Anti – TNFα Use in Children With Inflammatory Bowel Disease

Document Control:

For Use In:	Norfolk and Norwich University Hospitals (NNUH) Jenny Lind Children's Department – Registered Paediatric Nurses and Medical Staff		
Search Keywords	Infliximab infusion, [TNFα] Therapy, Adalimumab		
Document Authors:	Catharine Searle and Sue Underhill-Smith – Paediatric Gastroenterology Specialist Nurses Members of East of England Paediatric Gastroenterology Network (EEPGN)		
Document Authors' Line Manager:	Dr Mary-Anne Morris, Paediatric Gastroenterologist Member of EEPGN - Consultant Paediatrician		
Document Owner:	Women's and Children's Division - Paediatrics		
Approved By:	Clinical Guidelines Assessment Panel		
Ratified By:	Clinical Safety and Effectiveness Sub-Board		
Approval Date:	18/04/2023	**Date to be reviewed by:** This document remains current after this date but will be under review	18/04/2026
Implementation Date:	N/A		
Reference Number:	CA2110, Trust Docs ID: 1257		

Version History:

Version	Date	Author	Reason/Change
1	Dec 2011	Paediatric Gastroenterology Specialist Nurses	To originate document
6	Dec 2019	Consultant Paediatrics/Paediatric Gastroenterology	Section 5: Changes in duration of infusion and pre-treatment. Updated references.
7	Feb 2023	Consultant Paediatrics/Paediatric Gastroenterology	Document transferred to updated template

Previous Titles for this Document:

Previous Title/Amalgamated Titles	Date Revised
None	Not applicable

Distribution Control

Printed copies of this document should be considered out of date. The most up to date version is available from the Trust Intranet.

Consultation

The following were consulted during the development of this document:
Dr Marco Gasparetto, Paediatric Gastroenterologist Member EEPGN.

Paediatric gastroenterology teams at Royal Free, Alder Hey and Norfolk and Norwich University Hospitals.

EEPGN meeting (8.12.2008) with final comments returned by 31.12.2008.

Members of inital guideline group:

MB Mary Brennan, Clinical Nurse Specialist in Paed Gastro, AH
GLB Graham Briars, Paediatric Gastroenterologist, NNUHT
NG Nigel Gooding, Senior Paediatric Pharmacist, AH
RBH Rob Heuschkel, Paediatric Gastroenterologist, AH
FL Frances Latcham, Consultant Paediatrician with interest in Gastroenterology, Hinchingbrooke Hospital
MAM Mary-Anne Morris, Consultant Paediatrician with interest in Gastroenterology, NNUHT Chair of East of England Paediatric Gastroenterology Network
GNJ Gabi Noble-Jamieson, Associate Specialist in Paediatric Gastroenterology, AH
CS Catharine Searle, Paediatric Gastroenterology Specialist Nurse, NNUHT
SUS Sue Underhill-Smith, Paediatric Gastroenterology Specialist Nurse NNUHT

Members of 2022 revision group

MG Marco Gasparetto Paediatric Gastroenterologist, NNUHT
MAM Mary-Anne Morris, Paediatrician Gastroenterologist, NNUHT
CS Catharine Searle, Paediatric Gastroenterology Specialist Nurse, NNUHT
SUS Sue Underhill-Smith, Paediatric Gastroenterology Specialist Nurse NNUHT
EG Eleanor Goodall, Paediatric Gastroenterology Specialist Nurse NNUHT

Monitoring and Review of Procedural Document

The document owner is responsible for monitoring and reviewing the effectiveness of this Procedural Document. This review is continuous however as a minimum will be achieved at the point this procedural document requires a review e.g. changes in legislation, findings from incidents or document expiry.

Relationship of this document to other procedural documents

This document is a clinical guideline applicable to Jenny Lind Children's Hospital, NNUH please refer to local Trust's procedural documents for further guidance.

Guidance note

This guideline has been approved by the Trust's Clinical Guidelines Assessment Panel as an aid to the diagnosis and management of relevant patients and clinical circumstances. Not every patient or situation fits neatly into a standard guideline scenario and the guideline must be interpreted and applied in practice in the light of prevailing clinical circumstances, the diagnostic and treatment options available and the professional judgement, knowledge and expertise of relevant clinicians. It is

advised that the rationale for any departure from relevant guidance should be documented in the patient's case notes.

The Trust's guidelines are made publicly available as part of the collective endeavour to continuously improve the quality of healthcare through sharing medical experience and knowledge. The Trust accepts no responsibility for any misunderstanding or misapplication of this document.

Anti – TNFα Use in Children With Inflammatory Bowel Disease

Contents

Anti – TNFα Use in Children With Inflammatory Bowel Disease

1. Introduction

1.1. Rationale

This guideline provides the framework for provision of biologics to children and young people with IBD. It provides a regional consensus on indications (based on NICE and ECCO guidelines), safe administration and monitoring.

1.1.1. Is there a beneficial clinical effect?

- Extended guideline ECCO 2014 Ruemmele et al [37] and NICE report benefits to defined patient groups
- A large prospective randomised study has shown Infliximab (5mg/kg) to be more effective in children than adults with moderate to severe Crohn's Disease at inducing a clinical remission (66% at 10 weeks) and maintaining this with repeated infusions (56% at 54 weeks) [5].
- Regular infusions of Infliximab reduces antibody formation and maintains better mucosal healing than episodic therapy [6].
- There have been several reports in children that have found Infliximab to be a safe and effective treatment in managing fistulizing Crohn's disease [7][8][9].
- Adults with fistulizing Crohn's Disease have been shown to have significant fistula closure with repeated infusions of Infliximab [10].
- Adalimumab has been shown to have a similar effect as Infliximab in adults with Crohn's disease [11][12].
- Adalimumab has also been shown to have some benefit in treating adults intolerant to / losing response to Infliximab [13][14].
- Infliximab has been shown to delay / prevent emergency surgery in children with acute severe Crohn's colitis [15].
- Some adults with ulcerative colitis have also been shown to respond to Infliximab in prospective studies [16].
- In the case of treatment-resistant UC in adults, the use of Infliximab achieved a clinical response in about 65% at 8 weeks and 45% response at 54 weeks [16]. Given the significantly better results in children with Crohn's disease receiving Infliximab, it is likely that children with UC will also respond better than adults.
- There is some evidence that Infliximab may delay emergency surgery in adults and children with acute severe ulcerative colitis [17][18].
- There are currently no published randomised prospective studies using anti-TNFα in children with UC, although numerous case series have been published [19][20].
- The avoidance of an un-planned, emergency colectomy in a child or adolescent is paramount for both medical and psychological reasons. The benefit of delaying a colectomy, even if only for a few months, allows preparation of the child and family for the impact of life with a stoma. Although the option of Cyclosporin in acute Colitis still exists; this is not a maintenance therapy. The use of Infliximab in the acute setting therefore allows an assessment of response at 10-14 weeks, with the potential of continuing maintenance therapy if a clinical remission has been achieved.

