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Norfolk and Waveney Integrated Care System

ULCERATIVE COLITIS TREATMENT PATHWAY 2023

Norfolk and Waveney Integrated Care System

1. Table of Contents

2. Document Control Sheet

Title	Ulcerative colitis treatment pathway 2022
Description of policy	NWICB high cost drug pathway for ulcerative colitis
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
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2.1 Revision History

Revision Date	Summary of changes	Author(s)	Version Number
20/07/22	First draft	M. Sully	0.1
22/07/22	Formatting, minor revisions	M. Sully, A. Charlwood	0.2
05/09/22	Amended to reflect advice from specialists, added further detail to chapter 12-14	M. Sully, A. Charlwood	0.3
23/06/23	Added Ozanimod, Upadacitinib. Added note for Ustekinumab, updated supporting information (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
Name	Title	Date of Issue	Version Number

ULCERATIVE COLITIS TREATMENT PATHWAY
Assumes primary care treatment pathway has been followed
Excluding treatment of acute severe ulcerative colitis

3. Introduction

3.1 Relevant NICE technology Appraisals

Technology Appraisal*	Title
TA329	Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy
TA342	Vedolizumab for treating moderately to severely active ulcerative colitis
TA547	Tofacitinib for moderately to severely active ulcerative colitis
TA633	Ustekinumab for treating moderately to severely active ulcerative colitis
TA792	Filgotinib for treating moderately to severely active ulcerative colitis
TA828	Ozanimod for treating moderately to severely active ulcerative colitis
TA856	Upadacitinib for treating moderately to severely active ulcerative colitis

*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.

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 evidence-based medicine.

The pathway includes biologic & non-biologic agents:

- Anti-TNFs: Infliximab, Adalimumab & Golimumab
- Interleukin-12 & 23 inhibitors: Ustekinumab
- $\alpha_4\beta_7$-integrin inhibitor: Vedolizumab
- JAK-inhibitor: Filgotinib, Tofacitinib, Upadacitinib
- S1PR modulator: Ozanimod

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.

Ulcerative colitis (UC) is a chronic non-infectious inflammatory bowel disorder of unknown aetiology characterised by chronic inflammation of the large bowel. It is likely the rectum is involved, with or without a variable length of the proximal colon.

Patients present with faecal urgency, diarrhoea and rectal bleeding and extent of disease can be classified as:

- Ulcerative proctitis — inflammation is limited to the rectum and does not extend proximally to the sigmoid colon. This is more common in adults.
- Left-sided colitis — inflammation does not extend proximally beyond the splenic flexure.

- Extensive colitis — inflammation extends proximally beyond the splenic flexure, including pancolitis (disease involving the entire colon).

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[1]

4.1 Lifestyle

All patients with IBD who smoke should be encouraged to stop. UC patients may flare when stopping smoking and this should be managed, bearing in mind the overall benefits of stopping smoking. This may require a temporary increase in medication to control the flare.

4.2 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

4.3 Specialist treatments

Specialist drug treatment for ulcerative colitis is generally given for induction and maintenance of remission. Treatment options depend on the severity, extent, and pattern of disease and previous response to treatment. (The least expensive preparation should be chosen considering patient's clinical need, adherence, and side effects)

- Aminosalicylates (5-ASA) — mesalazine and sulfasalazine prescribed topically (suppository or enema) initially and orally if required.
- Corticosteroids – time-limited course topically, orally, or intravenously.
- Calcineurin inhibitors — tacrolimus or ciclosporin may be added.
- Immunosuppressive drugs — the thiopurines (azathioprine, mercaptopurine)

