South African National Department of Health
Brief Report of Rapid Review
Component: Tertiary

TITLE: Evaluation of adalimumab and infliximab (biological medicines targeting Tumour Necrosis Factor Alpha) in the management of patients with Luminal Crohn's Disease (PICO 2), who are refractory to conventional therapies.

UPDATE: Revision of medicine review document for TNF inhibitors in patients with Crohn's Disease (CD) tabled at the National Essential Medicines List Committee (NEMLC) meeting held on the 30th November 2023. Medicine review revised to address proposed changes by the NEMLC and reformatted into two different PICOs with corresponding documents. Proposed plans for each PICO were circulated electronically to NEMLC chairs in February 2023. PICO 1 – Fistulising CD was presented at the NEMLC meeting held on the 14th March 2024 (see Medicine Review – PICO 1 – Fistulising CD). This document relates to PICO 2 – Luminal / Non-Specific CD.

Date: May 2024

Medicine (ATC): Tumour Necrosis Factor Alpha inhibitors (anti-TNFs): Adalimumab (L04AB04), Infliximab (L04AB02)
Indication (ICD10): Luminal / Non-Specific Crohn's Disease (K50.9)
Patient population: Patients of all ages with Luminal / Non-Specific Crohn's disease who are refractory to conventional therapies.
Prevalence: There is a paucity of South African data, last study in 1984 reported an incidence of 2.6/100 000 per year(1). Based on expert opinion – an estimated 36 patients (refractory to conventional therapy) with luminal CD nationally.
Level of Care: Tertiary and Quaternary Hospital Level
Prescriber level: Gastroenterologist
Current Standard of Care/ Comparator(s): Conventional therapy: methotrexate, azathioprine, 6-mercaptopurine

Key findings

- Conventional therapies for Crohn's Disease (CD) listed on the Essential Medicines List (EML) include methotrexate, azathioprine, 6-mercaptopurine with acute flares treated with corticosteroids. A motivation was received to include Tumour Necrosis Factor Alpha (anti-TNFs) Inhibitors, specifically infliximab and adalimumab, onto the EML for individuals who are refractory or intolerant to conventional therapies.
- We conducted a review of the literature to explore the safety and efficacy of the addition of adalimumab or infliximab to standard of care compared to standard of care alone for patients with luminal CD who are refractory to conventional therapy.
- We extracted data from 15 publications (6 SRs for adult population, 2 SRs for paediatric population, and 7 guidelines), representing different comparisons and outcomes relevant to our review.

- **Comparison 1: Adalimumab vs Standard of care in adults**
  - Number of participants with maintained clinical remission
    Fewer participants with failure to maintain clinical remission (at 52-56 weeks) in the adalimumab group compared to placebo (RR: 0.70 in favour of adalimumab, 95% CI [0.64 to 0.77], P<0.0001, **NNT 4** 95% CI [3 to 5], 3 RCTs, n=683) – high certainty of evidence.
  - Number of participants with induced clinical remission (CDAI **< 150**)
    Among TNF inhibitor naïve patients, a lower proportion of those receiving adalimumab failed to achieve clinical remission at 4 weeks compared to placebo (RR= 0.76, 95% CI [0.60 to 0.96], I^2= 82%, **NNT 5** 95% CI [4 to 8], 2 RCTs, n=494; P=0.02 – moderate quality evidence (JADAD score – downgraded one for inconsistency).
  - Number of participants with maintained clinical response
    A lower percentage of adalimumab receiving participants failed to maintain clinical response at 52 to 56 weeks as compared to placebo (RR=0.68 in favour of adalimumab, 95% CI [0.62 to 0.75], i^2=0%, **NNT 4** 95% CI [3 to 5], P<0.00001, 6 RCTs, n=733) – moderate certainty (downgraded 1 for unclear risk of bias).
  - Number of participants with induced clinical response (= ≥100-point CDAI decrease from baseline)
    Lower proportion of adalimumab receiving participants who failed to achieve clinical response at 4 weeks compared to placebo (RR= 0.77 in favour of adalimumab, 95% CI [0.69 to 0.86], I^2= 35% - moderate heterogeneity, **NNT 6**, 95% CI [4 to 9], 3 RCTs, n=714; P<0.0001) – high certainty of evidence.
  - Number of participants with maintained endoscopic improvement

Fewer adalimumab receiving participants failed to maintain endoscopic remission or response at 52 weeks as compared to placebo (Endoscopic remission: RR=0.74 in favour of adalimumab, 95% CI [0.63 to 0.87], i^2=NA, **NNT 4** 95% CI [3 to 8], P=0.0002, 1 RCT, n=129 – moderate certainty of evidence, downgraded by one level due to sparse data; Endoscopic response: RR 0.76 in favour of adalimumab, 95% CI [0.66 to 0.88], i^2=NA, **NNT 5** 95% CI [3 to 8], P=0.0001, 1 RCT, n=129 – GRADE not reported).

- Safety – Maintenance Therapy
  There is probably no difference in adverse events at 52 to 56 week follow-up between adalimumab and placebo (RR=1.01 95% CI [0.94 to 1.09], P=0.72, 4 RCTs, n=1012 – high certainty of evidence. However patients on adalimumab maintenance therapy had a lower percentage of serious adverse events (events included infectious complications including tuberculosis, abscess formation and wound infections, multiple sclerosis, pulmonary embolism) compared to placebo (RR=0.56 in favour of adalimumab, 95% CI [0.39 to 0.80], P=0.002, 4 RCTs, n=1012 – moderate certainty of evidence.
- Safety – Induction Therapy
  No difference found in adverse events between adalimumab and placebo at 4 weeks (RR=0.90, 95% CI [0.74 to 1.09], P=0.28 – not significant, 3 RCTs, n=531 – moderate certainty of evidence (GRADE from Abbass 2019, downgraded by 1 one level due to serious inconsistency (i^2 = 53%). No difference found in serious adverse events between groups (RR=0.44, 95% CI [0.17 to 1.15], P=0.09 – not significant, 3 RCTs, n=531 – low certainty of evidence (GRADE from Abbass 2019, downgraded by 2 levels due to very serious imprecision (19 events).

Comparison 2: Infliximab vs Standard of Care in adults

- Number of participants with maintained clinical remission
  More participants in the placebo groups with clinical relapse (at 30-32 weeks – CDAI > 150) compared to infliximab (RR=0.73 in favour of infliximab, 95% CI [0.63 to 0.84], i^2= 0%, P<0.00001, **NNT 6** 95% CI [4 to 10], 2 RCTs, n=408) – moderate certainty of evidence (downgraded one level due to concerns about risk of randomisation, selective reporting and other bias).
- Number of participants with achieved clinical remission
  More participants in the infliximab 5-10mg/kg group who achieved clinical remission at week 4 compared to placebo (RR=4.55 in favour of infliximab, 95% CI [1.53 to 13.50], i^2= NA, P=0.006, **NNT 3**, 95% CI [2 to 5], 1 RCT, n=80) – low certainty of evidence (downgraded one level due to serious concerns with risk of bias (selective reporting and unclear randomisation), and one level due to serious concerns with imprecision due to low event numbers).
- Number of participants with maintained clinical response (as defined by the study)
  More participants had a loss of clinical response in the placebo group compared to the infliximab group (RR: 0.59 95% CI [0.37 to 0.96], P=0.03, **NNT 4**, 95% CI [3 to 26], 1 RCT, i^2=NA, n=73) – very low certainty of evidence (downgraded two levels due to serious imprecision from very low participant and event numbers, downgrade one level due to concerns about risk of blinding, and selective reporting).
- Number of participants with achieved clinical response (as defined by the study)
  More participants in the infliximab 5-10mg/kg group who achieved clinical response at week 4 (reduction of CDAI score > 70 from baseline) compared to placebo (RR=4.09 in favour of infliximab, 95% CI [1.63 to 10.25], i^2= NA, P=0.003, **NNT 3**, 95% CI [2 to 4], 1 RCT, n=80) – low certainty of evidence (downgraded one level due to serious concerns with risk of bias (selective reporting and unclear randomisation), and one level due to serious concerns with imprecision due to low event numbers).
- Number of participants with maintained endoscopic improvement
  More participants had a loss of endoscopic response in the purine analogue only group compared to the infliximab and purine analogue combination group (RR: 0.38 95% CI [0.25 to 0.59], P<0.0001, **NNT 3**, 95% CI [2 to 4], 1 RCT, n=73, i^2=NA) – (GRADE not evaluated in Gordon 2024).
- Safety - Maintenance therapy
  Fewer withdrawals due to adverse events at 48 weeks in infliximab and purine analogue combination group (4 withdrawals) compared to the purine analogue alone group (8 withdrawals) however the CI did cross the null (RR 0.47 95% CI [0.15 to 1.49], P=0.20, 1 trial, n=115) – very low certainty of evidence (downgraded twice due to serious imprecision from very low participant and event numbers and once due to concerns about risk of bias for randomisation, blinding, attrition and selective reporting). More serious adverse events (at 48 weeks – 2 years) in infliximab and purine analogue combination group (12 events) compared to the purine analogue alone group (10 events) however the CI did cross the null (RR 1.19 95% CI [0.54 to 2.64], P=0.80, i^2=0%, 2 trials, n=257) – very low certainty of evidence (downgraded twice due to serious imprecision from very low participant and event numbers and once due to concerns about risk of bias for randomisation, blinding, attrition and selective reporting.
- Safety - Induction therapy
  Fewer adverse events in infliximab and purine analogue combination group (82 events) compared to the purine analogue alone group (97 events) however the CI did cross the null (RR 0.88 in favour of combination group 95% CI [0.65 to 1.20], P=0.42, 2 RCTs) – GRADE not reported.

- **Adalimumab in paediatric patients with luminal CD**
  - Maintenance of remission

    Fifty-seven percent of participants on adalimumab maintained remission (95% CI [55% to 79%], i^2=92.1% - high heterogeneity (severity at baseline, infliximab exposure, P=0.000). Proportion of participants with maintained remission significantly higher in infliximab naïve subgroup (0.75, 95% CI [0.65 to 0.86], compared to infliximab exposed subgroup.
  - Induction of remission

    Fifty-nine percent of participants on adalimumab achieved induction of remission (95% CI [25 to 61%], i^2=98.6% - high heterogeneity (severity at baseline, infliximab exposure, P=0.000). Proportion of participants with induced remission significantly higher in the infliximab naïve subgroup (0.94, 95% CI [0.90 to 0.98]), compared to infliximab exposed group.
  - Maintenance of response

    Sixty-three percent of participants on adalimumab achieved induction of remission (95% CI [30 to 87%], i2=94.4% - high heterogeneity (dose, study design and infliximab exposure, P=0.000). Results were dose dependent; < 40mg (0.42, 95% CI [0.32 to 0.52], 40mg (0.57, 95% CI [0.35 to 0.78]), >40mg (0.91, 95% CI [0.80 to1.03]). Adalimumab was found to be significantly more effective in the infliximab naïve subgroup (0.84, 95% CI [0.72 to 0.97]).
- **Infliximab in paediatric patients with luminal CD**

  Higher proportion of patients in the first line infliximab group achieved clinical and endoscopic remission at week 10 vs conventional therapy group (clinical remission: 59% vs 34%, p=0.021 and endoscopic remission: 59% vs 17%, p=0.001). No significant difference in maintenance of clinical remission at week 52 (p=0.421), however there were significantly more patients in the first line infliximab group (19/46, 41%) in clinical remission on azathioprine monotherapy without need for treatment escalation vs conventional therapy group (7/48, 15%, p=0.004).

- High quality guidelines recommend infliximab and adalimumab for luminal/non-specific CD who are refractory to conventional therapy (adults and children).
- The intervention is incrementally more costly than the standard of care. Adalimumab is estimated to be more affordable than infliximab. To reduce formation of antibodies, an immunomodulator (e.g. azathioprine) is likely to be required for infliximab (increased risk of antibody formation). Infliximab will require additional resources for intravenous administration whereas adalimumab is subcutaneous and can be given as monotherapy.

- **Recommendation:**

  The Tertiary/Quaternary Expert Review Committee suggests using anti-TNFs for patients (adults and children) with luminal Crohn's Disease who are refractory to conventional therapy subject to the requirement for further costing analyses.

See Appendix 1 – evidence to decision framework

TERTIARY AND QUATERNARY EXPERT REVIEW COMMITTEE RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option or to use the alternative **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
				X	

The Tertiary and Quaternary Expert Review Committee suggests using anti-TNFs (class including adalimumab and infliximab, with the most affordable agent procured) for patients (adults and children) with luminal Crohn's Disease who are refractory to conventional therapy. Further costing analyses may be required in the context of the incremental cost associated with the use of these medicines and the chronic nature of the disease.

Rationale: The majority of patients with refractory CD will require numerous hospitalisations and/or surgeries. In patients where conventional therapy has failed; there is a need for a next line of therapy to prevent morbidity and increased resource requirements in these patients.

Both adalimumab and infliximab have been shown to be beneficial over standard of care in achieving and maintaining clinical remission and response in patients with luminal/non-specific CD refractory to conventional therapies. Limited data suggests superiority over placebo for reduction in CD related hospitalisations and surgeries and improvement in quality of life. No difference was found in adverse events. There is limited evidence available for the paediatric population however benefit shown for adalimumab and infliximab. High quality clinical practice guidelines recommend the utilisation of both agents in the luminal / non-specific CD patients who are refractory to conventional therapy.

Adalimumab and infliximab therapy would be associated with an incremental cost however only direct administration costs of the drugs were included in the analyses. Consumables, other therapies, and health service costs were not included as well as potential reduction in surgeries or hospitalisations.

Monitoring: Although there was limited evidence to show concerns regarding safety around infections, in the South African potential increased risk of infection such as TB is an important consideration for monitoring and initiating treatment. All patients should be assessed for latent or active tuberculosis prior treatment initiation.

Level of Evidence: High Quality Systematic reviews (AMSTAR 2), evidence certainty considered to be moderate to high for adalimumab over standard of care for majority of outcomes and very low to moderate for infliximab compared to standard of care.

NEMLC RECOMMENDATION 16th May 2024:

The NEMLC accepted the TQ ERC recommendation for luminal / non-specific CD and recommends that both adalimumab and infliximab be added onto the TQ EML for this indication. It is recommended that adalimumab be listed as the preferred option, as the agent is favourable in terms of efficacy, cost, decreased risk of antibody formation and route of administration. The treatment algorithm developed for fistulising Crohn's disease will be expanded to include luminal Crohn's disease and be circulated to the NEMLC with the finalised medicine review.

SUMMARY OF FINDINGS TABLES

Comparison 1 (adalimumab in addition to standard of care versus standard care alone), extracted from Abbass 2019

Figure 1 - Outcomes 1.2, 1.4, 1.8, 1.9

Adalimumab compared with placebo for induction of remission in Crohn's disease

Patient or population: Patients with active Crohn's disease

Settings: Outpatient

Intervention: Adalimumab

Comparison: Placebo

Outcomes Analysis 1.4	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Risk with placebo	Risk with Adalimumab				
Failure to achieve clinical remission **Follow-up: 4 weeks**	**913 per 1000**	**776 per 1000** (721 to 821)	**RR 0.85** (0.79 to 0.90)	714 participants (3 RCTs)	⊕⊕⊕⊕ **High**	Clinical remission was defined as CDAI < 150.
Failure to achieve clinical response (70-point response) **Follow-up: 4 weeks**	**658 per 1000**	**447 per 1000** (388 to 520)	**RR 0.68** (0.59 to 0.79)	714 participants (3 RCTs)	⊕⊕⊕⊕ **High**	Clinical response was defined as a reduction of at least 70 points in the CDAI score from baseline.
Failure to achieve clinical response (100-point response) **Follow-up: 4 weeks**	**757 per 1000**	**583 per 1000** (522 to 651)	**RR 0.77** (0.69 to 0.86)	714 participants (3 RCTs)	⊕⊕⊕⊕ **High**	Clinical response was defined as a reduction of at least 100 points in the CDAI score from baseline.
Endoscopic response	Not reported					This outcome was not reported.
Quality of life (QoL) **Inflammatory Bowel Disease Questionnaire (IBDQ) (scale: 32 to 224; higher score = better QoL)** **Follow-up: 4 weeks** **Short-Form 36 health survey (SF-36) (scale: 0 to 100; higher score = better QoL)** **Follow-up: 4 weeks**	One study reported significantly higher IBDQ scores at week 4 in the adalimumab 160 mg/80 mg and 80 mg/40 mg dose groups compared to placebo. One study reported a mean IBDQ score at 4 weeks of 150 in the adalimumab group compared to 139 in the placebo group (P < 0.001). One study reported significantly higher SF-36 scores in adalimumab 160 mg/80 mg and 80 mg/40 mg dose groups at four weeks compared to placebo. IBDQ scores were higher at 4 weeks in the adalimumab 160 mg/80 mg group compared to placebo (P > 0.05).			714 participants (3 RCTs)	⊕⊕⊕⊖[1] **Moderate**	Data did not allow for meta-analysis (means and/or standard deviations not reported). An increase in the IBDQ score of 16 to 32 points from baseline constitutes the lower and upper bounds of clinically meaningful improvement in QoL.
Adverse events **Follow-up: 4 weeks**	**715 per 1000**	**643 per 1000** (529 to 779)	**RR 0.90** (0.74 to 1.09)	531 participants (3 RCTs)	⊕⊕⊕⊖[2] **Moderate**	The most commonly reported adverse events included injection site reactions, abdominal pain, fatigue, worsening Crohn's disease and nausea.
Serious adverse events **Follow-up: 4 weeks**	**49 per 1000**	**22 per 1000** (8 to 57)	**RR 0.44** (0.17 to 1.15)	531 participants (3 RCTs)	⊕⊕⊖⊖[3] **Low**	The most commonly reported serious adverse events included infections, worsening Crohn's disease, abscesses and dehydration.
Withdrawals due to adverse events **Follow-up: 4 weeks**	**30 per 1000**	**12 per 1000** (3 to 40)	**RR 0.38** (0.11 to 1.30)	531 participants (3 RCTs)	⊕⊕⊖⊖[4] **Low**	Adverse events that led to study withdrawal included worsening Crohn's disease, abdominal abscess and liver abscess.

[1] Downgraded one level due to serious imprecision (narrative synthesis was conducted, estimates were not precise).
[2] Downgraded one level due to serious inconsistency (I^2 = 53%).
[3] Downgraded two levels due to very serious imprecision (19 events).
[4] Downgraded two levels due to very serious imprecision (11 events).

Comparison 1 (adalimumab in addition to standard of care versus standard care alone), extracted from Townsend 2020

Figure 2 - Outcomes 1.1, 1.3, 1.5, 1.9

Summary of findings 1. Adalimumab compared to placebo for maintenance of remission in Crohn's disease

Adalimumab compared to placebo for maintenance of remission in Crohn's disease

Patient or population: People with quiescent Crohn's disease
Setting: Outpatient
Intervention: Adalimumab (40 mg/week or 40 mg every other week)
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with Adalimumab				
Failure to maintain clinical remission Follow-up: 52 to 56 weeks	Study population 858 per 1000	600 per 1000 (549 to 660)	RR 0.70 (0.64 to 0.77)	683 (3 RCTs)	⨁⨁⨁⨁ HIGH	Clinical remission defined as a CDAI < 150
Failure to maintain clinical remission Follow-up: 24 to 26 weeks	Study population 793 per 1000	523 per 1000 (412 to 658)	RR 0.66 (0.52 to 0.83)	554 (2 RCTs)	⨁⨁⨁◯ MODERATE[a]	Clinical remission defined as a CDAI < 150
Failure to maintain endoscopic remission Follow-up: 52 weeks	969 per 1000	717 per 1000 (611 to 843)	RR 0.74 (0.63 to 0.87)	129 (1 RCT)	⨁⨁⨁◯ MODERATE[b]	Endoscopic remission defined as an absence of mucosal ulceration
Adverse events Follow-up: 52 to 56 weeks	Study population 854 per 1000	862 per 1000 (802 to 930)	RR 1.01 (0.94 to 1.09)	1012 (4 RCTs)	⨁⨁⨁⨁ HIGH	Commonly-reported adverse events included CD aggravation, arthralgia, nasopharyngitis, urinary tract infections, headache, nausea, fatigue and abdominal pain
Serious adverse events Follow-up: 52 to 56 weeks	Study population 144 per 1000	80 per 1000 (56 to 115)	RR 0.56 (0.39 to 0.80)	1012 (4 RCTs)	⨁⨁⨁◯ MODERATE[c]	Reported serious adverse events included infectious complications including tuberculosis, abscess formation and wound infections, multiple sclerosis, pulmonary embolism

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a]Downgraded by one level due to serious inconsistency (I^2 = 55%).
[b]Downgraded by one level due to sparse data (109 events).
[c]Downgraded by one level due to sparse data (105 events).
[d]Downgraded by one level due to sparse data (93 events).
[e]Downgraded by one level due to sparse data (237 events).

