Sussex Partnership
NHS Foundation Trust

Use of Clozapine in In-Patient Units Policy

(Previously Procedure and Guidance for the Use of Clozapine Version 2.3)

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POLICY SPONSOR	Chief Medical Officer
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EXECUTIVE SUMMARY:

Clozapine is an antipsychotic medication that is prescribed for treatment resistant schizophrenia for which it has a good evidence base. Research shows it is often more effective than other antipsychotics. However, it has side effects that need close monitoring including neutropenia (low levels of white blood cells that can affect ability to fight infection) which can lead to agranulocytosis - an acute and severely low level of white blood cells which can be fatal. Constipation is a very common side effect which if unmonitored or untreated can cause bowel perforation and death

This policy is intended to be used in all situations where treatment with clozapine is initiated and continued in the community settings. This policy is for all health care staff who are involved in any aspect of prescribing, supplying, administering or monitoring clozapine. It ensures that patients receive clozapine appropriately, safely and effectively and manages the risk that clozapine can pose to them.

If you require this document in another format such as large print, audio or other community language please contact the Corporate Governance Team on: 0300 304 1195 or email: policies@sussexpartnership.nhs.uk

Did you print this document yourself?

Please be advised that the Trust discourages the printing and retention of hard copies of policies and can guarantee that the policy on the Trust website is the most up-to-date version.

As a contingency a full set of up-to-date Trust policies are held by the Corporate Governance Team based at Trust HQ, Swandean

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1. Introduction

1.1. Purpose of the policy

This document sets out the practice criteria to be followed by all Trust healthcare professionals for the prescribing, administration, side effect management and monitoring of clozapine in inpatient units. The aim of this document is to enable the safe and effective use of clozapine in the Trust in the treatment of mental illness.

1.2. Definitions/Glossary

DMS (Britannia, Nov 2019)
Denzapine Monitoring Service. Telephone number: 0333 2004141.
Website: https://www.denzapine.co.uk/

Named Supply
Dispensed from pharmacy with the individual patient's name on it. Administration of clozapine must be from the named supply. It is a serious medication error to dispense from another patient's supply.

Agranulocytosis
A severe lack of one major class of infection-fighting white blood cells. People with this condition are at very high risk of serious infections due to their suppressed immune system.

Neutropenia
Abnormally low levels of white blood cells called neutrophils

White blood cells (WBCs) and neutrophils
WBCs are an important part of the immune system, they help fight infections by attacking bacteria, viruses, and germs that invade the body. White blood cells originate in the bone marrow but circulate throughout the bloodstream. There are five major types of white blood cells: neutrophils, lymphocytes, eosinophils, monocytes and basophils

Green Result
WBC more than $3.5x10^9$/L and neutrophils more than $2.0\ x10^9$/L and no decreases of more than 10% or repeatedly decreasing values in the previous test(s).
Clozapine may be prescribed and dispensed.

Amber Result
WBC $3.0\text{-}3.5\ x10^9$/L and/or neutrophils $1.5\text{-}2.0\ x10^9$/L.
If the patient's medical condition is satisfactory, clozapine treatment may continue. The DMS will contact the registered consultant and telephone clozapine supply service and request twice-weekly samples until counts stabilise or increase.

Red Result
WBC less than $3.0\ x10^9$/L and/or neutrophils less than $1.5\ x10^9$/L and/or platelets less than $50\ x10^9$/L.
Clozapine treatment must be stopped immediately and all supplies of clozapine removed from the patient. DMS will contact the registered consultant and telephone clozapine supply service to inform them of this, and to request that a further blood sample is taken urgently and analysed locally. The patient should be monitored for signs of infection and further blood tests will need to be taken daily until a green result has been achieved. If either of the blood tests on the following 2 days produce a red result, this will be deemed a confirmed red result. The patient should not routinely be re-exposed to clozapine.

Yumizen machine
A machine that provides rapid blood test results on site.

1.3. Scope of the policy

This policy is intended to be used in all situations where treatment with clozapine is initiated and continued in inpatient units. This policy is for all health care staff who are involved in any aspect of prescribing, supplying, administering or monitoring clozapine. It ensures that patients receive clozapine appropriately, safely and effectively and manages the risk that clozapine can pose to them.

1.4. Principles

Clozapine is an atypical antipsychotic licensed for treatment resistant schizophrenia. The Medicine and Healthcare Products Regulatory Authority (MHRA) has restrictions on its prescribing, which includes extensive monitoring (especially white blood cell [WBC] counts). Failing to follow correct procedure could result in harm to patients.

1.5. Training Expectations.

1.1.1. A full understanding of the Clozapine Policy for community teams is essential for all qualified staff working in inpatient units that may be called upon to prescribe and/or administer clozapine.

1.1.2. It is deemed **essential** that all qualified medical and nursing staff working in inpatient units complete the mandatory training for medication management which includes clozapine within this.

1.1.3. The responsibility to ensure adequate training is undertaken lies with ward managers and modern matrons (for nursing staff) and with consultants and local tutors (for medical staff) and should extend to include locum, agency and bank staff.

1.1.4. Nursing staff working in inpatient units in substantive or 'bank' posts will undertake clozapine training as part of their Medicines Management Update day. Ward managers and matrons will ensure that each member of their nursing staff has undertaken and successfully completed the e-learning module. Newly qualified staff will also be expected to pass the Medicines management competencies as outlined in the Trust Preceptorship Policy.

2. POLICY STATEMENT

Clozapine is an atypical antipsychotic licensed for treatment resistant schizophrenia (NICE Feb 2014). The Medicine and Healthcare Products Regulatory Authority (MHRA) has restrictions on its prescribing, which includes extensive monitoring (especially white blood cell [WBC] counts). Failing to follow correct procedure could result in harm to patients. Therefore, it is important that Trust staff are appropriately trained and supported in order to ensure the safe administration of clozapine and the monitoring of its effects on the patient.

3. DUTIES OF THE STAFF GROUPS

INDIVIDUAL/GROUP	RESPONSIIBILTY
Policy committee/Drugs and Therapeutics committee	• This is the group that ratifies this policy ensuring the development of the clozapine policy to reflect current practice within the Trust
Chief Pharmacist	• Is accountable for establishing and maintaining a safe and secure system for medicines management throughout the Trust • Is responsible for reporting to Trust wide Clinical Governance Group in relation to medicines management

Clinical Directors/Leads and Service Directors/Leads	• Are responsible for ensuring that their staff are aware of this policy
Service Manager	• Ensure provision and governance arrangement around clozapine clinics or alternatives • Ensure allocation of a Lead Practitioner in addition to the Prescribing Consultant
Prescribing Consultant - some of these can be delegated to other prescribers in the team:	• Discuss benefits and side effects of clozapine with patient and carers • Arrange baseline blood and QTc measurements, register patient with clozapine provider and ensure adequate arrangements if being commenced in community • Ensure dosage is correct and provide prescriptions as requested by pharmacy • Review at least annually usually face to face, by phone or by digital depending on patient circumstances • Ensure that the service provides the patient with an annual physical health check, annual serum clozapine level and an annual GASS-C and review these to ensure ongoing prescribing is safe • Review clozapine dose in relation to side effects, clozapine levels or at the request of the Lead Practitioner, Clozapine Clinic or pharmacy • Inform DMS of any changes to the patient's named consultant • Ensure the patient's GP is informed when starting clozapine and any changes. This should be included in the discharge summary.
Lead Practitioner (when a patient is admitted to a ward many of these tasks will be performed by the wards staff)	• Support the Clozapine Clinic or patient directly to ensure that Full Blood Counts are taken regularly at required frequency and medication is supplied if results are green • Devise care plan jointly with patient, family and care provider addressing side effects and to reflect any changes in care needed if the person becomes constipated, changes their smoking pattern or has amber or red blood result. • Contact the patient taking clozapine regularly to review the above monthly • Ensure the patient has an ALL- physical assessment completed on Carenotes each year (including smoking status, weight/ BMI, Hba1c and Lipid Profile) • Ensure the person has an annual serum clozapine level or more frequently if significant side effects or a change in smoking habit if necessary if conjunction with prescribing consultant • Ensure a GASS-C is completed at least annually • Liaise with the acute hospital and clozapine coordinator if the patient is admitted to hospital
Clozapine Clinics	

Some areas have clozapine clinics which take over some of the roles of the Lead Practitioner. Functions will depend on staffing. This can include taking bloods and dispensing medication if green result. Some clinics may assist in completing the annual physical health check	• Ensure any on site equipment such as Yumizen machines are calibrated and working properly • To ensure that clozapine is stored in a separate cupboard when quarantined pending a FBC result • To take a blood sample and analyse via the Yumizen machine • To confirm the result and upload this onto the DMS database and get a confirmed RED/AMBER/GREEN result • To give the patient a supply of clozapine based on the result • To send off a blood sample for plasma assay analysis if any side effects are reported, suspected non-adherence or requested by the supervising community team • Make an entry on Care Notes to indicate patient attendance (either by making a clinical note or as a diary appointment), include a brief summary of the person's clinical presentation. • Liaise with Lead Practitioner if the patient does not attend their appointment for regular blood tests • Check for a current green result and for any dose change before dispensing the medication • Screen for significant side effects, constipation (including red flag signs) or changes to smoking and alert Lead Practitioner if concerned • Liaise with Lead Practitioner and prescribing consultant if any abnormal blood results
Clozapine supply service	• To provide support and advise other healthcare professionals on pharmaceutical matters that need to be considered when prescribing, monitoring or administering clozapine. • To assist and advise on the development of policies and procedures to ensure safe, appropriate and timely patient selection, prescribing, monitoring, administration and supply of clozapine. • To check that suitable blood results are available before supplies of clozapine are made. • To arrange delivery/collection of dispensed supplies according to each individual patient's schedule. • To provide a medicines information service for professionals, patients and carers. • To liaise with manufacturers and national medicines safety agencies to maintain a sound knowledge base on the use of clozapine for patients cared for by the Trust. • The patients existing medication is reviewed by the team or ward pharmacist. Some drugs will need to be discontinued e.g. carbamazepine and antipsychotic depot injections.
Medicines management team	• To monitor the safe and effective use of clozapine by checking the accuracy of prescriptions. • To advise on all aspects of clozapine therapy, and interpret and advise on the appropriateness of prescriptions, interactions, management of side effects and contraindications • Advise patients on the use of clozapine. The choice and medication website may be used as a resource • Monitor the dispensing and supply of clozapine • To follow up and advise on late blood tests

	• Are responsible for ensuring that their staff are aware of this policy • To deliver medicines management training to all health care professionals working within the lead practitioner and care co-ordinator roles. This will include specific details on clozapine including indications, contra-indications, side-effects and red flag events that could occur as a consequence of treatment with clozapine.
Patient responsibilities	• To report any side effects, signs of constipation, illness or signs of infection as soon as possible to the team. • To inform the team if running low of clozapine • To inform team of any changes to the treatment • Arrange prior to going away on holiday the procedure for blood tests and clozapine supply with the team.

