Biologics pathways for Inflammatory Bowel Disease in Adults

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Version 2.0
This version supersedes version 1.0

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DOCUMENT CONTROL

Revision history

The latest and master version of this document is held on the GMMMG website.

REVISION DATE	ACTIONED BY	SUMMARY OF CHANGES	VERSION
September 2017	IBD working group	Added ustekinumab following publication of NICE TA456	1.1
October 2017	IBD working group	Changes to special situations	1.2
November 2017	IBD working group	Changes made following consultation	1.3
November 2017	Sarah Jacobs	Final changes to vaccinations & special situations. Amendments to flow charts.	1.4

Changes to version 1.0

The pathway has been updated with the following additions:

- Ustekinumab for the treatment of moderate to severe Crohn's disease (NICE TA456)
- Ustekinumab has been added to the pathway in all relevant sections.

Other minor amendments have been made as follows:

- Cover sheet
- Added statement regarding the use of NICE approved treatments between iterations of the IBD pathway.
- Changed IFR wording to include ustekinumab.
- Added a statement about switching between treatments.

Approvals

This document must be approved by the following before distribution:

NAME	DATE OF ISSUE	VERSION
IBD working group	November 2017	1.4
HCDSG	November 2017	1.4
GMMMG	December 2017	2.0

Final version available on GMMMG website

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Biologics Pathways for Inflammatory Bowel Disease in Adults

1. Background

These pathways are to be used as guidelines in the initiation and maintenance of biologic agents in the management of inflammatory bowel disease (IBD). These pathways have been written using up to date published research and evidenced based medicine. This has been a clinical project implemented by MAHSC and a joint project between the gastroenterology departments of the Greater Manchester hospital trusts.

2. NICE guidance

The links to relevant NICE guidance are listed below. Any new high cost drugs that are approved by NICE between GMMMG IBD pathway iterations will be considered for placement in this pathway. The use of any new NICE approved high cost drugs prior to inclusion in the pathway will be allowed, provided that the total number of drugs allowed in pathway has not been exceeded. 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.

2.1. Crohn's disease

NICE (2012 - updated 2016): Crohn's disease: management CG152[1]

a) NICE (2010): Infliximab and adalimumab for the treatment of Crohn's disease TA187[2]

Infliximab and adalimumab, are recommended as treatment options for adults with severe active Crohn's disease whose disease has not responded to conventional therapy (immunosuppressive and/or corticosteroid) or who are intolerant of or have contraindications to such therapy.

Severe active Crohn's disease is defined as very poor general health, plus ≥1 symptom of: weight loss, fever, severe abdominal pain, and 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 > 300, or a Harvey-Bradshaw score (see section 8) of >8.

Infliximab is recommended as 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.

Biologic treatment should normally be started with the less expensive drug as per GMMMG (2016): Prescribing of high cost biosimilar biological medicines.

Infliximab or adalimumab should be given until treatment failure, or the need for surgery, or until 12 months after the start of treatment, whichever is shorter. People should then have their disease reassessed to determine whether on-going treatment is still clinically appropriate. Treatment should only be continued if there is clear evidence of on-going active disease as determined by clinical symptoms, biological markers and investigation, including endoscopy if necessary.

People who continue treatment should have their disease reassessed at least every 12 months to determine whether on-going treatment is still clinically appropriate.

A trial withdrawal should be considered in patients in stable clinical remission.

People whose disease relapses after treatment is stopped should have the option to start treatment again.

b) NICE (2015): Vedolizumab for treating moderately to severely active Crohn's disease after prior therapy TA352[3]

Vedolizumab is recommended as an option for treating moderately to severely active Crohn's disease only if a tumour necrosis factor-alpha inhibitor has failed (that is, the disease has responded inadequately or has lost response to treatment), or a tumour necrosis factor-alpha inhibitor cannot be tolerated or is contraindicated.

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 on-going clinical benefit. People who continue vedolizumab should be reassessed at least every 12 months to decide whether continued treatment is justified. For people in complete remission at 12 months, consider stopping vedolizumab, resuming treatment if there is a relapse.

Vedolizumab is recommended only if the company provides it with the discount agreed in the patient access scheme.

c) NICE (2017): Ustekinumab to treat moderately to severe Crohn's disease after previous treatment TA456[4]

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.

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).

Ustekinumab should be given 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 in accordance with NICE's recommendations for infliximab and adalimumab for the treatment of Crohn's disease (NICE TA187) to see whether treatment should continue.

d) **Golimumab** has not been included in clinical trials for Crohn's disease and is not licensed for use in Crohn's disease. Therefore it is should not be considered as a treatment option for Crohn's disease, even as an individual funding request.

2.2. Ulcerative colitis

NICE (2013): Ulcerative colitis: management CG166[5]

a) NICE (2015): Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy TA329[6]

Infliximab, adalimumab and **golimumab** are recommended, as options for treating moderately to severely active ulcerative colitis in adults whose disease has responded inadequately to conventional therapy (e.g. corticosteroids, mercaptopurine or azathioprine), or who cannot tolerate them, or who have a medical contraindication for such therapies.

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.

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.

Therapy should be given as a planned course until treatment fails (including the need for surgery) or until 12 months after starting treatment, whichever is shorter. The treatment should be continued 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 on-going treatment is still clinically appropriate.

A trial withdrawal from treatment should be considered 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.

b) NICE (2008): Infliximab for acute exacerbations of ulcerative colitis TA163[7]

Infliximab is recommended as an option for the treatment of acute exacerbations of severely active ulcerative colitis. It is only recommended in patients in whom ciclosporin is contraindicated or clinically inappropriate, based on a careful assessment of the risks and benefits of treatment in the individual patient. Infliximab in this guidance relates to only an induction course of three doses of infliximab.

Treatment of acute exacerbations of UC with infliximab or ciclosporin should be the decision of the responsible gastroenterologist.

The guidance on continuation of treatment is covered by NICE TA329 (see section 2.2a).

c) NICE (2015): Vedolizumab for treating moderately to severely active ulcerative colitis TA342[8]

Vedolizumab is recommended as an option for treating moderately to severely active ulcerative colitis only if the company provides vedolizumab with the discount agreed in the patient access scheme.

