Humber Teaching
NHS Foundation Trust

CLOZAPINE GUIDELINES

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Author/Lead **Job Title**	Alberto Ortiz-Moya Principal Pharmacist Mental Health
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CHANGE RECORD

Version	Date	Change details
1.0	*No date*	
2.0	*29/11/12*	*Re-written guidelines*
2.1	*08/05/13*	*Addition of Clozapine Therapy Management Plan*
3.0	*01/07/20*	*Re-formatted guidelines, addition of physical monitoring table for initiation, links reviewed and updated, documents replaced by links; MHRA Pharmacovigilance Committee recommendations on toxicity monitoring added as a link.*
3.1	*30/11/23*	*Updated and checked references that have been updated since last update of this guideline in 2020. Reviewed/replaced links. Changed "Dispensing Pharmacy" by "HTFT Clozapine Dispensing Service"; updated Telephone Numbers. Re-alignment of monitoring table on page 12. Deleted mention of previous paper HTFT Prescription forms, as currently all clozapine is prescribed using Lorenzo Clozapine Prescription Form. Approved at Drugs and Therapeutic Group (30 November 2023).*

Contents

1 INTRODUCTION

1.1 Indication

Licensed Indications

Clozapine is indicated for patients with treatment-of resistant schizophrenia or those with schizophrenia who have severe, untreatable neurological adverse reactions to other antipsychotic agents, including atypical antipsychotics. It is also indicated for psychotic disorders occurring during the course of Parkinson's disease, where standard treatment has failed**.**

Off Licence Indications

Within HTFT, before initiation for any indication other than those listed in 0 a named patient application should be made to the HTFT Drug and Therapeutics Committee. This includes any patient who has previously been permanently prohibited due to RED result as outlined in Section 8, Red Re-challenge.

1.2 Brand

The brand of Clozapine that is used by Humber NHS Foundation Trust (HTFT) is Clozaril® manufactured by Novartis. (For the purpose of these guidelines Clozapine refers to the Clozaril® brand). In the exceptional circumstances where a liquid formulation is required, please contact pharmacy for advice regarding using alternative brand with oral formulation available.

1.3 Licensing Requirements and Registrations

The licensing requirements of Clozapine place strict restrictions on the treatment and management of patients prescribed Clozapine.

Patient Registration

All patients receiving Clozapine must be enrolled with the Novartis Clozaril® Patient Monitoring service (CPMS) and must be under the supervision of an appropriate specialist physician (usually a psychiatrist).

Prescriber Registration

All specialists who are responsible for prescribing Clozapine must be registered with the CPMS. Applications can be made using the Supervising Specialist Registration Form from the log in screen at CPMS website without the need to log in.

Non-Medical Prescribers and Junior Medical Prescribers

Within HTFT Clozapine may only be initiated by or under the direct supervision of a consultant psychiatrist. This requirement does not preclude the initiation and prescribing of Clozapine by suitably experienced Junior Medical Staff or Non-Medical Prescribers (NMPs) on either an independent or supplementary basis provided this is under direct supervised by a consultant psychiatrist. All prescribers should register with the electronic portal for CPMS (eCPMS) using the Clozaril® Website Access Formwhich is available from the log in screen at www.clozari.co.uk without the need to log in.

Pharmacist Registration
All pharmacists who dispense Clozapine must be enrolled with CPMS and only pharmacies registered with the CPMS can obtain supplies of Clozapine.

Additional Personnel Registration
Other personnel such as nurses and non-nursing care co-ordinators and Care home managers can also register to access blood results on the eCPMS using the Clozaril® Website Access Form

Blood Tests and Supplies of Medication
All patients treated with Clozapine must have regular blood tests the frequency of which is stipulated by the CPMS. Supplies of medication are restricted and the amount that can be supplied depends on the availability of a valid blood result.

1.4 CPMS

CPMS provides information and advice about all aspects of Clozapine treatment via the telephone on 08457698269 via eCPMS.

CPMS guidance within Humber Foundation Trust
The guidance provided by CPMS does not take into account HTFT Trust policies, procedures and guidelines which govern the management of Clozapine treatment within the Trust. *The Clozapine Guidelines*, *HTFT Procedures for The Safe and Secure Handling of Medicines* and all HTFT Medicines Management Guidelines should be read in conjunction with the CPMS guidelines. Under licensing requirements CPMS retain responsibility for keeping both a national patient register and a full record of haematological monitoring for all patients (including de-registered patients) to regulate the treatment and management of Clozaril® across all treatment settings and geographical boundaries. Staff should therefore contact CPMS (or access eCPMS) to obtain the most accurate and up-to-date information as it is not always practical for Trust paper records to reflect the current situation or history from other trusts.

The HTFT Clozapine Dispensing Service and where appropriate the Trust pharmacy should be the first point of contact for any queries regarding the local management of clozapine.

1.5 Using eCPMS

Up to date records on any patient can be obtained from eCPMS which is a secure, validated web-based database of patient registered for treatment with Clozaril®. Once registered users will receive a unique user identification number and password to allow access to relevant Clozapine patients' blood histories. Access can be obtained by sending a completed Clozaril® Website Access Form. All forms must be approved by a Supervising Specialist or Lead Pharmacist who is registered with the CPMS.

2 INITIATION AND DOSE CHANGES

2.1 Investigations required prior to initiation

Physical health

As patients should be treated only if expected benefits clearly outweigh the risks. Clinically relevant responses to Clozapine have been reported in 30% of patients after six weeks of treatment and 60% of patients after one year.

Before initiating Clozapine check the patient's history and a full physical examination should be done. If the patient has a history of cardiac illness or has abnormal cardiac findings on examination they should be referred to a specialist for other investigations (which might include an ECG). Consider seizure risk, Clozaril® is contraindicated in uncontrolled epilepsy. With all patients, treating physicians should consider performing a pre-treatment ECG. In addition baseline BCP (U+Es & LFTs), FBC, TFTs and BP monitoring should be completed.

If you require any further information regarding Clozaril and Cardiovascular events, contact the Pharmacy Department

Baseline blood tests

Prior to starting Clozaril® patients must have a satisfactory pre-treatment white blood cell (WBC) count and absolute neutrophil count (ANC) (WBC >3.5 x 10^9/L, neutrophil count >2.0 x 10^9/L).

The results of a pre-treatment blood sample, less than 10 days old, are required to enable full registration and allocation with a CPMS patient number. Refer to Section 3.2 on Sampling methods

It is also very important to establish that the patient has not previously experienced an adverse haematological reaction to Clozapine that necessitated discontinuation.

Patients who have low WBC counts because of benign ethnic neutropenia (BEN) should be given special consideration and may only be started on Clozaril® with the agreement of a haematologist. Details on this are available in section 8 on Red Re-challenge.

Medication review

NICE guidance CG178 Psychosis and schizophrenia in adults: prevention and management suggests Clozapine as an intervention for people with schizophrenia whose illness has not responded adequately to treatment. An adequate period of treatment to assess response is generally accepted as a minimum of six weeks.

Offer clozapine to people with schizophrenia whose illness has not responded adequately to treatment despite the sequential use of adequate doses of at least 2 different antipsychotic drugs. At least 1 of the drugs should be a non-clozapine second-generation antipsychotic.. NICE.

Before considering clozapine, establish that there has been adherence to antipsychotic medication, prescribed at an adequate dose and duration. Consider other causes of non-response, such as comorbid substance misuse (including alcohol), the concurrent use of other prescribed medication or physical illness.

Consider concomitant medications, their indications and potential to have additive adverse effects prior to starting clozapine. Clozapine as mono-therapy can induce the rare but life-threatening blood dyscrasia; agranulocytosis.

Some co-prescribed medications may contribute to the risk of agranulocytosis by acting synergistically, especially drugs that are known to cause agranulocytosis themselves. Cases of

blood dyscrasias with clozapine have been reported with concomitant carbamazepine, valproate, lamotrigine, olanzapine and mirtazapine. The peak incidence of both neutropenia and agranulocytosis occurs in the first 18 weeks of clozapine treatment. Co-prescription with other drugs that are known to depress bone marrow function should also be avoided as these could increase the risk of patients on clozapine developing neutropenia or agranulocytosis.

Long-acting depot antipsychotics should not be used with clozapine as they have the potential to depress bone marrow function and cannot be rapidly removed from the body in the event of neutropenia or agranulocytosis.

Additional medication should be reviewed to avoid concomitant medications with the potential to cause the same adverse effects as clozapine. Consideration should be given to switching to alternatives if appropriate. Contact Pharmacy If you require further advice.