4. POLICY AND PROCEDURAL PRACTICE

4.1. Decision to treat

4.1.1. Before initiating a patient on clozapine

Ensure the following is carried out

- Complete the pre-clozapine checklist (appendix 1) and upload to Carenotes labelled as 'pre-clozapine checklist'.
- A full psychiatric and medical history.
- Checking that there are resources available to provide safe clozapine treatment, including ongoing supply and support on discharge.

4.1.2. Indications

The licensed indications for clozapine are:

- Treatment resistant schizophrenia defined as a lack of satisfactory clinical improvement despite the use of adequate doses of at least two different antipsychotic agents, including an atypical antipsychotic agent, prescribed for adequate duration (Brittania, Nov 2019).
- In schizophrenia patients who have severe, untreatable neurological adverse reactions to other antipsychotic agents, including atypical antipsychotics.
- Psychotic disorders occurring during the course of Parkinson's disease, in cases where standard treatment has failed

4.1.3. Unlicensed (off label) use of clozapine

- For unlicensed use refer to the Trust Medicines code (Use off unlicensed medicines). https://www.sussexpartnership.nhs.uk/node/1430/attachment
- The consultant psychiatrist for an individual patient must accept clinical responsibility for any unlicensed/off-label use of clozapine.
- The Denzapine Monitoring Service (DMS) must be contacted prior to unlicensed prescribing by the consultant, regarding the correct procedure to be followed. An 'off-label treatment agreement' form, available from the DMS website, should be completed.
- Clozapine is unlicensed for use in children under the age of 16 years. The Trust will support the appropriate use of clozapine in children under the age of 16 years and adolescents, if they fulfil the indications.
- Unlicensed clozapine can be used when a patient is prohibited due to not obtaining a valid green result. This needs to be considered by the Trust ethics committee and therefore must be discussed as soon as possible to allow the off label use to be agreed.

4.1.4. Contraindications to the use of clozapine

- Full details of contraindications can be found on the Denzapine® SmPC (www.medicines.org.uk)

4.1.5. Special precautions for the use of clozapine

Refer to the Denzapine® SmPC for a full set of special precautions in the use of clozapine (www.medicines.org.uk).

4.1.6. Interactions with clozapine

Refer to the Denzapine® SmPC for a full set of special precautions in the use of clozapine (www.medicines.org.uk).
Refer to the Denzapine® SmPC for an exhaustive list of interactions with clozapine. All healthcare professionals responsible for prescribing medication to clozapine treated patients should be aware of potential drug interactions. It is the prescriber and pharmacists validating the prescriptions responsibility to ensure that all medications prescribed for the patient do not cause significant interactions with clozapine.

4.2. Standards for prescribing

4.2.1. Prescriber

- The **initiation** of clozapine in the Trust is restricted to consultant psychiatrists registered with DMS. Nominated pharmacists and patients must also be registered. DMS can be accessed via https://www.denzapine.co.uk/
- For **ongoing prescribing**, clozapine is normally prescribed by the patient's consultant psychiatrist, but may be prescribed by another registered medical practitioner or non-medical prescriber involved in the care of the patient.
- The named consultant is responsible for ensuring that all required physical health checks and side effect monitoring is carried out at initiation.
- Whenever the care of a patient is transferred then the new details of the patient's consultant must be communicated to DMS
- Complete a HDAT form (https://www.sussexpartnership.nhs.uk/node/1577/attachment) if required.
- Ensure the patient's GP is informed when starting clozapine and any changes.

4.2.2. Prescribing

- Ensure consent and capacity has been assessed before starting clozapine.
- Ensure prescribing is covered by the relevant MHA paperwork when required.
- Once a GREEN result (see below) has been given clozapine can be prescribed on an inpatient titration chart for initiation.
- Where a patient has been admitted on clozapine the dose and adherence must be verified before prescribing. Please note clozapine does not always show on the GP Summary Care Record.
- Clozapine needs to be prescribed on one of the standard inpatient's titration charts or on the Drug prescription and Administration Chart.
- Any prescription outside of the standard charts will need to be clinical screened by a pharmacist prior to dispensing of clozapine
- Make reference to the titration chart on the main prescription chart.
- Consider special precautions or co-morbidities (see SmPC www.medicines.org.uk) and consider using a slow inpatient titration if required.
- Review the current prescription; consider any interactions (see SmPC www.medicines.org.uk) reduce or stop medication as necessary.
- Complete a HDAT form (https://www.sussexpartnership.nhs.uk/node/1577/attachment) if required.

4.2.3. Titration charts

Standard Inpatient titration chart (Appendix 2)

- Gradual titration and a divided dosage regime for clozapine initiation are necessary to minimize the risks of hypotension, seizure, and sedation. The Trust titration chart for in-patient clozapine initiation is shown in appendix 2 with an initial daily dose of 12.5mg. The usual minimum effective clozapine dose is around 300mg, which is normally reached two to three weeks after starting.

Slow Inpatient titration chart (Appendix 3)

- When a patient has co-morbid medical conditions or clozapine is being used for the indication of psychosis in Parkinson's disease or the patient has not tolerated the standard titration then the slow titration chart should be used.
- If problematic side effects occur, consider slower dose titration or decreasing dose to one previously tolerated or use the slow titration chart.

Quick Inpatient titration chart (Appendix 4)

- When a patient has previously been on clozapine and tolerated a normal titration a quick titration sheet can be used. This should only be used where the person is fit and well with no other co-morbid conditions.

4.2.4. Dose changes

- At the end of the titration the dose should be written on the Drug prescription and Administration Chart.
- Target dose must be adjusted according to effectiveness, side effects and plasma levels but also consider the expected target ranges
    - Target doses female non-smoker = 250mg/day
    - Male non-smoker = 350mg/day
    - Female smoker = 450mg/day
    - Male smoker = 550mg/day.
- Dose should not be increase more than 50mg - 100mg a week (maximum 50mg per dose), unless the patient is known to tolerate the higher does. Above 600mg enzyme saturation is more likely and increases should be slower.

4.3. Standards for administration

- Ensure consent and capacity has been assessed before starting clozapine.
- Ensure prescribing is covered by the relevant MHA paperwork when required.
- Clozapine needs to be prescribed on one of the standard inpatient's titration charts or on the Drug prescription and Administration Chart.
- Once a GREEN result (see below) has been given and the clozapine has been supplied for that patient as a named patient supply it can be administered.
- Another patient's clozapine should not be given unless this has been agreed with the local pharmacist or the on-call pharmacist (see emergency supplies below)
- The administration should be endorsed on the titration chart or on the Drug prescription and Administration Chart (where there is no Titration chart).
- Ensure monitoring is carried out, hourly for the first 6 hours, then twice a day during titration and recorded on the NEWs2 clozapine form.
- Postural drops will not be picked up on the NEWs2 form - if there is concerns or side effects such as dizziness then postural drops should be monitored.
- Ensure the clinical response is actioned as specified on the NEWs2 form to Total scores above 1 or if one parameter is above 3, (see NEWs2 form for advice appendix 6)
- If the first dose is given at night only AVPU monitoring is required for the first 6 hours.
- Complete the inpatient monitoring form for clozapine (appendix 7) daily whilst the clozapine is being titrated.

- If a medicine is no longer required, then with the patient's or their relatives' consent or a best interest decision, the medicines must be disposed of safely in a medication waste bin and the consent or best interest decision recorded in the patient's care notes.

4.4. Emergency supply of clozapine

- Ward staff should make sure clozapine is ordered from the pharmacy in a timely manner after routine blood tests, to ensure continuity of supply.
- If a patient requires clozapine out of hours, then the following process should be followed
    - The on-call pharmacist must be contacted who will check on the patient monitoring service website and confirm the current blood result for the patient.
    - If the patient has a current green result then the pharmacist will give permission for another patient's supply or the emergency clozapine supply to be administered.
    - The emergency supply of clozapine should be recorded on the emergency supply form.
    - To replace the emergency clozapine supply, contact your pharmacy team.

4.5. Clozapine for psychosis in Parkinson's disease (PD)

- Clozapine is licenced for use in Parkinson's disease. The dose tolerated is much lower, with a usual starting dose of 6.25mg and then a slower titration. The target maintenance dose is normally between 25mg and 50mg. Pharmacy can be contacted for a bespoke clozapine titration form.
- The decision should be an MDT one involving the patient, carer, consultant psychiatrist, GP, PD consultant, PD specialist nurse and pharmacist is required when initiating clozapine for Parkinson's disease.
- Co-morbidity is more prevalent and the necessary physical health checks must be carried out.