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 on-going clinical benefit. People who continue vedolizumab should be reassessed at least every 12 months to see whether continued treatment is justified. For people in complete remission at 12 months, consider stopping vedolizumab, resuming treatment if there is a relapse.

3. Biosimilars

In February 2016 the British Society of Gastroenterology (BSG) published guidance on the use of biosimilar infliximab in inflammatory bowel disease:

BSG (2016): Guidance on the Use of Biosimilar Infliximab in Inflammatory Bowel Disease [9]

The guidance states that there is sufficient data from observational studies to show that safety and clinical efficacy of biosimilar infliximab are comparable to the originator drug, with similar immunogenicity, and that switching from Remicade to a biosimilar is safe and effective.

GMMMG (2016): Prescribing of high cost biosimilar biological medicines.is available for adoption by gastroenterology centres using this pathway.

a) Initiating treatment with a biologic

- The choice of biologic used should be guided by clinical judgement, national or local guidance, and the overall value proposition offered by the individual medicines. The rationale for choice should be documented.
- If more than one treatment is suitable, the least expensive should be chosen (taking into account administration costs, dosage, price per dose and treatment frequency).
- When the biologic treatment with a particular drug has been selected, the least expensive product, either biosimilar or originator should be prescribed.
- If the least expensive product is not prescribed, the reasons why must be documented and made available to commissioners if required.
- Where NICE has already recommended the originator biological medicine, the same guidance will apply to the biosimilar medicine.

- In line with the MHRA guidance (2008): Biosimilar products biologics, including biosimilars must be prescribed by brand name (i.e. the brand of biosimilar or originator product) to support on-going pharmacovigilance of the individual products.

- Pharmacovigilance is essential for any new biological medicine including biosimilars and additional monitoring is indicated through the Black Triangle Scheme. Patients prescribed a biologic should be enrolled on to the relevant biologic registry which serve data collection on the safety and effectiveness of medicines in clinical practice.

b) Changing from originator to a biosimilar

- There is accumulating evidence that patients who are in a stable clinical response or remission may be changed over to a biosimilar at the same dose and dose interval as the originator drug. This should only be done after discussion and agreement with individual patients with an explanation for the reason for changing.

- The switch from a biologic originator medicine to a biosimilar should be done at the point of prescribing and not at the point of dispensing or administration.

4. Individual funding requests (IFR)

- IFRs for Crohn's disease will not be required for any of the 4 biologics included in this pathway.

- IFRs for ulcerative colitis will not be required for any of the 4 biologics included in this pathway.

- All treatment options exceeding the allowed number of biologics or drugs not included in this pathway will require commissioner's funding approval via IFR prior to commencing the treatment.

- Golimumab has not been included in clinical trials for Crohn's disease and is not licensed for use in Crohn's disease. Therefore it is should not be considered as a treatment option for Crohn's disease, even as an individual funding request.

- Blueteq forms which comply with these pathways are available. Where Blueteq has been introduced to the trust as part of the contractual arrangements, funding approval for the PbR excluded high cost drugs will be required by submission of the relevant Blueteq form prior to treatment administration. The Blueteq forms contain a list of relevant criteria that the patient must meet in order to secure funding. Any patients who do not meet these criteria will require an IFR.

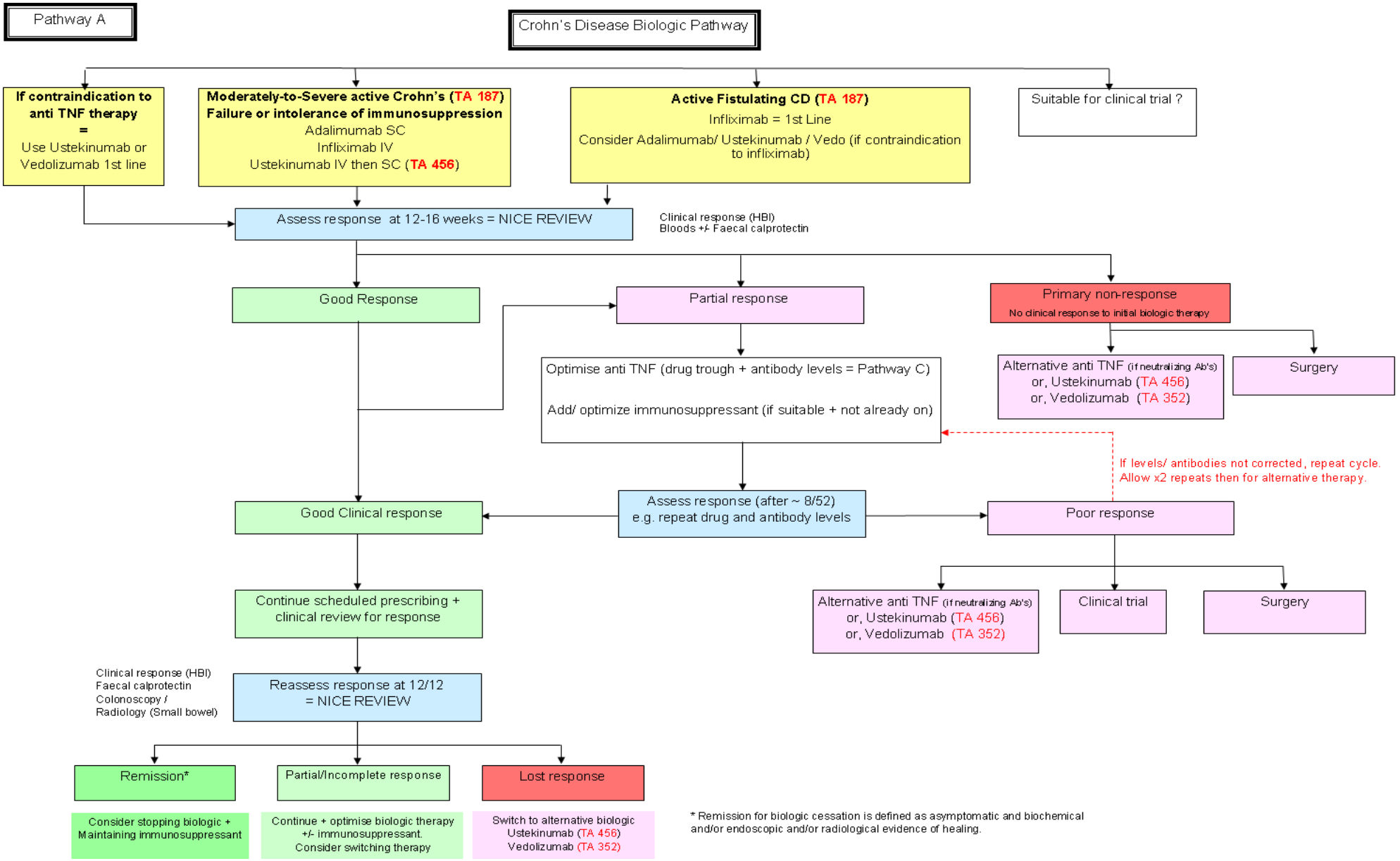
5. Checklist for Patient Screening on Initiation of Biologic Agents