1.1.2. What is the effect on growth?

- The cause of growth failure in children with IBD (particularly Crohn's disease) is multi-factorial. The inflammatory process itself plays a pivotal role in slowing linear growth [21].
- TNFα has been shown to suppress osteoblast formation and bone growth independent of malnutrition in animal models [22].
- Infliximab induction treatment is reported to reverse growth hormone resistance associated with IBD through suppression of systemic inflammation [23].
- Several studies have now documented increased linear growth velocity following Infliximab therapy [24][25][26].

1.1.3. Does Infliximab heal gut mucosa?

- Studies have shown sustained endoscopic healing after with regular infusions of Infliximab in adults [27] as well as in paediatric patients with Crohn's disease [26].
- Regular infusions of Infliximab maintain mucosal healing better than episodic therapy [6].
- There is some evidence that achieving mucosal healing improves long-term outcome in adults with Crohn's disease [6].

1.1.4. Are there any risks?

- See attached patient information sheet
- There is an increased risk of infectious complications (particularly if patients are on concomitant immunosuppression e.g. corticosteroids, cyclosporin) More of a risk of therapy inactive TB
- There have been about 31 cases of hepatosplenic T-cell lymphoma in young, predominantly male patients with IBD receiving combination treatment with azathioprine and infliximab [28] [39]. The risks are currently quoted between 1/1000 and 1/10,000.
- Varicella – if patient not immune manage contact varicella as per "green book". Advise patient of risk and importance of reporting contact to team or CAU.

1.2. Objectives

- To promote understanding of anti- Tumour Necrosis Factor alpha (TNF) use and its risks in children with IBD.
- To ensure the safe administration of anti-TNF agents.
- To ensure minimum standards for anti-TNF use.
- To demonstrate a regional consensus on anti-TNF agent use in children with IBD.
- To provide a document to support the funding of anti-TNF agents within the region.

1.3. Scope

The decision to start a child with IBD on anti-TNFα therapy should be made in discussion with a Consultant Paediatric Gastroenterologist. The patient should have disease distribution and severity

reassessed before treatment. An ileo-colonoscopy (+/- radiographic imaging) should ideally be done within 4 weeks of the first infusion.

1.4. Glossary

NNUH	Norfolk and Norwich University Hospitals
TNF	Tumour necrosis factor
EEPGN	East of England Paediatric Gastroenterology Network
AH	Alder Hey
TB	Tuberculosis
PCDAI	Paediatric Crohn's Disease Activity Index
PUCAI	Paediatric UC Activity Index
IBD	Inflammatory bowel disease
EMEA	European Medicines Evaluation Agency
UC	Ulcerative colitis
CAU	Children's Assessment Unit
ECCO	European Crohn's and Colitis Organisation
ESPGHAN	European Society for Paediatric Gastroenterology Hepatology and Nutrition
URTI	Upper respiratory tract infection
UTI	Urinary tract infection
BP	Blood pressure
FBC	Full blood count
LFT	Live function tests
ESR	Erythrocyte sedimentation rate
CRP	C-reactive protein
IV	Intravenous
BNFC	British National Formulary for Children
MDT	Multidisciplinary team
EPMA	Electronic Prescribing and Medicines Administration
APLS	Advanced Paediatric Life Support
EPLS	European Paediatric Life Support
BTS	British Thoracic Society
BCG	Bacillus Calmette-Guerin vaccine
PCT	Primary Care Trust
HSTCL	Hepatosplenic T-Cell Lymphoma

2. Responsibilities

- Paediatric Gastroenterology Consultants: treatment decision, prescribing and monitoring of effectiveness
- Paediatric Gastroenterology Specialist nurses: completion of pre-biologics screening, provision of information to families and patients, entry into biologics audit, submission of BlueTeq form
- Children's Day Ward nursing team: administration of biologic, booking of next admission

3. Processed to Follow

What are anti-TNFα therapies?

Anti-TNFα therapies use antibodies to TNFα to block / reduce the production of TNFα [1]

- TNFα is a pro-inflammatory cytokine that plays a pivotal role in the inflammatory cascade that causes ulceration in the intestinal mucosa of patients with IBD [2].
- Infliximab (Remicade) is a chimeric (murine & human) monoclonal antibody which inhibits TNFα and is given by intravenous infusion. This is licensed for use by EMEA in children with Crohn's disease over 6 years of age.
- Adalimumab (Humira) is a more recently developed (fully humanised) monoclonal antibody that inhibits TNFα, but is given by subcutaneous injection [3].
- Children with Crohn's Disease have an increased number of cells in their gut mucosa producing TNFα [4].

3.1.1. A. Crohn's disease

NICE and ECCO guidelines 2014 are in place for Biologics induction of Infliximab and Adalimumab

I. A patient with either of the following is prescribed Infliximab

a. The patient has severe Crohn's Disease and;

b. The patients condition is refractory to treatment with immunomodulating drugs and corticosteroids or the patient is intolerant of or experienced toxicity from these treatments and;

c. Surgery is inappropriate for the patient.

or

d. Serious Perianal Disease.

II. Infliximab treatment is repeated for patients who meet 1a-c above in the following circumstances

a. The patient has responded to the initial or subsequent treatment course and then relapsed and;

b. The decision is made by gastroenterologist experienced in the management of Crohn's Disease.

Exception - Patient declines repeated treatment after being fully informed of the potential risks and benefits of repeated treatment

III. Infliximab is not provided to patients with fistulating Crohn's Disease except when the patient meets the other criteria for eligibility

Other indications where the use of Infliximab has been shown to have some efficacy:

1. Once a patient is defined as having a clinical response / remission at 14-22 weeks, regular maintenance therapy typically with 8 weekly infusions of Infliximab at 5mg/kg/dose should be commenced. At present Infliximab responders have azathioprine discontinuing considered after about 6 months of Infliximab therapy. Patients are then reviewed at 6 monthly intervals to assess the ongoing clinical efficacy and need for ongoing therapy. This may include reinvestigation by endoscopy if clinical response is lost.
2. Growth failure in the presence of active Crohn's disease [25].

3. As bridging therapy (i.e. use of 3 infusion induction course) in severe Crohn's disease not responding to corticosteroids, where additional bridging therapy is required to reach full immunomodulator efficacy.
4. Pyoderma gangrenosum resistant to conventional therapy [31][32].

3.1.2. B. Ulcerative colitis

There are currently no national recommendations on anti-TNFα use in children with ulcerative colitis. However ESPGHAN guidelines Turner et al 2012 [38] state TNF as medical management in acute severe ulcerative colitis.

The following two indications for Infliximab use are increasingly accepted as appropriate for children with a confirmed diagnosis of ulcerative colitis:

1. Acute severe ulcerative colitis not responding to intravenous corticosteroid therapy, where emergency colectomy is to be avoided and additional bridging therapy (i.e. 3 infusion induction course) is required to await maximal immunomodulator efficacy.
2. Acute severe ulcerative colitis resistant to / dependent on corticosteroids where conventional immunomodulator maintenance therapy has become ineffective. Although this is less efficacious in adults with UC than indication 1, it is felt that surgery (i.e. subtotal colectomy and ileostomy) is now inappropriate for children and adolescents BEFORE a trial of anti-TNFα induction therapy, as there are a significant number of children in whom a colectomy may be delayed for many months [33].