It is necessary to monitor BP for a few days prior to commencing clozapine treatment (ambulant BP monitor) to check for significant autonomic instability.

4.6. Guidance for managing clozapine for patients admitted to acute hospitals

- When patients are admitted to any acute Trusts who are prescribed clozapine it is important to inform the Clozapine supply service as soon as possible.
- All patients prescribed clozapine admitted to the acute trust should be referred to the liaison psychiatry team for ongoing monitoring.
- Key messages include
    - Check adherence to clozapine, if non-adherence for over 48 hours then clozapine needs to be re-titrated
    - Confirm dose and brand, GP summary care records don't always have clozapine recorded on the system
    - Clozapine risk of constipation and neutropenia
    - Interactions with other medications particular antibiotics and smoking
- See for https://www.sussexpartnership.nhs.uk/node/4526/attachment for more details

4.7. Risk Management

4.7.1. Monitoring

4.7.1.1. Blood Monitoring

- Clozapine can cause a reduction in the number of white blood cells in a minority of people and regular blood sampling is required as set out in the SmPC www.medicines.org.uk
- **Pharmacy will not dispense clozapine unless there is a valid blood test result, unless there is an agreed quarantine procedure.**

- In the UK, a white cell count with a differential count must be monitored:
  - One blood test within the 10 days prior to starting clozapine
  - At least weekly for the first 18 weeks of treatment
  - At least fortnightly between weeks 19 and 52
  - After 1 year of treatment with stable neutrophil counts, patients may be monitored at 4-week intervals
  - Monitoring must continue during treatment and for at least 4 weeks after stopping as specified in the SmPC www.medicines.org.uk

- Blood monitoring must be completed as per the schedule and either sent to
  - A Local pathology laboratory
  - A local Yumizen machine (where agreement has been sort)
- A grey/white **blood pack** should be used for blood samples that are sent to DMS for full blood count analysis (routine blood monitoring). This blood pack can be ordered from SPIRE direct by calling 020 8238 6830.
- DMS provides an alert system which gives guidance on the suitability of each patient's blood result for dispensing by assigning a traffic light alert color scheme. These are as follows:

Blood cell count		**Action required**
WBC/mm^3 (/L)	**ANC/mm^3 (/L)**	
GREEN **≥3500 (≥3.5 x 10^9)**	**≥2000 (≥2.0 x 10^9)**	**Continue clozapine treatment**
AMBER ≥3000to <3500 (≥3.0 x 10^9 to <3.5 x 10^9)	**≥1500 to <2000 (≥1.5 x 10^9 to <2.0 x 10^9)**	**Continue clozapine treatment, sample blood twice weekly until counts stabilise or increase**
RED <3000 (<3.0 x 10^9)	**<1500 (<1.5 x 10^9)**	**Immediately stop clozapine treatment, sample blood daily until haematological abnormality is resolved, monitor for infection. Do not re-expose the patient.**

4.7.1.2. Missed blood tests

- If a patient has missed the regular day for their blood test and is close to becoming prohibited, a sample must be sent urgently to a local acute hospital trust pathology department for testing. It is the responsibility of the ward to arrange this.
- **A postal (DMS/Spire) blood testing kit must not be used for missed bloods, red or amber results. A point of care testing (Yumizen) machine or the local pathology laboratory must complete the testing.**
- A Full Blood Count must be requested on a hematology form. Details of the patient must be fully completed also include:
  - Urgent
  - Patient on clozapine
- Please phone the Clozapine Supply Service at Worthing General on 01273 446091 or email uhsussex.pharmacyclozapine@nhs.net or the Trust's on call pharmacist if out of normal working hours. Inform them the bloods have been taken and where they are being analysed.
- DMS will require the following to provide a result:
  - Patient Name
  - Date of Birth
  - DMS Number
  - Sample Date
  - White blood cell count
  - Platelet count
  - Neutrophil count

- When a blood test is sent for analysis at a local pathology lab, the name of the hospital and the time/date the sample was taken should be recorded in Carenotes.
- Importantly the ward will need to inform the Clozapine Supply Service at Worthing General that the blood is being tested locally and at which pathology lab or it can also be tested at a Yumizen machine.
- The blood test results should be either entered by staff with access to the DMS website or communicated to the team pharmacist or in their absence the Clozapine Supply Service at Worthing General Hospital. Out of hours the on-call pharmacist will enter them.
- Once a green result has been given, pharmacy can supply the medication or an emergency supply can be agreed.
- If a blood test has been missed, pharmacy, under the advice of DMS, may be able to supply a few days' supply of clozapine, providing there is a valid green result to cover that period.
- An unlicensed use could be considered but only after agreement with the senior pharmacy team, the consultant and an off label form has been approved by Denzapine

4.7.1.3. Therapeutic drug monitoring – Clozapine levels

- Metabolism of clozapine will vary greatly between individuals therefore it is difficult to predict the therapeutic dose of clozapine for a given patient. The clozapine dose prescribed should be based on the patient's clinical presentation and clozapine plasma level (Flanagan RJ, 2006).
- Clozapine plasma levels should be taken to ensure that a therapeutic level has been reached and when the dose of clozapine is increased.
- Clozapine plasma levels should be monitored on an annual basis. Consider more often in patients with dose related risk factors such as metabolic syndrome (i.e. type 2 diabetes, metabolic syndrome or those with a BMI over 30 kg/ m2) or with high plasma levels (see appendix 11 for more details).
- Additional clozapine plasma levels may be useful when:
  - Dose changes (increase or decrease)
  - When non-adherence is suspected
  - If a patient is experiencing side effects which are likely to be dose related (constipation, sedation or hypersalivation)
  - When response to an adequate dose seems poor
  - When high doses are being used
  - If the patient is prescribed hepatic enzyme inducing/inhibiting medications (see appendix 13)
  - If a patient changes their smoking habits their plasma levels of clozapine can rise by up to 70% when a patient stops smoking. This is because the induction of hepatic enzyme is caused by hydrocarbons in the smoke is no longer present. The levels will rise when a patient stops smoking or swops smoking for e cigarettes or Nicotine Replacement therapy as these agents do not contain hydrocarbons.
- Plasma levels can take several days or weeks to return. If there is any concern about side effects, then the dose should be reduced prior to receiving the plasma level result.
- When a plasma level is order or it is the yearly test the plasma level must be followed up by the responsible clinician and acted upon as soon as possible. Results from ASI should be copied into care notes in the medication tab, labelled with clozapine plasma levels and dated.
- Higher plasma levels increase the risk of seizures and other adverse drug reactions (>0.6mg/l is associated with an increased risk of seizures), though there is a great deal of individual variability. The usual indicated therapeutic range is **0.35 – 0.6mg/l**, with values >1mg/l requiring consideration of cautious dose reduction and physical health monitoring and consider seizure prophylaxis.
- For details of how to take plasma blood samples and how to interpret plasma results see appendix 11

4.7.2. Physical health monitoring

- Physical health checks must be completed as per appendix 6
- This should be completed on an ALL - physical assessment form on care notes. This is to determine the risk of metabolic syndrome as clozapine patients are at an increased risk of both cardiovascular disease and diabetes.
- If a patient does not wish to have a physical health check then this must be documented in their Carenotes records and the patient should continue to be offered.
- Smoking status, alcohol and illicit drug use must be established and relevant health promotion advice offered.
- Advice on preventing and treating constipation must also be offered.
- Discuss risk of stopping laxatives and the increased risk of partial or full bowel obstruction. Lifestyle factors contributing to overall health such as diet and exercise should be considered and relevant advice given and documented.
- Results of physical health checks must be forwarded to the SPT consultant/discussed in MDT reviews.

4.8. Clozapine adverse effects

4.8.1. Serious adverse events

Any drug may produce unwanted or unexpected adverse reactions. Detection and recording of these are important. Adverse reactions should be reported to the Medicines and Healthcare Products Regulatory Agency (MHRA). Doctors, pharmacists, nurses and patients are all eligible to report. Pre-paid yellow cards for reporting can be found at the back of the British National Formulary or electronic submissions made at: www.yellowcard.gov.uk

Some major side effects (neutropenia, eosinophilia or thrombocytopenia) can contra-indicate the continued use of clozapine. Long term discontinuation may not be in the best interest of the patient and in these circumstances a discussion with the MDT must take place and provided that pre-cautions are taken to minimise the possibility of the serious adverse effect from reoccurring then the re-initiation of clozapine can be considered. This would be off licence and requires a form to be completed prior to re-initiation (see the off-label section 4.1.3)

The major groups of side effects are detailed in appendix 9

4.8.2. Common side effects

- The most common side effects and recommended treatment strategies can be found in appendix 10
- Please note this list is not exhaustive. For further details on side-effects, please refer to the Denzapine® SmPC www.medicines.org.uk.
- A GASS clozapine (GASS-C) can be found on care notes under medication tab. These should be complete prior to starting treatment, during titration and at least yearly to assess patient's side effects.
- Some of the side-effects above may also be caused by other prescribed medication the patient may be on (e.g. lithium, anticholinergics). Ensure this is considered and managed appropriately.
- Constipation is a potentially life-threatening side effect and must be discussed at all clinic appointments or patient contacts.

4.8.3. Clozapine Red alert

When the DMS detects a red result the registered contact will be notified. The registered contact would normally be the consultant psychiatrist or nominated deputy and the Clozapine Supply Team at Worthing General Hospital.

