

Appendix 1 (part 1 of 3): Search strategies for a study of infliximab in pediatric Crohn disease.

Search strategy: MEDLINE (PubMed)

- 1 Search "Crohn Disease"[Mesh]
- 2 Search crohns
- 3 Search crohn
- 4 Search crohn's
- 5 Search Ileitis
- 6 Search Regional Enteritis
- 7 Search Granulomatous Enteritis
- 8 Search Inflammatory Bowel Disease 1
- 9 Search Ileocolitis
- 10 Search 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
- 11 Search infliximab [Supplemental concept]
- 12 Search remicade
- 13 Search inflectra
- 14 Search remsim
- 15 Search avakine
- 16 Search revellex
- 17 Search 11 or 12 or 13 or 14 or 15 or 16 or 17
- 18 Search "Adolescent"[Mesh]
- 19 Search "Child"[Mesh]
- 20 Search "Infant"[Mesh]
- 21 Search "Pediatrics"[Mesh]
- 22 Search infant*
- 23 Search infancy
- 24 Search newborn*
- 25 Search baby*
- 26 Search babies
- 27 Search neonat*
- 28 Search preterm
- 29 Search prematur*
- 30 Search postmatur*
- 31 Search child*
- 32 Search kid
- 33 Search kids
- 34 Search toddler
- 35 Search toddler*
- 36 Search adoles*
- 37 Search teen*
- 38 Search boy
- 39 Search boys
- 40 Search girl*
- 41 Search pediatric*
- 42 Search paediatric*
- 43 Search 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43
- 44 Search 10 and 18 and 44

Search Strategy: Embase

- 1 exp Crohn disease/
- 2 crohns.mp.
- 3 crohn.mp.
- 4 crohn's.mp.
- 5 Ileitis.mp.
- 6 Regional Enteritis.mp.
- 7 Granulomatous Enteritis.mp.
- 8 Inflammatory Bowel Disease 1.mp.
- 9 Ileocolitis.mp.
- 10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
- 11 infliximab/
- 12 remicade.mp.
- 13 infliximab.mp.
- 14 inflectra.mp.
- 15 remsima.mp.
- 16 avakine.mp.
- 17 revellex.mp.
- 18 11 or 12 or 13 or 14 or 15 or 16 or 17
- 19 exp child/
- 20 exp adolescent/
- 21 exp infant/
- 22 pediatrics/ or exp neonatology/
- 23 infant*.mp.
- 24 infancy.mp.
- 25 newborn*.mp.
- 26 baby*.mp.
- 27 babies.mp.
- 28 neonat*.mp.
- 29 preterm*.mp.
- 30 prematur*.mp.
- 31 postmatur*.mp.
- 32 child*.mp.
- 33 kid.mp.
- 34 kids.mp.
- 35 toddler.mp.
- 36 toddler*.mp.
- 37 adoles*.mp.
- 38 teen*.mp.
- 39 boy.mp.
- 40 boys.mp.
- 41 girl*.mp.
- 42 pediatric*.mp.
- 43 paediatric*.mp.
- 44 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43
- 45 10 and 18 and 44

Note: [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

Appendix 1 (part 2 of 3): Search strategies for a study of infliximab in pediatric Crohn disease.

Search Strategy: CENTRAL

- 1 crohns.mp.
- 2 crohn.mp.
- 3 crohn's.mp.
- 4 Ileitis.mp.
- 5 Regional Enteritis.mp.
- 6 Granulomatous Enteritis.mp.
- 7 Inflammatory Bowel Disease 1.mp.
- 8 Ileocolitis.mp.
- 9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
- 10 remicade.mp.
- 11 inflectra.mp.
- 12 remsima.mp.
- 13 infliximab.mp.
- 14 10 or 11 or 12 or 13
- 15 infant*.mp.
- 16 infancy.mp.
- 17 newborn*.mp.
- 18 baby*.mp.
- 19 babies.mp.
- 20 neonat*.mp.
- 21 preterm*.mp.
- 22 prematur*.mp.
- 23 postmatur*.mp.
- 24 child*.mp.
- 25 kid.mp.
- 26 kids.mp.
- 27 toddler.mp.
- 28 toddler*.mp.
- 29 adoles*.mp.
- 30 teen*.mp.
- 31 boy.mp.
- 32 boys.mp.
- 33 girl*.mp.
- 34 pediatric*.mp.
- 35 paediatric*.mp.
- 36 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35
- 37 9 and 14 and 36
- 38 crohns.mp.
- 39 crohn.mp.
- 40 crohn's.mp.
- 41 Ileitis.mp.
- 42 Regional Enteritis.mp.
- 43 Granulomatous Enteritis.mp.
- 44 Inflammatory Bowel Disease 1.mp.
- 45 Ileocolitis.mp.
- 46 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45
- 47 remicade.mp.