Comparison 2 (infliximab in addition to standard of care versus standard care alone), extracted from Gordon 2024

Figures 3 and 4 - Outcomes 2.1, 2.3, 2.5 and 2.9

SUMMARY OF FINDINGS

Summary of findings 1. Infliximab compared to placebo

Infliximab compared to placebo

Patient or population: patients with Crohn's disease (mixed disease activity population with clinical response at baseline)
Setting: hospitals in several countries
Intervention: infliximab
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with infliximab				
Clinical relapse (at 30-32 weeks, CDAI > 150)	Study population 753 per 1000	550 per 1000 (475 to 633)	RR 0.73 (0.63 to 0.84)	408 (2 studies)	⊖⊖⊖⊖ Moderate[a]	NNTB = 5
Loss of clinical response (at 32 weeks, less than 70 points in CDAI change)	Study population 639 per 1000	377 per 1000 (236 to 613)	RR 0.59 (0.37 to 0.96)	73 (1 study)	⊖⊖⊖⊖ Very low[b]	
Withdrawal due to adverse events (at 32-54 weeks)	Study population 133 per 1000	88 per 1000 (49 to 159)	RR 0.66 (0.37 to 1.19)	355 (2 studies)	⊖⊖⊖⊖ Very low[b]	
Serious adverse events (at 54 weeks)	Study population 229 per 1000	137 per 1000 (82 to 229)	RR 0.60 (0.36 to 1.00)	282 (1 study)	⊖⊖⊖⊖ Very low[b]	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **OR:** odds ratio; **RR:** risk ratio;

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded once due to concerns about risk for randomisation, selective reporting and other bias
[b]Downgraded twice due to serious imprecision from very low participant and event numbers and once due to concerns about risk for blinding, and selective reporting

Summary of findings 2. Infliximab combined with purine analogues compared to purine analogues

Infliximab combined with purine analogues compared to purine analogues

Patient or population: Crohn's disease patients (in remission at baseline)
Setting: secondary care (multiple countries)
Intervention: infliximab combined with purine analogues
Comparison: purine analogues

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with purine analogues	Risk with infliximab combined with purine analogues				
Clinical relapse (at 48 weeks, CDAI of 150 or greater together with an increase in CDAI more than 70 points above baseline over 2 consecutive weeks or definitive clinical relapse requiring immediate intervention, as judged by the treating physician)	Study population 589 per 1000	118 per 1000 (59 to 248)	RR 0.20 (0.10 to 0.42)	115 (1 study)	⊖⊖⊖⊖ Moderate[a]	NNTB = 2
Loss of clinical response	-	-	-	-	-	
Withdrawal due to adverse events (at 48 weeks)	Study population 142 per 1000	67 per 1000 (21 to 212)	RR 0.47 (0.15 to 1.49)	115 (1 study)	⊖⊖⊖⊖ Very low[b]	
Serious adverse events (at 48 weeks to 2 years)	78 per 1000	94 per 1000 (42 to 206)	RR 1.19 (0.54 to 2.64)	257 (2 studies)	⊖⊖⊖⊖ Very low[b]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **OR:** odds ratio; **RR:** risk ratio;

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded once due to some concerns about bias from selective reporting
[b]Downgraded twice due to serious imprecision from very low participant and event numbers and once due to concerns about risk of bias for randomisation, blinding, attrition and selective reporting

Comparison 2 (infliximab in addition to standard of care versus standard care alone), extracted from Gordon 2023

Figure 5 – Outcome 2.2, 2.4, 2.9

Summary of findings 1. Infliximab 5–10 mg/kg compared to placebo

Infliximab compared to placebo

Patient or population: active Crohn's disease
Setting: hospitals and tertiary centres (Amsterdam, Belgium, the Netherlands, UK, USA)
Intervention: infliximab
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with infliximab				
Clinical remission defined as CDAI < 150 at week 4	120 per 1000	546 per 1000 (184 to 1000)	**RR 4.55** (1.53 to 13.50)	80 (1 study)	⊖⊖⊖⊖ **Low**[a]	—
Clinical response defined as improvement in the scores on the CDAI score ≥ 70 at week 4	160 per 1000	654 per 1000 (260 to 1000)	**RR 4.09** (1.63 to 10.25)	80 (1 studies)	⊖⊖⊖⊖ **Low**[a]	—
Withdrawals due to adverse events	—		—	—	—	—

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CDAI: Crohn's Disease Activity Index; **CI:** confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded one level due to serious concerns with risk of bias (selective reporting and unclear randomisation), and one level due to serious concerns with imprecision due to low event numbers.

BACKGROUND

Crohn's disease (CD) is a chronic, inflammatory disorder of the gastrointestinal tract with periods of active and quiescent disease. Symptoms of the condition include diarrhoea, nausea, vomiting, weight loss, fatigue, abdominal pain, fever and bleeding. Extraintestinal manifestations are also present in some patients such as osteoporosis, psoriasis and ankylosing spondylitis (2,3). The disorder can often have a progressive fulminant course resulting in surgery and hospitalisation. Given the nature of the condition, CD can have a profound impact on a patient's quality of life (4). Data on the prevalence of Crohn's disease (CD) in South Africa is scarce. The last formal published epidemiological study was performed in 1984. In this study the incidence of CD was reported to be 2.6/100 000 per year(1). An analysis of medical aid beneficiaries in South Africa, estimated a prevalence of CD for beneficiaries over the age of 20 years at about 0.2 per 1000(5).

Conventional therapies for CD listed on the Essential Medicines List (EML) include methotrexate, azathioprine, 6-mercaptopurine with acute flares treated with corticosteroids. A motivation was received to include Tumour Necrosis Factor Alpha (TNFs) Inhibitors, specifically infliximab and adalimumab, onto the EML for individuals who are refractory or intolerant to conventional therapies(4). Infliximab is administered intravenously 8-weekly (5mg/kg), following an initial loading period of 0, 2 and 6 weeks, and is often given in combination with an immunomodulator, usually azathioprine, to reduce the formation of antibodies and improve efficacy. Adalimumab is administered subcutaneously as monotherapy, every other week. Therapy is initiated with a loading period of 160mg at week 0, 80mg at week 2 and maintained at 40mg administered every alternate week.

The motivation noted that while some CD patients may be adequately controlled on immunomodulatory therapy such as azathioprine, 6-mercaptopurine, and methotrexate and corticosteroids, there are a number who remain uncontrolled requiring additional therapy including prolonged hospital admissions. Moreover, the motivation highlighted that corticosteroids are considered to have an unacceptable side effect profile and that all recent CD guidelines (including local guidelines) suggest limiting their use as much as possible by prescribing a corticosteroid sparing agent(4,6–9).

This review thus seeks to review the safety and efficacy of the addition of infliximab or adalimumab in the management of patients with Luminal / Non-Specific Crohn's disease who are refractory to standard of care therapies.

RESEARCH QUESTION: For patients of all ages with Luminal Crohn's Disease (CD) / non-specific CD who are refractory to conventional therapy, is the addition of a TNF inhibitor (namely adalimumab or infliximab) safe and effective?

METHODS

Eligibility criteria for review

Table 1: PICO for medicine review

PICO	
Population:	Individuals of all ages with Luminal / non-specific Crohn's Disease who are refractory* to conventional therapies
Intervention:	Infliximab therapy: 5mg/kg IVI at weeks 0, 2, and 6, and then 8-weekly OR Adalimumab therapy: 160mg SC at week 0, and then 80mg SC at week 2, and then 40mg SC every other week
Comparators:	Standard of care

Outcomes:	1. Maintenance of clinical remission as defined by the study 2. Induction of clinical remission = CDAI <150 3. Maintenance of clinical response as defined by the study 4. Induction of clinical response = ≥100-point CDAI decrease from baseline 5. Maintenance of endoscopic improvement 6. Induction of endoscopic improvement 7. Rates of hospitalization and surgeries 8. Quality of life 9. Safety
Study designs	Systematic reviews of RCTs, RCTs, guidelines

* There is no uniform definition for refractory patients and is generally at the clinician's discretion (using a combination of clinical, biochemical, endoscopic, or radiographic findings). The time at which response is evaluated depends on the agent – but generally at 6-9 months for methotrexate and azathioprine at optimal doses. Trials will be examined for inclusion criteria of patients and transparently outlined in characteristics of include studies.

Studies with patients undergoing surgery or including outcomes only related to fistulising CD were excluded. For paediatric populations, the study design criteria were broadened to include SRs of study designs other than RCTs.

Search Strategy

An updated search was developed based on the revised PICO and run in March 2024. The search strategy is outlined in Appendix 2. A general search for guidelines and HTAs was also conducted in Google Scholar, Google and targeted websites, for example Guidelines International Network (G-I-N), utilising a combination of the search terms such as 'paediatric', 'Crohn's disease', and 'luminal'.

Study Selection and assessment of methodological quality

Title and abstract screening as well as full text review was undertaken by two reviewers independently with conflicts resolved through discussion (JR and KM). Due to the number of eligible SRs for the adult population, studies published earlier than 2013 were excluded during screening. Eligible systematic reviews included after full text review were independently assessed for methodological quality using AMSTAR 2 by two reviewers (KM, JR or SD) (10). SRs for adult population were excluded if considered to be of critically low or low quality except where an SR focussed on an outcome not covered in a higher quality SR. Due to limited studies on the paediatric population, SRs of lower quality were included for data extraction. Cochrane Risk of Bias 1 assessments were extracted directly from the included SRs. Guidelines were assessed with the AGREE II tool by one reviewer (KM, JR or DF) and included if overall assessment was ≥5 out of 7.

Data extraction, management, analysis and quality assessment

Data extraction was undertaken by one reviewer (KM) and another reviewer checked it (JR). Descriptive data on all eligible studies were tabulated. Findings were summarised narratively. Where quality/certainty of evidence assessment results (such GRADE) were reported for included data estimates, we extracted the result directly. If a result was not reported, we assessed quality based on the RoB 1 assessment and number of events. Relevant recommendations were extracted and tabulated from included guidelines.

RESULTS

Identification of studies

The searches combined produced 249 results (241 database searches, 8 additional sources). After title and abstract screening (and removal of 38 duplicates), 40 articles remained. After full text review 21 records were excluded (See Appendix 3). Twelve SRs (9 adults and 3 paediatrics) met the PICO and were assessed for final inclusion (see Appendix 4 – Summary of Amstar 2 Assessments, Appendix 5 – Assessment of eligible studies). Seven guidelines were assessed for inclusion with AGREE II (See Appendix 6 – Summary of AGREE II assessments). Data was extracted from 8 SRs (2 paediatrics, 6 adults) and 7 guidelines (See below for description of included studies and section on guidelines). See Figure 6 below - PRISMA diagram.

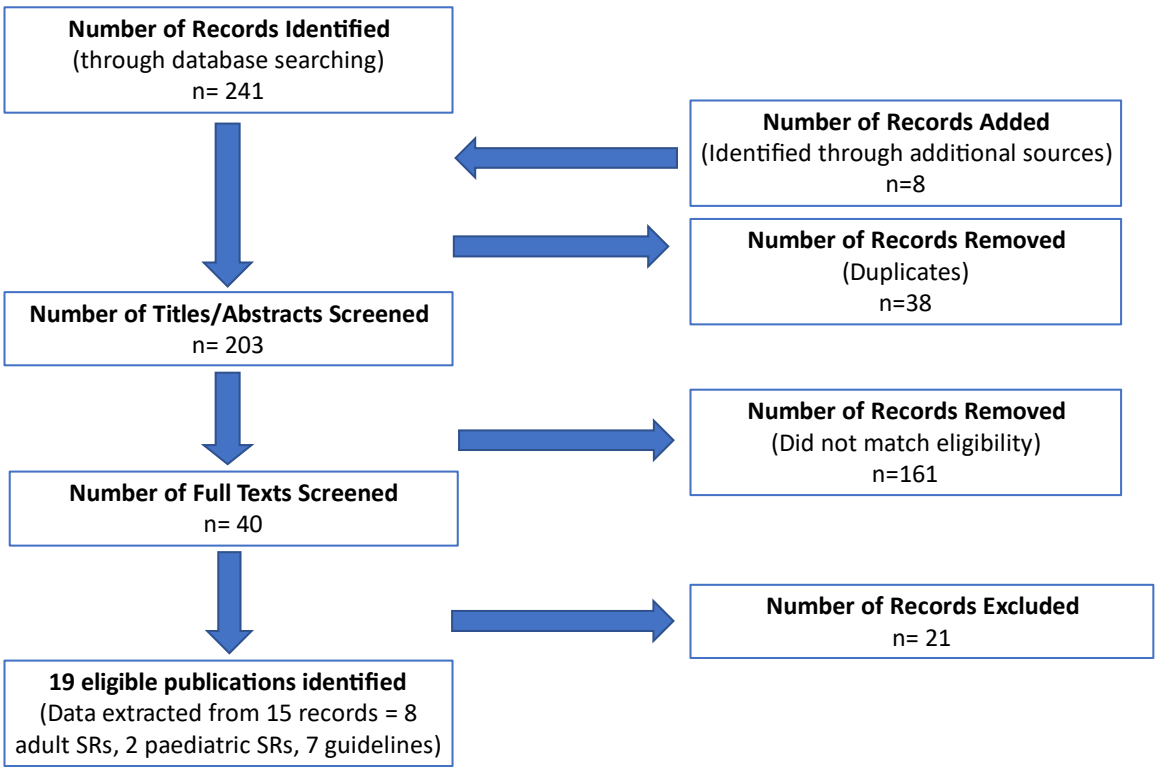


***Figure 6**: PRISMA Diagram – TNF inhibitors (adalimumab and infliximab) for Luminal Crohn's Disease*

Assessment of Methodological Quality

All eligible SRs were assessed with AMSTAR 2 (see Appendix 4 – Summary of Amstar 2 assessments); five high quality SRs were included for data extraction for adult population, Abbass 2019 (induction of response – adalimumab), Townsend 2020 (maintenance – adalimumab), Yin 2022 (induction of remission – adalimumab), Gordon 2023 (induction – infliximab) and Gordon 2024 (maintenance – infliximab). Mao 2017 was the only study included of lower quality (critically low quality), however it was the only study meeting the PICO that reported on outcomes of hospitalisation and surgeries. The SRs included for data extraction for the paediatric population, Chen 2024 and Martin-Garcia were evaluated as low and moderate quality respectively. See Guidelines section for detail on assessment of guidelines.

Description of included studies

Systematic Reviews

Adults

- Abbass 2019 conducted an SR of RCTs on adalimumab compared to placebo for individuals with CD. The primary outcome was the proportion of participants who failed to achieve clinical remission, as defined by the original studies. Secondary outcomes included failure to achieve clinical response, endoscopic response and remission, withdrawals due to adverse events, serious adverse events, quality of life, and total adverse events. The population of interest for the SR was not specifically refractory patients however the trials underpinning the analyses, for the specific outcomes of interest, met refractory definition according to the PICO (**Hanauer 2006; Watanabe 2012**(11,12)**). Sandborn 2007a** (13) however was conducted specifically on patients who had failed infliximab.
- Townsend 2020 (2) reported on an SR of RCTs exploring efficacy and safety of adalimumab compared to placebo in CD. The primary outcome was the proportion of participants with CD who failed to maintain clinical remission, as defined by the original trials. Secondary outcomes included maintenance of clinical response, endoscopic remission and response, and safety. The population of interest for the SR was not specifically refractory patients. However the trials underpinning the analyses, for the specific outcomes of interest, met refractory definition according to the PICO **(Colombel 2007; Rutgeerts 2012; Watanabe 2012; Sandborn 2007b**(11,14–16)).
- Yin 2022 (17) reported on an SR of RCTs on adalimumab on induction of clinical remission in CD patients as a primary outcome. The analysis also explored induction of clinical response, quality of life and safety. The review included a

more recent study, **Chen 2020** (18), in addition to the three RCTs included in the Abbass 2019 study thus the data for the specific outcome of induction of remission will be extracted.

- Gordon 2024 (19) reported on an SR of RCTs exploring efficacy and safety of infliximab compared to placebo and infliximab combined with purine analogues to purine analogues alone in patients with Crohn's disease (CD). The primary outcome was proportion of patients with clinical relapse (as defined by the trials). Secondary outcomes included clinical loss of response as defined by the trials, withdrawals due to adverse events, serious adverse events and total adverse events. The population of interest for the SR was not specifically refractory patients however the trials underpinning the analyses, for the specific outcomes of interest, met refractory definition according to the PICO (**Hanauer 2002; Rutgeerts 1999; Buhl 2022**(20–22)).
- Gordon 2023(3) conducted an SR of RCTs comparing infliximab with placebo and infliximab combined with purine analogues to purine analogues alone in CD. The primary outcomes were clinical remission and response (as defined by the included trials) and withdrawals due to adverse events. Secondary outcomes included endoscopic remission and response and serious adverse events. The population of interest for the SR was not specifically refractory patients however the trials underpinning the analyses, for the specific outcomes of interest, met refractory definition according to the PICO (**Targan 1997; Colombel 2010; Lemann 2006**(23–25)).
- Mao 2017(26) reported on an SR of RCTs evaluating efficacy of immunosuppressants and biologicals on reducing number of hospitalisations and surgeries for individuals with inflammatory bowel disease. The population of interest was not specifically refractory and one included trial was specifically fistulising CD patients (**Lichtenstein 2005**(27)). **Rutgeerts 2004**(28) conducted a post-hoc analysis on the ACCENT I trial **(Hanauer 2002**(20)**)** exploring infliximab and **Feagan 2008**(29) carried out a post-hoc analysis of the CHARM study exploring adalimumab **(Colombel 2007**(15)**)**.

Paediatrics

- Chen 2024(30) reported on an SR of RCTs and cohort studies exploring adalimumab in children and adolescents with inflammatory bowel disease. Outcomes of interest were induction of remission and response, maintenance of remission and response, and adverse events. Population of interest were not specifically refractory and no double blind placebo trials were found. Majority of included studies were cohort in design, the only two randomised studies included were **Hyams 2012**(31) and **Assa 2019**(32), which focussed on dosing and therapeutic monitoring respectively.
- Martin-Garcia 2023(33) reported on SR exploring TNF-inhibitors for children with inflammatory bowel disease and presented results narratively. Many of the studies included explored different dosing for infliximab and adalimumab. One trial was included evaluated infliximab versus standard of care (glucocorticoids and enteral nutrition) - **Jongsma 2022**(34) (TISKids study). The open label study explored first line treatment with infliximab in children with recently diagnosed moderate to severe Crohn's disease. One study was included for adalimumab, the same dosing study included in Chen 2024 (**Hyams 2012**(31)).

Risk of Bias Assessments

The SRs evaluating adults all conducted Cochrane RoB 1 assessments. Results were extracted directly from the SRs and tabulated below, see Table 2. For the SRs evaluating adalimumab, no studies were considered high risk of bias. Similarly to Townsend 2020 and Abbass 2019, Yin 2022 evaluated Watanabe 2012 to be of unclear risk of bias due to concerns with unclear bias in random sequence generation, allocation concealment, and blinding. In Gordon 2023, all domains were considered either low risk or unclear risk for the studies included in analyses of specific interest for this medicine review (Colombel 2010, Targan 1997, Lemann 2006). All domains in Gordon 2024 were considered either low risk or unclear risk for the studies included in analyses of specific interest for this medicine review (Buhl 2022, Hanauer 2002, Rutgeerts 1999). Louise 2022 was included in the serious adverse events analysis and did have two domains assessed to be of high risk of bias.

Table 2: SRs for adult population – extracted Cochrane Risk of Bias 1 assessments

Systematic review	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selection reporting (reporting bias)	Other bias
Abbass 2019							
Hanauer 2006	Low	Low	Low	Low	Low	Low	Low
Sandborn 2007a	Low	Low	Unclear	Low	Low	Low	Low
Watanabe 2012	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
Townsend 2020							
Colombel 2007	Low	Low	Low	Low	Low	Low	Low
Rutgeerts 2012	Unclear	Unclear	Low	Low	Low	Low	Low
Sandborn 2007b	Low	Low	Low	Low	Low	Low	Low
Watanabe 2012	Unclear	Unclear	Low	Low	Low	Low	Low
Yin 2022							
Chen 2020	Low	Low	Low	Low	Low	Low	Low
Hanauer 2006	Low	Low	Low	Low	Low	Low	Low
Sandborn 2007a	Low	Low	Unclear	Low	Low	Low	Low
Watanabe 2012	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
Gordon 2023							
Colombel 2010	Low	Low	Low	Low	Low	Low	Low
Targan 1997	Unclear	Low	Low	Low	Low	Unclear	Low
Lemann 2006	Low	Low	Low	Low	Low	Unclear	Low
Gordon 2024							
Buhl 2022	Low	Low	Low	Low	Low	Unclear	Low
Hanauer 2002	Low	Low	Low	Low	Low	Unclear	Unclear
Rutgeerts 1999	Unclear	Low	Low	Low	Low	Unclear	Low
Mao 2017							
Rutgeerts 2004	Low	Low	Low	Low	Low	Low	Low
Feagan 2008	Low	Unclear	Low	Low	Low	Low	Low

For the paediatric population Chen 2024 evaluated one domain in the Hyams 2012 study to be of high risk of bias, selection bias due to the open-label nature of the design - See Table 3. Martin-Garcia 2023 utilised Cochrane RoB 2 to assess clinical trials and assessed Hyams 2012 as 'some concerns' and Jongsma 2022 to be low risk.

Table 3 - SRs for paediatric population – extracted Cochrane Risk of Bias 1 assessments

Chen 2024							
Hyams 2012	Unclear	High	Low	Low	Low	Low	Low
Assa 2019	Low	Low	Low	Low	Low	Low	Low
Martin-Garcia 2023							
Hyams 2012	Some doubts						
Jongsma 2022	Low Risk						

For non-randomised studies Chen 2024 utilised the MINORS tool where a maximum of 16 points. Majority of studies were evaluated to be of moderate or high quality. See figure 7 below.

Study	The purpose of the research is clearly stated	Consistency of enrolled patients	Collection of expected data	Endpoints that appropriately reflect the purpose of the study	The objectivity of endpoint evaluation	Adequate follow-up time	Loss to follow-up rate is less than 5%	Whether the sample size was estimated	total
Rosh et al. [13]	2	2	2	2	0	2	0	2	12
Viola et al. [22]	2	2	2	2	0	1	2	1	12
Russel et al. [23]	2	2	2	2	0	2	2	1	13
Cozijnsen et al. [25]	2	2	2	2	0	2	1	1	12
Alvisi et al. [2]	2	2	2	2	0	2	2	1	13
Romeo et al. [27]	2	2	2	2	0	2	2	1	13
Rinawi et al. [28]	2	2	2	2	0	0	2	1	11
Rinawi et al. [28]	2	2	2	2	0	2	2	2	14

Figure 7 – MINORS tool for single arm studies extracted from Chen 2024.

Effects of Interventions

Data was extracted and summarised below for each comparison and corresponding outcome from selected studies as outlined in Appendix 5 - Tables 1 and 2.

Efficacy and Safety for adult population

Comparison 1: Subcutaneous adalimumab in addition to standard of care compared to standard of care alone

Outcome 1.1 Number of participants with maintained clinical remissions (as defined by the study)

Townsend et al. 2020(2) reported that fewer participants in the adalimumab failed to maintain clinical remission at **52 to 56 weeks** compared to those receiving placebo (RR=0.70 in favour of adalimumab, 95% CI [0.64 to 0.77], i^2=0%, P<0.00001, NNT 4 95% CI [3 to 5], 3 RCTs, n=683) – high certainty evidence as per Townsend 2020) – See Summary of Findings Table and figure 8 below. Superiority of adalimumab compared to placebo was also observed in subgroup analysis for different dose frequencies (40mg/kg weekly or two weekly) with no difference found between groups.

The systematic review also reported that a lower percentage of adalimumab participants failed to maintain clinical remission at **24 to 26 weeks** (RR=0.66 in favour of adalimumab, 95% CI [0.52 to 0.83], i^2=52% - moderate heterogeneity, P<0.0004, NNT=4 CI 95% [3 to 6], 2 RCTs, n=554) – *moderate certainty of evidence (GRADE from Townsend 2020, downgraded 1 for serious inconsistency*) – See Summary of Findings Table (pg. 4) and figure 9 below. Subgroup analysis for dose frequency (40mg/kg weekly or two weekly) produced estimates that favoured adalimumab over placebo however CIs for both groups crossed the line of no effect. Test for subgroup differences found no difference between groups.

