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Gloucestershire Health and Care
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CLINICAL POLICY
Clozapine

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Policy Number	CLP265
Version:	V5.1
Purpose:	The purpose of this policy is to set out the governance framework to be followed by GHC colleagues involved in the prescribing, ordering, dispensing, administration and monitoring of clozapine and those who support patients prescribed clozapine. It sets out the requirements for the initiation, maintenance and monitoring of clozapine in inpatient and outpatient settings and the requirements for monitoring physical health and side effects of patients prescribed clozapine. This policy provides a framework so that patients prescribed clozapine are supported to take it safely and to manage the risk that clozapine can pose to them.
Consultation:	Clozapine Governance Group / Medicines Optimisation Group / Clinical Policy Group Consultation Distribution List
Approved by:	Clozapine Governance Group – 28th August 2025 Medicines Optimisation Group – 11th September 2025
Ratified by:	Clinical Policy Group
Date Ratified:	18/11/2025
Date of Issue:	03/12/2025
Review Date:	01/12/2028
Author / Reviewer:	Reviewed by: Laura Bucknell. Chief Pharmacist
Audience:	This policy is for all GHC colleagues who are involved in ordering, prescribing and administration of clozapine and to all colleagues who support patients prescribed clozapine
Dissemination:	The policy will be published on the GHC intranet, and its update will be listed on the Clinical Policy update bulletin
Impact Assessments:	This Policy has been subjected to an Equality Impact Assessment. This concluded that this policy will not create any adverse effect or discrimination on any individual or particular group and will not negatively impact upon the quality of services provided by the Trust

Version History

Version	Date Issued	Reason for Change
V1	Sep 2014	Policy Review Paul Ward and Rachel Jackson
V2	Sept 2017	Policy Review Rachel Jackson, George Morris, Paul Ward, Helen Elliott, Veena Aggarwal, Henry Delacave
V2.1	Feb 2018	Updated to include revised Appendices
V2.2	June 2018	Revised following medication error risk for Denzapine® initiation and revised appendices - Rachel Jackson/Helen Elliott
V3	Oct 2019	Full Policy Review and New Format
V4	Mar 2020	Reference to Herefordshire services removed
V4.1	Oct 2020	Updated to reflect MHRA Drug Safety Update monitoring blood concentration for toxicity – Clozapine plasma monitoring section and information about Zaponex® brand
V4.2	Feb 2021	Amendment to section 6 Training Clozapine e learning for clinical staff working with patients on Clozapine Helen Elliott/Rachel Jackson
V4.3	12/05/2022	Policy under review included
V5	03/12/2025	Complete re-write of policy and inclusion of action cards
V5.1	16/12/2025	6.1 – Clarification of wording on who can prescribe by registered with ZTAS, 6.5.3 and Action Card 1 – clarification of wording on who can initiate clozapine, Appendix 2- inclusion of use of botulinum toxin and reference source for this.

SUMMARY

Clozapine is an atypical antipsychotic licensed for treatment-resistant schizophrenia (TRS) and psychotic disorders occurring during the course of Parkinson's disease where standard treatment has failed.

Clozapine can on rare occasions cause neutropenia and agranulocytosis, which has led to the MHRA mandating that the drug may only be used in combination with a strict blood test monitoring regime. This together with other aspects of clozapine's adverse effect profile have led to it being a specialist only prescribed drug in Gloucestershire and as the lead provider of mental health services, all prescribing is the responsibility of GHC.

The brand of clozapine currently used within GHC is Zaponex® produced by Leyden Delta and the Zaponex® Treatment Access System (ZTAS) is the Trust approved monitoring service for GHC.

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ABBREVIATIONS

Abbreviation	*Full Description*
ANC	Absolute neutrophil Count
AOT	Assertive Outreach Team
BEN	Benign Ethnic Neutropenia
BMI	Body Mass Index
BNF	British National Formulary
CGH	Cheltenham General Hospital
CMHT	Community Mental health team
CPK	Creatinine phosphokinase
CRHTT	Crisis Resolution and Home Treatment Team
ECG	Electrocardiogram
ED	Emergency Department
EDTA	Ethylenediaminetetraacetic acid
eGFR	Estimated Glomerular filtration rate
EHIC	European Health Insurance Card
FBC	Full Blood Count
GASS-C	Glasgow antipsychotic side-effect scale for clozapine
GHC	Gloucestershire Health and Care NHS Foundation Trust
GHIC	Global Health Insurance Card
GMC	General Medical Council
GORD	Gastro-oesophageal reflux
GRH	Gloucestershire Royal Hospital

IM	Intramuscular
LFT	Liver Function Test
MCA	Mental Capacity Act
MDT	Multidisciplinary Team
MHRA	Medicines and Health Products Regulatory Agency
NICE	National Institute for Health and Care Excellence
NMS	Neuroleptic Malignant Syndrome
NRT	Nicotine replacement therapy
POCT	Point of Care Test/Testing
RCT	Randomised controlled trial
RMO	Responsible Medical Officer
SCR	Summary Care Record
TDM	Therapeutic drug monitoring
TRS	Treatment Resistant Schizophrenia
WCC	White Cell Count
WHR	Waist- hip ratio
ZTAS	Zaponex Treatment Access System
ZTAS PIN	Zaponex Treatment Access System Patient Identification Number

ACTION CARD 1

CLOZAPINE INITIATION
Key points
(refer to Clozapine Policy section 6.5 for full details)

For use by: all GHC colleagues involved in ordering, prescribing and administration of clozapine or support patients prescribed clozapine

- The clozapine commencement pathway must be used when starting a patient on clozapine.
- Clozapine can only be initiated by consultant psychiatrists and suitably qualified speciality doctors delegated to by a consultant.
- Pre-existing physical health conditions, drug interactions and side/adverse effects must be considered prior to the initiation of clozapine.
- Appropriate health checks and assessment must be completed before initiating clozapine.

HEALTH CHECKS REQUIRED BEFORE INITIATING CLOZAPINE

- Full medical and psychiatric history.
- Blood tests
  - Full blood count (FBC) - baseline white cell count (WCC) and differential count.
  - Fasting blood glucose (Random blood glucose if fasting not possible) or HbA1c
  - Liver Function Tests (LFTs)
  - Urea and Electrolytes (including creatinine and eGFR)
  - Blood lipids – cholesterol and triglycerides (Fasting if possible)
  - Prolactin.
- Electrocardiogram (ECG)- A recent Electrocardiogram (ECG) (within the previous 6 months) is recommended before starting clozapine (as with all antipsychotics). If patients have a history of cardiac illness or abnormal cardiac findings on physical examination, consideration should be given to the balance of risk and cardiology opinion sought if there is doubt. Any discussion and the outcome must be documented in the patient record.
- Echocardiogram if clinically indicated.
- Weight and Obesity Measure.
- Blood Pressure and pulse.
- Smoking status including what is smoked and much per day.
- Baseline bowel habit – If there is pre-existing constipation, it must be adequately treated before initiating clozapine.
- During the titration phase, the reviewing doctor must review at least weekly:
  - Patient's mental state
  - Side/adverse effects to clozapine and manage as necessary
  - Other medication prescribed and reduced as necessary.

ACTION CARD 2

ORDERING FBC TESTING KITS AND PATIENT LABELS FROM ZTAS
(refer to Clozapine Policy section 6.8.2)

For use by: all GHC colleagues involved in ordering, prescribing and administration of clozapine or support patients prescribed clozapine

- All supplies of blood testing kits and labels come from Magna laboratories.

- Forms for ordering of the blood testing kits and patient's labels can be downloaded at www.magnalabs.co.uk/forms
- You will require the following forms:
    - Magna Labs Zaponex® (Clozapine) consumables request form
    - Clozapine Patient Blood Labels Request Form
- Complete the form then scan and to magnalabs.info@nhs.net. Requests/orders are NOT accepted over the phone.
- If emailing magna labs, please include the following information in your order:
    - Contact details of person ordering the supplies
    - Address to send the items to
    - What items you require and how many of each
        (if ordering sampling kits please specify that they are for FBC, routine monitoring, blue form)
        (if ordering labels, please specify the patient's initials, date of birth and ZTAS PIN (patient identification number))
- Magna labs will aim to dispatch the order within 3 working days of receipt of order.

BLOOD SAMPLING KITS and CONTENTS

- ZTAS blood sampling kits are pre-made and include the following:
    - Ethylenediaminetetraacetic acid (EDTA) sample tube, needle and needle protection device
    - Small sealable bag with swab for the sample
    - Blue sample form
    - Cardboard box and silver pre-addressed covering envelope.

- Taking the sample:
    - Take the FBC using the kit provided in the box
    - Place a patient bar coded label on the sample tube and on the blue sample form
    - Place the tube in the plastic sealed bag then place this in the box and seal it in the covering envelope
    - Put ready to go in the Royal Mail post.

ACTION CARD 3

REPORTING RESULTS TO ZTAS
(refer to section 6.8.2 of the Clozapine Policy)

For use by: all GHC colleagues involved in ordering, prescribing and administration of clozapine or support patients prescribed clozapine

- If local sampling is utilised for analysis either due to exceptional circumstances, weekly or extra sampling, THE COMMUNITY TEAM or WARD **MUST** REPORT THE RESULTS TO ZTAS.

Emailing results

- Results must be sent to ZTAS in written form, this can be done by email info@ztas.co.uk. Results cannot be phoned through
- ONLY include the following identifying information:
    - Patient initials
    - Date of birth
    - ZTAS PIN if available (this will be located in the alert section in RIO).

- Report the following information:
    - Date of sample
    - White cell Count
    - Neutrophil count
    - Platelet count
    - Eosinophil count (if available).

Reporting directly to the ZTAS website
'Proxy' access to the ZTAS website can be obtained so blood tests can be reported directly to ZTAS via their website – please speak with your team pharmacist to organise this.
ZTAS telephone number for advice - 020 7365 5842.
    - Put ready to go in the Royal Mail post.

ACTION CARD 4

MANAGING CLOZAPINE AFTER A RED FBC RESULT
(refer to section 6.9.5 and 6.12 of the Clozapine Policy)

For use by: all GHC colleagues involved in ordering, prescribing and administration of clozapine or support patients prescribed clozapine

- A red blood result alert is a clinical emergency; the patient is at risk of harm and immediate action must be taken.
- Other physical signs are flu-like symptoms e.g. fever, rapid pulse and respiration, sore throat, hypotension, mouth ulcers, swollen and tender gums and skin infections.
- Management of a red result is the clinical responsibility of patient's consultant psychiatrist who must liaise with the ZTAS and keep the patient and carer(s) informed of progress.

Action To Be Taken When a Red Alert Is Received

- ZTAS will contact the patient's registered contact. This is usually the consultant psychiatrist or nominated deputy and the registered pharmacist This person is responsible for ensuring the actions required are completed.
- **STOP CLOZAPINE IMMEDIATELY.** Instruct the patient to stop taking clozapine until further notice (remove the tablets as soon as possible) due to the risk of depressing white blood cells further.
- If another antipsychotic is started this must be done with caution and following consultation with wider team. Choose an antipsychotic with a lower risk of neutropenia.
- Fully explain to the patient and their carer if appropriate, the implications and the procedure to be followed.
- Ensure the following are updated on the situation
  - Consultant psychiatrist or nominated deputy
  - Team leader/ward manager or deputy
  - Dispensing pharmacist
  - Care co-ordinator
  - Crisis Resolution and Home Treatment Team (CRHTT) if appropriate.

- The consultant psychiatrist or deputy/nurse in charge must arrange an emergency blood test as soon as possible via the nearest pathology laboratory. This must be carried out locally and not sent to ZTAS for analysis due to the urgency.
- The clinician arranging the FBC test must ensure the pathology laboratory has a named contact to inform of the results in and out of hours (if appropriate).
- The clinician receiving the blood result from the pathology laboratory must relay it to ZTAS as soon as it has been received.
- Daily FBCs are required until the neutrophil count has risen to least $1.5x10^9$/L.
- Daily physical health checks are to be carried out. These should include as a as a minimum:
  - Body temperature
  - Blood pressure
  - Pulse rate
  - Respiratory rate

ACTION CARD 4

MANAGING CLOZAPINE AFTER A RED FBC RESULT
(refer to section 6.9.5 and 6.12 of the Clozapine Policy)

For use by: all GHC colleagues involved in ordering, prescribing and administration of clozapine or support patients prescribed clozapine

- Monitoring for clinical signs and symptoms of infection (e.g. fever, sore throat, mouth ulcers etc.).

- A haematologist must be contacted for advice If clozapine has been stopped and either:
  - WBC count falls below 2.0 x 10^9/L occur OR
  - Absolute Neutrophil Count (ANC) falls below 1.0 x10^9/L

- Advise the patient to avoid close contact with others due to the increased risk of infection.
- Monitor the patient's mental state on an on-going basis as a psychotic relapse can occur following sudden withdrawal of clozapine.
- Monitor the patient for other side effects of sudden withdrawal of clozapine. These can include
  - Restlessness
  - Agitation
  - Confusion
  - Profuse sweating
  - Diarrhoea
  - Dyskinesia
  - Headache
  - Insomnia
  - Nausea and vomiting.
    Treatment for these symptoms may have to be considered.
  - In rare cases clozapine discontinuation can present as catatonia.

- Update the patient's risk assessment and record all results and events on RIO as soon as possible, in order that the information is readily available to healthcare professionals.
- Continue FBC monitoring as advised by the ZTAS
- Ensure the patient/carer(s) and other team members are aware of the need to watch for signs of infection. If there are any concerns about the identification of signs of infection
- Following a two confirmed red results ZTAS will add the patient to the Central Non-Rechallenge Database.

ACTION CARD 5

REPORTING RESULTS TO ZTAS
(refer to section 6.8.2 of the Clozapine Policy)

For use by: all GHC colleagues involved in ordering, prescribing and administration of clozapine or support patients prescribed clozapine

MISSED DOSES AND TREATMENT BREAKS OF LESS THAN 48HRS

- If a patient misses one or more doses, but less than 48 hours have lapsed since they last took clozapine, their clozapine can be continued with the next prescribed dose. They must not try to 'catch up' by taking two doses at once.

- If the missed doses occurred during a titration however, the titration should be restarted at a logical point. See section 'Clozapine Initiation'.

- A repeat FBC is not required if the patient still has a valid green FBC result. Contact pharmacy for further advice if needed.

TREATMENT BREAKS OF MORE THAN 48HRS (2 DAYS) BUT LESS THAN 72HRS (3 DAYS)

- If clozapine has not been taken for more than 48 hours patients must have their clozapine re-titrated. This is due to the increased risks of cardiac complications when restarting clozapine (e.g. postural hypotension, tachycardia or bradycardia). Once the medicine has been discontinued the clozapine plasma level drops quickly. Large increases in doses following treatment breaks have caused death in patients that had already been taking clozapine. A rapid re-titration should be started as soon as possible. Refer to table 1 below.
- If there is any doubt as to the exact duration of a patient's treatment break it is advisable to re-titrate clozapine.

TREATMENT BREAKS OF MORE THAN 72HRS (3 DAYS)

- If the treatment break is more than 72 hours then the patient needs to have a valid FBC, taken within 7 days, prior to re-commencing the clozapine.

- The re-titration must commence at a dose of no more than 12.5mg - 25mg. The dose can then be increased according to patient tolerability. A more rapid titration than an initially used may be appropriate if the patient has previously tolerated clozapine, if the treatment break has been relatively short, there are no significant co-morbidities, and the patient is physically healthy.

ZTAS must be informed of any treatment breaks in excess of 72 hours, and the blood monitoring frequency may also change depending on the duration of the

- treatment break. See the summary table below for advice on haematological monitoring following treatment breaks.