- 48 inflectra.mp.
- 49 avakine.mp.
- 50 revellex.mp.
- 51 remsima.mp.
- 52 infliximab.mp.
- 53 47 or 48 or 49 or 50 or 51 or 52
- 54 infant*.mp.
- 55 infancy.mp.
- 56 newborn*.mp.
- 57 baby*.mp.
- 58 babies.mp.
- 59 neonat*.mp.
- 60 preterm*.mp.
- 61 prematur*.mp.
- 62 postmatur*.mp.
- 63 child*.mp.
- 64 kid.mp.
- 65 kids.mp.
- 66 toddler.mp.
- 67 toddler*.mp.
- 68 adoles*.mp.
- 69 teen*.mp.
- 70 boy.mp.
- 71 boys.mp.
- 72 girl*.mp.
- 73 pediatric*.mp.
- 74 paediatric*.mp.
- 75 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74
- 76 46 and 53 and 75

Note: [mp=title, original title, abstract, mesh headings, heading words, keyword]

Search Strategy: Clinicaltrials.gov

Advanced Search was selected.

The following search terms were entered:

Condition: crohn

Intervention: infliximab

Age group: child (birth - 17 years)

Search Strategy: EU Trials Register

Advanced Search was selected.

The following search terms were entered: infliximab

AND crohn

The following filters were applied: Age group - Children and Adolescent

Appendix 1 (part 3 of 3): Search strategies for a study of infliximab in pediatric Crohn disease.

Search Strategy: WHO International Clinical Trials Registry Platform

Advanced Search as selected. Trials in both Searches 1 and 2 were included in screening process.

Search 1:
infliximab AND crohn in Title
“Search for clinical trials in children” checked

Search 2:
Crohn in Condition
infliximab in Intervention
“Search for clinical trials in children” checked

After Search 1 and 2 were completed, duplicate entries were merged.

Search Strategy: Conference proceedings

Abstracts from the following conferences were identified through the respective conference websites, if available.

1. Digestive Diseases Week (American):
<http://www.ddw.org/>
2. Canadian Digestive Disease Week (Canadian):
<http://www.cag-acg.org/annual-conference-cddw>
3. United European Gastroenterology Week (European):
<https://www.ueg.eu/week/>
4. Advances in Inflammatory Bowel Disease (Crohn's & Colitis Foundation):
<http://www.advancesinibd.com/>
5. European Crohn's and Colitis Organisation (ECCO):
<https://www.ecco-ibd.eu/publications/congress-abstract-s/>

Search Strategy: Regulatory documents

Regulatory documents from FDA and EMA were searched:

EMA

Search terms: active substance or common name: infliximab
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion_-_Variation/human/000240/WC500051562.pdf

Pediatric decisions searched

FDA

Search terms: search by drug name: infliximab

Search Strategy: Manufacturer clinical trials

Searched “infliximab” in Janssen Clinical Trials Registry.

Search Strategy: Reference lists

Hand-searching of reference lists of relevant systematic reviews and included articles occurred after title and abstract screening and full-text screening.

Appendix 2: Outcome definitions from individual trials. Note: Reference numbering here is based on the reference list in the main article. For details about each study, see Table 1 in the main article.

Endoscopic remission (complete MH)

- Endoscopic lesion severity score using 10-cm visual analogue scale, 0 = healed, 10 = very severe disease (Baldassano et al. [2003]³⁵)
- HBI < 5, ESR < 20 mm/h, and/or fistula closure, completely weaned from steroids (Ruemmele et al. [2009]²⁶)
- CDEIS ≤ 3 (Luo et al. [2017]⁴²)
- CDEIS score = 2 (Muhammed et al. [2014]³¹)
- Disappearance of ulcerations, multiple erosions, bleeding, and friability (grade 0 - complete normalization) (Olbjørn et al. [2014]²⁹)
- SES-CD score = 0, no ulcers or other mucosal lesions like erosion and inflammation (Kang et al. [2016]⁴¹)
- SES-CD = 0–1, no signs of active inflammation of any colonic segment or in terminal ileum (Nutti et al. [2016]²⁴)