Patient concordance

Clozapine should only be considered following an MDT discussion ideally including a Pharmacist to ensure a collaborative approach. Treatment options should be discussed with patients and their relatives and carers where appropriate to allow informed consent to be made. Information about schizophrenia and its treatment is provided for patients at the Choice and Medication website
NICE guidance CG178 Psychosis and schizophrenia in adults: prevention and management promotes person centred care:

When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.

Information should be provided on the risk/benefits of treatment with clozapine, paying particular attention to the rare serious side effects of agranulocytosis, seizures,myocarditis and cardiomyopathy. Clozapine is associated with significant weight gain and associated risks which are included in the information on the Choice and Medication website which is accessible for service users. Printable information sheets can also downloaded from Choice and medication and a Patient Handbook is also available from Clozaril® Connect website which outlines the common side effects of clozapine. If you need advice regarding the effects of different lifestyles, smoking, alcohol and caffeine on Clozaril treatment seek advice from HTFT Pharmacy Department.

An agreement regarding the importance of compliance with Clozaril® and on-going blood monitoring needs to be reached with the patient**.**

2.2 Registering a new patient

Patients must be registered for treatment with Clozaril® with CPMS in one of two ways. It is important to check the patient has not previously been registered with CPMS and consideration should be given to changes in name, address and the use of aliases. Upon receipt of patient details the patient status for Clozaril® will be 'awaiting registration' until a satisfactory blood result has been received by CPMS.

Completing a Patient Registration/Re-registration form

Complete a Patient Registration Form (also available from eCPMS) and e-mail (cpms@mylan.co.uk) or fax (0845 769 8541/8379) to CPMS.

Using eCPMS Remote Patient Registration

It is possible to enter and save patient details on-line after which they will appear 'awaiting registration' until a satisfactory initial blood result is received blood. See Quick start guide on Remote Patient Registration Section 1.5.

Awaiting Registration Status and Initial Blood Result

Until a satisfactory initial blood sample is received by CPMS the patient is held on an 'awaiting registration' list for up to 10 days. If an initial blood result is not received by CPMS the patient will be de-registered after 10 days.

Initial blood samples can be sent to CPMS Central Laboratory for analysis or a result analysed locally, by a laboratory registered on the CPMS system, can be attached to the Registration Form. If the patient is 'awaiting registration' on the CPMS database an initial blood sample result can be submitted electronically (Section 3.2.3 Local Blood Samples).

2.3 Switching from a previous antipsychotic therapy

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.

Previous depot should be stopped prior to clozapine initiation. Refer to Medication review

2.4 Potential Clozapine Adverse Effects

Careful dose titration is necessary to minimize adverse effects as detailed.

Neuroleptic Malignant Syndrome

Neuroleptic Malignant Syndrome (NMS) is a serious and potentially fatal symptom complex cases have been reported in patients using clozapine either as mono-therapy or more commonly, in combination with lithium or other CNS agents, e.g. other neuroleptics. Although NMS is most often seen in early treatment especially within the first 10 days, it can occur at any time during therapy.

There appears to be an association with dose, with an increased risk reported in patients who:

- Are started on high doses
- Undergo rapid dose titration,
- Have had a significant dose alteration.

Other adverse reactions and their management

- Tachycardia and hypotension may present during initiation additionally myocarditis and cardiomyopathy risk is increased, especially during, but not limited to, the first 2 months of treatment.

- Rapid dose increases may increase seizure risk,

- The peak incidence of both neutropenia and agranulocytosis occurs during the first 6-18 weeks of Clozaril treatment. Refer to Section 3, Blood Samples, and Section 7, Red Results, for detailed information on blood disorders, monitoring and management.

- Hypersalivation and GI adverse effects may be transient.

- Constipation may persist

- Weight Gain, Diabetes and hyperglycaemia are expected complications of therapy

For patient advice on adverse effects refer to Choice and Medication website, which is accessible for service users.

For advice regarding the management of these side effects contact the Pharmacy Department.

Extra precautions in the elderly
The prevalence of Cardio-vascular adverse effects and blood disorders increases with age and in addition elderly patients are more likely to experience other serious side-effects. Extra care is necessary in elderly patients, including hypotension risk..

Lower starting doses and very slow dose titration is recommended in the elderly, contact HTT Pharmacy Department for advice if necessary

2.5 Dose Titration

Following baseline blood tests upon receipt of a "Green result" Clozaril® dose titration may commence. When Clozaril® 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. Previous depot should be stopped prior to Clozaril® initiation. See Section 2.1 Medication review

Initiating Pharmacy supply
Only Pharmacies registered with CPMS may supply Clozaril®, Section 10.3 HTFT Clozapine Dispensing Service, provides current Pharmacy contact details.

Prior to initiation for both In-Patient and Out-patient please liaise with the HTFT Clozapine Dispensing Service to agree and ensure process for effective and uninterrupted supply. Avoid Saturdays and Sundays when initiating patients onto Clozapine. See section 4.1 Pharmacy liaison

Initial Physical Monitoring Requirements
Pulse, temperature and standing and lying BP should be taken before the first dose of Clozaril® and then at hourly intervals for 3 hours. For elderly patients close observation for the first 24 hours may be necessary, especially in those patients with concurrent cardiovascular or cognitive impairment. See table below for details.
During initiation: Omit if temperature >38.5'C, postural drop >30mmHg or pulse > +/- 15% baseline, and inform the Doctor. Observations

Physical Monitoring Initiation: Observations (example table, to be expanded as necessary)

		Day (use the morning dose where possible)	Date	Time	Temp	Pulse	Respiratory rate (normal rate 12-18 breaths per minute)	Lying BP	Standing BP	Other side effects, particularly flu-like symptoms, hypersalivation, palpitations, chest pain, constipation, GASS-C
DAY 1	Evening Dose	Before dose								
		1hr post-dose								
		2hr post-dose								
		3hr post-dose								
		4hr post-dose								
		5hr post-dose								
		6hr post-dose								
Days 2-14	Morning Dose	Before dose								
		3-6hrs post-dose								
	Evening Dose	Before dose								
		3-6hrs post, if awake								
Days 14-onwards	Morning Dose	Before dose								
		3-6hrs post								

Ref. Maudsley 13th Edition/ Clozaril SPC/ CLozaril Initiation Document

In Patient Initiation
There is a requirement to titrate slowly to reduce emergence of adverse effects and facilitate their management. See Potential Clozapine Adverse Effects in Section 2.4. The initial dose of clozapine in patients with treatment-resistant schizophrenia is 12.5 mg once or twice on the first day, this will require tablet cutting, please consult HTFT Pharmacy department for advice.

For elderly patients initiation of treatment is recommended at a particularly low dose (12.5 mg given once on the first day), an even lower starting dose of clozapine 6.25mg may be suitable for some elderly patients with close observation for the first 24 hours. Subsequent dose increases are restricted to 25mg/day. For further information regarding starting clozapine in elderly patients please Contact HTFT Pharmacy Department.

For patients with psychotic disorders occurring during the course of Parkinson's disease, in cases where standard treatment has failed the starting dose must not exceed 12.5mg/day taken in the evening and again additional care is required with subsequent dose increases.

Prescribing and legislation
The titrating dose should be prescribed in Lorenzo as a Stepped Variable dose (Note: A standard clozapine titration shedule is available in Lorenzo ePMA for the first 2 weeks of treatment) Once a regular dose is attained prescribe as a regular dosing regime in ePMA. Ensure consent to treatment and inclusion on a T2/T3 form prior to initiation if appropriate. The review functionality can be used in Lorenzo ePMA to alert staff of the frequency of blood tests.Refer to Section 4.1 Monitoring frequency and associated supply.

Outpatient Initiation
Clozapine can be started on an out-patient basis, as an alternative to hospitalisation, see abridged HTFT **Clozapine Outpatient Initiation Guidelines here**

In addition to previous cautions:

- Clozapine initiation for psychotic disorders occurring during the course of Parkinson's disease is not possible within HTFT Home treatment guidance, due to requirement for extra care and an evening start dose.
- Elderly patients may also be unsuitable for out-patient initiation, due to extra care and monitoring required HTFT Guidelines for Clozapine Home Treatment

During Initiation
- A Psychiatrist should assess regularly and at a minimum once every week, to assess in a similar way to that which would occur if the patient were an inpatient.
- The patient should be visited by a health care professional every day for at least the first two weeks; the actual length of attendance is subject to review. Pulse, temperature and Blood pressure (BP) and mental state should be monitored and any changes reported to Psychiatrist.
- Each dose administered should be signed on the Trust's drug chart.
- Enquiry should be made daily into the occurrence of the following adverse drug reactions (ADRs) e.g. hypersalivation, nausea, vomiting, drowsiness, dizziness, sore throat and infections refer to B.N.F.

