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Norfolk and Waveney Integrated Care System

NHS
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Integrated Care Board

Crohn's Treatment Pathway 2023

Norfolk and Waveney Integrated Care System

1. Table of Contents

2. Document Control Sheet

Title	Crohn's treatment pathway 2023
Description of policy	NWICB high cost drug pathway for crohn's
Version	1.1
Scope	
Prepared by	Medicine optimisation team With input/advice from specialists at NNUH, QEH & JPH
Impact Assessment (Equalities and Environmental)	
Other relevant approved documents	
Evidence base / Legislation	Level of Evidence: ~~A. based on national research-based evidence and is considered best evidence~~ **B. mix of national and local consensus** ~~C. based on local good practice and consensus in the absence of national research based information.~~
Dissemination	Is there any reason why any part of this document should not be available on the public web site? ~~Yes~~ / **No**
Approved by	N&WICB Therapeutics advisory group
Authorised by	N&WICB Therapeutics advisory group
Review date and by whom	July 2025
Date of issue	07/07/2023

2.1 Revision History

Revision Date	Summary of changes	Author(s)	Version Number
20/07/22	First draft	M. Sully (ICB)	0.1
06/09/22	Formatting, minor revisions, approved by TAG	As above + A. Charlwood (ICB)	1.0
04/07/23	Added Risankizumab (TA888), Upadacitinib (TA905), updated information relating to pregnancy & breastfeeding, vaccination information, and corrected dose escalation information.	As above & local specialist input	1.1

2.2 Approvals

This document requires the following approvals either individual(s), group(s) or board.

Name	Title	Date of Issue	Version Number
Norfolk & Waveney ICB Therapeutics Advisory Group		06/09/2022	1.0
Norfolk & Waveney ICB Therapeutics Advisory Group		07/07/2023	1.1

3. Introduction

3.1 Relevant NICE technology appraisals

Technology Appraisal*	Title
TA187	Infliximab and adalimumab for the treatment of Crohn's disease
TA352	Vedolizumab for treating moderately to severely active Crohn's disease after prior therapy
TA456	Ustekinumab for moderately to severely active Crohn's disease after previous treatment
TA888	Risankizumab for previously treated moderately to severely active Crohn's disease
TA905	Upadacitinib for previously treated moderately to severely active Crohn's disease

*NICE recommendations **also apply to biosimilar products of the technologies** that have a marketing authorisation, allowing the use of the biosimilar for the same indication.

See Appendix 6 for full detail of listed TAs.

3.2 Background

This pathway is to be used to guide the initiation and maintenance of high-cost drugs in the management of inflammatory bowel disease (IBD) and have been written using up to date published NICE Technology Appraisals (TAs) and evidenced based medicine.

The pathways include biologic agents:

- Anti-TNF: Adalimumab & Infliximab
- $\alpha_4\beta_7$-integrin inhibitor: Vedolizumab
- Interleukin-12 & 23 inhibitors (IL-12/23i): Ustekinumab
- Interleukin-23 inhibitor (IL-23i): Risankizumab
- JAK inhibitors (JAKi): Upadacitinib

Drugs should be used in accordance with the relevant TA. The links are included in this document. Inclusion will be allowed for any new high-cost drugs that are approved by NICE prior to review of the pathway, provided that the relevant local "New Medicines" Policy and process has been followed. Those drugs should be used in accordance with the relevant NICE TA. The NICE recommendations also apply to biosimilar drugs, where marketing authorisations allow use of the biosimilar for the indication specified in the relevant NICE TA.

Crohn's disease (CD) is a chronic inflammatory bowel disorder of unknown aetiology which is characterised by a chronic inflammatory process which can affect any part of the GI tract. The disease is characterised by relapses and remissions and there is an increasing incidence of early onset CD, which has major implications for the provision of long-term care. It is incurable at the present time and a combination of medical and surgical therapies are often required for patients. Biologics may be offered in secondary care where the disease is active and severe and all other treatment options have failed.

Severe active Crohn's disease Severe active Crohn's disease is defined as very poor general health, plus >1 symptom of:

- weight loss
- fever
- severe abdominal pain
- frequent (3-4 or more) diarrhoeal stools daily.

People with severe active Crohn's disease may or may not develop new fistulae or have extra-intestinal manifestations of the disease.

Active fistulising Crohn's disease Fistulating Crohn's disease is a complication that involves the formation of a fistula between the intestine and adjacent structures, such as perianal skin, bladder, and vagina. It occurs in about one quarter of patients, mostly when the disease involves the ileocolonic area.

The disease is characterised by relapses and remissions. Most patients can be maintained in remission with medical therapy or surgical therapies.

4. Local Specialist and NICE Clinical Guideline Advice

4.1 Non-Drug Consideration

4.1.1 Lifestyle factors

Give all people with Crohn's disease and their family members appropriate lifestyle information. Crohn's patients who smoke have a higher risk of flare. All patients with IBD who current smokers are should be encouraged to stop. Advice and support should be provided in line with national guidance on smoking cessation, diet, nutrition, fertility, cancer risk, surgery, treatment side effects and medicines adherence.

4.1.2 Concurrent opioid medication

Patients with IBD taking long term opioids should be helped to reduce long term opioid use due to the increased risk of harmful effects.

4.2 Inducing remission[1,2] (Algorithm Appendix 1)

Specialist drug treatment for Crohn's disease and fistulating Crohn's disease is generally given for induction and maintenance of remission. Treatment aim is to reduce symptoms and improve quality of life and to maintain closure of fistula where these are present. Active treatment of acute disease should be distinguished from preventing relapse.

4.2.1 To induce remission in patients with a first presentation or a single inflammatory exacerbation of Crohn's disease in a 12-month period.