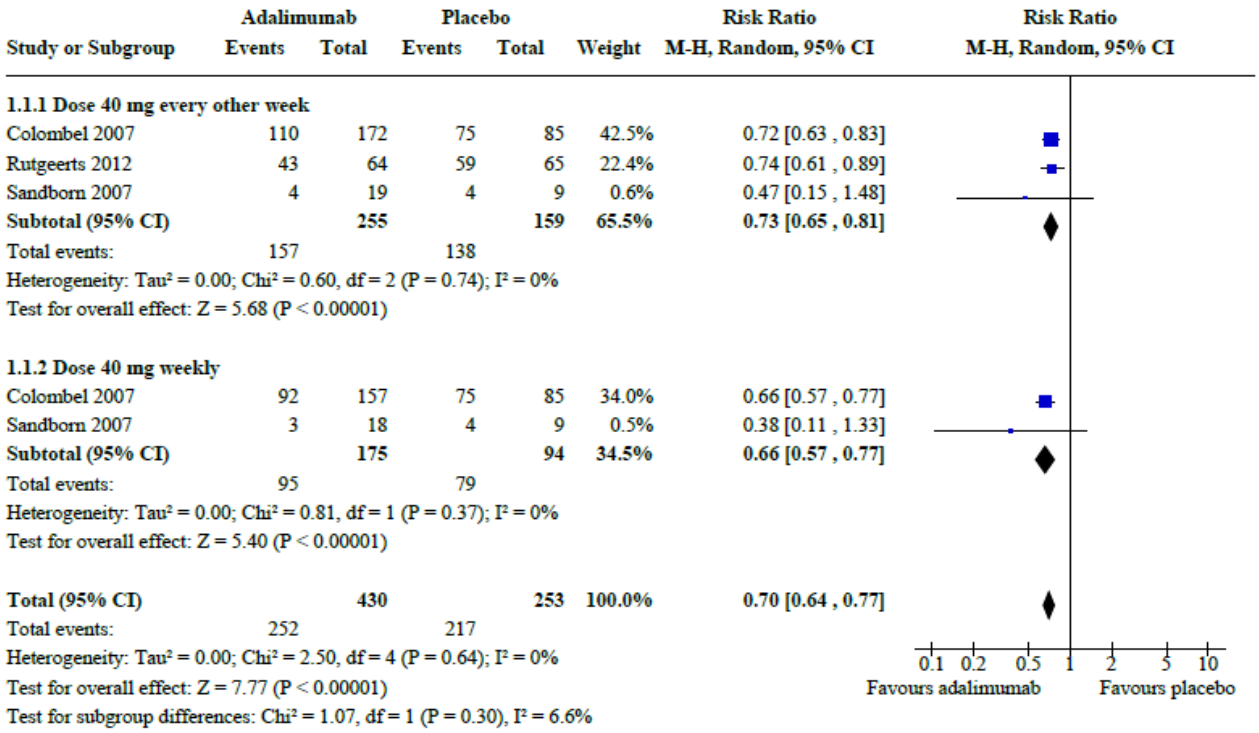


***Figure 8**: Comparison 1 (Adalimumab vs placebo); Outcome 1.1 (Number of participants with maintained clinical remission at 52 to 56 weeks (CDAI < 150)) – extracted from Townsend 2020.*

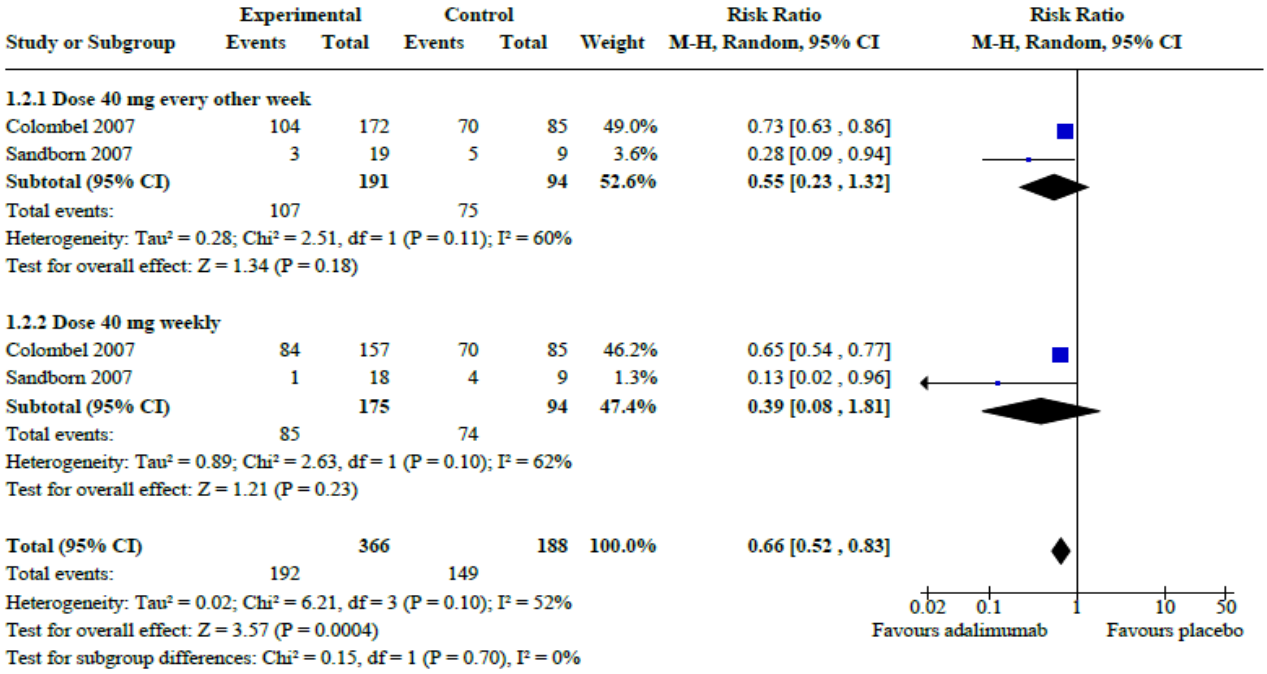


***Figure 9**: Comparison 1 (Adalimumab vs placebo); Outcome 1.1 (Number of participants with maintained clinical remission at 24 to 26 weeks (CDAI < 150)) – by dose – extracted from Townsend 2020.*

Outcome 1.2 Number of participants with induced clinical remission (CDAI < 150)

Yin 2022(17) found that among TNF inhibitor naïve patients, a lower proportion of those receiving adalimumab failed to achieve clinical remission at 4 weeks compared to placebo (RR= 0.76, 95% CI [0.60 to 0.96], I^2= 82%, NNT 5 95% CI [4 to 8], 2 RCTs, n=494; P=0.02 – *moderate certainty of evidence* (JADAD score from Yin 2022 – downgraded one for inconsistency). Subgroup analysis showed that adalimumab was also superior to placebo in TNF-inhibitor exposed patients and no difference was found between subgroups – See figure 10 below.

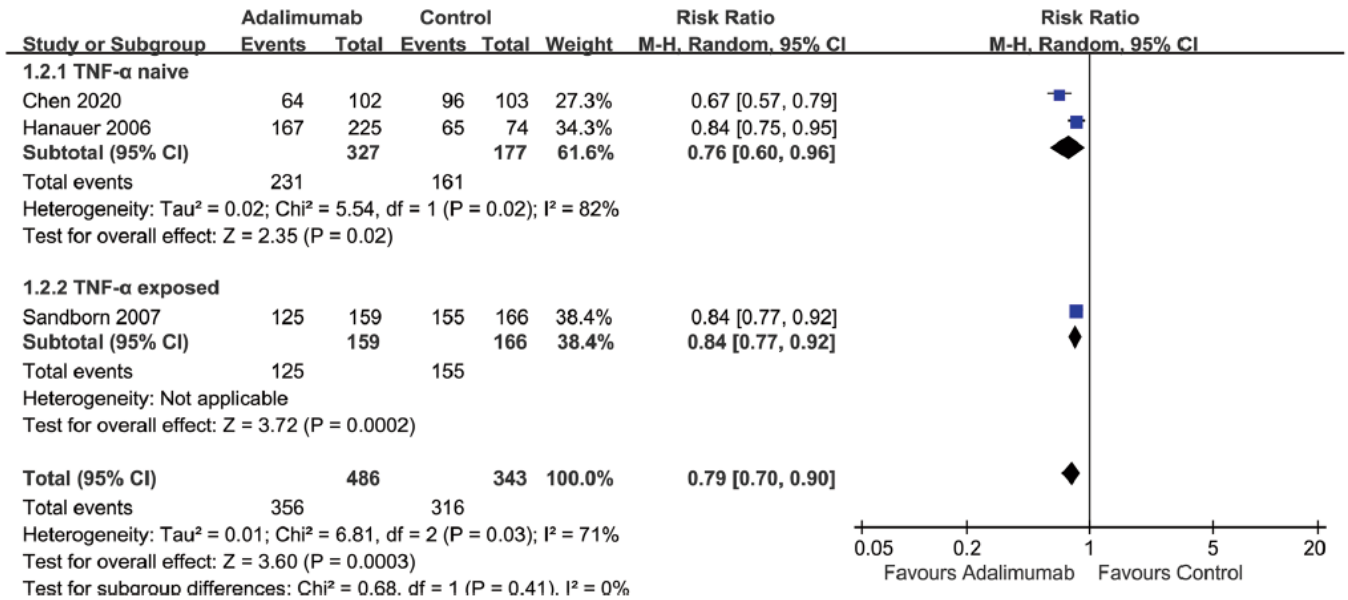


***Figure 10**: Comparison 1 (Adalimumab vs placebo); Outcome 1.2 (Number of participants who achieved clinical remission at 4 weeks (CDAI < 150) – by previous TNF exposure – extracted from Yin 2022.*

Abbass et al. 2019(35) reported on a subgroup analysis by dose and found a lower percentage of patients in the adalimumab 160/80mg dose failed to achieve clinical remission at 4 weeks compared to placebo (RR= 0.82, 95% CI [0.75 to 0.88], I^2= 0%, NNT[i] 6 95% CI [4 to 8], 2 RCTs, n=470; P<0.0001) – high certainty of evidence reported in Abbass 2019 - See Summary of findings table and figure 11.

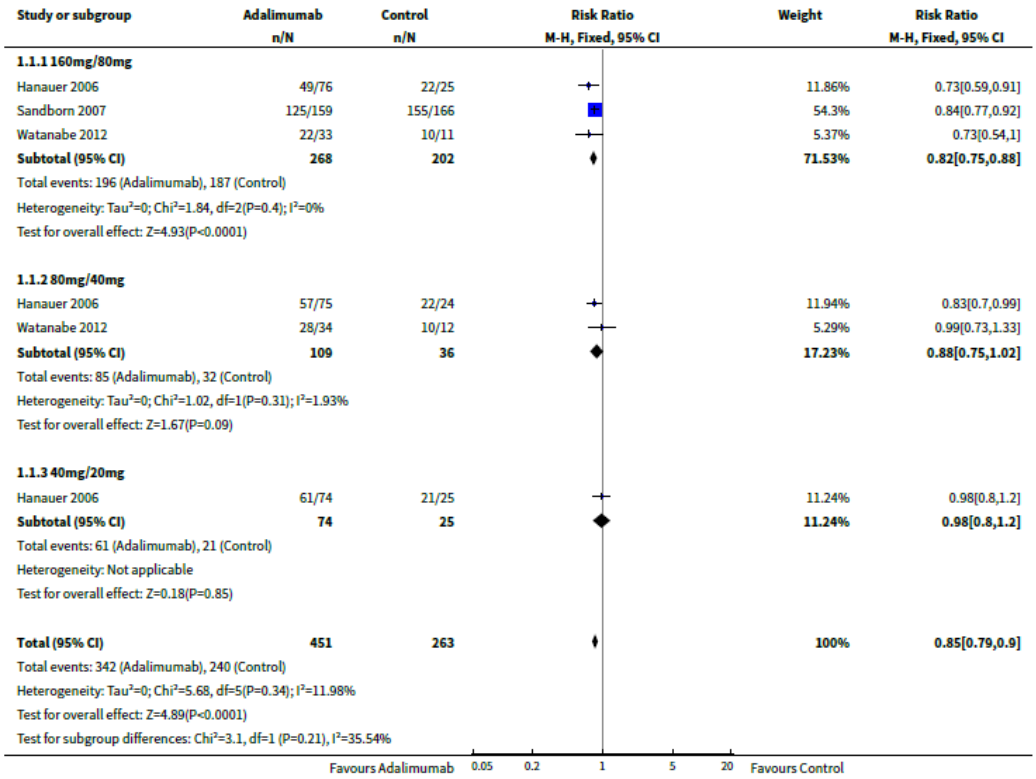


***Figure 11**: Comparison 1 (Adalimumab vs placebo); Outcome 1.2 (Number of participants who achieved clinical remission at 4 weeks (CDAI < 150)); by dose – extracted from Abbass 2019.*

[i] Unweighted NNT based on total events from the three trials

Outcome 1.3 Number of participants with maintained clinical response (as defined by the study)

The SR by Townsend et al. 2020(2) found that there was a lower percentage of adalimumab receiving participants (40mg/kg weekly or two weekly) who failed to maintain clinical response at **52 to 56 weeks** as compared to placebo (RR=0.68 in favour of adalimumab, 95% CI [0.62 to 0.75], i^2=0%, NNT 4 95% CI [3 to 5], P<0.00001, 6 RCTs, n=733) – GRADE not reported, aligning with other evaluations assessed to be moderate certainty, downgraded 1 for unclear risk of bias) – See figure 12 below. Superiority of adalimumab compared to placebo for this outcome was observed in subgroup analysis for dosing of 40mg/kg every other week however the CI result for the subgroup group for 40mg/kg weekly dosing included the null. Test for subgroup differences found no difference between groups.

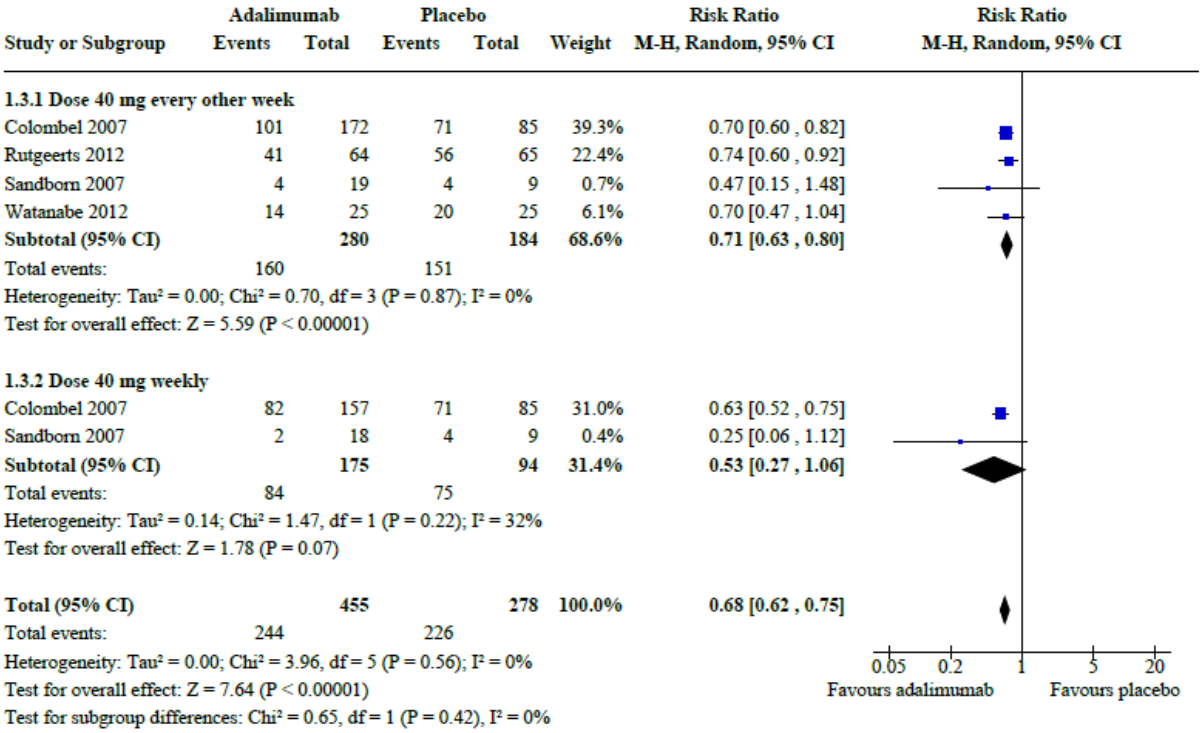


Figure 12: *Comparison 1 (Adalimumab vs placebo); Outcome 1.3 (Number of participants with maintained clinical response at 52-56 weeks) – extracted from Townsend 2020.*

Townsend et al. 2020 also found that there was also a lower proportion of participants who failed to maintain clinical response **at 24 to 26 weeks** on adalimumab as compared to placebo (RR=0.65 in favour of adalimumab, 95% CI [0.56 to 0.74], i^2=0%, P<0.00001, NNT 4, 95% CI [3 to 6], 2 RCTs, n=554) – GRADE not reported, aligning with other evaluations assessed to be moderate certainty, downgraded 1 for unclear risk of bias). Superiority of adalimumab compared to placebo for this outcome was observed in subgroup analysis for dosing of 40mg/kg every other week however the CI result for the subgroup group for 40mg/kg weekly dosing included the null. Test for subgroup differences found no difference between groups – See figure 13 below.

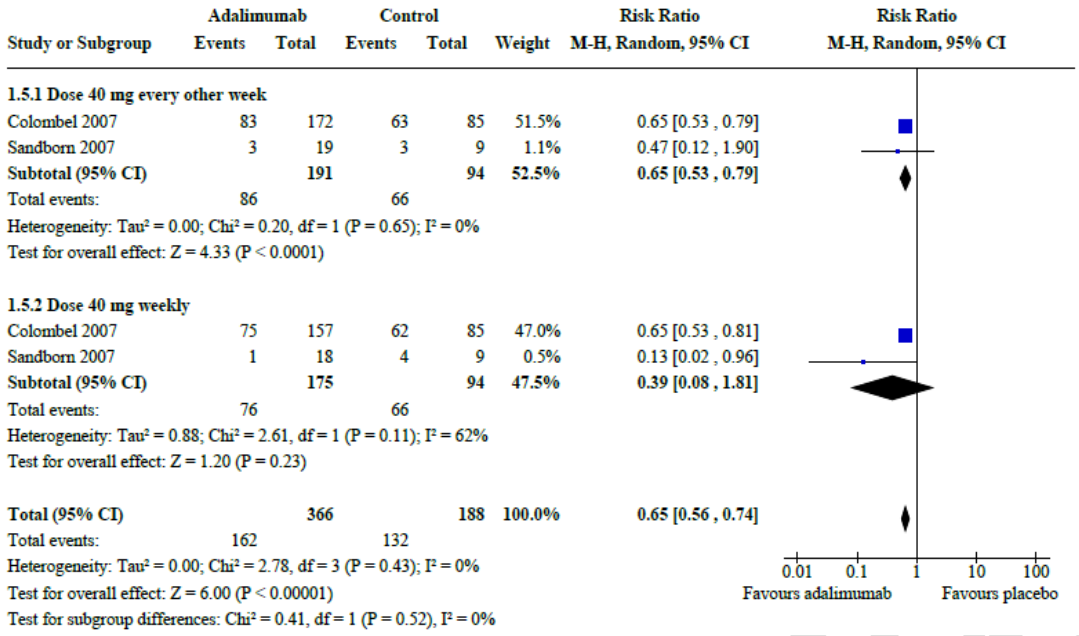


Figure 13: *Comparison 1 (Adalimumab vs placebo); Outcome 1.3 (Number of participants with maintained clinical response at 24-26 weeks) – extracted from Townsend 2020.*

Outcome 1.4 Number of participants with induced clinical response (= ≥100-point CDAI decrease from baseline)

Abbass et al. 2019(35) reported that there was a lower proportion of adalimumab receiving participants who failed to achieve clinical response at 4 weeks compared to placebo (RR= 0.77 in favour of adalimumab, 95% CI [0.69 to 0.86], I^2= 35% - moderate heterogeneity, NNT 6, 95% CI [4 to 9], 3 RCTs, n=714; P<0.0001) – *high certainty of evidence* (GRADE from Abbass 2019 – See Summary of findings table. On subgroup analysis, superiority for adalimumab was observed for group 1 (160mg/80mg) and group 2 (80mg/40mg) but not for group 3 (40mg/20mg). However test for subgroup differences found no differences between subgroups – See figure 14 below.

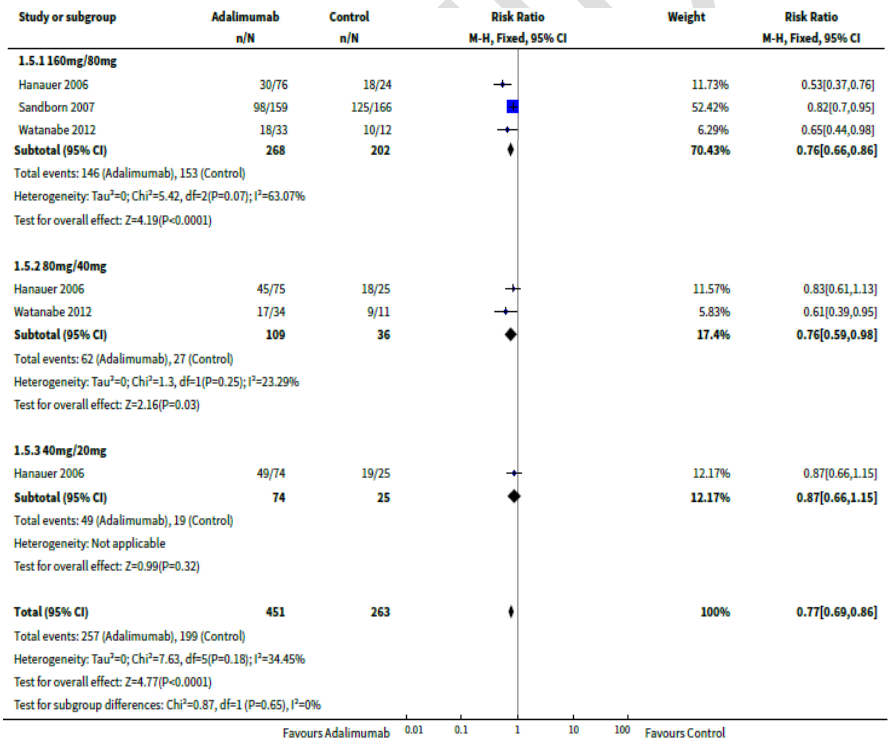


Figure 14: *Comparison 1 (Adalimumab vs placebo); Outcome 1.4 (Number of participants who achieved clinical response at 4 weeks); Test for subgroups – dosing – extracted from Townsend 2020.*

Sandborn 2007a(13) was conducted on patients previously exposed to infliximab. Adalimumab was found to be superior in both TNF-inhibitor naïve and exposed patients with no difference between subgroups (see figure 15).