4.4 Inducing remission of mild-moderate first presentation or inflammatory exacerbation.[1,2]

4.4.1 Proctitis

1st line treatment

- Offer topical 5-ASA to induce remission in people with mild-moderate first presentation or inflammatory exacerbation of proctitis.
- Local specialists advise use of 1g 5-ASA nightly suppository, reducing the dose as symptoms improve.
    - Enemas may bypass the rectum and should be reserved for proctosigmoiditis or left-sided disease.
- If remission is not achieved within 4 weeks, add oral 5-ASA.
- Patients with ulcerative proctitis who do not respond or are intolerant to oral/topical 5-ASA may be switched to corticosteroid suppositories.
    - The addition of a prednisolone 5mg suppository[1] in the morning while continuing 5-ASA suppositories at bedtime is worth trying.
- If further treatment is needed where there is an incomplete response to previous therapy,
- Consider time limited (4-8 weeks) course of oral or topical corticosteroid [2] . Treatment with immunomodulators/biologic therapy may be required if unresponsive to steroids or need for maintenance therapy.

[1] BSG advises addition of a prednisolone 5mg suppository in the morning while continuing 5-ASA suppositories at bedtime is worth trying

[2] BSG advises 40mg Prednisolone once daily weaning over 6-8 weeks to induce remission

4.4.2 Proctosigmoiditis and left-sided ulcerative colitis

1st line treatment

- Offer topical 5-ASA to induce remission
- Local specialists suggest where disease is beyond the rectum **oral 5-ASA** may be started from the beginning, then continued as maintenance
    - a steroid enema may be used in place of **topical 5-ASA**
- If remission not achieved within 4 weeks,
    - add **oral 5-ASA** (high dose) to topical 5-ASA treatment ***or***
    - switch to a **high-dose oral 5-ASA** and a time limited (4-8 week) course **of topical corticosteroid**
        - e.g., steroid suppositories with or without enema, reducing the dose as symptoms improve.
- If further treatment is needed, stop topical treatment, and offer oral 5-ASA + time-limited course of oral corticosteroid
- For people who decline any topical treatment:
    - consider a **high-dose oral 5-ASA alone**
        - explain that this is not as effective as a topical 5-ASA
    - if remission is not achieved within 4 weeks, offer a time-limited course of **an oral corticosteroid in addition to the high-dose 5-ASA**.

For people who cannot tolerate 5-ASAs, consider a time-limited course of a topical or an oral corticosteroid.

*Local specialists advise that for people with proctosigmoiditis or left-sided colitis**, 5-ASA enemas each night may be beneficial**.*

4.4.3 Extensive disease[1,2]

1st line treatment

- NICE advises offer **topical 5-ASA and a high-dose oral 5-ASA 4-4.8g daily** preferably as a once daily dose to induce remission in people with mild-moderate first presentation or inflammatory exacerbation of extensive ulcerative colitis.
- If remission is not achieved within 4 weeks
    - Stop the topical 5-ASA and start high dose oral 5-ASA[2] with a time-limited course of oral corticosteroid e.g., prednisolone 40mg daily, tapering over 6-8 weeks.
    - For people who cannot tolerate 5-ASAs, offer a time limited course of oral corticosteroid. [3]

4.5 Maintaining remission[1,2]

4.5.1 After mild-to-moderate inflammatory exacerbation

4.5.1.1 Proctitis & Proctosigmoiditis

- Consider using either [4]
    - a **topical 5-ASA** alone (daily or intermittent), ***or***
    - an **oral 5-ASA** with topical **5-ASA** (daily or intermittent) ***or***
    - an **oral 5-ASA** alone though the latter may not be as effective as combined treatment or oral therapy with intermittent topical therapy.

[3] Corticosteroids such as budesonide MMX(Cortiment(®) or beclometasone dipropionate (Clipper®) can be used as alternative treatments in cases of prednisolone intolerance.)

[4] BSG advises 1g suppository used regularly at bedtime – possibly alt night or every 3rd night may be suitable

4.5.1.2 Left-sided and extensive ulcerative colitis1

- Offer a low maintenance dose of **oral 5-ASA**. (The least expensive preparation should be chosen considering patient adherence and side effects)

4.5.1.3 All extents of disease[1,2]

- Consider **oral azathioprine** or **mercaptopurine** to maintain remission:
    - after 2 or more inflammatory exacerbations in 12 months that require treatment with systemic corticosteroids[5] **or**
    - if remission is not maintained by **oral 5-ASA**.

