Shared Care Guideline for Adult Inflammatory Bowel Disease (IBD)

High Risk Immunomodulators in IBD – Ulcerative Colitis (UC) & Crohn's Disease (CD)
Azathioprine, Mercaptopurine and Methotrexate Tablets

Executive Summary/ Critical Information

Indication	Route and Dose	Key aims of treatment in the long term	Monitoring undertaken by specialist before requesting shared care	Ongoing monitoring to be undertaken by GP	Duration of treatment	Stopping criteria	Follow up (weeks / months)
CROHN'S DISEASE **ULCERATIVE COLITIS**	**Azathioprine 2 - 2.5mg/kg daily** **Mercaptopurine 1 - 1.5mg/kg daily** **Methotrexate 25mg once weekly**	**To induce and maintain remission, and relieve symptoms.**	**Prior to starting azathioprine, mercaptopurine or methotrexate:** **Viral serology screen -** **Hepatitis B** **Hepatitis C** **HIV** **Cytomegalovirus (CMV)** **Epstein-Barr virus (EBV)** **Varicella Zoster virus (VZV)** **Thiopurine S-methyltransferase (TPMT) phenotype** **(*for azathioprine and mercaptopurine only*).**	**FBC** **Renal profile** **Alanine aminotransferase (ALT)** **Aspartate aminotransferase (AST)** **Alkaline phosphatase (ALP)** **measured every 12 weeks to ensure safe use of medication.**	**Dependent on response, but usually 3 - 5 years.**	**Loss of response** **Toxicity / adverse effects** **Interactions with other drugs**	**<u>Hospital IBD Team</u>** **Patient will be reviewed at week 0, 4, 8 and 12.** **Bloods will be monitored every 2 weeks for the first 12 weeks (induction period).** **Prescription supplies will be managed by the hospital during the 12 week induction period or until the patient can be safely moved to Primary Care.**

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			Baseline chest x-ray at discretion of clinician *(for methotrexate only).* **The following tests are monitored every 2 weeks for the first 12 weeks (induction period):** **C-reactive protein (CRP)** **FBC** **Renal profile** **Alanine aminotransferase (ALT)** **Aspartate aminotransferase (AST)** **Alkaline phosphatase (ALP)** **measured every 2 weeks for the first 12 weeks (induction period).** **Haematinics (serum folate, vitamin B12, ferritin)** **Bone profile (calcium, phosphate, albumin) will be checked, if required.** **Lipase – if azathioprine-induced pancreatitis suspected.** **For azathioprine and mercaptopurine, thioguanine metabolites (TGN) will be**	**C-reactive protein (CRP) will be monitored at the same interval to ensure adequate disease control.**			**Patient to be reviewed annually by the IBD clinician or more frequently if clinically indicated.** **<u>Primary Care (once patient stable)</u>** **<u>Bloods</u>: Monitor bloods every 12 weeks.** **Issue ongoing prescriptions.** **<u>Clinical Review</u>: Monitor the patient for loss of response or adverse effects.** **In the event of abnormal bloods including leucopenia, neutropenia, anaemia, renal impairment, elevated ALP, AST or ALT, please call the IBD helpline (see section 10) and ask patient to stop medication in the interim. A review will be organised by the hospital IBD Team.**

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			checked at week 6 - 8 to confirm appropriate dosing. **For all agents and if considered necessary by the clinician, the following clinical and objective markers will be checked at week 12:** **C-reactive protein (CRP)** **Faecal calprotectin (FCP)**				

Key Safety Notice (for instance: notification if prescribing must be brand specific or BNF cautionary and advisory warnings).

Mercaptopurine

Mercaptopurine 50mg tablets - only 50mg strength should be prescribed. Do not prescribe 25mg preparation or liquid as they are 'specials.'
DO NOT confuse Mercaptopurine with ***Mercaptamine***; care must be taken to ensure the correct drug is prescribed and dispensed.

Azathioprine – available as 25mg and 50mg tablets. Liquid must not be prescribed as it is a 'special'. Tablets can be crushed and dispersed in water. The preferred method is to disperse azathioprine tablets in 10 mL of water in the barrel of a syringe, as this is a closed system. Gloves should be worn during this procedure in case of accidental spillage.[(1)]

Methotrexate – ONCE WEEKLY dosing and always prescribe and dispense as **2.5mg tablets**. Folic acid – prescribe 5mg to be taken DAILY except on methotrexate days.
For patients being initiated on methotrexate:

- The hospital IBD team will send patients the MHRA link: https://www.gov.uk/drug-safety-update/methotrexate-once-weekly-for-autoimmune-diseases-new-measures-to-reduce-risk-of-fatal-overdose-due-to-inadvertent-daily-instead-of-weekly-dosing.
- Lloyds Pharmacy will supply a methotrexate alert book.