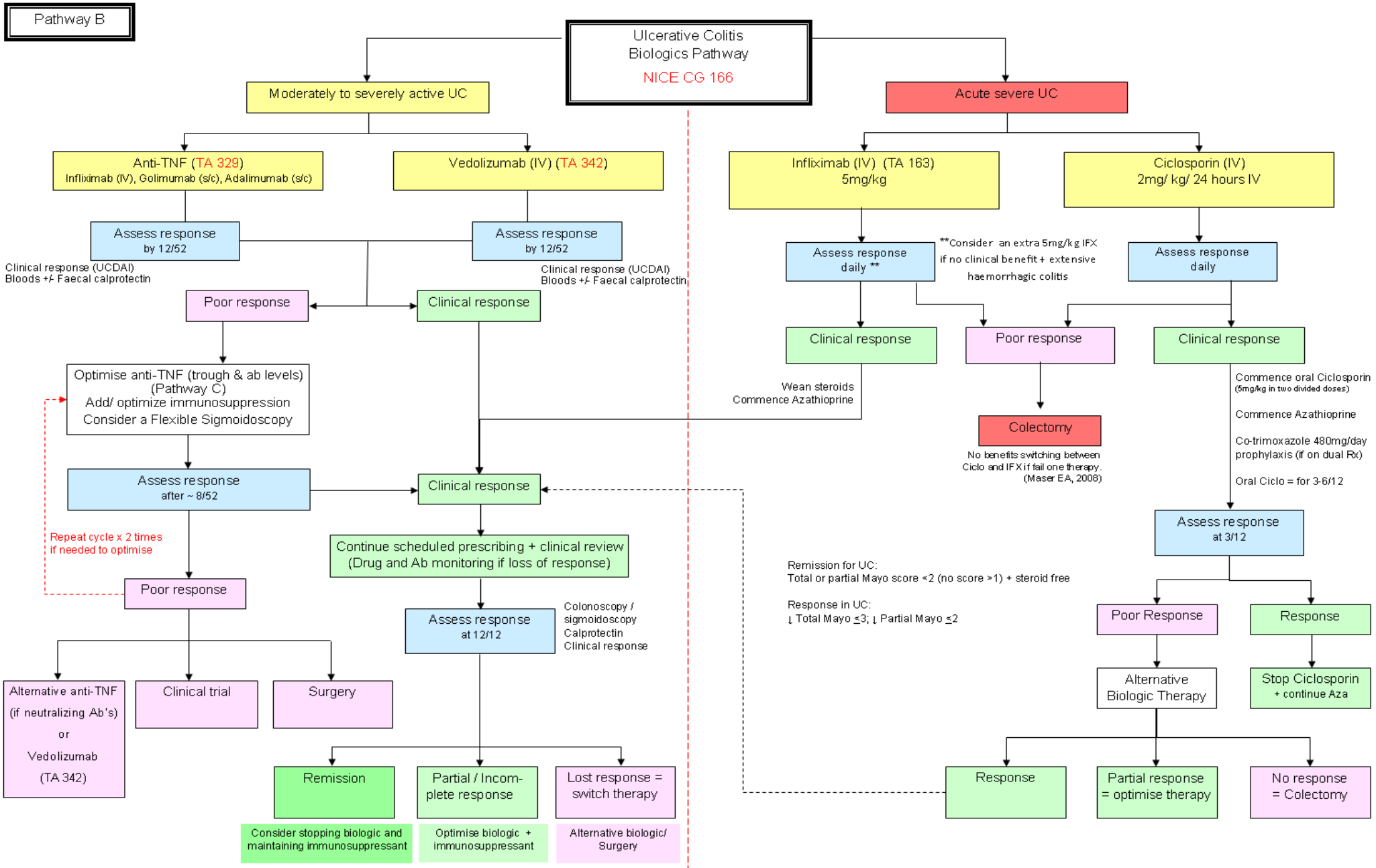
Name:……**Number:**……**Consultant:**……

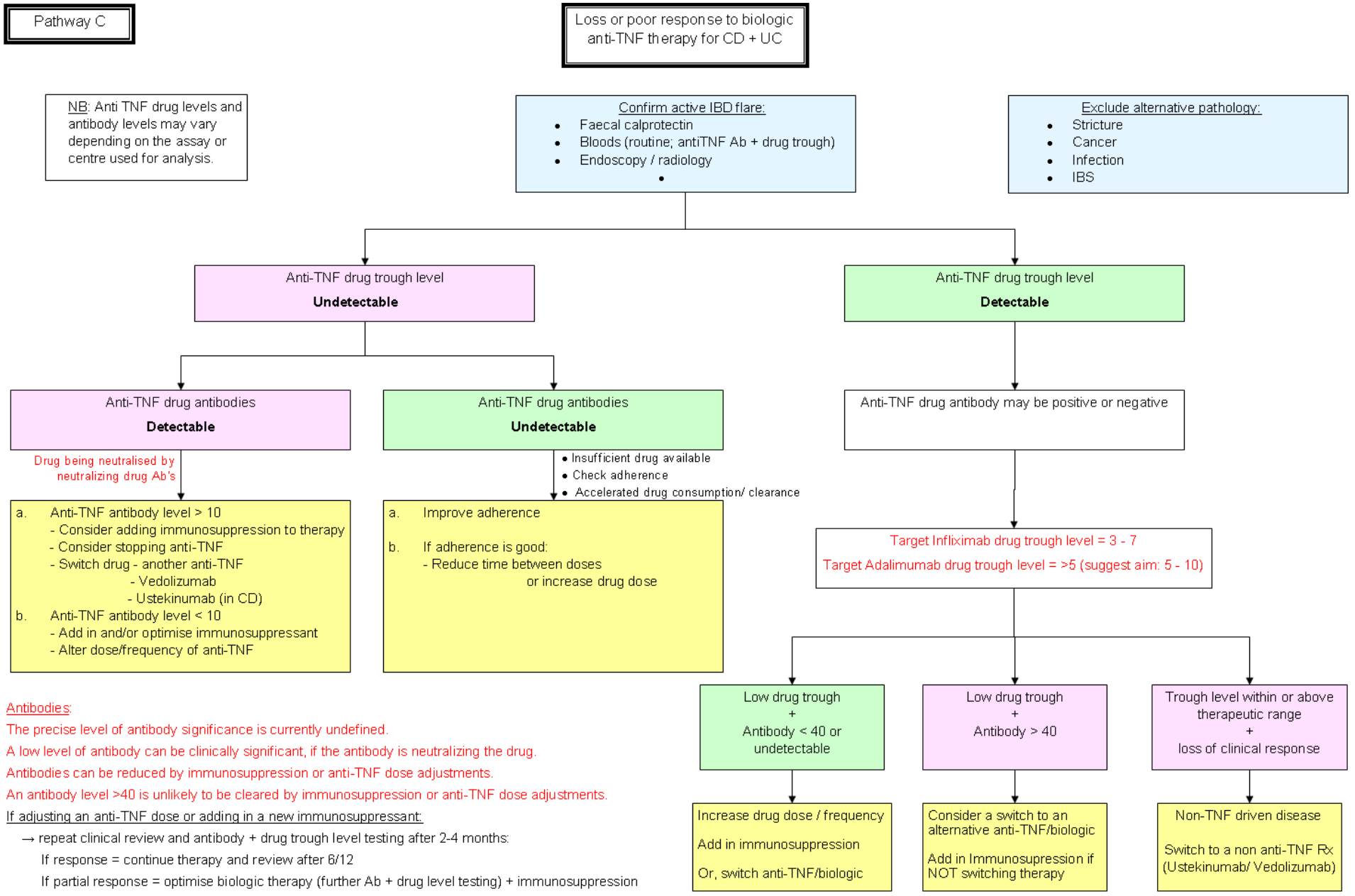
Screening Investigations Requested in Clinic			
	Y/N	**Initial**	**Results/Details**
FBC/U&E/LFT/CRP			
HIV **HBV** *(surface antigen, core antibody)*. *Reactivation has been reported in HbsAg-ve as well as HbsAg +ve patients stressing the importance of measuring not only HbsAg but also antibodies against HBc antigen to identify positive carrier status* **HCV** *(antibody test)* Consider **EBV, CMV** testing. *If positive result consider Hepatology/GUM referral*			
Varicella Zoster IgG (If negative inform GP and patient)			
TB screening *(g-IFN testing)* *If positive refer to Respiratory Unit*			
Chest X-Ray *(within the last 6 months)* **CXR checked by/date:**			
TPMT (Before commencing azathioprine therapy)			
Consider:			
Faecal Calprotectin level			
Ferritin, Vitamin B12, Folate levels			
Screening Questions Asked in Clinic			
	Y/N	**Initial**	**Details**
Previous TB/TB contact/ recent travel to high risk countries (*details*)			
History of demyelinating disorders of the CNS *(e.g. MS)* *(details)*			
History of heart failure (NYHA class III or IV) *(details)*			
History of recurrent infection *(details)*			
History of cancer *(Type/Date when occurred/Date of all clear)*			
Date of last mammogram (50yr +) *(Encourage patient to visit GP if >3 years)*			
Date of last smear (25yr +) *(Encourage patient to visit GP if >3 years)*			
History of infusion reaction to any agent *(To what/type of reaction)*			
Allergy (*details)*			
Education and Funding			
	Initial	**Details**	
Request for funding			
Pregnancy/breastfeeding advice given			
Influenza vaccine advice given			
Pneumococcal vaccine advice given			
Patient counselled and educated			
Patient education pack given			

