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Clozapine Initiation and Management Guideline

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Guideline context

- This document sets out agreed clinical practice regarding the use of clozapine within the Birmingham and Solihull Mental Health Trust.

- Clozapine is an antipsychotic for use in treatment resistant schizophrenia. Restrictions imposed by the Medicines and Healthcare Products Regulatory Authority (MHRA), as part of the respective product licenses, impose limitations as to who can prescribe clozapine. Mandatory routine monitoring of designated blood markers is also required regularly during treatment.

- Initiation of clozapine has important clinical, logistical and safety implications for patients and staff within inpatient areas, home treatment services and community services. This guideline aims to standardise the initiation of clozapine for patients within the trust ensuring that registration of patients, pre-initiation baseline monitoring, prescribing and physical monitoring during initiation are all undertaken in a timely, safe, and well-co-ordinated manner, wherever this may occur. It is essential that there is good co-ordination between the patient's community team and the inpatient or home treatment team managing initiation of clozapine. This guideline will help ensure all initiation and ongoing monitoring requirements associated with clozapine initiation are carried out appropriately.

- The IM formulation of clozapine is not licensed within the UK and as such has additional requirements for its use. It may be considered for patients who have never been exposed to clozapine previously or patients previously treated with clozapine and known to have responded but relapsed owing to non-compliance. The IM formulation can only be prescribed following MDT consultation and with approval from the PTC. All Mental Health Act (MHA) paperwork must be in place and the plan for use must be fully documented in the patient record.
  The request to use IM clozapine must be made on a case-by-case basis. Teams considering use of IM clozapine must have the relevant knowledge and skills, either from experience or by supervision from others experienced in using IM clozapine to ensure patient safety is maintained.

- In line with the monitoring requirements for clozapine, a red result will necessitate a suspension or discontinuation of treatment. This may be permanent or temporary and where treatment is to be restarted, several requirements around dosing and monitoring are mandated. This guidance sets out these requirements and the required consultation with the monitoring service as to the suitability of continued treatment and the documentation required to facilitate this.
- The use of clozapine carries significant risk of adverse effects for the patient and the guidance outlines the requirements for therapeutic drug monitoring (TDM) to reduce the risk and ensure patient safety. High plasma levels are associated with a significantly higher chance of adverse effects and poorer outcomes for patients and

Guideline requirement (see Section 2)
This guideline applies to all medical, nursing and pharmacy staff involved in the initiation, prescribing, administration, monitoring and supply of clozapine within the trust.

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1. Introduction

1.1 Rationale: The purpose of this guidance is to set out the standards for clinicians, pharmacy service providers, nursing staff and other health care professionals involved in the prescribing, administration, and monitoring of clozapine. It covers initiation of clozapine (inpatient and community setting) and continuation of monitoring following initiation.

1.2 Scope: This guideline applies to all medical, nursing and pharmacy staff involved in the initiation, prescribing, administration, monitoring and supply of clozapine within the trust. All staff involved in the process are responsible and accountable for ensuring they have read, understood, and follow these guidelines. It is the responsibility of all staff involved in any aspect of this guideline to inform their manager of any variation in practice or inability to follow the processes defined. Tasks should not be undertaken or delegated to a member of staff who is not legally entitled, authorised, or appropriately trained.

2. The Guideline & Procedure:

2.1 Clozapine Treatment: Initiation and Maintenance

Considerations prior to starting clozapine

Initiation of clozapine has important clinical, logistical and safety implications for patients and staff within inpatient areas and community services. This guideline aims to standardise the initiation of clozapine for patients within the trust ensuring that registration of patients, preinitiation baseline monitoring, prescribing and physical monitoring during initiation are all undertaken in a timely, safe, and well-co- ordinated manner.

Indications for clozapine

- **Treatment resistant schizophrenia (TRS)**: Clozapine is the gold standard medication for treatment resistant schizophrenia and is currently the only antipsychotic with proven efficacy in reducing symptoms and relapse in TRS. The definition of treatment resistance varies between clinicians and treatment centres but can be broadly defined as the "failure to achieve satisfactory control of the condition after use of two different antipsychotics, at clinically appropriate doses and duration".
- **Psychosis in Parkinson's disease:** where standard treatments, including second generation antipsychotics, have failed, or caused adverse effects.

Contraindications to treatment with clozapine

These must be considered prior to treatment being commenced and are taken from the Summary of Product Characteristics (SPC) for Denzapine.

Absolute contraindications:

- Hypersensitivity to the active substance or to any of the excipients
- Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine due to the inclusion of lactose in the formulation
- Patients unable to undergo regular blood tests.

Relative contraindications:

- History of toxic or idiosyncratic granulocytopenia/agranulocytosis (except for granulocytopenia/agranulocytosis from previous chemotherapy)
- History of clozapine-induced agranulocytosis
- Impaired bone marrow function
- Uncontrolled epilepsy
- Alcoholic and other toxic psychoses, drug intoxication, comatose conditions
- Circulatory collapse and/or CNS depression of any cause
- Severe renal or cardiac disorders (e.g., myocarditis)
- Active liver disease associated with nausea, anorexia or jaundice, progressive liver disease, hepatic failure
- Paralytic ileus.
- Denzapine treatment must not be started at the same time as commencing treatment with drugs known to have a substantial potential for causing agranulocytosis e.g., carbamazepine. Use with established medication should be carefully assessed before starting clozapine.
- concomitant use of depot antipsychotics is to be discouraged (see below)

[Note that treatment of patients who have had had a previous neutropenia may be possible under an off-label agreement with the Denzapine Monitoring Service (DMS) and with the agreement of a haematologist. Unlicensed use paperwork must be completed before initiation. Contact DMS directly to discuss]

General Requirements

- All clozapine patients must be managed under the supervision of a BSMHFT consultant psychiatrist who is registered with the Denzapine Monitoring Service. A nominated pharmacy should be designated and will be responsible for all supplies of clozapine during treatment.
- The consultant should assure themselves that all medical staff managing the clozapine treatment of patient(s) under their care are trained and competent to perform those duties safely and consistently. Senior nursing staff responsible for clozapine clinics and managers of wards providing clozapine treatment must also ensure all staff dealing with clozapine patients are also properly trained and registered. The consultant should liaise with nursing leads to ensure a holistic view of the service within their team.

- Patients must be registered with the specific clozapine monitoring service in line with the brand of clozapine provided. Within this Trust we only initiate treatment with the Denzapine brand and all new patients should be registered with the DMS.
- Previously, it has been recommended that clozapine treatment not be commenced over the weekend, due to the limitations on service provision at these times. For inpatient (IP) initiations, the access to clinical observations and intervention is relatively unchanged, though clinician supervision and ability to respond may be reduced. Therefore, while starting clozapine at the weekend is not prohibited but it is strongly discouraged. It is the responsibility of the consultant to consider any service limitations against the clinical risk posed by delaying treatment, agree the management of the patient within the multidisciplinary team and arrange treatment initiation and its management accordingly.
- For outpatients (OP) being initiated in the community, it is recommended that weekend initiation is avoided. In the exceptional cases that this is not possible, the consultant must clearly document the reasons and confirm that monitoring of physical observations can be done appropriately and on time with the responsible team.
- There should be provision for the supply of medication from either Central or Summerhill pharmacy and medication should be ordered and on hand before treatment is due to start.

All teams must ensure they have the capacity and capability to monitor and ensure the safety of clozapine patients before taking them on

There are three distinct stages to the prescribing of clozapine:
- Pre-initiation – registration with DMS, completion of pre-initiation checklist
- Initiation – Initial prescribing, assessments, and observations
- Maintenance – determination of ongoing dosing and monitoring

Pre-initiation with clozapine

Documentation in clinical notes
Prior to initiation, prescribers should ensure that the decision to consider clozapine is properly discussed with the patient and documented in their notes. This must include an explanation of the rationale for clozapine and likely side effects and an assessment of the patient's capacity to consent to clozapine. If the patient lacks the mental capacity to understand and consent to clozapine treatment, then a best interest meeting needs to be completed and documented accordingly. If the patient is under part IV of the Mental Health Act and requires a T2 form or a SOAD these also need to be completed. Clozapine can be commenced prior to a SOAD providing a rationale is given and a section 62 is completed Appendix 2 lists the information to be discussed with patients prior to initiation of clozapine. This is in addition to the pre-initiation checklist (Appendix 3)

2.1.2 Registration with clozapine monitoring service

Brand Choice:
Clozapine is currently licensed and available from three companies within the UK. Each company is responsible for providing monitoring services to clozapine prescribers.

All patients under the care of Birmingham and Solihull Mental Health Foundation Trust (BSMHFT) are to be **started on the Denzapine brand only**. Patients transferring in on other brands are normally required to switch to Denzapine as part of the transfer.

- DMS registration:
- Patients can only be commenced on clozapine once they have been registered with the Denzapine Monitoring Service (DMS)
- All provision of clozapine must be under the direct supervision of a BSMHFT consultant who is also registered with the DMS service.
- It is not appropriate for anyone to prescribe clozapine if not registered with the relevant monitoring service. Junior doctors prescribing on behalf of a responsible clinician should also be registered with the appropriate monitoring service.

- Please contact Pharmacy to be registered or contact DMS directly via:

  - Telephone: 0333 200 4141
  - E-mail: denzapine@britannia-pharm.com (general enquiries)
  - dms.britannia@nhs.net (confidential information)
  - E-registration forms: https://securesign.britanniapharm.co.uk/Home/Index2#RegMenu

  - Patients must also have a nominated pharmacist to act for and authorise clinical staff using the monitoring service (referred to as the "Clozapine Pharmacist" henceforth).
  - Clozapine is a specialist only medicine on the Birmingham and Solihull formulary. GPs are not normally authorised to prescribe clozapine and should not normally be requested to do so unless this has been agreed by all parties and is in the patient's best interest.

All staff involved in clozapine management including **prescribers, pharmacists, pharmacy technicians and nurses** running clozapine clinics or inpatients prescribed clozapine **MUST** be able to check blood results on the DMS monitoring service. This requires sufficient staff to be registered with DMS to enable the prompt access to the results.

It is the **responsibility of the responsible clinician** to ensure the team is sufficiently prepared to support the use of clozapine. If they and the ward manager or deputy are confident that there are enough staff with access available on each shift and results can be checked on the appropriate monitoring service as needed, then not all staff need to be registered.

Pre-initiation Checklist **(See Appendix 3)**

The pre-initiation checklist needs to be completed and uploaded to the patients notes. This needs to be completed for both inpatients and outpatients.

- Following discussion with the patient and explanation of the benefits and risks of clozapine treatment, patient consent should be obtained. If the patient is under a Mental Health Act section, then the appropriate section paperwork must be completed
- Register the patient with DMS (see below)
- Organise second opinion paperwork / T2 or T3 if needed

- Perform ECG – if this cannot be done, the reason must be clearly documented on Rio.
- A blood sample should be taken for a full blood count (FBC) as part of the registration process. A patient will not be authorised for treatment by DMS without one. The result is valid for up to 10 days from the date of sampling and treatment must begin within this time, or a new sample will be required. If the sample is not a
  "green" result as indicated on the DMS site, treatment **cannot** be started.
- Teams must ensure that this sampling will be possible before initiating treatment.
- Dose titration should follow the titration schedule laid out in Table 1 below.
- This titration is intended to reach a standard maintenance dose reasonably quickly to allow assessment of the response whilst minimising the risk of side effects.

Pre-initiation (and ongoing) observations should be documented on the physical health observation section of RIO. A paper copy (Appendix 4) should only be used in exceptional circumstances and if used, a copy **must be uploaded onto the patient record**.

The minimum physical health monitoring requirements during and following initiation (inpatient and outpatient) are described below.

Parameter	Baseline	1 Month	3 Months	6 Months	9 Months	12 Months & Annually
Temperature	Daily during titration.					
BP and Pulse	Daily during titration.					
Weight & BMI						
Lipids (fasting if poss.)						
HbA1C (& fasting glucose iif possible)		(Fasting glucose only)				**Complete every 6 months**
LFTs						

ECG (especially if on multiple drugs increasing QTc)			Clozapine may cause cardiomyopathies and myocarditis. Plasma CRP and troponin should be checked if suspected. Use QTc as marker for Torsades des Points risk			
U&Es						
FBC	As per clozapine protocol. Weekly for 18 weeks, fortnightly up to 1 year and then 4 weekly. Additional monitoring may be required if appropriate.					
Side-effect Rating Scale [GASS]						
Echocardiogram		Clozapine may cause cardiomyopathies and myocarditis. Plasma troponin and CRP should be checked if suspected. An echocardiogram can be useful. Consult with a cardiologist.				
Smoking Habits		At each clinic appointment				
Clozapine plasma level	Consider at the end of initial titration period. Further levels taken when clinically indicated (See Section 5 also)					

For additional guidance on physical observation monitoring see Appendix 4.

2.1.3 Prescribing and initiation of clozapine

Once treatment is agreed, the prescription must be entered onto EPMA to allow the ordering of medication. The template is the same for both IP and OP initiation.
The EPMA template should be used unless a custom titration is required (See table 2 below). A faster titration may be possible in an inpatient setting or following a short treatment break but must be carefully considered and documented in the patient notes.

Inpatient initiation

The schedule has been redesigned as a single titration which can be started on any day. Patients should be monitored for any side effects during the titration. If needed, consider pausing dose escalation to properly assess these.
It is recommended that initiations on weekends are avoided unless clinically necessary. The titration schedule will take the patient through from first dose to maintenance after two weeks, allowing time to evaluate the effectiveness.

Community Initiation
When community initiation is deemed necessary by the Community Mental Health Teams (CMHTs), the role of monitoring **MUST** be managed by the Home Treatment (HT) teams. Some patients will require inpatient admission where problems are anticipated.
Home treatment teams will follow the same initiation schedule as inpatient teams, **but the first dose may be given in the morning to allow follow up observations**.

Observations in the community teams are more difficult as they are usually done in the patient's home, and it is not always practical or possible to wait there to take the readings. With this in mind, it may be appropriate to witness the administration of the medication and return to take the observations between 2-3 hrs later (time of peak dose effect). [See Observation record chart] – Appendix 5

2.1.4 Clozapine Dose Titration (Inpatient and Community)

Table 1: Normal titration (14 day)
Note only 25mg and 100mg tablets will be supplied during titrations

Day	Morning dose	Evening Dose	
1		12.5mg	**Supply 1** 18 x 25mg
2	12.5mg	12.5mg	
3	12.5mg	25mg	
4	25mg	25mg	
5	25mg	50mg	
6	50mg	50mg	
7	50mg	75mg	
8	75mg	75mg	**Supply 2** 15 x 25mg 12 x 100mg
9	75mg	100mg	
10	100mg	100mg	
11	100mg	125mg	
12	100mg	150mg	
13	100mg	175mg	
14	100mg	200mg	

If initiating in over 65s, a slow initiation with lower maintenance doses is required; this should be done in an inpatient setting. (See Table 2). In very rare situations a smaller starting dose of 6.25mg may be considered; including where there is an identified clinical risk associated with normal titrations or considered in community situations where there are problems with access for observations and a much slower titration may be used. See also section 2.5 below.

Table 2 - Slow titration (21 day)

Normally only 25mg and 100mg tablets will be supplied during titrations, however where a 6.25mg dose may be required, the liquid formulation may be supplied.

Days	Morning dose	Evening Dose	
1-2		12.5mg	**Supply 1** 10 x 25mg
3-5	12.5mg	12.5mg	
6-8	25mg	25mg	
9-11	25mg	50mg	**Supply 2** 21 x 25mg
12-14	50mg	50mg	
15-17	50mg	75mg	**Supply 3** 30 x 25mg 6 x 100mg
18-20	50mg	100mg	
21	75mg	100mg	

The normal EPMA order set is prescribed as a 14-day course and prescribers will need to ensure repeat bloods are taken in time for day 8. As the FBC bloods are required every 7 days, dispensing will be up to seven days at a time in line with the bloods.
If the slower titration is used, bloods are required in time for days 8 and 15.
Titration beyond day 21 is determined by the prescriber and should be guided by the patient response and any side effects.

***Note**; when prescribing on EPMA, the start date should be set as the day on which the titration is set to begin, and the time amended to **00:01** to allow for dose prompts. Prescribing after 12pm midday and not amending the time to 00:01 may result in missed doses or shifting of the scheduled doses forward in time.*

Initial doses should be given in the evening (6-8pm) rather than at night, which allows time for observations at 2hrs post dose. In exceptional circumstance during community initiations, the **first dose only** can be given in the morning to allow the full post-dose monitoring to be carried out. Subsequent PM doses can be given in the evening rather than at night.

NOTE: If significant side effects develop, then titrations can be paused, and the current dose maintained to see if they resolve. If following a clinical review, they are deemed sufficiently problematic, doses can be reduced, and a slower titration considered. This will need to be prescribed as a custom titration and the template will no longer be suitable.