2.6 Dose Changes

Avoid rapid dose increases; see Section 2.4 Potential Clozapine Adverse Effects. Caution is required when increasing the dose of clozapine at the weekend or on bank holidays due to monitoring requirements. Where clinically appropriate, implement dose changes to synchronise with the next supply schedule, consult Section 4 on Supplies.

Initial therapy

If the initial dose is well tolerated the daily dose can be slowly increased up to 400mg/day over at least 3-4 weeks Note requirement for extra care in elderly patients and psychotic disorders occurring during Parkinson's disease.

On-going dose adjustment

Clinically relevant responses to clozapine have been reported in 30% of patients after six weeks of treatment and 60% of patients after one year. Review response, assess compliance and presenting side-effects.

Response is usually seen within the range of 150 mg -900mg clozapine daily, average maintenance dose is 400mg daily. In most patients antipsychotic efficacy can be expected with 200-450mg/day in divided doses. A few patients may require larger doses, cautious increases (i.e., not exceeding 100mg) towards 900mg/day may be made. The total daily dose may be divided unevenly with the larger portion at bedtime.

Note restricted increments and lower doses in:

1. Elderly patients.
2. Psychotic disorders occurring during Parkinson's disease detailed in Clozaril ® SPC, with a mean effective dose 25-37.5mg/day and specification for a low dose of 50mg/day, not to be reached until the end of the second week.

At each consultation, remind the patient to contact the Responsible Clinician immediately if any kind of infection begins to develop. Particular attention is required for flu-like complaints such as fever and sore throat which may be indicative of neutropenia/agranulocytosis. In the event of any of these symptoms an immediate white blood cell count is required.
Clozapine assays may assist in detecting non-compliance, refer to Plasma Concentration assay (TDM) Section 3.4 for advice. Plasma Clozapine assays are only useful after the initial stages of treatment and if the dose has remained stable for at least one week.

Un-satisfactory Response

- Evidence suggests that treatment should be continued for 1 year as it may take this long for efficacy to become apparent.
- Review compliance; use plasma levels to detect non-compliance Refer to Plasma Concentration assay (TDM) section 3.4 and Possible applications of TDM. Assay may be considered to assess poor responders after 3-6 months; provided that the dose has been constant for a week or so before sampling. A plasma level of between 0.35mg/L and 0.6mg/L is considered a good target range. A plasma clozapine concentration **significantly less** than 0.35 mg/L indicates a dose increase is necessary.
- Consider gradually increasing the dose (guided by plasma clozapine assays), up to a maximum of 900mg/day if necessary. The possibility of increased adverse reactions (in particular seizures) occurs at doses over 450mg/day. Doses of 900mg/day are rarely justified in women but young male smokers may have rapid clearance and require higher doses, co-prescription of enzyme inducers necessitates higher doses, drug-drug interactions are included in Section 3.4.1. Requirement for TDM
- Lower doses are required in elderly patients and psychotic disorders occurring during Parkinson's disease. In Parkinson's disease adjustments above a specifically low dose of 50mg/day are only to be considered in exceptional circumstances when treatment at this

dose for at least one week fails to provide satisfactory therapeutic response, a maximum dose of 100mg/day must never be exceeded.

- Augmentation with a second anti-psychotic may only be considered after sufficient duration at adequate dose of clozapine mono-therapy. In selection of secondary agent consider the side-effects and the evidence for combined therapy with clozapine. Avoid the use of a depot in combination with Clozapine due to length of time required for terminal clearance if a subsequent adverse reaction develops.

Satisfactory Response
Consider establishing a lower maintenance dose. After achieving maximum therapeutic benefit many patients can be effectively maintained on lower doses. Perform a reference plasma concentration assay, consult section 3.4 Plasma Concentration assay, when the patient is established on an effective dose, careful downward titration is required. Lower doses are required in the elderly, females, non-smokers and patients co-prescribed enzyme inhibitors. If the maintenance dose does not exceed 200mg/day, once daily administration in the evening may be appropriate.

Side-effects
See section 2.4 for Potential Clozapine Adverse Effects and their management.

If side effects are serious or persistent consider Clozapine concentration assays, see Section 3.4 (TDM) for details and assess.

Clozapine Discontinuation
If an adequate trial of clozapine has been undertaken with lack of response or presence of unacceptable side-effects consider stopping clozapine gradually over 1-2 weeks referring to the SPC or the Pharmacy Department for advice. If abrupt discontinuation is necessary due to haematological reasons the patient should be carefully observed for the occurrence of withdrawal reactions. For either planned or immediate discontinuation of therapy monitoring must continue for at least 4 weeks or if necessary *until* haematological recovery has occurred, following CPMS advice. Patients/carers should be warned to contact the doctor if infection develops especially fever, sore throat or flu-like symptoms, and an urgent WBC and differential should be arranged.

3 BLOOD SAMPLES

Registration with CPMS regulates Clozaril® supply, specifying monitoring within the licensing requirements. Before any clozapine can be dispensed the status of the patient must become 'active' on CPMS, this is dependent on the results of a pre-treatment blood sample, **less** than 10 days old. Patients must have a normal pre-treatment WBC and differential (*both* WBC > 3.5 x 10^9/L and neutrophil count > 2.0 x10^9/L) to exclude Neutropenia, defined as a neutrophil count of less than 1.5 x 10^9/L and agranulocytosis, a neutrophil count of less than 0.5 x 10^9/L.

Development of granulocytopenia and agranulocytosis is a risk inherent to Clozapine treatment. Although generally reversible on withdrawal of treatment, agranulocytosis may result in sepsis and can prove fatal. Because immediate withdrawal of treatment is required to prevent the development of life-threatening agranulocytosis, monitoring of the WBC count is mandatory.

3.1 Monitoring frequency

Blood samples are required at routine intervals: **weekly, fortnightly or four–weekly,** the frequency for each patient is indicated by CPMS, dependent on both Risk factors,Section 3.1., (including duration of therapy) and Sample results, Section 3.4.

- **Risk factors**
  - The peak risk for neutropenia and agranulocytosis is between weeks 6-18, decreasing after the first year of treatment.
  - Both are idiosyncratic reactions and are **not dose-related**.
  - 70% of agranulocytosis cases occur within the first 18 weeks.
  - There is evidence for an increased risk of agranulocytosis with female gender and increasing age.
  - Co-prescribed medication may increase the risk of blood dyscrasias – detailed in Section 2.1. Medication review

It is mandatory to monitor the WBC and differential at least weekly for the first 18 weeks, at least fortnightly from 19-52 weeks and at least four weekly thereafter. Patients/carers should be warned to contact the doctor if infection develops especially fever, sore throat or flu-like symptoms, and an urgent WBC and differential should be arranged.

Monitoring must continue for 4 weeks following discontinuation of Clozaril® and if necessary until haematological recovery has occurred.

- **Associated Supply**
  The **quantity** of clozapine supplied depends on the patient's current Sampling Status and monitoring frequency, see Section 3.1 Sample results and Section 4.1 Monitoring frequency and associated supply. Samples are usually taken on the Monday or Tuesday of the week the supply is due, with deliveries made on the Thursday or Friday of that week.

- **Changes to sample day**
  Any major changes to the sample day require discussion and agreement with the HTFT Clozapine Dispensing Service /HTFT Pharmacy Department prior to making arrangements with the patient as this may impact upon the amount of clozapine that can be supplied.

- **Bank holidays**
  HTFT Clozapine Dispensing Service /HTFT Pharmacy Department will supply a Bank Holiday Sampling Guide for Christmas, New Year and Easter Bank Holidays. Remaining Bank Holidays are usually accommodated by sampling on the Tuesday instead of the Monday.

- **Patient's Holidays**
  The HTFT Clozapine Dispensing Service should be contacted to discuss any requirement to make changes to the sample date prior to agreeing changes with the patient. Contact the Pharmacy Department if you need more specific advice regarding arrangements for Clozapine patients going on holidays.

- **Additional samples**
  In addition to routine monitoring, Section 3.1 Monitoring frequency, CPMS may request samples on an individual basis prompted by a recent result. Additional sampling will not affect the regular sample or supply schedule dates unless the results are unsatisfactory.

3.2 Sampling methods

The HTF area Clozapine Clinics will take blood samples as per their SOPs (click on link for details)

- **Local Blood Samples**
  If a Clozapine blood result is required urgently, instead of sending the sample to the Clozaril® Patient Monitoring Service (CPMS) a sample can be processed by the local Pathology Lab. This is referred to as a Local Sample. Contact the Clozapine clinic in Miranda House or the Pharmacy Department for advice if this is required.

- **Advice for patients who are difficult to bleed**
  A finger prick sample may utilised, please contact HTFT Pharmacy Department for the current advice and requirements.

- **Urgent Sample Result**
  Contact HTFT Pharmacy Department.