For all medications - patients should be warned to report immediately the onset of sore throat, bruising and mouth ulcers, liver toxicity (nausea, vomiting, dark urine and abdominal discomfort) and respiratory effects (cough or shortness of breath for those taking methotrexate). They should also report high fever (>38°C).

Other

It is important that patients do not have a break in treatment. In the event of an interruption in supply due to drug shortages, inform the hospital via the IBD helpline number.

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1. Background

Inflammatory bowel disease (IBD) comprises Crohn's disease (CD) and ulcerative colitis (UC). Both are chronic, relapsing and remitting conditions that require anti-inflammatory or immunosuppressant medication.

Azathioprine and mercaptopurine are the most widely used immunosuppressive agents in IBD and have been in use since the 1960's. In addition, azathioprine, mercaptopurine and methotrexate can be prescribed in combination with biologic agents (infliximab, adalimumab, golimumab, vedolizumab and ustekinumab) to reduce anti-drug antibody formation, increase serum biologic drug levels and increase persistence on medication. Azathioprine or mercaptopurine SHOULD NOT be prescribed in combination with JAK inhibitors (tofacitinib, updatacitinib, filgotinib).

Mercaptopurine is the active metabolite of azathioprine. Azathioprine and mercaptopurine appear identical in their pharmacologic and biologic effects, but their exact mode of action is unknown. In IBD they are used in patients with steroid dependent, frequently relapsing disease. Both agents can cause serious adverse reactions including leucopenia and thus require regular monitoring, cautious dose titration and awareness of drug interactions. If tolerated, patients can remain on these medicines for up to 5 years.

Methotrexate is also used as a disease-modifying agent to induce and maintain remission of CD, and less commonly in UC. Currently methotrexate is positioned as a second-line immunosuppressive agent in patients resistant or intolerant of azathioprine or mercaptopurine.

Although all agents are unlicensed for these indications, their use has been endorsed by NICE guidance.[(2)(3)]

This guideline sets out prescribing and monitoring responsibilities to facilitate shared care of these medications.

2. Important information

Azathioprine is a pro-drug, which is metabolised by the enzyme thiopurine S-methyltransferase (TPMT) to mercaptopurine, then to pharmacologically active thioguanine nucleotide (TGN).

Mercaptopurine is also metabolised by TPMT to produce methylmercaptopurine (MMP) and xanthine ozidise (XO) to thiouric acid.

<u>Monitoring by Secondary Care</u>

Baseline monitoring

- TPMT should be measured PRIOR to patients starting on azathioprine or mercaptopurine.

- TGN / MMP levels are checked **after 6 weeks** (some centres do 8 weeks) of starting treatment and after any dose changes
    - Patients with **high TPMT levels** can produce high levels of MMP leading to **hepatotoxic side effects**.
    - Patients with **high TGN levels** can lead to dose-related adverse effects such as **bone marrow suppression.**

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Monitoring by Primary Care

Ongoing monitoring

After the induction phase, routine bloods (renal profile, AST, ALT, ALP, FBC, CRP) should be monitored every 12 weeks if patient is stable, or refer back to hospital specialist via IBD helpline number if toxicity is suspected.

3. Drug name, form, and licensed indications (unlicensed/off-label)

Azathioprine (available as 25mg and 50mg tablets) is used to induce and maintain remission in UC and CD (unlicensed).

Mercaptopurine (available as 50mg tablets) is used to induce and maintain remission in UC and CD (unlicensed).

Methotrexate (available as 2.5mg tablets) is used to induce and maintain remission in CD unresponsive to conventional therapy (steroid resistant or dependent), failed or intolerant to azathioprine or mercaptopurine (unlicensed).

4. Dose and Administration

Azathioprine
Starting dose of **2 - 2.5mg/kg per day** with normal or high TPMT levels
The maximum daily dose rarely exceeds 200mg. For any cases where the daily dose exceeds 200mg, patients will be monitored as per above.