Physical observations –Monitoring during Clozapine initiation (See appendix 5)

Day	Observation Time	Monitoring range
1	Prior to first dose	**Within 60 mins**
	1 hours post dose	Within 15 mins
	2 hours post dose	Within 15 mins
	6 hours post dose	Within 15 mins
2	Prior to administration of **each** dose	**Within 60 mins**
	2 hours post dose	Within 15 mins
	6 hours post dose	Within 15 mins
3-15	Prior to administration of **first** dose	**Within 60 mins**
	6 hours post dose	Within 15 mins

NB – in some very rare instances with community initiation, it may be appropriate to give the first dose earlier in the day to enable the 6 hrs post dose monitoring to occur within the teams working hours (e.g. in the morning or midday). In these cases, this should be documented clearly in the patient notes. This is not needed for inpatient initiations

Physical Observations	
Baseline	Blood Pressure*, Temperature, Pulse (Can be taken before first dose)
Day 1	Blood Pressure*, Temperature, Pulse **One, two and 6 hours after dose**
Day 2	Blood pressure, temperature, pulse **2hrs post AM dose** **6hrs post AM dose**
Day 3 -14	Blood pressure*, temperature, pulse
Day 15 and after (until stable dose reached)	Blood pressure*, temperature, pulse **Once daily on alternate days**
Follow up	Blood pressure*, temperature, pulse **Before each blood test**, or as indicated by presentation
Biochemistry and other monitoring	
Baseline	FBC, U+Es, LFTs, HbA1c
Weeks 1-4	FBC, U+Es, HbA1c
Week 5 onwards	As per schedule

(* **If patients mention dizziness following initiation of clozapine, consider adding in orthostatic BP measurements in addition to basic sitting BP**)

- All abnormal or out of range observations MUST be discussed with the consultant as soon as possible. Morning observations should be reported to the consultant the same working day, evening doses no later than the following morning
- At weekends, abnormal values must be discussed with the on-call doctor, who should also be registered with DMS.

The prescriber or deputised duty doctor MUST be contacted if any of the following are reported:

- Temperature greater than 38°C
- Any sustained upward trend in pulse, or a single pulse >100bpm

- A postural drop of greater than 30 mmHg (systolic or diastolic)
- Systolic BP >140 mmHg and/or diastolic >90mmHg
- Systolic BP <100 mmHg
- Diastolic <60 mmHg
- Patient appears over-sedated or any other adverse effect
- Any sore throat or fever (Urgent FBC advised)
- Evidence or mention of constipation
- Any red or amber blood monitoring result
- Any evidence of non-compliance with initiation regime

Where symptoms of myocarditis are present (e.g., tachycardia, fever, flu-like symptoms, fatigue, dyspnoea, chest pain) an urgent ECG must be performed. When this is accompanied by signs of heart failure, clozapine must be immediately discontinued. In all cases where myocarditis is suspected, seek advice from an appropriate medical specialist, including on-call/emergency services if necessary.

If any observation cannot be made then an entry must be recorded in the patient notes for each, explaining the reason and any follow up required.

2.1.5 Additional Monitoring Requirements for community (Home Treatment Team) Initiation

Patients must be considered suitable for out-patient care in view of their current symptomatology and safety risk **before** initiation in the community.

- At the point of deciding to initiate in a community setting, adequate facilities and staffing should be available to carry out all necessary clinical monitoring.
- Patient should have expressed a preference for home initiation, and be aware of the risks
- Must be accompanied **24 hours a day for the first day** of the titration period (family member, a friend or care home staff). If this is not possible, inpatient initiation should be strongly considered. Rationale for continuing without such monitoring should be clearly documented and all risks noted. After 24hrs, normal checks and supervision should be carried out as per the protocol.
- The current drug regimen should not be complex. Consider interactions and additive side effects – hypotension, sedation & effect on QTc
- There should be an understanding from the patient that admission may become necessary during the titration, and staff should be aware they may have to act to identify a bed if this situation arises
- **Outside of the titration schedule, dose increases on weekends and bank holidays schedule should be avoided if possible**
- There should be a named consultant psychiatrist available for the duration of the treatment [the prescriber]. The consultant psychiatrist should have experience of managing clozapine titrations. During the titration the client is to be seen by a doctor at least once a week. The consultant psychiatrist should also review the physical observations made by the team at least once a week
- The consultant should review the patient similarly to an inpatient initiation i.e., assessing mental state, adjusting the titration rate, managing any cross-titration of antipsychotic medication

- The patient must be provided with an emergency contact number for the treating team, this contact must be available in the evening and at weekends. There must be a contingency plan in case the patient defaults from visits, becomes non-adherent or experiences potentially serious side-effects.
- The patient must be able to be seen each day of the titration and observations taken
- Has the patient understood the possible side effects and what to do about them?
- At the end of the titration period, follow up arrangements including blood monitoring requirements should be explained and appointments made as necessary
- The patient's GP should be informed in writing of the ongoing prescribing, monitoring and supply of clozapine (see appendix 2), including any physical tests performed and on-going physical health concerns regarding clozapine.
- The patient MUST be seen **at least** once a day at the time of the first dose of the day.
- From day 5, and only if all previous observations have been stable and consistent, and where suitable monitoring equipment can be loaned to the patient, it MAY be appropriate to replace the 6hr post dose check with a phone call to the patient to confirm there are no problems. Two conditions MUST apply to this:
    - It must be considered clinically appropriate by the consultant to rely on remote observations and documented as such in the notes.
    - Staff must speak directly to the patient. If this is not possible, a visit must be arranged as soon as possible.

End of titration (Inpatient and Community)

By day 14 of the regime, if all goes to plan, the patient will be on a stable dose of 100mg AM and 200mg PM; if required the dose may then be further increased in increments of 50 to 100 mg preferably at weekly intervals, but no more than 25mg on any given day as an outpatient. These subsequent dose adjustments will not have an order set on EPMA as these will be bespoke for each patient. Further dose changes should be considered carefully, and the patient reviewed until stable. Due to the half-life of clozapine, allow between five to seven days for a patient's clinical presentation to settle enough to be assessed).

The total daily dose may be divided unevenly, with the larger portion at bedtime. This may limit the effect of sedation or dizziness

Note that some patients may achieve a good clinical response at lower doses or further titration may be limited by the development of adverse effects. The decision to increase a dose at any stage must balance any additional risk posed by a dose increase against the mental state of the patient, the risk they pose to themselves or others, or any side effects that are apparent at the time

Maintenance dose

After achieving maximum therapeutic benefit, treatment should be maintained for at least 6 months. It has been shown that as many as 60% of patients with a initially lesser respond over the period of 6-12 months. Subsequently, many patients may be maintained effectively on lower doses. Careful downward titration should therefore be considered but must be balanced by the clinical presentation. Clear documentation of any changes is vital. Where concordance is a problem, administration in the evening as a single dose may be acceptable and more convenient. Some patients may prefer a once-a-day dosing schedule, but the impact of the higher single dose must be carefully reviewed to avoid increased adverse

effects and discussed with the patient. Most single doses are given at night to avoid issues with excessive sedation.
Note doses of 400mg/day or more should be given as divided doses twice daily, with the larger dose given at night.

Higher / Maximum dose

To obtain full therapeutic benefit, a very few patients may require larger doses, in which case small incremental dose adjustments (i.e., not exceeding 100 mg can be considered, up to 900 mg/day. Plasma level monitoring is required to assess the impact of these higher doses and the risks of higher plasma levels if these occur. The clinical presentation and any side effects must be documented along with the plasma levels to ensure a clear benefit/risk determination can be made.

The possibility of increased adverse reactions (especially seizures) occurring at doses over 450 mg/day must be borne in mind and monitoring of levels should be considered, ideally every one to two weeks in the early stages of higher dosing, reducing once steady state levels are determined and side effects are not a problem.

In some cases, titration **may** proceed even above laboratory stated ranges as evidence suggests exploring levels up to 1000mcg/L as long as there are no **significant** adverse effects. There are very few patients who will respond above this level but see section 2.4.6 before considering this option.

Rapid and slow responders

Some patients may respond especially well to clozapine and show good clinical responses even at low doses. This can be seen at doses as low as 150mg/day. The clinical presentation of such patients should be monitored closely and reviewed at the end of the first few weeks of treatment to determine if further titration is really needed.
Where psychotic symptoms persist there is evidence that some patients who initially respond sub-optimally on clozapine can benefit from an extended period on clozapine and show improvements after six to eight months.

2.1.6 Maintenance Monitoring Requirements During Clozapine Treatment

Due to the risk of serious blood dyscrasias, namely neutropenia and agranulocytosis, all patients on clozapine are required to have regular haematological (full blood count, FBC) monitoring. The majority (around 70%) of observed cases of blood dyscrasia occur in the first 18 weeks of treatment, though the mechanism by which clozapine causes these is poorly understood. The risk is not dose related and the incidence of agranulocytosis decreases according to the length of time that clozapine has been taken.

Following the initial baseline blood test, clozapine therapy requires on going blood tests. The frequency of these varies depending on the length of treatment, but the monitoring parameters remain the same:

- Weeks 1-18 – Testing **ONCE a week** is required.
- Weeks 18 – 52 – Testing is required **every TWO weeks.**

- After 52 weeks – Testing is required **every FOUR weeks.**

Testing frequencies will alter following any untoward blood test (see below)

To reduce the likelihood of preventable mortality, pharmacy departments who supply clozapine to patients should only do so once a satisfactory blood test result has been received by the relevant clozapine monitoring. A traffic light scheme is used to visually classify the FBC results for patients, giving a **Red, Amber,** or **Green** result. It is important to enter results onto the correct monitoring system to confirm the current colour status and not rely on interpreting results directly from Pathology reports.

Table 3. Interpretation of clozapine blood tests (for Denzapine Monitoring Service)		
	Reference ranges: White blood cells (WBC) /L Absolute neutrophil count (ANC) /L	Additional information
GREEN	WBC ≥ 3.5 x 10^9 ANC ≥ 2.0 x10^9	Treatment to continue as planned
AMBER	WBC ≥ 3.0 x 10^9 to < 3.5 x 10^9 ANC ≥ 1.5 x10^9 to <2.0 x 10^9	Treatment to continue as planned, but blood testing required **TWICE a week** until counts increase or stabilise
RED	WBC< 3.0 x 10^9 ANC < 1.50 x10^9	Immediately stop clozapine treatment, sample blood **DAILY** until either two consecutive green or amber results, or a combination of two consecutive green or amber results are obtained. Do not re-expose the patient to clozapine. without appropriate discussion with DMS
		If clozapine has been withdrawn and either a further drop in the WBC count
		below 2.0 x 10^9/L occurs or the ANC falls below 1.0 x 10^9/L, further management must be guided by an experienced haematologist.

(Source – Summary of product characteristics; Denzapine, EMC)

2.1.7 Point of care testing versus Pathology service samples

Within our Trust we currently use two possible systems for processing routine clozapine blood tests. Each system has its own advantages and problems:

Samples sent via City Hospital Pathology - samples are taken and then sent via porters to City Hospital. This is available to both inpatients and community teams.

Advantages	Disadvantages
• Results are added to the Pathology results system automatically	• Results need to be manually uploaded to DMS • Delay in obtaining results

Samples analysed via Yumizen® machines – These point-of-care blood analysers are located in many of our community hubs around the Trust. These provide analysis of samples in the clinics and can negate the need for patients to return to collect medication once results come back from Pathology. Unfortunately, this is currently predominantly only available to community clinics at specific locations; it is not available for routine testing for inpatients due to the multiple and widespread location of such units.

Advantages	Disadvantages
• Samples take approximately 1 minute to be analysed • Results are automatically uploaded to DMS and current blood result status can be seen immediately • Patients can receive medication at the time of testing and avoid unnecessary repeat visits	• Results do not appear on Pathology service • Not easily available to inpatients

2.1.8 Management of blood results

Management of Green results

Where a patient has a green result, supplies can be made and issued to the patient in line with the validity of the blood result **(See appendix 6)**

Management of Amber and Red results

It is important that any amber or red results are identified and actioned as soon as possible to avoid any harm to the patient. Amber results are not normally a reason to interrupt treatment, but additional monitoring is required as indicated above.

Red results are always a matter for concern and require prompt management.

- Note that a below range result for **platelets** only does not constitute a RED result, but all three monitoring services will highlight this. DMS recommend discontinuation of treatment if platelets fall below 50,000/mm^3 (50 x 10^9/L). Treatment should not be restarted till levels are above 50 x 10^9/L.
- Some of the services (ZTAS, CPMS) also monitor the eosinophil count and this also would not trigger a RED result, but high levels may be associated with myocarditis. DMS state that if levels go above 3000/mm^3 (3.0 x 10^9/L) treatment with clozapine should be discontinued. Treatment can re-start when levels fall below 1000/mm^3 (1.0 x 10^9/L). Treatment above this level should only be carried out after discussion with the appropriate monitoring service.

Amber Results: Please also see the section for managing AMBER results. [Appendix 7] This is indicated by either a total white cell count between 3.0 x 10^9/L and <3.5 x 10^9/L, or a neutrophil count of between 1.5 x10^9/L to <2.0 x 10^9/L.

Amber results are not a reason to stop clozapine treatment, but they may be an indication of future concerns. An amber result can be triggered by a drop in any of the measured values, including platelets, but may not necessarily lead to agranulocytosis. More often it is an indicator of a downward trend in values which may eventually lead to an increased risk of infection. To mitigate the risk, bloods are checked on a twice a week basis until the levels drop further to a red level or improve and become green again. Clozapine doses normally remain unchanged unless a sustained downward trend is seen.

Red Results: Please also see the section for managing RED results. [Appendix 8] These are indicated by either a total white cell count below 3.0 x 10^9/L or a neutrophil count below 1.5 x10^9/L and may put the patient at significant risk of severe infection.
On receipt of an abnormal RED result, the team currently responsible must stop treatment immediately. This is managed easily for inpatients, but community teams will need to contact the patient or their carer and ensure that no further doses are taken. **Daily blood tests are required** until the abnormal results resolve and during this time period the patient needs to be monitored closely for infection. It is the responsibility of the consultant to ensure that these results are relayed to DMS promptly and that they are kept informed of any changes with the patient.

- If the initial red result is followed by a second red result, then the patient is considered "confirmed red" result. Traditionally these patients would not be considered suitable to re-start on clozapine, but more recently, some patients have been re-started after discussion with DMS. This requires direct discussion by the consultant with DMS. Not all patients are suitable for a re-challenge. In this case the patient is added to the Central Non-Rechallengable Database (CNRD) which is accessed by all UK manufacturers and would not normally be accepted for treatment by any of them.
- If the initial red result is followed by two non-red results, i.e., two greens, two ambers, or an amber and a green, then the red result is currently classified as an "unconfirmed red" and a patient may be considered as suitable to retry clozapine once the bloods settle down. (See section Three – Red result re-challenge)

2.1.9 Benign Ethnic Neutropenia (BEN)

Some patients from some ethnic groups may suffer from this condition which is characterised by a lower than "normal" level of circulating neutrophils. This mainly affects individuals of Afro-Caribbean, African and Middle Eastern descent. Clinically, these individuals do not appear to be at increased risk of infections compared to non-BEN individuals.
These patients are still suitable for initiation of clozapine following diagnosis and discussion with DMS and a haematologist and special altered dose ranges are used during their monitoring.

2.1.10 Monitoring clozapine plasma levels (See Section 5 – Therapeutic drug monitoring of clozapine)

Notifying GP services of clozapine initiation
Once clozapine titration has been successfully completed the patient's GP must be informed that treatment has been commenced. This is especially important for community teams where GPs may be required to support the ongoing monitoring and review of patient wellbeing. Appendix [9] provides a template letter for this purpose. A copy sent through to

the GP and a copy should be added to the patient record. There are editable letter templates on RIO under clinical documentation for initiation and to notify of red results.

Switching from a previous antipsychotic therapy to clozapine
It is generally recommended that clozapine should not be used in combination with other antipsychotics. When clozapine therapy is to be initiated in a patient undergoing oral antipsychotic therapy, it is recommended that the other antipsychotic should first be discontinued by tapering the dosage downwards. However, a more practical approach to prevent a mental health relapse requires slow reduction in dose of the previous oral antipsychotic at the same time cautiously titrate the dose of clozapine up [Cross-taper approach].

Medication	Effect
First generation depot antipsychotics	Can potentiate the risk of agranulocytosis and are contraindicated with clozapine. Treatment with clozapine should not be initiated until at least 5 half-lives after the last depot injection.
Risperidone long-acting injection (2 weekly dose) **Risperdal Consta**	Ideally treatment with clozapine should not be initiated until at least 4 weeks after the last depot injection.
Paliperidone long-acting injection (Monthly dose)	Ideally treatment with clozapine should not be initiated until at least 8 weeks after the last depot injection.
Paliperidone long-acting injection (**Three** Monthly dose) **Trevicta**	Ideally treatment with clozapine should not be initiated until at least **6 Months** after the last depot injection.
Paliperidone long-acting injection (**Six** Monthly dose) **Byannli**	Ideally treatment with clozapine should not be initiated until at least **12 months** after the last depot injection.
Aripiprazole long-acting injection (Monthly dose)	Ideally treatment with clozapine should not be initiated until at least 8 weeks after the last depot injection.
Olanzapine long-acting injection (Monthly dose)	Ideally treatment with clozapine should not be initiated until at least 8 weeks after the last depot injection.