ACTION CARD 5

REPORTING RESULTS TO ZTAS
(refer to section 6.8.2 of the Clozapine Policy)

For use by: all GHC colleagues involved in ordering, prescribing and administration of clozapine or support patients prescribed clozapine

Table 1:

Table 1 Re-starting clozapine[2]	
Time since last clozapine dose	**Action to re-start**
Up to 48 hours	Restart at previous dose – no re-titration required
48 – 72 hours	Begin rapid re-titration as soon as possible On day 1, re-start with half of the previously prescribed total daily dose given in divided doses 12 hours apart. Then give 75% of previous daily dose on day 2 and, if prior doses have been tolerated, the whole of the previous daily dose in the normal dosing schedule on day 3
72 hours – 1 week	Begin re-titration with 12.5 or 25 mg clozapine Try a second dose 12 hours later if the first is well tolerated. Increase to ´normal´ dose according to patient tolerability over at least 3 days
More than 1 week	Re-titrate as if new patient Aim to reach previously prescribed dose within 2-4 weeks. Increase according to tolerability

Taken from: Zaponex Fact Sheet Clozapine dosing, available in the ZTAS website via a secure login.

Table 2

Previous Sampling Frequency	Break in Treatment	Blood Monitoring on Restart
Weekly	72 hrs. (3 days) or less	Weekly, no need to re-start re-titration
	More than 3 days up to and including 7 days	Weekly, continuing the 18-week titration period. It will be ensured that the patient has at least 6 weeks of weekly monitoring prior to decrease of the monitoring frequency
	More than 7 days	Weekly, MUST restart 18-week titration period
Fortnightly	72hrs (3 days) or less	Fortnightly, continue
	More than 3 days up to and including 4 weeks	Weekly for 6 weeks, then continue fortnightly
	Longer than 4 weeks	Weekly, re-start 18-week titration period
4-Weekly	72hrs (3 days) or less	4-weekly, continue
	More than 3 days up to and including 4 weeks	Weekly for 6 weeks, then continue 4-weekly
	Longer than 4 weeks	Weekly, re-start 18-week titration period. After 18 weeks switch to 4 weekly

ACTION CARD 6

CLOZAPINE – THERAPEUTIC DRUG MONITORING
(Clozapine Plasma Levels and Assay)
(refer to section 6.15 of the Clozapine Policy)

For use by: all GHC colleagues involved in ordering, prescribing and administration of clozapine or support patients prescribed clozapine

- In addition to the routine mandatory FBC monitoring, plasma levels of clozapine can also be measured. This can guide clinicians in the optimisation of the clozapine dose and ensure that the potential benefits of the current clozapine dose outweigh the risks.
- GHC do not recommend carrying out clozapine therapeutic drug monitoring (TDM) at routine time intervals, but clozapine assays can be useful in optimising treatment.
- GHC recommend that checking clozapine levels must be considered in the following situations:
  - To guide clozapine dosing after commencement
  - Signs of clozapine toxicity
  - Excessive adverse effects
  - Change in smoking status
  - Commencing or discontinuing concomitant medicines that may interact to alter clozapine blood levels
  - Symptoms/signs of infection e.g. flu like symptoms and raised temperature but this list is not exhaustive
  - Symptoms/signs of inflammation
  - After surgery
  - Lack/incomplete clinical response to standard dosing
  - Poor/ non-adherence with clozapine is suspected
  - If a dose reduction is required following stabilization
  - If a disorder that may affect metabolism of clozapine is suspected e.g. liver disease.
- Trough blood samples must be used when checking plasma clozapine level. To achieve this take the sample pre-dose or 10-14 hours post dose.
- It is also important that the clozapine is at steady state so the patient should be on a stable dose for a minimum of 5 days before taking the blood sample. If there are doubts as to how reliable the result will be, it is recommended to postpone the test until a reliable result is more likely.
- Request plasma level assay forms from Magna Laboratories, the ZTAS central laboratory
- Complete the plasma assay request form with the following details to aid interpretation of the result and sent with the blood sample:
  - Patient name and demographics
  - Date and time of blood sample
  - Date and time of last dose
  - Current dose
- The blood sample must be sent to Magna Labs NOT **to the local lab**. Bloods sent incorrectly cannot be processed.
- Magna Laboratories will report the clozapine plasma assay results directly to the Trust via the BloodResults web-application.

ACTION CARD 7

Template for Information Slip for Patients Requiring a CLOZAPINE Assay Blood Test
(refer to section 6.15.2 of the Clozapine Policy)

For use by: all GHC colleagues involved in ordering, prescribing and administration of clozapine or support patients prescribed clozapine

Your Doctor has requested that an assay blood test be completed.

An Assay tells us the level of clozapine in your blood and if you are taking the right amount of clozapine

For this blood test to be completed you will need to take your usual dose of clozapine at

……(Time& date)

And attend …… …… (Place)

At ……(time)

On……(Date)

If you have any questions please contact your care co-ordinator

ACTION CARD 8

CLOZAPINE – PHYSICAL HEALTH MONITORING REQUIREMENTS AND FREQUENCY

(refer to section 6.16 of the Clozapine Policy)

For use by: all GHC colleagues involved in ordering, prescribing and administration of clozapine or support patients prescribed clozapine

Ongoing physical health monitoring and frequency - The below list is not exhaustive. Additional physical health checks should be carried out if clinically indicated for the service user

TEST	FREQUENCY	ACTIONS IF OUTSIDE REFERENCE RANGE	COMMENTS
Full Blood Count (FBC)	• Baseline • Weekly – First 18 weeks of treatment • Fortnightly – weeks 19-52 of treatment • Every 4 weeks thereafter	Contact ZTAS and follow their guidance.	All FBC results should be reported to ZTAS; See action card 5 Results of FBC determine whether service user continues on clozapine – see section 6.6.
Weight and body mass index (BMI)	• Baseline • At each blood test (see comments)	Offer lifestyle advice. If BMI is above 30 or weight gain is rapid refer to consultant/RMO for review. Consider referral to Gloucestershire Healthy Lifestyles, see action card 8	Minimum of every 4 weeks when receiving fortnightly blood tests OR a minimum of every 8 weeks once 4 weekly blood tests
Bloods cholesterol and lipids (Fasting if possible)	• Baseline • 3 monthly for first 12 months • After 12 months, annually as part of routine physical health check	Offer lifestyle advice. Refer to GP to consider initiating statin therapy	BMI above 30 is clinically obese
HbA1c OR Plasma Glucose	• Baseline • After 1 month (plasma glucose only) • Every 4-6 months	If fasting glucose is above 6mmol/L and/or HbA1c is above 42mmol/mol (6%) highlight when reporting to GP. If random blood glucose is above 7.1mmol/L, check fasting blood glucose.	All results should be reported to the GP, and any abnormal ones should be highlighted.

ACTION CARD 8

CLOZAPINE – PHYSICAL HEALTH MONITORING REQUIREMENTS AND FREQUENCY

(refer to section 6.16 of the Clozapine Policy)

For use by: all GHC colleagues involved in ordering, prescribing and administration of clozapine or support patients prescribed clozapine

		If random blood glucose is above 11.1mmol/L and/or HbA1c is above 47mmol/mol (6.4%) diagnosis of diabetes is likely but needs confirming by GP.	
Blood pressure and Pulse	• Baseline • Hourly after first dose for 6 hours • Twice daily before each dose from second dose until stable dose reached • Weekly with each routine blood test until week 18 • Fortnightly weeks 19-52 of treatment • Every 4 weeks thereafter	If severe hypotension or hypertension is observed during titration, consider slowing the rate of increase. Treat hypertension in line with NICE guidelines. If pulse is above 100bpm refer to prescriber/GP for review. If postural changes in blood pressure and tachycardia occur, consider if myocarditis/cardiomyopathy are present	Additional readings should be taken if outside required range and/or a postural drop in blood pressure occurs. Consider increasing frequency of checks following dose increases. Clozapine is associated with blood pressure changes.
Liver function tests (LFTs)	• Baseline • Annually as part of routine physical health check		Clozapine is associated with hepatic failure. Clozapine is known to transiently raise liver enzymes. Refer to Prescriber/GP for advice if LFTs are more than 3 times upper limit. Consider whether clozapine should be stopped.
ECG	• Baseline	Discuss with cardiology if abnormality detected.	

ACTION CARD 8

CLOZAPINE – PHYSICAL HEALTH MONITORING REQUIREMENTS AND FREQUENCY

(refer to section 6.16 of the Clozapine Policy)

For use by: all GHC colleagues involved in ordering, prescribing and administration of clozapine or support patients prescribed clozapine

	• Annually as part of routine physical health check		
Urea and Electrolytes (including eGFR)	• Baseline • Annually as part of routine physical health check	Investigate any abnormalities detected	
Prolactin	• Baseline • Repeat (if elevation noted at baseline)		Clozapine is NOT associated with an elevation in prolactin. Monitoring is important if prolactin is high at baseline and elevation is due to previous antipsychotics. Warn of return of menses if amenorrhoea present and also pregnancy.
Creatinine phosphokinase (CPK)	• If Neuroleptic Malignant Syndrome (NMS) suspected	Stop clozapine and refer to acute hospital for assessment and treatment of NMS if other symptoms present.	

ACTION CARD 9

CLOZAPINE SIDE/ADVERSE EFFECT
(refer to section 6.17 of the Clozapine Policy)

For use by: all GHC colleagues involved in ordering, prescribing and administration of clozapine or support patients prescribed clozapine

Similarly to other medications clozapine can cause a range of side effects affecting different systems in the body. A full list of side effects is available at Zaponex 100 mg Tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk).

There is also information regarding side effects and their management in the BNF (BNF (British National Formulary) | NICE) and the Maudsley Prescribing Guidelines.

There are a range of fact sheets and information for patients about clozapine and its side effects available on www.choiceandmedication.org/2gether.

There are also a variety of factsheets relating to different side effects of clozapine, their mechanism and management on the secure area of ZTAS website (www.ztas.co.uk). These cover areas such as constipation, hypersalivation, tachycardia, metabolic side effects, myocarditis/cardiomyopathy, seizures.

Recommend that patient completes an annual GASS -C (Glasgow Antipsychotic Side Effect Scale – Clozapine) in order to assess their overall side effect burden from clozapine and to ascertain the most problematic side effects for the patient.
GASS-C can be found on GHC intranet GASS - Interact

The following action card covers a small number of side effects from clozapine and focuses on those which are:

- Common and less serious
- Serious but manageable
- Serious and require discontinuation of clozapine.

COMMON and LESS SERIOUS

Side effect	Brief description	Frequency/time course	Management/comments
Sedation	Feeling excessively tired including during the daytime	Mostly during dose titration but may persist.	Usually wears off to some extent. Consider a reduction in dose. Give a smaller dose in the morning and larger dose at night. (ZTAS suggest that if daily is no larger than 200mg, all the dose could be given in the evening). If morning waking is a problem, evening dose may be given earlier. Sedation may be worsened by concomitant medicines.
Hypersalivation	Excess saliva	First few months	Consider non-pharmacological

ACTION CARD 9

CLOZAPINE SIDE/ADVERSE EFFECT
(refer to section 6.17 of the Clozapine Policy)

For use by: all GHC colleagues involved in ordering, prescribing and administration of clozapine or support patients prescribed clozapine

/ sialorrhea	which can result in drooling	but often persists. Sometimes wears off. Often more troublesome at night.	treatment if appropriate such as chewing gum during the day, elevating pillows and placing a towel on pillow to prevent soaking. Hyoscine hydrobromide (Kwells®) 300mcg can be sucked/chewed and swallowed up to three times daily. Other options can be considered. See Clozapine Policy Appendix 2 on management of clozapine induced hypersalivation Here is also a link to choice and medication patient fact sheet on hypersalivation handyfactsheethypersalivationuk.pdf (choiceandmedication.org)
Dizziness	Feeling lightheaded	Can occur due to time of dosing, size of the dose, dehydration and/or low blood pressure.	Consider a reduction in dose. Advise the patient to sit and rest until dizziness passes. Ensure adequate fluid intake (2-3L per day) Monitor blood pressure to establish if related (see below). Dizziness may be worsened by concomitant medicines.
Postural hypotension	Felt as dizziness on standing	Mostly during dose titration. Should improve once dose is stable.	Advise to take time when standing up. Consider reduction in daily dose. Consider slowing down rate of titration Ensure adequate fluid intake (2-3L per day) If severe, consult medical team/GP advice (may prescribe additional medicine)
Tachycardia	Fast heart rate, may feel as palpitations in chest.	Mostly during dose titration. Sometimes persists.	Usually benign. May be dose related. Check ECG for any changes. Consider bisoprolol/atenolol or ivabradine if hypotension or contraindications for beta-blockers. If prolonged it can precipitate cardiomyopathy (see below).

ACTION CARD 9

CLOZAPINE SIDE/ADVERSE EFFECT
(refer to section 6.17 of the Clozapine Policy)

For use by: all GHC colleagues involved in ordering, prescribing and administration of clozapine or support patients prescribed clozapine

			If persistent at rest and associated with fever, hypotension or chest pain may indicate myocarditis (see below).
Hypertension	May have no symptoms. Detected by regular blood pressure monitoring.	Mostly during dose titration but may persist.	Monitor closely. Consider a slower rate of dose increase. May need to treat with antihypertensives.
Gastro-oesophageal reflux (GORD)	Stomach acid leaks up in to the food pipe and causes a burning sensation.	Can occur at any time.	Lifestyle advice such as reduce spicy and fatty foods, reducing caffeine and alcohol intake. Consider use of antacids such as Gaviscon; H2 antagonists such as famotidine or Proton pump inhibitors (PPIs) – lansoprazole is preferred choice due to interactions.
Nocturnal Enuresis and urinary incontinence	Not able to pass urine or loss of bladder control that can lead to Involuntary urination that occurs while asleep	Common May occur at anytime Sometimes resolves spontaneously	Consider dose reduction or manipulating dose schedule to try and avoid periods of deep sleep Avoid fluids at bedtime Consider scheduled nighttime toileting Consider a trial of desmopressin (10mcg/mL nasal spray into each nostril at night, or 200–400mcg orally at night) or aripiprazole 10-15mg daily Other options can include oxybutynin, trihexyphenidyl, imipramine, amitriptyline and verapamil but consider patient frailty and medical complexity Monitoring for hyponatraemia is essential

ACTION CARD 9

CLOZAPINE SIDE/ADVERSE EFFECT
(refer to section 6.17 of the Clozapine Policy)

For use by: all GHC colleagues involved in ordering, prescribing and administration of clozapine or support patients prescribed clozapine

POTENTIALLY SERIOUS BUT MANAGEABLE

Side effect	Brief description	Frequency/ time course	Management/comments
Constipation	Infrequent, irregular and difficult opening of bowels.	First 4 months are highest risk but usually persists. Close monitoring required.	**Ensure patients are not constipated before starting clozapine.** Advise patients of the risks of constipation and consequences. Regularly ask about constipation at each routine full blood count appointment). Recommend the use of Bristol Stool scale for assessment (Bristol Stool Chart - Interact (ghc.nhs.uk)) **If not detected and treated may result in bowel impaction and subsequent perforation which may result in death.** Offer lifestyle advice such as increased fluids, regular exercise and increased dietary fibre. Consider laxative treatment. Consider dose reduction. Consider stopping other potentially constipating medicines. See GHC guidelines on management of clozapine induced constipation Guidance on the Management of Clozapine Associated Constipation - Clinical Guideline (CLG085) - Interact (ghc.nhs.uk) Here is also a link to the patient fact sheet on choice and medication on constipation handyfactsheetclozapineandconstipationuk.pdf (choiceandmedication.org)
Weight gain	Increase in body weight often as a result of increased	Most common in first year of treatment but may continue.	Weight gain with clozapine can be significant (4.5kg in first 10 weeks). Advise the patient of the importance of

ACTION CARD 9

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For use by: all GHC colleagues involved in ordering, prescribing and administration of clozapine or support patients prescribed clozapine

	appetite and increased food intake.		good dietary habits and exercise and of the risks of weight gain prior to commencement. Once weight gain has occurred, dietary measures and exercise are the best method to reduce. Additional medicines are sometimes used such as metformin. Refer to the Trust Guideline, CLG105 Managing Weight Gain Associated with Antipsychotic Medication in Adults
Seizures	Sudden burst of electrical activity in the brain causing changes to the way someone feels, behaves, moves and to their levels of consciousness.	Can occur at any time.	Often related to clozapine dose, plasma level and speed of dose titration. Review the dose, adherence and check plasma level. Assess if there are other causes for the seizure. If plasma level is less than 0.6mg/L and other causal factors for a seizure are not identified or addressed, consider prophylactic anticonvulsant treatment such as valproate or lamotrigine (NB: valproate should not be prescribed for women of child-bearing age). **If seizure occurs, withhold clozapine for 1 day, consider starting an anticonvulsant medication and restart clozapine at half the previous dose.**
Fever	Feel excessively hot	Usually in first 4 weeks but can occur at any time if patient has infection.	Check full blood count to ensure no evidence of neutropenia. Check for other causes of fever such as myocarditis, neuroleptic malignant syndrome or pneumonia. Give paracetamol to settle fever.