3.1.3. Exclusions

- Patients with sepsis (i.e. fever > 38°C), or with clinically apparent infection or abscesses (discuss with consultant). Less serious infections (e.g. URTIs or simple UTIs) are not contra-indications but should be discussed with the responsible consultant.
- Patients who are hypersensitive to Infliximab (or other anti-TNF agents) or any other excipients.
- Female patients who may be / may become pregnant (should not become pregnant within 6 months of last dose).
- Patients with moderate or severe heart failure.
- Previous demyelinating disease (e.g. optic neuritis/MS.
- Evidence of prior history of TB or of current active TB. Recent close contact with an individual with active TB (see Appendix i).

3.2. Definitions

3.2.1. A. Crohn's Disease

Moderate to severe Crohn's Disease:

Patient with very poor general health with weight loss & sometimes fever, severe abdominal pain and frequent diarrhoeal stools (> 3-4/day).

Patients may/may not be developing new fistulae or have extra-intestinal manifestations of disease.

This corresponds to a PCDAI (Appendix ii) > 30 [34].

Refractory / intolerant to treatment with immunomodulators:

Patient has received a full and adequately dosed course of Azathioprine (2.5mg/kg for minimum of 4 months) / methotrexate (25mg SC OW for minimum 12 weeks)
Clinician to agree locally as to what constitutes intolerance or toxicity of treatment.

Refractory to / dependent on corticosteroids:

Continuing disease activity unresponsive to corticosteroids (maximum dose of 2mg/kg or 40mg OD for > 2 weeks / equivalent IV dose) or dependence on corticosteroids (relapse during / soon after reducing course requiring other rescue therapy).

Surgery may be deemed 'inappropriate' when there is:

- Diffuse / panenteric disease and/or a risk of short bowel syndrome.
- Pancolitis that would require subtotal colectomy with fashioning of a long-term ileostomy.
- Severe perianal Crohn's disease.
- Child / family refusing surgical intervention.

Clinical response: Decrease from baseline PCDAI of ≥ 15 points and a total PCDAI score of ≤ 30 points.

Clinical remission: PCDAI score of ≤ 10 points. Stool calprotectin <250microgrammes/ml

Loss of response: An increase in the PCDAI score of ≥ 15 points from baseline at 2 consecutive visits at least 7 days apart **OR**

The subject's overall PCDAI score is > 30 points at any point

3.2.2. B. Ulcerative colitis

There is now a validated clinical disease activity index for children with ulcerative colitis (Appendix iii) [35] PUCAI

Activity scores:

< 10 = inactive disease
10 - 34 = mild disease
35 – 64 = moderate disease
> 65 = severe disease

Response	Small	≥ 10 points
	Moderate response)	≥ 20 points (moderate change represents clinically 'significant'
	Large	≥ 35 points

3.3. Admission schedule

Use in conjunction with checklist for 1st and Follow-up infusions – (Appendix iv)

- Administration of Infliximab is appropriate as a daycase.
- Patients should ideally be scheduled in small groups (3-4) to minimise drug wastage (Vial sharing should be approved in each unit administering Infliximab).

- It is not necessary for a patient to be seen by a doctor at every visit.
- All children are to be seen by an appropriate member of the gastroenterology team to record the **first** (week 0) or **assessment** (Week 14) PCDAI / PUCAI and complete the infusion checklist on each admission and data collected for biologic audit.
- Record base line observations (pulse, BP, temperature, weight and height).
- Medical review is required if there are signs of infection / history of recent contact with infection (mild viral illnesses / upper respiratory tract infections are not contra-indications to treatment).
- Apply EMLA / cold spray as appropriate.
- At each infusion, blood tests including FBC, LFT's, ESR, CRP, (consider Ca, P, Ferritin, B12 & folate) should be taken at cannula insertion.
- Ensure access to resuscitation trolley and appropriate medication (ie anaphylaxis medication).
- Ensure oxygen mask and tubing are connected.
- Ensure paediatric doctor is aware infusion will be in progress and is available within 5 minutes if called (senior nursing staff to give first-line anaphylaxis treatment as necessary).
- Administer infusion (see below).

3.4. Prescription

Infliximab	5 mg/kg as IV infusion over **2 hours** (see reconstituted information below) at 0, 2 & 6 weeks, then 8 weekly until infusion has been given for 6 months. After first 6 months give 5mg/kg as IV infusion over **1 hour** unless there has been a reaction (42,43,44)
	Only to be continued if clinical response achieved at 14 weeks.

Infliximab dose intensification 10mg/kg infusions may be used in an attempt to regain Infliximab efficacy where therapeutic drug levels have been demonstrated to be suboptimal (<5microgrammes/ml in luminal disease and <12.5microgrammes/ml is severe fistulating disease. This is usually given as 3 10mg/kg doses over 2 hours before returning to 5mg/kg doses at 8weekly intervals. Alternatively the dosing interval may be reduced following discussion with the lead clinician.

If there is a delay of **10 weeks or more** since the last infusion, paediatric gastroenterology consultant advice should be sought before the infusion as there is an increased risk of adverse reaction due to possible development of antibodies (see Appendix v). In this case prophylactic chlorphenamine (Piriton) and hydrocortisone should also be considered.

Pre-treatment with oral chlorphenamine (Piriton, dose as per BNFc) and IV hydrocortisone (4 mg/Kg, max 200 mg) may also be considered in the following circumstances:

1. Patient has experienced a previous low level reaction to Infliximab but not anaphylaxis
2. High antibody levels have been detected but no adverse reaction has occurred

In this situation the MDT discussion and decision to continue Infliximab should be documented in patients notes and on EPMA.

3.5. Preparation

- Infliximab must be stored at 2-8 degrees centigrade. Do not freeze.
- Calculate dose at 5mg/kg (each vial contains 100 mg Infliximab) and round up to the nearest 10mg.
- Reconstitute each vial with 10mls of Water for Injection using a 21 gauge needle or less. Swab vial top with a 70% alcohol swab and allow to dry.
- Inject the water against the glass wall of the vial. Do not use the vial if the vacuum is not present.
- Swirl the solution gently by rotating the vial to dissolve the powder. **DO NOT SHAKE THE VIAL**. It is not unusual to see some foaming of the solution.
- Allow to stand for 5 minutes. Solution should be colourless to light yellow and opalescent. It is normal to see a few fine translucent particles as Infliximab is a protein. Do not use if there are opaque particles, discolouration or foreign particles present.
- Withdraw the same total volume as the reconstituted drug from 250ml Sodium Chloride 0.9%. Slowly add the total volume of reconstituted Infliximab to the 250ml infusion bag. Gently mix. Fix additive drug label according to Trust policy.
- Infliximab infusions should be administered via a sterile giving set and a 0.2 micron epidural filter. Connect the infusion with a y-connector and prime giving set with Infliximab solution. Infusions must be administered via a volumetric pump.
- If the last infusion was given > 10 weeks ago, a test dose of 10mls should be infused over 10 minutes (1ml/min) and the patient should be observed closely for any signs of anaphylaxis. If there are no adverse reaction or signs of hypersensitivity the infusion may continue at the normal rate.
- Administer infusion over a period of 1-2 hours
- Following reconstitution and dilution the infusion must be started as soon as possible and **AT THE LATEST** within 3 hours. Do not store any unused portion for later re-use.
- The Batch Number and Lot Number of vials must be recorded in the patient's notes.