The above data is based on manufacturer recommendations and should be considered a safe compromise between levels of the depot beginning to fall and complete clearance of the depot from the system. It is anticipated that there may be interactions, but for the majority of the high-risk patients, any decision to start clozapine earlier than the recommendations will be at the sole responsibility of the named consultant.
Such decisions must be documented within the patient notes and full clinical reasons given, clearly indicating the risk/benefit considerations.

2.1.11 Clozapine discontinuation

Clozapine is associated with the most common and severe withdrawal symptoms of the antipsychotics, probably due to the potent anticholinergic side-effects.
In the event of planned termination of clozapine therapy, a gradual reduction in dose over at least a 1-to-2-week period is recommended to reduce the likelihood of experiencing discontinuation symptoms. A widely accepted schedule for this is 100mg reduction per week until a 100mg/day dose is reached and then decrease by 25mg every 4-7 days until discontinued. Stopping clozapine treatment should be managed very carefully as it often represents the patient's best hope of recovery from treatment resistant schizophrenia.

Stopping more abruptly may be clinically indicated when patients are at risk but there are significant risks with abrupt discontinuation (e.g., severe infection) the patient should be carefully observed for the occurrence of withdrawal and rebound reactions:

- Clozapine discontinuation rebound psychosis
  Patients who stop clozapine suddenly are at risk of developing a rebound psychosis which can occur rapidly and be very severe. Unless contra-indicated it is advised to recommence clozapine titration as soon as possible. Use of IM clozapine may need to be considered if the patient is not cooperative with oral medication due to the severity of their presentation.

- Cholinergic rebound – this is caused by the abrupt removal of muscarinic receptor antagonism in patients who have developed a tolerance for this over time. The size of the response may be related to the prior cholinergic load.
  Symptoms may develop as much as 5-7 days after discontinuation and may be mild or life-threatening. Symptoms include: ○ Mild – sleep disturbance, vivid dreams, nightmares
  ○ Moderate – anxiety, nausea, diarrhoea, sweating, urinary urgency ○ Severe – confusion, delirium, catatonia

If clozapine cannot be re-initiated within 48hrs, then altering the regimen should be considered to prevent rebound. These may include the use of antipsychotics with anticholinergic properties (e.g., olanzapine) or procyclidine as an addition to prescribed antipsychotics.
Patients who develop mild rebound symptoms during withdrawal titration should be paused and the previous higher dose re-initiated for a while and the patient reviewed before continuing the withdrawal.

Notifying DMS after clozapine discontinuation

DMS **must** be notified when treatment is ceased, with the requirement for an **additional 4 weeks of blood results** after the last dose using the patient's established monitoring frequency.

2.1.12 Restarting clozapine after a treatment break

After a period of non-concordance
Clozapine needs to be retitrated if the patient has not taken any clozapine doses for more than 48 hours. Titration can be faster than initial titration if clozapine has been well tolerated previously

After an unconfirmed red
Following an unconfirmed red result (red followed by two green or amber results) treatment can restart after discussion with DMS and a haematologist. The discussion should determine the rate at which the retitration occurs

After a confirmed red
Following a confirmed red result (two or more red results without two consecutive green or amber results) the patient cannot be re-challenged with clozapine, unless this is done off license (See Section Four – Management of clozapine red results and clozapine rechallenge) Any decision concerning the continued treatment of a patient following a red result is the responsibility of the responsible consultant. It is at their discretion to re-start clozapine therapy; however, **the clozapine monitoring service (DMS) must be informed**, and this is considered an off-license indication for which an off-licensed agreement needs to be completed and documented on DMS before starting.

2.1.13 Smoking & Clozapine levels

Smoking may reduce clozapine plasma levels by up to 50% depending on the number and type of cigarettes smoked. Consistently heavy smokers often require higher doses of antipsychotic medications. Thus, patients who smoke and who are not responding to clozapine treatment may have their plasma levels checked to ensure that the clozapine dose is high enough to obtain full therapeutic effect. This effect is unrelated to nicotine and is caused by polycyclic aromatic hydrocarbons (PAHs) present in tobacco smoke. The hydrocarbons in tobacco smoke induce the production or activity of various liver enzymes, in particular cytochrome CYP1A2, an enzyme associated with the metabolism of several psychotropic drugs including clozapine. Following smoking cessation, the service user is no longer exposed to PAHs and metabolism of these psychotropic drugs decreases, resulting in increased plasma levels. Plasma levels will rise regardless of whether a patient is treated with NRT, bupropion, varenicline or e-cigarette.
When discharging patients from inpatient services the risk of smoking increasing in the community needs to be considered and a discussion about this documented with the patient.

If smoking cessation is planned, a baseline clozapine plasma level should be taken before implementing the change. On stopping smoking the clozapine dose should be reduced gradually (over a week) until around 75% of the pre-cessation dose is reached. A clozapine plasma level should be repeated one week after stopping smoking. Further dose reductions should be considered if necessary and the patient should be reviewed weekly for up to four weeks.
If the service user subsequently re-starts smoking, the clozapine dose should be increased cautiously to their previous 'normal' smoking dose over one week. A clozapine plasma level should then be taken after a further week and dose adjustments made if necessary.

2.1.14 Clozapine side effects (See Section six – Management of Clozapine side effects)

Reporting Side Effects

Upon review of a patient's health and blood result any abnormalities in the blood parameters (excluding those mentioned above) or significant changes in physical or mental symptoms considered to be clinically significant, should be reported as adverse events. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard.

Adverse events must also be reported to the clozapine monitoring service (DMS).

2.2 Use of IM Clozapine

2.2.1 What is IM clozapine?

Intramuscular clozapine is an unlicensed product made in the Netherlands and imported to the UK via Durbin PLC or Mawdsley's Unlicensed. It is a clear yellow solution for injection. The strength of the injection is 25mg/ml, and each ampoule contains 5mls (125mg). It is administered by deep intramuscular injection into the gluteal muscle. The injection may be painful and the maximum volume that can be injected into each site is 4ml (100mg). For doses greater than 100mg, the dose may be divided and administered into two sites.

2.2.2 What is the objective of using IM Clozapine?

The aim of using clozapine injection is a short-term intervention to a)
initiate clozapine for patients who refuse oral clozapine

OR

b) to maintain patients on clozapine who refuse existing oral doses when there is a significant risk to the patient or to others if clozapine is not administered. This is always with a view to convert to oral clozapine as soon as possible.

2.2.3 Who can have IM clozapine?

IM clozapine is an unlicensed product which may be considered only for inpatients registered with a clozapine monitoring service (ZTAS/CPMS/DMS) who are refusing oral clozapine treatment. It can be considered for patients who have never been exposed to clozapine previously or patients previously treated with clozapine and known to have responded but relapsed owing to noncompliance. The need for clozapine injection must be agreed by the MDT, included within the appropriate MHA consent paperwork, and fully documented in the patient record (see Appendix 10 for an example of information to be included in a care plan).

Clozapine injection may only be prescribed and administered on the prescription written by or authorised by the consultant Psychiatrist with the agreement of the Chair and/or Deputy Chair of the Pharmacological Therapies Committee (PTC) i.e., Assistant Medical Director (Pharmacological Therapies) and/or Chief Pharmacist. The request to use IM clozapine must be made on a case-by-case basis (see Appendix 11 – request form for IM clozapine). Teams considering use of IM clozapine must have the relevant knowledge and skills, either from experience or by supervision from others experienced in using IM clozapine to ensure patient safety is maintained.

2.2.4 Process for requests for IM clozapine for treatment initiation

The following must be completed before IM clozapine can be prescribed for treatment initiation:

- Discussion with MDT and team / locality pharmacist
- Discussion with a peer consultant
- Discussion with a SOAD and inclusion of IM clozapine on Form T3 if MHA Consent to Treatment applies. If consultation with a SOAD will create a clinically unacceptable delay, the use of IM clozapine for treatment initiation must be discussed & documented at least with a peer consultant psychiatrist before completion of Section 62 form.
- Documentation in the patient record regarding use of IM clozapine (Appendix 2)
- Completion of request form for IM clozapine (Appendix 3). This form must be signed by the requesting consultant and the peer consultant prior to submission to PTC.
- To avoid unnecessary urgency, requests for IM clozapine may be made in anticipation of need rather than at the urgent point of need.
- Email the IM clozapine request form to the Chair and Deputy Chair of the Pharmacological Therapies Committee (PTC) i.e., Assistant Medical Director (Pharmacological Therapies) and/or Chief Pharmacist for discussion and authorisation at the following PTC meeting. If this will create a clinically unacceptable delay, authorisation may be requested outside of the following PTC meeting, and then the request will be subsequently presented at the following PTC meeting for information.
- Team to consider whether restrictive physical interventions will be needed to administer IM clozapine. Are there any health risks or additional observation likely to be needed post-administration? Care plan for IM clozapine must include details of this assessment. See Prevention and Management of Violence Policy, and contact AVERTS team for advice and support on a case-by-case needs led basis.

2.2.5 Process for requests for IM clozapine to avoid a clozapine treatment break

The following must be completed before IM clozapine can be prescribed to avoid a clozapine treatment break:

- Discussion with MDT and team / locality pharmacist
- Discussion with a peer consultant
- The use of IM clozapine to avoid a clozapine treatment break must be discussed & documented with a peer consultant psychiatrist before completion of Section 62 form if MHA Consent to Treatment applies. Referral must also be made for discussion with a SOAD and inclusion of IM clozapine on Form T3.
- Documentation in the patient record regarding use of IM clozapine (Appendix 2)
- Completion of request form for IM clozapine (Appendix 3). This form must be signed by the requesting consultant and the peer consultant prior to submission to PTC.
- To avoid unnecessary urgency, requests for IM clozapine may be made in anticipation of need rather than at the urgent point of need.
- Email the IM clozapine request form marked as urgent to the Chair and Deputy Chair of the Pharmacological Therapies Committee (PTC) i.e., Assistant Medical Director (Pharmacological Therapies) and/or Chief Pharmacist. The request will be reviewed, and a response provided within one working day. The request will be subsequently presented at the following PTC meeting for information.
- Duration of approval:

- When a request for IM clozapine is initially approved, treatment may be prescribed under Section 62 if treatment is required urgently while waiting for a SOAD
- At the earliest opportunity, IM clozapine should be added to a Form T3. IM clozapine should be included either if it is currently prescribed, or if it is not currently prescribed but it is anticipated it will be required as part of the treatment plan during potential periods of clozapine non-adherence
- Provided there is no change to the reasons for IM clozapine AND it is included on the Form T3, further future requests for use are not required to be submitted to PTC after the initial approval.

2.2.6 Registration of patients for IM Clozapine

All patients for IM clozapine must be registered with a clozapine monitoring service (ZTAS/CPMS/DMS) as the objective is to use the injection for the shortest possible time before switching to oral treatment. The clozapine monitoring service must be informed of the plan to use IM clozapine. The usual clozapine mandatory baseline and routine blood monitoring and the necessary precautions for amber and red warnings apply. NOTE: ZTAS/CPMS/DMS do not have any responsibility for the patient when they are not taking oral clozapine.

2.2.7 How long can the treatment continue for?

Clozapine injection should be used for the shortest duration possible. Before administering each injection, the patient should be offered clozapine orally. The need for ongoing IM treatment must be reviewed regularly by the MDT.

In general, the injection should be used for no longer than a cumulative total of two weeks. In exceptional cases, the injection may be used for a cumulative total of longer than two weeks following discussion with a peer consultant psychiatrist. This discussion must be documented in the patient's clinical notes and communicated with the Chair and Deputy Chair of the PTC. This process must be followed after each subsequent cumulative use of two weeks.

2.2.8 What is the oral equivalent of the IM?

The oral bioavailability of clozapine is about half that of the intramuscular injection. For example, 50mg daily of the IM injection is roughly equivalent to 100mg daily of oral formulations.

2.2.9 How to prescribe clozapine injection

The dose of IM clozapine will be half of the current dose of oral clozapine. The patient should always be offered the tablets or liquid first on a dose-by-dose basis. Only if the patient continues to refuse should the injection be administered. All prescriptions for IM clozapine must be included on the MHA consent paperwork if applicable.

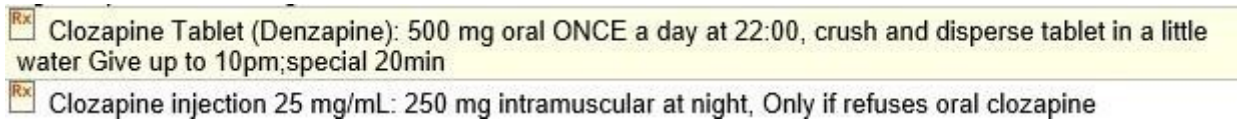
2.2.10 Clozapine initiation

For new clozapine prescriptions, see Section 2.1.3 (above) for requirements to initiate clozapine. All inpatient initiations will be prescribed on EPMA, either as a standard titration from an EPMA order set or as a custom titration to allow for dose adjustments outside of the set titration schedule e.g., rapid re-titration, older patients or a previous poor tolerability to clozapine. A custom titration would be prescribed manually i.e., individual doses prescribed. As the dose of oral and therefore IM clozapine will vary depending upon the stage of titration, the IM dose of clozapine will be prescribed individually as a STAT dose *'to be given if refuses oral clozapine'* and amended as the titration progresses.

2.2.11 To avoid clozapine treatment break

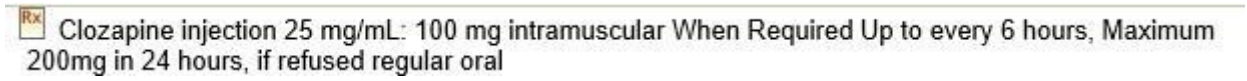
Either:

IM clozapine can be prescribed as a regular dose with instructions to administer if oral clozapine dose is refused (see example below)



Or:

IM clozapine can be prescribed as a PRN dose with instructions to administer if oral clozapine dose is refused.



Or:

IM clozapine can be prescribed as a STAT dose with instructions to administer if oral clozapine dose is refused or at the time when the decision is made to administer IM clozapine.

2.2.12 Administration of IM clozapine

- IM clozapine is available as 25mg/ml x 5ml ampoule. The solution does not need dilution before administration.
- The remainder of the ampoule must be discarded after use.
- The injection may be painful. Doses >100mg (>4ml) will need to be divided and administered over two sites.
- The solution is administered as a deep intramuscular injection into the gluteal muscle. Access to upper/outer gluteal region while resisting will require face down restraint and this needs to be specifically referenced in the care plan before administration. An Eclipse for must also be completed for any restraint in the prone position.
- If at any point the patient changes their mind and wishes to take oral clozapine – give oral clozapine.
- If IM lorazepam is required leave at least ONE HOUR between administration of IM clozapine and IM lorazepam.

2.2.13 Monitoring of patients on IM clozapine

Follow the trust recommended guidance on monitoring clozapine. It is anticipated that if required, daily monitoring of blood pressure, pulse, respiratory rate, and temperature will be difficult for many patients; every effort must be made to obtain these, and patient refusal of observations must be documented. Importantly, patients should be observed for any signs of being unwell, such as pallor, cough, shortness of breath, sweating etc.
After each injection has been given the patient must be observed every 15 minutes for the first two hours to check for excessive sedation. The usual clozapine monitoring blood tests must be performed whilst on treatment; the sample could be taken at the same time as the administration of clozapine injection if needed.

2.2.14 Costs

Clozapine injection costs around £100 per ampoule (or part thereof, as any unused portion must be discarded)

2.3 Management of clozapine red results and clozapine rechallenge

2.3.1 Clozapine and blood dyscrasias

See Section 2.6 for routine monitoring frequencies and FBC reference ranges.

The medical and scientific literature gives different criteria for the definition of neutropenia and agranulocytosis; an understanding of the nature of the blood dyscrasia that a the patient experiences is important and can guide on future treatment options.

Agranulocytosis is defined as “a deficiency of granulocytes in the blood, causing increased vulnerability to infection.”

Neutropenia is defined as “is an abnormally low concentration of neutrophils in the blood.”

Agranulocytosis may be a decrease in one or more type of granulocyte, neutropenia is specific to the neutrophils. Neutropenia increases the risk from bacterial infections and the possibility of developing sepsis.

2.3.2 Clozapine – immediately after a red result

2.3.2a Actions following a red result

If a patient has a red result, the following actions need to take place:

- stop clozapine immediately and refer to the acute care pathway
- arrange for daily FBC testing until two successive green results are achieved
- identify other medications which may be contributing to a red result

- record blood pressure, pulse, and temperature measurements at least once daily
- ask a haematologist for management advice, seek clarity about the nature of the blood dyscrasia (see above)
- consider appropriate antipsychotic treatment for initial psychosis management (discuss with pharmacy and / or DMS) including consideration of whether and when to re-start clozapine
- consider the risk and monitor for signs of clozapine rebound psychosis (See Section 1)
- close monitoring for any signs or symptoms of infection and immediate action if any suspicion of infection e.g., raised temperature
- if the patient is at home, advise the patient to take additional temperatures if they are feeling warm or unwell
- advise the patient to report immediately if any signs of infection develop, for example, sore throat, fever, or other flu-like symptoms

2.3.2b Consequence of a red result

Two consecutive red results are classified as a *confirmed* red result and the patient will be added to the Central Non-Rechallenge Database (CNRD) which is shared with all clozapine UK brands in order to avoid inadvertent rechallenge with a different clozapine brand. Following a confirmed red result, it is recommended that patients do not continue on clozapine.