Completing Clinician Signature…… Date…….....

Nurse Practitioner Signature…… Date…….....


Pathway A
Crohn's Disease Biologic Pathway
If contraindication to anti TNF therapy = Use Ustekinumab or Vedolizumab 1st line
Moderately-to-Severe active Crohn's (TA 187) Failure or intolerance of immunosuppression Adalimumab SC Infliximab IV Ustekinumab IV then SC (TA 456)
Active Fistulating CD (TA 187) Infliximab = 1st Line Consider Adalimumab/ Ustekinumab / Vedo (if contraindication to infliximab)
Suitable for clinical trial ?
Assess response at 12-16 weeks = NICE REVIEW
Clinical response (HBI) Bloods +/- Faecal calprotectin
Good Response
Partial response
Primary non-response No clinical response to initial biologic therapy
Optimise anti TNF (drug trough + antibody levels = Pathway C)
Add/ optimize immunosuppressant (if suitable + not already on)
Alternative anti TNF (if neutralizing Ab's) or, Ustekinumab (TA 456) or, Vedolizumab (TA 352)
Surgery
If levels/ antibodies not corrected, repeat cycle. Allow x2 repeats then for alternative therapy.
Good Clinical response
Assess response (after ~ 8/52) e.g. repeat drug and antibody levels
Poor response
Continue scheduled prescribing + clinical review for response
Alternative anti TNF (if neutralizing Ab's) or, Ustekinumab (TA 456) or, Vedolizumab (TA 352)
Clinical trial
Surgery
Clinical response (HBI) Faecal calprotectin Colonoscopy / Radiology (Small bowel)
Reassess response at 12/12 = NICE REVIEW
Remission*
Partial/Incomplete response
Lost response
Consider stopping biologic + Maintaining immunosuppressant
Continue + optimise biologic therapy +/- immunosuppressant. Consider switching therapy
Switch to alternative biologic Ustekinumab (TA 456) Vedolizumab (TA 352)
* Remission for biologic cessation is defined as asymptomatic and biochemical and/or endoscopic and/or radiological evidence of healing.


