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 Fistulising Crohn's Disease (PICO 1), 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 30 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. This document relates to PICO 1 – Fistulising CD and the document for PICO 2 – Luminal / Non-Specific CD expected to be presented at the next NEMLC meeting to be held in May 2024 (see accompany document – Proposed plan for PICO 2 – TNF-inhibitors for Luminal / Non-Specific CD.

Date: March 2024

Medicine (ATC): Tumour Necrosis Factor Alpha (anti-TNFs): Adalimumab (L04AB04), Infliximab (L04AB02)
Indication (ICD10): Fistulising Crohn's Disease (K50.9)
Patient population: Patients of all ages with Fistulising 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 19 patients (refractory to conventional therapy) with fistulising 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 fistulising CD who are refectory to conventional therapy.
- We extracted data from 6 publications reporting on 2 SRs (2 publications) and 2 RCTs (4 publications).
- **Comparison 1: Adalimumab vs Placebo in adults**
  - Number of participants with induced fistula remission (100% fistula closure)
    More participants with fistula remission at week 26 in the combined adalimumab (40mg weekly or every other week) group (RR: 2.35, 95% CI [1.03 to 5.38], P=0.043, **NNT 6** 95% CI [4 to 51], n=117) – very low quality evidence. Similarly at week 56 there were more participants with fistula remission in the combined adalimumab group compared to the placebo group (RR: 2.58. 95% CI [1.14 to 5.84], P=0.016, **NNT 5** 95% CI [3 to 22], n=117 – very low quality evidence.
  - Number of participants with maintained fistula remission (100% fistula closure)
    No difference found between adalimumab and placebo in maintenance of fistula closure (100% maintained in both groups), n=117 very low quality evidence. Two years after baseline, 59% of patients on adalimumab still in remission (no placebo comparator in trial extension).
  - Safety
    Adverse events - RR 1.04 [95% CI 0.88 to 1.24), P=0.34, n=117 – **not significant**. Severe adverse events (placebo 10.6%; adalimumab 12.9%, RR 1.21 [95% CI 0.43 to 3.39], P=0.7, n=117 – **not significant**). There were more infectious adverse events in the adalimumab group (44.3%) compared to the placebo group (34%) (RR 1.3 [95% CI 0.81 to 2.10], P=0.3 – **not significant**) – very low quality evidence**.**
- **Comparison 2: Infliximab vs Placebo in adults**
  - Number of participants with induced fistula response (at least 50% fistula closure)
    More participants in the infliximab groups who achieved fistula response compared to placebo (RR=1.94, 95% CI [1.10 to 3.41], i^2= 14%, P=0.02, **NNT 4** 95% CI [3 to 9], 2 RCTs, n=181) – very low certainty.

- Number of participants with induced fistula remission (100% fistula closure)
  More participants in the infliximab group who achieved fistula remission compared to placebo (RR=3.57, 95% CI [1.38 to 9.25], i2= 0%, P=0.009**, NNT 4** 95% CI [2 to 10], 1 RCTs, n=94) – very low certainty**.**
- Number of participants with maintained fistula response (at least 50% fistula closure)
  More participants in the infliximab group still had a response at week 54 compared to the placebo group (RR: 1.96 95% CI [1.29 to 3.00], P=0.001, **NNT 5**, 95% CI [3 to 11], n=195 responders) – moderate quality evidence.
- Mean number of hospitalisations and surgeries
  - Mean number of hospitalisation days due to CD (MD: 2 days in favour of infliximab, P<0.05, n=195); % of responder participants hospitalised CD related causes (MD 10.9% in favour of infliximab, P<0.05, n=195) – moderate quality evidence**.**
  - Mean number of inpatient surgeries and procedures per 100 patients (MD 61 in favour of infliximab, P<0.01, n=195) – moderate quality evidence**.**
  - Mean number of major surgeries per 100 patients (MD 9 in favour of infliximab, P<0.05, n=195) – moderate quality evidence**.**
- Safety – induction of remission
  - More withdrawals due to adverse events in the infliximab group (RR 2.50 95% CI [0.12 to 50.54], P=0.55 – **not significant**, 1 trial, n=94) - very low certainty of evidence).
  - Serious adverse events higher in the infliximab group (RR 5.50 95% CI [0.31 to 96.40], P=0.24 – **not significant**, 1 trial, n=94, GRADE not conducted in Gordon 2023.
  - More total adverse events in the infliximab group (RR 1.48 95% CI [0.90 to 2.41], P=0.12 – **not significant**, 1 trial, n=94, GRADE not conducted in Gordon 2023)
- Safety – maintenance of response
  - Lower percentage of participants in infliximab maintenance group reported adverse events leading to discontinuation compared to placebo (placebo=8%, infliximab 4%, P=0.1 – **not significant**). Higher percentage of infections requiring antimicrobial treatment in the infliximab group (34%) compared to placebo (27%) group however not significantly different (P=0.20 – **not significant**). Differences in serious infections were not significantly different between group (placebo=6%, infliximab=3%, P=0.18 – **not significant**) – moderate quality evidence.
  - Higher percentage of participants who developed antinuclear antibodies in the infliximab group (56 out of 122, 45.9%) compared to the placebo group (24 out of 132, 18.2%) (RR 2.53 [95% [1.68 to 3.80, NNH 4 [95% CI 3 to 6) P<0.001). Results were similar for the development of antibodies against double-stranded with a higher percentage in the infliximab group (infliximab 27 out of 116, 23.3%, placebo 8 out of 127, 6.3% (RR 3.7 [95% CI 1.80 to 7.81], NNH 6 [95% CI 4 to 12], P <0.001) – moderate quality evidence.

➡ **Paediatric Population**

- Limited evidence available for the paediatric population. Evidence from a low quality SR (AMSTAR II) including multiple study designs reported potential benefit for adalimumab and infliximab for achieving and maintain clinical remission as well as complete perianal closure (over 50% of patients). No placebo RCTs found for any outcomes**.** Withdrawal due to adverse events was reported in 3 studies (120 patients) and occurred in 9% of patients ([95% CI: 5–16]), with serious infections being the most reported reason for withdrawal (8 out of 11 withdrawals) (no placebo comparison).

➡ Guidelines recommend infliximab and adalimumab for fistulising CD, only one guideline specifies the refractory population and infliximab is recommended (NICE 2019).

➡ 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.

➡ Rates of infections were reportedly higher in the adalimumab and infliximab groups however results were not statistically different over placebo. For paediatric setting with limited evidence, serious infections were cited as the most reported reason for withdrawal (no placebo comparator). Although evidence is limited for increased risk of infections, in the South African setting, potential risk of TB infection is an important consideration; as well as the requirement to test for latent TB and provide IPT.

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 Hospital Level Committee suggests using anti-TNFs (class including adalimumab and infliximab, with the most affordable agent procured) for patients (adults and children) with fistulising Crohn's Disease who are refractory to conventional therapy.

Rationale: 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.

Both adalimumab and infliximab have been shown to be beneficial over placebo in achieving fistula remission. There are data to show that the benefit of infliximab over placebo in maintaining fistula remission, achieving fistula response and reduction in number of hospitalisations and surgeries as well as hospitalisation duration. There is limited evidence from observational studies showing benefit of adalimumab and infliximab for the paediatric population.

Adalimumab and infliximab therapy would be associated with an incremental cost. However, it is proposed that access in patients with fistulising CD be prioritised on the grounds of limited patient estimates as well as the costs incurred in terms of disease management including surgeries and hospitalisations. Although these is more data to support infliximab, the agent is more costly (SEP), requires additional resources for intravenous infusion, antibody testing and potential addition of an immunomodulator and/or corticosteroid whereas adalimumab is subcutaneous and suitable for monotherapy. Thus it is recommended that the most affordable agent be procured, and that the same agent be procured for both adults and children.

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.[7]

Level of Evidence: Systematic reviews and RCTs, evidence quality considered to be very low to low (adalimumab) and very low to moderate (adalimumab).

NEMLC RECOMMENDATION:

The NEMLC accepted the TQ ERC recommendation for fistulising CD however recommends that both adalimumab and infliximab be added to the TQ EML. It is further recommended that adalimumab be listed as the preferred option despite lower quality evidence, as the agent is favourable in terms of cost and route of administration and is associated with a decreased risk of antibody formation. It was also recommended that a document outlining treatment and monitoring of patients on adalimumab or infliximab be added as an annexure to this review (See accompanying annexure and Appendix 6).

SUMMARY OF FINDINGS TABLES

Infliximab vs Placebo – Outcomes 2.1 (induction of fistula response), 2.2 (Induction of fistula remission), and 2.7 (safety) – extracted from Gordon 2023(2)

Summary of findings 2. Infliximab 5–10 mg/kg compared to placebo for exclusively fistulating population

Infliximab compared to placebo for exclusively fistulating population

Patient or population: active Crohn's disease
Setting: not reported (multiple countries)
Intervention: infliximab (combined 5 and 10 mg/kg dosages)
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with infliximab				
Clinical remission defined as absence of any draining fistulas at ≥ 2 consecutive visits, at a median 12 weeks	129 per 1000	460 per 1000 (178 to 1000)	**RR 3.57** (1.38 to 9.25)	94 (1 study)	⊖⊖⊖⊖ **Very low**[a]	—
Clinical response defined as reduction of 50% in the number of draining fistulas at ≥ 2 consecutive visits, at a median 12 weeks	200 per 1000	388 per 1000 (220 to 682)	**RR 1.94** (1.10 to 3.41)	181 (2 studies)	⊖⊖⊖⊖ **Very low**[a]	—
Withdrawals due to adverse events	3 per 1000	7.5 per 1000 (0 to 152)	**RR 2.50** (0.12 to 50.54)	94 (1 study)	⊖⊖⊖⊖ **Very low**[a]	—

***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 two levels due to very serious concerns with risk of bias for randomisation, blinding and selective reporting, 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). Fistulising disease is a severe manifestation of CD affecting about 35% of CD patients and can sometimes necessitate multiple surgical interventions due to abscess formation(2,4,6).