A red alert is a clinical emergency, the patient is at risk of harm and immediate action must be taken. Management of a red result is under the clinical leadership of the patient's consultant psychiatrist and the patient's ward team. They must arrange for the following procedure to be carried out without delay. If it is out of hours the responsibility will be with the on-call consultant.

If the neutrophil count is below $1.5x10^9$/L and /or the WCC is below $3.0x10^9$/L and the patient develops or shows signs of fever, their management must be guided by a haematologist or A&E. Other physical signs are flu-like symptoms e.g. fever, rapid pulse and respiration, sore throat, hypotension, mouth ulcers, swollen and tender gums and skin infections.

Procedure for Red results

- **STOP** CLOZAPINE IMMEDIATELY and advise the patient to stop taking clozapine until further notice.

  Advice to the patient
  - Fully **explain** to the patient/carer(s) the implications and the procedure to be followed.
  - The patient must be monitored for signs of infection and given advice on what signs of infection they will need to look out for and seek immediate medical attention should they experience any of them.
  - The information which the patient is given must meet the individual's communication needs.
    - **Explain how and where blood samples will be taken.**
    - **Monitor** daily FBC until there has been at least 2 green results.
    - **If another red result occurs then clozapine treatment will be discontinued.** Arrange to remove all supplies of clozapine from the patient.

Healthcare Staff
- Blood test
  - Arrange an emergency local blood test as soon as possible via the nearest pathology laboratory.
    - The blood sample must be sent to the local pathology laboratory for testing. **Not in a posted grey/white (DMS/Spire) blood testing kit (as this takes 2 days to process).**
  - When a blood test is sent for analysis at a local pathology lab, the name of the hospital and the time/date the sample was taken should be recorded in Carenotes.
  - Importantly the person arranging the blood test must inform their local pharmacist or the Clozapine Supply Service at Worthing General Hospital or the on-call pharmacist (if out of hours) that the blood test has been taken locally and at which pathology laboratory. They will enter the results into the DMS website.
  - Pharmacy or the on-call pharmacist will inform the patient's ward team to say they can restart the clozapine.
- Physical observations
  - Healthcare professionals to carry out daily checks as a minimum on the patient's temperature, BP, pulse rate and respiratory rate. Monitor for clinical signs and symptoms of infection (e.g. fever, sore throat, mouth ulcers etc.). The medical team should be updated on the patient's progress and informed if any physical health concerns occur.
  - Other side effects of sudden withdrawal of clozapine may be restlessness, agitation, confusion, profuse sweating, diarrhoea, dyskinesia, headache, insomnia, nausea and vomiting.
- Mental state examinations
  - Monitor mental state on an on-going basis as a psychotic relapse can occur following sudden withdrawal of clozapine. Due to the risk of reducing white blood count further, another antipsychotic must be used with caution. If necessary, choose an antipsychotic with a lower risk of neutropenia.

- Risk assessment
  - Update risk assessment, record all results and events on Carenotes as soon as possible, inotesn order that the information is readily available to healthcare professionals.

How to request an urgent local blood test

- A Full Blood Count must be requested on a hematology form. Details of the patient must be fully completed also include:
  - Urgent
  - Patient on clozapine
- DMS will require the following to provide a result:
  1. Patient Name
  2. Date of Birth
  3. DMS Number
  4. Sample Date
  5. White blood cell count
  6. Platelet count
  7. Neutrophil count

- If two green results have been given, pharmacy can supply the medication.
- There must be close liaison with the DMS and the clozapine supply team at Worthing hospital throughout the process.

Confirmed red Result

A red blood test is taken to be confirmed if either of the blood tests on the following 2 days produce a red result. Following a true red result clozapine would become contraindicated. If clozapine is still felt to be the best treatment option for the patient following a conformed red result then the decision to re-challenge needs to be made with the full MDT including pharmacy and haematology.

4.8.4. Clozapine Amber alert

- When the DMS detects an amber alert the registered contact will be notified. The registered contact would normally be the consultant psychiatrist or nominated deputy or a designated pharmacy.
- Management of an amber result is under the clinical leadership of the patient's consultant psychiatrist. They must arrange for the following procedure to be carried out without delay.
- Pharmacy will only supply 7 days of medication

Procedure for Amber alert

- **If at any stage the result becomes red then the red procedure must be followed.**
- **Monitor** FBC twice a week until a green result has occurred.
- Fully **explain** to the patient/carer(s) the implications and the procedure to be followed. The information which the patient is given must meet the individual's communication needs.
- There must be close liaison with the DMS.
- Arrange the twice a week local blood test.
- The blood sample must be sent to the local pathology laboratory for testing. **Not in a posted grey/white (DMS/Spire) blood testing kit (as this takes 2 days to process).**
- When a blood test is sent for analysis at a local pathology lab, the name of the hospital and the time/date the sample was taken should be recorded in Carenotes.

- Importantly the person arranging the blood test must inform their local pharmacist or the Clozapine Supply Service at Worthing General Hospital or the on-call pharmacist (if out of hours) that the blood test has been taken locally and at which pathology laboratory. They will enter the results into the DMS website.
- Once a green result has been given, pharmacy can supply the medication fully.
- There must be close liaison with the DMS and the clozapine supply team at Worthing hospital throughout the process.

4.9. Discontinuing clozapine therapy

- Clozapine must be discontinued if the patient has a blood dyscrasia, bowel obstruction caused by clozapine induced constipation, intolerable side effects and/or a failure to respond. DMS and the Clozapine supply Service must be notified.
- When a patient has to discontinue due to adverse events, long term discontinuation may not be in the best interest of the patient and in these circumstances a discussion with the MDT must take place and provided that pre-cautions are taken to minimise the possibility of the serious adverse effect from reoccurring then the re-initiation of clozapine can be considered. This would be off licence and requires a form to be completed prior to re-initiation (see section 4.1.3).
- The dose should be reduced gradually over at least a 1 to 2 week period unless abrupt discontinuation is necessary e.g. red blood result or partial or full bowel obstruction If abrupt discontinuation is necessary observe the patient carefully for return of psychotic symptoms and symptoms related to cholinergic rebound (profuse sweating, headache, nausea, vomiting and diarrhoea).
- Follow-up blood samples must be taken for four weeks after cessation of treatment with clozapine. This means sample once more for four weekly monitoring, twice for fortnightly monitoring and four times for weekly monitoring.
- **If clozapine therapy has been discontinued for any reason, all stock held by the patient should be removed in order to prevent any unauthorised re-initiation by the patient.**

4.10. Re-initiation of therapy

4.10.1. Following non-adherence

- Following a break in treatment DMS must be contacted to clarify the necessary monitoring requirements. The Clozapine Supply Service at Worthing General Hospital should also be informed prior to restarting clozapine.
- Clozapine plasma level once the drug has been discontinued drops quickly. Based on an average half-life of between 7 and 14 hours, after 35-70 hours (5 times the half-life) there will be no detectable clozapine remaining. Along with the rapid decline in plasma levels the tolerability to the adverse effects rapidly declines.
- Patients who have not had clozapine for more than 48 hours (taken from the last dose given) should be re-titrated from 12.5mg per day, with a maximum dose titration possible of 50mg/day. For patients who have not had clozapine for 48-72 hours off licence fast titration could be consider (see section 4.10.2)
- The speed of the titration depends on the original acceptance and tolerability of clozapine, however it should be noted that a slower titration (appendix 3) is preferable to prevent adverse reactions. Hypotension, tachycardia and seizures are risks when re-starting clozapine.
- When a patient has previously been on clozapine and they tolerated the standard titration, a quick titration sheet can be used (appendix 4). This must not be used for patients with other medical conditions.

DMS On/Off treatment assessment guidelines

The last dose administered is considered the time off clozapine.

Monitoring Frequency	Time Off clozapine ≤ 48 hours	Time Off clozapine >48 hours BUT <7 days	Time Off clozapine >7 days
Weekly	No change to monitoring frequency	No change to monitoring frequency. Retitration dose as per initial titration	Restart at 18 weeks of weekly monitoring. Retitration dose as per initial titration

Monitoring Frequency	Time Off clozapine ≤ 48 hours	Time Off clozapine >48 hours BUT <3 days (72 hrs)	Time Off clozapine >3 days (72 hrs) BUT <28 days	Time Off clozapine >28 days
Fortnightly & Monthly	No change to monitoring frequency	No change to monitoring frequency. Retitration dose as per initial titration	**Treatment Break** Weekly for 6 weeks and then return to previous monitoring frequency	Restart 18 weeks of weekly monitoring

4.10.2. Off licensed rapid re- titration

When a patient has been off clozapine for greater than 48 hours but less than 72 hours a rapid re-titration can be carried out. This is off licensed therefore needs to be approved by the pharmacist (or the on-call pharmacist if out of hours) and the consultant psychiatrist. Patients must only be started on the rapid re-titration if there is no renal, hepatic, cardiac or neurological impairment and has previously tolerated titrations well with no adverse effects. (Taylor, 2018). The decision to use rapid re-titration must be recorded fully in the patient's Carenotes. This should only be carried out in the inpatient setting.

Dosage

- On day 1, restart with half of the previously prescribed total daily dose on given in divided doses 12 hours apart.
- Then give 75% of the previous daily dose on day 2.
- If prior doses have been tolerated, the whole of the previous daily dose in the normal dosing schedule on day 3.