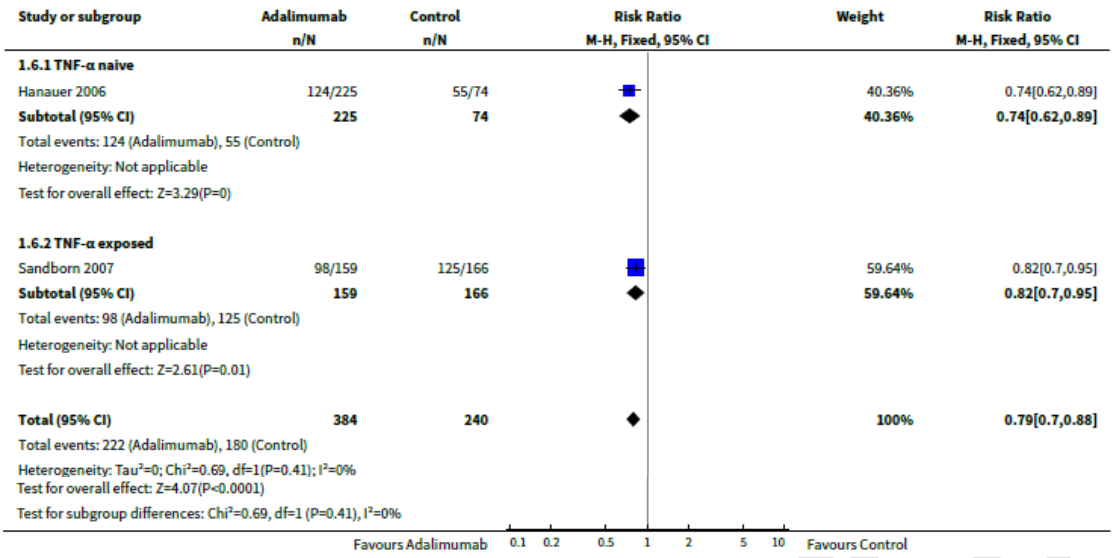
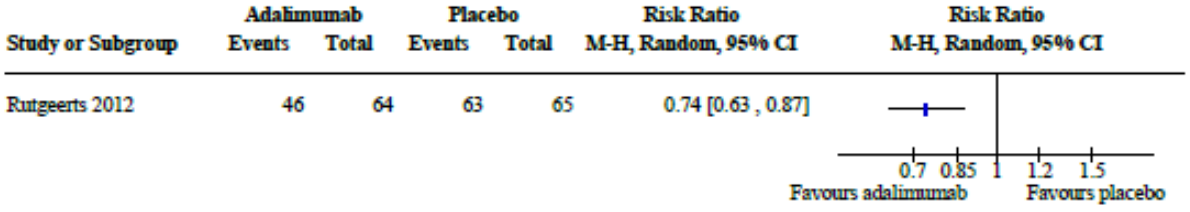


Figure 15: *Comparison 1 (Adalimumab vs placebo); Outcome 1.4 (Number of participants who achieved clinical response at 4 weeks); Sub-group analysis by previous TNF exposure – extracted from Townsend 2020.*

Outcome 1.5 Number of participants with maintained endoscopic improvement

Townsend et al. 2020(2) reported that a fewer adalimumab receiving participants failed to maintain endoscopic remission or response **at 52 weeks** as compared to placebo (Endoscopic remission: RR=0.74 in favour of adalimumab, 95% CI [0.63 to 0.87], i^2=NA, NNT 4 95% CI [3 to 8], P=0.0002, 1 RCT, n=129 – moderate certainty of evidence (GRADE from Townsend 2020 – downgraded by one level due to sparse data); Endoscopic response: RR 0.76 in favour of adalimumab, 95% CI [0.66 to 0.88], i^2=NA, NNT 5 95% CI [3 to 8], P=0.0001, 1 RCT, n=129 – GRADE not reported) – See figure16 below.



Analysis 1.7. Comparison 1: Adalimumab versus placebo, Outcome 7: Failure to maintain endoscopic response at 52 weeks

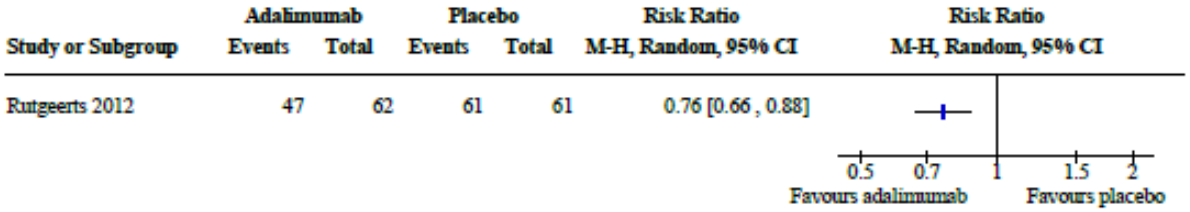


Figure 16: *Comparison 1 (Adalimumab vs placebo); Outcome 1.5 (Number of participants with maintained endoscopic improvement) – extracted from Townsend 2020.*

Outcome 1.6 Number of participants with induced endoscopic improvement

Outcome not reported

Outcome 1.7 Mean number of hospitalisations and surgeries

Mao 2017(26) reported that TNF inhibitors were more effective that placebo in reducing Crohn's disease related hospitalisations (OR 0.46, 95% CI [0.36 to 0.60]) and surgeries (OR 0.23, 95% CI [0.13 to 0.42]). Adalimumab ranked lower than infliximab but higher azathioprine. The analysis was not specifically on refractory patients and included patients with fistulising CD. However one included study, Feagan 2008, focussed on patients from the CHARM trial, which was on individuals with refractory Luminal/non-specific CD (as per the medicine review PICO definition) and assessed adalimumab specifically. The estimates reported for reducing hospitalisations and surgeries were OR 0.50, 95% CI [0.32 to 0.79), 1 study, n=778 (high quality[ii]) and OR 0.15 [0.04 to 0.54], 1 study, n=778 (high quality [ii]) respectively – See Figure 17 below.

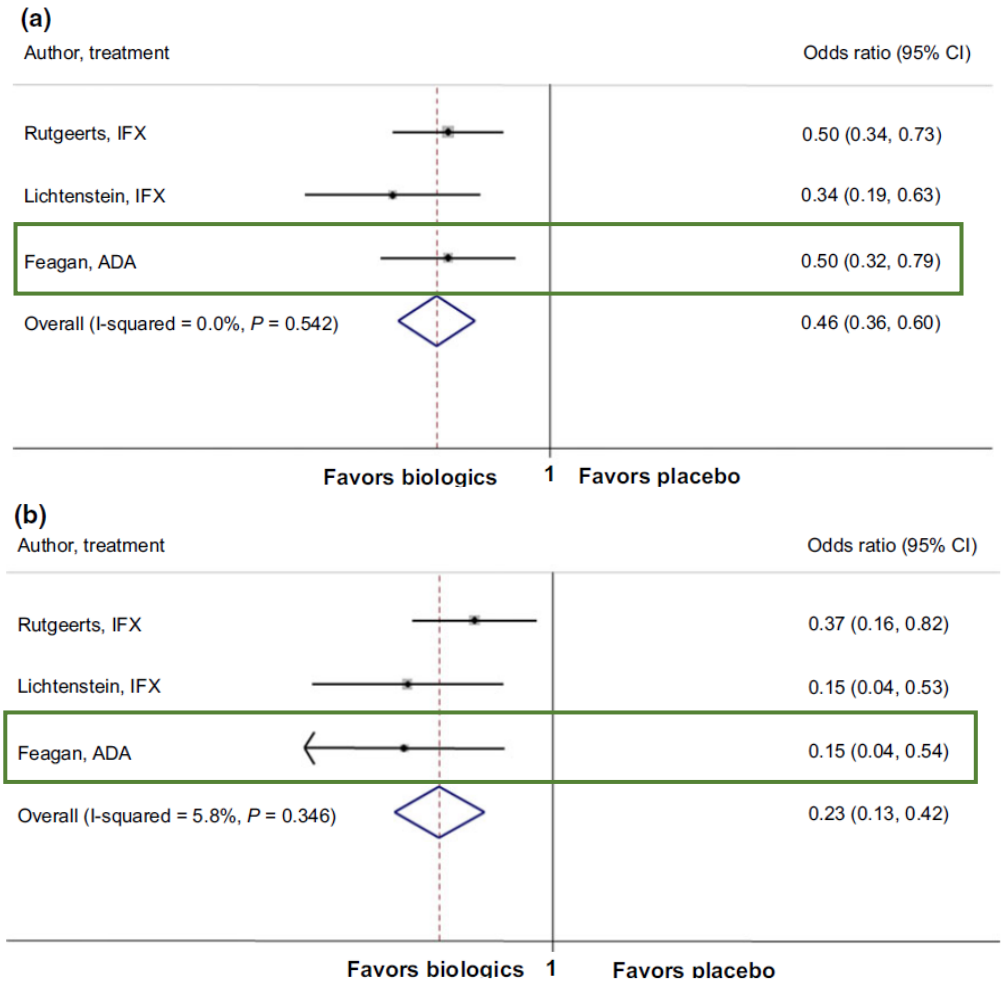


Figure 17: *Comparison 1 (Adalimumab vs placebo); Outcome 1.7 (Reductions in A. hospitalisations and B. surgeries) – extracted from Townsend 2020.*

Outcome 1.8 Quality of life

Abbass et al. 2019(35) reported on quality of life for induction of response or remission but presented results narratively as the data did not allow for meta-analysis (n=714, 3 RCTs) – Summary of Findings Table –*moderate certainty of evidence (*GRADE result extracted Abbass 2019*, downgraded 1 level due to sparse data*. All included RCTs reported on the quality of life utilising the Inflammatory Bowel Disease Questionnaire (IBDQ) (scale 32-224 with higher score representing better quality of life). Hanauer 2006 reported significantly higher IBDQ scores at week four in the adalimumab 160 mg/80 mg dose group compared to placebo. Sandborn et al. 2007 reported a higher mean IBDQ score at four weeks in the adalimumab group (150) compared to the placebo group (139) (P < 0.001). Watanabe 2012 also reported that IBDQ scores were higher at four weeks in the adalimumab 160 mg/80 mg group compared to placebo, although the difference was not statistically significant. However Watanabe 2012 also evaluated quality of life with the Short-Form 36 Health survey (scale 0-100 with higher score representing better quality of life) and reported that

[ii] Only RoB 1 conducted, low risk of bias, no issues with imprecision, indirectness or inconsistency.

the SF-36 score was significantly higher in the adalimumab 160 mg/80 mg dose group at four weeks compared to placebo.

Yin 2022 reported that Chen et al. found significantly higher IBDQ scores at week 4 in the ADA 160 mg/80 mg group compared with the placebo group (P < 0.01).

Outcome 1.9 Safety

Maintenance therapy

Townsend et al. 2020(2) reported that for patients undergoing maintenance therapy there is probably no difference in adverse events at 52 to 56 week follow-up between adalimumab and placebo (RR=1.01 95% CI [0.94 to 1.09], P=0.72, 4 RCTs, n=1012 – *high certainty of evidence (GRADE from Townsend 2020 – See Summary of Findings Table)*. However patients on adalimumab maintenance therapy had a lower percentage of serious adverse events (events included infectious complications including tuberculosis, abscess formation and wound infections, multiple sclerosis, pulmonary embolism) compared to placebo (RR=0.56 in favour of adalimumab, 95% CI [0.39 to 0.80], P=0.002, 4 RCTs, n=1012 – *moderate certainty of evidence (GRADE from Townsend 2020, downgraded for sparse number of events*) – See Summary of Findings Table and figure 18 below.

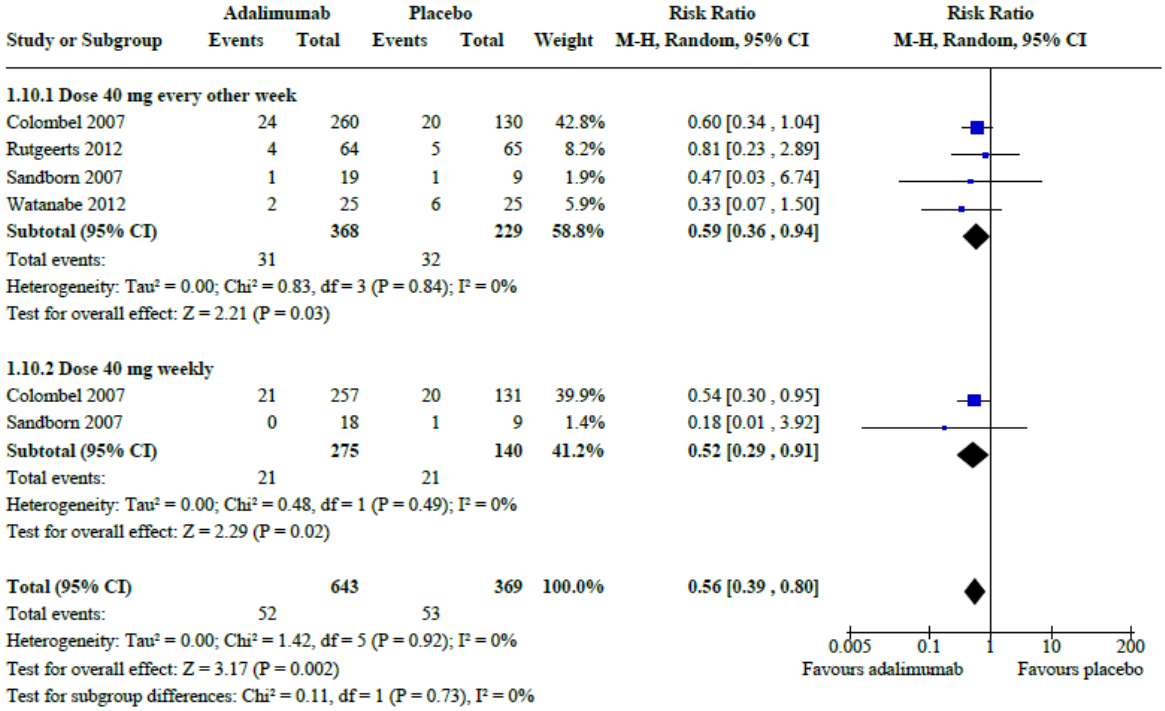


Figure 18: *Comparison 1 (Adalimumab vs placebo); Outcome 1.9 (Safety – serious adverse events for patients undergoing maintenance therapy) – extracted from Townsend 2020.*

Induction therapy

Abbass et al. 2019(35) reported that for patients undergoing induction therapy there was no difference in adverse events between adalimumab and placebo at 4 weeks (RR=0.90, 95% CI [0.74 to 1.09], P=0.28 – *not significant,* 3 RCTs, n=531 – *moderate certainty of evidence (GRADE from Abbass 2019, downgraded by 1 one level due to serious inconsistency (i^2 = 53%).* The review similarly found that there may be no difference in serious adverse events between groups (RR=0.44, 95% CI [0.17 to 1.15], P=0.09 – *not significant,* 3 RCTs, n=531 – *low certainty of evidence (GRADE from Abbass 2019, downgraded by 2 levels due to very serious imprecision (19 events)* – See Summary of Findings Table and Figure 19 below.

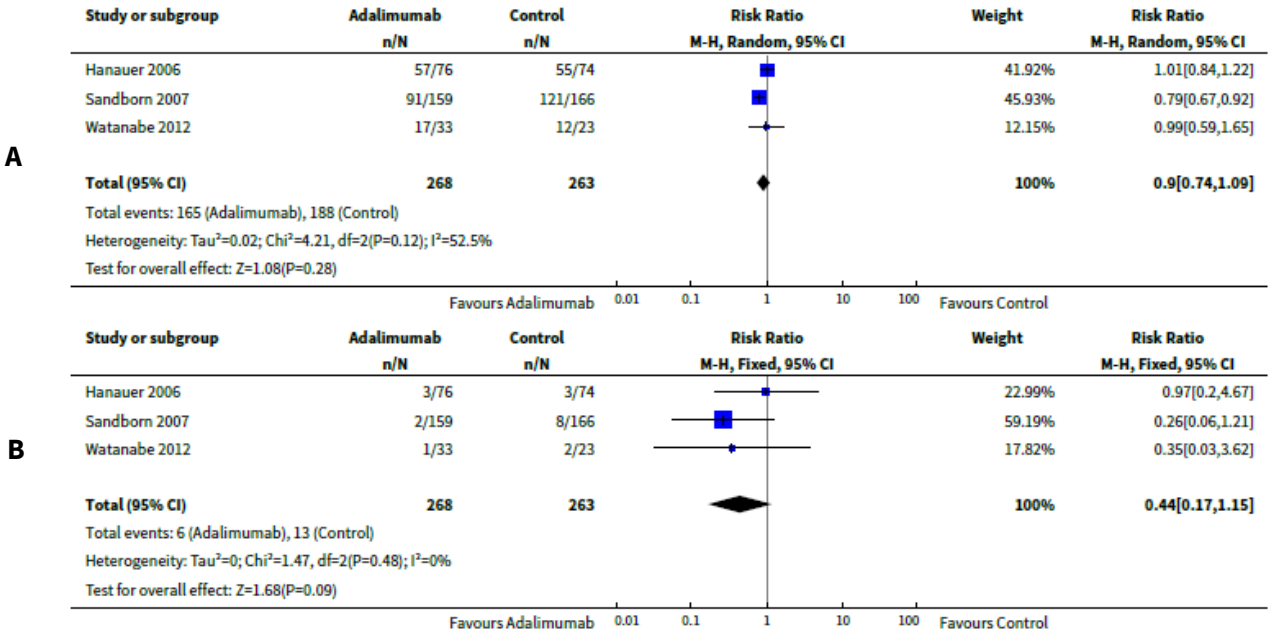


Figure 19: *Comparison 1 (Adalimumab vs placebo); Outcome 1.9 (Safety – (A) adverse events and (B) serious adverse events for patients undergoing induction therapy) – extracted from Abbass 2019.*

Comparison 2: Intravenous infliximab in addition to standard of care versus standard of care alone

Outcome 2.1 Number of participants with maintained clinical remission (as defined by the study)

Gordon 2024(19) reported that there were more participants in the placebo groups with clinical relapse (at 30-32 weeks – CDAI > 150) compared to infliximab (RR=0.73 in favour of infliximab, 95% CI [0.63 to 0.84], i^2= 0%, P<0.00001, NNT 6[iii] 95% CI [4 to 10], 2 RCTs, n=408) – *moderate certainty of evidence (GRADE from Gordon 2024 - downgraded one level due to concerns about risk of randomisation, selective reporting and other bias*). See Summary of findings table and Figure 20.

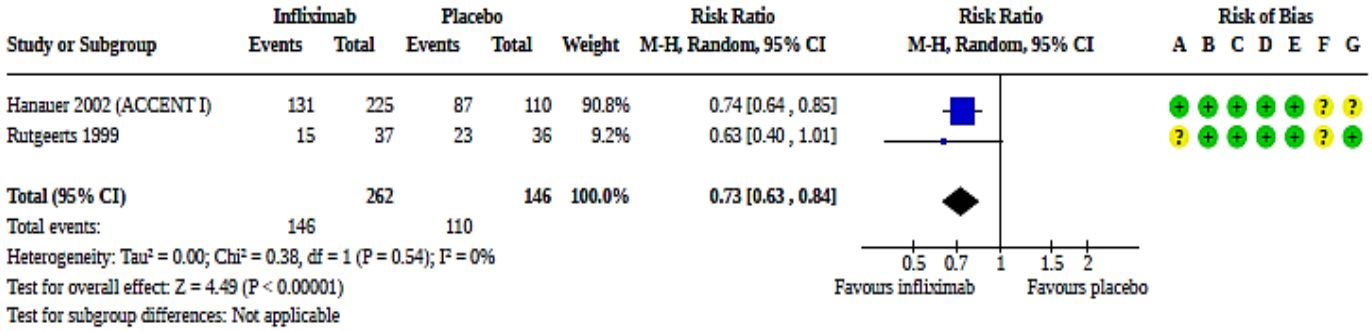


Figure 20: *Comparison 2 (infliximab vs placebo); Outcome 2.1 (No. of participants with clinical relapse) – sourced from Gordon 2024* (19)

Gordon 2024(19) reported that there were less participants in the infliximab and purine analogue combination group with clinical relapse as defined by the study, at 48 weeks compared to the purine analogue only group (RR=0.20 in favour of infliximab combination, 95% CI [0.10 to 0.42], i^2= NA, P<0.0001, NNT 3 95% CI [2 to 4], 1 RCTs n=115) – *moderate certainty of evidence (GRADE from Gordon 2024 - downgraded one level due to some concerns about bias from selective reporting*). See Summary of findings table and Figure 21.

[iii] Unweighted NNT based on total events from both trials

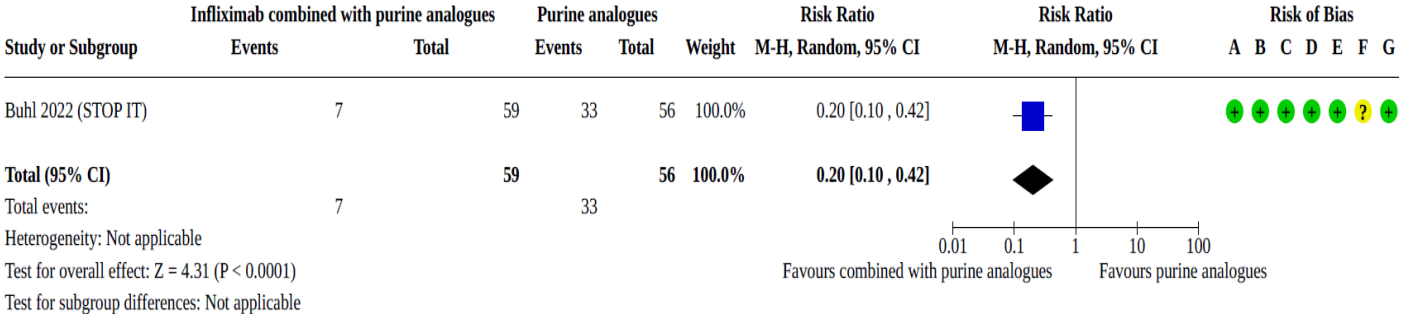


Figure 21: *Comparison 2 (infliximab combined with analogue purines vs analogue purines alone); Outcome 2.1 (No. of participants with clinical relapse) – sourced from Gordon 2024* (19).

Outcome 2.2 Number of participants with induced clinical remission (CDAI < 150)

Gordon 2023(3) reported that there were more participants in the infliximab 5-10mg/kg group who achieved clinical remission at week 4 compared to placebo (RR=4.55 in favour of infliximab, 95% CI [1.53 to 13.50], i^2= NA, P=0.006, NNT 3 95% CI [2 to 5], 1 RCT, n=80) – *low certainty of evidence (GRADE from Gordon 2023, downgraded one level due to serious concerns with risk of bias (selective reporting and unclear randomisation), and one level due to serious concerns with imprecision due to low event numbers*). See Summary of findings table and Figure 22.