ACTION CARD 9

CLOZAPINE SIDE/ADVERSE EFFECT
(refer to section 6.17 of the Clozapine Policy)

For use by: all GHC colleagues involved in ordering, prescribing and administration of clozapine or support patients prescribed clozapine

			If occurs during dose titration, consider reducing rate of titration if other causes have been ruled out.
Pneumonia	Chest infection with excess sputum, fever, chills and difficulty breathing.	Can occur at any time.	Infections may be more common with clozapine treatment. Due to excess salivation aspiration pneumonia may also be a causative factor. Clozapine plasma levels may increase if infection is present due to inflammation. Monitor for any increase in clozapine related side effects and consider taking clozapine plasma level. Take an extra full blood count and report to ZTAS to ensure no signs of neutropenia. Refer patient to GP/NHS111/general hospital for further investigations and treatment for infection. Consider dose reduction during the period of infection if excess side effects occur. handyfactsheetclozapineinfectionsuk.pdf (choiceandmedication.org)

VERY SERIOUS AND REQUIRE CLOZAPINE TO BE STOPPED

Side effect	Brief description	Frequency/time course	Management/comments
Neutropenia and Agranulocytosis	Low white blood cell count. Should be detected by mandatory full blood count monitoring.	Highest risk in first 18 weeks of treatment. Can occur at any time.	Adhere to mandatory white cell count monitoring throughout clozapine treatment, follow ZTAS guidelines following any abnormal results. See section in policy on blood monitoring. **Clozapine should be stopped if neutrophils drop below $1.5x10^9$**

ACTION CARD 9

CLOZAPINE SIDE/ADVERSE EFFECT
(refer to section 6.17 of the Clozapine Policy)

For use by: all GHC colleagues involved in ordering, prescribing and administration of clozapine or support patients prescribed clozapine

Myocarditis	Inflammation of the heart muscle.	Most likely in first 6-8 weeks of treatment but can occur at any time.	Symptoms include hypotension, tachycardia, fever, flu-like symptoms, chest pain, shortness of breath and fatigue. Myocarditis is potentially fatal. **If myocarditis is suspected clozapine should be STOPPED IMMEDIATELY.** Refer to a cardiologist for further advice.
Cardiomyopathy	Increased difficulty with heart pumping blood around the body.	Usually, some months into clozapine treatment but can occur any time.	May be asymptomatic but should be suspected if patient shows signs of heart failure. Symptoms include palpitations, chest pain, syncope, sweating, reduced exercise capacity and breathing difficulties. **If cardiomyopathy suspected clozapine should be STOPPED IMMEDIATELY.** Refer to a cardiologist for further advice.

All serious side effects experienced with clozapine should be reported via the Yellow Card system (www.mhra.gov.uk/yellowcard).
Reports can be submitted by anyone including healthcare professionals, patients and family/carers.

ACTION CARD 10

CLOZAPINE – SIDE/ADVERSE EFFECT MONITORING FOR PATIENTS WHO DO NOT ATTEND POCT CLINIC
(refer to section 6.17 of the Clozapine Policy)

For use by: all GHC colleagues involved in ordering, prescribing and administration of clozapine or support patients prescribed clozapine

- At each medication collection the patient must have side effect monitoring.
- It is the responsibility of the care coordinator to ensure these checks happen
- Documentation of side effects must be entered into the progress notes using the template below
- If there are any concerns this must be escalated to a medical colleague.

Patient Details:	Date of check:	Name of person carrying out the check:
Current Clozapine dose:		
Recent medication changes:		
Side effect- Constipation	(Prompts) Bristol Stool Chart: Bowel Movements: Any current laxatives	
Side effect – hypersalivation		
Side effect – sedation		
Smoking status **Changes in smoking status**		
Additional relevant information		
Is follow up/escalation required	YES/NO IF YES – name of person escalated to Date of escalation	

ACTION CARD 11

LETTER TEMPLATE FOR PATIENTS ATTENDING ED WITH CONSTIPATION

(refer to section 6.17.2 of the Clozapine Policy)

For use by: all GHC colleagues involved in ordering, prescribing and administration of clozapine or support patients prescribed clozapine

Dear ED team,

My community mental health team have advised me to attend ED for emergency medical attention due to severe constipation which is a side-effect of the antipsychotic medication Clozapine. I have with me a Handy Fact Sheet on Clozapine and Constipation for your information. My mental health team would also like to draw your attention to a warning about this side-effect in the BNF which points to a national MHRA alert from 2017 about constipation. These resources will inform you of the risks.

Please do not stop or change my dose of Clozapine without consultation with the prescriber in my mental health team:

Name of Prescriber:

Name of care co-ordinator:

Name of community mental health team:

Phone number of community mental health team

If it is the weekend or I need to be admitted, please contact the Mental Health Liaison team to review my prescription.

It is important that I do not miss doses of Clozapine, if more than 48 hours elapses between doses the medication must be re-titrated, otherwise there is a risk of significant hypotension and seizures.

If I need to be admitted and I do not have my medication on me, please contact the mental health pharmacy service immediately on 0300 422 6289 or if out of hours contact GHFT switchboard and ask for the on-call pharmacist.

Thank you,

My name:……

ACTION CARD 12

SMOKING AND CLOZAPINE
(refer to section 6.18 of the Clozapine Policy)

For use by: all GHC colleagues involved in ordering, prescribing and administration of clozapine or support patients prescribed clozapine

Tobacco smoke can have a significant effect on clozapine blood levels. It can turn speed up the metabolism of clozapine leading lower levels. Patients who smoke tobacco are likely to need a higher dose than patients who do not.

Reducing/stopping smoking tobacco

- If a patient reduces or stops smoking their liver enzyme activity slows down. This occurs as 50% reduction every 2 days until a steady level is achieved.
- Clozapine plasma levels will increase, sometimes substantially.
- **A dose reduction in clozapine will usually be necessary**.

Action to be taken on stopping smoking or reducing to less than 7-10 cigarettes a day

- Take clozapine plasma level before stopping/reducing tobacco smoking.
- Once tobacco smoking is stopped/reduced, reduce dose gradually (over a week) until around 75% of original dose reached (i.e. reduce by 25%).
- Repeat clozapine plasma level one week after stopping.
- Anticipate further dose reductions
- Monitor the patient for an increase in side effects or any changes to their symptoms.
- Provide the patient with the Handy fact Sheet 'Stopping Smoking if you are taking Clozapine' available to be printed from the Choice and Medication Website handyfactsheetsmokingandclozapineuk.pdf (choiceandmedication.org)

Initiating or restarting smoking tobacco

- If smoking is re-started, enzyme activity increases, plasma levels fall and clozapine dose increases are then required. The process is complicated, and effects are difficult to predict.
- Additional complexity is introduced by intermittent smoking and repeated attempts at stopping completely. Close monitoring of plasma levels (where useful), clinical progress and adverse effect severity are essential

Actions to be taken on restarting/increasing

- Take plasma level before re-starting/increasing.
- Increase dose to previous smoking dose over one week.
- Repeat plasma level.

ACTION CARD 13

CONSIDERATIONS FOR PATIENTS GOING ON HOLIDAY
(refer to section 6.20 of the Clozapine Policy)

For use by: all GHC colleagues involved in ordering, prescribing and administration of clozapine or support patients prescribed clozapine

Useful source of information Mental health abroad - GOV.UK

Date of planned departure and supply

- Discuss medication requests with the prescriber and pharmacy at the earliest opportunity and ideally at least 8 weeks before the patient is due to go on holiday.
- If possible, synchronise with usual dates of routine/planned clozapine clinic/blood tests
- Plan for any extra pre-departure clinics/bloods to coincide with departure dates
- Plan and book date of first appointment back in clinic after trip
- Discuss quantity of medication needed with pharmacy
- Risk assess and document and risk associated with any extra supplies e.g. overdose risk
- Consider and discuss with the patient if there are any travel restrictions for any of their medication.

Physical Health and FBC

- Review recent health and blood results- is there any risks of neutropenia or constipation, etc
- Encourage the patient/family to get travel insurance and apply for the European Health insurance card (EHIC) or Global Health Insurance Card (GHIC) Applying for healthcare cover abroad (GHIC and EHIC) - NHS
- Encourage the patient/family to identify potential clinics for blood tests at their holiday destination.

Governance

- Develop a care/crisis plan: share with patient, family, travel companions

Patient and family education

- Revisit signs and symptoms of adverse/side effects e.g. neutropenia, constipation, etc. Provide information leaflets, available on the Choice and Medication website » Clozapine
- Ensure shared understanding of risk, plan, safety netting etc
- Letter from doctor summarising medication carried (all, not just clozapine), current medical status, required monitoring and dates, FBC normal values, actions for neutropenia/constipation etc.
- Include contact details for care plan, crisis plan, home team, clinician contact details.

ACTION CARD 14

INTRAMUSCULAR (IM) CLOZAPINE
(Refer to Section 6.21 of the Clozapine Policy)

For use by: all GHC colleagues involved in ordering, prescribing and administration of clozapine or support patients prescribed clozapine

- Clozapine is available as a short-acting intramuscular (IM) injection.
- It is an **unlicensed product** therefore the prescribing consultant retains responsibility for its use.
- It is only suitable as a short-term intervention, as a substitute for doses of oral clozapine for patients with treatment-resistant schizophrenia, who are admitted and detained under the Mental Health Act and are refusing oral clozapine.
- The aim of using the IM formulation is to ensure clozapine treatment is sustained on a daily basis, with the view to administering it orally as soon as possible. IM clozapine should only be used when other approaches to encourage adherence with the oral formulation have failed and with the agreement of the Drugs and Therapeutics Committee.

Who can Prescribe IM Clozapine?
It can only be prescribed by a consultant; use must be approved by the chair of the Drugs and Therapeutics Committee on an individual patient basis.
Refer to General Medical Council (GMC) guidance for further information about prescribing an unlicensed treatment Prescribing unlicensed medicines - professional standards - GMC

Patient Criteria for IM Clozapine

- ✓ Only patients meeting the following criteria should be considered for IM clozapine:
- ✓ Inpatients aged 18 years an over
- ✓ Have a treatment-refractory psychotic disorder.
- ✓ Be registered with Zaponex Treatment Access System (ZTAS) although ZTAS does not hold any responsibility for the use of IM clozapine, this rests with the Consultant
- ✓ Lack capacity or insight to consent.
- ✓ Is refusing oral clozapine despite significant attempts
- ✓ All contraindications, precautions and interactions have been considered by the consultant.
- ✓ There is documented evidence in the patient's notes that:
  - the MDT (which must include the consultant, pharmacist and ward manager) agree potential benefits outweigh risks
  - there's a high likelihood that sufficient physical monitoring and observations could be carried out to ensure patient's safety.

The Product
It is a clear yellow solution for injection in a glass ampoule. The strength of the injection is 25mg/ml, each ampoule contains 5mls (125mg). It should be stored at room temperature.

How Should IM Clozapine be Prescribed?
Refer to the Clozapine Injection prescription chart at the end of the action card

- ✓ Each dose on the titration sheet must be signed and dated by the prescriber.
- ✓ All other aspects of the Clozapine Initiation Pathway should be followed.
- ✓ As soon as IM clozapine has been stopped and switched solely to oral clozapine, oral

ACTION CARD 14

INTRAMUSCULAR (IM) CLOZAPINE
(Refer to Section 6.21 of the Clozapine Policy)

For use by: all GHC colleagues involved in ordering, prescribing and administration of clozapine or support patients prescribed clozapine

clozapine must be prescribed on the EPMA and the paper clozapine IM titration chart crossed out and updated onto the patient's RIO record.

How Should IM Clozapine be Administered?

- ✓ It should be administered by deep IM injection into the gluteal muscle.
- ✓ Before administering **each** dose, the patient should be encouraged to take it orally, if this is refused the dose should be administered by IM injection, this may need to be administered under restraint. If they accept oral clozapine, DO NOT administer IM clozapine.
- ✓ The injection is painful. The maximum volume that may be injected into each site is 4ml (100mg). For doses greater than 100mg daily the dose may be divided and administered into two sites. (Injection sites should be rotated as per usual IM practice). Any unused portion of the ampoule must be discarded.
- ✓ After administration nurses must clearly indicate the route of administration on the prescription.

What is the oral equivalent of the IM?
The oral bioavailability of clozapine is about half that of the IM injection, therefore 100mg in tablets is roughly equivalent to 50mg IM injection. If the patient switches to or from IM clozapine during titration, the dose prescribed and administered must be adjusted accordingly.

How long can the treatment continue for?
Clozapine injection should be used for the shortest duration possible. The need for ongoing IM treatment must be reviewed regularly by the MDT. In general, the injection should be used for no longer than two weeks.

How is IM Clozapine Obtained?
It is manufactured in the Netherlands by Brocacef and imported to the UK via Durbin PLC. Clozapine injection is not held as stock in any Trust units or in GRH pharmacy. It can only be obtained for named patients against a special order and will normally take some time to arrive from the time of ordering.

Monitoring of patients on IM clozapine treatment
The usual clozapine **mandatory full blood count monitoring** should be performed and the associated procedures for amber and red warnings apply. Legally blood samples can be taken under restraint; full discussion must take place with the PMVA team on correct restraint methods if this is planned.

Routine physical health checks should be completed as per prescribing oral clozapine, and in line with the Clozapine policy.

Before each injection: 30 minutes before the injection the patient's blood pressure (lying and standing), pulse, respiratory rate and temperature should be measured. If the patient refuses this should be documented, but respiration rate and consciousness should still be recorded.

ACTION CARD 14

INTRAMUSCULAR (IM) CLOZAPINE
(Refer to Section 6.21 of the Clozapine Policy)

For use by: all GHC colleagues involved in ordering, prescribing and administration of clozapine or support patients prescribed clozapine

After each injection: the patient must be observed every 15 minutes for at least an hour. The following should be checked each time, if the patient refuses this should be documented, but respiration rate and consciousness should still be recorded.

- ✓ Blood pressure
- ✓ Pulse
- ✓ Respiratory rate
- ✓ Temperature.

If the patient refuses this should be documented, but respiration rate and consciousness should still be recorded.

Patients should be observed for excess sedation and any other signs of being unwell, e.g. pallor, sweating, etc. and if observed these should be reported to the consultant and recorded in the clinical record. The NEWS2 form should be used.