- **GP Sampling**
  Sampling may be performed by GP practices but this requires co-ordination by the patient's CPN, Care Co-ordinator, Primary Carer (Case Manager) or Care Home Manager.

3.3 Sample results

Supply of Clozapine is dependent upon a current, satisfactory blood result.

Following sample analysis of current WCC, neutrophils and platelets the results are translated into current patient status within a colour range as below.

WCC/neutrophils 10^9/L	Status	Clozaril® Supply
>3.5 / > 2.0	Green	to be supplied
3.0-3.5 / 1.5-2.0	Amber	to be supplied *but* sampling will need to be repeated as indicated by e-CPMS until blood count results stabilise or increase .
<3.0/ <1.5	RED	to be discontinued immediately *unless* supply confirmed by CPMS and within a patient specific care plan in collaboration with haematology.

Weekly patients who have a blood result which is the lowest seen to date will be assessed by CPMS and an extra sample requested if necessary.

- **Management of an Amber result/alert**
  Follow CPMS advice and monitoring requirements.
  If a patient has an amber blood result a full blood count (FBC) must be performed TWICE weekly until either the count stabilises in this range or increases.

  Advice is included in the information on the Choice and Medication website which is accessible for service users. A printable patient information leaflet is available on this site.

- **Management of a Red result/alert**
  If a patient's WBC is less than 3.0 x 10^9/L and/or the neutrophil count is less than 1.5 x 10^9/L this is known as a **RED ALERT** and the following action must be taken:

  - **STOP CLOZARIL TREATMENT IMMEDIATELY**
  - If the red alert is confirmed **THE PATIENT MUST NOT RESTART CLOZARIL TREATMENT**
  - Full Blood Counts with Differential should be performed **DAILY** whilst the blood counts remain in the RED range and the patient must be observed closely for infection, i.e., sore throat, fever. The results should be reported to the CPMS as soon as they are available.

  For full details please refer to Section 7, Red Results
  Advice is included in the information on the Choice and Medication website which is accessible for service users. A printable patient information leaflet is available on this site.

- **Benign Ethnic Neutropenia (BEN) sampling and results**
  For Benign Ethnic Neutropenia please refer to the BEN CPMS Alert Ranges in Section 8.2
  Collaboration with HTFT Pharmacy Department and haematology is essential.

  A treatment plan will need to be approved for a Red Re-challenge, contact HTFT Pharmacy Department for Advice.

3.4 Plasma Concentration assay (TDM)

Also referred to as Therapeutic Drug Monitoring (TDM), this is distinct from the routine monitoring required by CPMS to monitor for blood dyscrasias which are unrelated to dose. At higher doses there may be an increased risk of other side-effects, please review Section 2.4. Other adverse reactions and their management for details.

- **Requirement for TDM**
  Whilst TDM is not mandatory, plasma monitoring may help to optimise treatment regimens. A plasma level of between 0.35mg/L and 0.6mg/L is considered a good target range for effective response whilst reducing the risks of serious side-effects. Seizure risk may increase above daily doses of between 450mg and 600mg and plasma levels above 0.6mg/L, with a definite link between seizures and plasma levels > 1.0 mg/L.
  Clozapine assays also assist in detecting non-compliance. A low clozapine: norclozapine ratio < 0.5 may suggest non-compliance during the previous days (norclozapine is a major clozapine metabolite).

- **Method of TDM**
  Clozapine assays are only useful after the initial stages of treatment and if the dose has remained stable for at least one week. The assay requires a trough sample (six hours or more after last dose) of plasma to determine clozapine and nor-clozapine (a major clozapine metabolite) levels.

  CPMS specific advice for plasma assay/TDM:
  Blood (2.7ml EDTA Monovette or 5ml EDTA tube) is best collected either immediately before a normal morning dose or, in the morning after an evening dose ('trough' sample). It is important to note the time of sampling with respect to dosage since this may influence interpretation of the result.

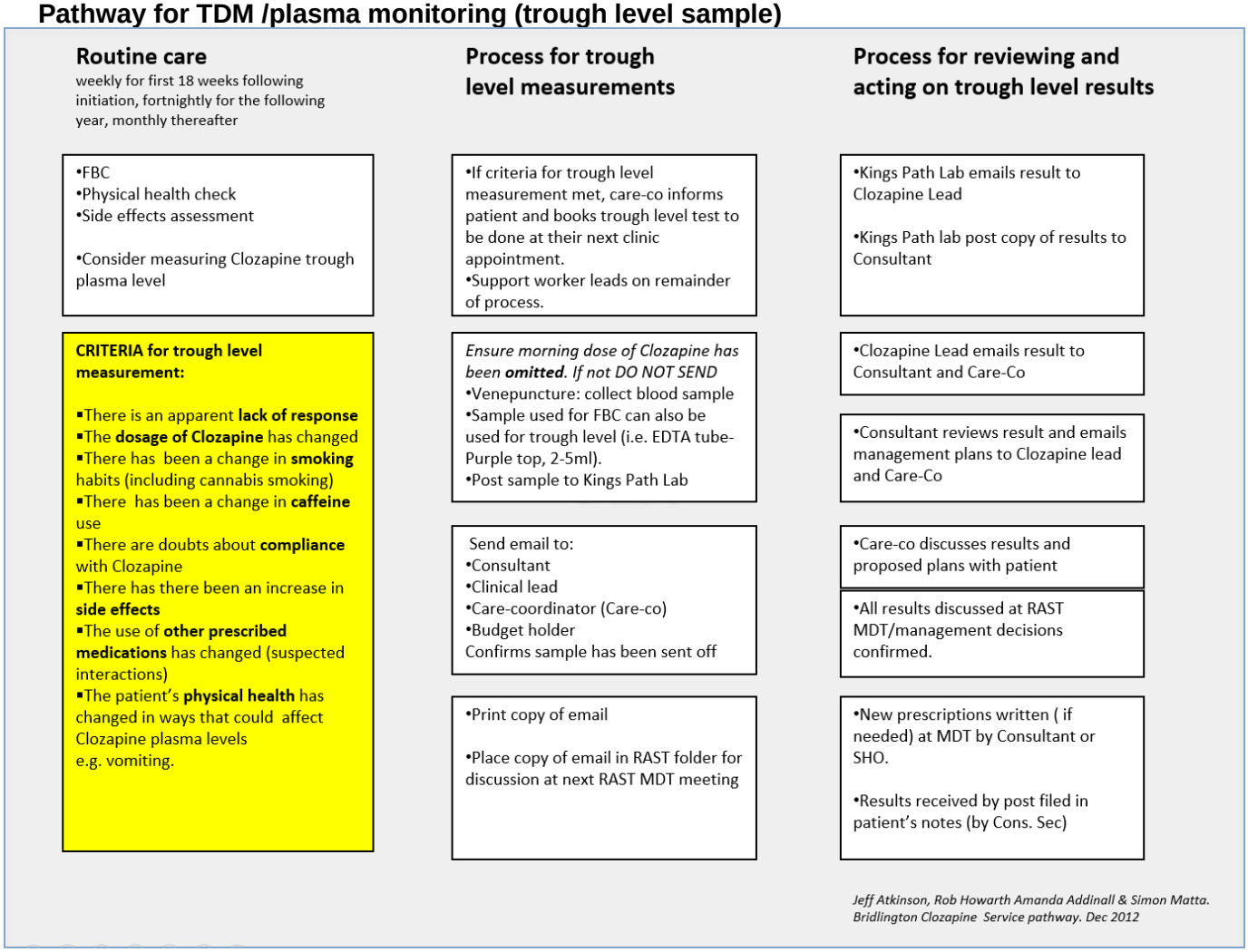
- **Possible applications of TDM**
  - To monitor adherence, non-compliance is detectable, partial adherence is harder to detect.
  - To optimise dosage.
  - On increasing doses from a currently high dose to minimise the risk or severity of side-effects
  - When side effects suggest a high serum level.
  - To establish a lower maintenance dose following maximum therapeutic benefit
  - On planned addition of another drug likely to interact or to investigate and measure suspected drug-drug interactions.
  - To monitor the effects of changes in smoking habit, stopping and (re)starting.
  - It may be helpful to measure 'baseline' plasma clozapine and nor-clozapine during successful therapy in case problems occur later.

In addition Clozapine TDM should be considered in the early stages of treatment to help identify patients who metabolise clozapine very slowly and who may therefore benefit from receiving the drug at a lower dose.

The MHRA have issued guidance in a Drug Safety Update, summarising indications for checking clozapine levels

For advice on interpreting plasma levels with respect to non-compliance/ partial adherence please consult HTFT Pharmacy Department

Pathway for TDM /plasma monitoring (trough level sample)



4 CLOZAPINE SUPPLIES

4.1 Monitoring frequency and associated supply

Registration with CPMS and the licensing requirements of Clozaril® indicate:

- The **supply** of clozaril® is dependent on a current, satisfactory blood result
- The current Monitoring frequency, of the patient determines **the quantity** of clozaril® supplied.