4.10.3. Re-initiation following Red blood result

- Consideration of re-initiation of clozapine after a red result is only appropriate in specific circumstances. The risks and benefits of re-challenge of clozapine therapy need to be considered by the whole MDT.
- Neutropenia during clozapine therapy needs to be assessed for the likelihood of being directly attributable to clozapine and not from any other cause, such as concomitant myelosuppressive drugs (e.g. Carbamazepine, chemotherapy, concomitant long acting antipsychotic injections and underlying physical conditions e.g. benign ethnic neutropenia). Determination if neutropenia is due to clozapine or another cause cannot be made with certainty.
- Risk factors for true clozapine induced neutropenia are a low baseline WBC, Afro-Caribbean ethnicity and young age. True clozapine induced neutropenia usually develops early in treatment e.g. in the first 18 weeks decreasing rapidly over 1-2 weeks, with a slow return to normal levels.
- The final decision for re-challenge of clozapine therapy rests with the named consultant and should be initiated on a named-patient basis with completion and filing in the patients notes of a new consent form as in such circumstances use will be 'off-licence'. (See appendix ..). The patient and family/carers where appropriate must have a fully documented discussion with the clinician regarding the risks associated with a re-challenge of clozapine.

- DMS needs to be informed and an Off Label Treatment agreement filled out and signed by consultant. This form is available form www.denzapine.org.uk

4.10.4. Lithium therapy

- If there is sufficient strong evidence that true clozapine induced neutropenia has not occurred and that the neutropenia was caused by another factor then lithium therapy may be considered to elevate WBC levels. Consideration of concomitant lithium therapy must be made with specialist pharmacy advice. Lithium will not elevate WBC's if a true clozapine induced neutropenia has occurred.
- Initiation of lithium therapy requires baseline U&Es, TFTs and FBC with initial prescribing of 400mg nocte and a target plasma level range between 0.6-0.8mmols/L for 1-2 weeks, with WBC checked after this trial period. If there is sufficient elevation of WBC's then re-initiation of clozapine if thought to be of sufficient clinical benefit can be considered, with appropriate blood monitoring (Blier et al, 1998).

N.B. Clozapine and lithium combination can increase the risk of neuroleptic malignant syndrome

Lithium therapy for raising WBC's should not be considered when a patient is high risk:

- Severe neutropenia/agranulocytosis – (In such cases granulocyte colony-stimulating factor (G-CSF) could be considered following specialist advice
- Red WBC result was inconsistent with previous WBC results
- A prolonged neutropenia

4.10.5. GCSF Therapy

Granulocyte colony-stimulating factor (G-CSF) has been used to support clozapine re-initiation after neutropenia with the aim of maintaining the neutrophil count. This would be off licence and therefore needs support from the MDT and a haematologist. A follow up plan needs to be developed and agreed with the supervising community team to ensure appropriate monitoring is carried out.

- To re-start clozapine after an event like this, if it is felt to be in the patient's best interests, a discussion with the MDT must take place and provided that pre-cautions are taken to minimise the possibility of the serious adverse effect from reoccurring then the re-initiation of clozapine can be considered. Dependant on the side effect an off licence form must be completed – these are available from the www.denzapine.co.uk

4.11. Augmentation of clozapine

For people with complex psychosis whose symptoms have not responded adequately to an optimised dose of clozapine alone, consider augmenting clozapine with the following, depending on target symptoms:

- an antipsychotic, for example aripiprazole or amisulpride for schizophrenia and related psychoses and/or a mood stabiliser for psychosis with significant affective symptoms and/or
- an antidepressant if there are significant depressive symptoms in addition to the psychotic condition.

Consult the Maudsley guidelines (Taylor, 2018) or your local pharmacy team for more information.

Be aware of potential drug interactions and note that not all combinations of treatments may be in accordance with UK marketing authorisations. Any off-licence prescribing should be communicated in writing with the person's GP. Seek specialist advice if needed, for example from another psychiatrist specialising in treatment-resistant symptoms or a specialist mental health pharmacist.

Do not offer valproate to women of childbearing potential, unless other options are unsuitable and the pregnancy prevention programme is in place. Follow the MHRA safety advice on valproate use by women and girls.

4.12. Intramuscular (IM) clozapine

IM clozapine is not licensed for use in the UK. The Trust has approved its use, in exceptional circumstances and clozapine injection can only be obtained by following this the IM clozapine protocol which can be found on (need pigeon hole).

In summary:-

- Only for patients in PICUs and secure units ONLY between the ages of 18 and 60.
- Must be approved by a SOAD
- Only prescribed by a consultant and approved by the clinical director on an individual basis.
- It is expensive a dose titration over 2 weeks costs £2,000
- Needs to be imported in which can take some time to be delivered.
- Often requires blood via PMVA techniques and the PMVA team advice should be sort.

4.13. Discharge

Most patients will be attending a clozapine clinic after discharge and most clozapine clinics are supplied by Worthing hospital.

On discharge ensure:-

- The next clozapine blood test is organised prior to leaving and the patient is given the appointment date, clozapine clinic details and details of where to collect the clozapine.
- Inform the local pharmacist that the patient is being discharged.
- A discharge summary is written and sent to Worthing hospital for supply if required. The discharge summary should state where blood tests and collection will be.
- The supply from the ward is given to the patient. This may need to be reduced in cases of risk but the medication should be given to the team responsible for the patients care.
- Ensure the patient's GP is informed via the discharge summary when starting clozapine and any changes.

4.14. If a patient prescribed clozapine moves out of area:

- In the event of moving residence out of the Sussex Partnership area, patients prescribed clozapine and/or their carers should inform their lead practitioner and Clozapine Clinic as soon as they know their new address. Such patients will need to be re-registered with a local clozapine provider.
- The lead practitioner and responsible clinician have a duty to arrange suitable secondary care follow-up in the new area. The lead practitioner and responsible clinician will inform the Worthing Hospital of the details of new follow-up arrangements as soon as these have been agreed.

4.15. Care planning

- This Trust sets out the standards and principles that should be applied when care planning is provided.
- All patients must have a responsible clinician and a lead practitioner. If the lead practitioner is not a nurse then a named nurse should be assigned.

5. DEVELOPMENT, CONSULATION AND RATIFICATION.

This policy was developed by the clozapine management group which comprises of a MDT team. The group utilised the previous approved guidance, actions from the trust risk group and undertook an extensive review process to ensure safe and effective use of clozapine.

The policy was taken to the Drugs and Therapeutics group for approval and then to the policy group for ratification.

6. EQUALITY IMPACT ASSESSMENT (EHRIA)

All patients covered by this policy, regardless of their race, gender, gender identity, sexuality, religion, spiritual beliefs or disability, will be treated equally within the principles of the policy and with equal dignity and respect (undertaken in May 2021).

7. MONITORING COMPLIANCE

This policy will be used to measure, monitor and evaluate that the process of prescribing, administering and monitoring of clozapine is within the minimum requirements.

The clozapine management group with use this policy alongside the POMHUK and National Clinical audit or psychosis to ensure these standards are met.

The Clozapine management group will devise and audit tool and KPIs to ensure these standards are met and carry out this audit once a year. Results from this audit will be shared.

8. DISSEMINATION AND IMPLEMENTATION OF POLICY

The policy will be circulated via communication form the trust, including policy on a page. There will also be mention of the policy in the Drugs and Therapeutics Newsletter. For training the slides will be updated with the addition of the policy. Training is currently within the medication management training.

9. DOCUMENT CONTROL INCLUDING ARCHIVE ARRANAGEMENTS

The previous guidance will be archived.

- Details of process and responsibility for recording, storing, controlling and updating documents detailed in the policy and ultimately archive arrangements.
- This section should cross reference to the Policy for Procedural documents and possibly the Policy for the Management of Corporate Records, Policy for the Management of Health Records and Information Governance Policy.

10. REFERENCE DOCUMENTS

Barnes TR and Schizophrenia Consensus Group of British Association for Psychopharmacology (2020). Evidence-based guidelines for the pharmacological treatment of schizophrenia: Updated recommendations from the British Association for Psychopharmacology. J Psychopharmacol 34(1):3-78

Blier P et al. Lithium and clozapine-induced neutropenia/agranulocytosis. International Clinical Psychopharmacology 1998; 13:137-140

Britannia Pharmaceuticals Limited UK Denzapine® 25mg, 50mg, 100mg and 200mg tablets Summary of Product Characteristics last updated 15/11/2019 accessed online via https://www.medicines.org.uk/emc/product/6120/smpc

British National Formulary. Accessed on line via www.medicinescomplete.com

Flanagan RJ. Therapeutic monitoring of antipsychotics. CPD Clin Biochem 2006; 7: 3 -18.

National Institute for Health and Care Excellence. Psychosis and schizophrenia in adults: treatment and management. [CG178] February 2014

National Institute for Health and Care Excellence. Rehabilitation for adults with complex psychosis. [NG181] August 2020.