4.5.2 After a single episode of severe UC

Consider oral azathioprine or mercaptopurine, or use an oral 5-ASA if azathioprine or mercaptopurine are contraindicated/not tolerated

4.5.3 5-ASA dosing

Consider once daily dosing for oral 5-ASA when used for maintaining remission. This regime may have more side effects but can be more effective. British society of gastroenterology (BSG) guidance advises that there is little to choose from between the different5-ASA preparations.

4.5.4 Monitoring

Therapeutic drug monitoring should be carried out at regular intervals for IBD patients as specified in the Specialist Pharmacy Service guidance to drug-monitoring, unless the local shared care arrangement states otherwise.

4.6 Medicines Adherence

Patients should be routinely asked about medicines adherence as non-adherence is common. It is estimated that 30% of all IBD patients, most frequently those on 5-ASAs, do not take their medication as prescribed. Such patients should have a review and offered strategies to improve adherence.

5. Secondary care: Biologics and Janus Kinase Inhibitors for moderate to severe active ulcerative colitis

Biologic therapy and Janus Kinase Inhibitors are useful in inducing and maintaining remission in people with severe active disease which has not responded to conventional therapy (incomplete response), or where conventional therapy is not tolerated. See appendix 1 for full algorithm.

6. Initiating treatment with high-cost drugs

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[6] 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.

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[5] Budesonide (Cortiment®), Beclometasone (Clipper®) or Prednisolone in the BSG guidance

6.1 Choice of therapy:

See Appendix 1 for full algorithm. Biosimilar Adalimumab should be selected as a first line treatment option where clinically and cost-effectively appropriate as above. In terms of cost,

- Golimumab and Ustekinumab are similar annual costs per patient per year.
- Tofacitinib is lower cost than Golimumab and Ustekinumab and therefore Tofacitinib may be a suitable treatment option for patients requiring oral therapy
- JAK inhibitors at standard maintenance dose are more cost effective than IV Vedolizumab & Ozanimod
- IV Vedolizumab is the most costly option

6.1.1 Ustekinumab

Ustekinumab (NICE TA633) can only be used first line when Anti-TNFs are not clinically suitable. It can be used second line if Anti-TNFs have responded inadequately, or patient has lost response to treatment.

6.1.2 Ozanimod

Ozanimod (NICE TA828) can only be used first line, when Infliximab is not suitable. It can be used second line if biologic treatment is not tolerated/not working well enough. Note that an ECG is required before initiation to determine whether any pre-existing cardiac abnormalities are present as per SPC.

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

See **appendix 2** for summary breakdown**.**

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

Use Mayo score to assess treatment response and to guide treatment choices. If endoscopic findings are not available, the remaining 3 categories constitute a “Modified” or “Partial” Mayo score. T&W is more suited for severe disease.

Scores should be compared to previous scores taken for a patient. The higher the score, the more severe the ulcerative colitis. Remission is a Mayo score of 2 or less.

- **Rectal bleeding**: Indicate the most severe bleeding of the day. Three points requires patients to have 50% or more of bowel movement with visible blood AND 1 or more bowel movement with blood alone
- **Clinical response** is defined as reduction of Mayo score by ≥3 points and a decrease of 30% from the baseline score with a decrease of at least 1 point on the rectal bleeding subscale or an absolute rectal bleeding score of 0 or 1
- **Clinical remission** is defined as a Mayo score ≤2 and no individual sub score>1
- **Mucosal healing** is defined as mucosa sub score of ≤1
- **Disease activity**: Mild= 3-4, Moderate 6-10, Severe 11-12

9.1 Truelove & Witts Severity Index

Symptoms	Mild	Moderate	Severe
Bowel movements (Number per day)	<4	4-6	6+ plus at least one of the features of systemic upset marked * below
Blood in stool	Small traces of blood	Between mild and severe	Visible blood
Pyrexia >37.8C*	No	No	Yes
Pulse >90bpm*	No	No	Yes
Anaemia*	No	No	Yes
ESR mm/hr*	30 or less	30 or less	>30