Allopurinol has a clinically significant interaction with azathioprine / mercaptopurine that can lead to increased toxicity. However, this combination may be recommended by the hospital specialist, particularly in patients who are unable to tolerate or do not respond to treatment with azathioprine / mercaptopurine. In this setting it is essential that the dose of azathioprine / mercaptopurine is reduced (normally to 25% of the original dose). The use of low dose azathioprine / mercaptopurine in combination with allopurinol will increase the possibility of patients tolerating / responding to I mmunomodulator therapy.

Mercaptopurine
Starting dose of **1 - 1.5mg/kg per day** with normal or high TPMT levels.
If TPMT low (carrier status): start with 50% of normal dosage and monitor.
Concomitant use with allopurinol warrants a dose reduction to 25% of the original dose.

Methotrexate
Starting dose of **25mg ONCE A WEEK as a single dose** (maximum dose).
A low starting dose of 2.5mg is often used for the elderly or those with renal impairment.
Folic acid is co-prescribed: 5mg once daily, except for methotrexate day, and is useful if nausea, abdominal discomfort, diarrhoea or anorexia associated with methotrexate is a problem.
Clinical response is usually evident in 4 - 6 weeks.
Metoclopramide may be used to prevent nausea, 10mg taken, 30 minutes before methotrexate.

All dose titrations will be carried out by the specialists in secondary care.

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5. Contraindications / Cautions

Immunisation with LIVE vaccines	Patients on azathioprine, mercaptopurine and methotrexate must NOT receive immunisation with LIVE vaccines, such as polio, MMR, BCG, Zostavax, or yellow fever. Annual influenza vaccination (provided it is not a LIVE vaccine) is recommended and pneumococcal vaccination should be considered.
Chickenpox/Shingles	Patients should avoid contact with those who have ACTIVE chickenpox or shingles and should report any such contact immediately to the hospital specialist to allow a management plan to be made.
Pregnancy/Breastfeeding	Patients planning on becoming pregnant should consult their specialist so that optimal disease control and modification of medical strategy can be considered. Female patients should STOP methotrexate at least 6 months prior to conception due to proven teratogenic impact of this medication. There is less evidence that male patients should stop methotrexate should they want to father a child and careful discussion with the IBD team is recommended. If a female becomes pregnant whilst on methotrexate this should be stopped immediately and urgent advice sought from the IBD team and obstetric department. There is no need for either male or female patients to stop azathioprine or mercaptopurine should they be considering or become pregnant. Those patients who become pregnant whilst on treatment may need reviews more frequently. It is important that the mother's disease is under control prior to and throughout pregnancy to ensure optimal birth outcome. Methotrexate is contraindicated during breastfeeding. Azathioprine and mercaptopurine can be continued whilst breastfeeding after discussion with the hospital IBD team.
Obesity, Diabetes Mellitus or excessive alcohol intake	Increased risk of liver damage in patients on methotrexate.
Renal / Hepatic impairment	Dose reduction may be necessary in moderate to severe renal or hepatic impairment. This will be discussed with the IBD specialist if a change is required.
TPMT deficiency (homozygous state)	AVOID azathioprine and mercaptopurine as resultant elevated thioguanine nucleotide levels can cause serious toxicity early after commencing treatment. Patients with **reduced TPMT levels** (heterozygotes) should be started on half the initial dose as greater risk of myelosuppression.
Digoxin	Reduced absorption of digoxin (methotrexate only)

For a complete list of cautions/contraindications, please refer to the SPC: https://www.medicines.org.uk/emc

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6. Drug interactions

NSAIDS	Not recommended in IBD as they can worsen IBD symptoms and may trigger a flare up.
Allopurinol	Enhanced effects and toxicity of allopurinol when taken together with azathioprine and mercaptopurine. Dose of azathioprine or mercaptopurine should be reduced to 25% and requires regular monitoring of FBC and TGN levels.
Warfarin	Azathioprine and mercaptopurine reduces anticoagulant effect.
Clozapine	Increased risk of agranulocytosis.
Vaccines	Refer to LIVE vaccines under cautions / contraindications.
Phenytoin **Sodium valproate** **Carbamazepine**	When co-prescribed with azathioprine, the absorption of these anti-epileptic drugs may be reduced.
Co-trimoxazole and trimethoprim	Increased risk of haematological toxicity (leucopenia).
5-aminosalicylates (mesalazine)	Possible increased risk of nephrotoxicity.