Following a confirmed red result or another serious adverse drug reaction to clozapine (which would usually preclude its use) some patients may be re-exposed to clozapine as part of a planned clozapine rechallenge, often on an off-licensed basis (see Section 2.3 below).

If the two follow-up blood test results are both non-red (i.e., either amber or green), the RED result is considered unconfirmed and following discussion with pharmacy and / or DMS, Denzapine can be continued. If treatment has stopped for less than 2 days continue on the same dose. If over 2 days, re-titrate from 12.5mg.

2.3.3 Initial psychosis treatment following a red result

When clozapine is discontinued abruptly the risk of relapse is particularly high and relapses can be of significant severity (see section 1 – treatment following abrupt cessation of clozapine). The decision to initiate alternative antipsychotic treatment during this vulnerable period is a clinical decision which should be taken in context of the risks and benefits. Most antipsychotics are associated with reports of blood dyscrasias, and some may prolong clozapine-induced blood dyscrasias[9]. Olanzapine or Amisulpride may be the safest options after clozapine-induced neutropenia or agranulocytosis due to the low number of case reports of neutropenia in monotherapy and absence of case reports of prolonged clozapineinduced neutropenia. The DMS haematologist can support teams in developing an individualised medication plan and advise on suitable antipsychotic alternatives if required.

Alongside discussion with pharmacy and / or DMS, consideration must be made regarding whether to re-start clozapine as a matter of priority following an unconfirmed red result in order to minimise the risk of relapse. Rapid re-titration must only take place in an inpatient

setting. See Section 4.6 for guidance on blood test results required prior to re-commencing clozapine after a treatment break.

2.3.4 Record keeping - Alerts

Where a patient experiences a serious adverse effect to clozapine (or any medication) this should be recorded in the alerts section on RiO, and completion of a Yellow Card ADR report must be considered.

2.3.5 Clozapine rechallenge following a confirmed red result

Clozapine re-challenge following a confirmed red result is often a successful process and may offer a patient an opportunity for improved symptom control compared to treatment with other regimes. A systematic review of the literature suggests that clozapine rechallenge success rates vary according to the original tolerability issue.

Original Tolerability Issue	Success Rate
Neutropenia	70%
Agranulocytosis	20%
Neuroleptic Malignant Syndrome	100%
Myocarditis	75% (although CI of 30 to 90%)

It was concluded that clozapine rechallenge should be carefully considered for those patients who have previously derived benefit from clozapine and who have discontinued this treatment due to neutropenia or NMS but not agranulocytosis or myocarditis.

DMS consider all clozapine rechallenges in patients who have had a previous confirmed red result to be *off-license* and as such the prescribing clinician takes additional responsibility for the outcome of treatment. It is usual for additional haematological monitoring to be agreed during the initial phase of clozapine titration in such cases. DMS will consider each request for clozapine rechallenge on its individual merits and will always require evidence that the patient and/or an advocate (such as a carer or family member) has consented to this.

Criteria for re-challenge

Clozapine rechallenge may be reasonably considered when:

a) the patient derived significant benefit from treatment with clozapine
b) the patient has demonstrated a lack of response to other treatment options
c) there has been a previous episode of neutropenia (but not agranulocytosis)
d) written evidence is documented that advice has been sought from a consultant haematologist (either local haematologist or DMS haematologist)
e) there is doubt that clozapine was the cause of the previous tolerability issue
f) the benefits of proceeding are deemed to outweigh the risks
g) the patient and/or their advocate specifically requests this

Clozapine re-challenge following a confirmed red result is a high-risk procedure and it is expected that this be performed in a highly supported environment; where hospitalisation is not an option, it must be performed under the care of a Home Treatment Team.

Process for clozapine rechallenge - **See Appendix 12**

2.3.6 Blood tests following re-challenge

In cases of clozapine re-challenge following a red result, DMS will usually suggest an increased frequency of haematological monitoring. The frequency of monitoring will be determined by discussion and agreement between DMS, the consultant psychiatrist and the haematologist and will be titrated according to the level of risk and time course/nature of the previous red result.

Week of Treatment	Monitoring Frequency
1 to 12 weeks	Twice a week
13 to 18 weeks	Weekly
19 to 52 weeks	Fortnightly
Thereafter	Fortnightly Monthly monitoring may be proposed in the 2nd year, according to risk evaluation

2.3.7 Other Issues

2.3.7a - The use of G-CSF in clozapine re-challenge

In some cases, granulocyte-colony stimulating factor (G-CSF) may be recommended by haematologists in the acute and ongoing management of cases. Where this is the case an individualised plan of care will be required.

2.3.7b - The use of lithium in clozapine re-challenge

Lithium is known to cause leucocytosis and is sometimes used adjunctive to clozapine therapy to raise neutrophil levels, but this is somewhat controversial. The mechanism of this is unclear but seems to be not just a redistribution of existing neutrophils but also a true proliferative response. Where this approach is considered, it is important to implement the additional haematological monitoring associated with the use of lithium. The indication and clinical plan for concomitant use should be clearly documented in the patient notes.

The prescriber should also ensure that the patient understands the issues that surround treatment with lithium. There are concerns that this combination may simply mask impending agranulocytosis, making this approach dangerous, although there is little evidence to suggest this. The combination of lithium and clozapine may occasionally be associated with reversible neurological adverse effects, usually characterised by ataxia, coarse tremor and myoclonus.

2.3.7c Concomitant medication

If clozapine is prescribed following a confirmed or unconfirmed red result, the risk should be minimised by review of concomitant medication and discontinuation of any other medicines known to exert effects on the blood/bone marrow. In particular, if an anticonvulsant is required, sodium valproate should be ideally avoided with lamotrigine being considered as a safer alternative.

2.3.8 Effect of circadian rhythm / diurnal variation and exercise on white blood cells

Some patients may exhibit pronounced circadian rhythm in their leukocyte count, with counts showing more than twice the number of neutrophils in the afternoon compared to a morning sample. 8 out of 10 patients showed an increase in neutrophil count if the sample was taken 2 hours after waking / mobility compared to sampling immediately on waking. In addition, moderate and heavy exercise has been shown to substantially increase leukocyte counts, including neutrophils. If a patient's blood sample results are low when drawn in the morning, consider sampling later in the day or after the patient has had a period of activity.

2.4 Clozapine Therapeutic Monitoring (TDM)

Clozapine has well-documented tolerability problems, ranging from minor to fatal in severity and from transient to chronic in their time course. Clozapine is associated with potentially fatal blood dyscrasias and cardiac disorders, particularly during the early stages of treatment.

The SPC for clozapine states that between 7.1% and 15.6% of patients discontinued clozapine during clinical trials due to tolerability problems. The most common reasons were leukopenia, somnolence, dizziness (excluding vertigo) and psychotic disorder.

The following table outlines the adverse effects that are most commonly experienced by people taking clozapine:

		Adverse Effect
Very Common	≥1 in 10 people	Drowsiness/sedation, dizziness, tachycardia, constipation, hypersalivation
Common	≥1 in 100 to <1 in 10 people	Nausea, vomiting, anorexia, dry mouth, weight gain, dysarthria, blurred vision, syncope, hypertension, postural hypotension, urinary retention, urinary incontinence, blood dyscrasias (neutropenia, eosinophilia, leucocytosis), fever, fatigue, benign hyperthermia, disturbances in sweating/temperature regulation, ECG changes, elevated liver enzymes.

Before a trial of clozapine is commenced, the patient should be given information about the risks and benefits of clozapine treatment so that an informed decision can be reached where this is possible.

The ongoing monitoring of people taking clozapine, after the initiation period, is important to ensure that any adverse effects are identified and managed optimally. Many of the adverse effects of clozapine that people experience commonly are not thought to be dangerous but can be troublesome for the individual. These adverse effects can negatively affect the person's quality of life and contribute to stigmatisation. Specific consideration should be given to advice and support for obese patients as this can increase both the short and longterm cardiovascular effects of clozapine treatment.

Some adverse effects may be managed by the patient or medical management. In some cases, the use of simple, prescribed treatments may reduce the severity of the adverse effect.

All requests for a plasma level assay must only be made after discussion with the consultant or senior doctor within the responsible clinical team. This is to ensure that they are aware of the request and can intervene or follow up on the results.

Blood levels should only be needed under specific conditions (see below) and the patient should be assessed at the time of the sample for any signs of toxicity, and this should be recorded in the notes.

Note - If patients present with signs of toxicity or new or increased intolerable side effects at the time of a blood test, they should be reviewed face-to-face **within 24hrs. (see section 2.4.6)**

KEY RECOMMENDATIONS

- People taking clozapine should be monitored according to the haematological monitoring guide (see appendix 14)
- People taking clozapine should complete the GASS for Clozapine self-reporting scale (see Appendix 15) when attending for blood tests
- People taking clozapine should be asked about their bowel habits at each face-toface contact with clinical staff, such as blood tests and supply of medication. A questionnaire has been developed for use at the clinics. (See appendix 18)

Any abnormalities in the above should be reported to the care co-ordinator and escalated where necessary.

- The information given below should be used to support management

Effective clozapine level monitoring is often poorly implemented due to an incomplete understanding of its intended purpose. Clozapine level monitoring should not be confused with routine full blood count sampling as mandated by the manufacturer's licence agreements.

TDM can be useful in assisting clinicians to assess adherence and optimise treatment with clozapine. It is important that clozapine plasma levels are considered in the context of the patient's clinical presentation, particularly observations of efficacy and tolerability. An expression often used with regards TDM of many medicines is 'treat the patient, not the numbers' and in the absence of potentially toxic levels, this holds true for clozapine.

The literature suggests that there is a link between response to clozapine in the management of acute psychosis and plasma levels.

Clozapine blood levels correspond to both clozapine effectiveness and side effects. However, there is large variation between patients in blood levels. There is also substantial variation within patients (plus or minus 30% in some studies). Given the inter-patient variability, there is no minimum effective clozapine level and no maximum safe level. A clozapine plasma trough concentration of greater than 350mcg/L has been associated with efficacy in treatment resistant schizophrenia.

The mean threshold response for people with treatment resistant schizophrenia is 350 mcg/l. If a patient still has positive symptoms and has a clozapine level <350 mcg/L, prescribers should consider increasing the clozapine dose to correspond with a level >350 mcg/L. Patients rarely respond to levels >1000 mcg/L.

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There is no clearly established upper limit for plasma clozapine levels, although trough concentrations above 600mcg/L have been associated with increased risk of adverse effects, specifically marginal increase in seizure risk in some studies.

The risk of seizures is significantly increased with levels greater than 1mg/L. The reference range for clozapine is usually quoted as 350-600mcg/L. This should not be interpreted as therapeutic range. It is important to note that clozapine does not have a narrow therapeutic index and some individuals will be maintained at plasma levels out with the quoted reference range.

There is little or no value in taking clozapine levels routinely along with full blood counts unless there is a specific indication to do so. **Clozapine plasma assays should therefore only be done when clinically indicated and not as a routine intervention.**

Therapeutic drug monitoring of clozapine may be considered appropriate under the following circumstances:

a. Attempting to establish if a dosage is adequate during initiation

Advice: Titrate to a target dose (usually 200mg to 400mg) and maintain this dose for 7 days before sampling

b. Assessing recent adherence

Advice: Take samples at irregular intervals in order that the patient cannot pre-load with clozapine in the few days before testing

c. Attempting to manage emergent tolerability problems

Advice: Triangulate the plasma levels with mental state presentation, reported tolerability problems and their severity; consider if the issue is dose-related and where this is likely adjusting the dose by small amounts (25 to 50mg) – re-check levels at intervals of no less than 7 days

d. Managing drug-drug interactions or change in smoking status

Advice: wherever possible take a baseline level for comparison purposes: (See also section 2.13)

- consider making an adjustment (reduction) in clozapine dose where an enzyme inhibitor is added or smoking reduced/stopped, review progress weekly for 4 weeks
- where an enzyme inducer is added or smoking starts/increases, review progress weekly for 4 weeks – dose adjustment (increase) may be needed when induction is at its peak (after 2 to 3 weeks)

e. When Higher doses are being used

Advice: Where doses in excess of 450mg a day are being used, levels should be checked once a maintenance dose has been implemented and has been stable for at least five to seven days. Levels should be repeated as clinically required, or if the patient's presentation changes. Specific reviews to determine the development of signs of any side effects or toxicity while being managed on higher doses should be done at each clinic session and recorded in the notes.

Guidance issued by the MHRA in August 2020 sets out additional criteria for monitoring of clozapine levels in certain clinical situations. These include when:

- a patient stops smoking or switches to an e-cigarette (as above)
- concomitant medicines may interact to increase blood clozapine levels (as above)
- **a patient has pneumonia or other serious or systemic infection**
- **poor (reduced) clozapine metabolism is suspected**
- **toxicity is suspected**

In these instances, clozapine plasma levels must be undertaken and reviewed by the patient's responsible clinician and clinical team.

These criteria are intended to highlight when clozapine levels can be affected by other factors and are in addition to reasons 1 to 5 above.

Clozapine is metabolised primarily through the CYP1A2 liver metabolic pathway and the impact of smoking and some drug-drug interactions on this are well documented. The effect of severe infections on this is less well known and this additional caution is now included in the SPC for all clozapine brands.

Note that infection with COVID has been linked to increased clozapine levels; while the exact mechanism is unclear and is probably multifactorial; systemic infection and changes in smoking habit may all contribute to increased levels.

2.4.1 Taking Samples

For TDM of clozapine, 'trough' samples must be taken, unless the sample is taken for compliance monitoring, in which case a random sample should be considered and marked as such. For those patients who take clozapine **once a day**, sampling must be performed 12 hours after the last dose (one hour tolerance either side is deemed acceptable). For patients who take clozapine more than once a day sampling must be performed before the morning dose, which may be deferred by up to 2 hours to allow a 12-hour period to elapse since the previous night dose.

Samples should be clearly labelled with the patient's name, the date and time that the sample was taken. Samples missing the time of sampling should not be used to determine current levels; without a true trough level interpretation of levels against the patient's clinical presentation is difficult at best.

Dosing decision based on non-trough samples should be avoided.

2.4.2 Changes in Metabolism with Advancing Age

As with any drug, clozapine will be affected by changes in a person's ability to metabolise foreign substances, including medication, as they age. This is a natural consequence of the aging process and although the timing and impact of this varies person to person, it can have a significant effect on drug clearance. It is generally accepted that the risk increases with age. It has been shown that by 80 years of age the dose-adjusted levels of clozapine can be twice that of those at the age of 40 and tripled at 90 years of age.

There is no recommended age at which additional monitoring should be considered, but any changes in presentation or physical health or tolerability (as indicated in point 3 above) in those over the age of 50 should indicate more frequent reviews of clozapine plasma levels and where necessary, dosage.

2.4.3 Clozapine and Norclozapine

Norclozapine is a partially active metabolite of clozapine, the levels of which are often reported alongside clozapine levels. It has a longer half-life than clozapine and therefore its levels are subject to less fluctuation including between peaks and troughs. The norclozapine level is normally reported as being around 70% of the clozapine level, but this may vary between 40-80%.
The primary interpretation of clozapine blood levels is done using the clozapine level itself. The main use of the norclozapine level is to explore how a patient metabolizes clozapine. This is typically assessed by calculating the ratio of clozapine to norclozapine at steady state based on a 12-hour trough. This ratio is the metabolic ratio or MR.
The pathway for metabolism of clozapine into norclozapine can be saturated and the ratio increases in a clozapine level-dependant manner (i.e., when metabolism is saturated, any increase in the clozapine dose will increase the clozapine and not the norclozapine level – the ratio will therefore increase).

The important consideration is that in a patient who is established on a dose and is routinely compliant, the ratio will be consistent if there are no other factors affecting metabolism. On average, the clozapine to norclozapine (C:N) ratio, is suggested as 1.32 across all dose ranges. The C:N ratio may provide an additional clinical indicator of stability as it isn't as affected by incorrect sampling times as the clozapine plasma level. While the levels may alter between tests, a consistent C:N ratio between tests may indicate compliance.

When the ratio of clozapine to norclozapine appears to be at variance from previous test results for a patient, this may indicate (triangulate with clinical presentation):

- recent non-adherence
- changes in metabolism e.g., due to a drug interaction or change in liver function
- pre-test loading (taking clozapine at high doses in the days before a test in order to mask non-adherence)

When interpreting the ratio:

Where the clozapine level is much greater than the norclozapine level? (>3 fold i.e., ratio >3)

- It may not be a true 'trough' sample. Attempt to confirm if it is a trough sample before taking any further action.
- Clozapine N-demethylation may have become saturated. If saturation is suspected, consider cautious dose reduction, but be aware that the level may take some time to decrease.
- May suggest recent missed doses over preceding days and a subsequent attempt at compliance, possibly prior to an appointment or review.