3.6. Administration & Monitoring

- The patient should be monitored closely during the infusion period and should stay in ward area for the duration of the infusion and for at least 1 hour after the infusion has finished.
- Observations of BP, pulse and temperature must be recorded every 30 minutes for the first hour, then every 30 minutes until the infusion is completed and for 1 hour post infusion.
- Observe the cannula site for extravasation and the infusion for any changes in colour or consistency.
- Report and record any adverse reactions to the child's named consultant.
- The cannula must remain in-situ until the patient is ready for discharge and should then be removed.

- All patients on Infliximab should have contact details of appropriate staff in case of a delayed reaction.
- Ensure patient is given Infliximab Alert card after first infusion.
- Ensure patient has forms for blood monitoring if appropriate.
- Make appointment for next infusion (schedule 6 monthly / annual clinic review as necessary.
- Ensure that appropriate discharge information is sent out.

3.7. Infusion-related reactions & Adverse Events

- Acute - within 24 hours of initial or subsequent infusions.
- Delayed - any reaction, which occurs from 24 hours-14 days post Infliximab treatment [36].

An acute infusion reaction may occur during an infusion, or within 1-2 hours post infusion. Patients must remain within the clinical environment for 1 hour for post infusion monitoring.

Signs and symptoms of infusion related reactions:

- Approximately 5% of Infliximab infusions are accompanied by acute reactions.
- About 3% were reported as mild, of these:
    - 1% were accompanied by urticaria, pruritus, fever and/or chills.
    - 1% were accompanied by chest pain, hypotension, hypertension and shortness of breath.
- 1% had severe reactions.
- Delayed reactions occurred in <1% of infusions. ie rash, fever, polyarthralgia, headaches and sore throat.

3.8. Treatment for infusion reactions

- Anaphylaxis (see Appendix v)
    - Discontinue the infusion and call for immediate medical attention according to APLS/EPLS guidelines.
    - Adrenaline IM 10 micrograms /kg.
    - Adrenaline nebuliser 5ml of 1/1000.
    - Salbutamol nebuliser 2.5mg.
    - Normal saline 20mls/kg IV bolus.
    - Steriods or Piriton.
- Moderate to severe reactions - discontinue infusion and seek a paediatric consultant decision about recommencement.
- Mild rash, nausea, headache or pruritus. Stop infusion, paediatric medical review. Administer Paracetamol and consider giving IV chlorphenamine. Consider restarting the infusion at 25% of the normal rate, increasing rate again if tolerated.

- Any infusion reaction should be reported to paediatric gastroenterology Consultant as a more severe reaction may occur at the next infusion.

3.9. Follow up

6 monthly assessment by:
Paediatric Gastroenterologist or Consultant with expertise in Paediatric Gastroenterology
Includes:

- Review of concomitant immunosuppressant use.
- Assessment of anti-TNFα efficacy.
- Discuss need for continuing therapy.
- Discuss risks of pregnancy.
- Assess growth and pubertal status.

Annual assessment by:
Paediatric Gastroenterologist
In addition to 6 month assessment:

- PCDAI / PUCAI score.
- Discuss benefit of annual endoscopic assessment.
- Review long-term treatment strategy.
- Transition planning, if appropriate.

4. Training & Competencies

Children's Day Ward administration to be undertaken by trained paediatrics nurse with assessed competencies in IV infusions.

5. References/ source documents

1. Van den Brande, J.M., et al., Infliximab but not etanercept induces apoptosis in lamina propria T-lymphocytes from patients with Crohn's disease. Gastroenterology, 2003. **124**(7): p. 1774-1785.
2. Breese, E.J., et al., Tumor necrosis factor alpha-producing cells in the intestinal mucosa of children with inflammatory bowel disease. Gastroenterology., 1994. **106**(6): p. 1455-1466.
3. Shen, C., et al., Adalimumab induces apoptosis of human monocytes: a comparative study with infliximab and etanercept. Aliment Pharmacol Ther, 2005. **21**(3): p. 251-8.
4. Murch, S.H., et al., Serum concentrations of tumour necrosis factor alpha in childhood chronic inflammatory bowel disease. Gut, 1991. **32**(8): p. 913-917.
5. Hyams, J., et al., Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. Gastroenterology, 2007. **132**(3): p. 863-73; quiz 1165-6.
6. Rutgeerts, P., et al., Scheduled maintenance treatment with infliximab is superior to episodic treatment for the healing of mucosal ulceration associated with Crohn's disease. Gastrointest.Endosc., 2006. **63**(3): p. 433-442.

7. Teitelbaum, J.E., et al., Infliximab in pediatric Crohn disease patients with enterovesicular fistulas. J Pediatr Gastroenterol Nutr, 2007. **44**(2): p. 279-82.
8. Ruemmele, F.M., et al., Efficacy of infliximab in pediatric Crohn's disease: A randomized multicenter open-label trial comparing scheduled to on demand maintenance therapy. Inflamm Bowel Dis, 2009, **15**(3): p. 388-94.
9. Baldassano, R., et al., Infliximab (REMICADE) therapy in the treatment of pediatric Crohn's disease. Am J Gastroenterol, 2003. **98**(4): p. 833-8.
10. Present, D.H., et al., Infliximab for the treatment of fistulas in patients with Crohn's disease. N Engl J Med, 1999. **340**(18): p. 1398-1405.
11. Colombel, J.F., et al., Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology, 2007. **132**(1): p. 52-65.
12. Hanauer, S.B., et al., Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. Gastroenterology, 2006. **130**(2): p. 323-33; quiz 591.
13. Sandborn, W.J., et al., An open-label study of the human anti-TNF monoclonal antibody adalimumab in subjects with prior loss of response or intolerance to infliximab for Crohn's disease. Am J Gastroenterol, 2004. **99**(10): p. 1984-9.
14. Peyrin-Biroulet, L., C. Laclotte, and M.A. Bigard, Adalimumab maintenance therapy for Crohn's disease with intolerance or lost response to infliximab: an open-label study. Aliment Pharmacol Ther, 2007. **25**(6): p. 675-80.
15. Afzal, N.A., et al., Infliximab delays but does not avoid the need for surgery in treatment-resistant pediatric Crohn' disease. Dig Dis Sci, 2007. **52**(12): p. 3329-33.
16. Rutgeerts, P., et al., Infliximab for induction and maintenance therapy for ulcerative colitis. N.Engl.J.Med., 2005. **353**(23): p. 2462-2476.
17. Jarnerot, G., et al., Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: a randomized, placebo-controlled study. Gastroenterology, 2005. **128**(7): p. 1805-11.
18. Halfvarson, J. and G. Jarnerot, Treatment of choice for acute severe steroid-refractory ulcerative colitis is remicade. Inflamm Bowel Dis, 2009. **15**(1): p. 143-5.
19. Fanjiang, G., G.H. Russell, and A.J. Katz, Short- and long-term response to and weaning from infliximab therapy in pediatric ulcerative colitis. J Pediatr Gastroenterol Nutr, 2007. **44**(3): p. 312-7.
20. Cucchiara, S., et al., Infliximab for pediatric ulcerative colitis: a retrospective Italian multicenter study. Dig Liver Dis, 2008. **40 Suppl 2**: p. S260-4.
21. Heuschkel, R., et al., Guidelines for the management of growth failure in childhood inflammatory bowel disease. Inflamm Bowel Dis, 2008. **14**(6): p. 839-49.
22. Varghese, S., et al., Effects of serum from children with newly diagnosed Crohn disease on primary cultures of rat osteoblasts. J.Pediatr.Gastroenterol.Nutr., 2002. **35**(5): p. 641-648.
23. Vespasiani Gentilucci, U., et al., Infliximab reverses growth hormone resistance associated with inflammatory bowel disease. Aliment Pharmacol Ther, 2005. **21**(9): p. 1063-71.