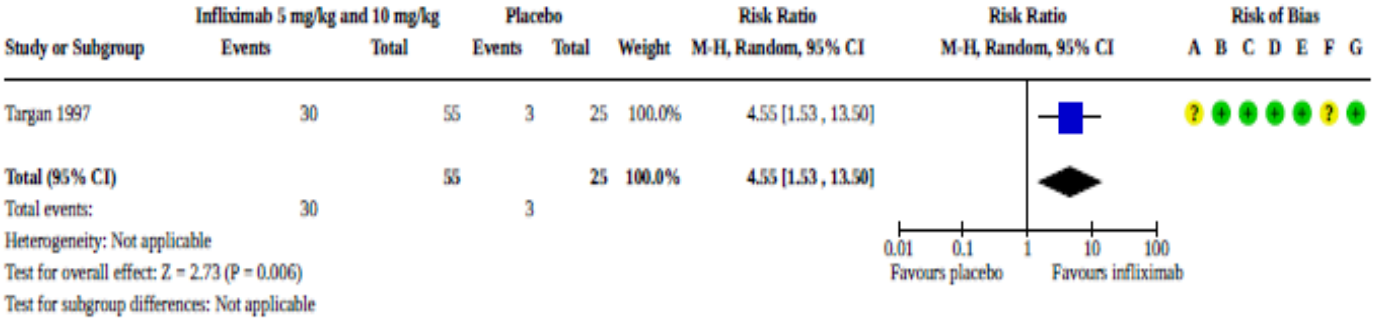


Figure 22: *Comparison 2 (infliximab vs placebo); Outcome 2.2 (No. of participants with induced clinical remission) – sourced from Gordon 2023*(3).

Outcome 2.3 Number of participants with maintained clinical response (as defined by the study)

Gordon 2024 (19) reported that more participants had a loss of clinical response in the placebo group compared to the infliximab group (RR: 0.59 95% CI [0.37 to 0.96], P=0.03, NNT 4, 95% CI [3 to 26], 1 RCT, n=73) – *very low certainty of evidence (GRADE from Gordon 2024, downgraded two levels due to serious imprecision from very low participant and event numbers, downgrade one level due to concerns about risk of blinding, and selective reporting*). See Summary of findings table and Figure 23.

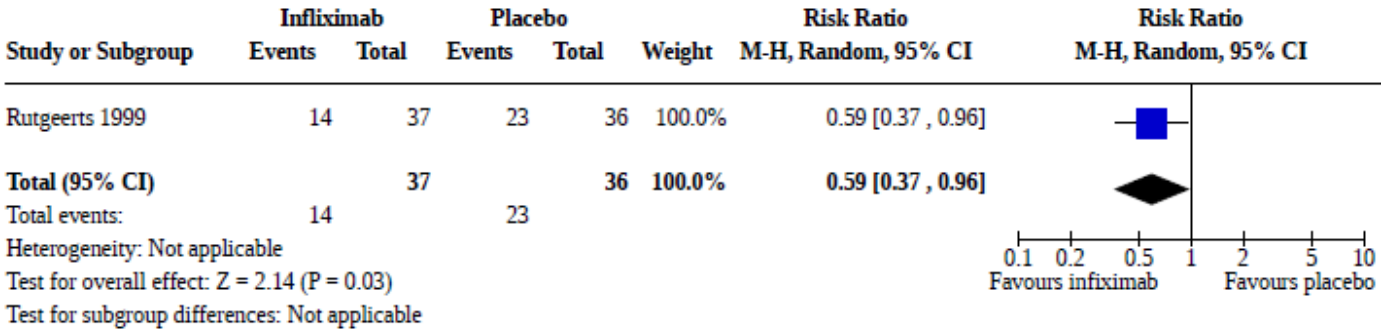


Figure 23: *Comparison 2 (infliximab vs placebo); Outcome 2.3 (No. of participants with loss of clinical response) – sourced from Gordon 2024* (19).

Outcome 2.4 Number of participants with induced clinical response

Gordon 2023(3) reported that there were more participants in the infliximab 5-10mg/kg group who achieved clinical response at week 4 (reduction of CDAI score ≥ 70 from baseline) compared to placebo (RR=4.09 in favour of infliximab,

95% CI [1.63 to 10.25], i^2= NA, P=0.003, NNT 3 95% CI [2 to 4], 1 RCT, n=80) – *low certainty of evidence (GRADE from Gordon 2023, downgraded one level due to serious concerns with risk of bias (selective reporting and unclear randomisation), and one level due to serious concerns with imprecision due to low event numbers*). See Summary of findings table and Figure 24.

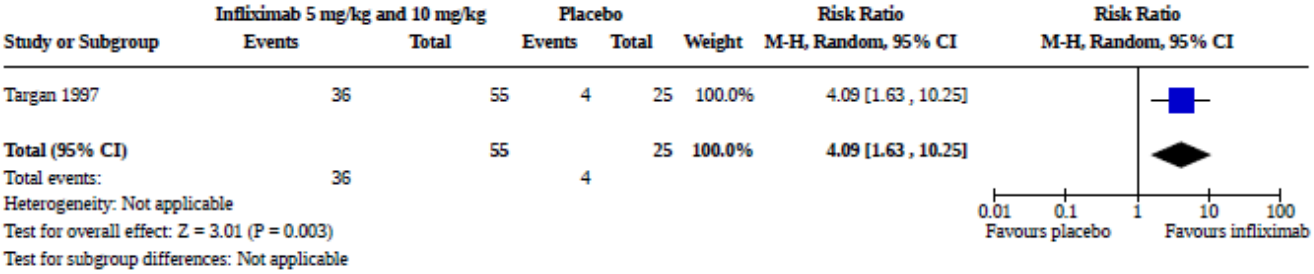


Figure 24: *Comparison 2 (infliximab vs placebo); Outcome 2.2 (No. of participants with induced clinical response) – sourced from Gordon 2023*(3).

Outcome 2.5 Number of participants with maintained endoscopic improvement

Gordon 2024 (19) reported that more participants had a loss of endoscopic response in the purine analogue only group compared to the infliximab and purine analogue combination group (RR: 0.38 95% CI [0.25 to 0.59], P<0.0001, NNT 3, 95% CI [2 to 4], 1 RCT, n=73) – *(GRADE not evaluated in Gordon 2024)* - See Figure 25.

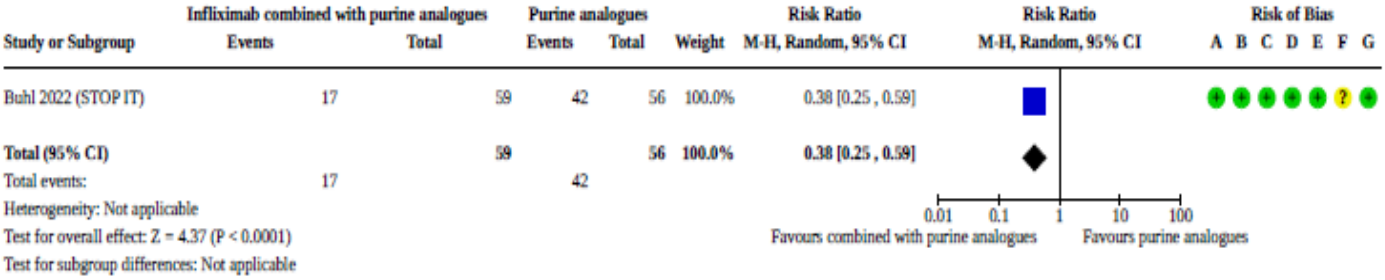


Figure 25: *Comparison 2 (infliximab combined with analogue purines vs analogue purines alone); Outcome 2.3 (No. of participants with maintained endoscopic improvement) – sourced from Gordon 2024* (19).

Outcome 2.6 Number of participants with induced endoscopic improvement

Outcome not reported.

Outcome 2.7 Mean number of hospitalisations and surgeries

Mao 2017(26) reported that TNF inhibitors were more effective that placebo in reducing Crohn's disease related hospitalisations (OR 0.46, 95% CI [0.36 to 0.60]) and surgeries (OR 0.23, 95% CI [0.13 to 0.42]). Infliximab ranked higher than adalimumab and azathioprine. The analysis was not specifically on refractory patients and included patients with fistulising CD. However one included study, Rutgeerts 2004, focussed on patients from the ACCENT I trial, which was on individuals with refractory Luminal/non-specific CD (as per the medicine review PICO definition) and assessed infliximab. The estimate reported for hospitalisations was OR 0.50, 95% CI [0.34 to 0.73), 1 study, n=573 (high quality[iv]) and 0.37 [0.16 to 0.82], 1 study, n=573 (high quality [iv]) respectively – See Figure 26 below.

[iv] Only RoB 1 conducted, evaluated by reviewers as high quality based on low risk of bias, no issues with imprecision, indirectness or inconsistency.

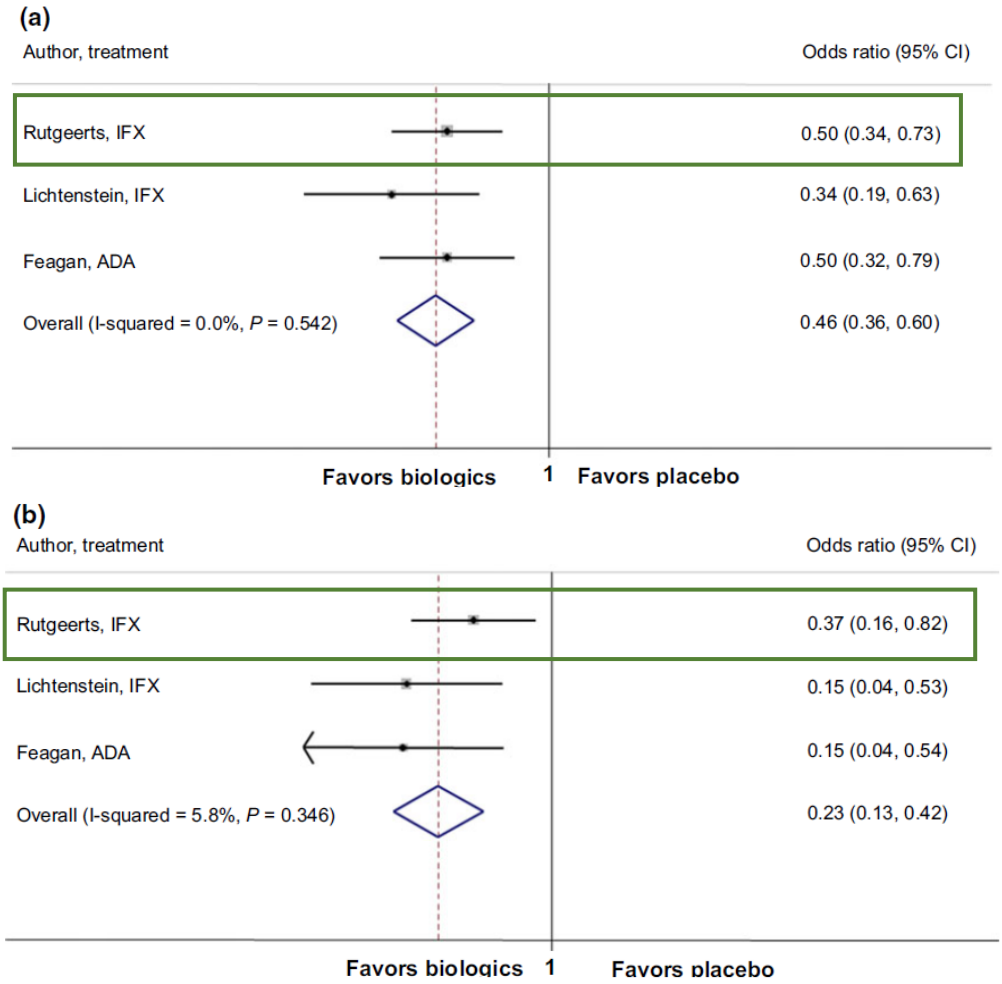


Figure 26: *Comparison 1 (Infliximab vs placebo); Outcome 2.7 (Reductions in A. hospitalisations and B. surgeries) – extracted from Townsend 2020.*

Outcome 2.8 Quality of life

None of the included articles reported on this outcome specifically.

Outcome 2.9 Safety

Maintenance therapy

Gordon 2024(19) reported less withdrawals due to adverse events at 48 weeks in infliximab and purine analogue combination group (4 withdrawals) compared to the purine analogue alone group (8 withdrawals) however the CI did cross the null (RR 0.47 95% CI [0.15 to 1.49], P=0.20, 1 trial, n=115) – *very low certainty of evidence (GRADE from Gordon 2024, downgraded twice due to serious imprecision from very low participant and event numbers and once due to concerns about risk of bias for randomisation, blinding, attrition and selective reporting)*. See Summary of findings table and Figure 27.

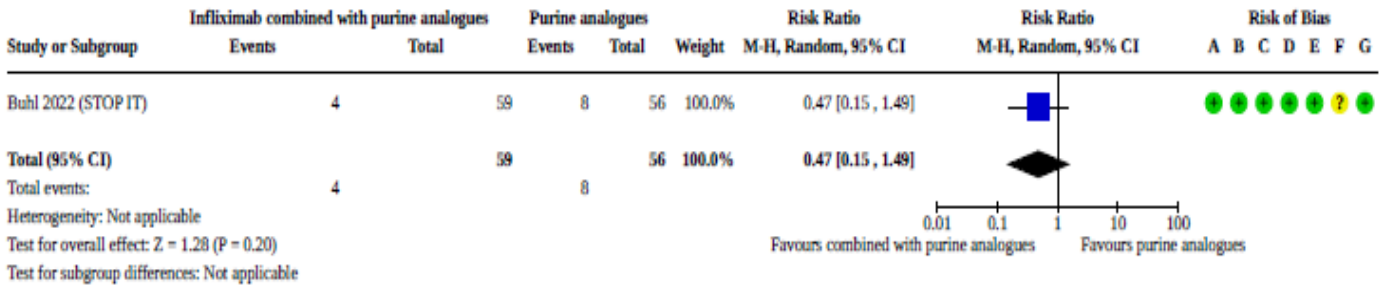


Figure 27: *Comparison 2 (infliximab and purine analogues vs purine analogues alone); Outcome 2.9 (Safety – withdrawals due to adverse events) – sourced from Gordon 2024*(19).

Gordon 2024 reported more serious adverse events (at 48 weeks – 2 years) in infliximab and purine analogue combination group (12 events) compared to the purine analogue alone group (10 events) however the CI did cross the null (RR 1.19 95% CI [0.54 to 2.64], P=0.80, i^2=0%, 2 trials, n=257) – *very low certainty of evidence (GRADE from Gordon 2024, downgraded twice due to serious imprecision from very low participant and event numbers and once due to concerns about risk of bias for randomisation, blinding, attrition and selective reporting)*. See Summary of findings table and Figure 28.

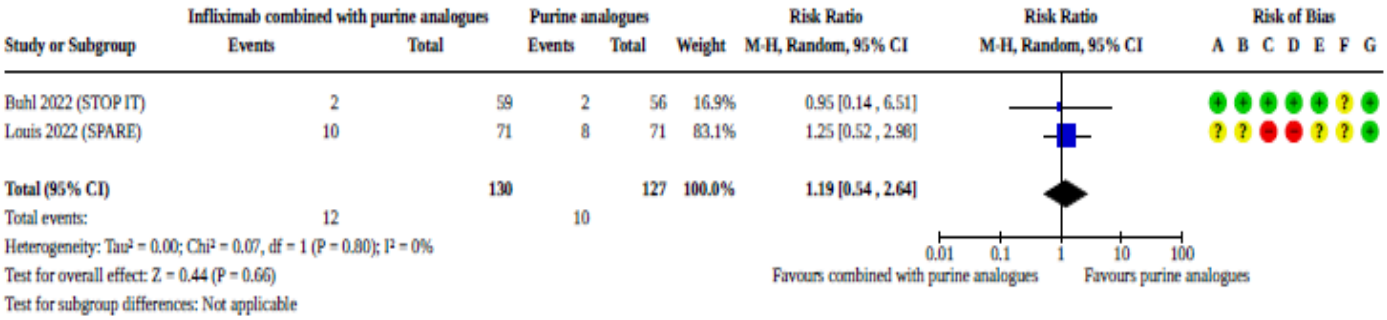


Figure 28: *Comparison 2 (infliximab and purine analogues vs purine analogues alone); Outcome 2.9 (Safety – serious adverse events) – sourced from Gordon 2024*(19).

Induction therapy

Gordon 2023 reported less total adverse events in infliximab and purine analogue combination group (82 events) compared to the purine analogue alone group (97 events) however the CI did cross the null (RR 0.88 in favour of combination group 95% CI [0.65 to 1.20], P=0.42, 2 RCTs) – *(GRADE not conducted for this outcomes in Gordon 2023)* - See Figure 29.

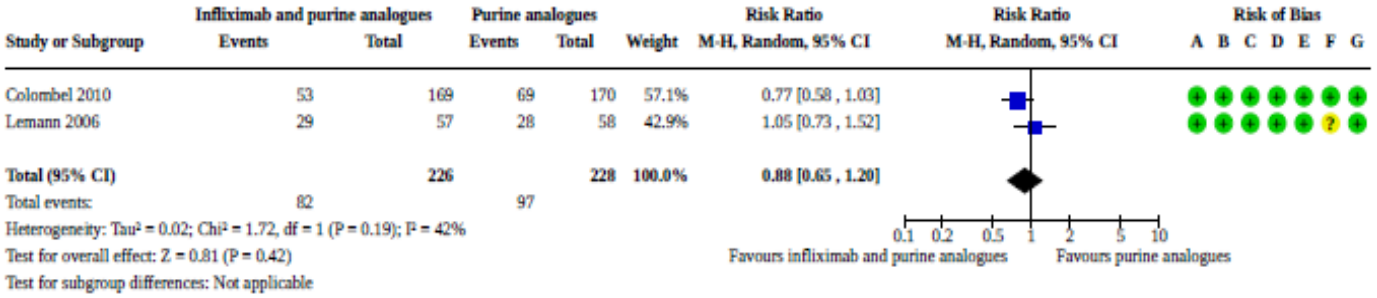


Figure 29: *Comparison 2 (infliximab combination vs purine analogues alone); Outcome 2.9 (Safety – total adverse events) – sourced from Gordon 2023*(3).

Efficacy and safety in paediatric population

Adalimumab – Chen 2024(30)

Maintenance of remission

Chen 2024 reported that analysis utilising pooled weighted proportions that 57% of participants on **adalimumab** maintained remission (95% CI [55% to 79%], i^2=92.1% - high heterogeneity, P=0.000) – See Figure 30. The high heterogeneity was explored in subgroup analyses. It was found that severity at baseline impacted the results; maintenance was significantly higher in children with PCDAI < 30 (0.69, 95% CI [0. 59 to0.80]) at baseline than in those with ≥ 30 (0.39, 95% CI [0.24 to 0.54]). No significant difference was found between 40mg or >40mg subgroups however there was a significantly lower proportion of patients with maintained remission in the <40mg dose sub-group. The proportion of participants with maintained remission was significantly higher in the infliximab naïve subgroup (0.75, 95% CI [0.65 to 0.86], compared to the TNF exposed sub-groups.

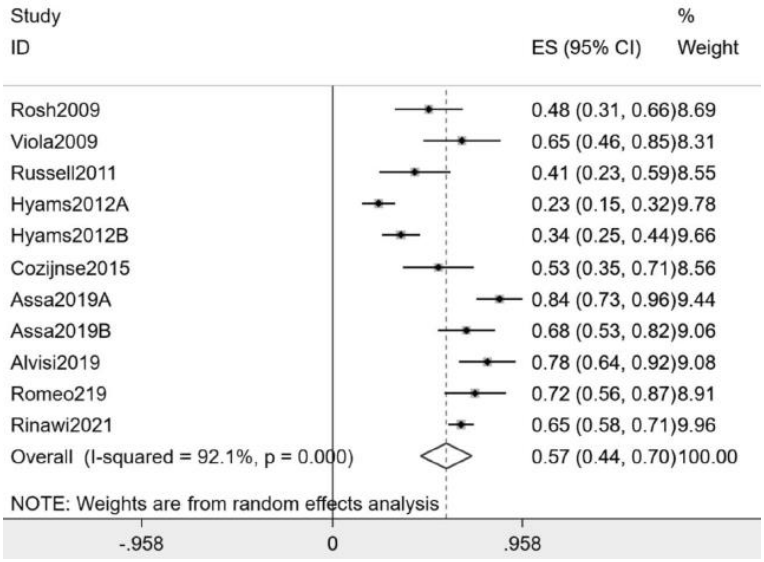


Figure 30: Adalimumab compared to placebo for maintenance of remission in children – extracted from Chen 2024.

Induction of remission

Chen 2024 reported that analysis utilising pooled weighted proportions that 59% of participants on adalimumab achieved induction of remission (95% CI [25 to 61%], i^2=98.6% - high heterogeneity, P=0.000) – See Figure 31. The high heterogeneity was explored in subgroup analyses. It was found that severity at baseline impacted the results; induction was significantly higher in children with PCDAI < 30 at baseline (0.76 95% CI [0. 57 to 0.95]) than in those with ≥ 30 (0.34, 95% CI [0.20 to 0.49]). A difference was also found between subgroups by infliximab exposure, with a significantly higher proportion of participants with induced remission in the infliximab naïve subgroup (0.94, 95% CI [0.90 to 0.98]).

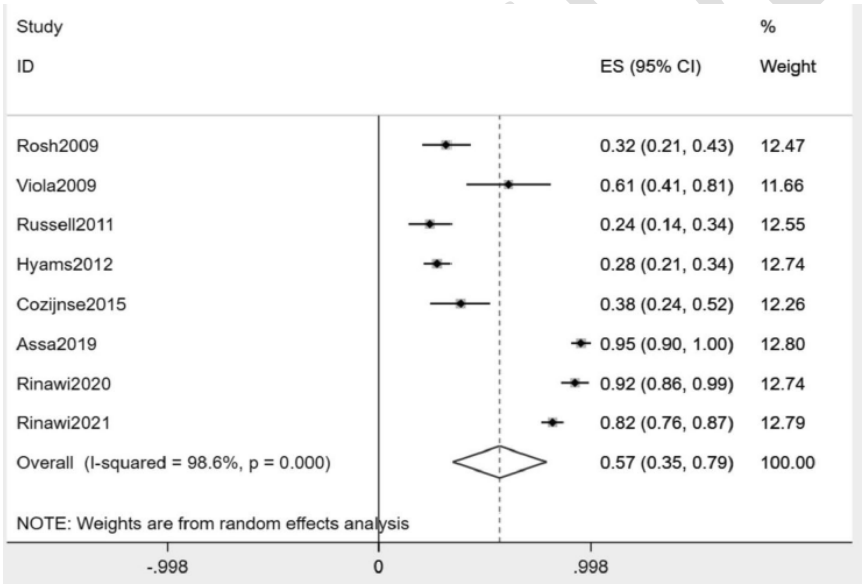


Figure 31: Adalimumab compared to placebo for induction of remission in children – extracted from Chen 2024.

Maintenance of response

Chen 2024 reported that analysis utilising pooled weighted proportions that 63% of participants on adalimumab achieved induction of remission (95% CI [30 to 87%], i^2=94.4% - high heterogeneity, P=0.000) – See Figure 32. The high heterogeneity was explored in subgroup analyses. It was found that study design impacted the results; maintenance of response was greater in non-RCTs than RCTs (0.72, 95% CI [0.56 to 0.88] vs. 0.35, 95% CI [0.22 to 0.48]). Results were also dose dependent; < 40mg (0.42, 95% CI [0.32 to 0.52], 40mg (0.57, 95% CI [0.35 to 0.78]), >40mg (0.91, 95% CI [0.80 to1.03]). Adalimumab was found to be significantly more effective in the infliximab naïve subgroup (0.84, 95% CI [0.72 to 0.97]).