Concurrent prescribed medicines
If IM lorazepam is required, at least ONE HOUR must be left between its administration and the administration of IM clozapine.

Purchase costs
Clozapine injection is relatively expensive. It costs approximately £1,000 per box of 10 ampoules: £100 per injection.

ACTION CARD 15

ESSENTIAL INFORMATION FOR PATIENTS ON CLOZAPINE TO GO INTO MY CARE PLAN
(refer to section 6.22 of the Clozapine Policy)

For use by: all GHC colleagues involved in ordering, prescribing and administration of clozapine or support patients prescribed clozapine

'I am taking clozapine. This is being prescribed by my mental health consultant.

*I collect my clozapine every _____ **(frequency in weeks)** from _____ **(collection point i.e. Pullman Place, Weaver's Croft).***

Or:

*My Clozapine is delivered to my home by GHC staff every _____ **(frequency in weeks)**.*

*I have my blood test done at _____ **(location i.e. GP clinic, POCHI Clinic, hospital)** every _____ **(frequency in weeks).***

If I cannot collect my clozapine medication or attend for my blood test, myself or my support staff will contact my key worker as soon as possible.

Myself and those supporting me know that I must not stop taking clozapine.

If I miss any doses of clozapine I must report this immediately to my care co-ordinator during office hours or the Crisis resolution Home Treatment team (Tel: 0800 168 0398) outside office hours.

I am aware that if I miss 2 days of treatment, I will need to restart the clozapine slowly from the beginning again.

If I want to consider stopping clozapine, then I will discuss this with my care co-ordinator and psychiatrist.

*Any **side effects** or **infection** must be discussed with my key worker during normal working hours or with Crisis Resolution Home Treatment team (Crisis 0800 169 0398) if out of hours.*

*Common side effects are **constipation, increased saliva** and **drowsiness.***

ACTION CARD 16

TRANSFER OF PATIENTS FROM GHC TO ANOTHER TRUST
(refer to section 6.23 of the Clozapine Policy)

For use by: all GHC colleagues involved in ordering, prescribing and administration of clozapine or support patients prescribed clozapine

Clozapine Communication Transfer Form

This form should be completed by the pharmacist when a patient is leaving GHC care

Patient details		
Name		
Date of birth		
NHS Number		
ZTAS PIN		
Planned date of transfer		
	Care transferring **from**	Care transferring **to**
Ward or team		
Consultant		
Named nurse/care coordinator		
Full Blood Count monitoring		
Monitoring frequency?	Weekly / 2-weekly / 4-weekly (delete as appropriate)	
Date of last green result		
Date of next blood test		
Site of next blood test		
Medication supply		
Next supply of medication needed by		
Adherence aid (blister pack)	No	
New prescriber		
Prescription requested by	(Name of person requesting, date and method of communication)	
Other information and smoking		
For example high-risk side-effects requiring monitoring, plans for plasma level checks *Is smoking status likely to change after transfer?*		

Preparation for transfer	**Date**	**Sign By whom**	**Comments**
Form sent to GRH pharmacy clozapine team			
Form sent to receiving MH team &			

ACTION CARD 16

TRANSFER OF PATIENTS FROM GHC TO ANOTHER TRUST
(refer to section 6.23 of the Clozapine Policy)

For use by: all GHC colleagues involved in ordering, prescribing and administration of clozapine or support patients prescribed clozapine

pharmacy				
ZTAS informed of transfer				
Blood tests arranged and labels ordered if needed				
Patient informed of arrangements				
Form uploaded to Clinical Documents in RiO				

1. INTRODUCTION

1.1 Clozapine is a second-generation antipsychotic licensed for the following indications:

- Treatment-Resistant Schizophrenia (TRS) – Clozapine is indicated in patients living with treatment-resistant schizophrenia and in those patients who have severe, untreatable neurological adverse reactions to other antipsychotic agents, including atypical antipsychotics. Treatment resistance is defined as a lack of satisfactory clinical improvement despite the use of adequate doses of at least two different antipsychotic agents, including an atypical antipsychotic agent, prescribed for at least 6 weeks each.
- Parkinson's Disease - Psychotic disorders occurring during the course of Parkinson's disease where standard treatment has failed.

1.2 Clozapine can cause neutropenia and agranulocytosis. Although these are rare adverse effects, they are very serious, and this has led to the Medicines Healthcare Products and Regulatory Agency (MHRA) mandating that the drug may only be used in combination with a strict blood test monitoring regime.

1.3 Initiation and ongoing prescribing of clozapine in Gloucestershire must only be done by GHC specialist mental health practitioners. Clozapine prescribing must not be done by primary care prescribers. If a patient already prescribed clozapine is admitted to a physical health hospital (either acute or community) prescribing is continued by the hospital prescriber with the support of GHC mental health teams.

1.4 Zaponex® Treatment Access System (ZTAS) is the approved clozapine provider and monitoring service for GHC.

1.5 Zaponex® is only available from Gloucestershire Royal Hospital pharmacy and is available as standard and Oro dispersible tablets (25mg and 100mg). Or dispersible tablets must only be prescribed where clinically indicated e.g. supervised administration, swallowing difficulties.

2. PURPOSE

2.1 The purpose of this policy is to set out the governance framework to be followed by GHC colleagues involved in the prescribing, ordering, dispensing, administration and monitoring of clozapine and those who support patients prescribed clozapine.

2.2 This policy sets out the requirements for the initiation, maintenance and monitoring of clozapine in inpatient and outpatient settings.

2.3 This policy sets out the requirements for monitoring physical health and side effects of patients prescribed clozapine.

2.4 This policy contains information on the following issues related to clozapine:

- Initiation
- Monitoring requirements – blood tests and physical health
- Side/adverse-effects and their monitoring and management
- Clozapine use in people over 65 years of age
- Clozapine in Parkinson's Disease
- Missed doses and re-titration

- Stopping clozapine treatment
- Therapeutic Drug Monitoring of clozapine
- Clozapine and tobacco smoking and cessation
- Supply of clozapine – routine and in an urgent/emergency situation
- Intramuscular administration of clozapine
- Care planning.

2.5 This policy provides colleagues with information on how to support patients taking clozapine and their carer and ensures they are alerted to side effects and their management.

2.6 This policy provides a framework so that patients prescribed clozapine are supported to take it safely and to manage the risk that clozapine can pose to them.

3. SCOPE

3.1 This policy applies to all GHC colleagues who are involved in ordering, prescribing and administration of clozapine and to all colleagues who support patients prescribed clozapine.

4. DUTIES

4.1 General Roles, Responsibilities and Accountability

Gloucestershire Health and Care NHS Foundation Trust (GHC) aim to take all reasonable steps to ensure the safety and independence of its patients and service users to make their own decisions about their care and treatment.

In addition, **GHC** will ensure that:

- All employees have access to current, evidence-based policy documents.
- Appropriate training and updates are provided to support staff in their roles
- Staff have access to equipment that meets safety standards and maintenance requirements.

Managers and Heads of Service will ensure that:

- All staff are aware of and have access to relevant policy documents.
- All staff are supported to access training and development as appropriate to individual employee needs.
- All staff participate in the appraisal process, including the review of competencies.

Employees (including bank, agency and locum staff) must ensure that they:

- Practice within their level of competency and within the scope of their professional bodies where appropriate.
- Familiarise themselves with and adhere to relevant GHC policies and procedures.
- Identify any areas for skill update or training required.
- Participate in the appraisal process.
- Ensure that all care and consent complies with the Mental Capacity Act (2005) – see section on MCA Compliance below.

4.2 Roles, Responsibility and Accountability Specific to this Policy

Inpatient Teams:

- **When admission occurs to a Mental Health inpatient ward, it is the responsibility of the mental health inpatient consultant to ensure that they are registered as the patient's supervising specialist with ZTAS whilst under their care as an inpatient**.
- It is the responsibility of the patient's ward team to ensure clozapine is prescribed and administered/taken correctly during an inpatient stay
- It is the responsibility of the patient's ward team to ensure that the patients FBCs are monitored and reported to ZTAS
- Whilst an **inpatient within a GHC community hospital** or Gloucestershire Hospitals NHS Trust the ZTAS supervising specialist remains as the patient's mental health community team consultant or speciality doctor, unless otherwise discussed and agreed with the Mental Health Liaison Team Consultants. During their inpatient stay at a GHC community hospital the following must be added to a patient record on SystmOne:
    - ZTAS PIN
    - Frequency of full blood count monitoring
    - The status and date most recent FBC results (RAG colour) and when the next test is due.
- All the above information can be obtained from the patient's mental health team.

Community Mental Health Team:

- **It is the responsibility of the mental health community consultant/speciality doctor to ensure that they are registered as the patient's supervising specialist with ZTAS whilst under their care in the community team.**
- It is the responsibility of the patient's community mental health team to ensure clozapine is prescribed and administered correctly and to support the patient to take clozapine correctly in the community.
- If the patient is admitted to hospital, it is the responsibility of the community mental health team to handover information about the clozapine prescription to the hospital inpatient team
- In addition to the usual prescription requirements the community prescription must contain details of:
    - The patient's ZTAS PIN (documented in the patient alert section of RiO)
    - Usual full blood count monitoring frequency.
    - The RMO / Consultant, care coordinator and team, including the nominated contact details and phone number, in case of problems.
    - Where to send the medication when it has been dispensed by pharmacy.
    - What quantity to supply to the patient on collection/delivery if different from the monitoring frequency.

The Care Co-ordinator is responsible for ensuring:

- The clozapine prescription is in date (community prescription cards are valid for up to 6 months).
- The patient has their blood test taken at the correct times.
- The patient has collected their clozapine as required.

- Checks of patient's adherence to clozapine therapy are undertaken and escalating to medical team if any concerns.
- The required physical health checks have been completed and a record of the results recorded on patient's electronic record.

The Consultant or Registered Speciality Doctor must ensure that:

- Their details are registered correctly with ZTAS and updated as soon as possible if there are any changes in responsibility.
- When a patient is transferred to their care, the ZTAS patient record is updated as soon as possible so correspondence goes to the correct team.
- The regular prescription is written as required.
- Any changes to the clozapine dose are updated on the prescription as soon as possible following their review.
- An entry is made, regarding the changes, in the progress notes.
- If a speciality doctor, they must be on the GMC Specialist list.

The Mental Health Pharmacy Team (based at the Mental Health Pharmacy at Gloucester Royal Hospital (GRH)):

- They are the registered pharmacy for dispensing prescriptions for clozapine and can send dispensed prescriptions and medication to the pharmacy at Cheltenham General Hospital and other GHC Trust sites for ease of collection.
- The pharmacy team are available for advice, queries and support to safely manage patients on clozapine.
- The pharmacy team will update the alert section of RiO to indicate that the patient is prescribed Zaponex® and add their ZTAS PIN.
- The POCT (Point of Care Testing) clozapine clinics are run by pharmacy technicians supported by a clinical pharmacist.
- On each weekday (Monday-Friday, excluding bank-holidays) the pharmacy team regularly check ZTAS to ascertain those patients who have satisfactory blood results in order for medication to be supplied.
- The pharmacy team will update the therapeutic drug monitoring section of RiO after each blood test with the date and status of the result as well as when the next blood test is due.

5. MENTAL CAPACITY ACT COMPLIANCE

5.1 Where parts of this document relate to decisions about providing any form of care treatment or accommodation, staff using the document must do the following: -

- Establish if the person is able to consent to the care, treatment or accommodation that is proposed. (Consider the 5 principles of the Mental Capacity Act 2005 as outlined in section 1 of the Act. In particular principles 1,2 and 3) Mental Capacity Act 2005 (legislation.gov.uk).
- Where there are concerns that the person may not have mental capacity to make the specific decision, complete and record a formal mental capacity assessment on the GHC Trust approved MCA forms. These are available as templates on clinical record systems and on the GHC intranet.
- Where it has been evidenced that a person lacks the mental capacity to make the specific decision, complete and record a formal best interest decision making process

using the best interest checklist as outlined in section 4 of the Mental Capacity Act 2005 Mental Capacity Act 2005 (legislation.gov.uk). Evidence of Best Interests decision making must be provided on the GHC Trust approved forms. These are available as templates on clinical record systems and on the GHC intranet.

- Where a person is admitted to hospital for the treatment of a physical health condition and is assessed as being unable to consent to admission, care or treatment, an application for an Urgent DOLS Authorisation must be submitted to the Local Authority. This applies in all cases where the person lacks capacity, regardless of their compliance with or objection to their admission. Establish if there is an attorney under a relevant and registered Lasting Power of Attorney (LPA) or a deputy appointed by the Court of Protection to make specific decisions on behalf of the person (N.B. they will be the decision maker where a relevant best interest decision is required. The validity of an LPA or a court order can be checked with the Office of the Public Guardian) Office of the Public Guardian - GOV.UK (www.gov.uk).
- If a person lacks mental capacity, it is important to establish if there is a valid and applicable Advance Decision before medical treatment is given. The Advance Decision is legally binding if it complies with the MCA, is valid and applies to the specific situation. If these principles are met it takes precedence over decisions made in the person's best interests by other people. To be legally binding the person must have been over 18 when the Advance Decision was signed and had capacity to make, understand and communicate the decision. It must specifically state which medical treatments, and in which circumstances the person refuses and only these must be considered. If a patient is detained under the Mental Health Act 1983 treatment can be given for a psychiatric disorder.

6. CLOZAPINE POLICY DETAIL

6.1 Clozapine Monitoring Service

- The Trust approved clozapine monitoring service is the Zaponex® Treatment Access System (ZTAS).
- Only Consultant psychiatrists and suitably qualified speciality doctors delegated to, by a consultant ,can be registered with ZTAS.
- All patients must be registered with ZTAS before they can be prescribed clozapine and the patient details recorded on ZTAS must be kept up to date.
- The information required by ZTAS is:
    - Patient's full name
    - Patient's date of birth
    - Patients NHS number
    - Ward patient is currently on (if an inpatient)
    - Contact address and telephone number for the clinician to be contacted if the sample result is abnormal
    - Contact address and telephone number for ZTAS to provide results
    - Name of supervising specialist
    - Dispensing Pharmacy – for GHC this will always be Gloucestershire Royal Hospital Mental Health Pharmacy.
- **Out of date information/incorrect information about both the patient or the consultant can lead to delays in teams being notified of urgent and potentially life-threatening blood results.**
- **The Consultant on the ward the patient is admitted to (for inpatients) or the receiving community Consultant (in the community) is responsible for ensuring**

the patient information is correct with ZTAS.

6.2 Consent and Patient Agreement

- Consent to start treatment with clozapine must be carefully discussed with the patient and documented in line with the GHC Consent to Examination and Treatment Policy (CLP213). It is good practice to involve the family/carers in the decision to initiate treatment with clozapine where appropriate.
- Prior to initiation, clinicians must have a full discussion with the patient and where appropriate their family/carers, explaining the risks and benefits of treatment, the range of common potential side/adverse effects, and the need for regular monitoring and contact with their clinicians.
- Written information about clozapine must be provided to the patient (see section 6.3)
- Clinicians must ensure that patient and their family/carers know who to contact if they have concerns both in and out of hours.
- All discussions must be documented in the patient's record.

6.3 Information for the Patient and their Support Network

- Before treatment with clozapine is started, the patient must be given the following, and this must be documented in the patient's record:
    - Clozapine information leaflet from choice and medication website www.choiceandmedication.org/2gether
    - A clear explanation of the requirement for blood tests, the duration and frequency of these.
    - A clear explanation of potential side/adverse effects, especially constipation and what they must do if they experience these.
    - An explanation of why good adherence is important.
    - What they must do if they miss a dose of clozapine especially if this is for more than 48 hours.
    - Contact numbers for their care co-ordinator and community team for contact during working hours and the Crisis Resolution and Home Treatment Team (CRHTT) for support outside of working hours.
    - If the patient is undergoing an outpatient titration, they must also be given emergency contact numbers for the team undertaking the titration.