- Offer monotherapy with conventional glucocorticosteroids
- If steroids are contra-indicated or not tolerated for people who have one or more of distal ileal, ileocaecal or right sided colonic disease and no severe presentations or exacerbations consider budesonide[1]

4.2.2 If there are two or more inflammatory exacerbations in a 12-month period or if the steroid dose cannot be tapered (Algorithm Appendix 2)

- **Add on azathioprine or mercaptopurine** (subject to TPMT activity) under local shared care arrangements. Local specialists advise as per British Society of Gastroenterology (BSG) that for patients with moderate to severe Crohn's disease responding to prednisolone, early introduction of maintenance therapy with thiopurines or methotrexate should be considered, to minimise risk of flare as prednisolone is withdrawn.
- In people who cannot tolerate azathioprine or mercaptopurine or in whom TPMT activity is deficient. **Add on methotrexate to steroid or budesonide** under local shared care arrangements if there are two or more inflammatory exacerbations in a 12-month period or if the steroid dose cannot be tapered.
- NICE does not include Allopurinol use in its guidance, but co-prescription with thiopurines can improve tolerance in many people.

4.3 Medicines Adherence

Patients should be routinely asked about medicines adherence as non-adherence is common. Such patients should have a review and offered strategies to improve adherence.

[1] BSG advise ileal release budesonide (Budenofalk® or Entocort®) where CDAI<150 but less effective than steroids where CDAI>300

5. Secondary care: Biologics for moderate to severe active Crohn's disease

Biologic therapies are useful in inducing and maintaining remission in people with severe active disease which has not responded to conventional therapy, or where conventional therapy is not tolerated. When using biologics, the most cost-effective appropriate treatment should be selected, considering drug administration costs, clinical appropriateness, and patient choice. See algorithm Appendix 3.

6. Initiating treatment with Biologics

6.1 Choice of therapy

NICE advises the least costly clinically appropriate option should be selected for treatment, including patient preferences and drug and administration costs i.e., overall value proposition offered by the individual medicines (considering administration costs, dosage, price per dose and treatment frequency). Use of biosimilars has become routine clinical practice. All NICE guidance on biologics applies to biosimilar medicines. The rationale for choice should be documented.

Biologics including biosimilars[3] must be prescribed by brand name in line with MHRA guidance (i.e., the brand of biosimilar or originator product) to support on-going pharmacovigilance of the individual products. Patients prescribed a biologic should therefore be enrolled on to the relevant biologic registry which serves data collection on the safety and effectiveness of medicines in clinical practice.

Biosimilar Adalimumab should be selected as a first line treatment option where clinically and cost-effectively appropriate as above. In terms of cost, IV Vedolizumab is currently the costliest option.

6.2 Contraindication to Anti-TNF therapy

If a patient is contraindicated to Anti-TNFs, or are otherwise unsuitable, Ustekinumab, Risankizumab, Upadacitinib & Vedolizumab can be considered as first line choices. See Appendix 3 for full treatment algorithm.

7. Contraindications, special warnings, and precautions for treatment with drugs

See appendix 4 for full summary page.

7.1.1 MHRA warning - Janus kinase (JAK) inhibitors

There have been several MHRA warnings since 2020 for individual JAK inhibitors. In March 2023 the MHRA released information for risk minimisation which has been previously recommended for tofacitinib & upadacitinib, would now apply to all JAK inhibitors. Points of interest[3] include:

- following a review, these risks are considered class effects across JAK inhibitors used for chronic inflammatory disorders and therefore it is advised to avoid prescribing these medicines unless there are no suitable alternatives in patients with the following risk factors:
    - age 65 years or older
    - current or past long-time smoking
    - other risk factors for cardiovascular disease or malignancy
- use caution if prescribing in patients with risk factors for VTE other than those listed above (see below for more details)

It is recommended to read the full guidance here for the full details on caution

8. Blueteq – all drugs except Anti-TNF biosimilars

Blueteq forms which comply with this pathway are available. Funding approval for the tariff excluded high-cost drugs will be required by submission of the relevant Blueteq form prior to treatment administration for all drugs except Anti-TNF biosimilars. The Blueteq forms contain a list of relevant criteria that the patient must meet to secure funding. Any patients who do not meet these criteria will require an individual funding request, further information found on Knowledge Anglia. All use is subject to external audit.

9. Monitoring disease[1]

Measure baseline Crohn's Disease Activity Index (CDAI) or Harvey Bradshaw Index (HBI) Score. Clinical response should be assessed at set points during each of the biologic therapeutic dosing regimens (see individual dosage schedules for details). Patients who continue treatment should have their disease reassessed at least every 12 months to determine whether ongoing treatment is still clinically appropriate.

9.1 Crohn's Disease Activity Index (CDAI)

This should be measured based on the clinical diary of symptoms in the **previous 7 days.** The CDAI score ranges from 0 to over 600 and measures symptoms, weight, bowel response, and haematocrit and other disease related measurements. A score of 150 or lower represents inactive disease, whereas scores over 450 represent severe, active disease[2].

9.2 Harvey Bradshaw Index (HBI) Score

The HBI score is a clinical indicator scoring of the activity of Crohn's disease and considers scoring for, general well-being, abdominal pain, number of liquid or soft stools per day, abdominal mass, and additional complications of Crohn's such as aphthous ulcers and uveitis. Scoring ranges from <5 as remission to >16 as seen in severe disease.

9.3 Faecal calprotectin as a biomarker of intestinal inflammation

Faecal calprotectin is excreted in excess into the intestinal lumen during the inflammatory process and so can act as a marker for inflammatory diseases of the lower gastrointestinal tract. The test is intended to help distinguish between inflammatory bowel diseases and non-inflammatory bowel diseases.

It may provide a high negative predictive value, low positive predictive value but may be useful biomarker for endoscopic histological disease activity to inform treatment

It is recommended by NICE as an option to support clinicians with the differential diagnosis of inflammatory bowel disease (IBD) or irritable bowel syndrome (IBS) in adults with recent onset lower gastrointestinal symptoms for whom specialist assessment is being considered if cancer is not suspected, having considered the risk factors (for example, age) described in the NICE guideline on cancer and appropriate quality assurance processes and locally agreed care pathways are in place for the testing.