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. Adalimumab is administered subcutaneously, every other week, following an initial loading period of 160mg at baseline followed by 80mg at week 2. Infliximab is given in combination with an immunomodulator, usually azathioprine, to reduce the formation of antibodies and to improve the efficacy of the drug and current guidelines recommend adalimumab as monotherapy.

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 corticosteroid sparing agent(4,7–10).

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

RESEARCH QUESTION: For patients of all ages with fistulising Crohn's Disease who are refractory to conventional therapy, is the addition of TNF inhibitors (namely adalimumab and infliximab) safe and effective?

METHODS

Eligibility criteria for review

PICO	
Population:	Individuals of all ages with Fistulising 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. Induction of fistula response defined as closure of at least 50% of draining fistula (at 2 or more consecutive visits or at week 4 or after) 2. Induction of fistula remission defined as complete close of draining fistula (at 2 or more consecutive visits or at week 4 or after) 3. Maintenance of fistula response 4. Maintenance of fistula remission 5. Rates of hospitalization and surgeries 6. Quality of life 7. Safety
Study designs	Systematic reviews of RCTs, RCTs, guidelines

* There is no uniform definition for refractory CD 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 for fistulising CD to be included if the patients had at least one draining fistula of at least 3 months duration or diagnosis of moderate to severe CD of at least 4 months with at least one draining fistula.

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

Search Strategy

An updated search was developed based on revised PICO and run in February 2024. The search strategy is outlined in Appendix 2 (Tables 1 – 6). A general search for guidelines was conducted in Google Scholar, Google and targeted websites utilising a combination of the search terms such as 'paediatric', 'Crohn's disease', and 'fistulizing'.

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). Two reviewers (KM, JR) independently assessed the methodological quality of included systematic reviews using AMSTAR 2 (11). For included primary studies, the risk of bias assessments conducted in the systematic review that included a particular study was used, and for primary studies not included in any eligible SR, we assessed the risk of bias using the Cochrane Risk of Bias tool (RoB) tool 1 (KM, JR).

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. Where data estimates for the same outcomes were available from more than one review or primary study, we extracted data from the highest quality studies available. Findings were summarised narratively and not meta-analysed. 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 or data extracted from a primary study, we assessed quality based on the RoB 1 assessment and number of events.

RESULTS

Identification of studies

The searches combined produced 111 results (108 database searches, 5 additional sources). After title and abstract screening (and removal of 40 duplicates), 21 articles remained. After full text review, 8 publications met the PICO and were assessed for eligibility for data extraction (See Appendix 4 – Summary of Amstar Assessments, Appendix 5 – Assessment of eligible studies). Data was extracted from 6 publications (See below for description of included studies). A list of excluded studies can be found in Appendix 3. See Figure 1 below - PRISMA diagram.

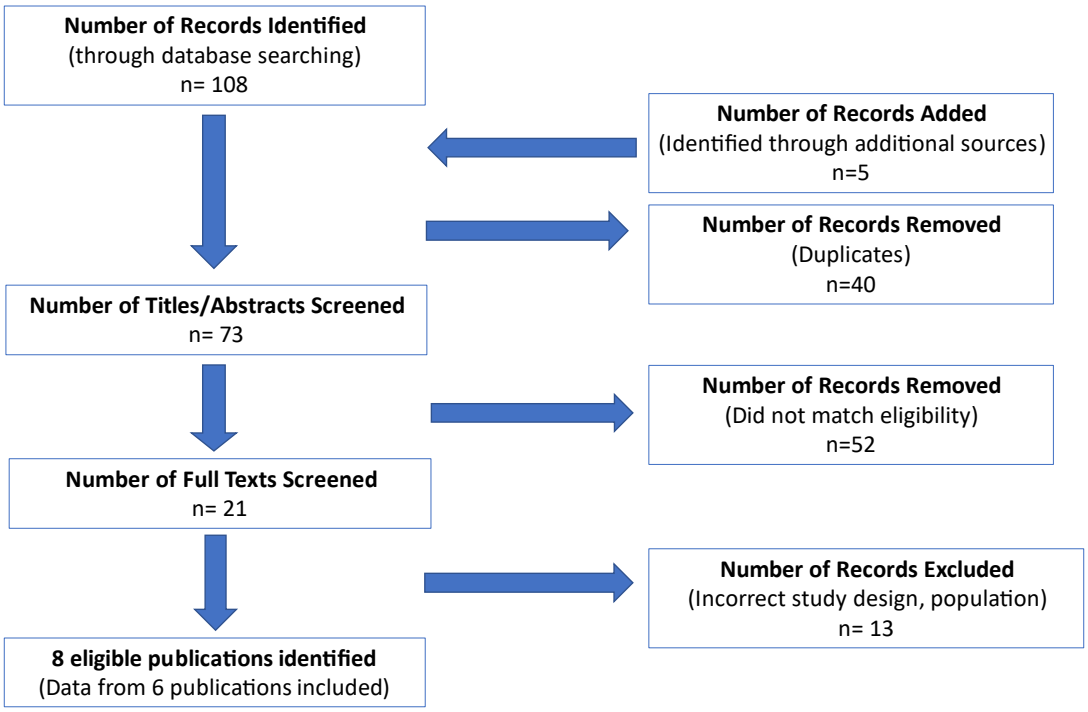

***Figure 1**: PRISMA Diagram – TNF inhibitors (adalimumab and infliximab) for Fistulising Crohns Disease*

Description of included studies

Systematic Reviews

- Gordon 2023(2) conducted a SR of RCTs conducted on **infliximab** compared to placebo in adults with fistulising CD for **induction of remission** (defined as absence of any draining fistulas at consecutive visits) and **induction of clinical response** (defined as reduction of 50% in the number of draining fistulas at 2 or more consecutive visits) and **adverse events**. The population of interest for the analysis was not specifically refractory patients however the trials underpinning the analyses for infliximab (**Present 1999**(12)**, Sands 2004**(13)) against placebo met refractory definition according to the PICO.
- Carnovale 2020(14) conducted a SR (including multiple study designs) to explore safety and efficacy of TNF inhibitors (infliximab and adalimumab) for individuals aged 9 months to 18 years who have perianal CD. Outcomes of interest included proportion of patients with fistula response, clinical response, clinical remission and adverse events.

Randomised Controlled Trials

ACCENT II (A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-term Treatment Regimen in Patients With Fistulizing Crohn's Disease)

- Sands 2004(13) reported on the ACCENT II trial exploring the efficacy and safety of **infliximab** 5-10mg/kg compared to placebo in adults for maintenance of fistula response. Participants had to have CD and ≥ 1 draining abdominal or perianal fistulas of ≥ 3 months' duration. All participants received 5mg/kg at 0, 2 and 6 weeks and thereafter participants classified with fistula response (at least 50% in number of draining fistulas observed at week 10 and 14) where randomised to either receive infliximab 5-10mg or placebo 8-weekly to evaluate **maintenance of fistula response** every 8 weeks to the study endpoint at 54 weeks. Concomitant therapy with conventional treatment was permitted at stable doses.
- Lichtenstein 2005(5) reported on a post-hoc analysis of data from ACCENT II trial specifically exploring rates of hospitalisation and surgeries during the randomised component of the trial (5m/kg infliximab or placebo on maintenance of fistula response during weeks 14 to 54 of the trial).

CHARM (Crohn's Trial of the fully Human Antibody Adalimumab for Remission Maintenance)

- Colombel 2007 – reported on the CHARM trial on adults with moderate to severely active CD (CD activity index 220-450) for ≥4 months. Prespecified subgroup analysis was also conducted for fistulising CD patients who had draining fistulas at baseline of the study. All participants received open label adalimumab induction therapy of 80mg at week 0 and 40mg at week 2 and thereafter were randomised to receive 40mg/kg adalimumab weekly or 40mg/kg adalimumab every other week, or placebo. Participants were also stratified based on clinical response (decrease in the Crohn's disease activity index (CDAI) of >70 points compared with baseline). Outcomes of interest were percentage of participants with fistula healing defined as no draining fistulas at the last two consecutive post-baseline evaluations in the double-blind period before and on that visit by week 26 and 56 (induction of fistula remission) and percentage of those with remission at 26 weeks still in remission by week 56 (maintenance of remission). Concomitant therapy with conventional treatment was permitted at stable doses.
- Colombel 2009(15) reported on a post-hoc analysis of the CHARM data on fistulising CD patients specifically. Estimates for number of mean fistulas by week 56 in the adalimumab combined groups (40mg weekly and every other week) compared to placebo were presented for all randomised patients as well as specifically for those classified as responders in the trial after open label adalimumab induction. Long term data for safety and remission were also reported.

Assessment of Methodological Quality

All eligible SRs were assessed with AMSTAR 2 (see Appendix 4 – Summary of Amstar 2 assessments); the two SRs included for data extraction, Gordon 2023 and Carnovale 202 were evaluated as high and low quality respectively.

Cochrane Risk of bias 1 assessments for Colombel 2007(16), Colombel 2009(15), Sands 2004(13) and Lichtenstein 2005(17) are tabulated below (Table 2). Colombel 2007 and 2009 (CHARM trial) had domains evaluated to be high risk of bias and considered to be high risk of bias overall. The domain for attrition bias was evaluated to be high risk of bias for Colombel 2007 and 2009 as there were different rates of withdrawals between groups. Colombel 2009 additionally had one domain considered to be of unclear risk of bias which was selective reporting as some of the outcomes of interest, and analysis thereof, were not prespecified in the original CHARM trial. Sands 2004 and Lichtenstein 2005 (ACCENT II trial) had some domains which were evaluated to be unclear and were considered to be of unclear risk of bias overall. Although it was reported that patients and study investigators were blinded to the treatment allocation, and that patients and physicians remained blinded to crossovers, it does not state explicitly whether study investigators remained blinded. Selective reporting was also considered unclear risk of bias for Lichtenstein 2005 as the outcomes of interest and analysis thereof were not prespecified in the ACCENT II trial.