9.2 Mayo score

Mayo Index	0	1	2	3
Stool frequency	Normal	1-2 stools per day more than normal	3-4 stools per day more than normal	>4 stools per day more than normal
Rectal bleeding	None	Streaks of blood with stool less than half the time	Obvious blood with stool half the time or more	Passing blood alone
Mucosal appearance at endoscopy	Normal or inactive disease	Mild disease (erythema, decreased vascular pattern, mild friability)	Moderate disease (marked erythema, absent vascular pattern, friability, erosions)	Severe disease (spontaneous bleeding, ulceration)
Physician rating of disease activity	Normal	Mild disease	Moderate disease	Severe disease

9.3 Partial Mayo score

Mayo Index	0	1	2	3
Stool frequency	Normal	1-2 stools per day more than normal	3-4 stools per day more than normal	>4 stools per day more than normal
Rectal bleeding	None	Streaks of blood with stool less than half the time	Obvious blood with stool half the time or more	Passing blood alone
Physician rating of disease activity	Normal	Mild disease	Moderate disease	Severe disease

9.4 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
- High negative predictive value, low positive predictive value
- May be useful biomarker for endoscopic histological disease activity to inform treatment
- 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

9.5 Treatment response review for high-cost drug therapy[3]

Treatment should only be continued if there is clear evidence of response to drug treatment. 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
Filgotinib	10 weeks – continue till 22 weeks if needed for induction
Golimumab	12 weeks
Infliximab	8 weeks
Ozanimod	10 weeks
Tofacitinib	8 weeks – continue till 16 weeks if needed for induction
Upadacitinib	8 weeks – continue till 16 weeks if needed for induction
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:

- Adalimumab weekly for up to 12 weeks
- Infliximab biosimilar 10mg/kg every 8 weeks for 3 doses
- Infliximab biosimilar 5mg/kg four to six weekly for up to 12 weeks (i.e., 2-3 doses over 12 weeks)
- Tofacitinib 10mg twice daily
- 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 –

- **Anti-TNFs** - In patients with clear objective evidence of response to escalated dose (e.g., Anti-TNF drug & antibody level) consider trial of maintenance escalated dose.
- **Ustekinumab** - De-escalate to standard dose if considered clinically appropriate. In patients with clear objective evidence of response to escalated dose and/or loss of response on de-escalation to standard dose consider trial of maintenance escalated dose.

- **JAK inhibitors** - Maintain elevated dose.

This maintenance escalated dose is commissioned for:

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

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.

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 routinely required.

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. Perioperative infection risk management

By temporarily discontinuing a patient's biologic medication, the chance of a post-operative infection should be reduced, but this should be carefully weighed against the risk of a peri-operative flare. Consider halting medication 3-5 half-lives before surgery if there is a high chance of infection or if infection could cause substantial harm. As shown in the table below, some biologics need up to 23 weeks to achieve 3-5 half lives.

Locally, there are joint guidelines for the management of interruption of biologic therapies for elective surgery in adults and children, produced by the rheumatology departments across the NWICB, which suggest a shorter interruption of biologic treatment may be appropriate[4]. For further information refer to the guidance linked.

Biologic	Mean half-life as per SPC	Time to stop treatment prior to surgery (3-5 half-lives)	Local guidelines; Time between last dose and surgery
Tofacitinib	3 hours	1 day	2 days
Filgotinib	19 hours	2-4 days	2 days
Upadacitinib	11.5 hours	1.5-3 days	2 days
Infliximab	8-9.5 days	4-7 weeks	5, 7 or 9 weeks
Adalimumab	2 weeks	6-10 weeks	3 weeks
Golimumab	12 days	5-9 weeks	5 weeks
Ustekinumab	15-32 days	7-23 weeks	13 weeks
Vedolizumab	26 days	11-19 weeks	No guidance

Post-operatively, once infection has been ruled out and the wound has healed, treatment should resume. Consider maintaining treatment in situations when there is a low chance of infection or a high risk of illness flare-up. If possible, surgery might be planned for a period when it is anticipated that drug levels will be low.