Where the norclozapine level is greater than clozapine level? (ratio <1)

- May suggest poor adherence over 24 hours prior to assay (i.e., clozapine level decreases, but norclozapine with longer half-life remains high)

2.4.4 Interpretation of Clozapine Levels

Rough Clozapine Plasma Level (micrograms/L)	Clinical Response	Comment
<10 micrograms/L or undetectable	Any	Clozapine unlikely to have been taken for at least a week unless in the very early stages of initiation.
<350 micrograms/L	Good	Continue current dose, repeat levels annually or sooner if response deteriorates, or adverse reactions become troublesome.
	Poor or Incomplete	If poor adherence is suspected, consider education, supervised consumption, reminder cards, compliance aids or using crushed tablets. If no improvement, consider a cautious dose increase, monitoring response and tolerability. Repeat level after 1 week at new dose.
350-600 micrograms/L	Good	Continue current dose, review regularly for continuing response and tolerability. Consider repeating levels annually e.g., for patients who are older or more physically frail.
	Poor or Incomplete	If clozapine has continued for at least 3 to 6 months and still incomplete response, consider augmentation with another suitable psychotropic.

601-999 micrograms/L	Good with no features of toxicity	Consider a cautious dose reduction, weighing against response, risk, and tolerability. If the patient has a history of not responding at lower doses, consider continuing at current dose. If dose reduction is considered necessary, it should be done cautiously suggested reduction is 25mg/day for first week and further 25mg/day in week two closely monitoring for emergence of break through symptoms. Consider using a prophylactic anticonvulsant to protect against seizures if this is considered to be a significant risk (usually lamotrigine or valproate). Monitor closely for tolerability and response. Valproate is contraindicated in women of childbearing age. Evidence for significant increased risk of seizures in those with no previous history of seizures is not strong and needs to weighed against the adverse effects of anticonvulsants , patient choice and compliance.
	Poor, incomplete or features of toxicity	Consider a cautious dose reduction, weighing against response, risk and tolerability. Repeat levels once stabilized on new dose. Response can occur at blood levels up to 1000mcg/l in cases who are symptomatic over a 6 month period consider this in any decision making.
Any level >1000 micrograms/L	Good with no features of toxicity	Review promptly. Consider a cautious dose reduction to bring levels down below 1000 micrograms /L and ideally below 600 micrograms/L, weighing against risk, response, and tolerability.
	If signs of toxicity are present	If clinical signs of toxicity (severe sedation, delirium, falls, seizures) consider withholding clozapine for up to 24 hours and re-introducing at a lower dose. Consider the risk of anticholinergic rebound when reducing the dose. Consider initiating an anticonvulsant to protect against seizures. Repeat levels once the lower dose is stabilized.

Erratic adherence may result in inconsistent plasma levels making interpretation difficult or impossible. In cases of poor compliance, regular level monitoring may be useful to indicate trends – specific values should not be interpreted in isolation.

2.4.5 Documentation of results

The results from any clozapine assay must be documented within the patient notes. There is a dedicated form within Rio for this. It is on Rio in the following location:

- Access the "Reviews" folder from the main patient screen
- Select "Clozapine Review" form and complete the listed sections.
- A note should also be added to the progress notes to direct clinicians to the results in the Clozapine Review folder

2.4.6 Management of patients on high clozapine plasma levels

See Appendix 17
The generally accepted normal range for clozapine levels is 350-600mcg/L and while many patients will be well controlled within the range, there are a significant number who may need to be managed at levels above this. As a specialist Mental Health provider with several psychiatric intensive care units, and complex community patients under the care of assertive outreach teams and community mental health teams it is expected that we will be responsible for many patients, who will be more difficult to treat than those with a more routine level of complexity.
While the 600mcg/L limit is not an absolute limit, but careful consideration is needed in managing patients above this level. There is no universally agreed safe blood level and no absolute maximum level for clozapine. While the lowest effective dose should be used, each patient needs to be managed according to their presentation and risk. Clinicians managing patients with higher levels are expected to have a good understanding of the clinical evidence and the associated risks of doing so.

It is important to be clear of the difference between expected mild adverse effects and signs of toxicity. Side effects often resolve over time or are able to be managed or ameliorated by additional medication (See section 2.5); signs of toxicity always need prompt management. Signs of toxicity include (but are not limited to) ataxia, over-sedation, hypersalivation, seizures, visual changes etc.

It is also recognised that plasma levels vary widely within a short period of time due to short term infections, changes of medication for other health conditions and life style changes (such as intake of caffeine) . Any decision making needs to consider this.

Plasma level assays should only be requested in line with guidance in section 2.4. However, it is often the case that high levels are also found when plasma level assays are done in error, either along with or instead of the normal full blood count for routine monitoring. When a level above the laboratory normal range of 600mcg/L there following actions should be carried out and the details and outcomes clearly documented in the patient notes:

1. Confirmation of sampling time – is this a true trough value? If not, then consider a repeated sample taken 12hrs (+/- 1hr) after the last clozapine dose. If it is likely to be a true trough value, then depending on the level, the patient should be seen as a priority
   Levels above 1000mcg/L, <u>which are confirmed as trough levels,</u> require a timely review and it is recommended this should be within **seven days**, unless there are any signs of toxicity noted, in which case a more rapid clinical review should be

arranged. If toxicity is noted at the time of sampling, the patient should be reviewed within 24hrs and the review should not be delayed while waiting for the assay result.

2. **All** patients with features of toxicity need to be reviewed face to face as a priority and action taken.
3. Face to face review with the patient – The patient should be assessed to determine if there are any clinical signs of toxicity or side effects. They should be informed of the result and the potential clinical risk this may pose. They should be asked specifically about the signs of toxicity and their response noted. Where there are any side effects (as opposed to toxicity) these must also be noted, along with the impact on the patient and how they are managing them. Details of any medication prescribed for this should also be noted. An ECG should be considered; any decision not to do one and the reasons, should be documented.
4. Where trough levels are reported between 600mcg/L and 1000mcg/L, and after reviewing the patient **IS** showing signs of toxicity or intolerable side effects, then a dose reduction should be strongly considered. This should be managed according to the severity of the symptoms, but abrupt withdrawal must be avoided due to the risk of cholinergic rebound.
5. Where a trough level is between 600mcg and 1000mcg/L and there are no signs of toxicity, then while a dose reduction may be considered, maintaining the patient at the same dose may be warranted. Repeat levels should be considered at the next clinic appointment, or as clinically indicated. Where a decision is made around the risk of maintaining the dose and the risk of relapse if reduced, this must be documented. Ongoing review of the clinical presentation and the presence/absence of side effects and toxicity should be documented at each face-to-face meeting. Patients must be advised to urgently report any new side effects or changes.
6. There will be a small number of patients who may need to be maintained between 1000-1200mcg/L and may relapse when doses are lowered. These will need regular review and a clear plan for managing them in the notes.
7. When managing patients with plasma levels above 600mcg/L it is extremely important to pay close attention to the metabolic ratio (MR) between clozapine and norclozapine levels (see Section 2.4.3).
8. Historic evidence of a “late response” of up to six months after starting clozapine has not been shown in later studies, so patients who are not responding but have no adverse effects **should not** be left at the same plasma level for months on end – i.e. either stop clozapine or trial a further increase – review after changes should allow 23 weeks for a full clinical response.
   The clozapine/norclozapine ratio can be a helpful guide to indicate recent noncompliance or saturated metabolism however if the plasma levels themselves are within the recommended range and the patient is responding well with minimal side effects it should not be used as an indicator for dose adjustment.

Where levels are reported above 1000mcg/L, an urgent review outside of the normal planned reviews is **NOT** needed if:

- There were no features of toxicity when the sample was taken **AND** this is documented in the notes from the appointment
- the result is expected i.e., a known compliance test done outside of the trough period or a patient whose level is above 1000 mcg/l and this has been maintained at this level, or is having dosing adjusted as part of a considered clinical decision.

2.5 Management of clozapine related side effects.

A questionnaire has been developed with a series of six questions to help identify problems as early as possible and manage them more effectively. The questions should be asked of every patient when seen by a health care professional (see appendix 18). It is expected that this is completed no less than once for each blood test required. This can be either asked at the clinic appointment or given as a paper slip for patients to fill in while waiting for their appointment. This will be added to RiO and can either be entered directly or updated following the receipt of forms filled in by the patient before their appointment.

Treatment with clozapine is associated with several significant side effects.

2.5.1 Sedation

Clozapine is reported as causing more sedation than other atypical antipsychotics and nearly half of patients report sedation of one kind or another. Clozapine-related sedation is thought to be a result of blockade of H_1 histamine receptors. Sedation is also a risk factor for urinary incontinence (see later).

Tolerance to sedation usually develops in the first 2 to 3 months of treatment in the majority of cases; in a minority of cases sedation can be persistent and severe. Clozapine has been shown to improve sleep and increase total sleep time without having negative effects on sleep architecture, unlike some other sedative medicines.

MANAGEMENT

- Assess regularly for sedative side effects
- Where sedation occurs early in treatment, offer reassurance that tolerance usually develops over the first 2 to 3 months of treatment
- Give advice on driving (if applicable) and other accident prevention
- Review and attempt to discontinue the use of other sedative medicines e.g., benzodiazepines, hypnotics, augmenting agents
- Review the dose of clozapine:
    - ensure that it is not supra-therapeutic
    - give a higher proportion of the total dose at night
    - split the night-time dose where deep sedation at night is problematic
    - give the night-time dose earlier if hangover present (morning sedation) Some small studies and case reports have examined the use of stimulants with clozapine to improve wakefulness e.g., modafinil, methylphenidate. **This approach should not be considered due to the lack of good evidence to support it and risks of worsening of psychosis, agitation and tachycardia.**

2.5.2 Hypersalivation

Clozapine is reported as causing hypersalivation in approximately one in three patients, with some studies quoting the incidence as high as 80%. The mechanism by which clozapine causes this adverse effect is unclear. In some cases, hypersalivation is transient but others experience persistent symptoms.
Hypersalivation is often embarrassing for patients and can contribute to social isolation and stigmatisation. Hypersalivation is rarely associated with life-threatening aspiration pneumonia, making the need for prompt management essential.

Hypersalivation can be treated with pharmacological options such as hyoscine hydrobromide (off label use) or pirenzepine (unlicensed product). Where these approaches are unsuccessful, a range of other treatment options exist with varying levels of evidence to support their use. Pharmacological treatment should be reviewed and withdrawn periodically to assess the need for continued use.
Prescribers must also be aware of the risk of severe constipation with antimuscarinic effects of medication used to treat hypersalivation. This can significantly increase the risk already present from clozapine induced constipation.

MANAGEMENT

- Assess regularly for the presence of hypersalivation
- Where present, establish if a dose reduction is feasible or if clozapine levels may have increased for any reason and adjust accordingly
- Where hypersalivation causes embarrassment in social situations, consider chewing sugar-free sweets or gum which encourages swallowing and is considered socially acceptable
- Where nocturnal hypersalivation is most problematic, advise the patient to sleep on more than one pillow (to reduce sensation of choking and waking as a result) and cover pillows with a towel or plastic pillow covers
- Offer pharmacological treatment with **hyoscine hydrobromide** (see below)
- Where hyoscine hydrobromide is not effective or not tolerated, offer pharmacological treatment with **pirenzepine** – (see table below)
- Where hyoscine hydrobromide and pirenzepine are not effective or not tolerated, consider augmenting with or use of an alternate pharmacological treatment (*contact pharmacy for further advice*)
- Periodically re-assess the need for pharmacological treatment of hypersalivation by attempting the withdrawal of this, particularly when the patient is no longer symptomatic

Option	Dosing	Monitoring	Comments
Hyoscine hydrobromide	Start tablets at 300 micrograms at night –	For anticholinergic adverse effects e.g., **constipation**,	Advise patient to suck or chew the tablets

	these should be sucked or chewed Increase weekly up to a maximum of 900 micrograms a day if necessary (in divided doses). Another consideration could be the use of patches- 1.5mg every 72 hours	dizziness, blurred vision, or urinary problems.	Off-label Use Patch should be placed behind the ear. If patch causes excessive drying, the location can be moved to the arm or shoulder
Pirenzepine	Start at 50mg at night. Increase weekly up to a maximum of 150mg a day (in divided doses) if necessary.	For peripheral anticholinergic effects e.g., blurred vision, **constipation,** or urinary problems.	Unlicensed in the UK

2.5.3 Constipation

(See appendix 16 for Clozapine Constipation Clinic Poster)
Constipation is reported by up to 60% of those taking clozapine. Constipation may be under-reported by patients due to cognitive impairments, altered pain sensation and the embarrassing nature of the subject. The importance of clozapine-induced constipation can be underestimated by clinicians yet there have been a number of reports of deaths from problems associated with constipation e.g., bowel obstruction. Estimates suggest clozapine is associated with severe and life-threatening complications in around 0.3% of patients. The onset of such complications can be rapid, and symptoms may include constipation, abdominal pain or cramps, fever, nausea, diarrhoea (overflow), distended abdomen, pneumonia, or drowsiness.

Before clozapine is started, the following risk factors should be considered and where identified, addressed with the patient, with support from dietetics where necessary:

- Poor quality or low-fibre diet
- Dehydration (drink 6 to 8 medium glasses of fluid a day)
- Lack of exercise (do at least 150 minutes of physical activity per week)
- Obesity
- Known issues with constipation
- Prescribed other medications with a risk of constipation

Laxatives can help with constipation although the evidence base to support their use or relative efficacy in clozapine-induced constipation is weak. Choice of laxatives usually depends on the symptoms present, treatment urgency and tolerability:

Option	Mechanism	Prefer when…	Ensure…	Comments
Osmotic laxatives e.g., Lactulose, Macrogol 3350	Ensures more liquid is present in large bowel	Routine use Use enema forms or high dose when impacted	Adequate fluid intake	Use regularly. May take 48 hours to take effect.

Bulk forming laxatives e.g., Ispaghula husk	Increase faecal mass and stimulate peristalsis	Small, hard stools **NOT** when impaction present	Adequate fluid intake	Do not take after 6pm
Stimulant laxatives e.g., Senna	Stimulate peristalsis	When rapid action (usually within 12 hrs) is required. **NOT** when impaction present		Can be useful where other laxatives are ineffective
Stool softeners e.g., Docusate, arachis oil enema	Softening of stool and local lubrication	When rapid action (usually within 12 hrs) is required		Often used in combination with other laxatives

MANAGEMENT

- Ask about bowel habits and constipation regularly, ideally at every contact
- Promote good diet (inclusion of soluble/insoluble fibre, inclusion of fruit/vegetables), fluid intake and regular exercise at every opportunity, further information available at: https://www.bda.uk.com/resource/fibre.html
- Consider risk factors for constipation (above) and address any identified risks
- Where constipation is present, review and consider stopping any concomitant medicines that can cause or worsen constipation
- Where constipation is present, review and consider the dose and plasma level of clozapine (may be a sign of over-treatment or recent onset increase in levels)
- Where constipation is present, start an appropriate laxative (see table above) and follow-up regularly
- Ensure that laxative use is governed and the effects on fluid balance and electrolytes are considered and monitored accordingly
- Seek advice or support from dietetic services
- When patients on clozapine experience diarrhoea or loose stools, consider if the presentation might be severe constipation with overflow diarrhoea **before** considering a reduction or pause in laxative medication
- Where constipation does not respond to laxatives or in cases of sudden onset or deteriorating health, seek urgent advice from a specialist

2.5.4 Urinary Problems

Clozapine appears to cause or worsen underlying urinary incontinence in up to 40% of patients, compounding social isolation and leading to non-adherence. Risk factors for the general population for developing urinary incontinence include:

- Being of female sex
- Older age
- Being overweight or obese
- Previous obstetric events
- Frequent urinary infections
- History of stroke or prostatectomy

Accurate diagnosis of clozapine-induced urinary incontinence is challenging as many patients are reluctant to discuss such a personal issue. The mechanism by which this happens is unclear and probably multifactorial. It is important to establish if deep sedation is a contributing factor (e.g., waking up wet) or bladder dysfunction/poor mobility (e.g., waking up and not getting to the toilet in time) in order to decide on the best way to proceed.