For a complete list of drug interactions, please refer to the SPC: https://www.medicines.org.uk/emc

7. Side effects which require managing

Drug	Bone marrow suppression *Leukopenia* *Anaemia* *Thrombocytopenia*	Hepatoxicity *Hepatitis* *Biliary stasis*	Nephrotoxicity *Uraemia* *Renal failure* *Haematuria* *Cystitis*	Gastro-intestinal disturbances *Anorexia* *Oral mucositis* *Nausea/Vomiting* *Diarrhoea* *Pancreatitis (rare)*	Pulmonary toxicity	CNS disturbances *Headache* *Drowsiness* *Fatigue* *Blurred vision*	Fevers Rash Rigors	Alopecia
Azathioprine	✓	✓		✓		✓	✓	✓
Mercaptopurine	✓	✓		✓		✓	✓	✓
Methotrexate	✓	✓	✓	✓	✓	✓	✓	✓

For complete list of side effects, please refer to the SPC: https://www.medicines.org.uk/emc.

8. Process for Referral Back to Secondary Care

If a GP has taken blood tests for the general medical management of a patient and blood test results fall into any of the categories listed below or the patient reports one of the adverse events listed in section 7, the patient should be told to stop the immunosuppressant and the hospital IBD team should be informed by calling the IBD telephone helpline. Further assessment and / or medication will be organised from secondary care.

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Adverse effects	Action
Lymphocytes < 0.5 x 10^9/L **WBC < 4.0 x 10^9/L** **Neutrophils < 2.0 x 10^9/L**	Withhold medication and discuss with specialist – call IBD helpline number.
Platelets < 150 x 10^9/L	Withhold medication and repeat blood test. Discuss with specialist if remains low **(< 150 x 10^9/L).**
Significant reduction in renal function	Withhold medication and discuss with specialist – call IBD helpline number.
Liver Function Tests **> 2-fold rise in AST, ALT (from ULN)** **> 4-fold rise in AST, ALT (from ULN)**	Withhold azathioprine and mercaptopurine. Look for alternative cause. Repeat LFTs, if abnormal discuss with specialist. **Stop methotrexate** and contact specialist immediately.
MCV > 105 fl	Check B12, folate and thyroid function tests (TFTs). If low, start appropriate supplementation. Check alcohol status. If no cause found, discuss with specialist.
New or increasing dyspnoea or persistent cough (with no other obvious cause – suspected pneumonitis)	**Stop methotrexate** and discuss with specialist – call IBD helpline number. A chest x-ray may be required.
Rash or oral ulceration	**RASH** - Withhold until symptoms clear. Consider re-challenging at a lower dose. If rash recurs, stop medication and discuss with specialist. **MOUTH ULCERS** – Check FBC for leucopenia. May respond to increasing folic acid or by treating with an OTC mouth ulcer medication. If severe despite extra folic acid stop methotrexate and refer to a specialist for advice.
Hypersensitivity reactions	Fever, malaise, rash, vomiting, muscle / bone pain, dizziness. Stop medication and discuss with specialist.
Abnormal bruising, bleeding or sore throat	Withhold medication until FBC result available.
Upper abdominal and back pain	Stop azathioprine or mercaptopurine, check lipase and discuss with specialist.

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Nausea, vomiting, diarrhoea	Recommend taking azathioprine, mercaptopurine or methotrexate tablets after meals to reduce nausea. An anti-emetic or dose reduction may help (or splitting the dose in divided doses). If symptoms persist, stop medication and discuss with specialist.
Suspected infection requiring antibiotics	Check FBC for leucopenia. Withhold medication temporarily until infection clears.

9. Monitoring and Responsibilities

a. Hospital specialist:

- Initiate, stabilise and prescribe treatment during the *induction phase* (12 weeks) and until the GP formally agrees to share care (as a minimum, supply the first 12 weeks treatment or until patient is stabilised). This will include monitoring safety, adverse events, and clinical response to therapy as well as drug levels where appropriate.
- Send a letter to the GP requesting shared care for this patient – complete "*Shared Care Guideline Prescribing Agreement' (Appendix 1)*
- Clinical and laboratory supervision of the patient either face to face in an outpatient clinic setting, a telephone clinic appointment or via virtual review on a regular basis for the 12 week induction period.
- Send a letter to the GP after each clinic attendance ensuring current dose and most recent blood results are documented. Where monitoring is via virtual contact, a letter will be sent to update the GP of any dose change.
- Evaluation of any reported adverse effects by GP or patient.
- Advise GP on review, duration or discontinuation of treatment where necessary.
- Inform GP of patients who do not attend clinic appointments.
- Inform GP, by letter, of clinic visits and action taken for management of patient.