Table 2: Risk of Bias 1 Assessments of included studies

	Colombel 2007	Colombel 2009	Sands 2004	Lichtenstein 2005
Random Sequence Generation (selection bias)	**Low**	**Low**	**Low**	**Low**
Allocation Concealment (selection bias)	**Low**	**Low**	**Unclear**	**Unclear**
Blinding of participants and personnel (performance bias)	**Low**	**Low**	**Low**	**Low**
Blinding of outcome assessment (detection bias)	**Low**	**Low**	**Low**	**Low**
Incomplete Outcome Data (attrition bias)	**High**	**High**	**Low**	**Low**
Selective Reporting (reporting bias)	**Low**	**Unclear**	**Low**	**Unclear**
Other Bias	**Low**	**Low**	**Low**	**Low**
OVERALL	**High**	**High**	**Unclear**	**Unclear**

Based on the Cochrane RoB 1 assessment extracted from Gordon 2023, Present 1999 had one domain that was evaluated as high risk (selective reporting – primary outcome not prespecified) – see Figure 2.

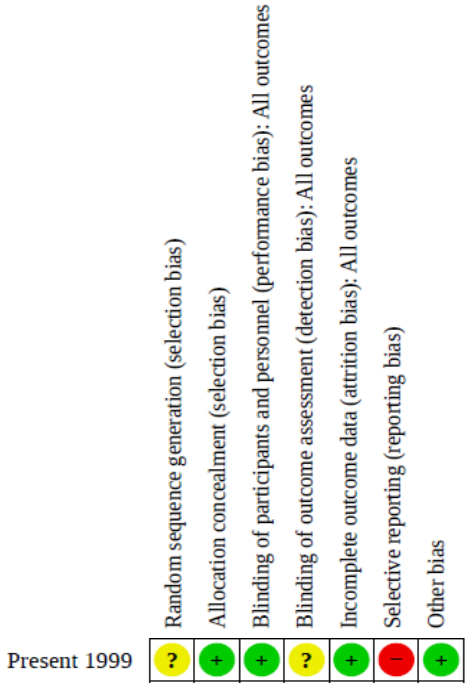

***Figure 2**: Risk of Bias Diagram extracted from Gordon 2023*(2) *conducted on Present 1999*

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 induced fistula response (at least 50% fistula closure)

None of the selected articles reported on this outcome

Outcome 1.2 Number of participants with induced fistula remission (100% fistula closure)

Colombel 2007(16) reported that in the CHARM RCT there were more participants with fistula remission at week 26 in the combined adalimumab (40mg weekly or every other week) group (n=21, 30%) compared to the placebo group (n=6, 13%) (RR : 2.35 in favour of adalimumab, 95% CI [1.03 to 5.38], P=0.043, NNT 6 95% CI [4 to 51], n=117) – *very low quality evidence* [i]. Similarly at week 56 there were more participants with fistula remission in the combined adalimumab group (n=23, 33%) compared to the placebo group (n=6, 13%) (RR:2.58 in favour of adalimumab, 95% CI [1.14 to 5.84], P=0.016, NNT 5 95% CI [3 to 22], n=117) – *very low quality evidence*[i].

The analyses above were conducted on all participants regardless of whether they were classified as responders or not after the open-label induction phase (week 4 CDAI decreases >70 points vs baseline). Colombel 2009 reported in

[i] See section on quality – serious concerns with risk of bias and small number of events

the post-hoc analysis that for those who had a clinical response, the mean number of fistulas was higher in the placebo group (1.15) compared to the adalimumab combined group (0.76) (MD 0.39, p=0.043, n=64) after 56 weeks. The results were similar for all participants (responders and non-responders) with a reported mean number of draining fistulas per day of 1.34 for placebo compared with a mean of 0.88 for the combined adalimumab groups (MD 0.46 more in the placebo group, p=0.002, n=117) – *very low quality evidence* [i].

Outcome 1.3 Number of participants with maintained fistula response (at least 50% fistula closure)

None of the selected articles reported on this outcome

Outcome 1.4 Number of participants with maintained fistula remission (100% fistula closure)

Colombel 2007 (16)reported that of patients with complete fistula closure at week 26, 100% in both adalimumab and placebo groups continued to have complete fistula closure at week 56 – *very low quality evidence* [i].

Colombel 2009(15) reported on data from the open-label extension ADHERE trial. Patients with fistula remission at the end of CHARM were eligible to continue receiving 40mg adalimumab either weekly or every other week. There was no placebo comparator. After two years from baseline of treatment with adalimumab 22 out of 37 (59%) patients remained in remission.

Outcome 1.5 Mean number of hospitalisations and surgeries

None of the included articles reported on this outcome specifically.

Outcome 1.6 Quality of life

None of the selected articles reported on this outcome.

Outcome 1.7 Safety

The Colombel 2009 reported on the safety data for the fistulising CD sub-group specifically and found a similar percentage of total adverse events in both groups (placebo 80.9%; adalimumab 84.3%, RR 1.04 [95% CI 0.88 to 1.24], P=0.34, n=117 – not significant) as well as severe adverse events (placebo 10.6%; adalimumab 12.9%, RR 1.21 [95% CI 0.43 to 3.39], P=0.7 – not significant, n=117). There were more infectious adverse events in the adalimumab group (44.3%) compared to the placebo group (34%) (RR 1.3 [95% CI 0.81 to 2.10], P=0.3 – not significant) – *very low quality evidence* [i]. See Figure 3.

Event	Placebo (n = 47) No (%)	All adalimumab (n = 70) No (%)
Adverse event	38 (80.9)	59 (84.3)
Serious adverse event	5 (10.6)	9 (12.9)
Adverse event leading to discontinuation of study medication	3 (6.4)	4 (5.7)
Infectious adverse event	16 (34.0)	31 (44.3)
Serious infectious adverse event*	2 (4.3)	5 (7.1)
Abscess (all)	5 (10.6)	8 (11.4)
Malignant neoplasm	0	0
Injection-site reaction (all)	2 (4.3)	3 (4.3)
Opportunistic infection†	1 (2.1)	0
Congestive heart failure	0	0
Demyelinating disorder	0	0
Death	0	0

*Both of the placebo-treated patients had an abdominal abscess. The serious infectious adverse events for the five adalimumab-treated patients were a pulmonary embolus with pneumonia (n = 1); intra-abdominal abscess (n = 1); perianal abscess (n = 2) and scrotal abscess (n = 1). †Oral candidiasis. CHARM, Crohn's Trial of the fully Human Antibody Adalimumab for Remission Maintenance.

***Figure 3**: Summary of safety in adalimumab and placebo treated patients with fistulas after 56 weeks – sourced from Colombel 2009* (15).

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

Outcome 2.1 Number of participants with induced fistula response (at least 50% fistula closure)

Gordon 2023 reported that there were more participants in the infliximab groups who achieved fistula response compared to placebo (RR=1.94 in favour of infliximab, 95% CI [1.10 to 3.41], i^2= 14%, P=0.02, NNT 4[ii] 95% CI [3 to 9], 2 RCTs, n=181) – *very low certainty of evidence (GRADE from Gordon 2023 - downgraded two levels due to very serious concerns with risk of bias, and one level due to serious concerns with imprecision due to low event numbers*). See Summary of findings table (pg. 4) and Figure 4.

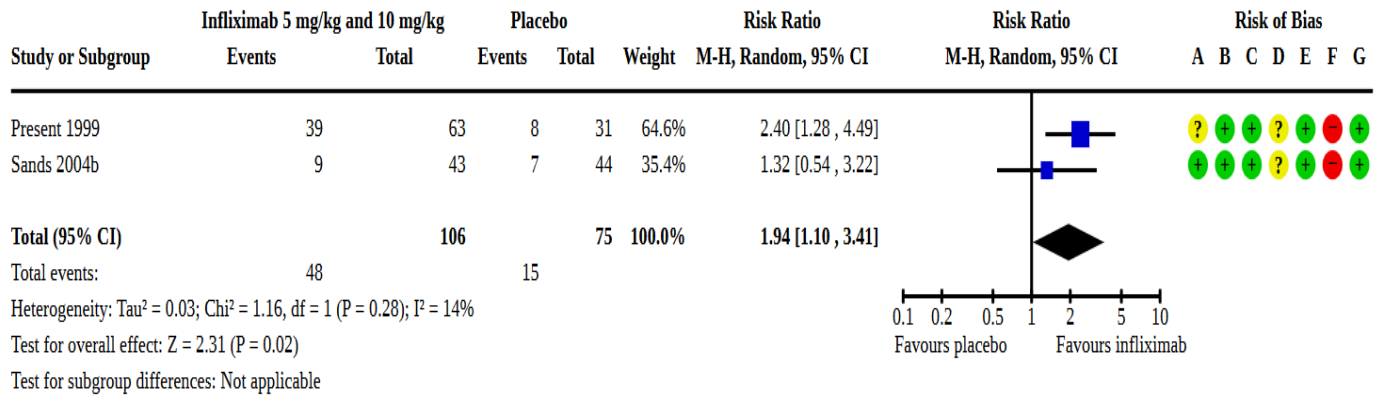

Figure 4: *Comparison 2 (infliximab vs placebo); Outcome 2.1 (No. of participants with induced fistula response) – sourced from Gordon 2023*(2).

Outcome 2.2 Number of participants with induced fistula remission (100% fistula closure)

Gordon 2023 reported that there were more participants in the infliximab group who achieved fistula remission compared to placebo (RR=3.57 in favour of infliximab, 95% CI [1.38 to 9.25], i^2= 0%, P=0.009, NNT 4 95% CI [2 to 10], 1 RCTs, n=94) – *very low certainty of evidence (GRADE from Gordon 2023, downgraded two levels due to very serious concerns with risk of bias, and one level due to serious concerns with imprecision due to low event numbers*). See Summary of findings table (pg. 4) and Figure 5.

