ Premature termination of study Adverse events including: o Early (up to 30 days) – Infection local wound or intra-abdominal abscess, other – Anastomotic dehiscence – Length of stay is a surrogate, (inpatient v outpatient), ITU – Cardiovascular (MI, thromboembolism) – Intestinal obstruction – Haemorrhage o Late – Wound herniation – Obstruction – Anaemia – B12 – Bile salt malabsorption Children Remission as defined by: • PCDAI ≤ 10 +/- fall of > 12.5 • IMPACT • Growth (height velocity)
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library and CINAHL. Randomised controlled trials (RCTs) will be considered. If no RCTs are found, well conducted cohort studies and observational studies may also be

Surgical resection limited to the distal ileum in Crohn's disease	
	considered. Studies will be restricted to English language only. No date restriction will be applied. Databases will be searched from their date of origin.
The review strategy	Meta-analyses will be conducted where possible. If there is heterogeneity the following subgroups will be analysed separately: • Disease severity o Mild-moderate active disease o Moderate-severe active disease o Severe-fulminating active disease OR • Active/quiescent • Age • Medication/nutritional therapy • Length of follow up

Treatment of stricture in Crohn's disease	
Component	Description
Review question	In individuals diagnosed with Crohn's disease what is the clinical and cost effectiveness of surgical treatment of stricture compared with • balloon dilation • balloon dilation plus intralesional glucocorticosteroid injections, conservative management?
Objectives	Evaluate the efficacy and safety of surgical treatment of stricture compared with balloon dilation or balloon dilation and glucocorticosteroid injections or conservative treatment
Population	Included: Patients of all ages with active Crohn's disease
Intervention	Surgical treatment of stricture by resection or strictureplasty
Comparison	Balloon dilation Balloon dilation plus glucocorticosteroid injections Conservative treatment
Outcomes	Incidence of perioperative complications Incidence of major complications Recurrence rate of symptomatic strictures requiring repeat procedure
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library and CINAHL. Randomised controlled trials (RCTs) will be considered. If no RCTs are found, well conducted cohort studies and observational studies will also be considered. Studies will be restricted to English language only. No date restriction will be applied. Databases will be searched from their date of origin.
The review strategy	Meta-analyses will be conducted where possible. If there is heterogeneity the following subgroups will be analysed separately: • Disease severity o Mild-moderate active disease o Moderate-severe active disease o Severe-fulminating active disease OR • Active/quiescent • Concurrent medications • Age • Disease location o Small bowel o Colon o Small bowel and colon

A.6 Monitoring

A.6.1 Monitoring for osteopenia

Monitoring for osteopenia	
Component	Description
Review question	In children diagnosed with Crohn's disease what is the risk of fracture?
Objectives	Evaluate the effect of monitoring with DEXA for osteopenia in patients with Crohn's disease
Population	Included: Children diagnosed with Crohn's disease
Intervention	None
Comparison	No monitoring
Outcomes	Fracture rates Change in bone density Hospitalisation for fracture
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, and CINAHL. The search will include observational data. Studies will be restricted to English language only. No date restriction will be applied. Databases will be searched from their date of origin.
The review strategy	Risk tables will be compiled

A.6.2 Monitoring for early relapse

Monitoring for early relapse	
Component	Description
Review question	Does predicting early relapse through monitoring: • Unintended weight loss • CRP • ESR • MRI • Calprotectin • Colonoscopy or capsule endoscopy • Growth in children compared with standard care, improve patient outcomes (quality of life, future surgery, hospitalization)?
Objectives	Evaluate the effect of monitoring for early relapse in patients with Crohn's disease
Population	Included: Patients of all ages with active Crohn's disease
Intervention	Monitoring for: • Unintended weight loss • CRP • ESR • MRI • Calprotectin • Colonoscopy or capsule endoscopy • Growth in children
Comparison	Standard care
Outcomes	Adult disease relapse as measured by • Crohn's Disease Activity Index > 150 +/- rise 70 • Harvey Bradshaw Index > 3 • Endoscopic relapse by Rutgeerts score • Recurrence of fistula • Hospitalisation • Surgery IBDQ score Adverse events Colorectal cancer Mortality Disease relapse in children and young people including: • PCDAI ≥ 10 • Growth as measured by height velocity or high velocity standard deviation score • IMPACT Questionnaire
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library and CINAHL. The search will include RCTs, systematic reviews and observational data. Studies will be restricted to English language only. No date restriction will be applied. Databases will be searched from their date of origin.

Monitoring for early relapse	
The review strategy	Meta-analyses will be conducted where possible. If there is heterogeneity the following subgroups will be analysed separately: • Medications, particularly glucocorticosteroid use • Age • Gender

A.7 Patient information and support

Component	Description
Review questions	What are the primary informational needs of adults with Crohn's disease in the UK? What are the primary informational needs of children and young people with Crohn's disease in the UK?
Objectives	To consider the primary informational needs of people with Crohn's disease in the UK
Population	Included: Patients of all ages with active Crohn's disease
Outcomes	• The information people with Crohn's disease wanted or found useful • If there are specific information requirements for people with Crohn's disease • If information received changed the perception of the disease
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library and CINAHL. The search will include all study designs including qualitative data. Studies will be restricted to English language only. No date restriction will be applied. Databases will be searched from their date of origin.
The review strategy	Appraisal of methodological quality. The methodological quality of each study will be assessed using NICE checklists. Data synthesis of data. Qualitative reporting will be conducted.