24. Thayu, M., et al., Improvement in biomarkers of bone formation during infliximab therapy in pediatric Crohn's disease: results of the REACH study. Clin Gastroenterol Hepatol, 2008. **6**(12): p. 1378-84.
25. Walters, T.D., A.R. Gilman, and A.M. Griffiths, Linear growth improves during infliximab therapy in children with chronically active severe Crohn's disease. Inflamm Bowel Dis, 2007. **13**(4): p. 424-30.
26. Borrelli, O., et al., Infliximab heals intestinal inflammatory lesions and restores growth in children with Crohn's disease. Dig Liver Dis, 2004. **36**(5): p. 342-7.
27. Rutgeerts, P., et al., Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease. Gastroenterology, 2004. **126**(2): p. 402-13.
28. Thayu, M., et al., Hepatosplenic T-cell lymphoma in an adolescent patient after immunomodulator and biologic therapy for Crohn disease. J Pediatr Gastroenterol Nutr, 2005. **40**(2): p. 220-2.
29. Hanauer, S.B. and M.B. Smith, Rapid closure of Crohn's disease fistulas with continuous intravenous cyclosporin A [see comments]. Am.J.Gastroenterol., 1993. **88**(5): p. 646-649.
30. de Ridder, L., et al., Infliximab therapy in 30 patients with refractory pediatric crohn disease with and without fistulas in The Netherlands. J.Pediatr.Gastroenterol.Nutr., 2004. **39**(1): p. 46-52.
31. Cocco, A., et al., Successful treatment with infliximab of refractory pyoderma gangrenosum in 2 patients with inflammatory bowel diseases. Inflamm Bowel Dis, 2007. **13**(10): p. 1317-9.
32. Batres, L.A., P. Mamula, and R.N. Baldassano, Resolution of severe peristomal pyoderma gangrenosum with infliximab in a child with Crohn disease. J.Pediatr.Gastroenterol.Nutr., 2002. **34**(5): p. 558-560.
33. Mamula, P., et al., Infliximab in pediatric ulcerative colitis: two-year follow-up. J.Pediatr.Gastroenterol.Nutr., 2004. **38**(3): p. 298-301.
34. Hyams, J.S., et al., Development and validation of a pediatric Crohn's disease activity index. J Pediatr Gastroenterol Nutr, 1991. **12**(4): p. 439-447.
35. Turner, D., et al., Development, validation, and evaluation of a pediatric ulcerative colitis activity index: a prospective multicenter study. Gastroenterology, 2007. **133**(2): p. 423-32.
36. Cheifetz, A., et al., The incidence and management of infusion reactions to infliximab: a large center experience. Am J Gastroenterol, 2003. **98**(6): p. 1315-24.
37 Ruemmele F.M, et al. Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohns disease. Journal of Crohns and Colitis. (2014) 8, 1179-1207.
38. Turner. D. et al. Management of Pediatric Ulcerative Colitis: Joint ECCO and ESPGHAN Evidence- based Consensus Guidelines. JPGN Vol 55, Number 3 Sept 2012
40. Siegel.C.A et al. Remicade blue book: Evaluating the risk of lymphoma with anti-TNF therapies. 2013
41. van Rheenen. P et al. The Medical Management of Paediatric Crohn's Disease: an ECCO-ESPGHAN Guideline Update *Journal of Crohn's and Colitis*, Volume 15, Issue 2, February 2021, Pages 171–194, https://doi.org/10.1093/ecco-jcc/jjaa161

42. Munsel EJ, et al. Rapid Infliximab Infusion in the Pediatric Population. J Pediatr Pharmacol Ther 2020; 25(8): 705-708.

43. El-Matary W, et al. Rapid Infliximab Infusion in Children with Inflammatory Bowel Disease: A Multicenter North American Experience. Inflamm Bowel Dis 2017; 23(12): 2104-2108.

44. Yeckes A, Hoffenberg E. Rapid Infliximab Infusions in Pediatric Inflammatory Bowel Disease. J Pediatr Gastroenterol Nutr 2009; 49(1): 151-4

6. Monitoring Compliance

Compliance with the process will be monitored through the following:

Key elements	Process for Monitoring	By Whom (Individual / group /committee)	Responsible Governance Committee /dept	Frequency of monitoring
Patient entered onto regional IBD & Biologic database	Frequency and severity of adverse reactions documented on regional database	PCDAI/PUCAI	Paediatrics Governance	Treatment onset, 10-14 weeks, and annually

The audit results are to be discussed at relevant governance meetings annually to review the results and recommendations for further action. Then sent to Paediatric Governance who will ensure that the actions and recommendations are suitable and sufficient.

7. Useful Contact Numbers:

Children's Day Ward	01603 287170
Children's Assessment Unit	01603 289774
Children's Gastroenterology Specialist Nurses	01603 286320
Paediatric Consultants (via secretaries)	01603 287174

Appendix A: Guidelines for TB screening prior to the use of anti-TNFα therapies

These guidelines are based on the 'BTS recommendations for assessing risk and for managing Mycobacterium Tuberculosis infection and disease in those patients due to start Anti-TNFα treatment. Thorax 2005;**60**:800-805.'

The use of anti-TNFα therapies is associated with a five fold increased risk of TB, mostly due to reactivation. Most cases of TB associated with Infliximab occurred within 3 cycles of treatment with a median time to onset of 12 weeks.

A risk assessment should be made to compare the risk of TB against an adverse event from Isoniazid prophylaxis. The absolute risk of TB varies with ethnicity and time since entry into the UK. The risk of an adverse event from Isoniazid prophylaxis is 278/100,000 in adults- there are no reliable data for children thus this figure should be used.

Risk Assessment

Before starting anti-TNFα therapies children should be assessed. This includes a clinical examination, history of any prior TB treatment or contact, a chest radiograph and, if appropriate, a tuberculin test. A tuberculin test is unreliable in children on immunosuppressants. These include oral steroids, azathioprine, 6-mercaptopurine, tacrolimus, methotrexate, cyclosporine, mycophenylate mofetil.

