National shared care protocol adapted for local use:

Rheumatological Conditions: Sulfasalazine for patients within adult services

Version 1

The content of this shared care protocol was correct as of November 2023. As well these protocols, please ensure that summaries of product characteristics (SPCs), British national formulary (BNF) or the Medicines and Healthcare products Regulatory Agency (MHRA) or NICE websites are reviewed for up-to-date information on any medicine.

Specialist responsibilities

- Assess the patient and provide a diagnosis; ensure that this diagnosis is within the scope of this shared care protocol (section 2) and communicated to primary care.
- Use a shared decision-making approach; discuss the benefits and risks of the treatment with the patient and/or their carer and provide the appropriate counselling (see section 11) to enable the patient to reach an informed decision. Obtain and document patient consent. Provide an appropriate patient information leaflet.
- Assess for contraindications, cautions (see section 4), and interactions (see section 7).
- Conduct required baseline investigations and initial monitoring (see section 8).
- Initiate and optimise treatment as outlined in section 5. Once the patient is known to be tolerating the medicine, transfer to shared care would normally take place. Before transfer to shared care, the patient is expected to have had at least one specialist review and be stable (no increase in mediation dose for at least 6 weeks alongside satisfactory investigation results). On transferring shared care, the specialist will provide at least 4 weeks of medication to enable the practice to receive and process the shared care agreement and set up prescribing and ongoing monitoring. Any bloods required within the 4 weeks should be requested/organised and followed up by the specialist.
- If shared care is considered appropriate, and once treatment is optimised, write to the patient's GP practice and request shared care; detailing the diagnosis, current and ongoing dose and formulation, baseline and most recent test results, confirm the monitoring schedule and when the next monitoring is required, details of monitoring arrangements and other relevant treatments being received by the patient. Include the specialist service contact information (section 13).
- The specialist should also provide the details of the treatment to be undertaken by the GP. Including the reasons for the choice of treatment, medicine combination, frequency of treatment, and the next review date by the specialist.

- Prescribe sufficient medication to enable transfer to primary care (usually 42 days). Further prescriptions will be issued where there are unforeseen delays to the transfer of care. The patient should not be put in a position where they are unsure where to obtain supplies of their medication. The specialist team will be responsible for monitoring and prescribing the medicine during this initial period.
- Conduct the required annual reviews and monitoring in section 8 and communicate the results in writing to primary care within 14 days, where possible. After each review, provide primary care with a written summary within 14 days, advising whether treatment should be continued, confirming the ongoing dose, and whether the ongoing monitoring outlined in section 9 remains appropriate.
- Provide advice to primary care on the management of adverse effects if required.
- Review patients annually. Review once every two years for patients under a Patient Initiated Follow-ups (PIFU) pathway.
- Provide the patient with a patient information sheet and details of their treatment, including any dosage changes made, follow-up appointments, monitoring requirements, and specialist team contact details. Highlight the importance of monitoring the patient and explain the potential withdrawal of treatment if monitoring appointments are not attended.
- Contact details for primary care prescribers will be made available.
- Details for fast-track referral will be supplied.

Primary care responsibilities

- If shared care is not accepted, inform the specialist of the decision in writing within 14 days with reasons as to why shared care cannot be entered into.
- If shared care is accepted, ensure knowledge and understanding of the therapeutic issues relating to the patient's clinical condition. Undergo any additional training necessary to carry out the prescribing and monitoring requirements.
- Agreeing that, in their opinion, the patient should receive shared care for the diagnosed condition unless good reasons exist for the management to remain within the secondary care.
- If accepted, prescribe ongoing treatment as detailed in the specialist's request and as per section 5, taking into account any potential drug interactions in section 7.
- Adjust the dose of sulfasalazine prescribed as advised by the specialist and communicate any changes made to the patient.
- Conduct the required monitoring as outlined in section 9. Communicate any abnormal results to the specialist. Discuss with the referring specialist team if there are any amendments to the suggested monitoring schedule.
- Ensure that the patient is given the appropriate appointments for follow-up and monitoring.
- If a patient fails to attend, contact the patient in a timely manner to arrange an alternative appointment. It is the GP's responsibility to decide whether to continue treatment in a patient

who does not attend follow-up and monitoring appointments. If the patient regularly fails to attend the monitoring appointment, the GP may withhold the prescription and inform the consultant responsible for the patient's care.