6.4 Communication with Primary Care

- Although GPs are not responsible for prescribing clozapine, they must be informed that their patient is prescribed clozapine and made aware of side/adverse effects and drug interactions.
- The GP must be notified, via either the discharge letter (inpatient initiation) or clinic letter (community initiation). The letter must include a request to the GP to add to the summary care record (SCR) that the patient is on clozapine. There is now a section in the SCR for GPs to record medications prescribed elsewhere.
- It is good practice to provide the GP with some basic information on clozapine including common side effects.

6.5 Clozapine Initiation for Treatment-Resistant Schizophrenia (TRS) – Refer to Action Card 1

6.5.1 Initiation of clozapine can take place either during an inpatient stay or in the community.

6.5.2 The clozapine commencement pathway (Appendix 1) must be used when starting a patient on clozapine.

6.5.3 Authority to Initiate Clozapine

- Clozapine can only be initiated by consultant psychiatrists and suitably qualified speciality doctors delegated to, by a consultant
- Pre-existing physical health conditions, drug interactions and side/adverse effects must be considered prior to the initiation of clozapine.

6.5.4 Health Checks Required Prior to Initiating Clozapine

- Full medical and psychiatric history- these should have previously been completed but please check
- Blood tests:
    - Full blood count (FBC)- baseline white cell count (WCC) and differential count. Refer to section 6.6.4 for ongoing blood test and their frequency
    - Fasting blood glucose or HbA1c
    - Liver Function Tests (LFTs)
    - Urea and Electrolytes (including creatinine and eGFR)
    - Blood lipids
    - Prolactin level.
- Weight and Obesity Measure – Body Mass Index (BMI) or other obesity measure e.g. abdominal girth or waist-hip ratio (WHR)
- Blood Pressure and pulse
- Smoking status including what is smoked and much per day – see section 6.18
- Baseline bowel habit – frequency and consistency of opening bowels must be recorded against the Bristol Stool Chart. Gastrointestinal history and/or abdominal examination are recommended in all patients prior to starting clozapine. If there is pre-existing constipation, it must be adequately treated before initiating clozapine
- A recent Electrocardiogram (ECG) (within the previous 6 months) is recommended before starting clozapine (as with all antipsychotics). If patients have a history of cardiac illness or abnormal cardiac findings on physical examination, consideration should be given to the balance of risk and cardiology opinion sought if there is doubt. Any discussion and the outcome must be documented in the patient record
- Echocardiogram if clinically indicated.

6.5.5 Community Initiation of Clozapine

Prior to initiation of clozapine in the community, it is the responsibility of the patient's Community Consultant e.g. recovery, assertive outreach team (AOT), to ensure:

- The patient has been provided with sufficient information as to the benefits and risks of treatment (in formats that best suit the patient need), to enable them to make an informed decision.
- The patient is capable of consenting to treatment, including community initiation.
- That pre-existing health conditions and potential drug interactions have been considered and discussed with the patient.
- That the patient is registered with ZTAS.
- The patient is referred to the Crisis Team to manage the community titration, and a

commencement date agreed.

- That all required physical investigations have been completed in time for the proposed commencement date.
- That there is a clinical handover with the Crisis Team Consultant (or a doctor working under their direct supervision), to include discussion of any potential variation from standard initiation schedule and plans for patient's other psychotropic medications during the initiation period.

During community initiation of clozapine, the Crisis Team Consultant:

- Must be the patient's named specialist with ZTAS and is responsible for informing ZTAS of this
- Is responsible for the prescribing of clozapine, reviewing the response to treatment and monitoring any adverse/side effects. These responsibilities may be delegated to any Specialist or Resident Doctor working under their direct supervision
- Should arrange for in person review of the patient to take place once weekly, either by them or a doctor under their direct supervision, to consider the following:
    - Patient's mental state
    - Side/adverse effects to clozapine and their management
    - Other medication prescribed and changed as necessary.
- It is recommended that the patient is not left alone during the first week of treatment. Ideally, someone (family/ social carer) should stay overnight with the patient during that period. The main reason for this is orthostatic hypotension (with or without syncope), which is common during clozapine therapy, especially during early titration. In rare cases, orthostatic hypotension can lead to profound collapse, which may be accompanied by cardiac and/or respiratory arrest.

6.5.6 Review of Initiation

- During the titration phase, the reviewing doctor must review the patient weekly and consider the following:
    - Patient's mental state
    - Side/adverse effects to clozapine and manage as necessary
    - Other medication prescribed and changed as necessary.

6.5.7 Supply of Clozapine on Initiation

- Clozapine is to be ordered weekly from pharmacy.
- Clozapine supply will be sent to the ward or designated community base by pharmacy following receipt of a green or amber blood result notified by ZTAS.
- Clozapine must only be used for the patient it has been dispensed for. If the patient does not have a supply, contact pharmacy immediately.

6.5.8 Once a patient has satisfactorily completed clozapine titration and the dose is stable, ongoing prescribing can be undertaken by another registered associate specialist, speciality doctor or competent independent non-medical prescriber involved in the care of the patient. This will be done under the direction and supervision of the patient's responsible consultant/registered supervising specialist.

6.6 Clozapine for Treatment-Resistant Schizophrenia (TRS) in Patients Over 65 Years of Age

- Clozapine prescribing in people over 65 is increasing as a result of an increasingly ageing population. Many patients over 65 who are prescribed clozapine will be treated within the recovery and AOT service as opposed to the later life community mental health teams (CMHTs).
- Clozapine is as effective and tolerated an antipsychotic in older people as it is in younger people. However, due to changes in pharmacokinetics and pharmacodynamics due to older age, as with many other medicines they will likely require a lower dose.
- Extra care must be taken when prescribing in older people due to potential comorbidities and side effects such as orthostatic hypotension, confusion, sedation and constipation.
- Clozapine must be titrated more slowly in older people, and it is recommended to take clozapine levels once a stable dose has been reached.
- In patients who have been prescribed clozapine for many years, the dose should be reviewed. Therapeutic drug monitoring (TDM) will help inform potential dose reductions (refer to 6.15).
- The Zaponex® license states that if the daily dose is 200mg or less, this can be given as a single evening dose. Doses greater than 200mg daily, must be split to help reduce risk of orthostatic hypotension and falls.

See also ZTAS factsheet for prescribing clozapine in elderly patients (available in the secure area of the ZTAS website: www.ztas.co.uk).

NB: there is separate information and guidance for initiating people on clozapine for Parkinson's Disease psychosis - see section 6.7.

6.7 Clozapine for Psychosis in Parkinson's Disease

- Clozapine is licensed for the treatment of Parkinson's Disease psychosis where other treatments have failed. It is recommended to be tried after other antipsychotics such as quetiapine have been tried and have not been effective or well tolerated.
- The dose of clozapine for psychosis in Parkinson's Disease is lower than for psychosis with a maximum dose of 100mg daily. Clozapine must be started at a very low dose (recommended 6.25mg daily) with maximum dose increments of 12.5mg. Doses must not be increased any faster than two increments per week. See full NICE guidelines Parkinson's disease in adults (nice.org.uk) for more information.
- Initiation will require a tailored initiation pathway which considers the patient safety issues and the patient's condition.

6.8 Clozapine Blood Monitoring

6.8.1 **Neutropenia** (low blood neutrophil count) and **agranulocytosis** (severe and dangerously low white cell count especially neutrophils) are rare but serous side/adverse effects of clozapine. (Incidence of 2-3% and 0.4-0.7% respectively). These conditions reduce a patient's ability to fight infection and can be life-threatening. As a result of the risk of neutropenia and agranulocytosis, Mandatory regular FBC testing is required to comply with the drug license. Clozapine will not be supplied without a current blood result.

- Routine blood samples are:
  - Taken and processed at a POCT clinic

or
- sent to the ZTAS laboratories for direct analysis using the addressed FBC blood packs supplied by the monitoring service
or
- on occasion, urgent samples may also be processed via local pathology labs.

- The required frequency of monitoring FBC is:

Treatment Period	Frequency of FBC
0-18 weeks	Every week
19-52 weeks	Every 2 weeks
After 1 year	Every 4 weeks

  - ZTAS will notify the supervising specialist when a patient's blood testing frequency can change
  - The FBC frequency may change if a patient has had a break in treatment.

- The supervising specialist must ensure ZTAS is notified of ALL treatment breaks of 48 hours or more

6.8.2 Taking Bloods and Processing Results

Options for blood testing is outlined below:

- **Clozapine Clinics using a Point of Care Test (POCT) machine**
  - Bloods are taken and analysed on site using a POCT machine.
  - Results are automatically uploaded to the ZTAS website within a few minutes, and clozapine is supplied by the pharmacy team.
  - The pharmacy team will support the patient with discussion around clozapine-related side/adverse effects, basic physical health checks and lifestyle monitoring and advice.
  - Referral to the clozapine clinic must be made as soon as possible following initiation of clozapine or transfer into the locality.
  - Use of the clozapine clinics is the preferred option for all patients in localities that have clinics.
  - For referral contact pharmacy and POCT nursing lead for respective venue.

- **Analysis by ZTAS**
  - Bloods to be sent to ZTAS must be taken at the beginning of the week to allow time for processing and results to be received by pharmacy. If bloods are taken at the end of the week/weekend there is a risk that processing may be delayed as the medical team may not be available to deal with any issues and test may be missed.
  - Bloods are to be taken at a designated site that is appropriate for the patient e.g. phlebotomy service at Cheltenham General Hospital (CGH) (West Block outpatients) or community team base. In exceptional circumstances the GP practice may be used (see below).
  - Patients must be encouraged to attend the same venue for all blood tests unless there are exceptional circumstances.
  - FBC blood sample packs can be ordered directly from ZTAS or can be supplied by the community team to the patients to take their blood test appointment - see

Action card 2.
    - Blood sample for FBC test must be sent to ZTAS using the stationery supplied by Magna laboratories.
    - ZTAS will analyse the blood test and upload FBC results to the ZTAs website.
    - Pharmacy will send the medication to the specified site once satisfactory blood results have been reported on the ZTAS website.
    - If a new patient is required to attend Phlebotomy at CGH for blood test, this must be organized by the patient's care coordinator.

- **GP Practice**
    - Routine FBC blood testing for clozapine monitoring must only be done in a GP practice in exceptional circumstances and with the agreement of the GP (not a GP commissioned service).
    - A clear plan must be written and easily available for the team in relation to blood taking arrangements which must include contact details for the GP practice, how the patient will be supported to attend and actions to be taken if the patient does not attend.
    - ZTAS must be notified of all blood tests either via direct transfer/upload to their secure website or via email. Refer to Action Card 3.
    - **It is the responsibility of the patient's ward/community team to inform ZTAS of the results of any bloods testing via local analysis.**

- **Local Analysis via GRH or CGH pathology labs is only to be used:**
    - For inpatients
    - Patients in the community without access to POCT testing who require weekly analysis
    - If an urgent test is required and POCT testing is not available
    - At the request of the clozapine provider (ZTAS)
    - If bloods are usually sent to ZTAS but there are potential known delays with the postal service.

- ZTAS must be notified of all blood tests either via direct transfer/upload to their secure website or via email to ZTAS. (see Action Card 3).
- It is the responsibility of the patient's ward/community team to inform ZTAS of the results of any blood tests analysed locally.

6.9 Blood Results

6.9.1 Blood results are classified using a RAG rating as follows

Blood cell count and status		
	White cell count ($x10^9$)	**Neutrophil count ($x10^9$)**
GREEN	3.5 and above	2.0 and above
AMBER	3.0 and above but less than 3.5	1.5 and above but less than 2.0
RED	Less than 3.0	Less than 1.5

6.9.2 GREEN Result

- Clozapine administration can continue at the prescribed dose.
- No concerns on monitored parameters.

- Continue until the next routine blood test.

6.9.3 Cautious GREEN Result

- This occurs when there is drop in white cell count by more than 3 x 10^9L.
- Clozapine administration can continue at prescribed dose.
- Supervising specialist and pharmacy will be notified by ZTAS.
- Additional blood tests are to be carried out as indicated by ZTAS – recommend to process via local analysis (see section 6.72) and report to ZTAS (Action card 3).
- ZTAS will advise on any further action on receipt of this repeat test.
- Monitor patient for signs of neutropenia e.g. flu like symptoms, sore throat, raised temperature.

6.9.4 AMBER Result

- Clozapine administration can continue at prescribed dose.
- Supervising specialist and pharmacy will be notified by ZTAS.
- Additional blood tests are to be carried out as indicated by ZTAS – recommend to process via local analysis (see section 6.82) and report to ZTAS (Action Card 3).
- Continue twice weekly blood tests until result is green then revert to routine sampling as before. (If a RED result occurs see section 6.8.5).
- Monitor patient for any signs of neutropenia e.g. flu like symptoms, sore throat, raised temperature.

6.9.5 RED Result – Refer to Action Card 4

- **STOP clozapine immediately.**
- Supervising specialist and pharmacy will be notified by ZTAS via telephone and email.
- Daily full blood count must be taken and processed locally (see section 6.7.2) and reported to ZTAS (Action Card 3) until a GREEN result is achieved.
- Monitor the patient for signs of neutropenia e.g. flu like symptoms, sore throat, raised temperature.

6.10 Eosinophils and Platelets

6.10.1 ZTAS also record and monitor eosinophil and platelet count. They will report as out of range:

- Eosinophil counts above 3.0x10^9/L
- platelet counts below 50x10^9/L.

6.10.2 Eosinophil Count

- A raised eosinophil count (eosinophilia) is a common side effect of clozapine. If asymptomatic it is usually benign and transient.
- Eosinophilia has been co-reported with approximately 14% of cases of myocarditis and also pericarditis/pericardial effusion. It is not known whether eosinophilia is a reliable predictor of carditis but should be used to raise awareness of the above plus other inflammatory conditions.
- Eosinophilia usually occurs within the first 4 weeks of clozapine treatment.
- If ZTAS detect an eosinophil count above 3.0x10^9/L they will:

- Send an ‘Out of Range’ email to the supervising specialist and the pharmacy.
- Advise that clozapine is discontinued -this is not mandatory. The decision to stop or continue sits with the supervising specialist.

- In cases of drastic increases of the eosinophil count, if the increase is persistent or the patient is symptomatic, it is advisable to stop treatment with clozapine.
- POCT analysis does not detect eosinophilia due to reporting on mixed cells, however it does facilitate identification of raised results by flagging any mixed cell results above 3.0x10^9/L ‘*Alert: Result is accepted and valid for Zaponex monitoring. However, one or more parameters fall in alert range. Further review is recommended.’*
- ZTAS advises to perform FBC with differential, analysed by a local lab. The results of this must be reported to ZTAS.

6.10.3 Platelet Count

- Clozapine is rarely associated with thrombocytopenia (low platelets) and thrombocythemia (elevated platelets).
- If ZTAS identify a platelet count below 50 x 10^9/L they will:
  - Send an ‘Out of Range’ email to the supervising specialist (and the pharmacy).
  - Advise that clozapine is discontinued- this is not mandatory. The decision to stop or continue sits with the supervising specialist.
  - Advice twice weekly full blood count monitoring until the platelet count is stabilised at below 50x10^9/L.
- The supervising specialist is advised to contact a haematologist if the platelet count drops below 20x10^9L or the patient presents with symptoms of unexplainable bruises, nosebleeds or unstoppable bleedings. In these patients, discontinuation of clozapine should be considered.