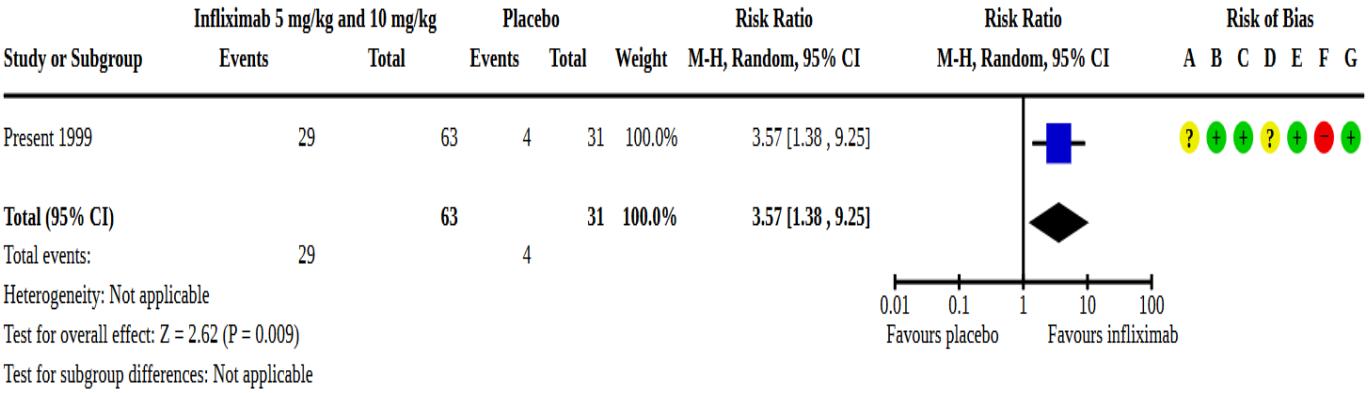

Figure 5: *Comparison 2 (infliximab vs placebo); Outcome 2.2 (No. of participants with induced fistula remission) – sourced from Gordon 2023*(2).

Outcome 2.3 Number of participants with maintained fistula response (at least 50% fistula closure)

Sands 2004 reported that among participants who had a response during open label induction, there more participants in the infliximab group (46%) who still had a response at week 54 compared to the placebo group (23%) (RR: 1.96 95%

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

CI [1.29 to 3.00], P=0.001, NNT 5, 95% CI [3 to 11], n=195 responders) – *moderate quality evidence*[iii]. After randomisation, the median time to the loss of response was 14 weeks in the placebo maintenance group, as compared with more than 40 weeks in the infliximab maintenance group. Efficacy was analysed for participants with antibodies against infliximab, those without, and those with inconclusive tests and were found to be similar at 32%, 31%, and 29% respectively.

Outcome 2.4 Number of participants with maintained fistula remission (100% fistula closure)

None of the selected articles reported on this outcome.

Outcome 2.5 Mean number of hospitalisations and surgeries

Lichenstein 2005(17) reported on the post hoc analysis of the ACCENT II trial (Sands 2004) that for those participants that were classified as responders after induction treatment, the mean number of hospitalisation days due to CD was lower in the 5mg/kg infliximab maintenance therapy group (0.5 days) than in the placebo group (2.5 days) after 46 weeks (MD: 2 days, P<0.05, n=195) – *moderate quality evidence*[iii]. For responder participants, there was also a reportedly lower percentage of participants hospitalised in the infliximab 5mg/kg maintenance group (7.3%) compared to the placebo group (18.2%) from CD related causes (MD 10.9%, P<0.05) – *moderate quality evidence*[iii]. Mean numbers (per 100 patients) for all surgeries and procedures, inpatients surgeries and procedures as well as major procedures were all lower in the 5mg/kg infliximab maintenance group compared to placebo for those participants classified as responders in the induction phase (See Figure 6 below). Results for all randomised patients (responders and non-responders) showed results in favour of the infliximab maintenance group however not all results were statistically significant – *moderate quality evidence*[iii].

	All randomized patients (n = 282)		Patients randomized as responders (n = 195)	
Variable	Placebo maintenance (n = 143)	5 mg/kg infliximab maintenance (n = 139)[a]	Placebo maintenance (n = 99)	5 mg/kg infliximab maintenance (n = 96)[a]
Hospitalizations[b]	31 (45)	14 (19) *P* < .05	31 (31)	11 (11) *P* < .05
Hospitalization days[c]	2.4	0.8 *P* = .110	2.5	0.5 *P* < .05
All surgeries and procedures[b]	118 (169)	60 (83) *P* < .01	126 (125)	65 (62) *P* < .05
Inpatient surgeries and procedures[b]	45 (65)	10 (14) *P* < .001	41 (41)	7 (7) *P* < .01
Major surgeries[b]	13 (18)	2 (3) *P* < .05	11 (11)	2 (2) *P* < .05

[a]*P* values are for comparisons between the 2 treatment groups.
[b]Each entry is the mean number per 100 patients with the total number in parentheses.
[c]Each entry is the mean number of days hospitalized per patient.

Figure 6 : *Comparison 2 (infliximab vs placebo); Outcome 2.5 (No. of CD related hospitalisations, hospitalisation days, surgeries and procedures) – sourced from Lichtenstein 2005* (17).

Outcome 2.6 Quality of life

None of the included articles reported on this outcome specifically.

Outcome 2.7 Safety

Gordon 2023 reported more withdrawals due to adverse events in infliximab group (2 withdrawals) compared to the placebo group (0 withdrawals) however the CI did cross the null (RR 2.50 95% CI [0.12 to 50.54], P=0.55, 1 trial) – very *low certainty of evidence (GRADE from Gordon 2023, downgraded two levels due to very serious concerns with risk of bias, and one level due to serious concerns with imprecision due to low event numbers)*. See Summary of findings table (pg. 4) and Figure 7.

[iii] See section on quality – unclear risk of bias

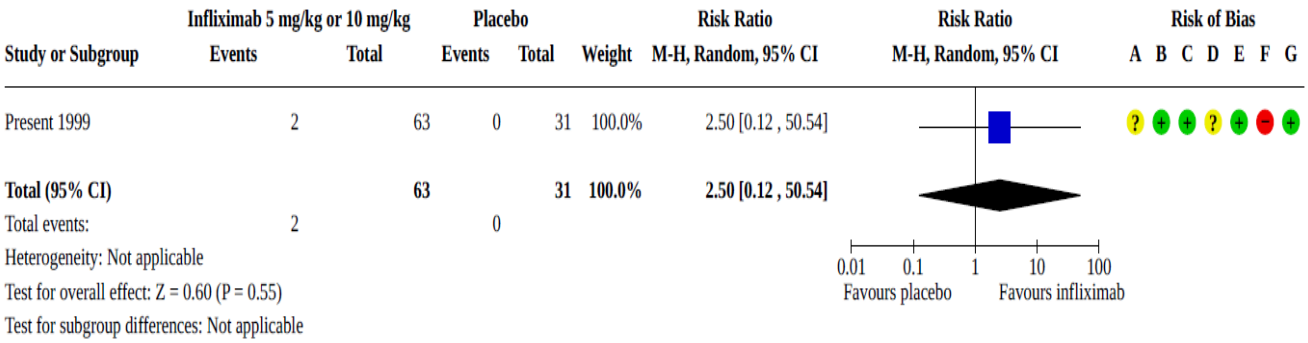

Figure 7 : *Comparison 2 (infliximab vs placebo); Outcome 2.7 (Safety – withdrawals due to adverse events) – sourced from Gordon 2023*(2).

Serious and total adverse events were also reportedly higher in the infliximab group however the CIs did cross the null (Serious adverse events: 5 vs 0; RR 5.50 95% CI [0.31 to 96.40], P=0.24, 1 trial, n=94, GRADE not conducted; Total adverse events: 36 vs 12; RR 1.48 95% CI [0.90 to 2.41], P=0.12, 1 trial, n=94, GRADE not conducted). See Figures 8 and 9 below.

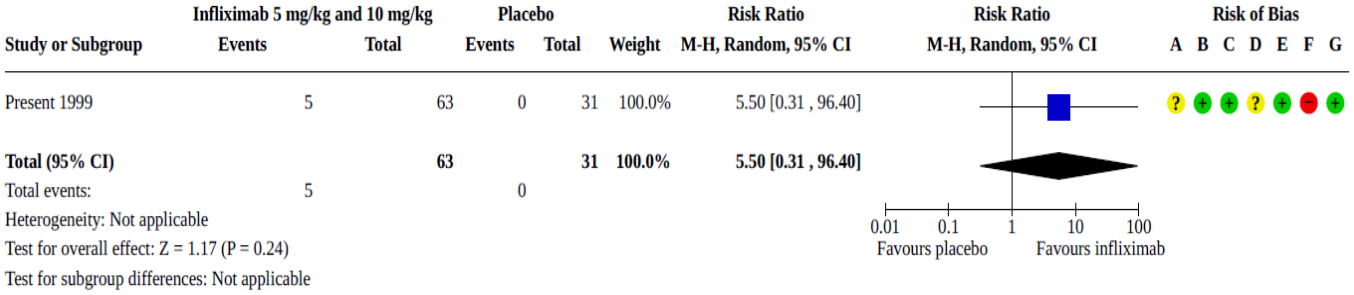

Figure 8 : *Comparison 2 (infliximab vs placebo); Outcome 2.7 (Safety – serious adverse events) – sourced from Gordon 2023*(2).