Monitoring Frequency	**Normal Supply (days)**	**Maximum supply allowable (days)** from **date of last sample**
Weekly	7	**10 (e.g. sample taken 1/6/12 supply covered up to and including 11/6/12)**
Fortnightly	14	**21**
Every 4weeks	**28**	**42**

Prescriptions should not be issued for periods longer than the interval between 2 blood counts.

- **Pharmacy liaison**
  The HTFT Clozapine Dispensing Service is able to advise when the next supply is due.

  Any changes to **supply schedule** should only be made after discussion with the HTFT Clozapine Dispensing Service/HTFT Pharmacy Department .

- **Local arrangement for the supply of Clozapine**
  Patients prescribed Clozapine are assigned to a specific dispensing group, determined by their current Monitoring frequency.

- **In-Patient supply**
  On each unit, Clozapine is stored as segregated stock. Following the in-patient prescription bring clinically screened and receiving a valid blood result a Pharmacy Technician will label the Clozapine for use.

- **Leave/Discharge**
  Supplies of Clozapine for leave and discharge will be prepared by a Pharmacy Technician. To facilitate timely supply of these, units are required to liaise with the ward based technicians or contacting the HTFT Pharmacy department.
  Refer also to Section 9, Transfers and Discharges

- **Out-Patient supply**

  Use HTFT Lorenzo Clozapine Prescription form (refer to current Safe and Secure Handling of Medicines Procedures) and See Section 4.3 Requirements to ensure routine clozapine supply

4.2 Emergency supply

During office hours contact HTFT pharmacy department to discuss the nature of the emergency and supply.

- **Conditions to emergency supply**

  The supply made is for maximum of 72 hours to cover a weekend or sufficient supply to cover a Bank Holiday.

  Supply can only be made against a **current and valid blood result**. The result must be confirmed via eCPMS or by contacting the CPMS directly. Tel: 0845 769 8269 or Out of hours: Tel:01276 692504.

4.3 Requirements to ensure routine clozapine supply

Clozaril® is classed as a "red drug" under HERPC local guidance. Currently HTFT retains responsibility for supply of this medication, including prescribing and monitoring.

- **General responsibilities**

  The unit/ward manager, team leader or Care home manager is required to ensure clozapine is competently managed by staff, including:

  - Registration and training on eCPMS
  - Staff awareness of guideline changes.
  - Ensuring CPMS monitoring requirements are met including any additional sample requests.
  - Appropriate handover of information, including any changes to sampling status/result.
  - Informing CPMS of changes to patient's details, medical conditions.
  - Ensuring timely receipt of clozapine prescriptions by HTFT Clozapine Dispensing Service, at least 24 hours prior to agreed delivery.
  - Liaising with HTFT Clozapine Dispensing Service regarding clozapine supply and delivery,
  - Maintenance of communication with the HTFT Clozapine Dispensing Service, HTFT Pharmacy Department and any GPs/practice nurses who share responsibility for delivering care to the patient.

It is the responsibility of the In-patient Named Nurse or Out-patient Primary Carer, to ensure that these processes are implemented and maintained.

- **Outpatient prescriptions**

  For **Out Patient prescriptions** it is the responsibility of the Primary Carer or Care Home Manager to inform the HTFT Clozapine Dispensing Service of any changes to the prescription. (Refer to current Safe and Secure Handling of Medicines Procedures on Prescribing of Medicines (HTFT Clozapine prescription form in Lorenzo.)

- **Care/nursing home requirements**

  It is the responsibility of the Named Nurse, or Home manager depending on the nature of the residential home, to ensure that processes are implemented and maintained. The home should hold up to date contact details for the patient's supervising specialist/psychiatrist and follow procedures for transfer of patients detailed in Section9 on Transfers and Discharges.
  An appropriate care plan is required for each **individual** patient, including the named person responsible for clozapine management, to ensure continuity of care and action to be taken when:

  - doses are missed- Section 6.3 Missed doses
  - a treatment break occurs- Section 6 Treatment Break and missed doses

- a patient presents with sore throat/flu like symptoms
- amber or red result received-see Section 3.3 Management of an Amber result/alert and Section 7, Red Results
- additional sampling/blood testing is requested by CPMS refer to 3.4 Additional samples
- A patient is admitted to hospital for *any* reason including routine surgery, discuss with HTFT Pharmacy Department, Tel: 01482 301732 and refer to Section 9 Transfers and Discharges

5 DELIVERY

Delivery frequency depends on the current sampling schedule. Consult Section 3.1. Monitoring frequency and Section 4.1 Monitoring frequency and associated supply. Delivery is usually arranged for the Thursday and Friday of the same week in which the sample is taken, unless otherwise arranged with the HTFT Clozapine Dispensing Service and HTFT Pharmacy Department.

5.1 Out-patients

- **Home Delivery Service**

  Arrangements *may* be made with the HTFT Clozapine Dispensing Service for Out-patients to have their Clozapine delivered to their home/relative/friend's address or their place of work. This is referred to as "Home Delivery Service."

  - This must be a secure and safe system and the patient must understand the requirements of this service.
  - The patient, or a responsible adult must, accept and sign for the delivery; the prescription will not be posted through the door.
  - A system for an alternate delivery point must be agreed, with all concerned, in the event that the patient or responsible adult is not at the agreed delivery address.

- **Alternative delivery address**

  There are various options available, please discuss with HTFT Pharmacy Department, Tel: 01482 301732 for suitability.

  - If the alternate delivery address has to be used, the delivery driver will leave notification at the primary delivery address stating where the medication has been taken. The HTFT Clozapine Dispensing Service will inform the prescribing Unit.
  - It is the responsibility of the Case Manager to ensure that the patient has collected their supply should the prescription be delivered to the alternate delivery address.
  - If the situation arises where the alternate address is repeatedly being used on the scheduled delivery day, then the option for 'Home Delivery' may be withdrawn and the medication will be delivered to the prescribing unit or another HTFT in-patient unit.

6 DELIVERY

Delivery frequency depends on the current sampling schedule. Consult Section 3.1. Monitoring frequency and Section 4.1 Monitoring frequency and associated supply. Delivery is usually arranged for the Thursday and Friday of the same week in which the sample is taken, unless otherwise arranged with the HTFT Clozapine Dispensing Service and HTFT Pharmacy Department.

6.1 Out-patients

Home Delivery Service

Arrangements *may* be made with the HTFT Clozapine Dispensing Service for Out-patients to have their Clozapine delivered to their home/relative/friend's address or their place of work. This is referred to as "Home Delivery Service."

- This must be a secure and safe system and the patient must understand the requirements of this service.
- The patient, or a responsible adult must, accept and sign for the delivery; the prescription will not be posted through the door.
- A system for an alternate delivery point must be agreed, with all concerned, in the event that the patient or responsible adult is not at the agreed delivery address.

Alternative delivery address

There are various options available e.g. the prescribing unit, a HTFT in-patient Unit. Please discuss with HTFT Pharmacy Department, Tel: 01482 301732 for suitability.

- If the alternate delivery address has to be used, the pharmacy delivery driver will leave notification at the primary delivery address stating where the medication has been taken. The HTFT Clozapine Dispensing Service will inform the prescribing Unit.
- It is the responsibility of the Case Manager to ensure that the patient has collected their supply should the prescription be delivered to the alternate delivery address.
- If the situation arises where the alternate address is repeatedly being used on the scheduled delivery day, then the option for 'Home Delivery' may be withdrawn and the medication will be delivered to the prescribing unit or another HTFT in-patient unit.

6.2 In-patient supply

Delivery will be made to the ward or inpatient unit where the patient is registered.

7 TREATMENT BREAK AND MISSED DOSES

7.1 General Advice

If a clozapine treatment break occurs for whatever reason:

- Inform CPMS, Tel: 0845 769 8269,Out of hours: Tel:01276 692504 /HTFT Clozapine Dispensing Service
- Refer to CPMS On/Off treatment-Assessment Guideline below.
- Consider the time interval since the previous dose, dosing may continue without re-titration only if it is less than 48 hours as per CPMS guidance.