Partial mucosal healing

- Disappearance of ulcerations, multiple erosions, bleeding, and friability (grade 1 - light hyperemia and granularity) (Olbjørn et al. [2014]²⁹)
- Reduction of 50% in SES-CD from baseline, no endoscopic healing, no variation or worsening of SES-CD (Nutti et al. [2016]²⁴)

Clinical remission

- PGA of inactive disease at every assessment point during follow-up (0–1, 1–2, 2–3 years) while receiving IFX without concomitant CS use or surgery (Hyams et al. [2009]⁴⁰)
- PCDAI < 10 or modified CDAI < 150 (Baldassano et al. [2003]³⁵)
- PCDAI ≤ 10 (Lee et al. [2015],¹⁸ Hyams et al. [2007],³⁸ Kang et al. [2016],⁴¹ Luo et al. [2017]⁴²)
- PCDAI ≤ 10 and CS-free (Walters et al. [2014]²⁰)
- PCDAI ≤ 10 and no symptoms related to CD (Nutti et al. [2016]²⁴)
- Inactive disease for ≥ 2 years follow-up on a 3-point scale based on PCDAI/PGA scores (Wauters et al. [2016]²²)
- PCDAI ≤ 10 and free of surgery (Hyams et al. [2013]²¹)
- Initial PCDAI perirectal subscore of 5 or 10 decreasing to 0 (Crandall et al. [2009]³⁹)

Clinical response

- PGA of mild or inactive disease at every assessment point during follow-up (0–1, 1–2, 2–3 years) while receiving IFX without concomitant CS use or surgery (Hyams et al. [2009]⁴⁰)
- ≥ 10 point improvement in PCDAI or ≥ 70 point reduction in modified CDAI (Baldassano et al. [2003]³⁵)
- Initial perirectal subscore of 10 decreasing to 5 (Crandall et al. [2009]³⁹)
- Decrease from baseline in PCDAI score of ≥ 15 points, with total score ≤ 30 (Hyams et al. [2007]³⁸)
- PCDAI reduction ≥ 15 or final PCDAI ≤ 10 (Lee et al. [2015],¹⁸ Luo et al. [2017],⁴² Chen and Luo [2016]⁴⁷)
- PCDAI reduction ≥ 15 (Nutti et al. [2016]²⁴)

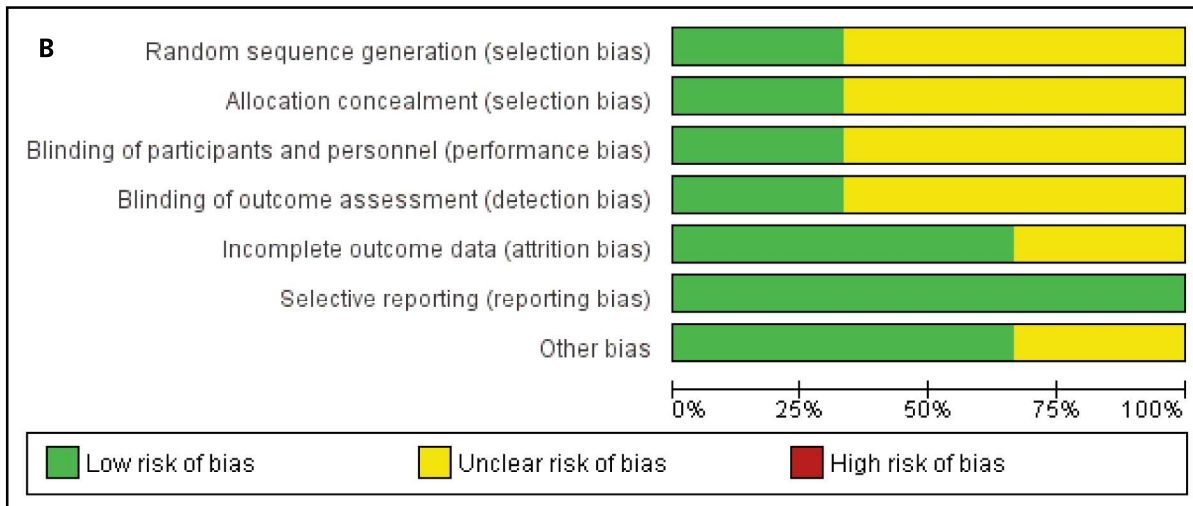
Definitions: CD = Crohn disease, CDEIS = Crohn Disease Endoscopic Index of Severity, CS = corticosteroid, ESR = erythrocyte sedimentation rate, HBI = Harvey–Bradshaw Index, IFX = infliximab, MH = mucosal healing, PCDAI = Pediatric Crohn Disease Activity Index, PGA = physician global assessment, SES-CD = Simple Endoscopic Score for Crohn Disease.