- The primary care clinician conducting the investigations is responsible for completing the patient's monitoring record with the necessary information and up-to-date results of investigations.
- Manage adverse effects as detailed in section 10 and discuss them with the specialist team when required. Refer the patient back to the specialist team if further investigation is required.
- Stop sulfasalazine and make an urgent referral to the specialist if signs of myelosuppression, hepatic or renal dysfunction develop, or a serious skin reaction or oral ulceration is observed.
- Sulfasalazine is safe for pregnancy. Prescribe folic acid 5mg daily supplementation when the patient becomes or plans to become pregnant.
- Stop treatment as advised by the specialist.
- Offer patients vaccination in line with the current Joint Committee on Vaccination and Immunisation advice (Immunisation against infectious disease).

Patient and/or carer responsibilities

- Take sulfasalazine as prescribed and avoid abrupt withdrawal unless advised by the primary care prescriber or specialist.
- Attend regularly for monitoring and review appointments with primary care and specialist and keep contact details up to date with both prescribers. Be aware that medicines may be stopped if they do not attend. If they are unable to attend any appointments, they should inform the relevant practitioner as soon as possible and arrange an alternative appointment.
- Report adverse effects to their primary care prescriber. Seek immediate medical attention if they develop any symptoms, as detailed in section 11.
- Report the use of any over-the-counter (OTC) medications to their primary care prescriber and be aware that they should discuss the use of sulfasalazine and any current medication with their pharmacist before purchasing any OTC medicines.
- Patients of childbearing potential should take a pregnancy test if they think they could be pregnant. Inform the specialist or GP immediately if they become pregnant or wish to become pregnant and take folic acid 5mg daily supplementation.
- Store their medication securely away from children.
- Read the information supplied by their GP, specialist and pharmacist, and contact the relevant practitioner if they do not understand any of the information given.
- Keep the patient-held monitoring booklet, if available, up-to-date with the results of investigations, dosage changes, and management alterations. Take any actions necessary.

Community pharmacist roles and responsibilities

- The community pharmacist will professionally check prescriptions to ensure they are safe for the patient and contact the GP if necessary.
- Fulfil the legal prescriptions for medication for the patient unless they are considered unsafe.
- Counsel the patient on the proper use of their medication.
- Be aware of patients who attend with symptoms such as unexplained bleeding, purpura, sore throat, fever or malaise, as these can be signs of toxicity or intolerance. Refer them back to the prescriber for further investigation. It is a good practice to maintain a record of any over-the-counter items supplied to the patient.

1. Background

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Sulfasalazine is of proven benefit as a disease-modifying antirheumatic drug (DMARD) used to treat a number of rheumatological conditions and to induce and maintain remission in certain inflammatory gastrointestinal diseases. Clinical improvement may take up to 3 months. NSAIDs and simple analgesics may need to be continued.

This shared care protocol applies to adults aged 18 and over.

2. Indications

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The licensed indications for sulfasalazine are:

- Rheumatoid arthritis (EC tablets only)

Sulfasalazine is also used off-label for other chronic inflammatory disorders, including:

- Seronegative spondyloarthropathies such as psoriatic arthritis and enteropathic arthritis.

3. Locally agreed off-label use

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To be agreed and completed locally (include supporting information)
National scoping did not identify any additional appropriate off-label indications.

4. Contraindications and cautions

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This information does not replace the Summary of Product Characteristics (SPC) and should be read in conjunction with it. Please see BNF & SPC for comprehensive information.

Contraindications:

- Known hypersensitivity to sulfasalazine, its metabolites or any of the excipients as well as sulfonamides or salicylates.
- Porphyria.