9.4 Treatment response review for biologic therapy[3]

Treatment should only be continued if there is clear evidence of response to drug treatment defined by a decrease in Harvey-Bradshaw Index by >3 points or CDAI by >70 points. After the start of treatment, people should have their disease reassessed to determine whether patients are responding adequately and if ongoing treatment is still appropriate. This should ideally be undertaken as suggested below:

Drug	Review of response after initiation at
Adalimumab	12 weeks
Infliximab	8 weeks
Risankizumab	12 weeks
Upadacitinib	12 weeks
Ustekinumab	16 weeks
Vedolizumab	14 weeks

10. Dose escalation

For patients who have responded to induction and maintenance treatment regime of a TNF inhibitor or Ustekinumab but then lost response an attempt to recapture response with a period of increased dose / shortened interval between doses may be made and is commissioned as below for initial escalation and maintenance:

[2] In clinical practice, CDAI is cumbersome to calculate, requires diary data from patients, is weighted towards diarrhoea (which is often caused by factors other than inflammation), is not usable in patients with stomas and is not validated for use after surgery

- Adalimumab biosimilar weekly for up to 12 weeks
- Infliximab biosimilar 10mg/kg for 3 doses
- Infliximab biosimilar 5mg/kg four to six weekly for up to 12 weeks (i.e., 2-3 doses over 12 weeks)
- Upadacitinib 30mg once daily
- Ustekinumab 90 mg every 8 weeks for 16 weeks (i.e., 2 doses at 8 weekly intervals)
- Vedolizumab dose escalation is not routinely commissioned at this time

If response to escalated dose is seen during short term escalation as above – de-escalate to standard dose if considered appropriate. Where drug levels and antibodies are adequate (in Anti-TNFs) and/or response on return to standard dose is lost, consider trial of maintenance escalated dose. This maintenance escalated dose is commissioned for:

- Adalimumab biosimilar weekly
- Infliximab biosimilar 10mg/kg
- Infliximab biosimilar 5mg/kg four to six weekly
- Upadacitinib 30mg once daily
- Ustekinumab 90 mg every 8 weeks

In patients with clear objective evidence of response to escalated dose (e.g., Anti-TNF drug & antibody level) and/or loss of response on de-escalation to standard dose.

Patients should be re-assessed after 6 months and then at least every 12 months to determine if ongoing escalated dose is necessary and clinically appropriate. De-escalation trial should be considered for patients without active disease and in stable clinical remission.

10.1 Vedolizumab

The product license for IV Vedolizumab allows for a dose increase to 300mg every 4 weeks, however, this dose increase was not considered by NICE and the cost effectiveness of such an intervention is unknown. Increased dosage has not been discussed with local specialists.

Where individual exceptionality to the routine commissioning policy can be demonstrated, an individual funding request application must be made to request funding for dose escalation. Routine commissioning of dose escalation will require a business case to be submitted to commissioners.

11. Anti-TNF Therapeutic Drug Monitoring

The decision to use drug and antibody levels will be a clinical decision based on individual patient factors and is not required routinely.

11.1 Managing Anti-TNF treatment failure

If there is an inadequate response to anti-TNF treatment (i.e., no/partial response, or loss of response):

- Check compliance to therapy
- Consider anti-TNF drug and antibody levels to guide further biologic therapy.

See appendix 1 for full treatment algorithm, and appendix 3 for guidance on interpreting anti TNF drug and antibody levels and further choice of therapy based on outcome of the monitoring.

12. Vaccination

The Department of Health Green Book[5] on NHS vaccinations advises:

'Patients on biologics may be at increased the risk of certain infections or may respond more poorly to vaccination, and should be considered for additional vaccination'

The British Association of Gastroenterologists provides advice on appropriate vaccination acknowledging that live vaccines are contraindicated in patients receiving immunosuppressants:

12.1 Statement 82

We recommend that a vaccination history should be obtained, and vaccinations updated for all patients with Crohn's disease, those with moderate to severe ulcerative colitis at diagnosis, and prior to commencing immunomodulator or biologics in all patients. Live vaccinations may be given at least 4 weeks before starting, and at a minimum of 3 months after stopping, but not whilst receiving immunosuppressive therapy (GRADE: strong recommendation, very low-quality evidence. Agreement: 93%).

12.2 Statement 83

We recommend that IBD patients receiving immunomodulators or biologics should receive influenza vaccination each autumn, and pneumococcal vaccination with a booster after five years (GRADE: strong recommendation, very low-quality evidence. Agreement: 95.5% Covid – 19 – SARS-Cov-2 Vaccination[6].

IBD patients receiving:

- long term immunosuppressive treatment for their condition
- immunosuppressive or immunomodulating biological therapy e.g., anti-TNF
- individuals treated with or likely to be treated with systemic steroids for more than a month at a dose equivalent to prednisolone at 20mg or more per day for adults

Some immunosuppressed patients may have a sub-optimal immunological response to the vaccine. For full information including patient groups and dosing schedules for Covid-19 – SARS-Cov-2 vaccination please see the Green book chapter 14a.

Prior to initiating biologic treatment, vaccination requirements should be evaluated and updated in accordance with Department of Health guidance.

12.3 Live vaccinations

Do not administer live vaccinations to individuals receiving biologic treatment. The British Society of Gastroenterology (BSG) recommend a period of 3 months[2] between stopping a biologic medication and administering live vaccinations.

Generally, biologic treatment may be started four weeks after a live vaccination is administered. Consult the drug's SPC, BSG guidelines, and the Green Book for more information.

The Green Book and the clinical risk category 'immunosuppression' should be used to determine immunisation needs during treatment. It is safe to provide inactivated vaccinations simultaneously with biologic treatment. To promote effective immune responses, inactivated vaccines should preferably be delivered at least 2 weeks prior to commencing treatment.