Appendix 3 (Part 1 of 3): Risk of bias in individual studies and across studies (see Table 1 for reference numbering).

A

	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)	Selective reporting (reporting bias)	Other bias
Baldassano 2003	?	?	+	+	+	+	+
Hyams 2007	?	?	?	?	+	+	?
Ruemmele 2009	+	+	?	?	?	+	+

Part A. Risk of bias in individual randomized controlled trials, assessed with the Cochrane risk-of-bias tool.



Part B. Risk of bias across randomized controlled trials, assessed with the Cochrane risk-of-bias tool.

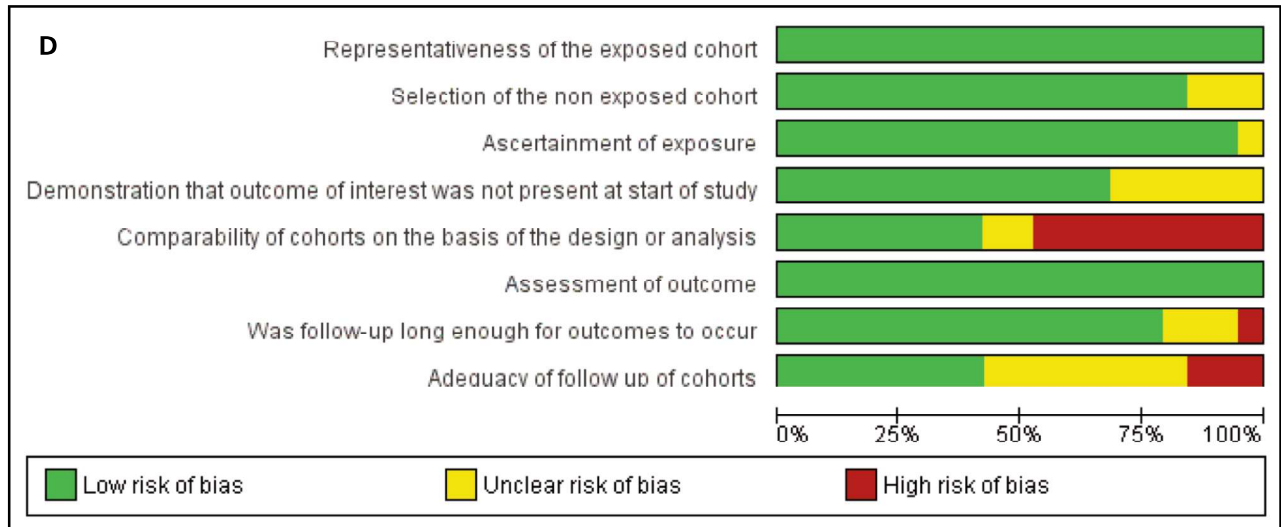
Appendix 3 (Part 2 of 3): Risk of bias in individual studies and across studies (see Table 1 for reference numbering).

C

	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts
Bellizzi 2011	+	+	+	?	-	+	+	+
Chanchlani 2017	+	?	+	+	-	+	+	-
Crowley 2017	+	?	?	+	-	+	+	?
Hyams 2009	+	+	+	+	-	+	+	+
Hyams 2017	+	+	+	+	?	+	+	?
Kang 2016	+	+	+	+	?	+	+	+
Keljo 2009	+	+	+	?	+	+	?	+
Lee 2015	+	?	+	+	+	+	+	?
Luo 2017	+	+	+	?	-	+	+	?
Mangiantini 2013	+	+	+	?	+	+	?	?
Muhammad 2014	+	+	+	+	-	+	?	?
Nuti 2011	+	+	+	+	-	+	+	-
Nuti 2016	+	+	+	+	+	+	+	+
Olbjørn 2014	+	+	+	+	-	+	+	+
Paganelli 2007	+	+	+	?	+	+	-	+
Pfefferkorn 2009	+	+	+	+	+	+	+	-
Walters 2014	+	+	+	+	+	+	+	+
Wauters 2016	+	+	+	?	+	+	+	?
Zarubova 2017	+	+	+	+	-	+	+	?

Part C. Risk of bias in individual prospective cohort studies, assessed with the Ottawa–Newcastle tool.

Appendix 3 (Part 3 of 3): Risk of bias in individual studies and across studies (see Table 1 for reference numbering).



Part D. Risk of bias across prospective cohort studies, assessed with the Ottawa–Newcastle tool.