Cautions:

- Hepatic or renal impairment.
- Pre-existing blood dyscrasias.
- Severe allergy or bronchial asthma.
- Glucose-6-phosphate dehydrogenase (G6PD) deficiency due to risk of haemolytic anaemia.
- Folic acid deficiency.
- Adequate fluid intake should be maintained during treatment to avoid crystalluria and kidney stone formation.
- Slow acetylator status increases the risk of sulfapyridine-related adverse drug reactions (ADRs) which can present as a drug-induced lupus-like syndrome.
- Pregnancy and breastfeeding – Sulfasalazine has been safely used in pregnancy, but a folic acid supplement of 5mg per day should be prescribed to those trying to conceive and during pregnancy. Small amounts of the medicine may be excreted in breast milk although these are not thought to be a risk to a healthy term infant.
- Sulfasalazine can be prescribed to men of childbearing potential, although there may be transient reversible oligospermia and infertility. Pregnancy may still occur, and contraception is needed.

5. Initiation and ongoing dose regimen

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- Once the patient is known to be tolerating the medicine, transfer to shared care would normally take place. Before transfer to shared care, the patient is expected to have had at least one specialist review and be stable (no increase in mediation dose for at least 6 weeks alongside satisfactory investigation results). On transferring shared care, the specialist will provide at least 4 weeks medication to enable the practice to receive and process the shared care agreement and set up prescribing and ongoing monitoring. Any bloods required within the 4 weeks should be requested/organised and followed up by the specialist.
- The duration of treatment & frequency of review will be determined by the specialist based on clinical response and tolerability.
- All dose or formulation adjustments will be the responsibility of the initiating specialist unless directions have been discussed and agreed upon with the primary care clinician.
- Termination of treatment will be the responsibility of the specialist.

Initial stabilisation:

Rheumatoid arthritis (using enteric coated (EC) tablets):

500mg daily, increasing by 500mg each week until 2-3g per day in divided doses is reached according to response. Only the enteric coated tablets are licensed in rheumatoid arthritis; use of other formulations is off-label.

For other indications take specialist advice.

The initial stabilisation period must be prescribed by the initiating specialist.

Maintenance dose (following initial stabilisation):
Rheumatoid arthritis and other indications (using EC tablets):
2-3g daily in divided doses.

The initial maintenance period must be prescribed by the initiating specialist.

Duration of treatment:
All DMARDs are long-term treatments. Onset of effect is slow and a marked effect may not be seen for up to 3 months.

Conditions requiring dose adjustment:

In patients with GFR <10 mL/min, start at very low dose and monitor.

6. Pharmaceutical aspects

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Route of administration:	Oral
Formulation:	500mg enteric coated (EC) tablets
Administration details:	EC tablets should be swallowed whole and not crushed or broken.
Other important information:	EC tablets are licensed for use in rheumatoid arthritis. Sulfasalazine may cause a yellow-orange discolouration of body fluids and skin. Certain types of extended-wear soft-contact lenses may be permanently stained.

	Sulfasalazine or its metabolites may interfere with ultraviolet absorbance, particularly at 340 nm, and may cause interference with some laboratory assays that use NAD(H) or NADP(H) to measure ultraviolet absorbance around that wavelength. Examples of such assays may include urea, ammonia, LDH, α-HBDH and glucose. It is possible that alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine kinase-muscle/brain (CK-MB), glutamate dehydrogenase (GLDH), or thyroxine may also show interference when sulfasalazine treatment is given at high doses. Consult with the testing laboratory regarding the methodology used. Caution should be exercised in the interpretation of these laboratory results in patients who are receiving sulfasalazine. Results should be interpreted in conjunction with clinical findings.

7. Significant medicine interactions

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The following list is not exhaustive. Please see BNF or SPC for comprehensive information and recommended management.

- **Digoxin:** Reduced absorption may be seen when used concomitantly with sulfasalazine.
- Sulfonamides are chemically similar to some **oral hypoglycaemic agents** and may cause hypoglycaemia. Patients receiving sulfasalazine and hypoglycaemic drugs should closely monitor blood glucose.
- **Azathioprine and 6-mercaptopurine:** Possible risk of bone marrow suppression and leucopenia
- **Folate** absorption and metabolism may be reduced by sulfasalazine**.**
- **Darolutamide and voxilaprevir** may increase exposure to sulfasalazine, manufacturer advises avoid.