Pathway B
Ulcerative Colitis
Biologics Pathway
NICE CG 166
Moderately to severely active UC
Acute severe UC
Anti-TNF (TA 329)
Infliximab (IV), Golimumab (s/c), Adalimumab (s/c)
Vedolizumab (IV) (TA 342)
Infliximab (IV) (TA 163)
5mg/kg
Ciclosporin (IV)
2mg/ kg/ 24 hours IV
Assess response
by 12/52
Assess response
by 12/52
Clinical response (UCDAI)
Bloods +/- Faecal calprotectin
Clinical response (UCDAI)
Bloods +/- Faecal calprotectin
Assess response
daily **
**Consider an extra 5mg/kg IFX
if no clinical benefit + extensive
haemorrhagic colitis
Assess response
daily
Poor response
Clinical response
Clinical response
Poor response
Clinical response
Optimise anti-TNF (trough & ab levels)
(Pathway C)
Add/ optimize immunosuppression
Consider a Flexible Sigmoidoscopy
Wean steroids
Commence Azathioprine
Colectomy
No benefits switching between
Ciclo and IFX if fail one therapy.
(Maser EA, 2008)
Commence oral Ciclosporin
(5mg/kg in two divided doses)
Commence Azathioprine
Co-trimoxazole 480mg/day
prophylaxis (if on dual Rx)
Oral Ciclo = for 3-6/12
Assess response
after ~ 8/52
Clinical response
Assess response
at 3/12
Repeat cycle x 2 times
if needed to optimise
Continue scheduled prescribing + clinical review
(Drug and Ab monitoring if loss of response)
Remission for UC:
Total or partial Mayo score ≤2 (no score >1) + steroid free
Response in UC:
↓ Total Mayo ≤3; ↓ Partial Mayo ≤2
Poor response
Assess response
at 12/12
Colonoscopy /
sigmoidoscopy
Calprotectin
Clinical response
Poor Response
Response
Alternative anti-TNF
(if neutralizing Ab's)
or
Vedolizumab
(TA 342)
Clinical trial
Surgery
Alternative
Biologic Therapy
Stop Ciclosporin
+ continue Aza
Remission
Partial / Incom-
plete response
Lost response =
switch therapy
Response
Partial response
= optimise therapy
No response
= Colectomy
Consider stopping biologic and
maintaining immunosuppressant
Optimise biologic +
immunosuppressant
Alternative biologic/
Surgery



Antibodies:

The precise level of antibody significance is currently undefined.

A low level of antibody can be clinically significant, if the antibody is neutralizing the drug.

Antibodies can be reduced by immunosuppression or anti-TNF dose adjustments.

An antibody level >40 is unlikely to be cleared by immunosuppression or anti-TNF dose adjustments.

If adjusting an anti-TNF dose or adding in a new immunosuppressant:

→ repeat clinical review and antibody + drug trough level testing after 2-4 months:

If response = continue therapy and review after 6/12

If partial response = optimise biologic therapy (further Ab + drug level testing) + immunosuppression

If no response = consider entry into a clinical trial / alternative biologic therapy / surgery

7. Contraindications, special warnings and precautions for biologic agents

Contraindications to anti-TNF's (infliximab, golimumab, adalimumab)[10,11,13]

- 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

*****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.

Special warnings and precautions for use with infliximab[10]
Medicines.org.uk: Infliximab special warnings and precautions

Special warnings and precautions for use with golimumab[13]
Medicines.org.uk: Golimumab special warnings and precautions

Special warnings and precautions for use with adalimumab[11]
Medicines.org.uk: Adalimumab special warnings and precautions

Contraindications to ciclosporin[16]

- Hypersensitivity to the active substance or to any of the excipients.
- Combination with products containing *Hypericum perforatum* (St John´s Wort)
- Combination with medicines that are substrates for the multidrug efflux transporter P-glycoprotein or the organic anion transporter proteins (OATP) and for which elevated plasma concentrations are associated with serious and/or life-threatening events, e.g. bosentan, dabigatran etexilate and aliskiren

Special warnings and precautions for use with ciclosporin therapy[16]
Medicines.org.uk: Ciclosporin special warnings and precautions

Contraindications to vedolizumab[12]

- 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)

Special warnings and precautions for use with vedolizumab[12]
Medicines.org.uk: Vedolizumab special warnings and precautions

Contraindications to ustekinumab

- Hypersensitivity to the active substance or to any of the excipients.
- Clinically important, active infection (e.g. active tuberculosis).

Special warnings and precautions for use with ustekinumab[14,15]
medicines.org.uk: Ustekinumab special warnings and precautions

8. Special situations

a) Drug and antibody testing (where available / commissioned)

The pathway includes three tumour necrosis factor-alpha inhibitors (anti-TNFs): infliximab, adalimumab and golimumab. Loss of clinical effect to anti-TNF therapy is common[21]. The intensification of therapy in this event has significant cost implications.

Currently, guidance relating to antibodies and drug levels for ustekinumab, golimumab and vedolizumab is not available.

Anti-TNF trough and antibody testing is recommended when a loss of response to therapy is suspected. Measurement of drug trough levels and antibody levels may help to identify specific reasons for therapeutic failure to aid clinical decision making[26,27]. See Pathway C

Anti-TNF drug and antibody levels may also be suggested prior to switching a patient's therapy to a biosimilar medicine. This is to firstly identify the on-going benefit of anti-TNF therapy in an individual, and secondly to reassure patients following a medication switch that drug efficacy had not altered[9].

The blood sample for anti-TNF drug and antibody trough levels should be collected prior to administration of the next scheduled dose of the drug.

The reference ranges for anti-TNF antibody and drug trough levels may vary slightly depending on the assay used.

b) Switching between treatments

Recommendations differ on the need for a washout period when switching from one biologic to another. A theoretical risk for increased susceptibility to infection has been proposed if washout time is not adequate between biologic therapies. However, there is very little published data on this topic. The half-life of the drug (table 1), clinical circumstances of the individual patient and drug levels should be considered in each case.

c) High risk patients

I. Early onset Crohn's disease

The course of Crohn's disease may be predicted by clinical factors at diagnosis and/ or at endoscopy. Onset before 40 years of age is a risk factor for a poor disease outcome.
Aggressive Crohn's disease causes increased relapse rates, increased admissions to hospital, the development of penetrating disease or structuring disease or abscesses plus the need for surgery.