MANAGEMENT

- Encourage the patient and any carers to report symptoms
- Enquire about bladder function regularly
- Where incontinence is present, assess for patterns of severity and impact
- Where incontinence is present, identify and treat any relevant co-morbidities e.g., urinary infection, poor mobility
- Consider the dose of clozapine and plasma level; dose reduction or manipulation may help to avoid over-sedation e.g., for nocturnal problems
- Use non-drug approaches such as urinating before going to bed, advice about full evacuation of bladder, avoiding taking in fluids late in the evening or incontinence products
- Where non-drug approaches are ineffective, or incontinence is significant and causes distress, refer to a specialist for review and treatment

2.5.5 Weight Gain

Studies suggest that all antipsychotics cause weight gain to some extent, with clozapine causing significantly more weight gain than other antipsychotic options. The most rapid weight gain usually takes place over the first three to four months but may continue indefinitely in some. Recent evidence suggests that one in five patients will experience an increase in body weight of 10% or more. Rapid, initial weight gain and low initial body weight are predictors for a larger degree of weight gain. Pro-actively offering advice about healthy diet and lifestyle is essential in all cases. The trust does not currently have any specific guidance around weight management, but Choice and Medication has an advice sheet on this, and additional resources are available from the British Dietetic Association at: https://www.bda.uk.com/

Three main theories exist to explain weight gain caused by clozapine[2]:

- Pharmacological theories (H_1 & 5-HT_{2C} antagonism)
- Hormonal changes (increased leptin levels)
- Genetic influences (multiple)

The treatment of clozapine-induced weight gain with a number of drug and non-drug approaches has been investigated. The studies supporting most approaches are small, have limitations and therefore the results may only be tentatively generalised. However, there are well evidenced interventions published in the NICE guidance for Weight Management, available at: https://www.nice.org.uk/guidance/PH53
The following recommendations reflect the current understanding of how weight gain should be managed:

- Treatment begins with counselling the individual on healthy diet and lifestyle before clozapine treatment begins and regularly during treatment

- Monitor weight and BMI regularly, refer to dietetics and/or weight management clinic where available
- Restrict calorie intake to nationally recommended levels and increase physical activity
- Involve a dietitian, physiotherapist, or health instructor where available
- Consider if psychological treatment is indicated for aberrant patterns of eating
- Refer to Trust Obesity guidelines where appropriate

Option*	Evidence	Dosing	Comments
Metformin	Substantial evidence database in (nondiabetic patients) supporting the use. Some negative studies, but clear and significant effect in meta-analyses	1.5g to 2g/day	Take with food to avoid GI side effects Off-label use

*Please note that this table is not complete, and illustrates only the most compelling options as recommended at the time of guideline development – the evidence for pharmacological options is not robust and requires significant further research

2.5.6 Seizures

Clozapine is associated with a higher risk of inducing seizures than other antipsychotic options; it is estimated that around 3% of people on clozapine will experience a seizure. EEG changes are common but are not predictive of developing seizures. The risk of seizures is thought to be related to the dose and more specifically, plasma levels of clozapine so, dose alone is not a sufficient indicator of risk. The utility of clozapine serum concentration for the purpose of seizure prevention is also debated within the literature, mainly because of the lack of a well-established concentration threshold. It would be a safe assumption that seizure is more likely at higher concentrations (i.e., > 1mg/mL), but similar to total oral dose, seizures still occur at lower concentrations (i.e., < 300 ng/mL or < 900 nmol/L). Seizures relating to clozapine have been reported with doses as low as 200mg/day,

Seizure prophylaxis should be considered for those patients who require high plasma levels of clozapine (≥1000microgram/L) or if on a high dose (≥ 500mg/day), particularly if there are other risk factors present. Factors have been identified which increase the risk of clozapineinduced seizures, such as:

- History of seizures
- History of head trauma/injury
- Alcohol or substance misuse
- Physical illness e.g., hypoglycaemia, hyponatraemia
- Concomitant medication that increases risk of seizures
- Increased plasma levels of clozapine e.g., due to drug interactions or smoking cessation

The evidence base for this subject is poor; the following pharmacological options are recommended by tertiary references for seizure prophylaxis in relevant patients.

Option*	Dosing	Comments	Considerations
Valproate	Use of doses from 500mg a day to 1500mg a day reported, dose usually limited by tolerability	Considered as drug of choice (quick, broad spectrum)	Avoid in women of child-bearing potential Counsel about liver disorders and pancreatitis.
		Mood stabiliser properties - may augment treatment	Rare reports of thrombocytopenia or pancytopenia - consider potential impact on blood results
Lamotrigine	25mg at night, increased by 25mg every 2 weeks to target dose of 200mg a day	Useful augmenter in partial response	Risk of rash – titrate slowly and counsel patient to stop and seek medical advice if rash develops

*Please note that this table is not complete, and illustrates only the most compelling options as recommended at the time of guideline development – the evidence for pharmacological options is far from robust and is recognised as an area for future study

Management of Clozapine-induced Seizures

If a patient experiences a seizure whilst taking clozapine, the following steps should be taken.

- Withhold clozapine for 24 hours
- Exclude common causes e.g., recent increase in levels due to drug interaction or smoking cessation or a significant change in caffeine intake.
- Re-introduce clozapine at a lower dose (usually 50% of previous dose)
- Request an EEG and referral to a neurologist if first seizure
- Monitor response and where it is clear that the full dose of clozapine needs to be reestablished, or where seizures recur, add an anticonvulsant as prophylaxis (see above)

Seizures are serious and usually warrant admission or transfer to an acute hospital for assessment and management therefore this will usually require liaison with the treating team at the hospital caring for the patient.

2.5.7 Cardiovascular Problems

Cardiovascular disease (CVD) is the leading cause of death globally. Treatment with clozapine is associated with a number of cardiac problems that range in severity from benign to fatal:

DYSLIPIDAEMIA

Dyslipidaemia is a major modifiable risk factor for developing CVD, with risks increasing with total cholesterol levels. People with schizophrenia are almost twice as likely to die of CVD compared to the general population. There is evidence to suggest that people on antipsychotic treatment are unlikely to receive treatment for dyslipidaemia. Dyslipidaemia,

when identified in patients taking clozapine should be managed in the same way as for the general population.

TACHYCARDIA

Tachycardia is very common in the initiation period (first four weeks) of treatment with clozapine, but sometimes persists. Benign sinus tachycardia can be treated with atenolol or bisoprolol, starting doses as given in the BNF such as 25mg and 1.25mg daily respectively and titrated according to response and tolerability. It is important to exclude myocarditis (see below) and **extreme caution** is advised when tachycardia is present in the context of chest pain or heart failure.

MYOCARDITIS and CARDIOMYOPATHY

- **Myocarditis** is a rare, yet potentially fatal adverse effect of clozapine treatment. It most commonly occurs in the initiation period (first 6 to 8 weeks) of treatment with clozapine. Signs and symptoms of myocarditis are tachycardia, fever, flu-like symptoms, fatigue, dyspnoea, and chest pain. The suspicion of myocarditis should provoke immediate cessation of clozapine and referral for a specialist opinion. Renewed monitoring should be initiated as per section 2.
- **Cardiomyopathy** is a rare adverse effect of clozapine treatment which can occur at any stage, although most commonly in the first year of treatment. Cardiomyopathy should be suspected in any patient showing signs of heart failure, such as shortness of breath, tiredness, and ankle oedema. The suspicion of cardiomyopathy should provoke immediate cessation of clozapine and referral for a specialist opinion.

THROMBOEMBOLISM

Venous thromboembolism (VTE) is a rare but potentially fatal adverse reaction associated with antipsychotic treatment. The mechanism by which this happens is unknown. The risk factors for VTE in people with psychiatric illnesses appear to be the same as for the general population. Anyone with signs and symptoms of VTE should be referred for immediate medical attention:

Deep Vein Thrombosis	Pulmonary Embolism
Increased temperature Pitting oedema Swelling, tenderness, unilateral leg pain Prominent superficial veins	Shortness of breath, haemoptysis Chest pain, focal signs in the chest Tachycardia, hypotension Tachypnoea, hypoxia

2.5.8 Reporting Side Effects

Upon review of a patient's health and blood result any abnormalities in the blood parameters (excluding those mentioned above) or significant changes in physical or mental symptoms considered to be clinically significant, should be reported as adverse events. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard.

Adverse events must also be reported to the clozapine monitoring service (DMS).

2.6 Development and Consultation process:

Developed by
XXXX Deputy Chief Pharmacist and Clozapine Pharmacist (Non-Secure) XXXX - Deputy Chief Pharmacist and Clozapine Pharmacist (Secure Services)

Reviewed by
XXXX
XXXX
XXXX
XXXX

This guideline will be reviewed in response to any significant change in national or local guidance, practice, or service provision pertinent to the subject matter and according to the organisational process of policy/guideline review. Local practice will be audited against the content of this guideline according to the PTC workplan.

Consultation summary		
Date guideline issued for consultation	October 2022	
Number of versions produced for consultation		
Committees / meetings where guideline formally discussed	**Date(s)**	
Where received	**Summary of feedback**	**Actions / Response**

3. Bibliography:

- Meyer, J., & Stahl, S. (2019). The Clozapine Handbook: Stahl's Handbooks (Stahl's Essential Psychopharmacology Handbooks). Cambridge: Cambridge University Press. doi:10.1017/9781108553575
- Bleakley S & Taylor, D. (2013) Clozapine Handbook (1st edition) Lloyd-Reinhold Communications
- Taylor, D. M., Barnes, T. R. E., & Young, A. H. (2021). The Maudsley prescribing guidelines in psychiatry (14th ed.). John Wiley & Sons
- Bazire, S (2020). The Psychotropic Drug Directory 2020/21. Lloyd-Reinhold Publications Limited
- British National Formulary (online) – Available at: https://bnf.nice.org.uk/ (details correct as of January 2023)

- Denzapine Summary of Product Characteristics (multiple strengths) – available at: https://www.medicines.org.uk/emc/ (details correct as of January 2023)
- Psychosis and schizophrenia in adults. Quality Standard QS80 (2015) – NICE, available at: https://www.nice.org.uk/guidance/qs80 (details correct as of January 2023)

Appendix 1 - Equality Analysis Screening Form

A word version of this document can be found on the HR support pages on Connect
http://connect/corporate/humanresources/managementsupport/Pages/default.aspx

Title of Proposal	**Use of Clozapine Guidelines Oct 2022**		
Person Completing this proposal	XXXX	**Role or title**	Deputy Chief Pharmacist
Division	Corporate	**Service Area**	Pharmacy
Date Started	4/10/22	**Date completed**	4/10/22
Main purpose and aims of the proposal and how it fits in with the wider strategic aims and objectives of the organisation.			
Clinical guidance			
Who will benefit from the proposal?			
Service users treated with clozapine			
Do the proposals affect service users, employees or the wider community? ***Add any data you have on the groups affected split by Protected characteristic in the boxes below. Highlight how you have used the data to reduce any noted inequalities going forward***			
No inequalities relating to guidance. Contains specific treatment options and monitoring for some ethnic groups			
Do the proposals significantly affect service delivery, business processes or policy? *How will these reduce inequality?*			
No			

Does it involve a significant commitment of resources? *How will these reduce inequality?*

No additional resources required – all patients receive same care through the guidance				
Do the proposals relate to an area where there are known inequalities? (e.g. seclusion, accessibility, recruitment & progression)				
Benign ethnic neutropenia is a possible condition in some Afro Caribbean and Asian communities and the policy recommends treatment where this is identified				
Impacts on different Personal Protected Characteristics – *Helpful Questions:*				
Does this proposal promote equality of opportunity? Y *Eliminate discrimination? N/A* *Eliminate harassment? N/A* *Eliminate victimisation? N/A*			*Promote good community relations? N/A* *Promote positive attitudes towards disabled people? N/A* *Consider more favourable treatment of disabled people? N/A* *Promote involvement and consultation? Y* *Protect and promote human rights? N/A*	
Please click in the relevant impact box and include relevant data				
Personal Protected Characteristic	**No/Minimum Impact**	**Negative Impact**	**Positive Impact**	**Please list details or evidence of why there might be a positive, negative or no impact on protected characteristics.**
Age	X			
Including children and people over 65 Is it easy for someone of any age to find out about your service or access your proposal? Are you able to justify the legal or lawful reasons when your service excludes certain age groups				
Disability	X			

Including those with physical or sensory impairments, those with learning disabilities and those with mental health issues Do you currently monitor who has a disability so that you know how well your service is being used by people with a disability? Are you making reasonable adjustment to meet the needs of the staff, service users, carers and families?				
Gender	X			
This can include male and female or someone who has completed the gender reassignment process from one sex to another Do you have flexible working arrangements for either sex?				

Is it easier for either men or women to access your proposal?				
Marriage or Civil Partnerships	X			
People who are in a Civil Partnerships must be treated equally to married couples on a wide range of legal matters Are the documents and information provided for your service reflecting the appropriate terminology for marriage and civil partnerships?				
Pregnancy or Maternity	X			
This includes women having a baby and women just after they have had a baby Does your service accommodate the needs of expectant and post-natal mothers both as staff and service users? Can your service treat staff and patients with dignity and respect relation into pregnancy and maternity?				
Race or Ethnicity	X			
Including Gypsy or Roma people, Irish people, those of mixed heritage, asylum seekers and refugees What training does staff have to respond to the cultural needs of different ethnic groups? What arrangements are in place to communicate with people who do not have English as a first language?				
Religion or Belief	X			

Including humanists and non-believers Is there easy access to a prayer or quiet room to your service delivery area? When organising events – Do you take necessary steps to make sure that spiritual requirements are met?				
Sexual Orientation	X			
Including gay men, lesbians and bisexual people Does your service use visual images that could be people from any background or are the images mainly heterosexual couples? Does staff in your workplace feel comfortable about being 'out' or would office culture make them feel this might not be a good idea?				
Transgender or Gender Reassignment	X			

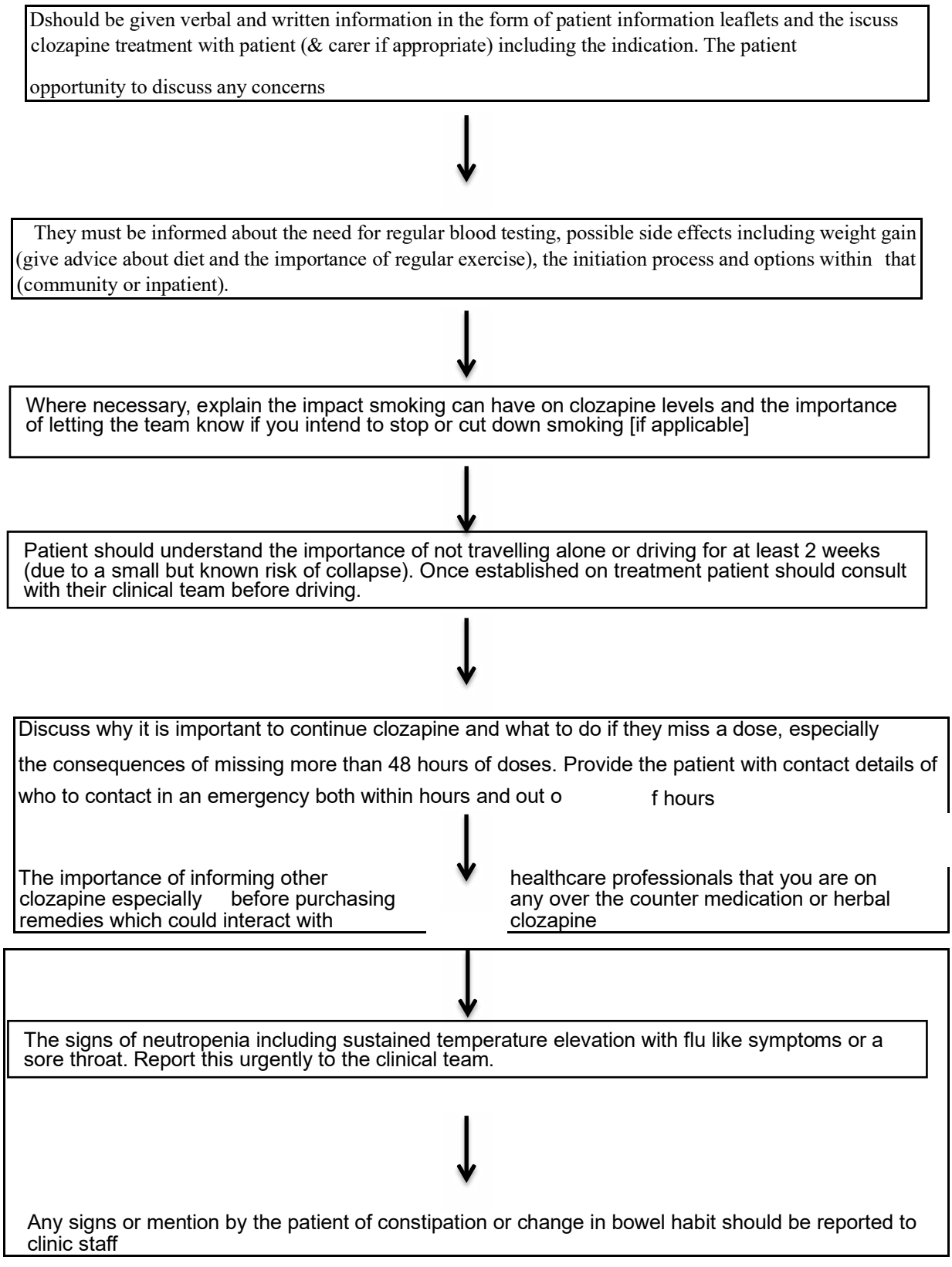
This will include people who are in the process of or in a care pathway changing from one gender to another Have you considered the possible needs of transgender staff and service users in the development of your proposal or service?				
Human Rights	X			
Affecting someone's right to Life, Dignity and Respect? Caring for other people or protecting them from danger? The detention of an individual inadvertently or placing someone in a humiliating situation or position?				
If a negative or disproportionate impact has been identified in any of the key areas would this difference be illegal / unlawful? I.e. Would it be discriminatory under anti-discrimination legislation. (The Equality Act 2010, Human Rights Act 1998)				