8. Baseline investigations, initial monitoring, and ongoing monitoring to be undertaken by specialists

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Monitoring at baseline and during initiation is the responsibility of the specialist; only once the patient is optimised on the chosen medication with no anticipated further changes expected in the immediate future will prescribing and monitoring be transferred to primary care.

Baseline investigations

- Urea and electrolytes (U&Es) including creatinine and creatinine clearance (CrCl)
- Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST), & albumin
- Full blood count (FBC)

- Weight
- Height and blood pressure
- Assess for co-morbidities which may influence DMARD choice
- Screening for HIV and hepatitis B and C should be undertaken at clinicians discretion.
- Screening for lung disease, including tuberculosis, should be undertaken at clinician discretion on a case-by-case basis.
- Provide or request appropriate vaccination prior to treatment initiation, according to local arrangements (e.g., pneumococcal, influenza, COVID-19)

Initial monitoring and at dose change:

- To be repeated every 2 weeks until the dose has been stable for 6 weeks, then monthly for three months, and then 3 monthly thereafter. BP
- FBC
- U&Es, including creatinine and CrCl
- AST and/or ALT, albumin, and bilirubin
- Rheumatology patients: C-reactive protein (CRP) &/or erythrocyte sedimentation rate (ESR) - may or may not be monitored by the specialist. The decision to monitor is dependent on the patient's risk.

Following a dose change, repeat every 2 weeks until the dose has been stable for 6 weeks, then revert to the previous schedule.

More frequent monitoring is appropriate in patients at higher risk of toxicity.

Ongoing monitoring:

The specialist will retain the responsibility for monitoring the patient's ongoing response to treatment and advise if a dose change or treatment cessation is appropriate. **This should usually be undertaken annually.**

After each review, advise primary care whether treatment should be continued, confirm the ongoing dose, and whether the ongoing monitoring outlined in section 9 remains appropriate.

9. Ongoing monitoring requirements to be undertaken by primary care

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See section 10 for further guidance on the management of adverse effects/responding to monitoring results.

Monitoring and advice	Frequency
• FBC • U&Es including creatinine and CrCl • ALT and/or AST and albumin • Rheumatology patients: CRP &/or ESR (only if requested by the specialist)	Three Monthly After 12 months no routine monitoring is required for the majority of patients. Annual serum creatinine or eGFR may be considered. **The decision to discontinue monitoring should be following advice from the specialist for the individual patient.**
• Patients aged from 50 years who are severely immunosuppressed and have not received the shingles vaccine before will be eligible for the shingles vaccine (varicella zoster). This will be provided as two doses of the non-live vaccine. If the patient is taking additional DMARDs, check advice for all drugs. Please refer to Green Book Chapter 6 and Chapter 28a (Shingles) for further details. • **Annual** influenza (The Green Book, Chapter 19) vaccinations are highly recommended • **COVID-19** vaccination is safe and recommended (see The Green Book, Chapter 14a). • Repeat pneumococcal vaccine. See The Green Book Chapter 25 for advice.	• Shingles vaccination: Chapter 28a (Shingles). • Influenza vaccination: annual. It is advisable to add the patient to the influenza vaccine list. • Other vaccinations as per national schedule, e.g., pneumococcal vaccine, COVID-19.
(If relevant) If monitoring results are forwarded to the specialist team, please include clear clinical information on the reason for sending, to inform action to be taken by secondary care.	

10. Adverse effects and other management

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Any serious adverse reactions should be reported to the MHRA via the Yellow Card scheme. Visit www.mhra.gov.uk/yellowcard

For a full list of side effects and information on incidence of ADRs, refer to the BNF or see relevant summaries of product characteristics

IF YOU ARE IN ANY DOUBT ABOUT ANY POTENTIAL ADVERSE REACTION, PLEASE CONTACT THE RHEUMATOLOGY SPECIALIST TEAM.