13. 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:

13.1 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%).

13.2 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.

13.3 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.

13.4 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.

14. Pregnancy & breastfeeding

14.1 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.

14.1.1 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
Filgotinib	No, use effective contraceptive during and for 1 week following treatment.		
Golimumab	No data		
Infliximab	Yes	Stop at 16 weeks	No
Ozanimod	No, use effective contraceptive during and for 3 months following treatment.		
Tofacitinib	No - contraindicated		
Upadacitinib	No - contraindicated		
Ustekinumab	No data		
Vedolizumab	No, use effective contraception until 18 weeks after last dose		

14.2 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.

14.2.1 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
Filgotinib	No - Contraindicated
Golimumab	Wait 6 months until after stopping to breastfeed
Infliximab	Wait 6 months until after stopping to breastfeed
Ozanimod	No - Contraindicated
Tofacitinib	No - Contraindicated
Upadacitinib	No - Contraindicated
Ustekinumab	Wait 15 weeks until after stopping to breastfeed
Vedolizumab	Consider benefit of therapy vs potential risks to the infant

15. Correspondence

15.1 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)

15.2 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

16. References

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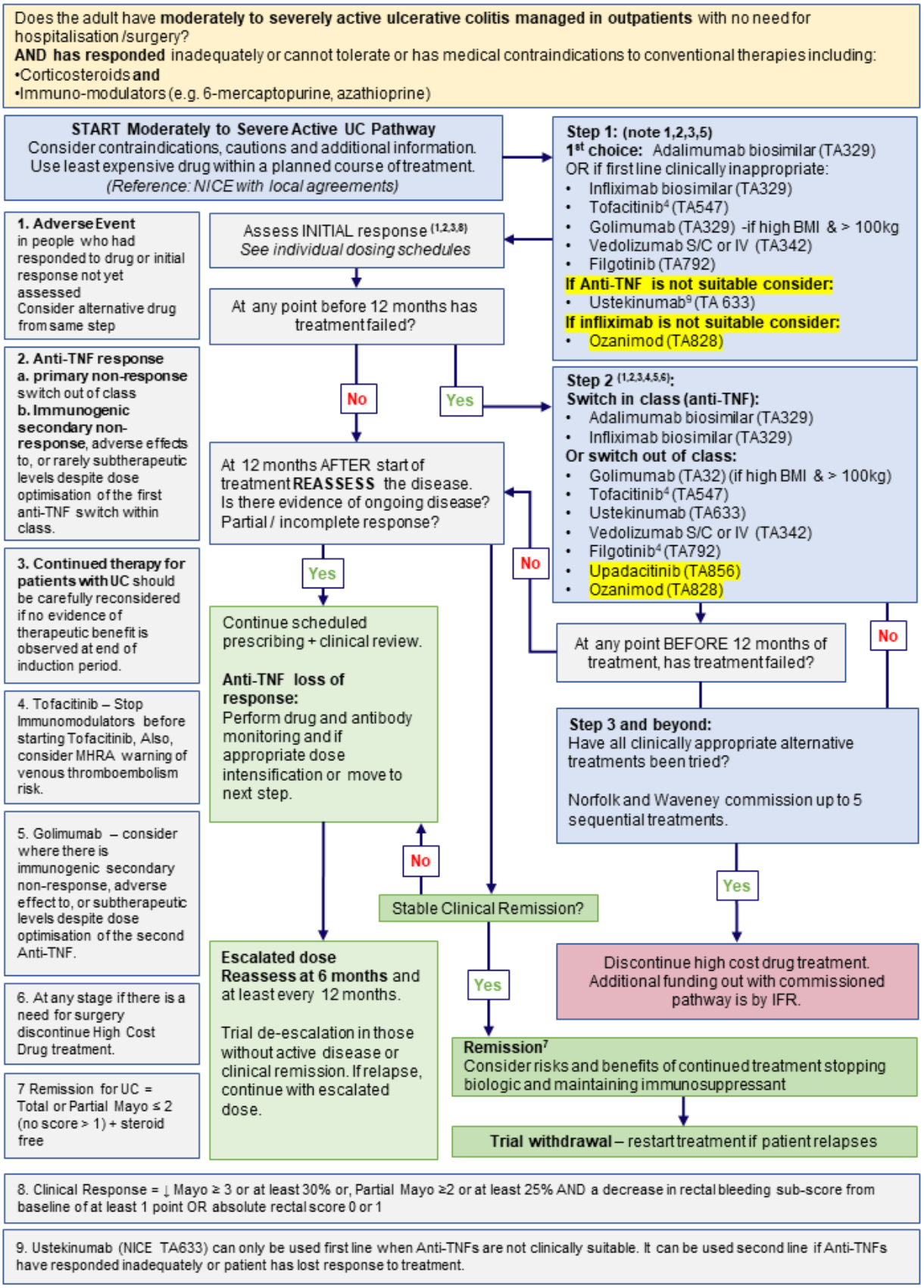
17. Appendix 1 - High-Cost Drugs Pathway