Pre-treatment monitoring	Viral serology screen (HIV, Hepatitis B, Hepatitis C, EBV, CMV and VZV)
	CRP, FBC, renal profile, ALT, ALP, AST, TPMT phenotype (thiopurines)
Monitoring during Induction	FBC – every 2 weeks for the first 12 weeks
	Renal profile – every 2 weeks for the first 12 weeks
	ALT / AST / ALP – every 2 weeks for the first 12 weeks
	CRP every 2 weeks for the first 12 weeks

b. General Practitioner / Primary Care:

- Monitor patient's overall health and well-being.
- In times of disease activity / flare ups, inform the hospital specialist.

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- After induction, monitor routine bloods (renal profile / liver function tests / FBC / CRP) every 12 weeks if patient is stable. Refer back to hospital specialist via IBD helpline number if toxicity is suspected – refer to section 8 above.
- Provide ongoing prescriptions every 12 weeks if appropriate.
- Report any adverse events to the consultant, where appropriate.
- Report any adverse events via the yellow card scheme, where appropriate.

c. Patient or parent / carer:

- Ensure their skin is adequately protected by using sunscreens and protective covering to reduce sunlight exposure (for azathioprine and mercaptopurine only).
- Patients should avoid "live" vaccines whilst on immunosuppressive therapy, and contact hospital specialist for advice if any vaccinations are required.
- Ensure they have a clear understanding of their treatment and potential adverse effects.
- Report any adverse effects to their GP and / or hospital IBD team.
- Report any changes in disease symptoms to GP and / or hospital IBD team.
- Alert GP and / or specialist of any changes of circumstance which could affect management of disease e.g. plans for pregnancy.

See Appendix 2 for IBD care pathway

10. Contact Information for Advice and Support

Number	
Main switchboard	0207 377 7000
Consultant Secretaries	0203 594 3700
Consultant Gastroenterologists (Royal London Hospital) Professor Lindsay Dr Langmead Dr Parkes Dr Rao Dr Kok Professor Rampton	0203 594 3200
Consultant Gastroenterologists (Newham) Dr Matt Guinane Dr Noor Jawad	020 7476 4000 (Ext. 5849) PA for Matt Guinane: 020 7363 8080 PA for Noor Jawad: 0207 363 3086
Consultant Gastroenterologist (Whipps Cross) Dr Sami Hoque Dr Elizabeth Carty	0208 539 5522 (Ext. 4458)
Clinical Nurse Specialists	0203 594 3700
Clinical Nurse Specialist (Young Adults)	0203 594 3700
Registrar on-call out of hours	*Air call via switchboard*
IBD helpline	0203 594 3700 or email bchnt.ibdhelpline@nhs.net
IBD Clinic Pharmacist	0203 246 0137

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11. References

(1) Handbook of enteral drug administration. Third edition 2015. White R and Bradnam V
(2) Crohn's disease: Management; NICE Clinical Guideline 129; Published date: May 2019
(3) Ulcerative colitis: Management; NICE Clinical Guideline 130; Published date: May 2019

12. Document Management

Document ratification and history	
Produced by:	Bart Health NHS Trust
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Appendix 1

Shared Care Guideline: Prescribing Agreement	
Section A: To be completed by the hospital consultant initiating the treatment	
GP Practice Details: Name: Tel No: Email (nhs.net):	**Patient Details:** Name: DOB: NHS Number (10 digits):
Consultant Details: Consultant Name: Secretary Contact Details: Tel No: Email (nhs.net):	
Diagnosis:	**Drug Name (to be prescribed by GP):** **Dose:** **Frequency:**
I will review the patient in clinic in weeks / months (*Delete as appropriate)*.	

Dear

Your patient started treatment with the above drug for the above diagnosis on (insert date) and in my view; his/her condition is now stable.

The patient has given consent to treatment under a shared care prescribing agreement and has agreed to comply with instructions and follow up requirements.

I am requesting your agreement to sharing the care of this patient from (insert date) in accordance with the attached Shared Care Prescribing Guideline.

This patient was reviewed on (insert date). These are the results relevant for the drug and/or condition, as outlined in the shared care document:

Test	Baseline	Date

Please continue to monitor the patient as outlined in the shared care guidelines. Refer to the attached guidelines for monitoring criteria.