D. Taylor, C. Paton, S.Kapur. The Maudsley Prescribing Guidelines. 13th Edition. The South London and Maudsley NHS Foundation Trust Oxleas NHS Foundation Trust. London 2018

11. BIBLIOGRAPHY

- D. Taylor, C. Paton, S.Kapur. The Maudsley Prescribing Guidelines. 13th Edition. The South London and Maudsley NHS Foundation Trust Oxleas NHS Foundation Trust. London 2018
- Bazire S, Psychotropic Drug Directory. 2018 edition. Lloyd-Reinhold Communications

A list of works that the author has used as a source of information or evidence, but is not referred to directly in the text

12. CROSS REFERENCE

- Essential Training Policy http://policies.sussexpartnership.nhs.uk/workforce/essential-training-policy
- Medicines Management Update for Qualified Nurses - Training Schedule (accessed via 'My Learning')
- Observation Policy http://policies.sussexpartnership.nhs.uk/clinical-3/461-observation-policy

- Physical Health Assessment and monitoring policy https://policies.sussexpartnership.nhs.uk/clinical-3/physical-examination-ongoing-healthcare-policy
- Venepuncture policy https://policies.sussexpartnership.nhs.uk/clinical-3/550-venepuncture-policy

APPENDIX 1 PRE-CLOZAPINE INITIATION CHECKLIST

This checklist must be completed by the lead practitioner (or ward nurse) in liaison with the Responsible Clinician

		Yes/No	Comments / date completed	Signature
1.	Establish that clozapine is in the best interest of the patient			
2.	The patient has been given **information** about the treatment in a form that can be understood including information about possible side effects, the likely consequences of not having the proposed treatment and the pros and cons of any alternative treatment.			
3.	The patient has given informed consent.			
4.	If the patient is deemed to lack capacity under the Mental Health Act or Mental Capacity Act then ensure prescribing of clozapine is covered under the MHA or MCA.			
5.	It is prescribed in line with the licensed indication (See section 2.2)			
6.	Contraindications to clozapine are absent. Please refer to clozapine SmPC www.medicines.org.uk			
7.	Cautions for clozapine have been considered Please refer to clozapine SmPC www.medicines.org.uk			
8.	Clozapine drug interactions have been considered. Please refer to clozapine SmPC www.medicines.org.uk			
9.	Has the G.P been contacted to complete medicines reconciliation, allergies and to request information relating to physical health concerns, investigations and treatments?			
10.	Is the patient likely to be adherent to oral medication?			
11.	Has the patient been given the Choice and Medication information leaflet and had an opportunity to speak to a member of the pharmacy team.			
12.	Is the patient aware of physical monitoring requirements for 4 week initiation period monitoring for 6 hours on day 1?			

13.	Is the patient aware of the need for regular blood tests and is willing to undergo weekly blood tests for the first 18 weeks, then fortnightly up until 1 year and then monthly thereafter			
14.	**Specifically, for community initiation/retitration** Check that there are resources available (particularly staff to follow up the patient in the community) to provide safe clozapine treatment.			
15.	**Specifically, for community initiation/retitration** Is patient aware of the need to remain with a member of staff at the initiation base or at the patient's home for monitoring for 6 hours on day one?			
16.	Has the patient been advised not to drive and not to drink alcohol?			
17.	Has the patient been given health living advice re: possible weight gain?			
18.	Has the patient's GP been informed and asked to make record on their own electronic recording system that this patient is receiving clozapine? Has the GP clozapine letter has been sent? (see appendix 13)			
19.	Has the patient been registered with Trust approved clozapine monitoring service (www.denzapine.co.uk)and the clozapine clinic (where necessary) and pharmacy team informed?			
20.	Have the required Baseline Monitoring have been completed (see appendix 6)		**Test Results**	
	Initial Full Blood Count and result communicated to DMS			
	Initial ECG (within 3 months if no major physical health changes)			
	Baseline glucose (fasting sample ideally) and HbA1c			
	Baseline weight, BMI and waist circumference			
	Baseline Blood Pressure (lying and standing) and pulse rate			
	Urea and Electrolytes			
	Liver Function Test			
	Cholesterol and lipids profile (ideally fasting)			
21.	Has the baseline measure of mental state been completed? (this includes suicidality)			

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Appendix 2

CLOZAPINE INPATIENT TITRATION PRESCRIPTION CHART-

Normal titration

This chart must be attached to the standard prescription chart, which must be endorsed with
'Clozapine as per titration chart'

If problematic side effects occur, consider slower dose titration or decreasing dose to one previously tolerated.

Ward		**Hospital/Unit**	
Patient Name		**DMS Number**	
Consultant		**Hospital No.**	
Allergies		**Date of Birth**	

If clozapine is omitted for greater than 48hrs it is essential to restart clozapine from initial starting doses. However, according to tolerance, upward dose titration may be faster than on first trial.
If previously on clozapine, date stopped :

DAY	DATE	DRUG	MORNING DOSE Time:	GIVEN BY	EVENING DOSE Time:	GIVEN BY
1		CLOZAPINE	First dose can be given earlier		12.5mg	
2		CLOZAPINE	12.5mg		12.5mg	
3		CLOZAPINE	25mg		25mg	
4		CLOZAPINE	25mg		25mg	
5		CLOZAPINE	25mg		50mg	
6		CLOZAPINE	25mg		50mg	
7		CLOZAPINE	50mg		50mg	
8		CLOZAPINE	50mg		75mg	
9		CLOZAPINE	75mg		75mg	
10		CLOZAPINE	75mg		100mg	
11		CLOZAPINE	100mg		100mg	
12		CLOZAPINE	100mg		125mg	
13		CLOZAPINE	100mg		150mg	
14	**Prescribe the dose on prescription chart.** Generally this dose is 100mg OM and 200mg ON.					
Should a higher dose than 300mg daily be required, increments are 50-100mg per week. Therefore, from day 18 aim for 100mg OM & 250mg ON, day 21 100mg OM & 300mg ON and day 28 100mg OM & 350mg ON.						
Target doses female non-smoker = 250mg/day (day 13), Male non-smoker = 350mg/day, Female smoker = 450mg/day and Male smoker = 550mg/day. Adjust according to plasma levels, consider taking after day 15.						
PRESCRIBER'S SIGNATURE				DATE		

Appendix 3

CLOZAPINE INPATIENT TITRATION PRESCRIPTION CHART

Slow titration

This chart must be attached to the standard prescription chart, which must be endorsed with **'Clozapine as per titration chart'**

Consider for patients with other medical conditions e.g. cardiac, hepatic or renal impairment.

If problematic side effects occur, consider slower dose titration or decreasing dose to one previously tolerated.

Ward		**Hospital/Unit**	
Patient Name		**DMS Number**	
Consultant		**Hospital No.**	
Allergies		**Date of Birth**	

If clozapine is omitted for greater than 48hrs it is essential to restart clozapine from initial starting doses. However, according to tolerance, upward dose titration may be faster than on first trial.

If previously on clozapine, date stopped:

DAY	DATE	DRUG	MORNING DOSE Time:	GIVEN BY	EVENING DOSE Time:	GIVEN BY
1		CLOZAPINE	First dose can be given earlier.	[redacted]	12.5mg	
2		CLOZAPINE	[redacted]		12.5mg	
3		CLOZAPINE	12.5mg		12.5mg	
4		CLOZAPINE	12.5mg		12.5mg	
5		CLOZAPINE	25mg		25mg	
6		CLOZAPINE	25mg		25mg	
7		CLOZAPINE	25mg		25mg	
8		CLOZAPINE	25mg		25mg	
9		CLOZAPINE	25mg		50mg	
10		CLOZAPINE	25mg		50mg	
11		CLOZAPINE	25mg		50mg	
12		CLOZAPINE	25mg		50mg	
13		CLOZAPINE	50mg		50mg	
14	**Prescribe the dose on prescription chart or 2nd sheet.**					

Should a higher dose be required, increments are 50-100mg per week, as the patient tolerates.

Target doses female non-smoker = 250mg/day, Male non-smoker = 350mg/day, Female smoker = 450mg/day and Male smoker = 550mg/day. Adjust according to plasma levels.

PRESCRIBER'S SIGNATURE		DATE	

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Appendix 4

CLOZAPINE INPATIENT RETITRATION PRESCRIPTION CHART

Quick titration

When a patient has previously been on clozapine and tolerated the titration. NOT for patients with medical conditions that may result in an increase in side effects e.g. cardiac or renal impairment.

This chart must be attached to the standard prescription chart, which must be endorsed with **'Clozapine as per titration chart'**

If problematic side effects occur, consider slower dose titration or decreasing dose to one previously tolerated.

Ward		Hospital/Unit	
Patient Name		DMS Number	
Consultant		Hospital No.	
Allergies		Date of Birth	

If clozapine is omitted for greater than 48hrs it is essential to restart clozapine from initial starting doses. However, according to tolerance, upward dose titration may be faster than on first trial.

If previously on clozapine, date stopped:

DAY	DATE	DRUG	MORNING DOSE Time:	GIVEN BY	EVENING DOSE Time:	GIVEN BY
1		CLOZAPINE	First dose can be given earlier.		12.5mg	
2		CLOZAPINE	12.5mg		12.5mg	
3		CLOZAPINE	25mg		25mg	
4		CLOZAPINE	25mg		50mg	
5		CLOZAPINE	50mg		50mg	
6		CLOZAPINE	75mg		75mg	
7		CLOZAPINE	100mg		100mg	
8		CLOZAPINE	100mg		150mg	
9		CLOZAPINE	100mg		200mg	
10		CLOZAPINE	100mg		250mg	
11		CLOZAPINE	100mg		300mg	
12		CLOZAPINE	100mg		350mg	
13		CLOZAPINE	100mg		400mg	
14	**Prescribe the dose on prescription chart.** **Consider the dose the patient was previously on.**					

Target doses female non-smoker = 250mg/day (day 8), Male non-smoker = 350mg/day (day 10), Female smoker = 450mg/day (Day 12) and Male smoker = 550mg/day. Adjust according to plasma levels.

PRESCRIBER'S SIGNATURE		DATE	

Appendix 5 **NEWS2 CLOZAPINE - PHYSICAL HEALTH OBSERVATIONS (INPATIENT TITRATIONS)**

NEWS key 0 1 2 3	FULL NAME	
	DATE OF BIRTH	DATE OF ADMISSION

Frequency: This should be done **prior to the first dose**, **hourly for the first 6 hours**, then **twice a day** during titration.
If the first dose is given at night only non-contact monitoring is required for the first 6 hours (if patient is asleep).

If you are unable to carry out Physical Health observations, or the patient refuses you must complete Non-Contact Observations of respiratory rate and level of consciousness using AVPU and record these on this chart.