New assessment methods for identifying latent TB are being developed. These tests measure interferon production of the subjects T-lymphocytes in response to tuberculous antigens (T SPOT TB and QuantiFERON-TB Gold). There is currently no data on the performance characteristics of these tests in children or adults about to start anti-TNFα therapies. Thus these tests should not be routinely requested before starting anti- TNFα therapies.

Any child with:

- A history of previous TB or contact with TB.
- Inadequately treated TB.
- Evidence of TB on chest X-ray or examination.
- Positive tuberculin test (if had BCG >15 mm; if no BCG >5 mm).
- A risk calculation that indicates the need for prophylaxis should be discussed with an infectious diseases consultant.

If there is inactive, adequately treated TB it is reasonable to commence anti-TNFα therapies but regular 3 monthly clinical assessments need to be made. These should include chest X-ray and sputum analysis if there are respiratory symptoms.
The onset of new respiratory symptoms, especially within 3 months of starting anti- TNFα therapy should be promptly investigated.

Recommended risk assessment:

If not on any immunosuppressant therapy for the previous 3 months:

History of prior TB/ TB contact
History of BCG

Clinical examination
Chest X-ray
Tuberculin test (2u)

If on immunosuppressant therapy

History of prior TB/ TB contact
History of BCG
Record ethnicity and place of birth (UK or other)
Clinical examination
Chest X-ray

Appendix B: PCDAI (Paediatric Crohn's Disease Activity Index)

Abdominal pain:			
None		= 0	
Mild – brief, does not interfere with activities		= 5	
Moderate/severe – daily, longer lasting, affects activities, nocturnal	= 10		____
Stools (per day):			
0 – 1 liquid stools, no blood		= 0	
Up to 2 semi-formed with small blood or 2 -5 liquid	= 5		
Gross bleeding, or 6 or more liquid, nocturnal diarrhoea		= 10	____
Well-being			
No limitation of activities, well		= 0	
Occasional difficulty in maintaining age appropriate activities, below par		= 5	
Frequent limitation of activity, very poor		= 10	____
Abdomen			
No tenderness, no mass	= 0		
Tenderness, or mass without tenderness	= 5		
Tenderness, involuntary guarding, definite mass		= 10	____
Perirectal disease			
None, asymptomatic tags	= 0		
1-2 indolent fistulae, scant drainage, no tenderness	= 5		
Active fistulae, drainage, tenderness, abscess		= 10	____
Extra-intestinal manifestations			
[Fever 38.5 for 3 days over past week, definite arthritis, uveitis, Erythema nodosum, P. gangrenosum]			
None		= 0	
One		= 5	
≥ Two		= 10	____
Height			
Diagnosis. (over last 4-6 months) <1 centile decrease	= 0		
≥ 1 <2 centile decrease		= 5	
>2 centile decrease		= 10	____
OR			
Follow-up height velocity (over last 6-12 months):			
≥-1 SD		= 0	
< -1 SD, >-2 SD		= 5	
< -2 SD		= 10	____
Weight			
Weight gain or voluntary stable/loss		= 0	
Involuntary weight stable, weight loss 1-9%	= 5		
Weight loss ≥ 10%		= 10	____
Laboratory			

HCT

< 10 yrs	≥33	= 0	Female 11-19 yrs ≥34	= 0	
	28-32	= 2.5	29-33	= 2.5	
	<28	= 5	<29	= 5	____
Male 15-19 yrs	≥37	= 0	Male 11-14 yrs >35	= 0	
	32-36	= 2.5	30-34	= 2.5	
	<32	= 5	<30	= 5	____

Albumin (g/l)	≥35	= 0	
	31-34	= 5	
	≥30	= 10	____
ESR (mm/hr)	<20	= 0	
	20-50	= 2.5	
	>50	= 5	____

Sum PCDAI (/100) _____

PUCAI (Paediatric UC Activity Index)

1. Abdominal pain		
No pain		0
Pain can be ignored		5
Pain cannot be ignored		10
2. Rectal bleeding		
None		0
Small amount only, in less than 50% of stools		10
Small amount with most stools		20
Large amount (_50% of the stool content)	30	
3. Stool consistency of most stools		
Formed	0	
Partially formed	5	
Completely unformed		10
4. Number of stools per 24 hours		
0 - 2		0
3 - 5		5
6 - 8		10
> 8		15
5. Nocturnal stools (any episode causing wakening)		
No		0
Yes		10
6. Activity level		
No limitation of activity		0
Occasional limitation of activity		5
Severe restricted activity	10	
Sum of PUCAI (/85)		_____

PUCAI User Guide

Most items contained in the PUCAI can be scored using the instructions provided within the instrument.

The following issues require additional clarification:

Time period for evaluation

- Answers should reflect a daily average of the last 2 days
- however, if clinical conditions are changing rapidly (eg during intense intravenous therapy), the most recent 24 hours should be considered and
- for patients undergoing colonoscopy, answers should reflect the 2 days before bowel prep was started.

Rectal bleeding

- "Large amount" should be selected if large amount of blood is present in most stools.

Number of stools per 24 hours

- Clustered several small stools over a very short period of time that could be related to tenesmus or incomplete evacuation should be considered as 1 stool.

Activity level

- Occasional limitation of activity = could attend school or equivalent but reduced activity (eg attends school but does not play at breaks) and
- severe restricted activity = could not attend school or equivalent activity.

Appendix C: Checklist/ clerking for children having 1st Infliximab infusion

Addressograph Label Date:

Action	Rationale	Tick each box below
Date and result of recent investigations documented in notes	Ensure up to date (ideally within 4 weeks) reassessment of disease extent / severity	Yes / No
Written patient information sheet provided and understood		Yes / No
Consent form signed by family and senior medical staff	Appropriate informed consent / assent of family +/- child	Yes / No
Annual review date confirmed	Detailed annual review of treatment strategy +/- endoscopic assessment	Date for annual review:
TB screening complete: History sheet, Chest x-ray performed & result reviewed and documented in the notes	TB screening prior to infusion start	Yes / No
Varicella titres measured	Ensure immunity / contingency plan for non-immune	Yes / No
Exit strategy discussed and documented	Make family aware of options if lack of treatment response	Yes / No
Advise that treatment response to be assessed between week 10-14 (ie before the 4th infusion)	Ensure that only patients responding to therapy continue on to maintenance 8-weekly infusions	Yes / No
Has funding been agreed by the PCT:	Unable to prescribe treatment unless funding agreed	Yes / No
Date for next infusion:	**Name, signature and designation**	

Regional Guideline On Anti – TNFα Use in Children With Inflammatory Bowel Disease