A specialist could consider potential disease modifying therapy in those with early onset and at least two of the following factors[25]

- Extensive small bowel disease
- Deep and extensive colonic ulceration
- Perianal / rectal disease
- Stricturing disease
- >5kg weight loss pre-diagnosis
- The requirement of corticosteroid at diagnosis
- Steroid dependency
- *Smoking (encourage smoking cessation)*

http://www.e-guide.ecco-ibd.eu/diseaseinfo/prognostic-factors

II. Acute severe ulcerative colitis

In acute severe ulcerative colitis where infliximab rescue therapy has been necessary, an undetectable serum anti-TNF drug level corresponds with a greater colectomy risk[26]. In patients with extensive haemorrhagic colitis who have not responded to treatment, a higher dose of infliximab (10mg/kg loading, or a second 5mg/kg at 24-48 hours) can be considered at the discretion of the clinician. This would be an immediate rescue treatment and not an individual funding request.

d) Surgery

I. Peri-operative risk

Potential post-operative infection may be reduced by temporarily stopping a patient's biologic treatment. The decision to do so should be made following a discussion between the gastroenterology and surgical teams given the specific circumstances of each individual patient[21].
The safe interval remains to be determined[21]. If treatment is to be **stopped prior to elective surgery**, if possible consider stopping the drug 3-5 times the half-life for the relevant drug (Table 1).

Biologic therapy should not delay urgent surgery.

Table 1

Biologic	**Half-life (days)***
Adalimumab	12-14
Golimumab	12-14
Infliximab	9
Ustekinumab	15-32
Vedolizumab	25

*summary of product characteristics (SPC)[10-15] www.medicines.org.uk

II. Post-operative recurrence

Biologic therapy should be considered for the treatment of post-operative recurrence of Crohn's disease if immunosuppression with azathioprine/6-mercaptopurine has failed or is not tolerated[22-24].
Biologic therapy is not normally considered for prophylactic use following surgery.

e) Pregnancy and breast feeding

I. Pregnancy

ECCO (2014) guidelines on pregnancy in IBD[29]:

- If conception occurs at a time of quiescent disease, the risk of relapse is the same as in non-pregnant women. Conception occurring at a time of active disease increases the risk of persistent activity during pregnancy.
- Appropriate treatment of IBD should be maintained in order to reduce the risk of disease flares during pregnancy.
- Acute flares in pregnancy carry a high risk of adverse maternal and foetal outcome, and are best treated appropriately and without delay.

The clinician should consider the half-life of the drug when giving family planning advice.

There is limited data for safety of biologic drugs in pregnancy and lactation.

The decision to continue biologic agents in pregnancy needs to be individualised, taking into account alternative therapies, the severity of the mother's condition prior to therapy, the risk of a disease flare caused by cessation of therapy, and the impact of a flare on the mother and the unborn child. This should be discussed by a multi-disciplinary team.

For patients who stop therapy during pregnancy, consider re-loading with biologic therapy soon after delivery.

Several studies have shown that treatment with **infliximab** and **adalimumab** does not increase the risk of adverse pregnancy outcomes during the first trimester[29,34,35].

Transfer of anti-TNF drug across the placenta is highest in the 2nd and 3rd trimesters[29,34,35]. Infliximab and adalimumab cross the placenta and their use beyond the second trimester results in neonatal levels exceeding maternal levels. This exposure can be limited by stopping treatment around gestational week 24-26 where appropriate[29,34,35].

There is little information on the use of **golimumab** in pregnancy[13,34,35].

There is limited amount of data on the use of **ustekinumab** or **vedolizumab** in pregnant women. Animal studies do not indicate any harmful effects. **Ustekinumab**[14,15] or v**edolizumab**[12] may be used in pregnancy only if the benefits outweigh any potential risk to mother or foetus[12, 14,15].

II. Breast feeding

There is limited data on compatibility with breast feeding or with paternal exposure.

There is insufficient information on the excretion of biologics in breast milk. Since immunoglobulins are excreted into human breast milk, a risk to the breastfeeding child cannot be excluded.

A decision on whether to continue/discontinue breastfeeding or to continue/discontinue therapy should be made taking into account the benefit of breastfeeding to the child and the benefit of therapy to the woman.

The manufacturers recommend that it is not advisable to breast feed during drug treatment or for a specified duration after treatment has stopped.

Low levels of **infliximab** and **adalimumab** can be detected in breast milk but the level of oral absorption by the infant is unclear. Follow-up of infants exposed in utero and breastfed during maternal infliximab therapy have found no adverse effects and normal development[30,31]

It is not known whether **golimumab, ustekinumab** or **vedolizumab** are excreted in human milk or absorbed systemically after ingestion. Due to the lack of data the manufacturer does not recommend breast feeding during treatment. It is therefore not advisable to breast feed during treatment[12-15,32,33].

f) Vaccination of infants

Any infant who has been exposed to immunosuppressive treatment from the mother either in utero during pregnancy or via breastfeeding should have any live attenuated vaccination deferred for as long as a postnatal influence on the immune status of the infant remains possible[29,35]. In the case of in utero exposure to a biologic medicine, this period should be until the infant is age 6 months, after which time vaccination should be considered[29,36].

MHRA have received 4 Yellow Card reports regarding neonates who have died from disseminated BCG or tuberculosis infection after exposure to a biologic medicine in utero; they were probably not known to be immunosuppressed at the time of vaccination[36].

Current vaccination strategies with non-live vaccines for infants who have been exposed to a biologic medicine in utero do not differ from those for unexposed infants[29].

The risk of a natural rotavirus infection is high. Although the vaccine is a live attenuated virus the benefit from vaccination may exceed the risk of infection. Vaccination should be discussed on an individual basis[37].

9. <u>Vaccinations</u>

During biologic therapy, patients should receive influenza vaccine annually and pneumococcal vaccine once. (Check titres every 5-10 years).

a) Live vaccines

The administration of live vaccines is contraindicated in patients on biologic agents[10-15,39].

It is safe to administer a live vaccine 4 weeks prior to commencing biologic therapy, when necessary.