Prior to biologic treatment, patients should obtain yearly influenza vaccination (intramuscular only), pandemic influenza vaccination when suggested, and pneumococcal immunisation. Clinicians should be aware that TNF antagonist monotherapy may result in diminished antibody responses to influenza vaccination, and that TNF antagonists in combination with methotrexate (alone) may result in diminished antibody responses to pneumococcal vaccine.

12.4 New-borns to mothers who have received biological therapy

New-borns (up to 6 months of age) whose mothers received biologic therapy after 16 weeks' gestation. Patients should be counselled about the need of avoiding live immunizations and the potential implications for international travel.

13. Pregnancy & breastfeeding

13.1 Pregnancy

There is limited data for safety of biologic medicines in pregnancy and breastfeeding. The decision to continue biologic medicines throughout pregnancy must be individualised. This should consider the various therapies, severity of the mother's health prior to therapy, risk of a disease flare if therapy is discontinued, and the impact of a disease flare on the mother and unborn child. This should be discussed by a multi-disciplinary team.

Patients who discontinue treatment during pregnancy should resume biological therapy as soon as possible following delivery.

13.1.1 Manufacturer guidance

See the table below for further details on specific biologics in the different stages of pregnancy, information is taken from the SPC of the relevant biologic.

Biologic	Compatible with trimester		
	1st	2nd	3rd
Adalimumab	Yes	Yes	No
Infliximab	Yes	Stop at 16 weeks	No
Risankizumab	No data		
Upadacitinib	No - contraindicated		
Ustekinumab	No data		
Vedolizumab	No, use effective contraception until 18 weeks after last dose		

13.2 Breastfeeding

There is little information available regarding the excretion of biologics in breast milk. Immunoglobulins are excreted in human breast milk, so a risk to a child cannot always be ruled out. The decision to breastfeed or continue/discontinue therapy should consider both the benefits of breastfeeding to the infant and the benefits of therapy to the mother.

13.2.1 Manufacturer guidance

See the table below for further details on specific biologics in breastfeeding, information is taken from the SPC of the relevant biologic. Where no data or recommendation is provided, it would be appropriate to use the "Time to stop treatment prior to surgery" listed in section 12 to determine time between discontinuing treatment and starting breastfeeding.

Biologic	Compatible with Breastfeeding
Adalimumab	Yes
Infliximab	Wait 6 months until after stopping to breastfeed
Risankizumab	No data
Upadacitinib	No - Contraindicated
Ustekinumab	Wait 15 weeks until after stopping to breastfeed
Vedolizumab	Consider benefit of therapy vs potential risks to the infant

14. Correspondence

14.1 Information to be included in correspondence from secondary to primary care:

- Main diagnosis/diagnoses: type & location of IBD, and date of diagnosis
- Date(s) of surgery
- Secondary diagnosis/diagnoses e.g., anaemia, vitamin D deficiency, osteoporosis, extraintestinal
- manifestations
- Date of last endoscopy with findings & timing of next planned endoscopy
- Date of next planned contact with secondary care
- Current medical therapy including any previous treatments with thiopurines, methotrexate or biologics and reasons for discontinuation
- Recommended length of current medical therapy
- Treatment recommendations in case of a flare: 5-ASA dose increase, prednisolone, budesonide, calcium, and vitamin D.
- Details of who to contact if treatment is initiated in primary care

- Contact details for local IBD team
- Weblink for advice and guidance for primary care (e.g., RCGP Spotlight Project toolkit www.rcgp.org.uk/ibd)

14.2 Information to be included in correspondence from primary to secondary care:

- Date last prescription issued
- All current and recent medications. Any recent antibiotics
- Number of courses of oral prednisolone issued in last 12 months
- Key results of last blood tests
- Functional impact e.g., impact of IBD on employment, family, and social functioning
- Any newly diagnosed co-morbidities

15. References

1. Lamb CA, Kennedy NA, Raine T, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. *Gut*. 2019;68(Suppl 3):s1. doi:10.1136/gutjnl-2019-318484

2. Overview | Crohn's disease: management | Guidance | NICE. Accessed July 1, 2022. https://www.nice.org.uk/guidance/ng129