		DATE / TIME		DATE / TIME
A+B Respirations Breaths/min	≥25		3	≥25
	21–24		2	21–24
	18–20			18–20
	15–17			15–17
	12–14			12–14
	9–11		1	9–11
	≤8		3	≤8
A+B SpO_2 Scale 1 Oxygen saturation (%)	≥96			≥96
	94–95		1	94–95
	92–93		2	92–93
	≤91		3	≤91
SpO_2 Scale 2† Oxygen saturation (%) Use Scale 2 if target range is 88–92%, eg in hypercapnic respiratory failure †ONLY use Scale 2 under the direction of a qualified clinician	≥97 on O_2		3	≥97 on O_2
	95–96 on O_2		2	95–96 on O_2
	93–94 on O_2		1	93–94 on O_2
	≥93 on air			≥93 on air
	88–92			88–92
	86–87		1	86–87
	84–85		2	84–85
	≤83%		3	≤83%
Air or oxygen?	A=Air			A=Air
	O_2 L/min		2	O_2 L/min
	Device			Device
C Blood pressure mmHg Score uses systolic BP only	≥220		3	≥220
	201–219			201–219
	181–200			181–200
	161–180			161–180
	141–160			141–160
	121–140			121–140
	111–120			111–120
	101–110		1	101–110
	91–100		2	91–100
	81–90		3	81–90
	71–80			71–80
	61–70			61–70
	51–60			51–60
	≤50			≤50
C Pulse Beats/min	≥131		3	≥131
	121–130		2	121–130
	111–120			111–120
	101–110		1	101–110
	91–100			91–100
	81–90			81–90
	71–80			71–80
	61–70			61–70
	51–60			51–60
	41–50		1	41–50
	31–40		3	31–40
	≤30			≤30
D Consciousness Score for NEW onset of confusion (no score if chronic)	Alert			Alert
	Confusion		3	Confusion
	V			V
	P			P
	U			U
E Temperature °C	≥39.1°		2	≥39.1°
	38.1–39.0°		1	38.1–39.0°
	37.1–38.0°			37.1–38.0°
	36.1–37.0°			36.1–37.0°
	35.1–36.0°		1	35.1–36.0°
	≤35.0°		3	≤35.0°
NEWS TOTAL				TOTAL
Monitoring frequency				Monitoring
Escalation of care Y/N				Escalation
Initials				Initials

Please record Patient Specific Variants in column below and Note: This protocol should NOT prevent a practitioner making an appropriate response based upon their clinical judgement.

Where NEWS 2 is used, ensure that patient's NEWS 2 is discussed at every medical and nursing handover. If a decision is made not to follow the clinical response guidance below, this MUST be documented in the patient's records with the rational for the decision.

NEW score	Frequency of monitoring	Clinical response
0	Minimum 12 hourly	• Continue routine NEWS monitoring
Total 1–4	Minimum 4–6 hourly	• Inform registered nurse, who must assess the patient • Registered nurse decides whether increased frequency of monitoring and/or escalation of care is required
3 in single parameter	Minimum 1 hourly	• Registered nurse to inform medical team caring for the patient, who will review and decide whether escalation of care is necessary
Total 5 or more Urgent response threshold	Minimum 1 hourly	• Registered nurse to immediately inform the medical team caring for the patient • Registered nurse to request urgent assessment by a clinician or team with core competencies in the care of acutely ill patients • Provide clinical care in an environment with monitoring facilities
Total 7 or more Emergency response threshold	Continuous monitoring of vital signs	• Registered nurse to immediately inform the medical team caring for the patient – this should be at least at specialist registrar level • Emergency assessment by a team with critical care competencies, including practitioner(s) with advanced airway management skills • Consider transfer of care to a level 2 or 3 clinical care facility, ie higher-dependency unit or ICU • Clinical care in an environment with monitoring facilities

Escalation Protocol SBARD

S Situation	Your name / designation / ward The patient's name is XX. I am concerned because XX. The NEWS2 score trigger is XX.	
B Background	Treatment Date Brief history Admission Date MHA Status Medication / therapy	
A Assessment	**A** Airway	Is the patient talking? Any airway noises; e.g. gurgling/stridor
	B Breathing	Respiratory Rate (RR)? Any respiratory noises e.g. wheeze? Is breathing laboured? Oxygen saturation levels % - Scale 1 or 2 (SpO2)? Air or Oxygen?
	C Circulation	Heart Rate (HR)? Capillary Refill Time (CRT)? Blood Pressure (BP)?
	D Disability	Level of consciousness (Alert, Newly Confused Voice Pain Unresponsive)? Blood sugar levels? Pupil reactions?
	E Exposure	Temperature? Exposure & environment. Bleeding / rashes, etc.? Any other abnormal signs?
R Recommend	I would like you to do /What would you like me to do?	
D Decision	Record what has been agreed on the patient's notes.	

***Use SBARD Tool (above) to notify Medical Team**

Appendix 6

Clozapine baseline and annual physical health monitoring

	Baseline	1 month	3 months	6 months	12 months	On going	ALL-Physical health assessment
FBC	As per clozapine protocol. Weekly for 18 weeks, then two weekly for up to 1 year then 4 weekly. Additional monitoring may be required.						
U&Es	✓				✓	***Annually***	
LFTs	✓			✓	✓	***Annually***	
Fasting Lipids	✓			✓	✓	***Annually***	✓
Blood glucose (random/fasting)	✓			✓	✓	***Annually***	✓
HbA1C	✓			✓	✓	***Annually***	✓
ECG (QTc Interval)	✓	Clozapine may cause cardiomyopathies and myocarditis. Check ECG when maintenance dose is reached and after any dose changes. Check annually if high doses (>600mg					
Weight, BMI, Abdominal Girth	✓		✓	✓	✓	***Annually***	✓
Constipation (Ask about bowel movements)	✓	✓	✓	✓	✓	**At every patient contact.**	
Prolactin	✓	Hyperprolactinaemia is rare with clozapine – check serum prolactin if symptoms occur (menstrual disturbance, galactorrhoea, gynaecomastia, sexual dysfunction). Consider other possible causes.					
BP and Pulse (BD whilst titrating)	✓	✓				***Annually***	✓
Temperature (BD whilst titrating)	✓	✓				***Annually***	
CPK	✓	If Neuroleptic malignancy syndrome (NMS) suspected					
EEG	✓	If at risk for seizures or experience a seizure.					
Troponin and CRP	✓	If suspecting cardiac complications					
Clozapine GASS-C	✓	✓	✓	✓	✓	***Annually***	
Clozapine Plasma level	Clozapine plasma levels should be taken to ensure that a therapeutic level has been reached following initiation or a re-titration. Clozapine plasma levels should be monitored on an annual basis (Section … for more details.					***Annually***	

Appendix 7 **Side effect monitoring form for Clozapine (based on GASS) - for initiation or re-titration)**

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

Score the side effects 0 point for never, 1 point for once, 2 points for a few times in a week, 3 points for every day.		Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	**Continue daily whilst titrating then weekly using the GASS form**
1	Sleepy during the day															
2	Drugged or like a zombie															
3	Dizzy when standing or have fainted															
4	Heart beating irregularly or unusually fast															
5	Experienced jerking limbs or muscles															
6	Drooling															
7	Vision blurry															
8	Dry mouth															
9	Sick (nauseous) or vomited															
10	Gastric reflux or heartburn															
11	Problems opening my bowels (constipation)															
12	Wet the bed															
13	Passing urine more often															
14	Thirsty															
15	More hungry than usual or have gained weight															
16	Having sexual problems															
	TOTAL															
Record below any other side effects **OR PHYSICAL PROBLEMS OR COMPLAINTS** that patient has experienced over the **past week**)																

Inform the medical team if it is severe or distressing for the patient

Appendix 8

GASS monitoring form 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	

Staff Information

- Allow the patient to fill in the side-effects scale themselves. All questions relate to the previous week

- **Scoring**

0 points	"Never"
1 point	"Once"
2 points	"A few times"
3 points	"Everyday)

- **Results**

0-16	Absent/mild side-effects
17-32	Moderate side-effects
33-48	Severe side-effects

- Side-effects covered include:

1-2	Drowsiness and sedation
3	Postural hypotension
4	Tachycardia
5	Myoclonus
6	Hypersalivation
7-8	Anticholinergic side-effects
9-10	Gastrointestinal side-effects
11	Constipation
12	Nocturnal enuresis
13-14	Screening for diabetes mellitus
15	Weight gain
16	Sexual dysfunction

- The column relating to the severity/distress experienced with a particular side-effect is not scored, but is intended to inform the clinician of the patient's views and condition.

- Questions 17 to 20 invite the patient to report any other side-effects or problems not already mentioned. These questions should not be scored but may instigate a discussion with the patient if clinically appropriate.