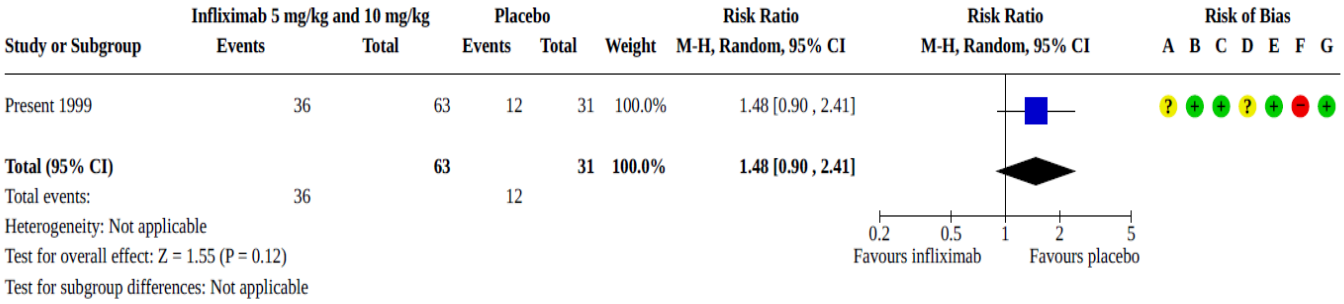

Figure 9 : *Comparison 2 (infliximab vs placebo); Outcome 2.7 (Safety – total adverse events) – sourced from Gordon 2023*(2).

Gordon 2023 only included the Present 1999 publication in safety data as the outcome of interest for their review was induction of remission however Sands 2004(13) reported similar rates of adverse events leading to discontinuation in the infliximab and placebo maintenance groups (placebo=8%, infliximab 4%, P=0.1). There was a higher percentage of infections requiring antimicrobial treatment in the infliximab group (34%) compared to placebo (27%) group however not significantly different (P=0.20). Differences in serious infections were not significantly different between group (placebo=6%, infliximab=3%, P=0.18).

There was a higher percentage of participants who developed antinuclear antibodies in the infliximab group (56 out of 122, 45.9%) compared to the placebo group (24 out of 132, 18.2%) (RR 2.53 [95% [1.68 to 3.80, NNH 4 [95% CI 3 to 6) P<0.001), P<0.001). Results were similar for the development of antibodies against double-stranded with a higher percentage in the infliximab (27 out of 116, 23.3%) group compared to placebo (8 out of 127, 6.3%) group (RR 3.7 [95% CI 1.80 to 7.81], NNH 6 [95% CI 4 to 12], P <0.001). The presence of antibodies had a reported impact on infusion reactions; 30% of participants with a positive antibody status developed at least one infusion reaction compared to 16% of those with a negative antibody status. Reportedly, participants on concomitant corticosteroids and/or immunomodulators at baseline had a benefit in preventing the development of antibodies (patient receiving corticosteroids AND immunomodulators=4%, patients receiving corticosteroids only=13%, patients receiving immunomodulators only=11%, patients receiving neither corticosteroids nor immunomodulators =24%).

Efficacy and safety in paediatric population

The Carnovale 2020 SR found only 2 RCTs (for infliximab) however they were not placebo controlled and had very small patient numbers. The evidence found was predominantly prospective observational, case series or case report study designs. The pooled analysis (of all study designs) included 565 patients and studies on infliximab or adalimumab.

Clinical remission (as classified by the study)

SR reported that at 2 weeks 21% of patients had achieved clinical remission (95% CI [10 to 37%], 3 studies, n=39). At 6 weeks 42% of patients had achieved clinical remission (95% CI [35 to 49], 8 studies, n=214). For maintenance therapy, it was reported that 64% of patients were in remission at 10 weeks (95% CI [62 to 76%], 3 studies, n=61) and 41% at 12 months (95% CI [34 to 49%], 5 studies, n=174) – *low quality evidence*.

Clinical response (as classified by the study)

Clinical response at 2 to 4 weeks was reported to 28% of patients (95% CI [19 to 39%), 5 studies, n=86) and 73% at 6 weeks (95% CI [65 to 80%], 6 studies, n=147) – *low quality evidence*.

Complete closure of perianal fistula

The SR report that 56% of patients achieved complete closure of perianal fistula (95% CI not reported, 12 studies, n=228) – *low quality evidence*.

Safety

Adverse events were reported in 10 of the included studies (n=105 patients, 91 events reported) with anaemia and allergic reactions the most common event reported (9 and 7 events reported respectively). Sixty five serious adverse events were reported with leucopoenia and varicella-zona virus infection the most frequent at 7 events. Withdrawal due to adverse events was reported in 3 studies (120 patients) and occurred in 9% of patients ([95% CI: 5–16]), with serious infections being the most reported reason for withdrawal (8 out of 11 withdrawals).

GUIDELINES

Five relevant guidelines on the treatment of TNF inhibitors for fistulising CD were found. These guidelines were produced by NICE 2019 (18), American College of Gastroenterology (ACG) (7), American Gastroenterological Association (19), British Society of Gastroenterology (BSC), and The European Crohn's and Colitis Organisation (ECCO)(8). The relevant recommendations from each guideline have been extracted and are presented in Table 2. Majority of the recommendations did not specify the refractory population (except for the NICE guidance) and provide recommendation in general for fistulising CD. All guidelines recommended infliximab and adalimumab in fistulising CD however recommendations for infliximab were all strong with moderate or low quality evidence reported. The strength of adalimumab recommendations varied from strong to weak with reported evidence to be of very low to low quality. The NICE guidance recommends infliximab for patients with fistulising CD who are refractory or intolerant to conventional therapies.

Table 2. Clinical guideline recommendations

Guideline	Recommendations	Strength of evidence
Crohn's Disease Management, NICE Guideline 2019 **(18)**	**INDUCTION OF REMISSION** • 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. • **1.2.16 Infliximab, within its licensed indication, is recommended as a treatment option for people with active fistulising Crohn's disease whose disease has not responded to conventional therapy (including antibiotics, drainage and immunosuppressive treatments), or who are intolerant of or have contraindications to conventional therapy. Infliximab 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.** • 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(20), strength of evidence not provided
	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**(7)**	<u>In Perianal/fistulizing disease:</u> Infliximab is effective and should be considered in treating perianal fistulas in Crohn's disease	GRADE: Strong recommendation, moderate level of evidence.
	Adalimumab and certolizumab pegol may be effective and should be considered in treating perianal fistulas in Crohn's disease	GRADE: Strong recommendation, low level of evidence.
AGA Clinical Practice Guidelines on the Medical Management of Moderate to Severe Luminal and Perianal Fistulizing	In adult outpatients with CD and active perianal fistula, the AGA recommends the use of infliximab over no treatment for the induction and maintenance of fistula remission.	GRADE: Strong recommendation, moderate level of evidence.
	In adult outpatients with CD and active perianal fistula, the AGA suggests the use of adalimumab, ustekinumab, or vedolizumab over no treatment for the induction or maintenance of fistula remission.	GRADE: Conditional recommendation, low level of evidence.

Crohn's Disease 2021**(19)**	In adult outpatients with CD and active perianal fistula without perianal abscess, the AGA recommends the use of biologic agents in combination with an antibiotic over a biologic drug alone for the induction of fistula remission.	GRADE: Strong recommendation, moderate level of evidence.
British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults 2019 **(9)**	Perianal Crohns Disease: Statement 65. We recommend that infliximab is used as the first-line biological therapy for complex perianal fistulae, and should be started as soon as adequate drainage of sepsis is achieved	GRADE: strong recommendation, high quality evidence. Agreement: 100%.
	We suggest that anti-TNF therapy may be used to control inflammation or maintain remission in the setting of non-perianal fistulising Crohn's disease	GRADE: weak recommendation, low-quality evidence. Agreement: 94.6%.
ECCO Guidelines on Therapeutics in Crohn's Disease: Medical Treatment 2020 **(8)**	We recommend infliximab for the induction and maintenance of remission in complex perianal fistulae in Crohn's disease	GRADE: Strong recommendation; low quality of evidence.
	We suggest adalimumab may be used for induction and maintenance of remission in complex perianal fistulae in Crohn's disease	GRADE: Weak recommendation, very low-quality evidence.
	In patients with Crohn's disease and complex perianal fistula there is insufficient evidence regarding the effect of adding immunomodulators to anti-TNF on fistula healing	GRADE: Weak recommendation, very low-quality evidence.

Quality

Evidence for adalimumab was considered to be very low quality for all outcomes due to serious concerns with potential risk of bias and very small sample size estimates. There were no concerns with heterogeneity or directness of the evidence. Evidence for infliximab varied per outcome from very low quality (Induction of response, Induction of remission, and safety) to moderate quality (maintained fistula response, hospitalisations and surgeries). Evidence for outcomes with very low quality was downgraded due to serious concerns with risk of bias and imprecision due to low event numbers. There were no concerns with heterogeneity or directness of the evidence. Evidence for outcomes with moderate quality was downgraded due to unclear risk of bias. There were no concerns with heterogeneity, directness of the evidence or number of events.

COSTS

Cost per patient for induction and maintenance as well as annual and 10 year budget impact were estimated.

Doses: Infliximab therapy: 5mg/kg IVI at weeks 0, 2, and 6, and then 8 weekly.
Adalimumab therapy: 160mg SC at week 0, and then 80mg SC at week 2, and then 40mg SC every other week

Table 3: Cost per patient per year (induction and maintenance) - 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		

cheapest generic product -SEP database December 2023 Amgevita® and Remiflex ®

Table 4: Budget impact SEP

19 patients/year - *Estimate from Prof Watermeyer based on survey from HODs across the country (35% estimate of CD for fistulising)*

	Active Ingredients	Price per patient per year (YEAR 1)	Price per patient per year (YEAR 2)	Budget impact based on 19 patients (year 1)	Budget impact based on 19 patients (subsequent years)
Single exit prices*	Infliximab	R68 075,18	R50 570,13	R1 293 428,33	R960 832,47
	Adalimumab	R49 941,75	R43 282,85	R948 893,25	R822 374,15

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

Table 5: Budget impact over 10 years

Incremental annual costs (19 new Fistulising CD patients per year)		
	SEP*	
	Infliximab	Adalimumab
Year 1	R1 293 428,33	R948 893,25
Year 2	R2 254 260,80	R1 771 267,40
Year 3	R3 215 093,27	R2 593 641,55
Year 4	R4 175 925,74	R3 416 015,70
Year 5	R5 136 758,21	R4 238 389,85
Year 6	R6 097 590,68	R5 060 764,00
Year 7	R5 247 707,28	R5 968 431,24
Year 8	R8 019 255,62	R6 705 512,30
Year 9	R8 980 088,09	R7 527 886,45
Year 10	R9 940 920,56	R8 350 260,60

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Additional resources have not been costed for infliximab; consumables for intravenous therapy, potential antibody testing, concomitant use of an immunomodulator and/or corticosteroids.