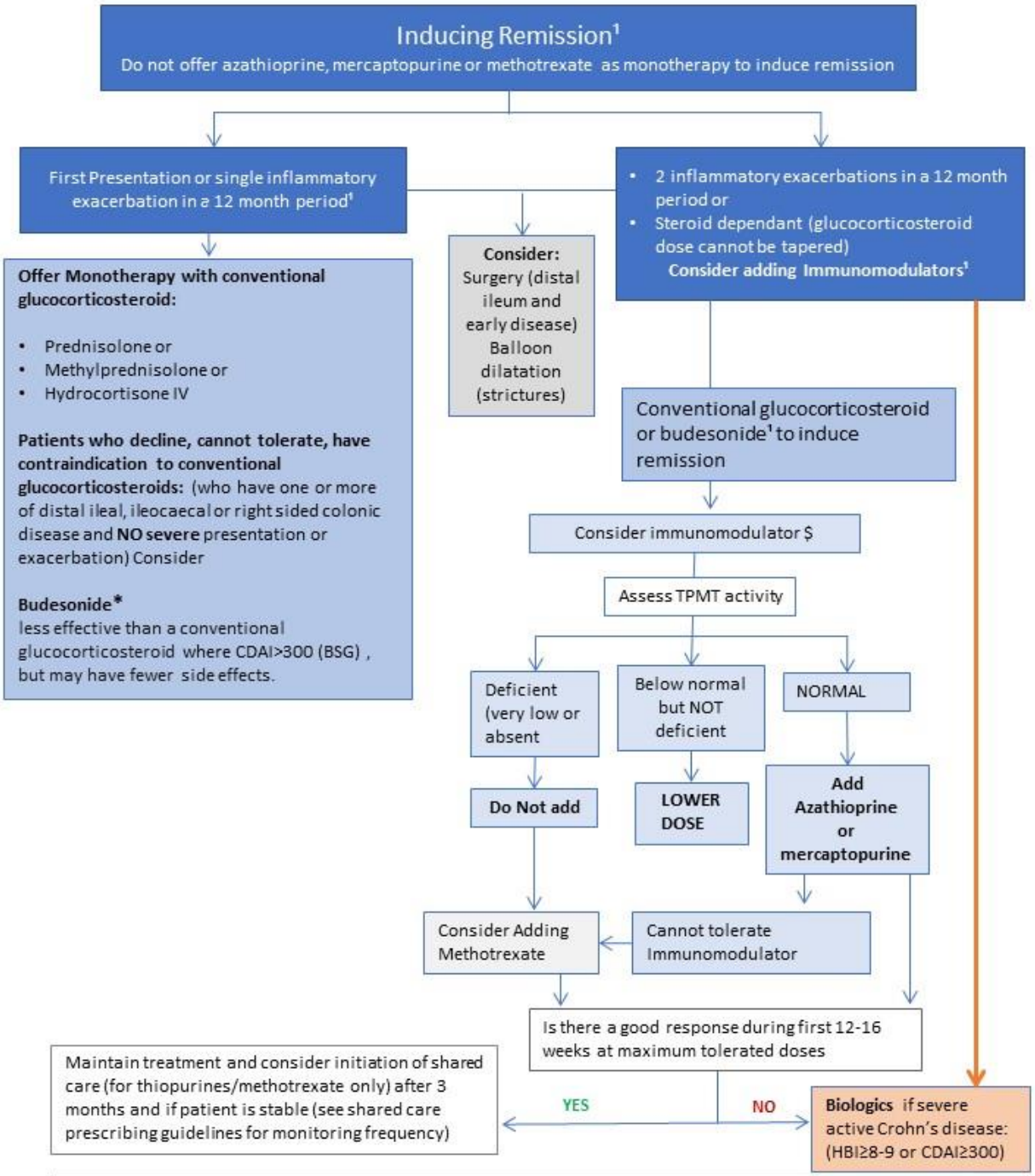
3. Medicines & Healthcare products Regulatory Agency. Guidance on the licensing of biosimilar products. GOV.UK. Accessed July 1, 2022. https://www.gov.uk/government/publications/guidance-on-the-licensing-of-biosimilar-products/guidance-on-the-licensing-of-biosimilar-products

4. UK Health Security Agency. *The Green Book of Immunisation - Chapter 7*.

5. COVID-19: the green book, chapter 14a. GOV.UK. Accessed July 1, 2022. https://www.gov.uk/government/publications/covid-19-the-green-book-chapter-14a

16. Appendix 1: Inducing Remission

Advice		Information
Discuss treatment options and monitoring. Give advice on:	If appropriate give information on:	
• Smoking Cessation • Patient Experience • Medicines Adherence • Fertility	• Diet and nutrition • Fertility, pregnancy and sexual relationships • Prognosis • Side effects of treatment	• Cancer Risk • Surgery • Support Groups