6.11 Benign Ethnic Neutropenia (BEN)

- Benign Ethnic Neutropenia (BEN) is an inherited cause of low neutrophil count that is most often seen in people of African or Middle Eastern descent.
- BEN is characterized by low white cell counts which might frequently fall below the lower limit of normal. These low white cell counts typically occur over many months and are in the absence of other cytopenias and other causes for neutropenia.
- People with BEN do not show an increased risk of infection and their response to infection is similar to those without the condition. People who have BEN are not at an increased risk of clozapine-induced agranulocytosis relative to those without the condition.
- For a patient with a confirmed BEN diagnosis a lower reference range for clozapine monitoring will be applied as follows.

Blood cell count and status		
	White cell count (x10^9)	**Neutrophil count (x10^9)**
GREEN	3.0 and above	1.5 and above
AMBER	2.5 and above but less than 3.0	1.0 and above but less than 1.5
RED	Less than 2.5	Less than 1.0

- All other parameters (eosinophils and platelets) remain the same as those patients who do not have BEN.

- In order for ZTAS to accept a patient with BEN and for them to be treated within license:
  - A diagnosis of BEN by a consultant haematologist is required.
  - ZTAS form ('confirmation of BEN monitoring criteria') must be completed. This is located in the secure area of the ZTAS website.
- If a patient has a more severe form of BEN, their FBC may be below the BEN range. In this circumstance individually adjusted monitoring criteria can be considered with ZTAS and the patient may be treated off license.
- Once accepted, ZTAS will confirm registration and the patient's ZTAS profile will flag 'BEN' criteria on the front page.

6.12 Stopping Clozapine

6.12.1 Stopping Clozapine

- There may be some circumstances where clozapine needs to be discontinued. This could include potentially dangerous side effects such as a red blood result (see Action Card 4) or as part of a considered shared decision treatment plan between the consultant and the patient.
- Each circumstance will require a different approach.
- Each case must be assessed individually weighing up the risks and benefits of cessation.
- Once clozapine has been discontinued:
  - All stock held by the patient must be removed for destruction.
  - ZTAS must be notified of discontinuation including the reasons for this.
  - Follow up FBC must be taken for 4 weeks after stopping treatment at the same frequency as the patient's routine monitoring.

6.12.2 Abrupt Discontinuation

- Abrupt discontinuation must be avoided due to the risk of relapse of symptoms and adverse effects, unless essential for potentially life- threatening side effects e.g. red blood results (see section 6.8.5), myocarditis or bowel impaction – Refer to section 6.16.
- Sometimes patients decide to stop clozapine without consultation, it is therefore important to discuss adherence with clozapine at each review with the patient.
- If abrupt discontinuation occurs the patient must be monitored closely and carefully for the following:
  - Return of their psychotic symptoms
  - Symptoms of cholinergic rebound which can include restlessness, agitation, confusion, profuse sweating, diarrhoea, dyskinesia, headache, insomnia, nausea and vomiting.
  - In rare cases clozapine discontinuation can present as catatonia.
- ZTAS must be informed that the patient's treatment has been discontinued (refer to Action Card 5).

6.12.3 Planned Discontinuation

- A patient may express a wish to review and potentially stop their clozapine; this can occur for a number of reasons including intolerable side effects.
- If there is agreement to stop clozapine in a planned manner, A gradual reduction in

Clozapine dose is recommended. Longer periods of reduction reduce the risks of potential relapse. It is recommended to reduce clozapine over at least 1-2 months. For some patients, a longer time frame may be needed.

- The decision to stop must take place following a shared consultation involving the patient and family/carer and the patient's consultant (or designated specialist doctor). The following must be considered and documented:
  - The rationale for stopping
  - Risks and benefits of continuing or stopping the clozapine.
  - A record of the patient's capacity and consent in relation to the decision to stop.
  - The immediate alternate treatment
  - A treatment plan should the patient relapse
  - The outcome.
- The prescriber should consider the risks involved in discontinuing clozapine. If the decision to stop clozapine is made the following must be put in place:
  - The patient's 'early warning signs of relapse'' must be completed and stored within the personal safety plan/crisis contingency plan and everyone involved in the patient's care made aware.
  - A personalised discontinuation management plan to manage the clozapine reduction and discontinuation which must include:
    - Frequency of reviews and physical/mental health checks to be carried out by a registered practitioner.
    - Frequency of reviews with the prescriber.
    - Contact details of who to contact if there are concerns regarding the patient's mental health.

The discontinuation plan must be regularly reviewed and updated.

- **All the above must be clearly documented in the patient's notes and all plans must remain in place until all the discontinuation has been successfully completed.**

6.13 Missed Doses and Treatment Breaks – Refer to Action Card 5

- Patients must be advised of the importance of good adherence to clozapine and the potential risks if doses of clozapine are missed or delayed. If they inadvertently miss a dose/s of clozapine they must be advised to contact their usual care team immediately for further advice.
- Adherence to clozapine must be, routinely checked as part of the patient's ongoing regular review and documented in progress notes and the patient must be reminded to contact the care team if doses be missed. If a patient misses more than 48 hours of consecutive clozapine treatment, clozapine must be re-titrated; this is to avoid any unnecessary adverse effects.
- The patient's consultant must be notified as soon as possible and a treatment plan put in place. Slower titrations are required after longer treatment breaks.
- Refer to Action Card 5 for the actions required.

6.14 Re-Initiation Following a Red Result

- If clozapine has been discontinued because of a confirmed red result it should not normally be restarted.
- In certain circumstances a clozapine 're-challenge' may be attempted by a consultant

following discussion with ZTAS and pharmacy. The risks and benefits of the re-challenge must be considered by a multidisciplinary team (MDT), with consideration for capacity and consent assessments, in discussion with ZTAS and the patient and carer(s), but the final decision will rest with the named RMO/consultant.
- Re-initiation of clozapine following a red result is off-license.
- The named RMO/consultant must have a full documented discussion with the patient and family/carer.

6.15 Therapeutic Drug Monitoring (TDM) / Plasma Levels / Assays

Refer to Action Card 6 for Guidance on Plasma Levels

6.15.1 Therapeutic Drug Monitoring (TDM) for Patients on Clozapine

- In addition to the routine mandatory FBC, plasma levels of clozapine can also be measured if clinically indicated.
- Clozapine TDM should not be carried out at routine intervals, but clozapine assays can be useful in optimising treatment and ensure that the potential benefits of the current clozapine dose outweigh the risks in specific patients.
- Checking clozapine levels should be considered in the following situations:
  - To guide clozapine dosing after commencement
  - Signs of clozapine toxicity
  - Excessive adverse effects
  - Change in smoking status
  - Commencing or discontinuing medicines that may interact to alter clozapine blood levels
  - Symptoms/signs of infection e.g. flu like symptoms and raised temperature but this list is not exhaustive
  - Symptoms/signs of inflammation
  - After surgery
  - Lack/incomplete clinical response to standard dosing
  - Poor/ non-adherence with clozapine is suspected
  - Dose reduction is required following stabilisation
  - If a disorder that may affect metabolism of clozapine is suspected e.g. liver disease.

6.15.2 Supporting Patients who Require a Clozapine Assay

- It is important that the patient understands the need for a blood test to support a clozapine assay, and they know where and when this is to happen.
- An patient information leaflet is available on the Choice and Medication website handyfactsheetclozapinebloodlevelsuk.pdf
- See Action Card 5 for an information slip that can be completed and given to patients.

6.16 Physical Health Monitoring

Refer to Action Card 8

The named consultant or specialty doctor is responsible for ensuring that all required physical health checks and side/adverse effect monitoring is carried out during the initiation phase and at the recommended interval.

6.16.1 Regular Physical Health Monitoring

- At each medication collection patients must have basic physical health checks completed:
  - Blood pressure and pulse -Results should be interpreted according to the National Institute for Health and Care Excellence (NICE) Guidelines. If it is above the range, advise the patient to see GP and inform the care coordinator. If the readings give cause for immediate concern inform the prescriber and care co-ordinator immediately.
  - Weight- Patients should be informed of the weight reading and their BMI value and interpretation (underweight, normal, overweight, obese). Discuss any significant loss or gain with the patient and provide relevant lifestyle advice. Any sudden unintentional weight gain or weight loss must be documented and care coordinator informed contacted.
- If a patient attends a clozapine clinic, basic physical health checks will be carried out by the pharmacy team as part of this service.
- If a patient does not attend a clozapine clinic the responsibility for the regular physical health checks lies with the care coordinator.
- Physical health checks must be entered into the physical health check section in RIO.
- If there are **any** concerns this must be escalated to a medical colleague.

6.16.2 Annual Physical Health Monitoring

- A full physical health review must take place at least ANNUALLY for all patients on clozapine.
- This review can be undertaken by the patient's GP, however if the review cannot happen in Primary Care, the prescriber must liaise with the GHC physical health team or the community mental health team to ensure full physical health monitoring happens.
- Physical health monitoring requirements and frequency are detailed in Action Card 8.
- Additional physical health checks must be carried out at the required frequency as clinically indicated for the patient.

6.17 Clozapine Side/Adverse Effect and Side/Adverse Effect Monitoring

6.17.1 Side Effects and Adverse Effects – General Information

- See Effects and Adverse Effects – General Information.
- See Action Card 9 for information on side/adverse effects and sources of information.
- Side/adverse effects of clozapine must be monitored as detailed in the clozapine commencement pathway (Appendix 1) during initiation and until a stable dose is achieved.
- Following stabilisation, the patient must have regular side/adverse effects checks. All side effects must be recorded and managed where possible to improve the patient's experience. Colleagues must be aware that some side effects are potentially much more serious and will require urgent action when reported of particular importance are bowel habits (see section 6.17.2), fever, chest infection, salivation and sedation.
- The patient must also be asked whether they are experiencing any new or worsening side/adverse effects and symptoms since the last review.
- The Glasgow Antipsychotic Side-effect Scale for Clozapine (GASS-C) must be completed at least annually for all patients prescribed clozapine and the completed document saved in the patient's clinical record. The GASS-C document can be accessed in the GHC intranet GASS - Interact.

- Side effects such as hypersalivation are common but can be distressing and uncomfortable for the patients. Refer to Appendix 2 Guidance on Management of Clozapine Induced Hypersalivation – for support to effectively manage this.
- Side/adverse effects must also be monitored more closely in the following circumstances:
  - Dose increase
  - Signs of infection/inflammation
  - Reduction/cessation of smoking.
- At each medication collection patients must have basic side effect monitoring. If a patient attends a clozapine clinic these checks will be carried out by the pharmacy team as part of this service. If a patient does not attend a clozapine clinic the responsibility for the side effect check lies with the care coordinator. Refer to Action Card 10 for required checks.
- Documentation of side effects must be entered in the progress notes.
- If there are any concerns this must be escalated to a medical colleague.

6.17.2 Constipation – See Appendix 3

- Constipation is a common but potential serious and, in some cases, fatal side effect of clozapine, caused by a slowing of transit time through the gut.
- Constipation can be dose related as it is associated with high plasma levels. The lowest effective dose of clozapine should be used.
- MHRA have published the following advice to health professionals:
  - The antipsychotic drug clozapine has been associated with varying degrees of impairment of intestinal peristalsis; this effect can range from constipation, which is very common, to very rare intestinal obstruction, faecal impaction, and paralytic ileus.
  - Exercise particular care in patients receiving other drugs known to cause constipation (especially those with anticholinergic properties), patients with a history of colonic disease or lower abdominal surgery, and in patients aged 60 years and older.
  - Clozapine is contraindicated in patients with paralytic ileus.
  - Advise patients to report constipation immediately.
  - Actively treat any constipation that occurs.
- When starting clozapine, a GI history must be taken and any pre-existing constipation treated. If possible, bowel habits should be established prior to treatment, including the frequency of bowel motions and this is to be recorded in the patient's record.
- Patients should be asked about their bowel habits regularly and advice on lifestyle, diet and exercise advised (Choice and Medication Clozapine and Constipation Handy Fact Sheet):
  - At every clozapine clinic appointment
    Or
  - At least monthly if the patient does not attend a clozapine clinic.
- Any significant change in bowel habit should be immediately reported to the relevant prescriber and **constipation actively treated**. In general prescribing for treatment of constipation should take place in primary care as the GP will be aware of all medication prescribed (constipation may not be due to clozapine). However, if the patient is unlikely/unwilling to engage with primary care or there may be a delay, GHC clinicians can prescribe. The patient's Responsible Clinician must always be informed.

If a patient is referred to the Emergency Department (ED) to manage symptoms of severe constipation, a letter must be sent with the patient to advise the ED team to NOT STOP clozapine. A letter template is attached as Action Card 11.

6.18 Smoking and Clozapine – Refer to Action Card 12

- The polycyclic hydrocarbons (PAHs) in tobacco smoke can have a significant effect on clozapine blood levels as they increase the activity of cytochrome P450 enzymes in the liver which breakdown clozapine. This in turn speeds up the metabolism of clozapine causing lower clozapine levels.
- Patients who smoke tobacco are likely to need a higher dose than someone who does not.
- Nicotine replacement therapy (NRT), e-burn and vaping **DO NOT** have the same impact on clozapine levels as smoking tobacco.
- A patient's smoking status must be noted **before** clozapine commencement and **regularly** for the duration of clozapine treatment.
- Smoking status is to be checked at every medication collection as part of physical health and side effect monitoring.
- Patients must be prompted to self-report any changes in tobacco smoking status including use of vapes/e-cigarettes/NRT/e-burn.
- A change in a patient's smoking status is more important than whether or not they smoke tobacco. These changes include the following scenarios:
  - Change the amount of tobacco they smoke each day
  - Change from smoking tobacco to nicotine replacement products such as NRT, e-burn or vaping
  - Admission or discharge from hospital- Due to constraints around smoking tobacco whilst in hospital, admission and discharge from hospital can have an impact on the amount of tobacco smoked.
- Patient's may use both e-burn/NRT/vaping AND smoke tobacco. This may reduce the quantity of tobacco smoked so should also be considered.
- Patients may smoke cannabis along with tobacco so this should also be counted in their overall tobacco intake.

6.19 Supply of Clozapine

Clozapine can be supplied to patients in a number of different ways depending on where they live and in some cases preference.

6.19.1 Supply from Clozapine Clinic

- Patients who attend a clozapine clinic will receive their clozapine on the same day as their routine FBC following a satisfactory result.
- The quantity they receive will be enough to last them until their next blood test unless otherwise specified by the care co-ordinator and documented on their prescription.
- If a patient only receives part of their clozapine supply the remaining supply will be securely stored in the relevant team's medicine cupboard.
- NB: Patients in the Cirencester area are offered a two-visit service on consecutive days (one for a blood test and the following day for clozapine supply and counselling by the pharmacy team).

6.19.2 Supply from Hospital Pharmacy

- Direct collection from GRH pharmacy is not encouraged except in exceptional circumstances and this must be agreed with pharmacy team.

6.19.3 Supply from Community Team Base

- Clozapine can be delivered from GRH pharmacy to the patient's community team base for collection by the patient or delivery by the care team. This is sometimes useful for patients who reside in more rural locations who are unable to attend a POCT clinic.
- Once collected/delivered, a record of this must be made in the patient's RIO notes.

6.19.4 Supply from GP Practice

- Collection from GP practice must be discouraged except when a patient lives at the extremities of the GHC locality. This option must be discussed with the community team pharmacist prior to organisation to ensure this is the only viable and pragmatic option.
- There needs to be an agreement with the GP surgery, and a clear care plan documented for this process. This must:
  - include name and address of GP
  - a contact at the GP surgery
  - actions in the event of non-collection including contact details of the community team base and care co-ordinator.
- The details of the GP surgery including contact telephone number must also be written on the patient's prescription chart.