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 fistulising CD. Fistulising CD is a severe manifestation of CD which can necessitate numerous surgeries, hospitalisations and costly investigations (CTs, MRIs) thus was prioritised for review first by the TQ ERC.

Quality of the data was generally low (high risk of bias) or very low (high risk of bias, small number of events) for outcomes reported for the adalimumab vs placebo comparison. 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. Data in favour of adalimumab over placebo was found for induction of fistula remission. Infliximab was found to be superior compared to placebo for induction of fistula response and remission, maintenance of fistula response, and rates of hospitalisations and surgeries. Adverse events and serious adverse events were reportedly similar between placebo and adalimumab. No difference was found between infliximab and placebo for serious adverse events and total adverse events. However there was a higher percentage of participants with antibodies at baseline (from infliximab or placebo groups) who had an infusion reaction compared to those without antibodies or inconclusive antibody tests. There was higher rate of antibody formation for infliximab therapy. The concomitant administration of immunomodulators and /or corticosteroids reportedly impacted the percentage of participants who had an infusion reaction. No placebo controlled randomised trials were found for the paediatric population however low quality evidence (based on a SR of study designs including descriptive studies) suggests

that adalimumab and infliximab may be beneficial for induction and maintenance of remission in children with perianal CD.

Utilisation of the therapy will result in an incremental cost however there is a potential that use of the agents may result in lower resource costs related to hospitalisations, surgeries and other procedures. The quality of data was varied (very low to moderate) however it is anticipated that no further trials will be conducted in this population as treatment has progressed globally; and is international standard of care. Due to the severity of the condition, low estimated patient numbers as well the potential reduction in hospitalisations and surgeries, it is proposed that access be considered in patients (adults and children) with fistulising CD as an add on therapy for those that have not responded to conventional therapies. Data was available for more outcomes for infliximab; however data was found in favour of both adalimumab and infliximab over placebo for the highest ranking endpoint (induction of fistula remission). 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. It is therefore recommended that the most affordable agent be procured. Both the package inserts for adalimumab(21) and infliximab(22) 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.

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

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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
- Solange Durao (SAMRC, Health Systems Research Unit)* 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.

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Appendix 1: Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High ☐ Moderate ☐ Low ☐ Very low ☒	**Comparison 1: Adalimumab in addition to standard of care vs standard of care alone** 1.2 Induced fistula remission (100% fistula closure) – RoB 1= High risk; Imprecision due to low event numbers 1.4 Maintained fistula remission (100% fistula closure) – RoB 1= High risk; Imprecision due to low event numbers 1.7 Safety – RoB 1= High risk; Imprecision due to low event numbers **Comparison 2: Infliximab in addition to standard of care vs standard of care alone** 2.1 Induced fistula response (at least 50% fistula closure) – GRADE result from SR, downgraded two levels due to very serious concerns with risk of bias, and one level due to serious concerns with imprecision due to low event numbers 2.2 Induced fistula remission (100% fistula closure) - GRADE result from SR, downgraded two levels due to very serious concerns with risk of bias, and one level due to serious concerns with imprecision due to low event numbers 2.7 Safety - GRADE result from SR, downgraded two levels due to very serious concerns with risk of bias, and one level due to serious concerns with imprecision due to low event numbers
	What is the certainty/quality of evidence? High ☐ Moderate ☒ Low ☐ Very low ☐	**Comparison 2: Infliximab in addition to standard of care vs standard of care alone** 2.3 Maintained fistula response (at least 50% fistula closure) – RoB 1 = Unclear Risk 2.5 Mean number of hospitalisations and surgeries – RoB 1 = Unclear Risk
	What is the size of the effect for beneficial outcomes? Large ☐ Moderate ☒ Small ☐ None ☐	**Comparison 1: Adalimumab in addition to standard of care vs standard of care alone** 1.2 Induced fistula remission (100% fistula closure) At 26 weeks - RR: 2.35 in favour of adalimumab (40mg weekly or every other week), 95% CI [1.03 to 5.38], P=0.043, NNT 6 95% CI [4 to 51], n=117. At 56 weeks - RR:2.58 in favour of adalimumab (40mg weekly or every other week), 95% CI [1.14 to 5.84], P=0.016, NNT 5 95% CI [3 to 22], n=117. **Comparison 2: Infliximab in addition to standard of care vs standard of care alone** 2.1 Induced fistula response (at least 50% fistula closure) RR:1.94 in favour of infliximab, 95% CI [1.10 to 3.41], i^2= 14%, P=0.02, NNT 4 95% CI [3 to 9], 2 RCTs, n=181 2.2 Induced fistula remission (100% fistula closure) RR:3.57 in favour of infliximab, 95% CI [1.38 to 9.25], i2= 0%, P=0.009, NNT 4 95% CI [2 to 10], 1 RCTs, n=94 2.3 Maintained fistula response (at least 50% fistula closure) RR: 1.96 95% CI [1.29 to 3.00], P=0.001, NNT 5, 95% CI [3 to 11], n=195 responders

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
		2.5 Mean number of hospitalisations and surgeries • Mean number of hospitalisation days due to CD (MD: 2 days in favour of infliximab, P<0.05, n=195). • % of responder participants hospitalised CD related causes (MD 10.9% in favour of infliximab, P<0.05). • Mean number of inpatient surgeries and procedures per 100 patients (MD 61 in favour of infliximab, P<0.01) • Mean number of major surgeries per 100 patients (MD 9 in favour of infliximab, P<0.05).
	What is the size of the effect for beneficial outcomes? Large [ ] Moderate [ ] Small [ ] None [X]	**Comparison 1: Adalimumab in addition to standard of care vs standard of care alone** 1.4 Maintained fistula remission (100% fistula closure) Colombel 2007 (16)reported that of patients with complete fistula closure at week 26, 100% in both adalimumab and placebo groups continued to have complete fistula closure at week 56.
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** **L**arge [ ] Moderate [ ] Small [ ] None [X]	**Comparison 1: Adalimumab vs placebo (conventional therapies both arms)** Outcome 1.7 – Safety • Adverse events - RR 1.04 [95% CI 0.88 to 1.24), P=0.34, n=117 – not significant • Severe adverse events (RR 1.21 [95% CI 0.43 to 3.39], P=0.7 – not significant, n=117). • More infectious adverse events in the adalimumab group (RR 1.3 [95% CI 0.81 to 2.10], P=0.3 – not significant). **Comparison 2: Infliximab in addition to standard of care vs standard of care alone** Outcome 2.7 – Safety • Lower percentage of participants in infliximab maintenance group reported with adverse events leading to discontinuation compared to placebo (placebo=8%, infliximab 4%, P=0.1 – not significant). • Higher percentage of infections requiring antimicrobial treatment in the infliximab group (34%) compared to placebo (27%) group however not significantly different (P=0.20). • Differences in serious infections were not significantly different between group (placebo=6%, infliximab=3%, P=0.18).
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** **L**arge [ ] Moderate [X] Small [ ] None [ ]	**Comparison 2: Infliximab in addition to standard of care vs standard of care alone** Outcome 2.7 – Safety • Higher percentage of participants who developed antinuclear antibodies in the infliximab group (RR 2.53 [95% [1.68 to 3.80, NNH 4 [95% CI 3 to 6) P<0.001). • Results were similar for the development of antibodies against double-stranded with a higher percentage in the infliximab group (RR 3.7 [95% CI 1.80 to 7.81], NNH 6 [95% CI 4 to 12], P <0.001).Results were similar for the development of antibodies against double-stranded with a higher percentage in the infliximab group (RR 3.7 [95% CI 1.80 to 7.81], NNH 6 [95% CI 4 to 12], P <0.001).