Appendix D: Adverse reactions during infusion

Type of reaction	Treatment Protocol (Dosages as below)	Prophylaxis for subsequent Infliximab Infusion
Mild Hyperaemia & Tachycardia Palpitations Diaphoresis (excessive sweating) Headache Dizziness Nausea	Slow infusion rate to 10ml/hr Chlorphenamine (IV) Paracetamol (oral) Monitor vital signs every 10 minutes until within normal limits. Wait 20 min then increase infusion rate as per regular protocol as tolerated. Monitor vital signs every 10 min until within normal limits	Pre-treat with oral paracetamol and chlorphenamine 1½ hours before infusion. Test dose Infliximab at 10ml/hr for 15 min If tolerated increase rate to infuse over 3 hours.
Moderate Hypo/hypertension (≥20points systolic blood pressure) Hyperaemia Chest discomfort (e.g. tightening, pressure) Shortness of breath Palpitations Urticaria	Stop or slow infusion rate to administer Chlorphenamine (IV) Paracetamol (oral) Monitor vital signs every 5 min until within normal limits Wait 20 min, then restart infusion rate at 10ml/hr and increase infusion rate as per regular protocol as tolerated Monitor vital signs every 5 mins until within normal limits	Pre-treat with oral paracetamol and chlorphenamine 1½hours before infusion Test dose Infliximab at 10ml/hr for 15 min If tolerated, increase infusion rate as per regular protocol as tolerated until 80ml/hour then increase to 150ml/hr until infusion finished
Severe Significant hypo/hypertension (≥40points systolic blood pressure) Elevated temperature with rigors Hyperaemia Chest discomfort (e.g. tightening, pressure) Significant shortness of breath Stridor (if potential to lose airway call crash team on 2222)	Stop infusion Infuse normal saline (10mls/Kg) Maintain airway; give oxygen if available Epinephrine 1:1000 (IM) Dose may be repeated every 5mins for 3 doses Hydrocortisone 100mg (IV) Chlorphenamine (IV) Paracetamol (Oral) Monitor vital signs every 2 min until within normal limits If patient stabilises restart infusion increasing as per regular protocol until 80ml/hr as tolerated until infusion finished If patient requires a second dose of adrenaline call the crash team on	Pre-treat with oral paracetamol and chlorphenamine 1½ hours before infusion. Hydrocortisone 100mg IV 20min before infusion Test dose Infliximab at 10ml/hr for 15 min If tolerated, increase infusion rate as per regular protocol as until 80ml/hour then increase to 100ml/hr until infusion finished

	2222	

Chlorphenamine (**ORAL**)
1month-2years 1mg twice daily
2-6years 1mg every 4-6 hourly (max 6mg daily)
6-12 years 2mg every 4-6 hours (max 12mg daily)
12-18 years 4mg every 4-6 hours (max 24mg daily)

Chlorphenamine (**Subcutaneous, Intramuscular or Intravenous injection**)
1month-2years 250micrograms/kg (max2.5mg) repeated if required up to 4 times in 24 hours
2-6years 2.5-5mg repeated if required up to 4 times in 24 hours
6-12 years 5-10mg repeated if required up to 4 times in 24 hours
12-18 years 4mg every 4-6 hours repeated if required up to 4 times in 24 hours (max 40mg daily)

Epinephrine 1:1000(**Intramuscular**)

Age	Dose	Volume of adrenaline **1:1000** (1mg/ml)
6months - 6 years	120micrograms	0.12ml
6 -12 years	250micrograms	0.25ml
12 -18 years	500micrograms	0.5ml

Regional Guideline On Anti – TNFα Use in Children With Inflammatory Bowel Disease

Appendix E: Information on Infliximab for the Treatment of Paediatric Crohn's Disease

What is Infliximab?

Infliximab (Infliximab) belongs to a group of treatments known as BIOLOGICS. It is one of several biologics which are more specifically known as anti-TNF-alpha agents. Infliximab is an antibody which recognises and binds to TNF-alpha neutralising its effects to reduce inflammation and the symptoms associated with Crohn's Disease.

What is Infliximab used for?

Infliximab has been used to treat over 1 million patients worldwide, for a range of inflammatory conditions which affect the gut, skin, joints or spine. It was first licensed in the UK for adults with Crohn's disease in 1999, then for rheumatoid arthritis in 2000 and then for psoriasis in 2005. Infliximab received approval for the treatment of paediatric Crohn's disease (patients aged 6 – 17 years old) in June 2007.

Although all of these conditions are different, the common factor is inflammation, which can cause pain and damage to the body's tissues and structures. Infliximab has been shown to be beneficial in the management of paediatric Crohn's Disease.

Your child may be prescribed Infliximab if they have severe active disease which is not responding to standard treatments and where surgery is not appropriate.

The underlying cause of Crohn's Disease

There are a number of theories about what causes Crohn's disease, but none have been proven. The human system is made up of cells and proteins which protect people from infection. The most common theory is that the body's immune system reacts abnormally in people with Crohn's disease, mistaking bacteria, foods, and other substances for being foreign. The immune systems response is to attack these "invaders". During this process, white blood cells accumulate in the lining of the intestines, producing chronic inflammation, which leads to ulcerations (breaks in the lining of the gut) and bowel injury.

One of the key molecules responsible for this chronic inflammation is called tumour necrosis factor alpha or TNF-α. It is one of a range of chemicals naturally produced by the body to fight infections as part of the immune response. In conditions such as Crohn's Disease, there is an overproduction of TNF-α, which leads to the chronic inflammation seen in Crohn's disease.

Family influence

Crohn's disease tends to run in families, and about 20 to 30% of people with the condition have a family member or relative with some form of inflammatory bowel disease.
There is no way of knowing which, if any, family members will develop Crohn's disease

Possible triggers

Foreign substances in the environment (such as a virus or bacterium) may also be the direct cause of the inflammation, or they may stimulate the body's immune system to produce inflammation without control.

How Does Infliximab Work?

Tumour necrosis factor alpha or TNF-α is one of the key molecules responsible for this chronic inflammation. It is one of a range of chemicals naturally produced by the body to fight infections

as part of the immune response. In conditions such as Crohn's Disease, there is an overproduction of TNF-α, which leads to the chronic inflammation seen in Crohn's disease.

Infliximab works by blocking the excess production of TNF-α which can reduce the inflammation in the gut. Patients may start to feel a difference within a few weeks after treatment has started.

How is Infliximab given?

Infliximab is a powder that is mixed with a water and salt solution to make up a clear liquid; this liquid is then given as an infusion. Infliximab is given into a vein, usually in the arm. The infusion will take about 2 hours. Your child will also be observed during the infusion and for 1 to 2 hours after the infusion has finished before being allowed to go home.

What is the dose of Infliximab?

The doctor will have decided the right dose; it is usually 5mg for every kilogram of weight. After the first infusion, the second infusion will be given 2 weeks later. The third infusion will be 4 weeks after the second infusion. Thereafter Infliximab may be given at 2 monthly intervals.

The appointment for the next infusion will be given to you before you leave the hospital. Please ensure that you attend the next appointment. If you miss the appointment, it may affect how the treatment works.

How long will Infliximab take to work?

The effects of Infliximab are often noticed within a few weeks of starting therapy. A check-up will be scheduled during the first 3 to 6 months of treatment to find out whether the treatment should be continued.

Will Infliximab work?