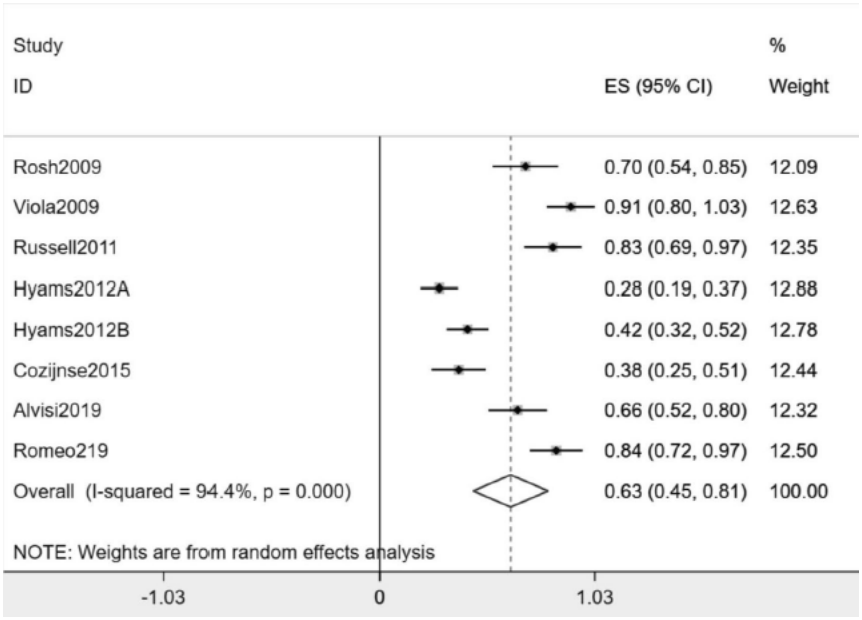


Figure 32: Adalimumab compared to placebo for maintenance of response in children – extracted from Chen 2024.

Induction of response

Chen 2024 reported that analysis utilising pooled weighted proportions that 60% of participants on adalimumab achieved induction of response (95% CI [6 to 35%], i^2=96.9% - high heterogeneity, P=0.000). – See Figure 33.

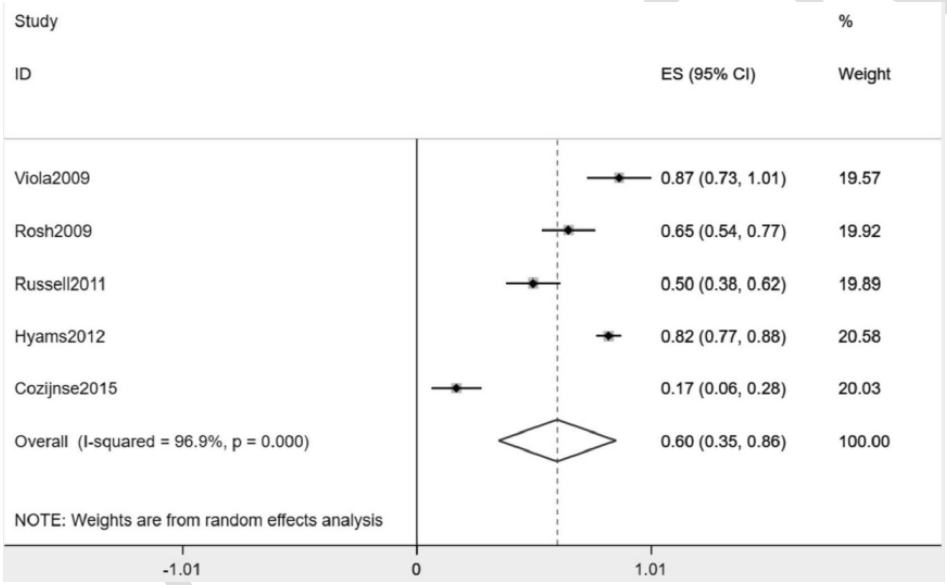


Figure 33: Adalimumab compared to placebo for induction of response in children – extracted from Chen 2024.

Safety

Infections and serious infections were the most commonly reportedly adverse event and severe adverse events respectively (infections = 134 patients, 15.1%; serious infections = 30 patients, 3.5%). Injection related reactions were reported in 39 patients (4.4%). One study reported two deaths due to central venous catheter sepsis.

Infliximab – Martin-Garcia 2022

One trial included in the Martin-Garcia 2022 SR reported on infliximab compared to conventional therapy (34). A higher proportion of patients in the first line infliximab group achieve clinical and endoscopic remission at week 10 compared to the conventional therapy group (clinical remission: 59% vs 34%, p=0.021 and endoscopic remission: 59% vs 17%, p=0.001). There was no significant difference in maintenance of clinical remission at week 52 (p=0.421),

however there were significantly more patients in the first line infliximab group (19/46, 41%) in clinical remission on azathioprine monotherapy without need for treatment escalation compared to the conventional therapy group (7/48, 15%, p=0.004). The RCT included in the Martin-Garcia 2023 review, Jongsma 2022 which compared infliximab first line with step up conventional therapy reported less adverse events in the infliximab group (44%) compared to conventional therapy (60%) group however the CI crossed the null (absolute difference 16%, 95% CI [-0.04% to 0.33%], p=0.215).

GUIDELINES

Seven relevant guidelines on the treatment of TNF inhibitors for luminal/non-specific CD were found. These guidelines were produced by NICE (36), American College of Gastroenterology (ACG)(6), American Gastroenterological Association (AGA)(37), British Society of Gastroenterology (BSG)(8), The European Crohn's and Colitis Organisation (ECCO)(7) and the Canadian Association of Gastroenterology (Adults(38) and paediatrics (39)). Appendix 6 provides a summary of the AGREE II assessments conducted for each guideline. The relevant recommendations from each guideline have been extracted and are presented **in Table 3** below along with the overall score from AGREE II and score for domain evaluating rigour. Four of the guidelines were rated as 5 out of 7 for overall score (ACG, AGA, ECCO, CAG – Paediatric) and the remaining three guidelines as 6 out 7 (BSG, NICE and CAG – adults). All guidelines recommended infliximab and adalimumab in luminal/non-specific CD who are refractory to conventional therapies The recommendations were all reported to be strong with evaluation of underlying evidence varying from very low (BSC) to moderate (ACG, AGA, ECCO, CAG – adults) to high (CAG – paediatrics – note evidence was predominantly based on adults).

Quality

Included SRs were evaluated to be high quality on AMSTAR 2 review, except for Mao 2017 (hospitalisation and surgeries – critically low quality), Chen 2024 (paediatrics – low quality) and Martin-Garcia 2022 (paediatrics – moderate quality). GRADE or JADAD results evaluated by the SR authors were extracted directly for majority of outcomes.

For the adult population, certainty/quality of evidence of efficacy outcomes for adalimumab compared to placebo ranged from **moderate** (Maintenance of clinical remission at 24-26 weeks; Induction of clinical remission (CDAI < 150) at 4 weeks; Maintained clinical response; Maintained endoscopic remission; and Quality of life) to **high** (Maintenance of clinical remission at 52-56 weeks; Induction of clinical response (= ≥100-point CDAI decrease from baseline) at 4 weeks; Reduction of hospitalisations and surgeries). Certainty of safety outcomes for adalimumab compared to placebo was considered **low** for serious adverse events during induction Therapy; **moderate** for serious adverse events in maintenance therapy and adverse events during induction therapy; and **high** for adverse events during maintenance therapy. See Summary of Findings Tables, Risk of Bias Assessments, and Appendix 1: Evidence to Decision Framework.

Certainty/quality of evidence for infliximab compared to placebo , in the adult population, for efficacy outcomes varied – **very low** (Maintained clinical response as defined by the study); **low** (Induction of clinical remission (CDAI < 150) at 4 weeks; Induction of clinical response at week 4 (reduction of CDAI score > 70 from baseline); **moderate** (Maintenance of clinical remission at 30-32 weeks – CDAI > 150); and **high** (reduction in hospitalisations and surgeries). Certainty of safety outcomes for purine analogues vs infliximab AND purine analogues was **very low** (Maintenance Therapy – adverse events; Maintenance Therapy). See Summary of Findings Tables, Risk of Bias Assessments, and Appendix 1: Evidence to Decision Framework.

Evidence for paediatric population was limited and certainty or overall quality of results was not conducted in the SRs. Both SRs (Chen 2024 and Martin-Garcia 2023) did however conduct RoB for the clinical trials included in the analyses. Overall quality is considered low due to some concerns with risk of bias (Chen 2024 and Martin-Garcia 2023), heterogeneity (Chen 2024) and small sample size (Chen 2024 and Martin-Garcia 2023).

Table 3. Clinical guideline recommendations

Guideline	Recommendations	Strength of evidence	AGREE II
Crohn's Disease Management, NICE Guideline 2019	**INDUCTION OF REMISSION** Adults • 1.2.12 Infliximab and adalimumab, within their licensed indications, are recommended as treatment options for adults with severe active Crohn's disease whose disease has not responded to conventional therapy (including immunosuppressive and/or corticosteroid treatments), or who are intolerant of or have contraindications to conventional therapy. Infliximab or adalimumab should be given as a planned course of treatment until treatment failure (including the need for surgery), or until 12 months after the start of treatment, whichever is shorter. People should then have their disease reassessed (see recommendation 1.2.16) to determine whether ongoing treatment is still clinically appropriate. Paediatrics • Infliximab, within its licensed indication, is recommended for the treatment of people aged 6 to 17 years with severe active Crohn's disease whose disease has not responded to conventional therapy (including corticosteroids, immunomodulators and primary nutrition therapy), or who are intolerant of or have contraindications to conventional therapy. The need to continue treatment should be reviewed at least every 12 months.	2010 NICE Technical Appraisal(40), strength of evidence not provided	**Overall assessment score:** 89%, 6 out of 7 **Score for rigour and methodology domain:** 85%
	MAINTAINING REMISSION • 1.2.16 Treatment with infliximab or adalimumab (see recommendations 1.2.12 and 1.2.15) should only be continued if there is clear evidence of ongoing active disease as determined by clinical symptoms, biological markers and investigation, including endoscopy if necessary. Specialists should discuss the risks and benefits of continued treatment with patients and consider a trial withdrawal from treatment for all patients who are in stable clinical remission. People who continue treatment with infliximab or adalimumab should have their disease reassessed at least every 12 months to determine whether ongoing treatment is still clinically appropriate. People whose disease relapses after treatment is stopped should have the option to start treatment again.		
ACG Clinical Guideline: Management of Crohn's Disease in Adults 2018	• 24.Anti-TNF agents (infliximab, adalimumab, certolizumab pegol) should be used to treat Crohn's disease that is resistant to treatment with corticosteroids. • 25. Anti-TNF agents should be given for Crohn's disease refractory to thiopurines or methotrexate • 26. Combination therapy of infliximab with immunomodulators (thiopurines) is more effective than treatment with either immunomodulators alone or infliximab alone in patients who are naive to those agents (strong recommendation, high level of evidence)	GRADE: Strong recommendation, moderate level of evidence.	**Overall assessment score:** 67%, 5 out of 7 **Score for rigour and methodology domain:** 81%
	• 49. Anti-TNF therapy, specifically infliximab, adalimumab, and certolizumab pegol, should be used to maintain remission of anti-TNF-induced remission	GRADE: strong recommendation, high level of evidence.	

	• 50. Anti-TNF monotherapy is effective at maintaining anti-TNF induced remission, but because of the potential for immunogenicity and loss of response, combination with azathioprine/6-mercaptopurine or methotrexate should be considered	GRADE: strong recommendation, moderate level of evidence.	
AGA Clinical Practice Guidelines on the Medical Management of Moderate to Severe Luminal and Perianal Fistulizing Crohn's Disease 2021	• Recommendation 1A. In adult outpatients with moderate to severe CD, the AGA recommends the use of anti-TNFa over no treatment for induction and maintenance of remission. • Recommendation 2A. In adult outpatients with moderate to severe CD who are naïve to biologic drugs, the AGA recommends the use of infliximab, adalimumab, or ustekinumab, over certolizumab pegol for the induction of remission. • Recommendation 4. In adult outpatients with moderate to severe CD, the AGA recommends the use of biologic drug monotherapy over thiopurine monotherapy for the induction of remission.	GRADE: Strong recommendation, moderate certainty evidence.	**Overall assessment score:** 75%, 5 out of 7 **Score for rigour and methodology domain:** 88%
British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults 2019	• Statement 43. We recommend that patients refractory to immunomodulator therapy despite dose optimisation should be considered for biological therapy. Choice between anti-TNF therapy, ustekinumab and vedolizumab should be made on an individual basis, considering patient preference, cost, likely adherence, safety data and speed of response to the drug	GRADE: strong recommendation, very low-quality evidence. Agreement: 95.7%.	**Overall assessment score:** 85%, 6 out of 7 **Score for rigour and methodology domain:** 77%
	• Statement 44. We recommend that combination therapy of infliximab with a thiopurine should be used as it is more effective than monotherapy infliximab in induction and maintenance of remission in active Crohn's disease	GRADE: strong recommendation, high-quality evidence. Agreement: 97.7%).	
ECCO Guidelines on Therapeutics in Crohn's Disease: Medical Treatment 2020	• Recommendation 1.5. We recommend the use of TNF inhibitors [infliximab, adalimumab, and certolizumab pegol] to induce remission in patients with moderate-to-severe Crohn's disease who have not responded to conventional therapy.	GRADE: Strong recommendation; moderate of evidence.	**Overall assessment score:** 72%, 5 out of 7 **Score for rigour and methodology domain:** 83%
	• Recommendation 1.6. We suggest against the combination of adalimumab and thiopurines over adalimumab alone to achieve clinical remission and response.	GRADE: Weak recommendation, moderate evidence.	
	• Recommendation 1.7. We recommend combination therapy with a thiopurine when starting infliximab to induce remission in patients with moderate-to-severe Crohn's disease, who have had an inadequate response to conventional therapy.	GRADE: Strong recommendation, moderate quality evidence.	
	• Recommendation 2.5. In patients with Crohn's disease who achieved remission with anti-TNF agents, maintenance treatment using the same treatment is recommended	GRADE: strong recommendation, moderate-quality evidence.	
	• Recommendation 2.11. In patients with Crohn's disease who have achieved long-term remission with the combination of infliximab and immunosuppressants, we suggest monotherapy with infliximab	GRADE: weak recommendation, very low-quality evidence.	
	• Recommendation 2.12. In patients with Crohn's disease who have achieved long-term remission with the combination of adalimumab and immunosuppressants, we suggest monotherapy with adalimumab	GRADE: weak recommendation, low-quality evidence.	

Canadian Association of Gastroenterology Clinical Practice Guidelines: The use of tumour necrosis factor-alpha antagonist therapy in Crohn's disease	• Statement 1 - Biologic therapy with infliximab, adalimumab or certolizumab is clinically effective for the induction of remission in patients who demonstrate continuing Crohn's disease symptoms despite conventional therapy (immunosuppressives [purine antimetabolites/methotrexate] and/or corticosteroids).	GRADE: High Vote: A 96% (strongly agree), B 4% (agree with minor reservation).	**Overall assessment score:** 80%, 6 out of 7 **Score for rigour and methodology domain:** 90%
	• Statement 4 - A TNF antagonist may be used in hospitalized patients with luminal or fistulizing Crohn's disease for situations in which a rapid onset of action is desired.	GRADE: Moderate Vote: A 68%, B 28%, C 4% (Agree with major reservation).	
	• Statement 8a - In patients who have responded to an induction regimen, maintenance therapy with infliximab (5 mg/kg every eight weeks), adalimumab (40 mg subcutaneously every two weeks) or certolizumab (400 mg subcutaneously every four weeks) has been shown to maintain remission	GRADE: High Vote: A 72%, B 28%.	
	• Statement 8b - Selected patients can be successfully maintained with an immunosuppressive drug alone following induction therapy with a TNF-antagonist.	GRADE: Medium Vote: A 40%, B 44%, C 12%, D 4% (Disagree with minor reservation).	
	• Statement 20: TNF antagonist therapy should be administered with caution to patients who have a history of recurrent bacterial or viral infections.	GRADE: High; Vote: A 60%, B 32%, C 8%.	
	• Statement 21: TNF antagonist therapy should be administered with caution to patients after consultation with the appropriate specialist in the following instances: I. HIV infection; II. hepatitis B and C; and III. organ-transplant recipients on multiple immunosuppressives.	GRADE: Low; Vote: A 80%, B 16%, C 4%.	
Canadian Association of Gastroenterology Clinical Practice: Guideline for the Medical Management of Pediatric Luminal Crohn's Disease	• Recommendation 17: In patients with moderate to severe inflammatory CD who have failed to achieve clinical remission with corticosteroids, we recommend anti-TNF therapy (adalimumab, infliximab) to induce and maintain clinical remission.	GRADE: Strong recommendation, high-quality evidence.*note evidence based also on adults Vote: strongly agree, 100%.	**Overall assessment score:** 73%, 5 out of 7 **Score for rigour and methodology domain:** 75%
	• Recommendation 18: In patients with moderate to severe inflammatory CD who fail to achieve or maintain clinical remission with a thiopurine or methotrexate, we recommend anti-TNF therapy to induce and maintain clinical remission.	GRADE: Strong recommendation, high-quality evidence.*note evidence based also on adults Vote: strongly agree, 93%; agree, 7%.	
	• Recommendation 19: In patients with severe inflammatory CD judged at risk for progressive, disabling disease, we suggest anti-TNF therapy as first-line therapy to induce and maintain clinical remission.	GRADE: Conditional recommendation, very-low-quality evidence. Vote: strongly agree, 47%; agree, 53%.	

COSTS

Table 4: Annual cost per patient - SEP

		Strength	Unit	PRICE*	Dose 60kg	Price per dose	Cost induction	Maintenance dose cost	Price per patient / year (YR 1)	Price per patient / year (YR 2)
Single exit prices	**Infliximab**									
	Induction	100	mg	R2 593.34	300	R7 780.02	R23 340.06		R68 075.18	R50 570.13
	Maintenance	100	mg	R2 593.34	300	R7 780.02		R7 780.02		
	Adalimumab									
	Induction	40	mg	R1 664.73	160	R6 658.90	R9 988.35		R49 941.75	R43 282.85
		40	mg	R1 664.73	80	R3 329.45				
	Maintenance	40	mg	R1 664.73	40			R1 664.73		

Table 5: Budget impact SEP

36 patients/year (for luminal/non-specific CD) - *Estimate from Prof Watermeyer based on survey from HODs across the country (65% estimate of 54 CD patients (luminal and fistulising CD patients)*

	Active Ingredients	Price per patient per year (YEAR 1)	Price per patient per year (YEAR 2)	Budget impact based on 36 patients (year 1)	Budget impact based on 36 patients (subsequent years)
Single exit prices*	Infliximab	R68 075.18	R50 570.13	R2 450 706.30	R1 825 524.68
	Adalimumab	R49 941.75	R43 282.85	R1 797 903.00	R1 558 182.60

***cheapest biosimilar product -SEP database December 2023;** adalimumab – amgevita®, infliximab - remiflex®*

Table 6: Budget impact over 5 years

Incremental annual costs (36 new Luminal CD patients per year)		
	SEP*	
	Infliximab	Adalimumab
Year 1	R2 240 645,76	R1 857 833,10
Year 2	R4 201 210,80	R3 475 945,80
Year 3	R6 161 775,84	R5 094 058,50
Year 4	R8 122 340,88	R6 712 171,20
Year 5	R10 082 905,92	R8 330 283,90

cheapest biosimilar product -SEP database December 2023

To note that costs were based on a 60kg patient. Due to the weight based regimen of infliximab an extra vial would be required per additional 10kg. A patient weighing 80kg would thus cost R82 987 and R72 614 in Year 1 and 2 respectively, whereas the cost of adalimumab would remain the same. Additional resources have not been costed for infliximab such as consumables for intravenous therapy, potential antibody testing, or concomitant use of an immunomodulator and/or corticosteroids. Potential savings in reduction of visits, hospitalisations or surgeries have not been included.

CONCLUSION

A motivation was received to include adalimumab and infliximab onto the TQ EML for patients with CD who have failed, or are intolerant to, conventional therapies. **Upon recommendations made by the NEMLC (meeting held 30 November 2023) the topic was split into two PICOs (PICO 1 – Fistulising CD; PICO 2 – Luminal/non-specific CD).** This review explored efficacy and safety of adalimumab and infliximab for patients with luminal CD. The majority of patients with CD will require numerous hospitalisations and/or surgeries. In patients where conventional therapy has failed; there is a need for a next line of therapy to prevent morbidity and increased resource requirements in these patients.

For adults adalimumab and infliximab were found to be superior to placebo for induction and maintenance of remission and response and reduction in CD related hospitalisations and surgeries. No difference was found between infliximab and adalimumab and placebo for serious adverse events and total adverse events. Quality of the data was generally moderate or high for outcomes reported for the adalimumab vs placebo comparison. Certainty of evidence was low to moderate for adverse events and serious adverse events. Quality was very low (high risk of bias, small number of events) to moderate (unclear risk of bias) for reported outcomes in the infliximab comparison. Limited data available for the paediatric population with no double blind, placebo controlled trials found, however findings show potential benefit for adalimumab and infliximab. Infection was the most frequently reported adverse event.

Utilisation of the therapy will result in an incremental cost however there is a potential that use of these agents may result in lower resource costs related to hospitalisations, surgeries and other procedures. The quality of data pertaining to this outcome was varied (very low to moderate for infliximab and moderate to high for adalimumab) however no further trials are anticipated in this population as treatment has progressed globally; and these agents are regarded internationally as the standard of care. Moreover, high quality clinical practice guidelines recommend adalimumab and infliximab for patients with luminal / non-specific CD who are refractory to conventional therapy.

In terms of feasibility, the route of administration for infliximab therapy is intravenous which will necessitate further resources as opposed to adalimumab therapy which is subcutaneous. Furthermore in order to reduce immunogenicity infliximab requires combination therapy with an immunomodulator. Both the package inserts for adalimumab and infliximab highlight the risk of potential active or latent TB development. In the South African context this is an important consideration for monitoring and initiating treatment. All patients should be assessed for latent or active tuberculosis prior treatment initiation.

The Tertiary and Quaternary Expert Review Committee thus recommends the inclusion of anti-TNFs (class including adalimumab and infliximab, with the most affordable agent procured) for patients (adults and children) with luminal Crohn's Disease who are refractory to conventional therapy. Further costing analyses may be required on account of the incremental cost associated with the use of these medicines and the requirement for ongoing use in the management of a chronic disease.