<table>
<tr><th></th><th>JUDGEMENT</th><th>EVIDENCE & ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td>BENEFITS & HARMS</td><td>Do the desirable effects outweigh the undesirable harms?
Favours intervention: [X] Favours control: [ ] Intervention = Control or Uncertain: [ ]</td><td></td></tr>
<tr><td>FEASABILITY</td><td>Is implementation of this recommendation feasible?
Yes: [X] No: [ ] Uncertain: [ ]</td><td></td></tr>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?
More intensive: [X] Less intensive: [ ] Uncertain: [ ]</td><td>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></td></tr>
</table>

Appendix 2: Search strategy

Table 1: PubMed – SEARCH RERUN 9 FEBRUARY 2024 – Systematic reviews

Search	Query	Search Details	Results
#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 ("fistul*"[Title/Abstract] AND ("Crohn's Disease"[Title/Abstract] OR "crohn disease"[MeSH Terms]))) AND (meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter])	50
#3	#1 AND #2	("tumor necrosis factor inhibitors"[MeSH Terms] OR "infliximab"[MeSH Terms] OR "adalimumab"[MeSH Terms] OR "TNF inhibitors"[Title/Abstract]) AND ("fistul*"[Title/Abstract] AND ("Crohn's Disease"[Title/Abstract] OR "crohn disease"[MeSH Terms]))	577
#2	Fistulising Crohns Disease	((fistul*[Title/Abstract]) AND (("Crohn's Disease"[Title/Abstract]) OR (crohn's disease[MeSH Terms]))	4786
#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]	19741

Tables 2 - 4: COCHRANE LIBRARY– SEARCH RERUN 9 FEBRUARY 2024

search	Query	Results
#1	MeSH descriptor: [Crohn Disease] explode all trees	2244
#2	MeSH descriptor: [Tumor Necrosis Factor Inhibitors] explode all trees	160
#3	#1 AND #2	11
#4	#3 in Cochrane Reviews	0

search	Query	Results
#1	MeSH descriptor: [Crohn Disease] explode all trees	2244
#2	MeSH descriptor: [adalimumab] explode all trees	1153
#3	#1 AND #2	161
#4	#3 in Cochrane Reviews	4

search	Query	Results
#1	MeSH descriptor: [Crohn Disease] explode all trees	2244
#2	MeSH descriptor: [infliximab] explode all trees	1064
#3	#1 AND #2	254
#4	#3 in Cochrane Reviews	7

search	Query	Results
#1	MeSH descriptor: [Crohn Disease] explode all trees	2244
#2	MeSH descriptor: [Tumor Necrosis Factor Inhibitors] explode all trees	**160**
#3	MeSH descriptor: [adalimumab] explode all trees	1153
#4	MeSH descriptor: [infliximab] explode all trees	1064
#5	#2 OR #3 OR #4	2186
#6	#1 AND #5	388
#7	MeSH descriptor: [Fistula] explode all trees	1219
#8	#6 AND #7	34
#9	#8 in Cochrane reviews	0

Table 5:Additional Searches for Paediatric Population – PUBMED

Search	Query	Search Details	Results
#5	Paediatric	(("tumor necrosis factor inhibitors"[MeSH Terms] OR "infliximab"[MeSH Terms] OR "adalimumab"[MeSH Terms] OR "TNF inhibitors"[Title/Abstract]) AND ("fistul*"[Title/Abstract] AND ("Crohn's Disease"[Title/Abstract] OR "crohn disease"[MeSH Terms])) AND ("meta analysis"[Publication Type] OR "randomized controlled trial"[Publication Type] OR "systematic review"[Filter])) AND (allchild[Filter])	10
#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 ("fistul*"[Title/Abstract] AND ("Crohn's Disease"[Title/Abstract] OR "crohn disease"[MeSH Terms]))) AND (meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter])	50
#3	#1 AND #2	("tumor necrosis factor inhibitors"[MeSH Terms] OR "infliximab"[MeSH Terms] OR "adalimumab"[MeSH Terms] OR "TNF inhibitors"[Title/Abstract]) AND ("fistul*"[Title/Abstract] AND ("Crohn's Disease"[Title/Abstract] OR "crohn disease"[MeSH Terms]))	577
#2	Fistulising Crohns Disease	((fistul*[Title/Abstract]) AND (("Crohn's Disease"[Title/Abstract]) OR (crohn's disease[MeSH Terms]))	4786
#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]	19741

Table 6: Additional Searches for Paediatric Population – COCHRANE LIBRARY

search	**Query**	**Results**
#1	MeSH descriptor: [Crohn Disease] explode all trees	2244
#2	MeSH descriptor: [Tumor Necrosis Factor Inhibitors] explode all trees	160
#3	MeSH descriptor: [Child] explode all trees	81197
#4	MeSH descriptor: [Adalimumab] explode all trees	1153
#5	MeSH descriptor: [Infliximab] explode all trees	1064
#6	MeSH descriptor: [Fistula] explode all trees	1219
#7	#1 AND #2 AND #3	1
#8	#6 AND #3	65
#9	#8 AND (#4 OR #5)	2

Appendix 3: List of excluded studies

Study Citation	Reason for exclusion
Crandall W, Hyams J, Kugathasan S, Griffiths A, Zrubek J, Olson A, Liu G, Heuschkel R, Markowitz J, Cohen S, Winter H, Veereman-Wauters G, Ferry G, Baldassano RN. Infliximab therapy in children with concurrent perianal Crohn disease: observations from REACH. J Pediatr Gastroenterol Nutr. 2009 Aug;49(2):183-90. doi: 10.1097/MPG.0b013e3181a70f21. PMID: 19561542.	Incorrect study design – post-hoc analysis of trial
Da W, Zhu J, Wang L, Lu Y. Adalimumab for Crohn's disease after infliximab treatment failure: a systematic review. Eur J Gastroenterol Hepatol. 2013 Aug;25(8):885-91. doi: 10.1097/MEG.0b013e32836220ab. PMID: 23817447.	Incorrect population – failed infliximab
Panaccione R, Colombel JF, Sandborn WJ, D'Haens G, Zhou Q, Pollack PF, Thakkar RB, Robinson AM. Adalimumab maintains remission of Crohn's disease after up to 4 years of treatment: data from CHARM and ADHERE. Aliment Pharmacol Ther. 2013 Nov;38(10):1236-47. doi: 10.1111/apt.12499. Epub 2013 Sep 22. PMID: 24134498; PMCID: PMC4670480.	Incorrect study design – narrative review
Peyrin-Biroulet L, Deltenre P, de Suray N, Branche J, Sandborn WJ, Colombel JF. Efficacy and safety of tumor necrosis factor antagonists in Crohn's disease: meta-analysis of placebo-controlled trials. Clin Gastroenterol Hepatol. 2008 Jun;6(6):644-53. doi: 10.1016/j.cgh.2008.03.014. PMID: 18550004.	Incorrect intervention – pooled analysis of TNF inhibitors beyond adalimumab and infliximab
Sands BE, Blank MA, Patel K, van Deventer SJ; ACCENT II Study. Long-term treatment of rectovaginal fistulas in Crohn's disease: response to infliximab in the ACCENT II Study. Clin Gastroenterol Hepatol. 2004 Oct;2(10):912-20. doi: 10.1016/s1542-3565(04)00414-8. PMID: 15476155.	Incorrect outcome, population
Shehab M, Alrashed F, Heron V, Restellini S, Bessissow T. Comparative Efficacy of Biologic Therapies for Inducing Response and Remission in Fistulizing Crohn's Disease: Systematic Review and Network Meta-Analysis of Randomized Controlled Trials. Inflamm Bowel Dis. 2023 Mar 1;29(3):367-375. doi: 10.1093/ibd/izac103. Erratum in: Inflamm Bowel Dis. 2023 Dec 5;29(12):2011-2012. PMID: 35604382.	Incorrect intervention – pooled analysis of TNF inhibitors beyond adalimumab and infliximab
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.	Only narrative available for outcome of interest, incorrect intervention – pooled analysis of TNF inhibitors beyond adalimumab and infliximab
Lee MJ, Parker CE, Taylor SR, Guizzetti L, Feagan BG, Lobo AJ, Jairath V. Efficacy of Medical Therapies for Fistulizing Crohn's Disease: Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 2018 Dec;16(12):1879-1892. doi: 10.1016/j.cgh.2018.01.030. Epub 2018 Jan 31. PMID: 29374617.	TNF inhibitors beyond adalimumab and infliximab
Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, Colombel JF, Panaccione R, D'Haens G, Li J, Rosenfeld MR, Kent JD, Pollack PF. Adalimumab induction therapy for Crohn disease previously treated with infliximab: a randomized trial. Ann Intern Med. 2007 Jun 19;146(12):829-38. doi: 10.7326/0003-4819-146-12-200706190-00159. Epub 2007 Apr 30. PMID: 17470824.	Incorrect population – failed infliximab
Hyams JS, Griffiths A, Markowitz J, Baldassano RN, Faubion WA Jr, Colletti RB, Dubinsky M, Kierkus J, Rosh J, Wang Y, Huang B, Bittle B, Marshall M, Lazar A. Safety and efficacy of adalimumab for moderate to severe Crohn's disease in children. Gastroenterology. 2012 Aug;143(2):365-74.e2. doi: 10.1053/j.gastro.2012.04.046. Epub 2012 May 2. PMID: 22562021.	Incorrect study design – no placebo randomised group
Ruemmele FM, Rosh J, Faubion WA, Dubinsky MC, Turner D, Lazar A, Eichner S, Maa JF, Alperovich G, Robinson AM, Hyams JS. Efficacy of Adalimumab for Treatment of Perianal Fistula in Children with Moderately to Severely Active Crohn's Disease: Results from IMAgINE 1 and IMAgINE 2. J Crohns Colitis. 2018 Nov 9;12(10):1249-1254. doi: 10.1093/ecco-jcc/jjy087. PMID: 29939254; PMCID: PMC6225974.	Incorrect study design – no placebo randomised group
Lionetti P, Bronzini F, Salvestrini C, Bascietto C, Canani RB, Dé Angelis GL, Guariso G, Martelossi S, Papadatou B, Barabino A. Response to infliximab is related to disease duration in paediatric Crohn's disease. Aliment Pharmacol Ther. 2003 Aug 15;18(4):425-31. doi: 10.1046/j.1365-2036.2003.01672.x. PMID: 12940928.	Incorrect study design – retrospective survey
Sudheer K Vuyyuru, Virginia Solitano, Neeraj Narula, Matthew J Lee, John K MacDonald, Jeffrey D McCurdy, Siddharth Singh, Christopher Ma, Vipul Jairath, Pharmacological Therapies for the Management of Fistulizing Crohn's Disease: A Systematic Review and Meta-Analysis, Journal of Crohn's and Colitis, 2023;, jjad185, https://doi.org/10.1093/ecco-jcc/jjad185	Incorrect population – not refractory and incorrect intervention – pooled analysis of TNF inhibitors beyond adalimumab and infliximab