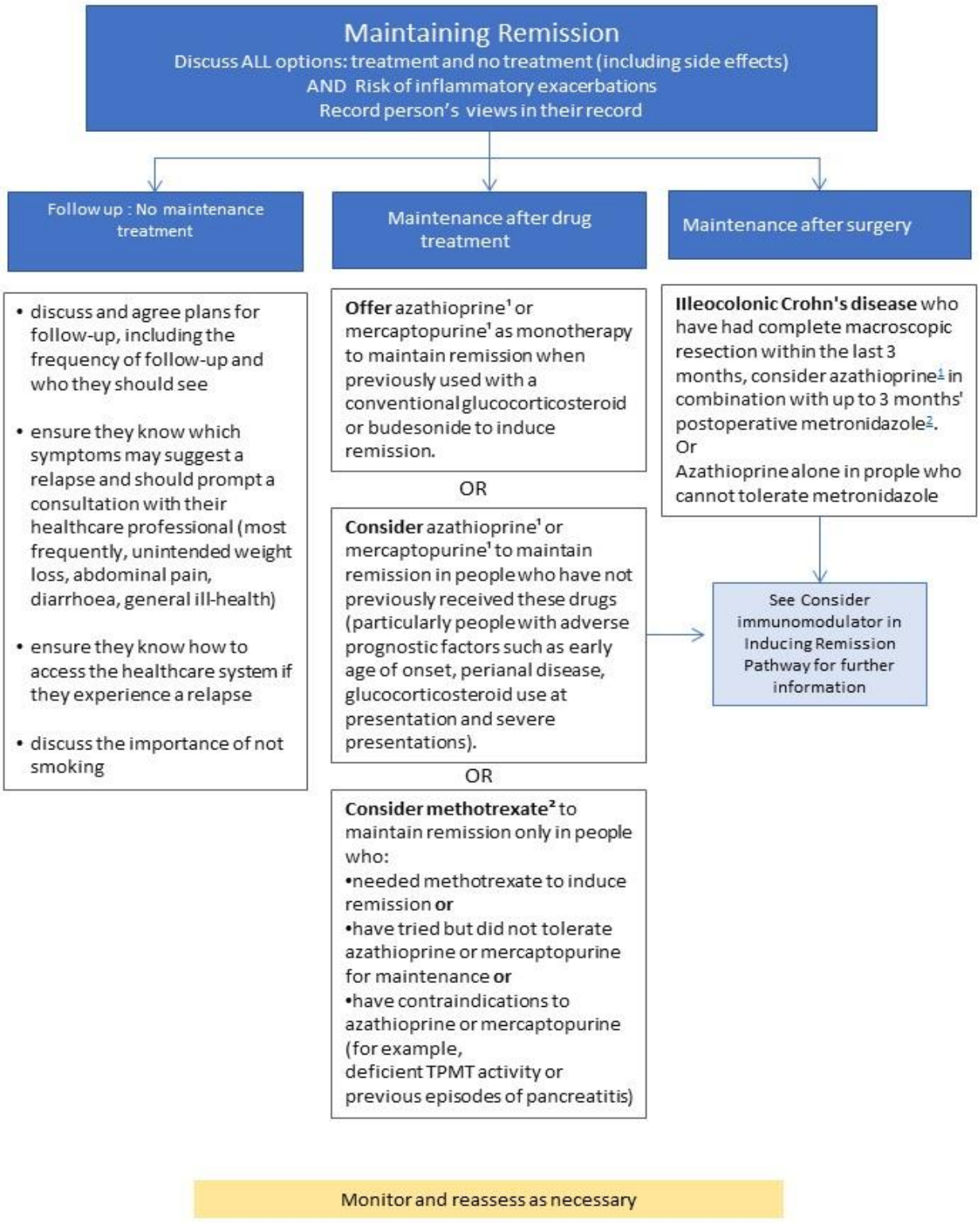


* BSG advise ileal release budesonide (Budenofalk or Entocort) where CDAI<150 but less effective than steroids where CDAI>300

$ NICE does not include Allopurinol use in its guidance, but co-prescription with thiopurines can improve tolerance in some people

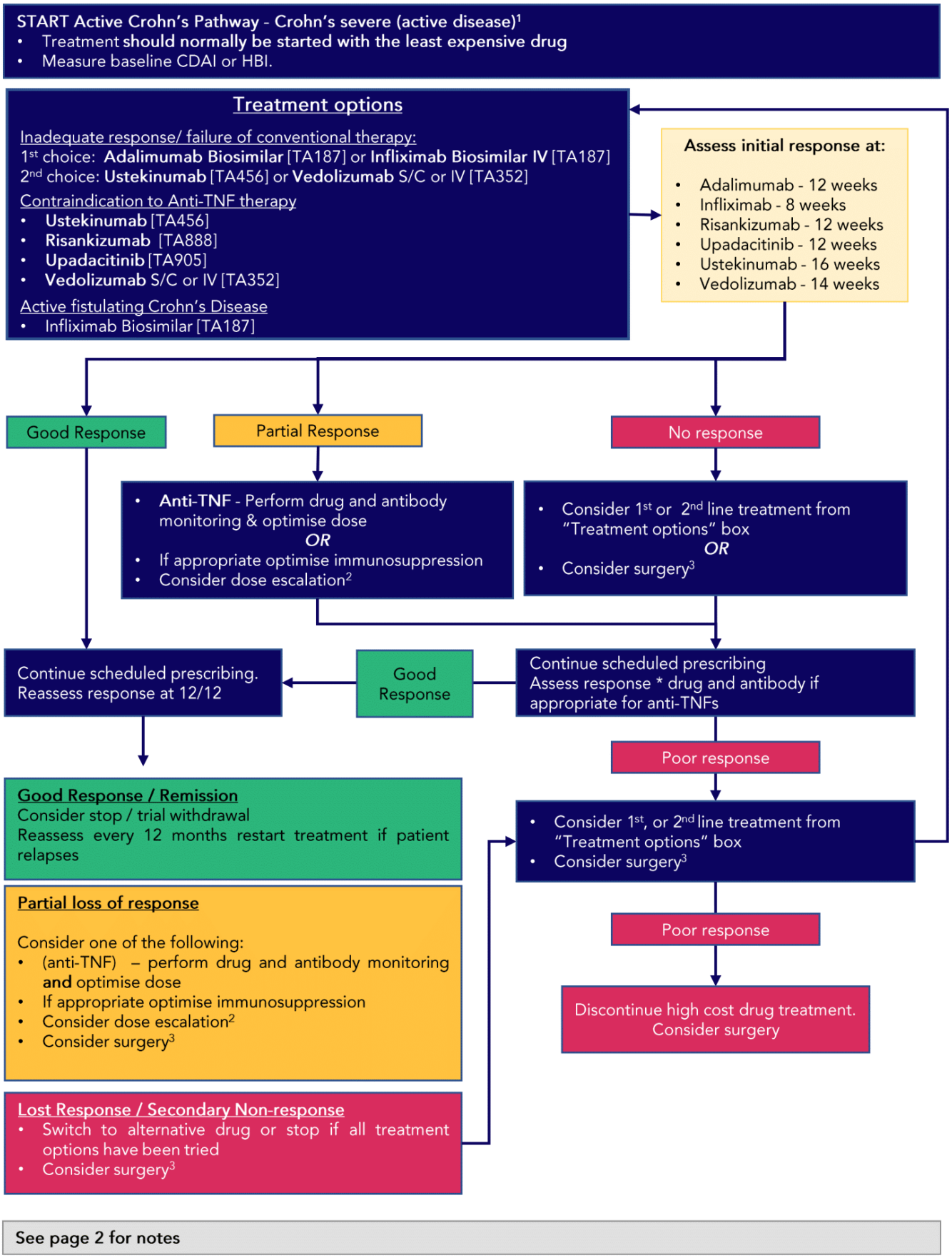
References:
1. NICE inducing remission in Crohn's disease Crohn's disease: management (2019) NICE guideline NG129
2. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults (2019)

17. Appendix 2: Maintaining Remission



Notes
1. mercaptopurine and most preparations of azathioprine did not have a UK marketing authorisation for this indication
2. not all formulations of methotrexate have UK marketing authorisation for this indication, and the licensed formulations only have a UK marketing authorisation for adults.

18. Appendix 3: Biologics Algorithm



See page 2 for notes

1) Crohn's severe (active disease) defined as normally, but not exclusively, corresponds to: Crohn's disease activity index score (CDAI) >300 **or** Harvey-Bradshaw score of >8-9 **has responded** inadequately or cannot tolerate or has medical contraindications to conventional therapies including: Corticosteroids **and/or** Immuno-modulators (e.g. 6-mercaptopurine, azathioprine. Consider contraindications, cautions and additional information.