	~~**Yes**~~	**No**		
What do you consider the level of negative impact to be?	**High Impact**	**Medium Impact**	**Low Impact**	**No Impact**
				X

If the impact could be discriminatory in law, please contact the **Equality and Diversity Lead** immediately to determine the next course of action. If the negative impact is high a Full Equality Analysis will be required. If you are unsure how to answer the above questions, or if you have assessed the impact as medium, please seek further guidance from the **Equality and Diversity Lead** before proceeding. If the proposal does not have a negative impact or the impact is considered low, reasonable or justifiable, then please complete the rest of the form below with any required redial actions, and forward to the **Equality and Diversity Lead.**
Action Planning:
How could you minimise or remove any negative impact identified even if this is of low significance?
Dependant on circumstance – no anticipated
How will any impact or planned actions be monitored and reviewed?
Dependant on circumstances
How will you promote equal opportunity and advance equality by sharing good practice to have a positive impact other people as a result of their personal protected characteristic.
Does not apply to clinical intervention, patients treated the same under guidelines
Please save and keep one copy and then send a copy with a copy of the proposal to the Senior Equality and Diversity Lead at bsmhft.edi.queries@nhs.net. The results will then be published on the Trust's website. Please ensure that any resulting actions are incorporated into Divisional or Service planning and monitored on a regular basis

Appendix 2 – Pre-initiation checklist: Patient Discussion

Quick Reference Flowchart [What patients should know]



Appendix 3 - Clozapine Pre-initiation Checklist

INTENDED START DATE: ……

Tasks to be completed prior to initiation	Date completed	Completed by: (Signature)
Thorough medical history and physical examination,		
Record smoking status and number of cigarettes smoked daily		
Clozapine treatment discussed with patient along with written and verbal information		
Patient registered with the clozapine monitoring system		
Obtain consent & document on form T2 or organise SOAD for T3 or S62 if required		
Perform ECG		
Organise pre-initiation FBC. Note this sample is only valid for 10 days (See notes 1, 2 and 3 below)		
Organise other baseline blood tests (Lipids & glucose, LFTs, U&Es, HBA1C)		
Organise initiation physical observations (See note 4)		
Prescribe titration order set on EPMA and ask ward staff to order clozapine from pharmacy		

1. The week before clozapine is started is counted as the first week of clozapine treatment. Which team organises the initial pre-treatment blood test must be negotiated locally to fit in with carer and patient needs. **The in-patient facility or home treatment team overseeing the initiation process should organise the prescription and ensure that everything that needs to have been done prior to the actual treatment starting has been done**. A clinic referral form will be needed.

2. Normally clozapine blood samples should be taken on a Monday or Tuesday. When pre-initiation bloods are taken on Wednesdays or later it may not be easy for pharmacy to dispatch the clozapine for receipt by the treating unit on Friday.

3. **ENSURE** that the pre-treatment blood sample is sent to the local lab (inpatients) or processed via a Yumizen machine or sent to the local lab (Community).

4. **Pharmacy will endeavour to dispatch clozapine to teams the day before the planned start, providing the above tasks are completed. In the rare instance clozapine must be started at a weekend, the pre-initiation tasks must be completed by the preceding Thursday.**

The checklist explained

This checklist gives structure to “things to do” before starting clozapine.
The schedule assumes that the use of clozapine will be considered and offered to patients long before an actual start.

Purpose:

- Ensuring that key tasks are completed in timely manner and not left to the last minute
- Ensuring that everyone involved with initiating clozapine is aware of each other’s role
- Minimising inconvenience to patients

By structuring the pre-start period in a transparent manner, this schedule will avoid last minute complications that can result in delayed treatment starts.

Although the entire process can be affected during the week immediately prior to starting this usually results in a last-minute scramble to get everything in place.

This schedule treats all clozapine using units as the same. (see **Untoward incidents** below). Adopting one scheme will be easier for everyone to follow than when there is more than one scheme in use.

Untoward incidents

Clozapine has many side effects. The risk of serious and profound cardiovascular incidents is reduced by a slow titration.

Planned admission for In-patient clozapine Initiation

If it is necessary for patients to be admitted for clozapine initiation the referring community team must register the patient and manage the pre-start schedule so that clozapine is available on the ward ready for use on the planned start date.

Unplanned admission for In-patient clozapine Initiation

If a decision to initiate clozapine is only made after an unplanned admission following a relapse or other acute episode, this schedule can be shortened.
Liaise with the community team that will assume post-ward care and establish provisional arrangements for taking bloods.

[RIO form needed]

Appendix 4 – Guidance on the recording of Physical Observations

The following section applies only to inpatient wards with access to the inpatient portal application.

For home treatment teams, a paper version (Appendix 5) will be available to document the physical observations. Both inpatient & home treatment teams should use progress notes to document any abnormal readings and the actions taken.

Inpatients Monitoring using the Observations App

- Physical observation monitoring via the Observations app needs to be set up via the service user's Rio profile under – Inpatient Management – Physical Observation. This form allows you to select the plan for the service user, there is a drop-down list and clozapine schedule can be selected. This plan entered into Rio will pull through to the inpatient portal and as long as the correct start date and time is entered into the initial plan the above physical monitoring schedule will be shown for that service user
- If for any reason the time of the first dose is delayed from that entered into the Rio physical observation form, there is a section under the "Plan" tab in the inpatient portal which allows you to enter the time the first daily dose was actually administered. The physical observation schedule will then be adjusted accordingly • An overall NEWs2 score will be generated for the service user's vital signs along with some guidance on the actions that should be taken as if the scores reach a certain threshold a senior nurse/clinician and or a doctor must be contacted to assess the patient. Actions taken should be clearly documented on Rio.
- Below shows the schedule and the specific time frames given to record the observations on the application; the reference to 10min threshold accounts for 10mins either side of the observation
- For a more detailed guide on how to use the Inpatient Physical Observation Application the I.T. guide can be found on this link:

http://connect/What's%20new%20in%20our%20Trust/paperless/Pages/Digital-Wards.aspx

Appendix 5 – Inpatient & Outpatient physical monitoring

Parameters	**Day 1** Pre-dose	**Day 1** 1 hr post- dose	**Day 1** 2 hrs post- dose	**Day 1** 6 hrs post-dose
Date				
BP				
Temp				
Pulse				

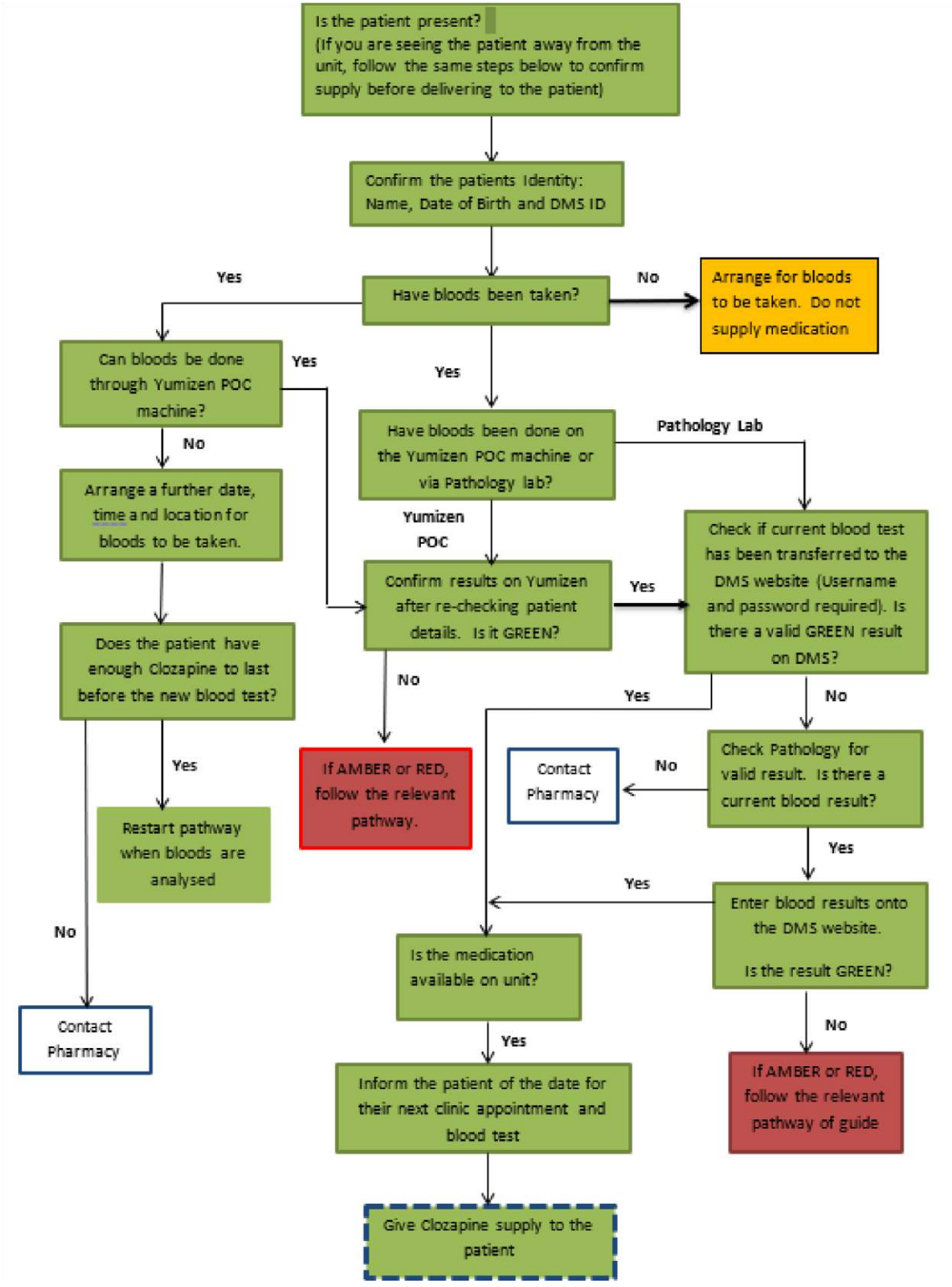
Parameters	**Day 2** Pre-dose	**Day 2** 2 hrs post- dose	**Day 2** 6 hrs post- dose	**Day 3** Pre-dose	**Day 3** 6 hrs post-dose	**Day 4** Pre-dose	**Day 4** 6 hrs post- dose	**Day 5** Pre-dose	**Day 5** 6 hrs post- dose
Date									
BP									
Temp									

Pulse									

Parameters	**Day 6** Pre-dose	**Day 6** 6 hrs post- dose	**Day 7** Pre-dose	**Day 7** 6 hrs post- dose	**Day 8** Pre-dose	**Day 8** 6 hrs post- dose	**Day 9** Pre-dose	**Day 9** 6 hrs post- dose
Date								
BP								
Temp								
Pulse								
Parameters	Day 10 Pre-dose	Day 10 6 hrs post- dose	Day 11 Pre-dose	Day 11 6 hrs post- dose	Day 12 Pre-dose	Day 12 6 hrs post- dose	Day 13 Pre-dose	Day 13 6 hrs post- dose
Date								
BP								
Temp								
Pulse								

Parameters	**Day 14** Pre-dose	**Day 14** 6 hrs post dose	**Day 15** Pre-dose	**Day 15** 6 hrs post dose	**Switch to Weekly monitoring with blood tests**
Date					
BP					
Temp					
Pulse					

Appendix 6 – Supply of clozapine from a clinic to patients with a GREEN result

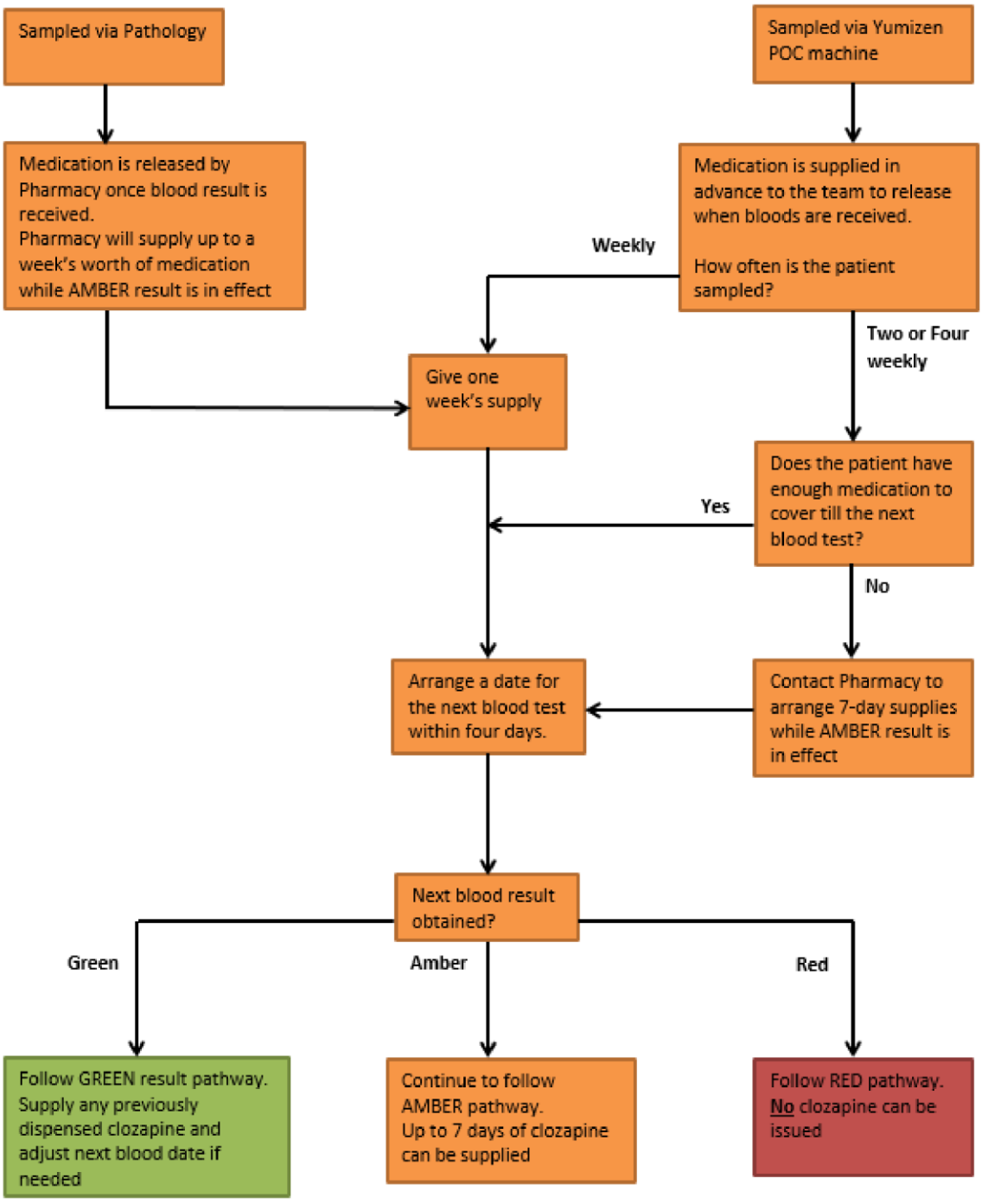


Appendix –

Appendix 7 Supply of clozapine from clinics to patients with an AMBER result

The process for managing this will depend whether the patient is sampled via the Yumizen POC machine or through Pathology services – see below.

While an AMBER result is in effect**, TWICE WEEKLY** blood tests are required until a green result is obtained and **MAXIMUM of seven days** medication may be given to patient.