There is no contra-indication for the administration of live vaccines to relatives or friends of patients on biologic or immunosuppressant drugs.

Table 2 shows all live vaccines available in the UK.

Table 2

Live Vaccine	Brand Name
BCG	Bacillus Calmette-Guerin Vaccine
Influenza	Fluenz Tetra®
Measles, Mumps and Rubella combined vaccine (MMR)	MMRvaxPRO®, Priorix®
Poliomyelitis (Live oral vaccine)	Poliomyelitis Vaccine, live (oral) GSK OPV (No longer available for routine use)
Rotavirus (Live oral vaccine)	Rotarix®
Typhoid (Live oral vaccine)	Vivotif®
Varicella-Zoster Vaccine	Varilrix®, Varivax®, Zostavax®
Yellow Fever	Stamaril®

When a live vaccine is required by a patient on a biologic, stopping treatment may enable a necessary vaccination to be administered.

The time period required between stopping biologic therapy and administering a live vaccine is not specified by the manufacturer, other than ustekinumab which specifies a time period of 15 weeks.

b) Non-live vaccines

Non-live vaccines are deemed safe to administer to people on immunosuppressant and on biologic therapies. Pneumococcal vaccine should be given 2-4 weeks before starting a biologic as response after starting treatment can be poor[38].

Table 3 gives a list of non-live vaccines available in the UK.

Table 3

Vaccine	Brand Name
Cholera Vaccine (Oral preparation only)	Dukural®
Diphtheria	The diphtheria vaccine is only given as part of combined products: ● diphtheria/tetanus/acellular pertussis/inactivated polio vaccine/ Haemophilus influenzae type b (DTaP/IPV/Hib) ● diphtheria/tetanus/acellular pertussis/inactivated polio vaccine (dTaP/IPV or DTaP/IPV) ● tetanus/diphtheria/inactivated polio vaccine (Td/IPV)
Hepatitis A	Avaxim®, Epaxal®, Havrix Monodose®, Vaqta Paediatric®
Hepatitis B	Engerix®, Fendrix®, HBvaxPRO®
Hepatitis A and B Combined	Ambirix®, Twinrix®
Influenza	Agrippal®, , Enzira®, Fluarix®, Imuvac®, Influvac® Sub-unit, , Optaflu®, Intanza® Influenza vaccine (non-proprietary).
Pneumococcal	Prevenar® Synflorix®, pneumococcal polysaccharide vaccine (non-proprietary)
Poliomyelitis (Injection)	See diphtheria.
Meningococcal Group C	Menjugate Kit®, NeisVac-C®, Meningitec®
Meningococcal polysaccharide A,C, W135 and Y vaccine	Menveo®, Nimenrix®
Rabies	Rabipur®, rabies vaccine (non-proprietary)
Haemophilus Influenzae type B with meningococcal group C	Menitorix®
Tetanus	*Single preparation no longer available. Tetanus/diphtheria/inactivated polio vaccine Td/IPV should be used where protection is required against tetanus, diphtheria or polio.
Human papillomavirus	Cervarix®, Gardasil®
Tick-borne encephalitis	TicoVac®
Typhoid (Polysaccharide injection for vaccination)	Typherix®, Typhim Vi®
Hepatitis A and Typhoid	Hepatyrix®, ViATIM®

10. Crohn's Disease Severity Scoring and Clinical Monitoring

HARVEY BRADSHAW	SCORE	Please tick your score
GENERAL WELL-BEING		
Very well	0	☐
Slightly below par	1	☐
Poor	2	☐
Very poor	3	☐
Terrible	4	☐
ABDOMINAL PAIN *(yesterday)*		
None	0	☐
Mild	1	☐
Moderate	2	☐
Severe	3	☐
NUMBER OF LIQUID STOOLS *(yesterday)*		.....
ABDOMINAL MASS		
None	0	☐
Dubious	1	☐
Definite	2	☐
Definite and tender	3	☐

COMPLICATIONS			
		None	☐
Mouth ulcer	☐	Skin Rash	☐
Sore Joints	☐	Anal fissure	☐
Sore eyes	☐	Abscess	☐
Bruising on legs	☐	New fistula	☐

Remission	<5
Mild disease	5-7
Moderate disease	8-16
Severe disease	>16

Adapted from: http://www.janssenmedicalinformation.ca/assets/pdf/HarveyBradshaw_English.pdf

11. Ulcerative Colitis Severity Scoring and Clinical Monitoring/ MAYO score

MAYO CRITERIA	SCORE	
STOOL FREQUENCY		**Please tick score**
Normal	**0**	□
1-2/day more than normal	**1**	□
3-4/day more than normal	**2**	□
≥ 5/day more than normal	**3**	□
RECTAL BLEEDING		
No blood seen	**0**	□
Streaks of blood with stool less than half the time.	**1**	□
Obvious blood with stool most of time.	**2**	□
Blood alone.	**3**	□
ENDOSCOPIC FINDINGS		
Normal or inactive disease	**0**	□
Mild disease (mild friability).	**1**	□
Moderate disease (Contact bleeding).	**2**	□
Severe disease (spontaneous bleeding).	**3**	□
PHYSICIAN'S GLOBAL ASSESSMENT		
Normal	**0**	□
Mild disease.	**1**	□
Moderate disease.	**2**	□
Severe disease.	**3**	□

The physician's Global Assessment acknowledges the Sub scores, the daily record of abdominal discomfort and functional assessment and other observations such as physical findings, and the patient's performance status

Full Mayo Index Score [sum of all above items]

Remission	≤2
Mild Disease	3-5
Moderate Disease	6-10
Severe Disease	11-12

Partial Mayo Index Score [sum of above items excluding endoscopic findings]

Remission =	0-1
Mild Disease	2-4
Moderate Disease	5-6
Severe Disease	7-9

Adapted from: Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med. 1987 Dec 24;317(26):1625-9.