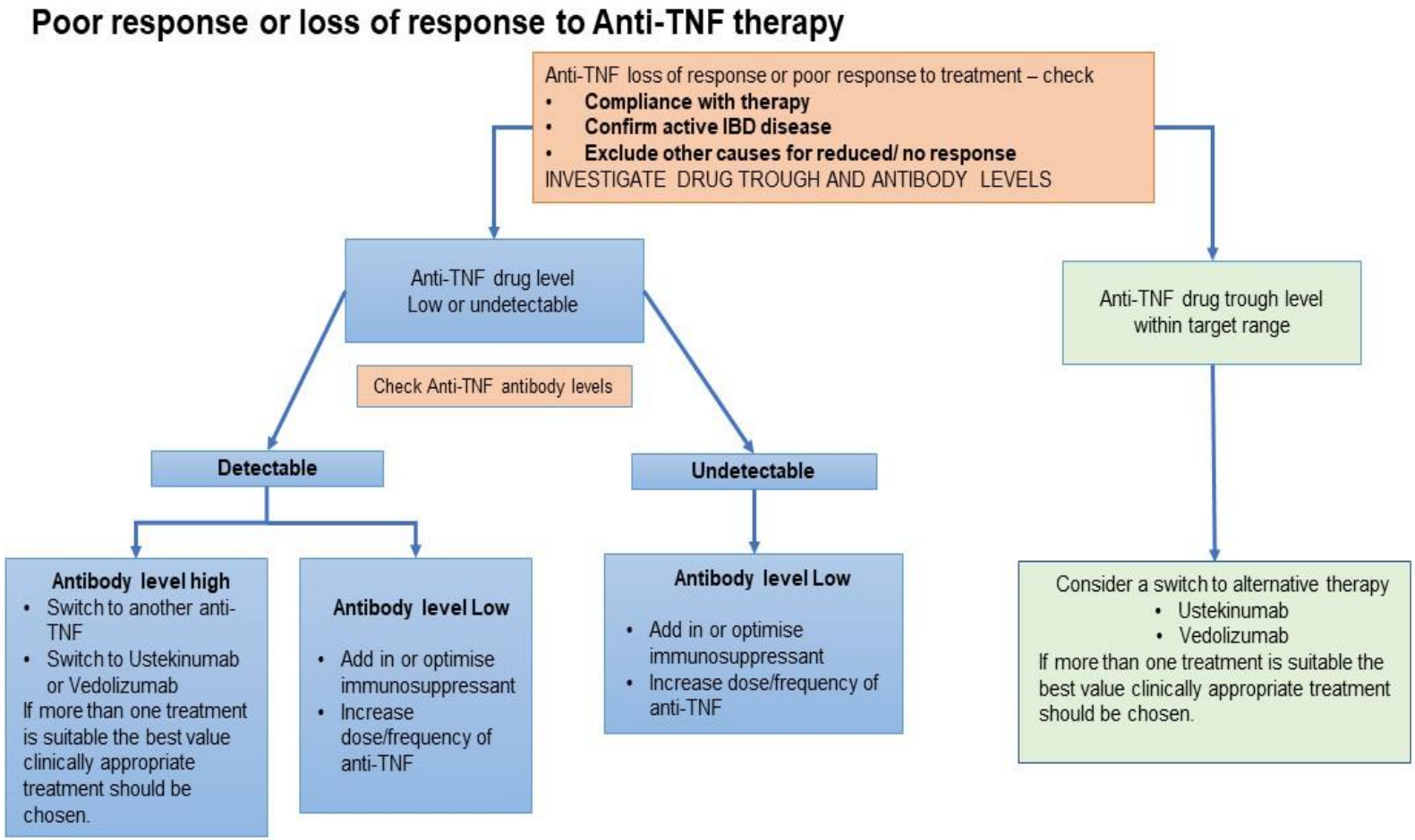
18. Appendix 2 – Contraindications, special warnings, and precautions for treatment with drugs