2) Dose escalation is commissioned and allowed temporarily as below and continued as maintenance depending on response:

- Adalimumab weekly for up to 12 weeks
- Infliximab 10mg/kg for 3 doses
- Infliximab 5mg/kg six to four weekly for up to 12 weeks
- Upadacitinib 30mg once daily
- Ustekinumab 90mg 8 weekly for 16 weeks (i.e 2 doses of 8 weekly intervals)
- Vedolizumab – no dose escalation commissioned

if response to escalated dose is seen, de-escalate to standard dose if considered appropriate. Where drug levels and antibodies are adequate (anti-TNFs) and/or response to return to standard dose is lost – consider maintenance escalated dose Re-assess at 6 months and annually to determine clinical appropriateness to continue.

3) Surgery:
BSG advises that response rates decline in people with longer disease duration and that where surgery is possible it should be considered

4) Response: Treatment should only be continued if there is clear evidence of response to drug treatment defined by a decrease in Harvey-Bradshaw Index by > 3 points or CDAI by > 100 points.

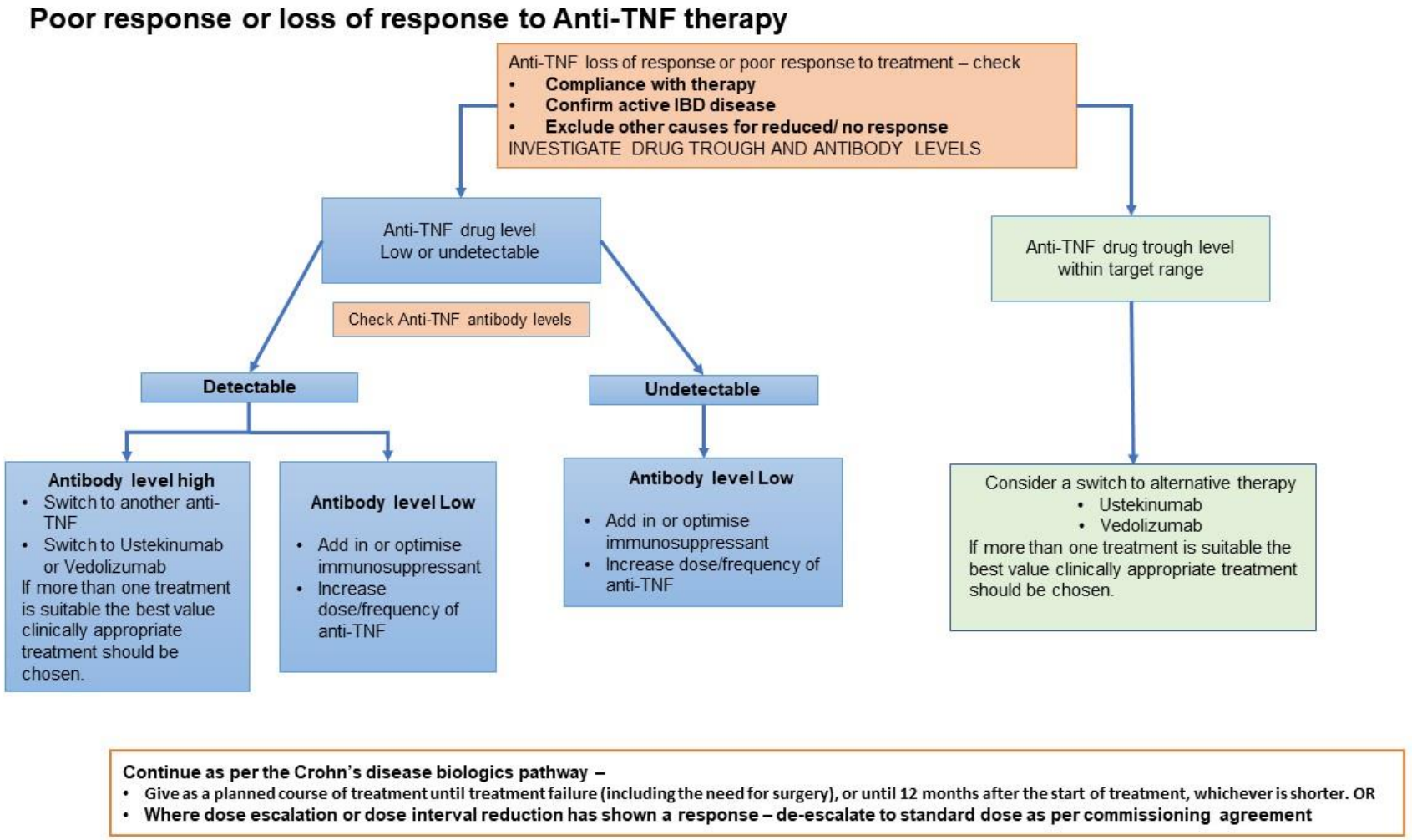
5) Disease assessment through symptoms, biomarkers and investigation including endoscopy if necessary where appropriate if not contra-indicated