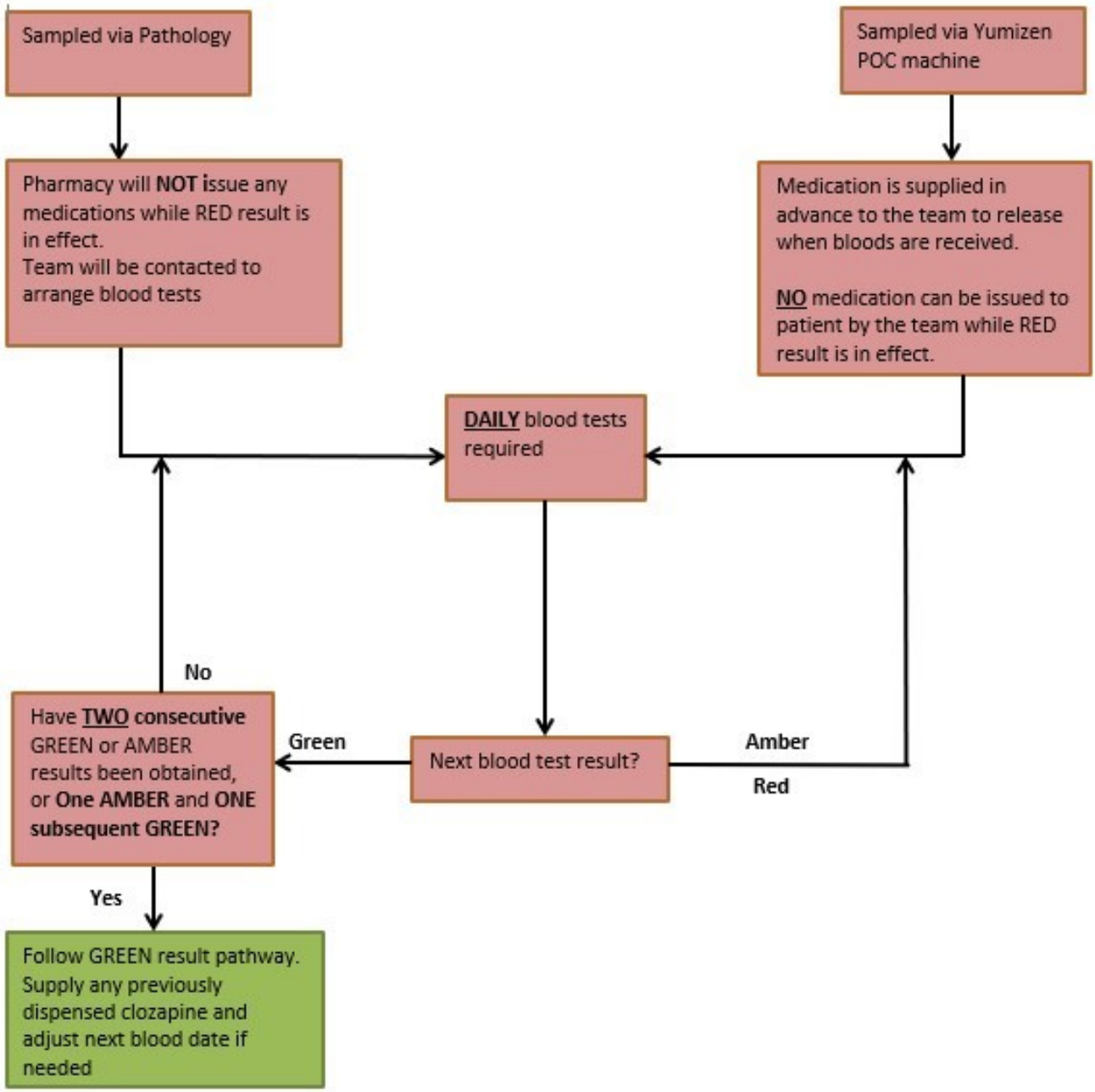


8 Supply of clozapine from clinics to patients with an RED result

The process for managing this will depend on whether the patient is sampled via the Yumizen POC machine or through Pathology services – see below.

While an RED result is in effect**, DAILY** blood tests are required until a green result is obtained, and **no clozapine** may be supplied to the patient. In all cases the team must ensure patient knows not to taken any until authorised to do so. If necessary, supplies should be removed and held by the team.

Appendix –


Sampled via Pathology
Sampled via Yumizen POC machine
Pharmacy will NOT issue any medications while RED result is in effect.
Team will be contacted to arrange blood tests
Medication is supplied in advance to the team to release when bloods are received.
NO medication can be issued to patient by the team while RED result is in effect.
DAILY blood tests required
No
Have TWO consecutive GREEN or AMBER results been obtained, or One AMBER and ONE subsequent GREEN?
Green
Next blood test result?
Amber
Red
Yes
Follow GREEN result pathway. Supply any previously dispensed clozapine and adjust next blood date if needed

Appendix – 9 Template GP Letter

Dear Dr _____ [Add team address]
Re: patient's name
Address DOB.

The above patient is prescribed clozapine at ____ mg/day and is under the care of Dr _____ (Consultant psychiatrist) based at _____.
Clozapine prescribing responsibility and supply are retained by secondary care mental health services, but we would recommend you add an alert to the patient's primary care file as clozapine can have profound effects on physical health.

A full white blood cell count is currently taken every____week(s)

A full physical health check is carried out every ____month(s).

Clozapine can present risks to physical health and requires close monitoring. Side effects include constipation, blood disorders, tachycardia, sedation, hypersalivation, hypotension, cholesterol changes, diabetes, and weight gain. We would be grateful if you would share any concerns you have about the patient's physical health with our team. In addition, clozapine has many important drug interactions (e.g., stopping or starting smoking, antidepressants, drugs which can affect white blood cells, other antipsychotics etc.).

If the patient reports any of the following symptoms, please contact our team or the Denzapine Monitoring Service on 0333 200 4141 immediately as further blood tests/ monitoring may be required.

- Breathlessness
- Flu like symptoms
- Any symptoms suggestive of or similar to those of heart problems
- Tachycardia

Should you have any questions or concerns with this patient or their Clozapine prescription, do not hesitate to contact either Dr _____ or the _____ Community Treatment Team.

Yours sincerely

10 - Suggested Care Plan Entry for IM Clozapine

An example of how this could be reflected in a care plan is:

Medication

Appendix

I plan to continue to take oral clozapine, but if for some reason I decide I do not want to take it, this can be a risk to my mental and physical health. The team will work to make sure I remain stable, and my physical health is cared for. I may need to be prescribed IM clozapine to prevent me showing early warning signs or becoming severely unwell.				
Intervention How am I going to get there	**Goal - Where I want to be**	**Evaluation**	**Who will do it**	**Action/Intervention Start date**
If I have refused oral clozapine for more than 24 hours, the team may prescribe IM clozapine if I am a significant risk to myself or others. If at any time I change my mind and decide I want to take oral clozapine; I will be able to take oral clozapine After each dose of IM clozapine, I will be observed every 15 minutes for two hours for excessive sedation. If I am late for my blood test, I will work with the team to have my blood test as soon as possible.	To agree a future treatment plan with my team. Maintain good physical and mental health and make sure my physical health is monitored.	Review at all reviews and CPAs.	Mental health team including doctors, nursing staff along with hospital pharmacist.	

Appendix 11 – Request Form for IM Clozapine

Request for IM Clozapine

This form must be completed before an initial supply of IM clozapine can be supplied from Pharmacy.

Patient's Name:			
Registration Number:		Date of Birth:	
Ward:		Consultant:	
Please PRINT clearly or use a registration label			
Does the patient have a history of noncompliance with oral medication?		□ Yes □ No	
Does the patient have a history of noncompliance with clozapine?		□ Yes □ No	
MHA consent to treatment paperwork completed?		□ S62 □ T3 □ CTT not applicable	
At what stage will IM clozapine be prescribed?		□ For clozapine initiation □ To avoid a clozapine treatment break	
Has the patient expressed a preference for IM clozapine?		□ Yes □ No	
Please give details as to why IM clozapine is considered necessary:			
Requested by (Consultant)			
Signed			
Print name			
Date			
Discussed with (peer Consultant)			
Signed			
Print name			
Date			
Accepted by (Assistant Medical Director for Pharmacological Therapies or Chief Pharmacist):			
Signed			
Print name			

Appendix

Date	

Appendix 12 - Process for Clozapine Rechallenge

Rechallenge with clozapine should only take place **once the following steps have been completed**. DMS and trust pharmacy services may be contacted for advice on how to proceed at any point.

1. Discuss the option of clozapine rechallenge and document the outcome of the discussion. Document the view of the patient and/or their advocate. If the patient is not able to be involved in the discussion, a second opinion may be considered if this is necessary.

2. Develop a patient-specific treatment plan, in collaboration with a Consultant Haematologist, which includes:

    a. the indication for clozapine treatment and rationale for rechallenge
    b. details of any planned augmentation strategies
    c. details of how and where rechallenge will take place
    d. the proposed monitoring schedules
    e. details of altered FBC criteria if agreed
    f. actions to be performed if blood results reach pre-ordained limits (Appendix 2)
    g. a contact number for emergency use (ideally available 24/7)

3. Complete a DMS clozapine rechallenge request form, which includes the off-label agreement (available from DMS either direct or via trust pharmacy services) and inform Pharmacy.

4. Submit in writing to DMS requesting them to authorise clozapine rechallenge, including:

    a. CPA review/MDT or ward round summary (see (1) above)
    b. treatment plan (see (2) above)
    c. DMS clozapine rechallenge request form
    d. DMS clozapine registration form (if treatment break is longer than 4 weeks)
    e. a special monitoring form if the patient is being re-challenged on altered criteria

5. Once agreement to rechallenge is gained, provide a satisfactory (green) FBC result. Liaise with trust pharmacy services regarding the initiation schedule, prescription paperwork and supply of clozapine.

Britannia contact details:
Tel: 0333 200 4141
Fax: 0333 200 4142
Email: denzapine@britannia-pharm.com

Appendix 13 - Action plan for recurrence of blood dyscrasia during clozapine rechallenge

This form should be completed and signed by the acute and long-term Consultant Psychiatrist, uploaded onto RiO and included in the Level 1 risk assessment and care plan. A copy should also be sent to the supplying Pharmacy who may be required to advise.

Emergency Contacts:

	Patient	Carer or nearest relative	Long-term Consultant	Pharmacy
Name				
Address: **Post Code**				
Home Phone No.				
Mobile Phone No.				
Out of Hours Contact				

Actions to be performed if an amber result is received:

e.g., increase frequency of blood monitoring to every 2 days until a green result is received, book an urgent OPA

Actions to be performed if a red result is received:

e.g., discontinue clozapine and monitor FBC daily, seek urgent medical advice, refer to home treatment team for close monitoring

Recommended treatment options in the event of clozapine discontinuation:

e.g., start amisulpiride or aripiprazole, start procyclidine to prevent cholinergic rebound

Other comments:

e.g., anything that you think my be of use to a colleague dealing with this patient on your behalf, in this event

Acute Consultant signature	Long-term Consultant signature
Date	Date

Appendix 14 – Physical Health Monitoring During Clozapine Treatment

This table does not include FBC monitoring which is mandated by the manufacturer and an ongoing requirement for treatment.

	Monitoring Required
Before Initiation	• Temperature • Blood Pressure and Pulse • Weight and BMI • Renal Function • Blood Lipids • HbA1c +/- Plasma Glucose • Liver Function Tests and Lipids • U+Es • Baseline Prolactin • ECG • Side effect ratings • Smoking Habits
After 1	• Temperature • Blood Pressure and Pulse • Weight and BMI • Blood Lipids • Fasting Glucose • ECG • Smoking Habits
After 3 months	• Temperature • Blood Pressure and Pulse • Weight and BMI • Blood Lipids • HbA1c • Smoking Habits
Annually	• Temperature • Blood Pressure and Pulse • Weight and BMI • Blood Lipids • HbA1c Every 6 months) • Liver Function Tests

Adapted from *BSMHFT Guidance for: Prescribing Guidance for the Treatment of Schizophrenia in Adults* (January 2016)

Appendix 15 – GASS Assessment Form for Clozapine

GASS for Clozapine

Name: _____ Current Medications: _____

Date: _____

Caffeine intake: .....cups/day

Smoker: Y / N .....cigarettes/day

Has there been a recent change in your smoking habit?: Increase/Decrease by.....cigarettes/day

This questionnaire is being used to determine if you are suffering from excessive side effects from your medication.
Please put a tick in the column which best indicates how often or how severely you have experienced the following side effects.

Over the **past week**:		Never	Once	A few times	Everyday	Tick if severe or distressing
1	I felt sleepy during the day					
2	I felt drugged or like a zombie					
3	I felt dizzy when I stood up or have fainted					
4	I have felt my heart beating irregularly or unusually fast					
5	I have experienced jerking limbs or muscles					
6	I have been drooling					
7	My vision has been blurry					
8	My mouth has been dry					
9	I have felt sick (nauseous) or have vomited					
10	I have felt gastric reflux or heartburn					
11	I have had problems opening my bowels (constipation)					
12	I have wet the bed					
13	I have been passing urine more often					
14	I have been thirsty					
15	I have felt more hungry than usual or have gained weight					
16	I have been having sexual problems					

I have also experienced: (please write down any other side effects OR PHYSICAL PROBLEMS OR COMPLAINTS that you may have experienced over the past week)	
17	
18	
19	
20	

Adapted from the Glasgow Antipsychotic Side-effects© 2007 by St John of God Hospital and South London and Maudsley Trust

Appendix 16 - Clozapine Clinic Poster

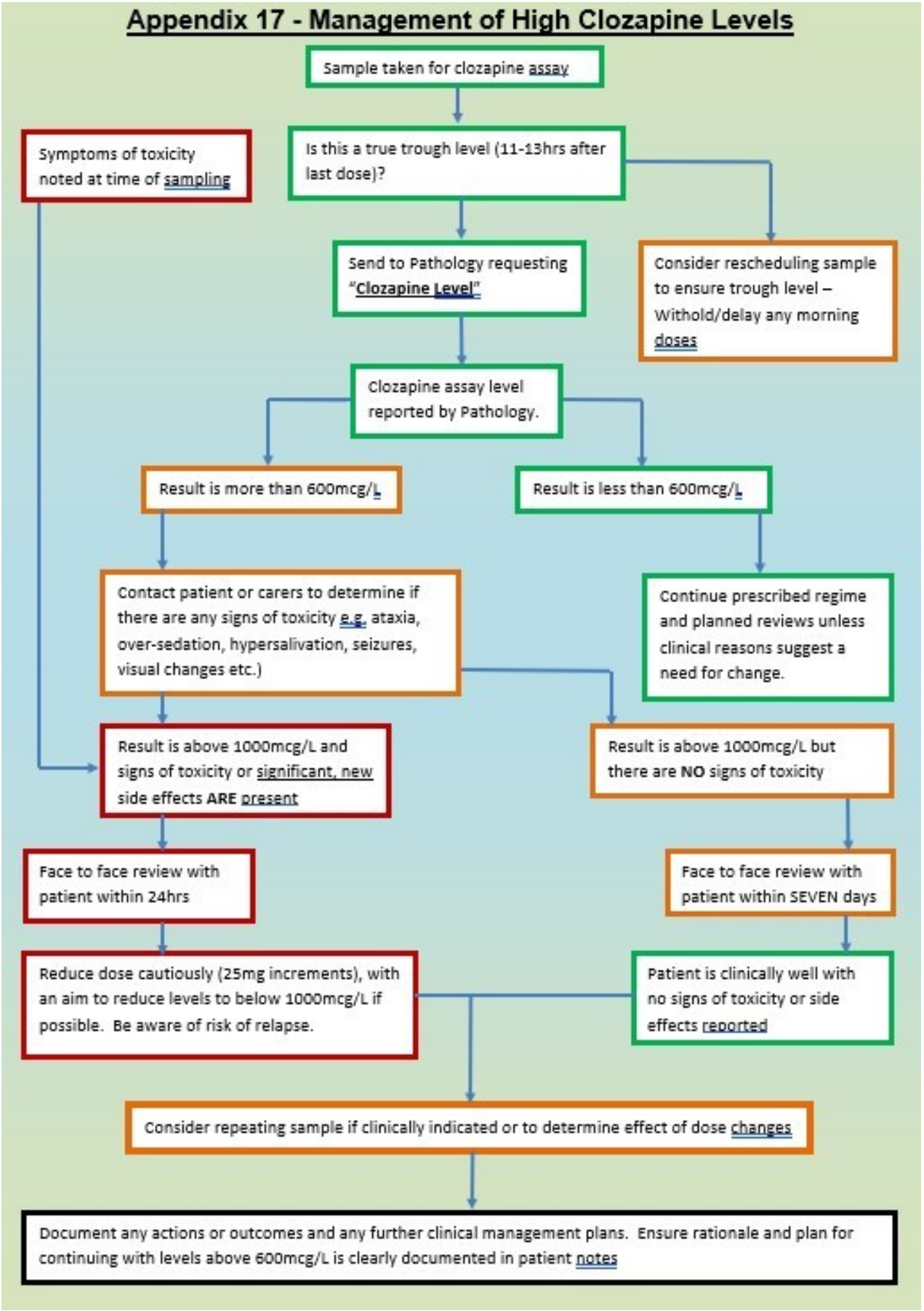
Struggling to go?
Let us know!

We want to know about any changes in your bowel habits.

Constipation may be caused by medicines like clozapine, procyclidine and amitriptyline.

Often, it can be relatively minor but can sometimes be very serious if not addressed quickly.

Appendix 17 - Management of High Clozapine Levels



Appendix 18 – Clozapine clinic questionnaire

This questionnaire can either be handed out to patients to fill in while waiting for their appointment or asked directly of them when seen. The outcomes should be documented on Rio in progress notes or on the Clozapine Pre-appointment questionnaire form (when available).

□	**Bloods checked on DMS/CPMS. Results indicate appropriate to hand out**
Since last appointment have you:	
□	**Stopped/started / changed smoking habits?**
□	**Have you unintentionally or not missed/ forgotten/ taken extra clozapine doses for any reason?**
□	**Started/stopped any other medication including medication from your GP or bought from a pharmacy or shop?**
□	**Had any infections diagnosed/ suspected since last blood test?**
□	**Any side effects or new symptoms that concern you?**
□	**Do you have any concerns about your bowel habits, or have your bowel habits changed?**

(The template for the forms is on the following page)