Infliximab has been prescribed because studies have shown that it improved Crohn's disease in the majority of patients who received it. However it is important to remember that no drug works for all patients.

Are extra health checks required with Infliximab?

There have been cases of tuberculosis (TB) reported in patients taking Infliximab; therefore all patients are screened for tuberculosis before starting Infliximab. Screening procedures may include a tuberculin skin test and a chest x-ray, depending on your hospitals TB screening policy. It is very important to let the doctor know if your child has had tuberculosis or if they have been in close contact with someone who has had tuberculosis.

Will there be any extra tests?

No, Infliximab does not require any extra tests but routine tests to monitor disease activity will still be required.

Can other medicines be taken with Infliximab?

It is a good idea to talk to your child's doctor or specialist nurse before taking any other medicines. Before starting Infliximab, the doctor or specialist nurse will perform a full review of your child's current medications. If your child should see another doctor, nurse or a dentist after they have started Infliximab, tell them that they are receiving Infliximab.

Other Considerations:

Vaccinations

Please discuss any vaccinations required with your child's doctor or specialist nurse before administration as the immune system is suppressed and on occasion can cause a severe reaction. It is advised that if possible, all vaccinations should be brought up to date in agreement with current vaccination guidelines, before your child starts their treatment with Infliximab.

It is recommended that the annual influenza vaccine (flu vaccine which is an injection) is given and this can be arranged through the family doctor. This should NOT be the nasal vaccination as it is a live vaccination.

Infections

If your child develops an infection the doctor or specialist nurse must be informed immediately. It is important that the next infusion of Infliximab is not given if your child has an infection or you suspect they may have an infection. If in doubt, speak with the doctor or specialist nurse.

Chicken Pox

Your child will be checked for their chicken pox status prior to starting infliximab. If they are not immune a vaccination will be offered if possible.

If your child comes into contact with an individual who has confirmed chicken pox ie a family member in the same house, immediate friendship group or on a sleep over whilst on Infliximab they will need checking again for antibody status even if previously immune.

If results are negative they will be offered either anti viral treatment or a vaccination as advised by NNUH virology.

Antibiotics

Infliximab has not been shown to react with antibiotics and they can be taken if required. However, if an infection develops the doctor or specialist nurse must be informed immediately. It is important that the next infusion of Infliximab is not given if your child has an infection or you suspect they may have an infection. If in doubt, speak with the doctor or specialist nurse.

Contraception

It is recommended that a reliable form of contraception is used whilst receiving Infliximab and for 6 months after the last infusion. If planning to start a family or already pregnant, contact the doctor or specialist nurse in advance to discuss as treatment with Infliximab will need to be stopped.

Are there any side effects?

Like all medicines, Infliximab can have side effects. Some side effects may appear up to 6 months after the last infusion. Remember medicines affect people in different ways and it is very possible that none of the side effects mentioned here will be experienced. However, the possible side effect of any medication needs to be balanced against the risk of problems if the disease is not treated properly.

The doctor or specialist nurse must be informed immediately if any of the following occur during the infusion

- Pain or tenderness in chest, muscles, joints or jaw.
- Swelling of the hands, feet, ankles, face, lips, mouth or throat.
- Any difficulty swallowing or breathing (e.g. shortness of breath).
- Bumpy skin or other signs of an allergic reaction.
- Fever.
- Rash.
- Itching.

Please inform the doctor or nurse as soon as possible if you notice your child experiencing any of the following symptoms at all other times

- Difficulty breathing and dry cough.
- Problems passing urine such as stinging sensation.
- Changes in heartbeat, for example if it is beating faster than usual.
- Light-headedness.
- Tiredness.
- Hoarseness.
- Headache.
- Tingling.
- Numbness.
- Double vision or other problems with the eyes.
- Weakness in arms or legs.
- Signs of liver problems for example: eyes or skin turning yellow. Dark brown urine, right-sided stomach pain.

The symptoms listed above can be signs of the more significant side effects. Below is a list of the full range of possible side effects with Infliximab

Common: headache, dizziness, nausea, abdominal symptoms, allergic reactions, rash, urinary, viral infections (for example herpes, influenza), respiratory infections (cold, sinus infections, bronchitis, pneumonia), infusion related reactions

Uncommon: depression, agitation, sleep disturbances, impaired wound healing, bacterial infections (for example tuberculosis, urinary tract infections, deep skin infections, sepsis), fungal infections, asthma, abnormal liver function, low blood cell counts including anemia, worsening of demyelinating nerve disease, autoimmune disease activation (SLE or systemic lupus erythematosus), worsening of heart failure, hair loss, bleedings, allergic anaphylactic reactions, injection site reactions.

Rare: gastrointestinal bleedings or perforation, circulatory failure, multiple sclerosis
Very Rare: Malignancies and lymphoproliferative disorders

In controlled studies of TNF-blocking agents, more cases of malignancies including lymphoma have been observed in patients receiving a TNF blocker compared to control patients.

One particular form of lymphoma has been observed in adolescent and young adult patients with Crohn's Disease. This form of lymphoma is called Hepatosplenic T-cell lymphoma (HSTCL). HSTCL is a very rare form of lymphoma in which the major sites of disease are the liver, spleen and bone marrow. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal, and is reported to occur most commonly in adolescent and young adult males.

The definition of a rare adverse event or reaction is one which has a likelihood of occurring in ≥ (greater than) 1 in 10000 people to ≤ (less than) 1 in 1000 people. HSTCL has been classified as being rare.

Additional liver tests (to see how well the liver is working) and blood tests may be done if any of the above symptoms occur.

If you notice any side effects that are not mentioned in this leaflet, please tell the doctor or specialist nurse.

8. Equality Impact Assessment (EIA)

Type of function or policy	Existing

Division	Womens and Childrens	**Department**	Paediatrics
Name of person completing form	Dr Mary-Anne Morris	**Date**	12/4/2023

Equality Area	Potential Negative Impact	Impact Positive Impact	Which groups are affected	Full Impact Assessment Required YES/NO
Race	N/A	N/A	N/A	NO
Pregnancy & Maternity	N/A	N/A	N/A	NO
Disability	N/A	N/A	N/A	NO
Religion and beliefs	N/A	N/A	N/A	NO
Sex	N/A	N/A	N/A	NO
Gender reassignment	N/A	N/A	N/A	NO
Sexual Orientation	N/A	N/A	N/A	NO
Age	None	Consistent care for Children and young people	Patients under Paed Gastro (usually <16years, sometimes 16-18)	NO
Marriage & Civil Partnership	N/A	N/A	N/A	NO
EDS2 – How does this change impact the Equality and Diversity Strategic plan (contact HR or see EDS2 plan)?	N/A			

- **A full assessment will only be required if: The impact is potentially discriminatory under the general equality duty**
- **Any groups of patients/staff/visitors or communities could be potentially disadvantaged by the policy or function/service**
- **The policy or function/service is assessed to be of high significance**

IF IN DOUBT A FULL IMPACT ASSESSMENT FORM IS REQUIRED

The review of the existing policy re-affirms the rights of all groups and clarifies the individual, managerial and organisational responsibilities in line with statutory and best practice guidance.