6.19.5 Non-Collection of Clozapine

- **Clozapine Clinic** - If a patient does not attend for their routine blood test and does not collect their medication, the medication is returned to pharmacy. Efforts must be made to contact the patient to rearrange their blood test by the clozapine clinic team. If the patients cannot be contacted this must be escalated to the care co-ordinator follow up urgently. If the patient arrives at clinic at a later date, the medication will be sent across to the team base once a FBC is taken and a satisfactory result received. The patient's care team will then organise getting the supply to the patient.

- **Community Team Base** – the Care co-ordinator is responsible for ensuring that patients receive their clozapine after it is delivered to the community team base.

- **GP Practice** – the Care co-ordinator is responsible for following up each collection/non-collection of clozapine and this must be documented in the patient's notes.

6.20 Patients Going on Holiday – Refer to Action Card 13

- Patients prescribed clozapine must be encouraged to plan holidays in advance and to inform their care team when they are organising a holiday.
- For patients who have recently commenced clozapine and are within the first 18 weeks of treatment, ZTAS recommend they must be encouraged NOT to travel abroad during this period.
- ZTAS have an information sheet in relation to patients going abroad including a reference form for them to take with them. Relevant contact details for patient's

community team must be included. The sheets are available in 12 different languages and are accessed via the secure area with the ZTAS website (www.ztas.co.uk).

6.21 Intramuscular (IM) Administration of Clozapine - Refer to Action Card 14

- Intramuscular (IM) clozapine is an unlicensed, short acting injectable form of clozapine.
- **IM clozapine is not routinely approved for use within the Trust. Named patient authorisation may be gained by request to the Chair of the Trust Drug and Therapeutics Committee.**
- It is only suitable as a short-term intervention to aid detained inpatients with treatment-resistant schizophrenia refusing oral clozapine with a view to convert to oral clozapine as soon as possible.
- It will be considered for people who have previously taken clozapine and who have tolerated it and responded but relapsed due to poor or non-compliance. It must only be used when all other approaches have failed.
- Where IM Clozapine has been approved and supplied to support initiation of Clozapine, it is the responsibility of the ward manager to return any unused IM Clozapine to pharmacy once the patient is on a stable dose.

6.22 Care Planning

- The 'My Care Plan' document must be completed to capture personalised care and conversations between the patient, their key worker, and GHC health professionals. It must identify what is important to the person, including their skills, strengths, support needs, and collaboratively agreed goals and actions, all in their own words.
- The Trust agreed has agreed a standardised text for patients on clozapine that must go into their My Care Plan in the 'Medication goals and actions' section – refer to Action Card 15.

6.23 Patient Transfers Between GHC Services

- Patients prescribed clozapine often move between different care teams and thus can have different supervising specialists responsible for the prescribing and oversight of their clozapine.
- Transfers between settings can occur in the following ways:
  - Between inpatient wards e.g. acute ward to rehabilitation ward
  - Between inpatient and community settings e.g. on admission to or discharge from hospital
  - Between community teams e.g. if the patient moves house or changes their GP
  - Admission/transfer to the local general hospitals due to physical health needs
- When patients are transferred their information with ZTAS must be kept up to date so that any alerts regarding late or abnormal blood tests are sent to the correct supervising specialist and care team.
- **IT IS THE RESPONSIBILITY OF THE TEAM (ward or community team) RECEIVING THE PATIENT TO ENSURE THAT THE DETAILS WITH ZTAS ARE UPDATED**.

6.24 Patient Transferring out of GHC Care

- If a patient is moving to another provider (i.e. leaving the care of GHC) the Clozapine Communication Form (Action Card 16) is to be completed by pharmacy and sent to the

new provider.

6.25 Out of Hours

- Occasionally patients/carers for those prescribed clozapine require support outside normal community team working hours. This could be in relation to blood testing e.g. red blood results which require daily testing or in relation to supply issues.

6.25.1 Urgent Bloods

- Contact the ZTAS out-of-hour service to discuss the need
- If bloods are required in the out-of-hour period (evenings, weekends, bank holidays) contact the Crisis Team to discuss the best option for the service user to have bloods taken.
- The bloods need to go to the local laboratory at Gloucestershire Royal Hospital.

6.25.2 Clozapine Supply

- If a supply of clozapine is required in the out-of-hours period, the GHFT call pharmacist must be contacted
  - Ring GHFT switchboard 0300 422 2222 and ask for the GRH on call pharmacist.

6.26 Resources

- **Choice and Medication website** Gloucestershire Hospitals NHS Foundation Trust Home
- **ZTAS website** ZTAS

7. DEFINITIONS

7.1 **Side Effect** - A side effect is an undesired effect that occurs when the medication is administered regardless of the dose. Side effects are mostly foreseen by the prescriber, and the patient is told to be aware of the effects that could happen while on the therapy.

7.2 **Adverse Effect** - an adverse effect is an undesired occurrence that results from taking a medication correctly. They occur less often than side effects and are influenced by patient-specific susceptibility factors such as drug allergies and intolerances. The event is not expected by either the prescriber or the patient and the effects can be reduced by lowering the dose or just stopping the medication all together.

8. PROCESS FOR MONITORING COMPLIANCE

Are the systems or processes in this document monitored in line with national, regional, trust or local requirements?	YES

Monitoring Requirements and Methodology	Frequency	Further Actions
Review of all Datix and AARs involving clozapine by the Clozapine Governance Group	Bimonthly	The group will share any learning and feedback to the Patient Safety Team if additional actions are required

Review of compliance with clozapine training by the Clozapine Governance group	Bimonthly	Areas of low compliance will be identified and service mangers contacted for an action plan on improvement

9. INCIDENT AND NEAR MISS REPORTING AND REGULATION 20 DUTY OF CANDOUR REQUIREMENTS

9.1 To support monitoring and learning from harm, staff should utilise the Trust's Incident Reporting System, DATIX. For further guidance, staff and managers should reference the Incident Reporting Policy. For moderate and severe harm, or deaths, related to patient safety incidents, Regulation 20 Duty of Candour must be considered and guidance for staff can be found in the Duty of Candour Policy and Intranet resources. Professional Duty of Candour and the overarching principle of 'being open' should apply to all incidents.

10. TRAINING

10.1 All colleagues, band 3 and above working in a Clinical role in mental health services must complete the Clozapine e-learning on Care 2 Learn on joining and as a refresher every 3 years.

11. REFERENCES

The Maudsley Prescribing Guidelines in Psychiatry, 14th edition (2021) David M. Taylor

Appendix 1 - Clozapine Commencement Pathway Document

Clozapine Commencement paperwork - Interact

Appendix 2 - Guidance on the Management of Clozapine Induced Hypersalivation

Guidance on the Management of Clozapine Induced Hypersalivation

Hypersalivation (also known as sialorrhoea or drooling) is a very common side effect of clozapine, with estimates of prevalence ranging from 30-92%. It is uncomfortable and often embarrassing and is a common reason for patients stopping treatment. It can also contribute to the development of conditions such as aspiration pneumonia.
It usually develops at the start of treatment; it may reduce over time and can be related to the dose or serum levels.

The mechanism behind this adverse effect remains unclear, although suggestions include M4 agonism, adrenergic α2 antagonism, and inhibition of the swallowing reflex.

There are no medications licensed in the UK to treat clozapine-induced hypersalivation, therefore the use of medication is off-label or unlicensed.

Pre-Treatment Prevention and Education

Provide the patient and carers/family with lifestyle advice and discuss the likelihood and management of hypersalivation prior to starting treatment, and again if this occurs.

Offer patient/carers the handyfactsheethypersalivationuk.pdf (or the Easy Read version) via the **Choice and Medication website**: Gloucestershire Hospitals NHS Foundation Trust Home

ASSESSMENT

Patients should be assessed for side effects at every Clozapine Clinic visit for their blood test. If patients do not attend a Clozapine Clinic, they should be monitored by their care coordinator at least monthly and recorded in progress notes on Rio. This should also be monitored during routine reviews with prescribers.

- Onset - most common in early months of treatment, may wear off, or persist for years
- Frequency - occasional or daily
- Timing – any time of day but most frequently at night
- Degree of distress caused (e.g. nighttime ‘choking sensation’, social stigma, disturbed sleep)
- It may not require any treatment
- Consider other possible causes (drugs, physical illness) and aggravating factors.

Tools like the Glasgow Antipsychotic Side-effect Scale for Clozapine (GASS-C) should be used to help identify hypersalivation and recorded in the patients’ progress notes on Rio.
GASS rand- Interact

OFF LABEL AND UNLICENSED MEDICATION USE

There is no medication specifically licensed for the treatment of hypersalivation and all medicines are either used “off label”, or in the case of pirenzepine unlicensed. The Trust guidance on use of unlicensed or off-label medicines should be followed and the patient informed of the off-label or unlicensed use.

Where medication use is in line with this guideline, completion of off-label or non-formulary use of medicines is not required. However, the use should be documented in the patients Rio notes.

TREATMENT

Non-Pharmacological

Hypersalivation commonly occurs when first starting treatment, it may ease over time. It tends to be worse at night.

At night

- Propping up or using extra pillows at night-time
- Using towels on pillows
- Nocturnal hypersalivation can lead to a choking sensation. Swallowing two or three times without inhaling (by compression of the nostrils) can reduce the sensation of choking.

During the day

- Advising to consciously swallow more frequently, may be helpful
- Chewing sugar-free chewing gum, to encourage regular swallowing.

Pharmacological Treatment

Review Existing Prescriptions

- - Divide clozapine dose throughout day if predominantly troublesome, give a higher dose at night.
- - Consider a clozapine dose-reduction, mental state permitting, as hypersalivation can be related to dose and serum levels. A clozapine level may guide this decision.
- - Review any co-prescribed anticholinergic medicines, as this may add to the anticholinergic action of clozapine which will increase the risk of constipation. Observe for: constipation, confusion, memory impairment and other cognitive deficits.

Table 1 – The main medications for management of clozapine-induced hypersalivation

Priority	Drug	Dose	Benefits	Limitations
First Line	**Hyoscine Hydrobromide (Kwells tablets/ Scopaderm™ patch)**	**Tablet (Kwells™)** 150-300micrograms up to THREE TIMES A DAY *Must be sucked or chewed. Ensure correct use before dose increase* *Suggest higher evening dose if night-time sialorrhoea is a problem – 600micrograms would generally be the maximum advised in one dose* **Patch (Scopaderm™)** 1.5mg (patch) applied every 72 hours	Used widely and known to be effective Maintains steady state drug concentration	One double-blind randomised controlled trial (RCT) Caution: can cause cognitive impairment, drowsiness, exacerbates constipation Off-label use

		If one formulation does not work then consider changing to the other		
Second Line	**Ipratropium 0.03% (21microgram/dose) (Rinatec™) (**	**Nasal Spray** 1-2 sprays up to THREE TIMES A DAY intranasally or sublingually	Minimal side effects mean that a trial may be considered	Limited evidence in literature Off-label use
Third Line	**Atropine 1% eye drops**	**Sublingually** 1-2 drops up to FOUR TIMES A DAY **As a mouthwash** 1-2 drops to a small amount of water, swish around mouth, then spit out	Quick onset of action within a few hours, provides fast relief – although full effect is not seen for several days Evidence for use in Parkinson's and Palliative care hypersalivation	Short duration of action Bitter unpalatable taste Not suitable for those with poor dexterity/ cognitive impairment as bottle not easy to use to administer dose Off-label use Not widely recommended

Other medications such as amisulpride, pirenzepine (unlicensed product) and trihexyphenidyl have less evidence to support their use and mixed suitability – discuss with pharmacy team with regards to these

In people with severe clozapine induced hypersalivation that has not responded to other treatments, there is published evidence of injecting botulinum toxin into the salivary glands that has proved to be successful. The effect of botulinum toxin injection can last up to 12 weeks. Any request to use botulinum toxin for this indication must be presents to the Trust Drug and Therapeutics Group for discussion/approval.

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Appendix 3 - Guidance on the Management of Clozapine Associated Constipation

Guidance on the Management of Clozapine Associated Constipation

Constipation

- **Constipation appears to be a dose related side effect of clozapine, as it is associated with high plasma levels (4,5). The lowest effective dose should be used to manage symptoms**

MHRA Advice to healthcare professionals (6):

- The antipsychotic drug clozapine has been associated with varying degrees of impairment of intestinal peristalsis; this effect can range from constipation, which is very common, to very rare intestinal obstruction, faecal impaction, and paralytic ileus
- Exercise particular care in patients receiving other drugs known to cause constipation (especially those with anticholinergic properties), patients with a history of colonic disease or lower abdominal surgery, and in patients aged 60 years and older
- Clozapine is contraindicated in patients with paralytic ileus
- Advise patients to report constipation immediately
- Actively treat any constipation that occurs

Pre-treatment, Prevention and Education

- A gastrointestinal history and/or abdominal examination are recommended in all patients prior to starting clozapine (1). If there is pre-existing constipation, it should be adequately treated before initiating clozapine.
- Provide the patient and carers/family with lifestyle advice and discuss the risk of constipation before starting and during treatment.
- Concurrent medication such as antimuscarinics, opioids, and tricyclic antidepressants increase the risk of constipation and so prescribing should be minimised where possible (1,4).
- Provide the patient/carers with the Clozapine and Constipation Handy Fact Sheet via the **Choice and Medication website** www.choiceandmedication.org/2gether/.

Assessment

- There are two distinct phases to clozapine treatment: a titration and stabilisation phase, then a maintenance phase. Assessment of clozapine induced constipation is appropriate in both phases. There must be systematic, documented assessment throughout clozapine treatment.
- Clozapine has a greater potential for gastro-intestinal side effects compared with other antipsychotics, possibly because of its anti-serotonergic properties. This may lead to slower colon transit, reduced gastro-colonic reflexes, increased colonic compliance, and perhaps reduced intestinal sensitivity to distension. This means that patients may

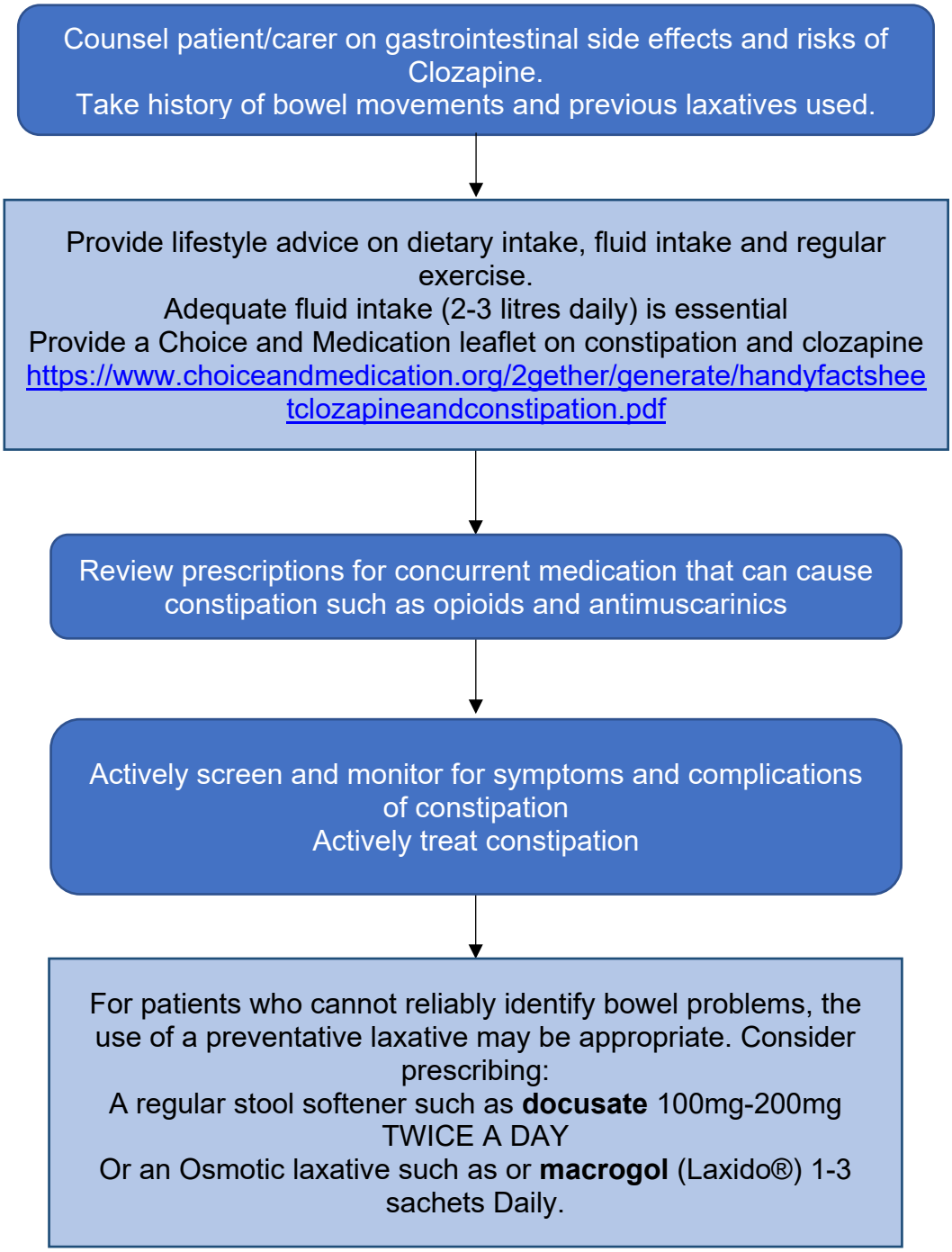
not complain about constipation and therefore should be asked regularly about bowel habit.