Reviewers: Kim MacQuilkan, Jane Riddin, Roger Wiseman, Marc Blockman

Acknowledgment:

- Gillian Watermeyer – support with formulation of PICO, hierarchy of outcomes and author of the motivation form submitted to the NDoH.
- Derusha Frank – support with AGREE II assessments

Declaration of interests:

- Kim MacQuilkan (GH-SCTA) has no interests to declare
- Jane Riddin (Essential Drugs Programme) has no interests to declare
- Roger Wiseman (Liberty Health (Pty) Ltd, South Africa) has no interests to declare.
- Marc Blockman (Department of Clinical Pharmacology, Groote Schuur Hospital, Cape Town, Western Cape, South Africa and the Department of Medicine, University of Cape Town, Cape Town, Western Cape, South Africa). Has no interests to declare
- Gillian Watermeyer (Department of Gastroenterology, Groote Schuur Hospital, Cape Town, Western Cape, South Africa and the Department of Medicine, University of Cape Town, Cape Town, Western Cape, South Africa). Has no interests to declare but to note that GM works with CD patients and uses TNF-inhibitors.
- Derush Frank (CHAI) has no interests to declare

Appendix 1: Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High: X Moderate: Low: Very low:	**ADULTS** **Comparison 1: Adalimumab in addition to standard of care vs standard of care alone** *Results extracted from High quality SRs (AMSTAR 2)* 1.1 Maintenance of clinical remission at 52-56 weeks; GRADE result extracted from Townsend 2020. 1.4 Number of participants with induced clinical response (= ≥100-point CDAI decrease from baseline) at 4 weeks; GRADE result extracted from Abbass 2019. *Results extracted from critically low quality SR (AMSTAR 2)* 1.7 Reduction of hospitalisations and surgeries **ADULTS** **Comparison 2: Infliximab in addition to standard of care vs standard of care alone** *Results extracted from critically low quality SR (AMSTAR 2)* 2.7 Reduction of hospitalisations and surgeries
	What is the certainty/quality of evidence? High: Moderate: X Low: Very low:	**ADULTS** **Comparison 1: Adalimumab in addition to standard of care vs standard of care alone** *Results extracted from High quality SRs (AMSTAR 2)* 1.1 Maintenance of clinical remission at 24-26 weeks; GRADE result extracted from Townsend 2020, downgraded 1 for serious inconsistency. 1.2 Number of participants with induced clinical remission (CDAI < 150) at 4 weeks; JADAD result extracted from Yin 2022, downgraded 1 for inconsistency. 1.3 Number of participants with maintained clinical response; GRADE not reported but aligning with how other outcomes were assessed was evaluated to moderate certainty (downgraded 1 for unclear risk of bias). 1.5 Number of participants with maintained endoscopic remission; GRADE result extracted from Townsend 2020, downgraded by one level due to sparse data. 1.8 Quality of life; GRADE result extracted Abbass 2019, downgraded 1 level due to sparse data. *Results extracted from High quality SRs (AMSTAR 2)* **ADULTS** **Comparison 2: Infliximab in addition to standard of care vs standard of care alone** 2.1 Maintenance of clinical remission (at **30-32 weeks** – CDAI > 150); GRADE from Gordon 2024 - downgraded one level due to concerns about risk of randomisation, selective reporting and other bias (**placebo vs infliximab**). 2.1 Maintenance of clinical remission (at **48 weeks** – CDAI > 150); GRADE from Gordon 2024 - - downgraded one level due to some concerns about bias from selective reporting (**purine analogues vs infliximab AND purine analogues**).

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
	What is the certainty/quality of evidence? High ☐ Moderate ☐ Low ☒ Very low ☐	**ADULTS** **Comparison 2: Infliximab in addition to standard of care vs standard of care alone** *Results extracted from High quality SRs (AMSTAR 2)* 2.2 No. participants with induced clinical remission (CDAI < 150) at 4 weeks; GRADE from Gordon 2023, downgraded 1 level due to serious concerns with risk of bias (selective reporting and unclear randomisation), and 1 level due to serious concerns with imprecision due to low events. 2.4 No. participants with induced clinical response at week 4 (reduction of CDAI score > 70 from baseline); GRADE from Gordon 2023, downgraded 1 level due to serious concerns with risk of bias (selective reporting and unclear randomisation), and 1 level due to serious concerns with imprecision due to low event numbers.
EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High ☐ Moderate ☐ Low ☐ Very low ☒	**ADULTS** **Comparison 2: Infliximab in addition to standard of care vs standard of care alone** *Results extracted from High quality SRs (AMSTAR 2)* 2.3 No. with maintained clinical response (as defined by the study); GRADE from Gordon 2024, downgraded 2 levels due to serious imprecision from very low participant and event numbers, downgraded 1 level due to concerns about risk of blinding, and selective reporting.
	What is the size of the effect for beneficial outcomes? Large ☐ Moderate ☒ Small ☐ None ☐	**ADULTS** **Comparison 1: Adalimumab in addition to standard of care vs standard of care alone** 1.1 No. participants with maintained clinical remissions (as defined by the study) at 52-56 weeks - RR=0.70 in favour of adalimumab, 95% CI [0.64 to 0.77], i^2=0%, P<0.00001, **NNT 4**, 95% CI [3 to 5], 3 RCTs, n=683. At 24-26 weeks - RR=0.66 in favour of adalimumab, 95% CI [0.52 to 0.83], i^2=52%, P<0.0004, **NNT 4**, CI 95% [3 to 6], 2 RCTs, n=554. 1.2 No. participants with induced clinical remission (CDAI < 150) at 4 weeks - Among TNF inhibitor naïve patients, RR= 0.76, 95% CI [0.60 to 0.96], P=0.02, I^2= 82%, **NNT 5** 95% CI [4 to 8], 2 RCTs, n=494). 1.3 No. participants with maintained clinical response (as defined by the study) at 52-56 weeks - RR=0.68 in favour of adalimumab, 95% CI [0.62 to 0.75], i^2=0%, **NNT 4** 95% CI [3 to 5], P<0.00001, 6 RCTs, n=733). At 24-26 weeks - RR=0.65 in favour of adalimumab, 95% CI [0.56 to 0.74], i^2=0%, P<0.00001, **NNT 4**, 95% CI [3 to 6], 2 RCTs, n=554). 1.4. No. participants with induced clinical response (= ≥100-point CDAI decrease from baseline): RR= 0.77 in favour of adalimumab, 95% CI [0.69 to 0.86], I^2= 35%, **NNT 6**, 95% CI [4 to 9], 3 RCTs, n=714; P<0.0001). 1.5. No. participants with maintained endoscopic improvement: (Endoscopic remission: RR=0.74 in favour of adalimumab, 95% CI [0.63 to 0.87], i^2=NA, **NNT 4** 95% CI [3 to 8], P=0.0002, 1 RCT, n=129; Endoscopic response: RR 0.76 in favour of adalimumab, 95% CI [0.66 to 0.88], i^2=NA, **NNT 5** 95% CI [3 to 8], P=0.0001, 1 RCT, n=129). 1.7 Reduction in hospitalisations and surgeries: Hospitalisations (OR 0.50, 95% CI [0.32 to 0.79), 1 study, n=778, high quality) and Surgeries (OR 0.15 [0.04 to 0.54], 1 study, n=778, high quality)

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large ☐ Moderate X Small ☐ None ☐	**ADULTS** **Comparison 2: Infliximab in addition to standard of care vs standard of care alone** 2.1 No. participants with maintained clinical remissions (at 30-32 weeks – CDAI > 150): RR=0.73 in favour of infliximab, 95% CI [0.63 to 0.84], i^2= 0%, P<0.00001, **NNT 6** 95% CI [4 to 10], 2 RCTs, n=408 **(infliximab vs placebo).** At 48 weeks with clinical relapse as defined by the study: RR=0.20 in favour of infliximab combination, 95% CI [0.10 to 0.42], i^2= NA, P<0.0001, NNT 3 95% CI [2 to 4], 1 RCTs n=115) **(purine analogues vs infliximab AND purine analogues).** 2.2. No. participants with achieved clinical remission: RR=4.55 in favour of infliximab, 95% CI [1.53 to 13.50], i^2= NA, P=0.006, **NNT 3** 95% CI [2 to 5], 1 RCT, n=80. 2.3 No. participants with maintained clinical response: RR: 0.59 95% CI [0.37 to 0.96], P=0.03**, NNT 4**, 95% CI [3 to 26], 1 RCT, i^2=NA, n=73). 2.4 No participants with achieved clinical response: RR=4.09 in favour of infliximab, 95% CI [1.63 to 10.25], i^2= NA, P=0.003, **NNT 3** 95% CI [2 to 4], 1 RCT, n=80). 2.5 No. participants with maintained endoscopic improvement: RR: 0.38 95% CI [0.25 to 0.59], P<0.0001, NNT 3, 95% CI [2 to 4], 1 RCT, n=73, i^2=NA **(purine analogues vs infliximab AND purine analogues).** 2.7 Reduction in hospitalisations and surgeries: Hospitalisations (OR 0.50, 95% CI [0.34 to 0.73), 1 study, n=573) and Surgeries (0.37 [0.16 to 0.82], 1 study, n=573) **PAEDIATRICS** **Comparison 1: Adalimumab in addition to standard of care vs standard of care alone** Maintenance of remission: 57% of participants on adalimumab maintained remission (95% CI [55% to 79%], i^2=92.1% P=0.000). Proportion with maintained remission significantly higher in infliximab naïve subgroup (0.75, 95% CI [0.65 to 0.86], compared to infliximab exposed subgroup. Induction of remission: 59% of participants on adalimumab achieved induction of remission (95% CI [25 to 61%], i^2=98.6%, P=0.000). Proportion with induced remission significantly higher in the infliximab naïve subgroup (0.94, 95% CI [0.90 to 0.98]), compared to infliximab exposed group. Maintenance of response: 63% of participants on adalimumab achieved induction of remission (95% CI [30 to 87%], i^2=94.4%, P=0.000). Results were dose dependent; < 40mg (0.42, 95% CI [0.32 to 0.52], 40mg (0.57, 95% CI [0.35 to 0.78]), >40mg (0.91, 95% CI [0.80 to1.03]). Adalimumab was found to be significantly more effective in the infliximab naïve subgroup (0.84, 95% CI [0.72 to 0.97]). **Comparison 2: Infliximab in addition to standard of care vs standard of care alone** Higher proportion of patients in the first line infliximab group achieved clinical and endoscopic remission at week 10 vs conventional therapy group (clinical remission: 59% vs 34%, p=0.021 and endoscopic remission: 59% vs 17%, p=0.001).

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
	What is the size of the effect for beneficial outcomes? Large: ☐ Moderate: ☐ Small: ☐ None: ☒	**PAEDIATRICS** **Comparison 1: Adalimumab in addition to standard of care vs standard of care alone** No significant difference in maintenance of clinical remission at week 52 (p=0.421), however there were significantly more patients in the first line infliximab group (19/46, 41%) in clinical remission on azathioprine monotherapy without need for treatment escalation vs conventional therapy group (7/48, 15%, p=0.004).
EVIDENCE OF HARMS	**What is the certainty/quality of evidence?** High: ☒ Moderate: ☐ Low: ☐ Very low: ☐	**ADULTS** **Comparison 1: Adalimumab in addition to standard of care vs standard of care alone** Results extracted from high quality SR (AMSTAR 2) **1.9 Safety** Maintenance Therapy – Adverse events; GRADE result extracted from Townsend 2020.
EVIDENCE OF HARMS	**What is the certainty/quality of evidence?** High: ☐ Moderate: ☒ Low: ☐ Very low: ☐	**ADULTS** **Comparison 1: Adalimumab in addition to standard of care vs standard of care alone** Results extracted from high quality SR (AMSTAR 2) **1.9 Safety** Maintenance Therapy – Serious adverse events; GRADE result extracted from Townsend 2020, downgraded 1 level due to sparse data. Induction Therapy – adverse events; GRADE from Abbass 2019, downgraded by 1 one level due to serious inconsistency.
EVIDENCE OF HARMS	**What is the certainty/quality of evidence?** High: ☐ Moderate: ☐ Low: ☒ Very low: ☐	**ADULTS** **Comparison 1: Adalimumab in addition to standard of care vs standard of care alone** Results extracted from high quality SR (AMSTAR 2) **1.9 Safety** Induction Therapy – serious adverse events; *GRADE from Abbass 2019, downgraded by 2 levels due to very serious imprecision.*
EVIDENCE OF HARMS	**What is the certainty/quality of evidence?** High: ☐ Moderate: ☐ Low: ☐ Very low: ☒	**ADULTS** **Comparison 2: Infliximab in addition to standard of care vs standard of care alone** Results extracted from high quality SR (AMSTAR 2) **2.9 Safety** Maintenance Therapy – adverse events; GRADE from Gordon 2024, downgraded twice due to serious imprecision from very low participant and event numbers and once due to concerns about risk of bias for randomisation, blinding, attrition and selective reporting **(purine analogues vs infliximab AND purine analogues).** Maintenance Therapy – serious adverse events; GRADE from Gordon 2024, downgraded twice due to serious imprecision from very low participant and event numbers and once due to concerns about risk of bias for randomisation, blinding, attrition and selective reporting **(purine analogues vs infliximab AND purine analogues).**

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large: [ ] Moderate: [ ] Small: [ ] None: [X]	**ADULTS** **Comparison 1: Adalimumab vs placebo (conventional therapies both arms)** **1.9 – Safety** Maintenance Therapy • Adverse events at 52 to 56 week follow-up between adalimumab and placebo (RR=1.01 95% CI [0.94 to 1.09], P=0.72, 4 RCTs, n=1012. Induction Therapy • Adverse events at 4 weeks (RR=0.90, 95% CI [0.74 to 1.09], P=0.28 – not significant, 3 RCTs, n=531. • Serious adverse events between groups (RR=0.44, 95% CI [0.17 to 1.15], P=0.09 – not significant, 3 RCTs, n=531. **ADULTS** **Comparison 2: Infliximab in addition to standard of care vs standard of care alone** **2.9 – Safety** Maintenance therapy • Withdrawals due to adverse events at 48 weeks in infliximab and purine analogue combination group compared to the purine analogue alone group: RR 0.47 95% CI [0.15 to 1.49], P=0.20, 1 trial, n=115). • Serious adverse events (at 48 weeks – 2 years) in infliximab and purine analogue combination group compared to the purine analogue alone group: RR 1.19 95% CI [0.54 to 2.64], P=0.80, i^2=0%, 2 trials, n=257). Induction Therapy • Total adverse events in infliximab and purine analogue combination group compared to the purine analogue alone group: RR 0.88 in favour of combination group 95% CI [0.65 to 1.20], P=0.42, 2 RCTs).
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large: [ ] Moderate: [ ] Small: [X] None: [ ]	**ADULTS** **Comparison 1: Adalimumab vs placebo (conventional therapies both arms)** **1.9 – Safety** Serious adverse events - (RR=0.56 in favour of adalimumab, 95% CI [0.39 to 0.80], P=0.002, NNT 16 95% [10 to 46], 4 RCTs, n=1012.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention: [X] Favours control: [ ] Intervention = Control *or* Uncertain: [ ]	
FEASABILITY	**Is implementation of this recommendation feasible?** Yes: [X] No: [ ] Uncertain: [ ]	

<table>
<tr><th></th><th>JUDGEMENT</th><th>EVIDENCE & ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?
More intensive: X
Less intensive:
Uncertain:</td><td>See Budget impact estimated 36 new patients a year
Cost of medicines/ year:<table><tr><th>Medicine</th><th>Year 1</th><th>Year 2</th></tr><tr><td></td><td colspan="2">Cost (ZAR) - SEP</td></tr><tr><td>adalimumab</td><td>R49 942</td><td>R43 283</td></tr><tr><td>infliximab</td><td>R68 075</td><td>R50 570</td></tr></table></td></tr>
<tr><td>VALUES, PREFERENCES, ACCEPTABILITY</td><td>Is there important uncertainty or variability about how much people value the options?
Minor: X
Major:
Uncertain:

Is the option acceptable to key stakeholders?
Yes: X
No:
Uncertain:</td><td>In a difficult to manage condition, with limited therapeutics options currently available, the addition of a biological either adalimumab or infliximab to EML for the management of this condition would be valued by relevant stakeholders.

Route of administration for adalimumab is subcutaneous whereas infliximab is intravenous</td></tr>
<tr><td>EQUITY</td><td>Would there be an impact on health inequity?
Yes:
No:
Uncertain: X</td><td>Funding availability</td></tr>
</table>

Appendix 2: Search strategy

Table 1: PubMed – SEARCH RUN 27 MARCH 2024 – Systematic reviews

Search	Query	Search Details	Results
#5	Meta-analyses, SRs	(("tumor necrosis factor inhibitors"[MeSH Terms] OR "infliximab"[MeSH Terms] OR "adalimumab"[MeSH Terms] OR "TNF inhibitors"[Title/Abstract]) AND ("Crohn's Disease"[Title/Abstract] OR "crohn disease"[MeSH Terms])) AND (meta-analysis[Filter] OR systematicreview[Filter])	172
#4	RCTS, meta-analyses, SRs	(("tumor necrosis factor inhibitors"[MeSH Terms] OR "infliximab"[MeSH Terms] OR "adalimumab"[MeSH Terms] OR "TNF inhibitors"[Title/Abstract]) AND ("Crohn's Disease"[Title/Abstract] OR "crohn disease"[MeSH Terms])) AND (meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter])	369
#3	#1 AND #2	("tumor necrosis factor inhibitors"[MeSH Terms] OR "infliximab"[MeSH Terms] OR "adalimumab"[MeSH Terms] OR "TNF inhibitors"[Title/Abstract]) AND ("Crohn's Disease"[Title/Abstract] OR "crohn disease"[MeSH Terms])	4808
#2	Crohn's Disease	(("Crohn's Disease"[Title/Abstract]) OR (crohn's disease[MeSH Terms]))	65462
#1	Tumour necrosis factor inhibitors (adalimumab, infliximab)	"tumor necrosis factor inhibitors"[MeSH Terms] OR "infliximab"[MeSH Terms] OR "adalimumab"[MeSH Terms] OR "TNF inhibitors"[Title/Abstract]	19893

Tables 2 - 4: COCHRANE LIBRARY– SEARCH RUN 27 MARCH 2024

search	Query	Results
#1	MeSH descriptor: [Crohn Disease] explode all trees	2252
#2	MeSH descriptor: [Tumor Necrosis Factor Inhibitors] explode all trees	161
#3	#1 AND #2	11
#4	#3 in Cochrane Reviews	0

search	Query	Results
#1	MeSH descriptor: [Crohn Disease] explode all trees	2252
#2	MeSH descriptor: [adalimumab] explode all trees	1156
#3	#1 AND #2	161
#4	#3 in Cochrane Reviews	4

search	Query	Results
#1	MeSH descriptor: [Crohn Disease] explode all trees	2252
#2	MeSH descriptor: [infliximab] explode all trees	1065
#3	#1 AND #2	255
#4	#3 in Cochrane Reviews	8

search	Query	Results
#1	MeSH descriptor: [Crohn Disease] explode all trees	2252
#2	MeSH descriptor: [Tumor Necrosis Factor Inhibitors] explode all trees	161
#3	MeSH descriptor: [adalimumab] explode all trees	1156
#4	MeSH descriptor: [infliximab] explode all trees	1065
#5	#2 OR #3 OR #4	2190
#6	#1 AND #5	389
#7	#6 in Cochrane reviews	11

Table 5: Additional Searches for Paediatric Population – PUBMED

Search	Query	Search Details	Results
#1	Paediatric	(("tumor necrosis factor inhibitors"[MeSH Terms] OR "infliximab"[MeSH Terms] OR "adalimumab"[MeSH Terms]) AND "crohn disease"[MeSH Terms]) AND ((systematicreview[Filter]) AND (allchild[Filter]))	13

Table 6: Additional Searches for Paediatric Population – COCHRANE LIBRARY

Search	**Query**	**Category**	**Results**
#1	MeSH descriptor: [Crohn Disease] explode all trees	MeSH	2252
#2	MeSH descriptor: [Tumor Necrosis Factor Inhibitors] explode all trees	MeSH	161
#3	MeSH descriptor: [Child] explode all trees	MeSH	81477
#4	MeSH descriptor: [Adalimumab] explode all trees	MeSH	1156
#5	MeSH descriptor: [Infliximab] explode all trees	MeSH	1065
#6	#2 OR #4 OR #5		2190
#7	#1 AND #2 AND #6		33
#8	#1 AND #3	Limits – Cochrane reviews	0