7.2 On/Off treatment assessment Guideline

Monitoring Frequency	OFF<48 HOURS	OFF>48 HOURS BUT< 7 DAYS	OFF 7 DAYS OR MORE Treatment Break	
WEEKLY	No change to Monitoring Frequency, **continue as normal**	No change to Monitoring Frequency. **Re-titration advice**.	To **Restart** 18 weeks of weekly monitoring. **Re-titration advice**	
Monitoring Frequency	OFF<48 HOURS	OFF>48 HOURS BUT <4 WHOLE DAYS	OFF 4 DAYS OR MORE BUT<28 WHOLE DAYS	OFF >28 DAYS

FORTNIGHTLY & EVERY 4 WEEKS	No change to Monitoring Frequency, **continue as normal**.	No change to Monitoring Frequency. **Re-titration advice**.	**To revert** to Weekly monitoring for 6 weeks and then back to previous monitoring frequency. **Re-titration advice**	To **Restart** 18 weeks of weekly monitoring. **Re-titration advice.**

7.3 Missed doses

- **Advice for patients**

  If a dose is missed, the next dose should be taken at the normal time; do not attempt to make up for the missed dose by giving more.

  Advice for patients on action required upon forgetting to take a dose of clozapine is included in the information on the Choice and Medication website which is accessible for service users. Printable patient information sheets can also down loaded from this site.

- **Requirements for Health Professionals**
  - If less than 48 hours has elapsed since the last dose: the patient may re-start on the last dose taken.
  - If more than 48 hours treatment is missed: inform the patient's psychiatrist as psychotic episodes may start to return before the patient's therapeutic dose can be reached. The patient should be started on 12.5mg a day, with careful dose titration, but titration to therapeutic level may occur at a faster rate than in Clozapine naive patients.
  - Patients who have been taking clozapine for more than 18 weeks and have missed treatment for more than 3 days but less than 4 weeks require extra weekly monitoring for 6 weeks. Patients who have missed over 4 weeks of treatment require weekly monitoring for 18 weeks. Please contact the CPMS for details. CPMS Telephone

  Note there is a requirement for cautious re-titration in any patient who previously experienced respiratory or cardiac adverse effects with initial dosing but was then successfully titrated to a therapeutic dose.

8 RED RESULTS

8.1 Notification of Red result

If a patient's WBC is less than 3.0 x 10^9/L and/or the neutrophil count is less than 1.5 x 10^9/L the result is categorised as a RED alert /result with requirement to**:**

- **Stop clozapine treatment immediately and re-test.**
- Quarantine clozapine tablets.
- Consider clozapine drug-drug interactions.
- Conduct careful psychiatric monitoring of the patient, as symptoms may recur quickly.

Make arrangements to undertake confirmatory blood counts on the 2 days following the date of the red alert sample. If either of these follow up blood counts is in the red alert range then red alert status is taken to be **confirmed.** Follow Section 7.2 Confirmed Red Result.

Consider repeat test at 2 pm or later to exclude reported morning pseudoneutropenia/fluctuating benign neutropenia.

Advice on Red Results is included in the information on the Choice and Medication website which is accessible for service users and includes a printable patient information leaflet.

If an initial red alert is followed by a subsequent (confirmed) red alert the patient becomes clozapine prohibited and treatment must not be re-started.

Neutropenia and agranulocytosis are usually reversible on cessation of Clozapine but agranulocytosis may result in sepsis and can be fatal.

For **Benign Ethnic Neutropenia** ranges and action upon red/amber results see Section 8, Red Re-challenge

Collaboration with HTFT Pharmacy Department and Haematology Department is essential.

- **Responsibilities following a red result/alert**

  Upon receipt of a red result ensure the following people are contacted as soon as possible:
  - Patient (immediately)
  - HTFT Pharmacy Telephone
  - CPMS (if not already aware) CPMS Telephone
  - Named nurse/Team leader/Primary Carer (iPM Case Manager)/Care Home Manager
  - Patient's Supervising Specialist/Psychiatrist or member of his/her team

  And if appropriate: in-patient Duty Doctor or out of hours Duty Doctor.

8.2 Confirmed Red Result

THE PATIENT MUST NOT RE-START CLOZAPINE TREATMENT

- **On-going action required**
  - Check the patient for any signs of infection e.g. fever, chills, fatigue, sore throat or mouth and contact the CPMS as soon as possible.
  - Avoid other antipsychotic drugs, only consider Haloperidol prn if absolutely necessary. See below.
  - Review **all** other medication. Consider clozapine drug-drug interactions. Consider stopping medications with potential to cause neutropenia, consider alternatives if still indicated.
  - Full Blood Counts with Differential should be performed **DAILY** whilst the blood counts remain in the RED range. The results should be reported to the CPMS as soon as they are available.
  - Careful psychiatric monitoring

  The patient should be carefully monitored for flu-like symptoms or any other signs of infection. See Choice and Medication website for a printable patient information leaflet.

  If antipsychotic medication is considered essential use agents with low potential to cause neutropenia and avoid depot preparations. All antipsychotics have potential to cause agranulocytosis but Haloperidol is acknowledged to be associated with the lowest risk. Haloperidol SPC recommends a baseline ECG prior to treatment.

  If clozapine has been withdrawn and *either* a further drop in the WBC count below 2.0 x 10^9/L *or* in the Neutrophil count (ANC) below 1.0 x 10^9/L occurs then the management must be guided by an experienced haematologist. See Section 7.4, Severe Neutropenia – Neutrophils <1.0 x 109/L for more details.

- **Responsibilities following a confirmed red result**

  The Patient's Supervising Specialist, (or member of his /her team), or duty doctor, (if out-of hours), is responsible for care of patient with support from pharmacy, nursing and other clinical staff.

- Observe for infection
- Monitor FBC, BP, pulse and temperature.
- Follow guidance from CPMS and HTFT Pharmacy Department.
- Review mental health and consider physical withdrawal symptoms, (a result of abrupt cholinergic re-bound) throughout the period of clozapine withdrawal; up to 2 weeks. Contact HTFT Pharmacy Department for advice, and also consider prescribing an anticholinergic agent e.g. Procyclidine/ trihexyphenidyl if necessary.
- Review **all** other medication. Consider clozapine drug-drug interactions. Consider stopping medications with potential to cause neutropenia, consider alternatives if still indicated.

8.3 Neutropenia –Neutrophils 1.0-1.5 x 10^9/L

- **Afebrile**
  - Follow advice from CPMS , especially regarding clozapine discontinuation
  - Check daily FBC,CRP-refer to Section 7.4.1 for details
  - Check patient's temperature, pulse and BP as advised or four hourly.
  - Check for symptoms of infection e.g. fever, chills, fatigue ,sore throat or mouth
  - Use standard infection prevention precautions.
  - Conduct careful psychiatric monitoring
  - Dietary Advice; avoid salads, yoghurt, unpeeled fruit, pâté or soft cheese in the patient's diet. Give sterilised milk, water or canned drinks.

- **Febrile**

  Discuss with a Specialist Haematologist

  Haematology Department based at Hull Royal Infirmary can be contacted on a telephone number: 01482 607777.

  Admit to a mental health ward for observations, if not already an in-patient. Consider a transfer to a ward with the facilities to provide care for neutropenic patients. If unable to contact the hospital haematologist immediately please contact a general medical physician and refer to the guidance below:
  - Check the patient's temperature, blood pressure and pulse **FOUR HOURLY.**
  - Nurse in protective isolation, ideally in a single room, taking care to wash hands, wear aprons etc. Explain the reason for isolation to the patient and carer. Remove flowers from the patient's room.
  - Contact infection control for further advice.
  - Follow dietary advice as in Section 7.3.1.
  - Give the patient an antibacterial and antifungal; mouthwash , prophylactically(e.g. chlorhexidine 10ml four times daily and either amphotericin lozenges 10mg four times a day or fluconazole (50mg/5ml) 10ml once daily.
  - If the patient's temperature rises above 38^0C at **any** time, take immediate blood cultures, examine the patient for a focus of infection and take appropriate swabs for MSU etc. Consider intravenous broad spectrum antibiotics as in Section 7.4.2.
  - Conduct careful psychiatric monitoring.

  (continue trying to contact the Specialist Haematologist)

8.4 Severe Neutropenia – Neutrophils <1.0 x 10^9/L

- **Afebrile**
  - Liaise with Haematology, Haematology Department based at Hull Royal Infirmary can be contacted on telephone number: 01482 607777.
  - Admit to a mental health ward if not already an in-patient, consider transfer to a ward with the facilities to provide care for neutropenic patients.
  - Follow any guidance from CPMS
  - Perform daily FBC to monitor neutrophil count until > **1.5 x 10^9/L**

- Check patient's temperature pulse and BP **four** hourly
- **Perform daily C-Reactive Protein (CRP) levels.** These may provide an index to developing infection.
- Monitor U&Es ,e GFR and LFTs to assess renal and liver function
- Nurse patient in protective isolation as in Section 7.3
- Contact Infection Control for further advice
- Conduct careful psychiatric monitoring
- Follow Dietary advice as in Section 7.3

Give granulocyte-colony stimulating factor (G-CSF) *if* advised by haematology Prescribe: stat dose of Lenograstim 236 micrograms once daily subcutaneously and order immediately. Continue until neutrophil count is in the normal range > 2.0 x 10^9/L or as directed by haematology.