Result	Action for primary care
As well as responding to absolute values in laboratory tests, a rapid change or a consistent trend in any value should prompt caution and extra vigilance Other benchmark values may be set by secondary care in specific clinical circumstances. This will be communicated by the specialist.	
Full blood count • White blood cells less than 3.5 $x10^9$/L • Lymphocytes less than 0.5 $x10^9$/L • Neutrophils less than 1.6 $x10^9$/L • Platelets less than 140 $x10^9$/L • Unexplained eosinophilia greater than 0.5 $x10^9$/L • Unexplained fall in albumin; less than 30g/L	Withhold treatment and discuss with specialist.
Signs or symptoms of bone marrow suppression, e.g., unexplained bleeding or bruising with or without sore throat, purpura, mouth ulcers.	Check FBC immediately, withhold treatment while awaiting results, and discuss with the specialist team. See haematological monitoring above.
Liver function tests: • ALT and/or AST greater than 100units/L • And/or a sudden increase (e.g., doubling of baseline) • Jaundice	Withhold and discuss with specialist team. Check any other reason for risk of hepatic dysfunction such as alcohol history and drug interactions, including OTC or complementary medication.
Renal function	Use clinical judgement and repeat in 1 week

• Creatinine increase of greater than 30% from baseline in the last 12 months or CrCl reduces to less than 60mL/min	If still more than 30% from baseline, withhold and discuss with specialist.
The following adverse effects and management below only apply during the initiation period as these are unlikely caused by established use of sulfasalazine.	
Gastrointestinal disorders • Nausea, vomiting, diarrhoea or unintentional weight loss	Review for reversible causes. Advise patient to take with food. If no improvement, contact specialist team.
Other symptoms • Skin/mucosal reaction, e.g., serious rash • Diffuse alopecia • Breathlessness or cough • Peripheral neuropathy • Oral ulceration	Consider withholding treatment and discussing with specialist. For widespread rash, discontinue and discuss with specialist urgently. For oral ulceration, withhold until discussed with the specialist.
Other symptoms • Dizziness/headache	Continue if possible. May reduce dose or stop if the symptoms are severe. Discuss with the rheumatology specialist if necessary.

11. Advice to patients and carers

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The specialist will counsel the patient with regard to the benefits and risks of treatment and will provide the patient with any relevant information and advice, including patient information leaflets on individual medicines.

The patient should be advised to report any of the following signs or symptoms to their primary care prescriber without delay:

- Sore throat, mouth ulcers, fever, malaise, swollen lymph nodes, or unexplained bleeding, purpura or bruising.

The patient should be advised to report any of the following signs or symptoms during initiation period only:

- Progressive skin rash with blisters or oral ulcerations – see below
- Nausea, vomiting, diarrhoea, jaundice, dark urine and unintentional weight loss.
- Hair loss
- Breathlessness, infection or cough

- Symptoms of peripheral neuropathy e.g., pins and needles, numbness or burning pain in extremities

The patient should be advised:

- Life-threatening skin reactions Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with the use of sulfasalazine. The highest risk for occurrence is within the first weeks of treatment. Patients should be advised to report a progressive skin rash often with blisters or mucosal lesions, or any other sign of hypersensitivity.
- Tell anyone who prescribes them a medicine that they are taking sulfasalazine. Always ask a pharmacist before purchasing any medicines over the counter, including herbal remedies, and ask if they are safe.
- That vaccination in line with current national advice (e.g., for COVID-19, influenza) is safe and recommended.
- Sulfasalazine may cause a harmless yellow-orange discolouration of body fluids and skin. Certain types of extended wear soft-contact lenses may be permanently stained.
- To maintain adequate fluid intake during treatment to reduce the risk of crystalluria and kidney stones.
- What shared care means for their treatment, what to expect, and their responsibilities under shared care.
- The patient should be given an approved information leaflet from Versus Arthritis. Further copies are available here.

Patient information:

- Versus Arthritis Sulfasalazine

12. Pregnancy, paternal exposure and breast feeding

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All patients should be informed of the risks and benefits of taking this medicine during pregnancy and breastfeeding. The specialist team should be contacted if a patient becomes pregnant or is planning to become pregnant or breastfeed.

The BSR and BHPR guideline on prescribing DMARDs in pregnancy and breastfeeding advises the following:

Pregnancy:

Sulfasalazine, with folate supplementation (5 mg/day), is compatible throughout pregnancy.
If a patient is considering conception, this should be discussed with the Rheumatology team at least 3 months in advance.