Appendix 4. Summary of AMSTAR 2 assessments of included reviews

AMSTAR-2 item	Gordon 2023 **High quality** Also includes GRADE assessment	Chehal 2023 **Low quality** No quality assessment, RoB 1	Carnovale **Low quality** No RoB, multiple study designs
1. Did the research questions and inclusion criteria for the review include the components of PICO?	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	Partial Yes
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Yes	Yes
4. Did the review authors use a comprehensive literature search strategy?	Yes	Yes	Partial Yes
5. Did the review authors perform study selection in duplicate?	Yes	Yes	Yes
6. Did the review authors perform data extraction in duplicate?	Yes	Yes	Yes
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Yes	No	No
8. Did the review authors describe the included studies in adequate detail?	Yes	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	Did not assess RoB, NRSI
10. Did the review authors report on the sources of funding for the studies included in the review?	Yes	No	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes	Yes	RCTs and NRSI
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	RCTs and NRSI
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes	Yes	No
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	No	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	Not applicable
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

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 2023(2)	SR of RCTs	10 RCTS, 1101 participants	Adults with CD including fistulising (sub-group analysis).	Infliximab 5mg/kg, 10mg/kg OR Placebo OR Active therapies	• 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	Yes, highest quality review, includes relevant studies. **Data extracted for comparison 2, outcome 2.1, 2.2, 2.7**
Carnovale 2020(14)	MA of multiple study designs	29 articles, 565 participants	Perianal CD patients aged 9 months to 18 years	Infliximab or adalimumab, placebo or active comparators	• Clinical remission as defined by the study • Clinical response as defined by the study • % with complete fistula closure • Withdrawals due to adverse events, serious adverse events, total adverse events	**AMSTAR – low quality** – Screening & extraction in duplicate, No RoB, No GRADE,	10/2018	Studies included: no placebo RCTs or active comparators studies	Included although MA of multiple study designs and no RCTs found for paediatric population that met PICO	Yes SR specifically for paediatric population – although low quality and wider scope of trial designs included.
Chahal 2023(23)	NMA of RCTs		Adult population where at least 90% of the subjects > 16 years old; Fistulising CD	Wide range including adalimumab and infliximab compared to active comparator or placebo	• Fistula remission at 8-12 weeks; at 16-24 weeks; and at 44 weeks. • Adverse events at 8-12 weeks; at 16-24 weeks; and at 44 weeks • Cessation of treatment due to adverse events	**AMSTAR – low quality** – Screening & extraction in duplicate, RoB 2, No GRADE	04/2022	Studies included: Present 1999 (INF); Sands 2004 (INF); Colombel 2009 (ADA)	SR did not specifically look at refractory CD - all types eligible but trials selected were refractory based medicine review PICO	No low quality review – extract from relevant RCTs (Colombel 2007, Colombel 2009, Sands 2004).

Table 2: Randomised Controlled Trials

Publication	Study type, duration, setting	Funding and COI	No. participants	Population	Intervention and comparator	Outcomes reported	Included in SRs	Notes	Effect measures to be extracted?
Present 1999(12)	• Double Blind placebo RCT • 18 weeks (primary outcomes) • 12 sites, multiple countries		94	Patients 18 to 65 years, who had single or multiple draining abdominal or perianal fistulas of at least 3 months' duration confirmed by radiography, endoscopy, or pathological examination.	Infliximab 5mg/kg biweekly OR 10mg/kg biweekly OR placebo	• Primary end point was a reduction of 50 percent or more from base line in the number of draining fistulas observed at 2 or more consecutive study visits (minimum 21 days between visits) – **Outcome 2.1 Induction of fistula response.** • Secondary end point was the closure of all fistulas – **Outcome 2.2 Induction of fistula remission.**	Chahal 2023 Gordon 2023	Not specific about moderate to severe - long standing and complication of CD. Patients could receive concomitant therapy. % balanced between groups - average years of CD balanced - all over 10 years - long standing CD - fistulising as a complication.	No – outcome data already included in Gordon 2023 SR which has been extracted.
Colombel 2007 (16) – CHARM Trial	• Double Blind placebo RCT • 56 weeks • 92 sites, multiple countries including SA	Abbott Laboratories, staff members involved with study design, analysis and manuscript preparation	854 in trial, 130 of which had fistulising CD	A subgroup of adults with moderate to severely active CD (CD activity index 220-450) for >or=4 months who had draining fistulas at baseline.	All patients received initial open-label adalimumab induction therapy (80 mg/40 mg at weeks 0/2). At week 4, all patients were randomly assigned to receive double-blind placebo OR adalimumab 40 mg every other week OR adalimumab weekly.	• Complete fistula healing/closure (assessed at every visit) was defined as no drainage, either spontaneous or with gentle compression – **Outcome 1.2 Inducted Fistula remission and outcome 1.4 maintenance of fistula remission** • Safety	Chahal 2023	Non-response in trial = Nonresponse was defined as failure to achieve 70-point response at any visit at or after week 12. Concomitant use of immunosuppressive agent (AZA, Metho, 6-Merc) in both groups. If had infliximab previously had to have last dose 12 weeks prior and recorded as a responder.	Yes, included in Chahal but low quality SR – extract from trial instead. **Data extracted for outcome 1.2 and 1.4**
Colombel 2009(15) – CHARM trial	• Subgroup post-hoc analysis of CHARM trial double blind RCT	As above	As above	As above	As above	• Mean number of draining fistulas per day during double-blind period and number at end of week 54 with complete fistula	Chahal 2023	Post hoc analysis, original trial not powered for secondary endpoints for fistulising CD	Yes but only as supplementary data for outcomes 1.2 and 1.4.

Publication	Study type, duration, setting	Funding and COI	No. participants	Population	Intervention and comparator	Outcomes reported	Included in SRs	Notes	Effect measures to be extracted?
Sands 2004(13) – ACCENT II	• Double Blind placebo RCT • 54 weeks • 45 sites, multiple countries	Centocor staff involved with study design and manuscript write-up but not analysis.	282 initial and 195 responders into randomised part of study.	Crohn's disease and ≥ 1 draining abdominal or perianal fistulas of ≥ 3 months' duration	Infliximab 5mg/kg every other week OR Placebo	• Primary end point was time to loss of response and secondary endpoints including % of patients who still had a response – **Outcome 2.3 Maintenance of fistula response (at least 50% in number of draining fistulas)**	Chahal 2023	Concurrent conventional therapies for Crohn's disease were permitted. All participants received infliximab initially then randomised to placebo or continued infliximab to assess maintenance of treatment	Yes, included in Gordon 2023 but not for outcome of interest. **Data to be extracted for outcome 2.3**
Lichtenstein 2005(17) – ACCENT II	• Post-hoc analysis of ACCENT II data	As above	As above	As above	As above	• Mean number of hospital days • Mean number (per 100) patients of hospitalisations • Mean number (per 100) patients of all surgeries and procedures • Mean number (per 100) patients of major surgeries **Outcome 2.6 Rates of hospitalisations and surgeries**	None of the SRs	Post-hoc analysis of ACCENT II – See Sands 2004	Yes, only study included to report on hospitalisation and surgeries **Data to be extracted for outcome 2.6**

Appendix 6 – Annexure Document - Therapeutic Drug Monitoring of adalimumab and infliximab

South African National Department of Health,
Tertiary and Quaternary Hospital Level
Annexure Document for Medicine Review

Adalimumab and infliximab in the management of patients with Fistulising Crohn's Disease who are refractory to conventional therapies.

This document was developed to guide use of adalimumab and infliximab in practice for the approved indication of fistulising Crohn's Disease (Approval: NEMLC 14th March 2024).

The use of Infliximab and Adalimumab in clinical practice

Both infliximab (IFX) and adalimumab (ADA) are approved for the treatment of fistulising Crohn's disease (CD). Both are monoclonal antibodies targeting TNF-alpha, and as foreign proteins carry the risk of immunogenicity. Given its chimeric structure, the risk of anti-drug antibody formation is highest for IFX, and as such is invariably given in combination with a low dose immunomodulator (IMM) such as azathioprine or methotrexate. Although ADA is less immunogenic than IFX, many patients still develop anti-drug antibodies, and, in clinical practice, is also frequently administered in combination with an IMM. Anti-drug antibodies are associated with both primary non-response, secondary loss of response, and infusion reactions.

Once ADA and IFX are prescribed for fistulising Crohn's disease, patients should be monitored for response as per facility/clinic protocol. Patients who fail to respond or who have lost response should undergo reactive therapeutic drug monitoring (TDM) to optimise therapy. TDM involves the measurement of plasma anti-TNF trough levels (TLs) and anti-drug antibodies. There are 3 possible scenarios that are encountered:

1. **A low trough level (TL) with the absence of anti-drug antibodies**. This reflects an insufficient plasma concentration of the anti-TNF agent. Once adherence is assured, it is recommended that the anti-TNF dose be increased.
   - For infliximab (IFX) this can be achieved by either increasing the dose from 5mg/kg 8 weekly to 10mg/kg 8-weekly, or, alternatively, shortening the dosing interval from 8 weekly to 6 weekly.
   - For adalimumab (ADA) the dosing interval may be reduced from 2-weekly to once weekly (at a dose of 40mg SC).

2. **A low TL with positive high anti-drug antibody titre**. In this case the presence of anti-drug antibodies results in rapid and enhanced drug clearance and increasing the dose will not be effective. In this scenario the anti-TNF needs to be switched to a 2nd in-class alternative (e.g. IFX to ADA, or ADA to IFX). This strategy is effective as these antibodies are not cross-reactive.

3**. Therapeutic TLs (regardless of anti-drug antibody titre).** This scenario is termed mechanistic failure, whereby the inflammation is no longer mediated by TNF-alpha but rather through alternative cytokine pathways**.** Patients need to switch out of class to another advanced therapy. In these circumstances, patients should be referred back to their specialist centre and/or to the local Pharmaceutical Therapeutics Committee for further consideration.

Acknowledgment and declaration: Thanks to Dr Gillian Watermeyer (Department of Gastroenterology, Groote Schuur Hospital, and the Department of Medicine, University of Cape Town, Cape Town, Western Cape, South Africa). GM has no interests to declare but to note that she works with CD patients and uses TNF-inhibitors.

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