Give Fluconazole orally 100mg once daily prophylactically. Continue until neutrophils are > 1.0 x 10^9/L and then discontinue.

Give Chlorhexidine mouthwash 10mls 4 x daily prophylactically. Continue until neutrophils are > 1.0 x 10^9/L and then discontinue.

- **Febrile**

Arrange admission to HRI or nearest acute general hospital, if the patient develops a fever, temperature above 38^0C on a **single** occasion.

The patient's neutropenic and febrile state must be stressed to the admitting Doctor.
Examine the patient for a focus of infection and take appropriate swabs for MSU etc.

Note **CPMS advice**

Check BP and pulse FOUR hourly. Consider taking immediate blood cultures if temperature rises above 38^0C and consider starting IV broad spectrum antibiotics, liaise with acute hospital as it is very important to initiate antibiotics prior to transferring to acute specialist setting. A combination of gentamicin and piperacillin or vancomycin and ceftazidime is suggested.

9 RED RE-CHALLENGE

The Red Re-challenge guidelines have been developed to assist clinicians manage medication and monitoring for a patient undergoing a clozapine re-challenge following a red result and to include management of a subsequent red result.

9.1 Background

The most well recognised side-effects of Clozapine are neutropenia and agranulocytosis. Neutropenia may be defined as a neutrophil count of less than 1.5 x 10^9/L and agranulocytosis is a neutrophil count of less than 0.5 x 10^9/L1.

Development of granulocytopenia and agranulocytosis is a risk inherent to Clozapine treatment. Although generally reversible on withdrawal of treatment, agranulocytosis may result in sepsis and can prove fatal. Because immediate withdrawal of treatment is required to prevent the development of life-threatening agranulocytosis, monitoring of the WBC count is mandatory.

- **Risk factors for neutropenia and agranulocytosis**

  The peak risk for neutropenia and agranulocytosis is between weeks 6-18 and the risk decreases after the first year of treatment. Both neutropenia and agranulocytosis are idiosyncratic reactions and are not dose-related. There is evidence for an increased risk of agranulocytosis with female gender and increasing age.

  Since the mechanism of Clozapine-induced agranulocytosis is not fully understood it is difficult to predict whether factors such as other medications could increase the risk. However, there are case reports of patients receiving carbamazepine and Clozapine concurrently who developed agranulocytosis. Also, surveys of agranulocytosis patients reported to Novartis show that many were receiving concomitant medication, often with drugs that are known to cause agranulocytosis themselves. Hence, Clozapine should not be used with other drugs that are known to depress bone marrow function as these could increase the risk of a patient on Clozapine developing neutropenia or agranulocytosis. Refer also to Section 2.3. Medication review.

  Long-acting depot antipsychotics should not be used with Clozapine as they have the potential to depress bone marrow function and cannot be rapidly removed from the body in the event of neutropenia or agranulocytosis.

- **Blood Results**

The CPMS categorise blood results according to the following colour-coded system: **Colour Alert**	**WBC count x 10^9/L**	**Neutrophil count x 10^9/L**
Green	> 3.5	> 2.0
Amber	3.0 - 3.5	1.5 - 2.0
Red	< 3.0	< 1.5

If a patient has an amber blood result a full blood count must be performed twice weekly until the count stabilises in this range or increases.

Weekly patients who have a blood result which is the lowest seen to date will be assessed by CPMS and an extra sample requested if necessary.

If a patient's WBC is less than 3.0 x 10^9/L and/or the neutrophil count is less than 1.5 x 10^9/L the result is categorised as a **RED ALERT requiring an immediate stop to clozapine treatment and re-test. If an initial red alert is followed by a subsequent (confirmed) red alert the patient becomes clozapine prohibited and treatment must not be re-started.** Refer to Section 7 Red Results for further information.

Neutropenia and agranulocytosis are usually reversible on cessation of Clozapine but agranulocytosis may result in sepsis and can be fatal.

9.2 Benign Ethnic Neutropenia (BEN)

CPMS defines Benign ethnic neutropenia (BEN) as "The occurrence of neutropenia, defined by normative data in white populations, in individuals of other ethnic groups who are otherwise healthy and who do not have repeated or severe infections".

It is not believed that individuals with BEN are at increased risk of infection. The level of neutropenia is usually mild and is not associated with an increased propensity to serious infection. Patients with BEN appear to have a normal response to infection and the outcome of infections appears to be no worse than in control groups.

Clozaril ® SPC states: Patients who have low WBC counts because of BEN should be given special consideration and may only be started on Clozapine with the agreement of a haematologist.

- **Registering BEN patients with the CPMS**
  In order for BEN patients to be registered with the CPMS, a letter is required from the consultant psychiatrist confirming that a haematologist has agreed to a probable diagnosis of BEN

- **CPMS Management of patients with BEN**
  After consultation with an expert haematologist and Novartis offices in other countries with experience in managing BEN patients, the CPMS has altered the traditional monitoring parameters for these patients. The aim is to minimise disruptions to therapy resulting from a normal variant, without compromising patient safety.

BEN CPMS Alert Ranges		
Alert Colour	**WBC x 10^9/L**	**Neutrophils x 10^9/L**
Green	> 3.0	> 1.5
Amber	2.5 - 3.0	1.0 - 1.5
Red	< 2.5	< 1.0

In BEN cases all the ranges have decreased by 0.5 x 10^9/L.
Any patients who develop a red or amber alert within the modified ranges are treated in accordance with standard CPMS procedures.

CPMS state 'There is no definitive diagnostic test for BEN. It is a diagnosis made on clinical judgement, however, before reaching the diagnosis it is important to exclude neutropenia due to infections, mal-absorption, malignant, premalignant and autoimmune disorders and neutropenia secondary to medication or toxins.'

9.3 Clozapine Re-Challenge after Clozapine prohibited

Clozapine re-challenge occurs following previous prohibition of clozapine therapy. Although a confirmed red alert will normally prompt a permanent discontinuation and prohibition of clozapine therapy the potential for benefit of clozapine re-challenge may be considered to outweigh the risk of harm on an individual patient basis. A subsequent diagnosis of BEN also requires special consideration and planning prior to clozapine re-challenge.

Re-challenge should only be undertaken within an inpatient setting.

- **Standard Re-challenge**
  - Re-challenge should only be undertaken within an inpatient setting.
  - An MDT discussion should be held including a member of HTFT Pharmacy Department, HTFT Pharmacy Telephone, to review previous treatments, determine the risk/benefit of potential re-challenge and whether the patient will undergo standard re-challenge or re-challenge under BEN criteria. Where it is not possible for a Pharmacist to attend, the consultant should liaise closely with a member of the Pharmacy team.
  - Where appropriate the opinion of the CPMS and/or a consultant hematologist should be sought, depending on the history of the previous of neutropenia or agranulocytosis.
  - The consultant Psychiatrist should apply to CPMS for consideration of re-challenge. Such treatment is 'off license' and therefore requires consideration of additional responsibilities outlined in the HTFT *Guidelines on the Use of Unlicensed Medications*.
  - After receiving the approval letter from CPMS the consultant Psychiatrist should sign the agreement form and return it to the CPMS in order to list the patient as an approved red re-challenge patient. **Without this form being signed and returned the patient with remain listed as Clozaril® prohibited.**
  - A *Request and Risk Assessment for the Use of Unlicensed Medicines* form should be submitted to the HTFT Drugs and Therapeutics Committee (DTC) should be made for approval to use clozapine 'off license'. Refer to HTFT Guidelines for Unlicensed

Prescribing . This should be sent with a copy of the CPMS approval, an individualised care plan and any other relevant supporting correspondence.
  - An individual care plan to be discussed at MDT and to be authorized prior to initiation of clozapine.

- **Benign Ethnic Neutropenia Re-challenge**

  Patients with diagnosed Benign Ethnic Neutropenia (BEN) may be considered for treatment or re-challenge with Clozapine, with the agreement of a haematologist. **Haematology Department based at Hull Royal Infirmary can be contacted on telephone number: 01482 607777**.

  In order for BEN patients to be registered with the CPMS, a letter is required from the consultant psychiatrist confirming that a haematologist has agreed to a probable diagnosis of BEN.

  In addition to the requirements 1 to 7 for standard re-challenge a copy of the letter from the haematologist supporting a probable diagnosis of BEN must be supplied with the *Request and Risk Assessment for the Use of Unlicensed Medicine*. Refer to HTFT Guidelines for Unlicensed Prescribing.

  For further information regarding the use of Clozapine in patients with BEN contact HTFT Pharmacy Department for advice.