Appendix 3: List of excluded studies

Study Citation	Reason for exclusion
Singh S, Fumery M, Sandborn WJ, Murad MH. Systematic review and network meta-analysis: first- and second-line biologic therapies for moderate-severe Crohn's disease. Aliment Pharmacol Ther. 2018 Aug;48(4):394-409. doi: 10.1111/apt.14852. Epub 2018 Jun 19. PMID: 29920733.	Update available Singh 2021 – included in eligible studies
Singh S, Garg SK, Pardi DS, Wang Z, Murad MH, Loftus EV Jr. Comparative efficacy of biologic therapy in biologic-naïve patients with Crohn disease: a systematic review and network meta-analysis. Mayo Clin Proc. 2014 Dec;89(12):1621-35. doi: 10.1016/j.mayocp.2014.08.019. Epub 2014 Oct 29. PMID: 25441399.	Update available Singh 2021 – included in eligible studies
Jiang CZ, Yu WL, Hua ZC. Clinical Efficacy of Infliximab in Patients With Crohn Disease in Different Locations of Disease Pathology: A Meta-Analysis. Clin Invest Med. 2021 Jun 21;44(2):E27-35. doi: 10.25011/cim.v44i2.36356. PMID: 34152704.	Incorrect comparator
Shah ED, Farida JP, Siegel CA, Chong K, Melmed GY. Risk for Overall Infection with Anti-TNF and Anti-integrin Agents Used in IBD: A Systematic Review and Meta-analysis. Inflamm Bowel Dis. 2017 Apr;23(4):570-577. doi: 10.1097/MIB.0000000000001049. PMID: 28230558.	Incorrect primary outcome
Moćko P, Kawalec P, Pilc A. Safety profile of biologic drugs in the therapy of Crohn disease: A systematic review and network meta-analysis. Pharmacol Rep. 2016 Dec;68(6):1237-1243. doi: 10.1016/j.pharep.2016.07.013. Epub 2016 Aug 1. PMID: 27686963.	Incorrect primary outcome
Lichtenstein L, Ron Y, Kivity S, Ben-Horin S, Israeli E, Fraser GM, Dotan I, Chowers Y, Confino-Cohen R, Weiss B. Infliximab-Related Infusion Reactions: Systematic Review. J Crohns Colitis. 2015 Sep;9(9):806-15. doi: 10.1093/ecco-jcc/jjv096. Epub 2015 Jun 19. PMID: 26092578; PMCID: PMC4558633.	Incorrect study design – only narrative summaries
Song YN, Zheng P, Xiao JH, Lu ZJ. Efficacy and safety of adalimumab for the Crohn's disease: a systematic review and meta-analysis of published randomized placebo-controlled trials. Eur J Clin Pharmacol. 2014 Aug;70(8):907-14. doi: 10.1007/s00228-014-1702-1. Epub 2014 Jun 1. PMID: 24880961.	Incorrect population
Cohen LB, Nanau RM, Delzor F, Neuman MG. Biologic therapies in inflammatory bowel disease. Transl Res. 2014 Jun;163(6):533-56. doi: 10.1016/j.trsl.2014.01.002. Epub 2014 Jan 7. PMID: 24467968.	Incorrect study design – narrative
Carnovale C, Maffioli A, Zaffaroni G, Mazhar F, Battini V, Mosini G, Pozzi M, Radice S, Clementi E, Danelli P. Efficacy of Tumour Necrosis Factor-alpha therapy in paediatric Crohn's disease patients with perianal lesions: a systematic review. Expert Opin Biol Ther. 2020 Mar;20(3):239-251. doi: 10.1080/14712598.2020.1718096. Epub 2020 Jan 23. PMID: 31971447.	Incorrect population
Forsdick VK, Tan Tanny SP, King SK. Medical and surgical management of pediatric perianal crohn's disease: A systematic review. J Pediatr Surg. 2019 Dec;54(12):2554-2558. doi: 10.1016/j.jpedsurg.2019.08.036. Epub 2019 Oct 15. PMID: 31708205.	Incorrect population
Horneff G, Seyger MMB, Arikan D, Kalabic J, Anderson JK, Lazar A, Williams DA, Wang C, Tarzynski-Potempa R, Hyams JS. Safety of Adalimumab in Pediatric Patients with Polyarticular Juvenile Idiopathic Arthritis, Enthesitis-Related Arthritis, Psoriasis, and Crohn's Disease. J Pediatr. 2018 Oct;201:166-175.e3. doi: 10.1016/j.jpeds.2018.05.042. Epub 2018 Jul 25. PMID: 30054164.	Incorrect study design
Dulai PS, Thompson KD, Blunt HB, Dubinsky MC, Siegel CA. Risks of serious infection or lymphoma with anti-tumor necrosis factor therapy for pediatric inflammatory bowel disease: a systematic review. Clin Gastroenterol Hepatol. 2014 Sep;12(9):1443-51; quiz e88-9. doi: 10.1016/j.cgh.2014.01.021. Epub 2014 Jan 22. PMID: 24462626.	Incorrect primary outcome
Jongsma MME, Aardoom MA, Cozijnsen MA, van Pieterson M, de Meij T, Groeneweg M, Norbruis OF, Wolters VM, van Wering HM, Hojsak I, Kolho KL, Hummel T, Stapelbroek J, van der Feen C, van Rheenen PF, van Wijk MP, Teklenburg-Roord STA, Schreurs MWJ, Rizopoulos D, Doukas M, Escher JC, Samsom JN, de Ridder L. First-line treatment with infliximab versus conventional treatment in children with newly diagnosed moderate-to-severe Crohn's disease: an open-label multicentre randomised controlled trial. Gut. 2022 Jan;71(1):34-42. doi: 10.1136/gutjnl-2020-322339. Epub 2020 Dec 31. PMID: 33384335; PMCID: PMC8666701.	Incorrect study design – SRs only included, included in Martin-Garcia
Hyams J, Walters TD, Crandall W, Kugathasan S, Griffiths A, Blank M, Johanns J, Lang Y, Markowitz J, Cohen S, Winter HS, Veereman-Wauters G, Ferry G, Baldassano R. Safety and efficacy of maintenance infliximab therapy for moderate-to-severe Crohn's disease in children: REACH open-label extension. Curr Med Res Opin. 2011 Mar;27(3):651-62. doi: 10.1185/03007995.2010.547575. Epub 2011 Jan 18. PMID: 21241207.	Incorrect study design – SRs only included, included in Martin-Garcia

Walters TD, Faubion WA, Griffiths AM, Baldassano RN, Escher J, Ruemmele FM, Hyams JS, Lazar A, Eichner S, Huang B, Li Y, Thakkar RB. Growth Improvement with Adalimumab Treatment in Children with Moderately to Severely Active Crohn's Disease. Inflamm Bowel Dis. 2017 Jun;23(6):967-975. doi: 10.1097/MIB.0000000000001075. PMID: 28301428.	Incorrect primary outcome
Harris RE, Aloi M, de Ridder L, Croft NM, Koletzko S, Levine A, Turner D, Veereman G, Neyt M, Bigot L, Ruemmele FM, Russell RK; PIBD SETQuality consortium and PIBDnet. Protocol for a multinational risk-stratified randomised controlled trial in paediatric Crohn's disease: methotrexate versus azathioprine or adalimumab for maintaining remission in patients at low or high risk for aggressive disease course. BMJ Open. 2020 Jul 1;10(7):e034892. doi: 10.1136/bmjopen-2019-034892. PMID: 32611737; PMCID: PMC7332179.	Protocol only – results not published
Matar M, Shamir R, Lev-Zion R, Broide E, Weiss B, Ledder O, Guz-Mark A, Rinawi F, Cohen S, Topf-Olivestone C, Shaoul R, Yerushalmi B, Assa A. The Effect of Adalimumab Treatment on Linear Growth in Children With Crohn Disease: A Post-hoc Analysis of the PAILOT Randomized Control Trial. J Pediatr Gastroenterol Nutr. 2020 Aug;71(2):237-242. doi: 10.1097/MPG.0000000000002728. PMID: 32324651	Incorrect primary outcome
Navas-López VM, Pujol Muncunill G, Llerena E, Navalón Rubio M, Gil-Ortega D, Varea-Calderón V, Sierra Salinas C, Martin-de-Carpi J. Efectividad y seguridad en nuestro entorno de adalimumab como tratamiento anti-TNF de primera linea en niños con enfermedad de Crohn [A real-world study focused on the effectiveness and safety of adalimumab as first-line anti-TNF treatment for pediatric Crohn's disease]. An Pediatr (Engl Ed). 2018 Feb;88(2):89-99. Spanish. doi: 10.1016/j.anpedi.2017.01.013. Epub 2017 Apr 21. PMID: 28434894.	Incorrect primary outcome, incorrect study design
Bonovas S, Piovani D, Pansieri C, Macaluso FS, Orlando A, Festa S, Papi C, Pugliese D, Armuzzi A. Use of biologics for the management of Crohn's disease: IG-IBD technical review based on the GRADE methodology. Dig Liver Dis. 2023 Jun;55(6):695-703. doi: 10.1016/j.dld.2023.02.019. Epub 2023 Mar 22. PMID: 36964060.	Incorrect study design
Bouhnik Y, Atreya R, Casey D, Górecki M, Baik D, Yoon SW, Kwon TS, Jang M. Cost-effectiveness Analysis of Subcutaneous Infliximab for Inflammatory Bowel Diseases in Sequential Biologic Treatment. Inflamm Bowel Dis. 2023 Jun 1;29(6):898-913. doi: 10.1093/ibd/izac160. PMID: 35942647; PMCID: PMC10233401.	Incorrect comparator
Ueno F, Doi M, Kawai Y, Ukawa N, Cammarota J, Betts KA. Number needed to treat and cost per remitter for biologic treatments of Crohn's disease in Japan. J Med Econ. 2020 Jan;23(1):80-85. doi: 10.1080/13696998.2019.1642900. Epub 2019 Aug 13. PMID: 31294641.	Incorrect study design

Appendix 4. Summary of AMSTAR 2 assessments of included reviews (for data extraction)

AMSTAR-2 item	Gordon 2024 **High quality** Also includes GRADE assessment	Gordon 2023 **High quality** Also includes GRADE assessment	Abbass 2019 **High quality** Also includes GRADE assessment	Townsend 2020 **High quality** Also includes GRADE assessment	Yin 2022 **High quality** Includes JADAD assessment	Mao 2016 **Critically Low quality**	Chen 2024 **Low quality**	Martin-Garcia 2022 **Moderate quality**
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes	Yes	Yes	Yes	Yes	No	Yes	Partial Yes
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. Did the review authors use a comprehensive literature search strategy?	Yes	Yes	Yes	Yes	Yes	No	Partial, yes	Partial Yes
5. Did the review authors perform study selection in duplicate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. Did the review authors perform data extraction in duplicate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Yes	Yes	Yes	Yes	Partial, yes	No	No	Partial Yes
8. Did the review authors describe the included studies in adequate detail?	Yes	Yes	Yes	Yes	Yes	Partial, yes	Partial, yes	YEs
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	Yes	Yes	Yes	Yes	Yes	No	No	Yes
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Appendix 5 – Assessment of eligible studies

Table 1: Systematic reviews

Study	Study type	No. of trials & participants	Population	Intervention and comparator	Outcomes reported	Quality	Search completed	Comprehensiveness	Notes	Effect measures to be extracted?
Gordon 2024	SR of RCTs	9 RCTs, 1257 participants	Adults with CD	Infliximab compared to placebo or active comparator	• Maintenance of clinical remission • Maintenance of clinical response • Withdrawals due to SAEs • Adverse events	AMSTAR – high quality: Screening & extraction in duplicate, RoB 1 assessment, GRADE	06/2023	Studies included: Hanauer 2002 (INF); Rutgeerts 1999 (INF); Sands 2004 (INF); Buhl 2022 (INF); Louis 2022 (INF); VanAssche 2012 (INF).	SR did not specifically look at refractory CD - all types eligible but trials selected were refractory based medicine review PICO for certain outcomes	Yes, high quality review, includes relevant studies. **Data extracted for comparison 2, outcome 2.1, 2.3, 2.5 and 2.9**
Gordon 2023	SR of RCTs	10 RCTS, 1101 participants	Adults with CD including fistulising (sub-group analysis).	Infliximab compared to placebo or active comparator	• Clinical remission defined as absence of any draining fistulas at consecutive visits • Clinical response defined as reduction of 50% in the number of draining fistulas at 2 or more consecutive visits • Withdrawals due to adverse events, serious adverse event, total adverse events	AMSTAR – high quality: Screening & extraction in duplicate, RoB 1 assessment, GRADE	03/2023	Studies included: Present 1999 (INF), Sands 2004 (INF)	SR did not specifically look at refractory CD - all types eligible but trials selected were refractory based medicine review PICO for certain outcomes	Yes, high quality review, includes relevant studies. **Data extracted for comparison 2, outcome 2.2, 2.4, 2.9**
Townsend 2020	SR of RCTs	6 RCTs, 1158 participants	Patients with CD in remission (as defined by the included studies) Patients not specific to luminal or fistulising but outcomes relevant to luminal	Adalimumab compared to Placebo or active comparator	Maintenance of clinical remission, Maintenance of endoscopic improvement, Maintenance of endoscopic remission, Quality of life, and Safety	**High quality** based on AMSTAR 2 assessment and includes GRADE assessment	15 April 2019	Studies included: Colombel 2007 (ADA); Rutgeerts 2012 (ADA); Sandborn 2007 (ADA); Savorino 2013 (ADA); Scapa 2015 (ADA); Watanabe 2012 (ADA) *Latest study Chen et al. 2020 not included	Trials include Sandborn and does not differentiate between TNF exposed and Naïve	YES, high quality Includes GRADE assessment Data to be extracted: Comparison 1, outcome 1.1, 1.3, 1.5, 1.9

Abbass 2019	SR of RCTs	3 RCTs, 714 participants	Patients with CD, Not specific to luminal or fistulising but outcomes for luminal	Adalimumab OR placebo or active comparator	Induction of clinical response, induction of clinical remission, safety	**High quality** – Screening & extraction in duplicate, RoB 1, GRADE	16 April 2019	Studies included: Hanauer 2006 (ADA); Sandborn 2007 (ADA); Watanabe 2012 (ADA) *Latest study Chen et al. 2020 not included	Active CD, not specific refractory depends on study (Sandborn not so exclude results, outcomes luminal, subgroup by TNF exposure	YES, highest quality Includes GRADE assessment Data to be extracted for comparison 1, outcome 1.2, 1.4, 1.8, 1.9
Yin 2022	SR of RCTs	4 RCTS, 919 participants	Patients with CD, not specifically refractory but 3/4 trials meet PICO - outcomes with SANDBORN not to be extracted or need to be stated that are previously INF exposed	Adalimumab compared to placebo or active comparator	Induction of clinical response, induction of clinical remission, quality of life, safety	**High quality** – Screening & extraction in duplicate, RoB 2, Jadad tool	30 May 2022	Studies included: Chen 2020 (ADA); Sandborn 2007 (ADA); Hanauer 2006 (ADA); Watanabe 2012 (ADA) *latest studies included	Sandborn previously INF exposed specific population; Colombel dose 80mg and not 160mg	Outcomes already covered by Abbass 2019, conducted GRADE but includes later study Chen 2020 thus will be extracted for the specific outcome (1.2).
Mao 2017	SR of RCTs	5 trials for CD	Patients with moderate to severe CD	Infliximab or adalimumab, conventional therapy	Rate of hospitalisation, rate of surgery	**Critically low quality** – Screening & extraction in duplicate, RoB 1, quality based on RoB	1st May 2016	Studies included: Faeagn 2008 (ADA); Lictenstein 2005 (INF); Rutgeerts 2004 (INF)	Not specifically CD,	Yes only SR to report on outcomes 1.7 and 2.7

Barberio 2023	SR and NMA of RCTs	25 trials, 8720 participants (induction of remission)	Patients with CD, specified luminal	Adalimumab and infliximab compared to placebo and active comparators	Induction of remission, Maintenance of remission, Induction of clinical response	**Low quality** - moderate – Screening & extraction in duplicate, RoB 1, Confidence in Network Meta-Analysis (CINeMA) – only on induction of remission outcome	1 July 2022	Studies included: Hanauer 2006 (ADA); Targen 1997 (INF); Sandborn 2007 (ADA); Colombel 2010 (INF); Watanabe 2012 (ADA); Hanauer 2002 (INF); Chen 2020 (ADA); Rutgeerts 1999 (INF); Colombel 2007 (ADA); Rutgeerts 2012 (ADA); Schreiber 2021 (INF) *latest studies included	Not specifically refractory	No, Low quality – outcomes already covered in higher quality SRs for ADA and INF
Singh 2021	SR and NMA of RCTs	15 RCTs, in 2931 participants	Patients with CD, Not specific to luminal or fistulising but outcomes for luminal	Adalimumab and infliximab	Induction of clinical remission, and maintenance of clinical remission	**Low quality** review – Screening & extraction in duplicate, RoB 1	3rd June 2021	Studies included: Hanauer 2006 (ADA); Targen 1997 (INF); Sandborn 2007 (ADA); Hanauer 2002 (INF); Watanabe 2012 (ADA); Rutgeerts 1999 (INF); Rutgeerts 2012 (ADA); Narula 2016 (INF); Colombel 2007 (ADA); Sandborn 2007 (ADA) *Latest study Chen et al. 2020 not included	Not specific refractory,	No, low quality SR and outcomes already covered in higher quality SRs
Stidham 2014	SR of RCTs	10 RCTS	Patients with moderate to severe CD	Infliximab or adalimumab or certolizumab pegol or placebo compared to placebo or active control	Induction and maintenance of clinical response, induction and maintenance of clinical remission	**Low quality** Screening & extraction in duplicate, RoB 1, quality based on RoB	31st August 2013	Studies (RCTS) included: Hanauer 2006 (ADA), Sandborn GAIN 2007 (ADA), Targan 1997 (INF), Colombel 2007 (ADA), Sandborn CLASSIC 2007 (ADA), Hanauer 2002 (INF)	Not specifically refractory for SR but underlying trials match PICO	No, low quality review. Outcome already covered in other reviews.

PAEDIATRICS

Chen 2024	SR of RCTs and cohort studies	10 studies (2 RCTs and 8 single arm cohort studies)	Children and adolescents with inflammatory bowel disease (CD and UC)	Adalimumab	Induction of remission or response, Maintenance of response or remission, SAEs and infections	Screening and extraction in duplicate, RoB 1, MINORS tool for NRCTs, quality based on RoB	6th January 2023	Studies (RCTs) included: Hyams 2012 (ADA); Assa 2019	Not specifically refractory, mainly observational data.	Yes
Dziechciarz 2016	All studies	14 studies (1 RCT and 13 case series)	Children and adolescents with CD	Adalimumab	Induction of remission, Maintenance of remission, Induction of response, Maintenance of response, adverse event, serious adverse event,and withdrawals due to adverse event.	Screening and extraction in duplicate,	July 2015	Studies included (RCTs): Hyams 2012 (ADA)	Not specifically refractory, mainly case-series study designs. Other SRs include cohort and more RCTs.	No
Martin-Garcia 2022		9 RCTs and 4 Economic evaluations	Children and adolescents with IBD with moderate or severe activity	Adalimumab and infliximab	Induction and maintenance	Clinical or endoscopic response and remission, quality of life, adverse events	20 May 2022	Studies included: Baldassano 2003 (INF); Hyams 2007 (INF); Reummele 2009 (INF); Hyams 2012 (ADA); Kierkus 2015 (INF); Jongsma 2022 (INF)	Not specifically refractory	Yes

Appendix 6 – SUMMARY OF AGREE II ASSESSMENTS

AGREE II assessment scores

ACG 2019 luminal CD

Scoring the guidelines

	Scope and purpose			Stakeholder involvement			Rigour of development								Clarity of presentation			Applicability				Editorial independence		Overall assessment
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16	Item 17	Item 18	Item 19	Item 20	Item 21	Item 22	Item 23	Overall
Appraiser 1	7	5	7	6	1	7	7	7	5	7	7	7	4	3	7	5	7	2	2	2	2	5	5	117
Item Total	7	5	7	6	1	7	7	7	5	7	7	7	4	3	7	5	7	2	2	2	2	5	5	117
Domain Total	19			14			47								19			8				10		117
Minimum possible score	3			3			8								3			4				2		23
Maximum possible score	21			21			56								21			28				14		161
Domain score	89%			61%			**81%**								89%			17%				67%		**67%**

Overall assessment: Guidelines are recommened for use in this context
5 out 7

CAG 2019 Luminal CD

Scoring the guidelines

	Scope and purpose			Stakeholder involvement			Rigour of development								Clarity of presentation			Applicability				Editorial independence		Overall assessment
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16	Item 17	Item 18	Item 19	Item 20	Item 21	Item 22	Item 23	Overall
Appraiser 1	6	6	7	6	6	7	7	7	6	7	7	7	6	4	7	6	7	4	4	3	5	5	5	135
Item Total	6	6	7	6	6	7	7	7	6	7	7	7	6	4	7	6	7	4	4	3	5	5	5	135
Domain Total	19			19			51								20			16				10		135
Minimum possible score	3			3			8								3			4				2		23
Maximum possible score	21			21			56								21			28				14		161
Domain score	89%			89%			**90%**								94%			50%				67%		**80%**

Overall assessment: Guidelines are recommened for use in this context
6 out 7

ECCO 2019 Luminal CD

Scoring the guidelines

	Scope and purpose			Stakeholder involvement			Rigour of development								Clarity of presentation			Applicability				Editorial independence		Overall assessment
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16	Item 17	Item 18	Item 19	Item 20	Item 21	Item 22	Item 23	Overall
Appraiser 1	5	6	6	5	6	6	7	6	5	6	6	6	6	6	6	6	6	3	6	3	3	5	5	125
Item Total	5	6	6	5	6	6	7	6	5	6	6	6	6	6	6	6	6	3	6	3	3	5	5	125
Domain Total	17			17			48								18			15				10		125
Minimum possible score	3			3			8								3			4				2		23
Maximum possible score	21			21			56								21			28				14		161
Domain score	78%			78%			**83%**								83%			46%				67%		**72%**

Overall assessment: Guidelines are recommened for use in this context
5 out 7

AGREE II assessment scores

AGA 2021 Luminal CD

Scoring the guidelines

	Scope and purpose			Stakeholder involvement			Rigour of development								Clarity of presentation			Applicability				Editorial independence		Overall assessment
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16	Item 17	Item 18	Item 19	Item 20	Item 21	Item 22	Item 23	Overall
Appraiser 1	6	6	5	3	4	6	7	5	6	6	7	6	7	6	6	6	6	5	5	6	3	7	5	129
Item Total	6	6	5	3	4	6	7	5	6	6	7	6	7	6	6	6	6	5	5	6	3	7	5	129
Domain Total	17			13			50								18			19				12		129
Minimum possible score	3			3			8								3			4				2		23
Maximum possible score	21			21			56								21			28				14		161
Domain score	78%			56%			**88%**								83%			63%				83%		**75%**

Overall assessment: Guidelines are recommened for use in this context
5 out 7 technical report must be read together with guideline

BSG 2019 Luminal CD

Scoring the guidelines

	Scope and purpose			Stakeholder involvement			Rigour of development								Clarity of presentation			Applicability				Editorial independence		Overall assessment
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16	Item 17	Item 18	Item 19	Item 20	Item 21	Item 22	Item 23	Overall
Appraiser 1	7	7	5	7	7	7	7	3	5	7	6	4	6	7	7	7	7	3	5	1	6	7	7	135
Item Total	7	7	5	7	7	7	7	3	5	7	6	4	6	7	7	7	7	3	5	1	6	7	7	135
Domain Total	19			21			45								21			15				14		135
Minimum possible score	3			3			8								3			4				2		23
Maximum possible score	21			21			56								21			28				14		161
Domain score	89%			100%			**77%**								100%			46%				100%		**85%**

Overall assessment: Guidelines are recommened for use in this context
6 out 7

NICE 2012_2019 Luminal CD

Scoring the guidelines

	Scope and purpose			Stakeholder involvement			Rigour of development								Clarity of presentation			Applicability				Editorial independence		Overall assessment
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16	Item 17	Item 18	Item 19	Item 20	Item 21	Item 22	Item 23	Overall
Appraiser 1	6	6	6	5	7	7	5	7	7	5	6	6	6	7	7	7	7	3	5	7	7	7	7	143
Item Total	6	6	6	5	7	7	5	7	7	5	6	6	6	7	7	7	7	3	5	7	7	7	7	143
Domain Total	18			19			49								21			22				14		143
Minimum possible score	3			3			8								3			4				2		23
Maximum possible score	21			21			56								21			28				14		161
Domain score	83%			89%			**85%**								100%			75%				100%		**89%**

Overall assessment: Guidelines are recommened for use in this context
6 out 7

AGREE II assessment scores																							
CAG Paeds Luminal CD																							
Scoring the guidelines																							
	Scope and purpose			Stakeholder involvement			Rigour of development								Clarity of presentation			Applicability				Editorial independence		Overall assessment
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16	Item 17	Item 18	Item 19	Item 20	Item 21	Item 22	Item 23	Overall
Appraiser 1	6	6	7	5	1	7	7	5	7	7	6	7	2	3	6	5	7	2	3	5	5	7	6	122
Item Total	6	6	7	5	1	7	7	5	7	7	6	7	2	3	6	5	7	2	3	5	5	7	6	122
Domain Total	19			13			44								18			15				13		122
Minimum possible score	3			3			8								3			4				2		23
Maximum possible score	21			21			56								21			28				14		161
Domain score	89%			56%			**75%**								83%			46%				92%		**73%**

Overall assessment: Guidelines are recommened for use in this context
5 out 7

Score: (e.g. domain 1)

$$\frac{\text{Maximum possible score = 7 (highest score) x no. of items x no. of appraisers}}{\text{Minumum possible score = 1 (lowest score) x no. of items x no. of appraisers}}$$

Score for each domain

$$\frac{\text{Obtained score - minimum possible score}}{\text{Maximum possible score - minimum possible score}} \times 100$$

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