12. References

1. NICE CG152. (2012). Crohn's disease: management. http://www.nice.org.uk/guidance/CG152
2. NICE TA187 (2010). Infliximab (review) and adalimumab for the treatment of Crohn's disease. http://guidance.nice.org.uk/TA187
3. NICE TA352 (2015) Vedolizumab for treating moderately to severely active Crohn's disease after prior therapy. http://guidance.nice.org.uk/TA352
4. NICE TA456 (2017) Ustekinumab for treating moderately to severe Crohn's Disease after previous treatment. http://guidance.nice.org.uk/TA456
5. NICE CG166 (2013). Ulcerative colitis- management in adults, children and young people http://www.nice.org.uk/guidance/CG166
6. NICE TA329 (2015). Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after failure of conventional therapy. http://guidance.nice.org.uk/TA329
7. NICE TA163 (2008). Infliximab for acute exacerbations of ulcerative colitis http://guidance.nice.org.uk/TA163
8. NICE TA342 (2015). Vedolizumab for treating moderately to severely active ulcerative colitis. http://guidance.nice.org.uk/TA342
9. BSG Guidance on the Use of Biosimilar Infliximab CT-P13 in Inflammatory Bowel Disease. 2016. British Society Gastroenterology. Available at: http://www.bsg.org.uk/images/stories/docs/clinical/guidance/bsg_infliximab_guidance_16.pdf
10. Summary of Product Characteristics. Remicade. 2015. Available at: http://www.medicines.org.uk/emc/medicine/3236
11. Summary of Product Characteristics. Humira 2016. Available at: http://www.medicines.org.uk/emc/medicine/31860
12. Summary of Product Characteristics. Entyvio 2015. Available at: http://www.medicines.org.uk/emc/medicine/28980
13. Summary of Product Characteristics. Simponi 2016. Available at: http://www.medicines.org.uk/emc/medicine/28316
14. Summary of Product Characteristics. Stelara 2017. Available at: http://www.medicines.org.uk/emc/medicine/32568
15. Summary of Product Characteristics. Stelara 2017. Available at: http://www.medicines.org.uk/emc/medicine/32569
16. Summary of Product Characteristics 2016. SANDIMMUN Concentrate for Solution for Infusion 50mg/ml. Available at: http://www.medicines.org.uk/emc/medicine/1317
17. Vande Casteele N, Compernolle G, Ballet V, et al. Individualised infliximab treatment using therapeutic drug monitoring: a prospective controlled Trough level Adapted infliXimab treatment (TAXIT) trial. J Crohn's Colitis 2012:6(Suppl 1):S1-221.
18. Roblin X , Rinaudo M , Del Tedesco E et al.. Development of an algorithm incorporating pharmacokinetics of adalimumab in inflammatory bowel diseases. Am J Gastroenterol 2014;109:1250-6.
19. European Crohn's and Colitis organisation. Algorithms. www.e-guide.ecco-ibd.eu/diseaseinfo/prognostic-factors).
20. Steenholdt C, Bendtzen K, Brynskov J et al. Cut-off levels and diagnostic accuracy of infliximab trough levels and anti-infliximab antibodies in Crohn's disease. Scand J Gastroenterol 2011;46:310-8.
21. Dignass A, Van AG, Lindsay JO, et al. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: current management. J Crohns Colitis 2010;4:28-62.
22. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Special situations. Journal of Crohn's and Colitis (2010) 4, 63–101
23. Mardini H.,Grigorian A.,Selby L.,Barrett T. Anti-TNF agents prevent endoscopic and clinical recurrence of Crohn's disease after surgical resection: A meta-analysis American Journal of Gastroenterology, October 2014, vol./is. 109/(S500),
24. De Cruz P.,Kamm M.,Hamilton A et al. Strategic timing of anti-TNF therapy in postoperative Crohn's disease: Comparison of routine use immediately postoperatively with selective use after demonstrated recurrence at 6 month endoscopy. Results from POCER. Journal of Gastroenterology and Hepatology, October 2013, vol./is. 28/(92),
25. European Crohn's and Colitis organisation. Prognostic Factors. Available at: http://www.e-guide.ecco-ibd.eu/diseaseinfo/prognostic-factors-0. Accessed May 2016.
26. C H Seow, A Newman, S P Irwin et al. Trough serum infliximab: a predictive factor of clinical outcome for infliximab treatment in acute ulcerative colitis. Gut 2010;59:49–54.
27. Steenholdt C, Brynskov J, Thomsen O et al. Individualised therapy is more cost effective than dose intensification in patients with Crohn's disease who lose response to anti-TNF treatment:a randomised, controlled trial.Gut 2014;63:919-927.
28. Dignass A, Lindsay JO, Sturm A et al. The second European evidence-based Consensus on the diagnosis and management of ulcerative colitis Part 2: Current management. J Crohn's Colitis 2012;991-1030.
29. Van der Woude CJ, Ardizzone S, Bengtson MB. The Second European Evidence-Based Consensus on Reproduction and Pregnancy in Inflammatory Bowel Disease. Journal of Crohn's and Colitis 2015;1-18.
30. Drug and Lactation Database (LACTMED). Infliximab. Available at: http://toxnet.nlm.nih.gov. Accessed May 2016.

31. Drug and Lactation Database (LACTMED). Adalimumab. Available at: http://toxnet.nlm.nih.gov. Accessed May 2016.
32. Drug and Lactation Database (LACTMED). Golimumab. Available at: http://toxnet.nlm.nih.gov. Accessed May 2016.
33. Drug and Lactation Database (LACTMED). Vedolizumab. Available at: http://toxnet.nlm.nih.gov. Accessed May 2016.
34. Christof Schaefer. Drugs During Pregnancy and Lactation. Third Edition.2015. Elsevier.
35. Briggs G, freeman R. Drugs in Pregnancy and Lactation. Tenth Edition. 2015. Wolters Kluwer Health.
36. MHRA Drug Safety Update. April 2016. Live attenuated vaccines: avoid use in those who are clinically immunosuppressed. Available at: https://www.gov.uk/drug-safety-update/live-attenuated-vaccines-avoid-use-in-those-who-are-clinically-immunosuppressed
37. Rotavirus. Green Book Chapter 27b. 2015. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/457263/Green_Book_Chapter_27b_v3_0.pdf
38. Pneumococcal. Green Book Chapter 25: 2013. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/263318/Green-Book-Chapter-25-v5_2.pdf
39. Contraindications and special situations. Green Book Chapter 6. Available at: http://media.dh.gov.uk/network/211/files/2012/07/Green-Book-Chapter-6-v2_0.pdf