19. Appendix 4: Contraindications, special warnings and precautions for treatment with drugs[3]

	Contraindications	Special warnings and precautions	Undesirable Effects / Adverse events
Anti-TNFs Infliximab SPC Adalimumab SPC	• Moderate or severe heart failure (NYHA class III/IV heart) • Tuberculosis or other severe infections such as sepsis, abscesses, and opportunistic infections • History of hypersensitivity to the active substance, to other murine proteins, or to any of the excipients	• Patients taking TNF-antagonists are more susceptible to serious infections – monitor closely for infection. • Autoimmune antibody formation • Use with caution in patients with mild heart failure (NYHA class I/II)	• Infection • Malignancy • Demyelination • Heart failure • Hepatobiliary events • Haematologic reactions
Ustekinumab SPC	• Hypersensitivity to the active substance or to any of the excipients • Clinically important, active infection (e.g. active tuberculosis)	• Ustekinumab may have the potential to increase the risk of infections and reactivate latent infections • Ustekinumab have the potential to increase the risk of malignancy • In some cases several days after treatment. Anaphylaxis and angioedema have occurred • Recommended that live viral or live bacterial vaccines are not to be given concurrently	• Infection • Malignancy • Anaphylaxis • Angioedema
Vedolizumab SPC	• Hypersensitivity to vedolizumab or to any of the excipients. • Active severe infections such as tuberculosis, sepsis, cytomegalovirus, listeriosis, and opportunistic infections such as Progressive Multifocal Leukoencephalopathy (PML)	• Acute hypersensitivity reactions including anaphylaxis. • All patients should be observed continuously during each infusion. For the first 2 infusions, they should also be observed for approximately 2 hours following completion of the infusion. All subsequent infusions, patients should be observed for approximately 1 hour following completion of the infusion. • Potential increased risk of opportunistic infections or infections for which the gut is a defensive barrier. • Monitor patients on vedolizumab for any new onset or worsening of neurological signs and symptoms	• Infection • Malignancy • Progressive Multifocal Leukoencephalopathy (PML)

[3] NB for up-to-date information on individual drug refer to https://www.medicines.org.uk/emc

20. Appendix 5: Poor response or loss of response to anti-TNF therapy



21. Appendix 6: NICE technology appraisal detail

TA187	Infliximab and adalimumab for the treatment of Crohn's disease 1. Infliximab and adalimumab, within their licensed indications, are recommended as treatment options for adults with severe active Crohn's disease (see 6) 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 4) to determine whether ongoing treatment is still clinically appropriate. 2. Treatment as described in 1 should normally be started with the less expensive drug (taking into account drug administration costs, required dose and product price per dose). This may need to be varied for individual patients because of differences in the method of administration and treatment schedules. 3. 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 4) to determine whether ongoing treatment is still clinically appropriate. 4. Treatment with infliximab or adalimumab (see 1 and 3) 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. 5. Infliximab, within its licensed indication, is recommended for the treatment of people aged 6–17 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. 6. For the purposes of this guidance, severe active Crohn's disease is defined as very poor general health and one or more symptoms such as weight loss, fever, severe abdominal pain and usually frequent (3–4 or more) diarrhoeal stools daily. People with severe active Crohn's disease may or may not develop new fistulae or have extra-intestinal manifestations of the disease. This clinical definition normally, but not exclusively, corresponds to a Crohn's Disease Activity Index (CDAI) score of 300 or more, or a Harvey-Bradshaw score of 8 to 9 or above. 7. When using the CDAI and Harvey-Bradshaw Index, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect the scores and make any adjustments they consider appropriate. 8. Treatment with infliximab or adalimumab should only be started and reviewed by clinicians with experience of TNF inhibitors and of managing Crohn's disease.
TA352	Vedolizumab for treating moderately to severely active Crohn's disease after prior therapy 1. Vedolizumab is recommended as an option for treating moderately to severely active Crohn's disease only if: 1.1. a tumour necrosis factor-alpha inhibitor has failed (that is, the disease has responded inadequately or has lost response to treatment) or 1.2. a tumour necrosis factor-alpha inhibitor cannot be tolerated or is contraindicated. 1.3. Vedolizumab is recommended only if the company provides it with the discount agreed in the patient access scheme. 2. Vedolizumab should be given as a planned course of treatment until it stops working or surgery is needed, or until 12 months after the start of treatment, whichever is shorter. At 12 months, people

	should be reassessed to determine whether treatment should continue. Treatment should only continue if there is clear evidence of ongoing clinical benefit. For people in complete remission at 12 months, consider stopping vedolizumab, resuming treatment if there is a relapse. People who continue vedolizumab should be reassessed at least every 12 months to decide whether continued treatment is justified.
TA456	Ustekinumab for moderately to severely active Crohn's disease after previous treatment 1. Ustekinumab is recommended, within its marketing authorisation, as an option for treating moderately to severely active Crohn's disease, that is, for adults who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNF-alpha inhibitor or have medical contraindications to such therapies. 2. The choice of treatment between ustekinumab or another biological therapy should be made on an individual basis after discussion between the patient and their clinician about the advantages and disadvantages of the treatments available. If more than 1 treatment is suitable, the least expensive should be chosen (taking into account administration costs, dosage and price per dose).
TA888	Risankizumab for previously treated moderately to severely active Crohn's disease 1. Risankizumab is recommended as an option for treating moderately to severely active Crohn's disease in people 16 years and over, only if: 1.1. the disease has not responded well enough or lost response to a previous biological treatment, or 1.2. a previous biological treatment was not tolerated, or 1.3. tumour necrosis factor (TNF)-alpha inhibitors are not suitable. 2. Risankizumab is only recommended if the company provides it according to the commercial arrangement. 3. If people with the condition and their clinicians consider risankizumab to be 1 of a range of suitable treatments, after discussing the advantages and disadvantages of all the options, use the least expensive. Take account of administration costs, dosage, price per dose and commercial arrangements. 4. These recommendations are not intended to affect treatment with risankizumab that was started in the NHS before this guidance was published. People having treatment outside these recommendations may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop. For young people, this decision should be made jointly by the clinician, the young person, and their parents or carers.
TA905	Upadacitinib for previously treated moderately to severely active Crohn's disease 1. Upadacitinib is recommended as an option for treating moderately to severely active Crohn's disease in adults, only if: 1.1. the disease has not responded well enough or lost response to a previous biological treatment or 1.2. a previous biological treatment was not tolerated or 1.3. tumour necrosis factor (TNF)-alpha inhibitors are contraindicated. 1.4. Upadacitinib is only recommended if the company provides it according to the commercial arrangement. 2. If people with the condition and their clinicians consider upadacitinib to be 1 of a range of suitable treatments, after discussing the advantages and disadvantages of all the options, use the least expensive. Take into account the administration costs, dosage, price per dose and commercial arrangements. 3. These recommendations are not intended to affect treatment with upadacitinib that was started in the NHS before this guidance was published. People having treatment outside these recommendations may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.