Information for healthcare professionals: Sulfasalazine in pregnancy (UKTIS)

Information for patients and carers: Sulfasalazine in pregnancy (Bumps)

Breastfeeding:
Sulfasalazine is compatible with breastfeeding in healthy, full-term infants.
There have been reports of bloody stools or diarrhoea in infants who were breastfeeding from mothers on sulfasalazine. In cases where the outcome was reported, bloody stools or diarrhoea resolved in the infant after discontinuation of sulfasalazine in the mother.
Information for healthcare professionals: https://www.sps.nhs.uk/medicines/sulfasalazine/

Paternal exposure:
Men taking sulfasalazine may have reduced fertility, due to oligospermia and impaired mobility, which may take 2-3 months to return to normal following treatment cessation.

13. Specialist contact information

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Name: **Named Rheumatology Consultant as per clinic letter**
Role and specialty: **Consultant Rheumatologist**
Daytime telephone number:
NUH: 0115 919 4477 Secretaries Extension: 78947,
SFH: 01623 676002 then choose option 2
Email address:
NUH: Nuhnt.ntcrheumatologysecretaries@nhs.net,
SFH: sfh-tr.rheumqueries@nhs.net

14. Additional information

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Where patient care is transferred from one specialist service or GP practice to another, a new shared care agreement must be completed. Ensure that the specialist is informed in writing of any changes to the patient's GP or their contact details.

15. References

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- Salazopyrin En tabs. Date of revision of the text 24/12/2021. Accessed via https://www.medicines.org.uk/emc/product/6686/smpc on 17.07.23.
- British Society of Rheumatology and British Health Professionals in Rheumatology. 2017. Guidelines for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs. Accessed via https://academic.oup.com/rheumatology/article/56/6/865/3053478.
- British Society of Rheumatology and British Health Professionals in Rheumatology. 2016. Guideline on prescribing drugs in pregnancy and breastfeeding – Part I: standard and

biologic disease modifying anti-rheumatic drugs and corticosteroids. Accessed via https://academic.oup.com/rheumatology/article/55/9/1693/1744535.
- eBNF – accessed via https://bnf.nice.org.uk/on 17.07.23.
- UK Teratology Information Service. Use of sulfasalazine in pregnancy. Version 3 October 2020. Accessed via https://uktis.org/monographs/use-of-sulfasalazine-in-pregnancy// on 17.07.23.
- Best Use of Medicines in Pregnancy. Last updated September 2020, accessed via https://www.medicinesinpregnancy.org/Medicine--pregnancy/Sulfasalazine/ on 17.07.23.
- NICE Clinical Knowledge Summaries - DMARD management. Last revised December 2021. Accessed via https://cks.nice.org.uk/topics/dmards/management/ on 17.07.23.
- Briggs G. Drugs in Pregnancy and Lactation, Ninth Edition. Sulfasalazine Monograph.

16. Other relevant national guidance

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- NHSE guidance – Responsibility for prescribing between primary & secondary/tertiary care. Available from https://www.england.nhs.uk/publication/responsibility-for-prescribing-between-primary-and-secondary-tertiary-care/
- General Medical Council. Good practice in prescribing and managing medicines and devices. Shared care. Available from https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/good-practice-in-prescribing-and-managing-medicines-and-devices/shared-care
- NICE NG197: Shared decision making. Last updated June 2021. https://www.nice.org.uk/guidance/ng197/.

17. Local arrangements for referral

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Define the referral procedure from hospital to primary care prescriber & route of return should the patient's condition change.

- The request for shared care should be accompanied by individual patient information, outlining all relevant aspects of the patient's care and which includes direction to the information sheets at the APC website.
- The specialist will request shared care with the GP in writing.
- If the GP doesn't agree to shared care, they should inform the specialist of their decision in writing within 14 days, outlining the reason for the decline. The agreement can be assumed if the GP does not provide a written decline.
- In cases where shared care arrangements are not in place or where problems have arisen within the agreement, and patient care may be affected, the responsibility for the patient's management, including prescribing, reverts to the specialist. Should the patient's condition change, the GP should contact the relevant specialist using the details provided with the shared care request letter.