	Contraindications	Special warnings and precautions	Undesirable Effects / Adverse events
Anti-TNFs Infliximab SPC, Adalimumab SPC Golimumab SPC	• Moderate or severe heart failure (NYHA class III/IV heart) • Tuberculosis[6] 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 increase the risk of infections & reactivate latent infections • Ustekinumab may 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)

[6] In acute severe ulcerative colitis waiting for result of Quantiferon test to rule out tuberculosis may not be possible. The decision should be made by the consultant gastroenterologist with referral for respiratory opinion if appropriate.

Tofacitinib SPC See section 5.1 for further information about MHRA warning	• Known risk factors for venous thromboembolism in addition to the underlying disease • Use of combined hormonal contraceptives or hormone replacement therapy, Heart failure, Previous venous thromboembolism, either deep venous thrombosis or pulmonary embolism, Inherited coagulation disorder, Malignancy, Patients undergoing major surgery • Hypersensitivity to the active substance or to any of the excipients • Active tuberculosis (TB), serious infections such as sepsis, or opportunistic infections • Severe hepatic impairment • Pregnancy and lactation	• Considering the increased risk of serious infections, myocardial infarction, and malignancies with tofacitinib in patients over 65 years of age, tofacitinib should only be used in these patients if no suitable treatment alternatives are available. • Use should be avoided in combination with biologics such as TNF antagonists, interleukin (IL)-1R antagonists, IL-6R antagonists, anti-CD20 monoclonal antibodies, IL-17 antagonists, IL-12/IL-23 antagonists, anti-integrins, selective co-stimulation modulators and potent immunosuppressants such as azathioprine, 6-mercaptopurine, ciclosporine and tacrolimus because of the possibility of increased immunosuppression and increased risk of infection. • Tofacitinib should not be initiated in patients with active infections, including localised infections • Tuberculosis • Viral reactivation and cases of herpes virus reactivation	• headache, nasopharyngitis, nausea, and arthralgia. • gastrointestinal disorders and infections • infections