Other relevant information:

Consultant Signature:	Date:

Section B: To be completed by the GP and returned to the hospital consultant as detailed in Section A above [If returned via e-mail, use NHS.net email account ONLY]

Please sign and return your agreement to shared care within 14 days of receiving this request.

☐ Yes, I accept sharing care as per shared care prescribing guideline.

☐ No, I am not willing to undertake shared care for this patient for the following reason:

(Please give reason)

GP Name:	GP Signature:	Date:

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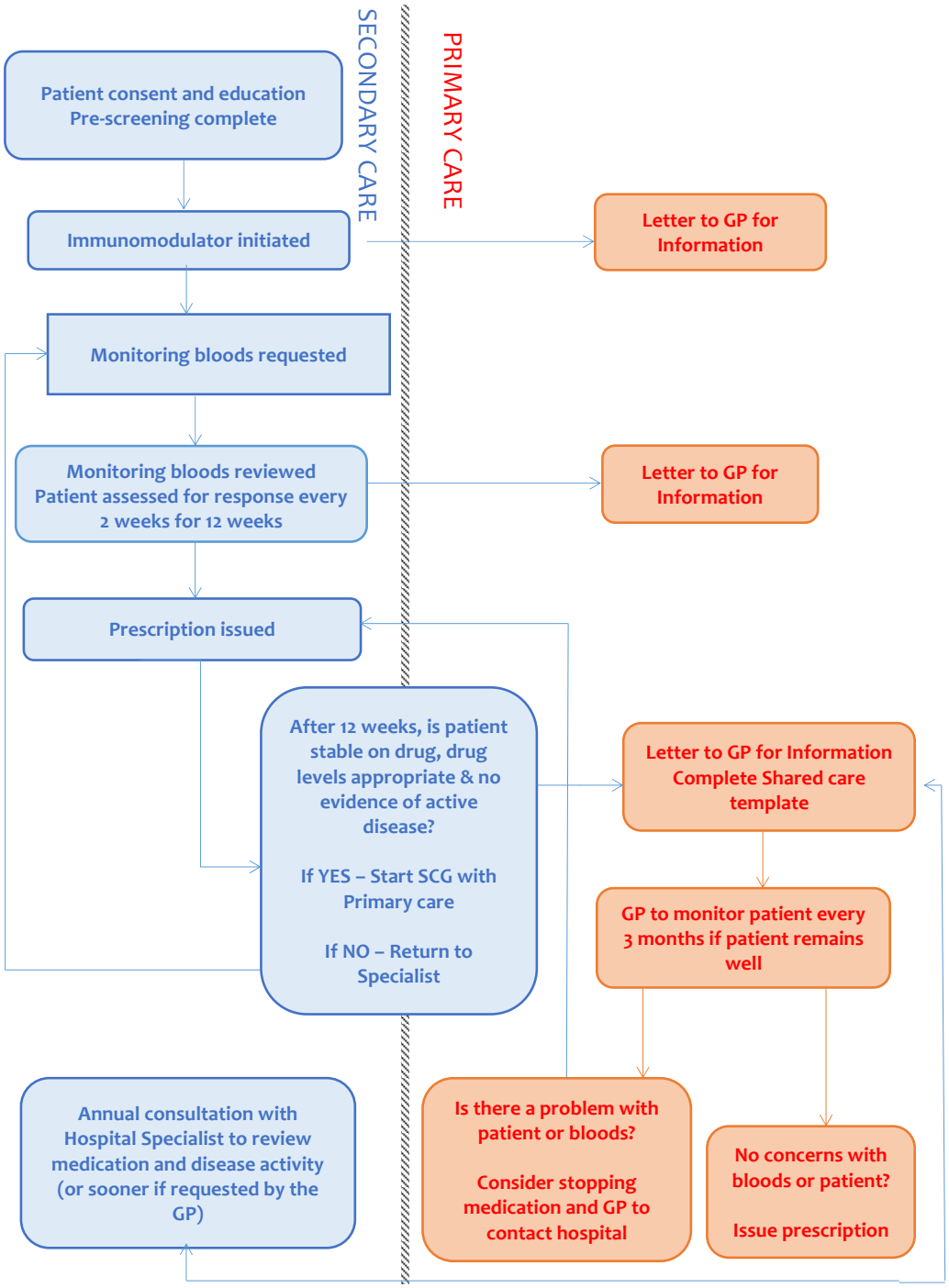
Appendix 2

CARE PATHWAY - Immunomodulators in Inflammatory Bowel Disease



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