9.4 Red Re-challenge care plans

A individual care plans must be discussed at MDT and finalised for submission to HTFT DTC with the *Named Patient Medication Approval Form* *for* standard re-challenge or BEN re-challenge.The patient specific care plan is required to clearly state:

- What should happen in the event of a red alert and in the event of the patient becoming neutropenic (Neutrophil <1.0 x 10^9/L or 0.7 x 10^9/L of BEN or WBC 2.0 x 10^9/L or if patient develops fever)
- Whether the patient is undergoing standard re-challenge or has a probable diagnosis of BEN confirmed by a haematologist.
- A requirement to follow CPMS advice.
- A specific threshold at which clozapine should be stopped.
- The physical observations to be undertaken including monitoring for sore throat and fever.
- The threshold at which to notify the haematologist of blood results and in event of patient developing fever.
- The threshold for initiation of G-CSF.
- The requirement for collaborative discussion with haematology regarding initiation of G-CSF following a red alert.
- Specifically when to contact haematologist to discuss further G-CSF doses.
- Chlorhexidine mouthwash (10ml four times daily) and fluconazole 50mg/5ml 10ml once daily suspension (anti-fungal) are to be prescribed in event of neutropenia or fever.
- G-CSF is to be kept at the in-patient unit and how many doses may be stored.
- GCSF is to be prescribed in prn section of the Medicines Administration Record Card (MAR). In indication/ special direction box add “as per care plan”.
- G-CSF is to be dispensed as a non- stock item supplied with a patient specific label.

In addition the care plan should

- Specify that all medications are to be obtained from, HTFT Clozapine Dispensing Service, immediately after prescribing
- Detail that all discussions with haematologist are to be recorded in the patient’s medical notes and that the CPMS is to be kept up-to-date.

- Note: off license use of G-CSF, should only be used in collaboration with haematologist on a specific patient basis, with requirement for care plan approval under HTFT policies. G-CSF of choice is lenograstim 263 mcg stat dose (33.6 million-unit; **non** weight adjusted).

10 TRANSFERS AND DISCHARGES

10.1 Transfer of a patient prescribed clozapine to another trust

The Named Nurse, Case Manager or Care Home manager is responsible for:

1. Ensuring that the CPMS (Telephone) are informed of all details either when transferring a patient.
2. Informing the HTFT Clozapine Dispensing Service of the transfer.

- **Acute Hospital admission**

  - If a patient has been admitted to an acute hospital the HTFT Clozapine Dispensing Service will need to liaise with the hospital to ensure continued safe management of clozapine if appropriate.
  - If an admission is planned for surgery with General Anaesthesia then contact HTFT Pharmacy Department for advice.
  - Consider requirement for Clozaril® Change of Patient Details Form

10.2 Receipt of a patient prescribed Clozapine from another trust

The Named Nurse, Primary Carer,(iPM Case Manager), or Care Home manager is responsible for following points 1+2 as above **and to ensure that in addition:**

- If a patient is transferred receiving an alternate brand of Clozapine that the treatment is changed to the Clozaril® brand before the next supply is required.
- The patient will be registered with a Supervising Specialist/Psychiatrist within the trust.
- Patient Registration with CPMS for Clozaril® treatment is completed. Section 1.3 Patient Registration
- If the patient is currently monitored by an alternative clozapine supplier contact CPMS. (CPMS Contact details)
- The patient will be de-registered from the alternate supplier of clozapine.

Refer to Section 4.1In-Patient supply

10.3 Transfer of a patient within the Trust

- Inform the HTFT Clozapine Dispensing Service of the transfer.
- Ensure the current Supervising Specialist/psychiatrist is known by CPMS.
- Consider requirement for Clozaril® Change of Patient Details Form

10.4 Discharge to home

Follow points 1 & 2 contained in section 9.1 above also:

- Contact the HTFT Clozapine Dispensing Service for advice regarding supplies for patients going on leave or being discharged. It may be necessary to send back tablets before the HTFT Clozapine Dispensing Service issue any leave or discharge clozapine as additional supplies may not be made.
- Liaise with the Community team to ensure the next appropriate supply is made (dictated by the current interval between blood tests, refer to Section 4.1 Monitoring frequency and associated supply) and the correct delivery address is used.
- Consider requirement for Clozaril® Change of Patient Details Form

Arrangements *may* be made with the HTFT Clozapine Dispensing Service for Out-patients to have their Clozapine delivered to their home/relative/friend's address or their place of work. This is referred to as "Home Delivery Service."

- This must be a secure and safe system and the patient must understand the requirements of this service.
- The patient, or a responsible adult must, accept and sign for the delivery; the prescription will not be posted through the door.
- A system for an alternate delivery point must be agreed, with all concerned, in the event that the patient or responsible adult is not at the agreed delivery address.

Regarding delivery address, there are various options available e.g. the prescribing unit, a HTFT in-patient Unit. Please discuss with HTFT Pharmacy Department, Tel: 01482 301732 for suitability.

- If the alternate delivery address has to be used, the pharmacy delivery driver will leave notification at the primary delivery address stating where the medication has been taken. The HTFT Clozapine Dispensing Service will inform the prescribing Unit.
- It is the responsibility of the Case Manager to ensure that the patient has collected their supply should the prescription be delivered to the alternate delivery address.
- If the situation arises where the alternate address is repeatedly being used on the scheduled delivery day, then the option for 'Home Delivery' may be withdrawn and the medication will be delivered to the prescribing unit or another HTFT in-patient unit.

11 CONTACT DETAILS

eCPMS: www.clozaril.co.uk

Service	Telephone Number	Out of Hours
CPMS	0845 769 8269	01276 692504
HTFT Pharmacy Department	01482 301732	
Clozapine Clinic Miranda House	01482 617553	
HTFT Clozapine Dispensing Service	Miranda House: 01482 617553 Pharmacy Procurement: 01482 301732	

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13 CLOZAPINE THERAPY MANAGEMENT PLAN

Name		**Date of Birth**	**Consultant**
NHS Number		**Gender**	**Care-co**
CPMS Number			

……...has been prescribed Clozapine, the risks, benefits and possible side effects of which have been explained to them by the prescribing doctor. Patient Information leaflet link

As part of this therapy,……..…undertakes to attend Clozapine Clinic for monitoring at intervals in accordance with the Clozaril Patient Management Service (CPMS)

At each attendance the following will be carried out and recorded:

- A blood sample will be taken by a trained phlebotomist.
- The sample will be tested for a differential White Cell count either in the department on the Point of Care Haemotology (PoCHi) machine, or posted to the CPMS laboratory.
- When using PoCHi, the result will be passed electronically to CPMS who analyse the result (ie white cell count in relation to the neutrophil count) and give an immediate determination of either ‘green’ (treatment may continue), ‘amber’ (treatment may continue with special precautions) or ‘red’ (treatment must be stopped). See over.
- If the sample is posted to CPMS the result will automatically be posted on the CPMS website by Thursday of that week. Adverse results will be reported by telephone for immediate action
- Sitting and standing Blood pressure(BP)
- Temperature.
- Weight and waist measurement
- Pulse.
- Side effects monitoring.
- Some patients will be able to receive their next supply of Clozapine from the clinic.
- Appointment card will be provided with the next due date

Every year, they will be offered a full blood screen and an ECG test.
It is an expectation that,…….will:

- Attend the clinic on the due date, or call to re-arrange if unable.
- Take Clozapine as prescribed.
- Liaise with their assigned mental health team worker or the clinic staff directly regarding any concerns.
- Tell the clinic staff of any holiday plans.
- Tell the clinic staff if they stop (or start) smoking.
- Inform staff if they have not taken their Clozapine for any reason.
- Inform staff if they do not have enough Clozapine.
- Carry an information card in case of medical emergencies

The clinic staff undertake to:

- Forward the monitoring results to their prescriber every 6 months or after 6 attendances (whichever is sooner)
- Send copies of same to the GP.
- Attend your CPA review where possible.
- Make the patient aware of any changes to clinic times because of bank holidays etc.
- Give the patient the opportunity to discuss their physical health as required.

Signed…….(The patient)
Signed…….(Clinic staff)

Green result	Treatment regime may continue uninterrupted
Amber result	Telephone contact will be made between clinic and CPMS who will determine the necessary procedure. This usually involves a retest within a few days, and the uninterrupted continuation of Clozapine.
Red result	The sample will be tested twice to verify the result and CPMS contacted, who will usually advise that Clozapine treatment must be stopped immediately. (Your doctor may wish to prescribe you an alternative) You will be asked to return for another blood sample to be taken and tested for the next 2 days.

<u>Useful Telephone Numbers</u>

Name	Telephone Number	Hours
Miranda House Clozapine Clinic	01482 617553	07.00-14.30 every day except Wednesday and weekends.
Insert local contacts		
Insert local contacts		