19. Appendix 3 – Poor response or loss of response to anti-TNF therapy



20. Appendix 4 – NICE technology appraisal detail

TA329	Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy 1. Infliximab, adalimumab and golimumab are recommended, within their marketing authorisations, as options for treating moderately to severely active ulcerative colitis in adults whose disease has responded inadequately to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or who cannot tolerate, or have medical contraindications for, such therapies. 1.1. Golimumab is recommended only if the company provides the 100 mg dose of golimumab at the same cost as the 50 mg dose, as agreed in the patient access scheme. 2. The choice of treatment between infliximab, adalimumab or golimumab should be made on an individual basis after discussion between the responsible clinician and the patient about the advantages and disadvantages of the treatments available. This should take into consideration therapeutic need and whether or not the patient is likely to adhere to treatment. If more than 1 treatment is suitable, the least expensive should be chosen (taking into account administration costs, dosage and price per dose). 3. Infliximab is recommended, within its marketing authorisation, as an option for treating severely active ulcerative colitis in children and young people aged 6–17 years whose disease has responded inadequately to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or who cannot tolerate, or have medical contraindications for, such therapies. 4. Infliximab, adalimumab or golimumab should be given as a planned course of treatment until treatment fails (including the need for surgery) or until 12 months after starting treatment, whichever is shorter. Specialists should then discuss the risks and benefits of continued treatment with the patient, and their parent or carer if appropriate: 5. They should continue treatment only if there is clear evidence of response as determined by clinical symptoms, biological markers and investigation, including endoscopy if necessary. People who continue treatment should be reassessed at least every 12 months to determine whether ongoing treatment is still clinically appropriate. 6. They should consider a trial withdrawal from treatment for all patients who are in stable clinical remission. People whose disease relapses after treatment is stopped should have the option to start treatment again.
TA342	Vedolizumab for treating moderately to severely active ulcerative colitis 1. Vedolizumab is recommended, within its marketing authorisation, as an option for treating moderately to severely active ulcerative colitis in adults only if the company provides vedolizumab with the discount agreed in the patient access scheme. 2. Vedolizumab should be given until it stops working or surgery is needed. At 12 months after the start of treatment, people should be reassessed to see 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 see whether continued treatment is justified.
TA547	Tofacitinib for moderately to severely active ulcerative colitis 1. Tofacitinib is recommended, within its marketing authorisation, as an option for treating moderately to severely active ulcerative colitis in adults when conventional therapy or a biological agent cannot be tolerated or the disease has responded inadequately or lost response to treatment. It is recommended only if the company provides tofacitinib with the discount agreed in the commercial arrangement.
TA633	Ustekinumab for treating moderately to severely active ulcerative colitis

	1. Ustekinumab is recommended as an option for treating moderately to severely active ulcerative colitis in adults when conventional therapy or a biological agent cannot be tolerated, or the disease has responded inadequately or lost response to treatment, only if: 2. a tumour necrosis factor-alpha inhibitor has failed (that is the disease has responded inadequately or has lost response to treatment) **OR** 3. a tumour necrosis factor-alpha inhibitor cannot be tolerated or is not suitable, **AND** 4. the company provides ustekinumab at the same price or lower than that agreed with the Commercials Medicines Unit. 5. This recommendation is not intended to affect treatment with ustekinumab that was started in the NHS before this guidance was published. People having treatment outside this recommendation 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.
TA792	Filgotinib for treating moderately to severely active ulcerative colitis 1. Filgotinib is recommended, within its marketing authorisation, as an option for treating moderately to severely active ulcerative colitis in adults: 1.1. when conventional or biological treatment cannot be tolerated, **OR** 1.2. if the disease has not responded well enough or has stopped responding to these treatments, **AND** 1.3. if the company provides Filgotinib according to the commercial arrangement.
TA828	Ozanimod for treating moderately to severely active ulcerative colitis 1. Ozanimod is recommended as an option for treating moderately to severely active ulcerative colitis in adults, only if: 1.1. conventional treatment cannot be tolerated or is not working well enough and infliximab is not suitable, **OR** 1.2. biological treatment cannot be tolerated or is not working well enough, **AND** 1.3. the company provides it according to the commercial arrangement.
TA856	Upadacitinib for treating moderately to severely active ulcerative colitis 1. Upadacitinib is recommended, within its marketing authorisation, as an option for treating moderately to severely active ulcerative colitis in adults: 1.1. when conventional or biological treatment cannot be tolerated, or 1.2. if the condition has not responded well enough or has stopped responding to these treatments, and 1.3. if the company provides upadacitinib according to the commercial arrangement. 2. Choose the most appropriate treatment after discussing the advantages and disadvantages of the treatments available with the person having treatment. If patients and clinicians consider upadacitinib to be one of a range of suitable options, choose the least expensive treatment (taking into account drug administration costs, dose needed and frequency, and product price per dose).

21.