- **Titration and Stabilisation Phase**

  - During the work up for clozapine treatment, patients should be assessed for risk factors for constipation including previous history, concurrent treatments likely to induce constipation, and lifestyle factors.
  - Educate patients and carers about the risk of constipation. Provide the Choice and Medication Clozapine and Constipation Handy Fact Sheet.
  - If possible, bowel habits should be established prior to treatment, including the frequency of bowel motions and recorded in the patient's record.
  - Patient preference and history of laxatives should be recorded.
  - Bowel function should be monitored throughout initiation. Tools such as the Bristol Stool Chart (Appendix 4) and the Glasgow Antipsychotic Side-effect Scale for Clozapine (GASS-C) (Appendix 5) should be used to help identify constipation (1,3) (Appendix 1). GASS-C is on the intranet Glasgow Antipsychotic Side -Effect Scale for Clozapine (GASS-c) - Interact
  - Any change in bowel habit should be immediately reported to the multi-disciplinary team and constipation actively treated

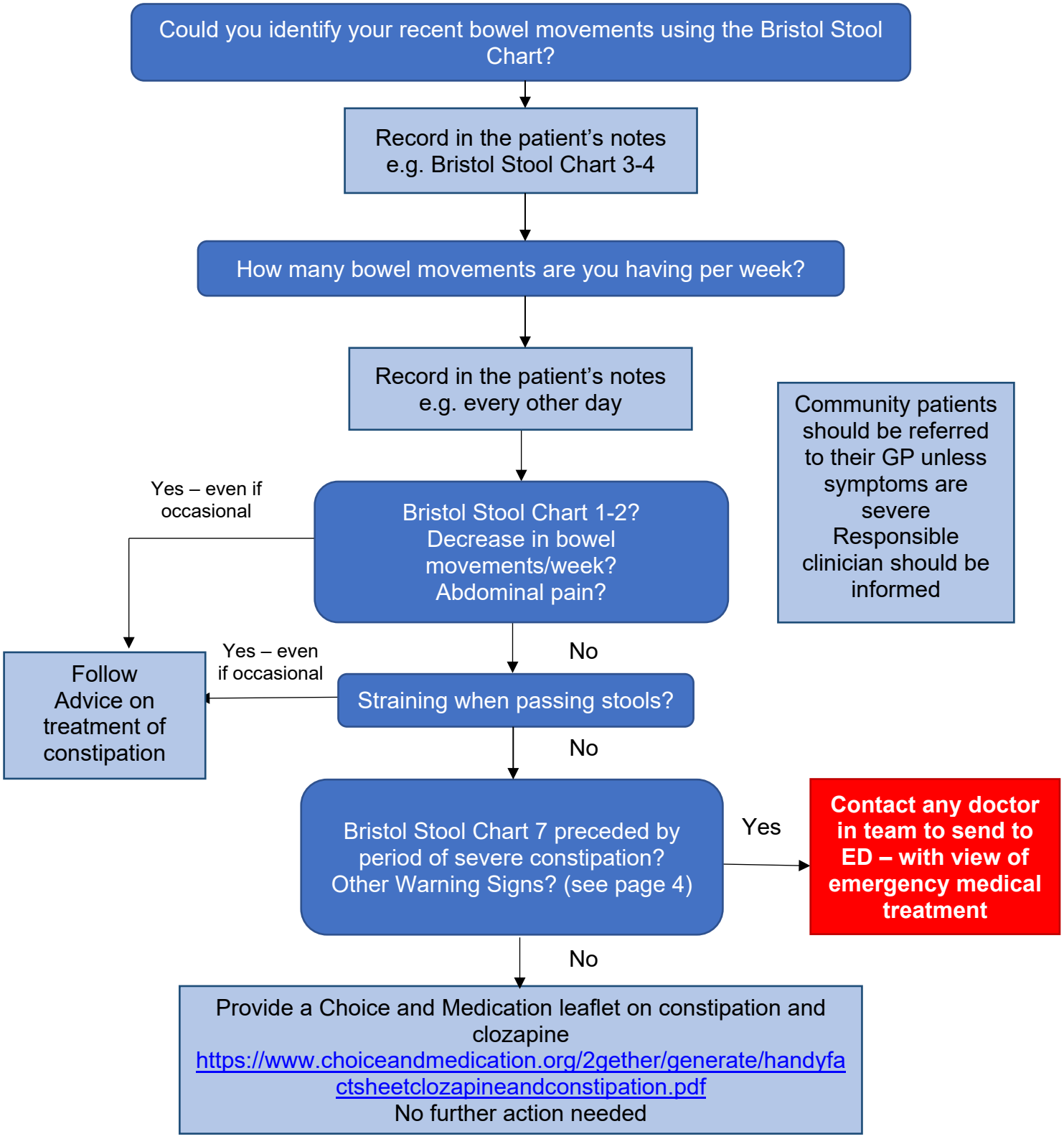
- **Maintenance Phase**
  - Patients should be assessed for constipation at every Clozapine Clinic. If patients do not attend clozapine clinic, constipation should be monitored by their care coordinator at least monthly and recorded in the patient's record, and during routine reviews with prescribers.
  - Tools such as the Bristol Stool Chart and the Glasgow Antipsychotic Side-effect Scale for Clozapine (GASS-C) should be used to help identify constipation (1,3) and recorded in the patient's record (Appendices 1 and 3). GASS-C is available on the intranet Glasgow Antipsychotic Side -Effect Scale for Clozapine (GASS-c) - Interact
  - Patient preference and history of laxatives should be recorded.
  - Any significant change in bowel habit should be immediately reported to the relevant prescriber and constipation actively treated (Appendices 4 and 5). The patient's Responsible Clinician must always be informed.
  - For community patients who do not attend a Clozapine Clinic, referrals should be directed to the patient's GP or if symptoms are severe to ED (see warning signs).
  - For inpatients contact the duty doctor.

Prevention of Clozapine Associated Constipation



Monitoring of Clozapine Associated Constipation

Follow these steps at each suitable meeting with the patient (i.e. during initiation on the ward or at every Clozapine Clinic visit)



WARNING SIGNS – SEND TO ED / CONTACT DUTY DOCTOR	
Absent or high-pitched bowel sounds	Vomiting
Severe abdominal pain	Overflow diarrhoea
Blood or mucus	Weight loss
Abdominal dilation	Temperature/fever

Recording Bowel Function

- Record findings in standardised manner in the progress notes, include numerical values for Bristol Stool Chart type and frequency. For example:
  - *"Bristol Stool Chart – 4*
  - *Bowel motion – Every 2 days"*

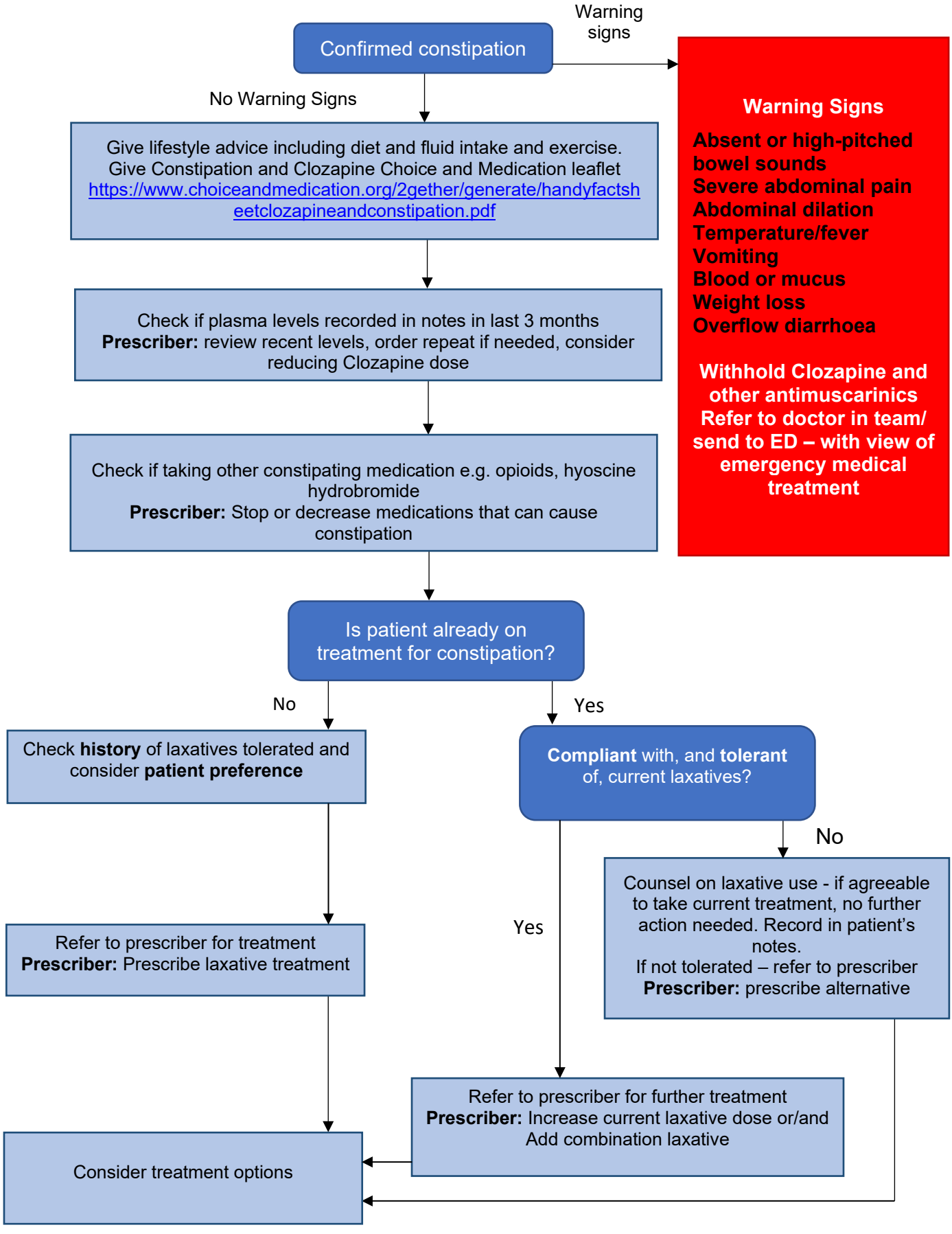
.

Treatment

- When clozapine induced constipation has been identified the following steps are recommended:
  - Recommend changes in lifestyle, diet, fluid intake and exercise – provide the patient with the Choice and Medication Clozapine and Constipation Handy Fact Sheet.
  - As constipation is related to high plasma levels (4,5), take a clozapine level and consider reducing the dose if clinically appropriate
  - Stop or reduce prescriptions for medications that can also cause constipation such as opioids or antimuscarinics.
  - Follow guidelines for pharmacological treatment of constipation (Appendices 4 and 5).
  - Patients presenting with diarrhoea may be constipated with the main symptom presenting as overflow – this should be excluded before any treatment is considered.

- For patients who cannot reliably identify bowel problems preventative laxative treatment with regular **docusate** or **macrogol** may be appropriate

Treatment of Clozapine Associated Constipation



Pharmacological Treatment Options for Clozapine Associated Constipation

To reduce risk of impaired peristalsis, **combinations of stimulant and softening laxatives**, such as **senna** and **docusate**, may be prescribed prophylactically or as treatment.
Macrogols may be used if these are ineffective, preferably alongside a stimulant laxative.

Laxative	Normal Dose Range	Maximum Dose	Method of action	Time for effect	Considerations
Docusate capsule	100-200mg twice a day	500mg/day	Stool softener, consider combining with stimulant	1-2 days	
Macrogol (Laxido®) sachet	1-3 sachets daily in divided doses	Max 12 sachets/day normally for faecal impaction	Osmotic (draws in water to bowel), consider combining with stimulant	1-2 days	Sachet is mixed with water
Senna tablet	7.5-15mg at night	30mg in one dose – only under medical supervision	Stimulant, consider combining with osmotic/softener, i.e. docusate	8 hours	**First line stimulant**
Bisacodyl enteric coated tablet	5-10mg at night	20mg/day	Stimulant, consider combining with osmotic/softener	10-12 hours	**Second line stimulant**

Alternative Options

Drug	Normal Dose Range	Max Dose	Method of action	Time for effect	Considerations
Glycerol suppository	4g as required	-	Lubricating/some Osmotic effects	15-60 mins	**First line** suppository option
Bisacodyl suppository	10mg in the morning	-	Stimulant	15-60 mins	**Second line** suppository option

NB. Lactulose used for constipation is **not** on the Gloucestershire Joint Formulary. Source: based on the Porirua protocol

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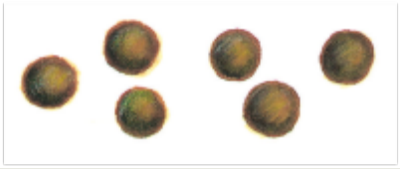
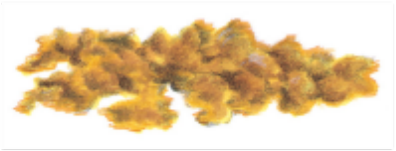
Appendix 4 - Bristol Stool Chart

The Bristol Stool Form Scale

Type 1		Separate hard lumps, like nuts (hard to pass)
Type 2		Sausage-shaped but lumpy
Type 3		Like a sausage but with cracks on its surface
Type 4		Like a sausage or snake, smooth and soft
Type 5		Soft blobs with clear-cut edges (passed easily)
Type 6		Fluffy pieces with ragged edges, a mushy stool
Type 7		Watery, no solid pieces ENTIRELY LIQUID

Appendix 5 - Zaponex Treatment Access System Reference Manual

A copy of the ZTAS manual can be found at ZTAS manual - Interact