Waddell, Taylor and Hyn es 2012
DT,IFG,AA,PH,RD comments

Appendix 9

Major side effects of clozapine

Neutropenia/ agranulocytosis	• Clozapine can cause neutropenia and in severe cases agranulocytosis. • Particular attention must be paid to flu-like symptoms such as sore throat and pyrexia which may be indicative of neutropenia. • DMS provides guidance on procedures to be followed in the event of neutropenia or agranulocytosis developing.
Eosinophilia	• Clozapine can cause eosinophilia • Can be a sign of cardiac issues and needs investigating. • Discontinuation of clozapine is recommended if the eosinophil count rises above 3000/mm^3 (3.0 x 10^9/L). • **Seek advice from local and DMS haemeotologist.** • Therapy should be restarted only after the eosinophil count has fallen below 1000/mm^3 (1.0 x 10^9/L).
Thrombocytopenia	• Clozapine can cause thrombocytopenia • Discontinuation of clozapine is recommended if the platelet count falls below 50 000/mm^3 (50 x 10^9/L). • **Seek advice from local and DMS haemeotologist.**
Pyrexia	• During clozapine therapy, approximately 5% of patients experience transient temperature elevations above 38°C, with the peak incidence within the first 3 weeks of treatment. • If a patient develops pyrexia and a flu-like illness, a medical examination and full blood count should be performed as soon as possible. • In the presence of a high fever, the possibility of neuroleptic malignant syndrome (NMS) must be considered. • Fever may indicate possible blood dyscrasia or Neuroleptic Malignant Syndrome; a Full Blood Count (FBC) should be taken. All possible causes of pyrexia should be considered. If the FBC is satisfactory, the pyrexia has resolved or the cause is unrelated to clozapine the patient may restart clozapine as per the standard titration schedule.
Seizures	• Clozapine lowers the seizure threshold and patients may develop a seizure disorder especially on high doses of clozapine. • The minimum effective dose should be prescribed. • Those patients requiring doses of clozapine that are at risk of causing seizures may be concomitantly prescribed an anticonvulsant that is not associated with bone marrow suppression. • Prophylactic sodium valproate (or lamotrigine for people of child bearing potential) should be considered for patients who are at high risk of clozapine induced seizures e.g. those on clozapine doses of 600mg daily and above.

Cardiovascular events	• A baseline ECG or other measurement of the QT interval must be taken before clozapine treatment is initiated and again when the maintenance dose is reached. • Troponin and CRP baseline levels must also be taken prior to starting clozapine. • Clozapine patients may have an increased risk of pulmonary embolism & VTEs Cardiomyopathy and fatal myocarditis has been associated with clozapine use with the risk of myocarditis greatest during the first 2 months of treatment. • Tachycardia is a common side effect with clozapine however persistent tachycardia can be a sign of more serious cardiac complications such as myocarditis or cardiomyopathy. • Cardiac complications should be suspected if patients experience persistent tachycardia at rest, palpitations, arrhythmias, chest pain or heart failure develops. In these cases clozapine should be immediately reviewed, and the patient referred to a cardiologist by their psychiatrist. Where clozapine is discontinued due to cardiac complications, such patients should not be re-exposed to clozapine. **Troponin levels should be tested for and compared to the baseline results.** • The risk of orthostatic hypotension can be minimised by slowly titrating the dose and spreading doses through the day.
Pneumonia	• Very rarely results from saliva aspiration or due to constipation • Pneumonia is a common cause of death in patients on clozapine • Infections may be more common and use antibiotics increased • Respiratory infections may give rise to elevated clozapine levels • Smoking is likely to be stopped. • Clozapine can be successfully reintroduced but has a high rate of reoccurance.
VTE	• Clozapine increase the risk of VTE including pulmonary embolism (PE) and DVTs. • Various mechanisms including o Sedation &weight gain (immobility), increase platelet aggregation, hyperprolacteamia. • Consider other risk factors • Complete a VTE assessment.
Constipation leading to intestinal obstruction	• Clozapine can cause constipation due to slowing of intestinal peristalsis and hence can cause obstruction, and a paralytic ileus which may be fatal. • Acute obstruction is a medical emergency. Symptoms include abdominal distension, pain and vomiting. When suspected the medical team must be alerted immediately and in the event that there is no medic available the patients GP needs to be contacted to see the patient. If this is not possible the patient

	will need to attend A&E for urgent treatment, usually requiring surgery. • The risk is greater with higher doses and when prophylactic laxatives have been stopped.
Diabetes and impaired glucose tolerance	• Clozapine has been strongly linked to hyperglycaemia, impaired glucose tolerance and diabetic ketoacidosis. • Up to one third of clozapine patients develop diabetes after 5 years of treatment. Patients and carers should be aware of the symptoms of diabetes and be encouraged to report these if present. • Routine baseline screening in the early months of treatment should detect evidence of glucose dysregulation, however if there is suspicion of abnormal glucose metabolism, a random blood glucose measurement should be undertaken. If this is abnormal, a fasting specimen should be obtained.

Appendix 10 **Management of other adverse effects**

Adverse Effect	Time course	Action
Sedation	First 4 weeks. May persist but usually wears off.	Give smaller dose in the mornings. Some patients can only cope with single night-time dosing. Reduce dose if necessary. Consider plasma level monitoring.
Hypersalivation	First few months. May persist but usually wears off. Often very troublesome at night.	Give hyoscine 300mcg (Kwells) **sucked** and chewed at night. Hyoscine patches may be considered as an alternative. Pirenzepine (not licensed in U.K, supplied via Worthing General Hospital) up to 100mg/day may be tried. Check whether troublesome to patient - treatment not always required. **Beware of increased risk of constipation**.
Constipation	Usually persists	Recommend high fibre diet. Stimulant laxatives must be prescribed for clozapine induced constipation e.g. docusate or an enema preparation. **Bulk forming laxatives are NOT effective at managing this type of constipation**.
Hypotension	First 4 weeks	Advise patient to take time standing up. Reduce dose or slow down rate of increase.
Hypertension	First 4 weeks, sometimes longer	Monitor closely and increase dose as slowly as is necessary. Consider antihypertensive therapy if suitable
Tachycardia	First 4 weeks, but often persists	Often occurs if dose escalation is too rapid. Inform patient that it is not usually dangerous. If pulse is persistently above 100bpm, consider cardiology referral. If persistent at rest, associated with fever, hypotension or chest pain may indicate myocarditis – seek cardiology referral. If accompanied by chest pain or shortness of breath. Seek immediate medical assessment. After ruling out myocardiatis or cardiac myopathy reduce the rate of the titration and if still persistent consider give a small dose of beta blockers if necessary e.g. bisoprolol or atenolol.
Weight gain	Usually during first year of treatment	Weight gain is common and often profound (5kg+) Dietary counseling is essential. Advice may be more effective if given before weight gain occurs. Advice on regular exercise and its role in mental wellbeing and contribution to maintaining a healthy weight
Fever	First 3 weeks	Give antipyretic and check FBC. **N.B.** This fever is not usually related to blood dyscrasias. If persists above 38.5C withhold clozapine and contact DMS. Consider myocarditis, seek medical attention and examine the patient for any other signs or symptoms of myocarditis e.g. breathlessness at rest.
Seizures	Dose dependent. Incidence rises at doses > 600mg / day or plasma level >0.6mg/l	Consider prophylactic sodium valproate (or lamotrigine for people of child bearing potential) if on high dose (>600mg/day or plasma level of >0.5mg/l). After a seizure – withhold clozapine for one day. Restart at reduced dose and prescribe a prophylactic anti-epileptic medication. (**Avoid carbamazepine**)
Nausea	First 6 weeks	May give anti-emetic.(Avoid prochlorperazine and metoclopramide if history of EPSE)

Nocturnal enuresis	May occur at any time	Try manipulating dose schedule. No fluids at bedtime. In severe cases, desmopressin is usually effective. Consider risk of hyponatraemia.
Hyperglycaemia	Any time. Usually known risk factors	Use oral hypoglycaemics or insulin.

Appendix 11

How to take plasma blood samples and how to interpret plasma results

Taking plasma level blood samples

- Collect at least 2mLs into an EDTA tube.
- The blood sample needs to be taken at trough (i.e. take the sample pre-dose or 10- 14 hours post dose).

If patient takes their clozapine in split doses they may need to omit/ delay their morning dose of clozapine on the day of the blood test to ensure the sample is taken at trough. It is also important that the clozapine is at steady state before taking a plasma level to ensure results are reliable (i.e. patient has taken the same dose of clozapine for at least 5 days prior to blood test).

- All clozapine plasma levels need to be sent to ASI labs for analysis (www.asilab.co.uk). **Please note** that local pathology labs cannot analyse clozapine plasma levels.
- A plasma level blood pack should be used for sending the blood sample to ASI for analysis. The pack contains an ASI request form as shown in appendix 15, which must be completed and sent together with the sample. ASI is totally independent laboratory and clozapine plasma must be sent directly to ASI. A plasma clozapine assay request form can also be downloaded from the ASI website: www.asilab.co.uk
- All clozapine prescribers should register with ASI via their website to view the results of the clozapine plasma levels. Prescribers will be forwarded an automatic notification from ASI when the results are available to view.
- The results of the clozapine plasma level should be reviewed by the consultant who is prescribing clozapine for that patient. Advice can be sought from pharmacy on the interpretation of the clozapine level if needed.

Interpretation of clozapine levels

Table below summarises interpretation of clozapine plasma levels.

The patient's clinical presentation should always be considered in combination with the clozapine plasma level when adjusted clozapine dose. Dose adjustments should not be made purely on interpretation of a clozapine level. Advice can be sought from your local pharmacist on interpretation of clozapine levels.

'Trough' clozapine (mg/L)	Clinical response	Comment
<0.01 ('not detected')	**Any**	Clozapine is unlikely to have been taken for at least a week before sampling except perhaps in the early stages of dose escalation (doses of 100 mg/d or less).
<0.35	**Good**	Consider repeating assay at 6 months, then annually unless response deteriorates or side effects become troublesome.
	Poor/ Incomplete	If poor adherence is suspected, consider psychoeducation or supervised administration. Review the patient and repeat the assay after adherence intervention. If there is no improvement, consider a cautious dose increase. (Be particularly cautious if the dose is already 450 mg/d or above because of the increased risk of side effects, notably seizures.) Monitor the patient's mental state and side effects. Review the patient and repeat the assay after at least 1 week on the new dose. (If suspension/ crushed clozapine tablets are prescribed ensure bottle shaken for full 90 seconds before administration.)
0.35-0.50	**Good**	Consider repeating the assay after 6 months, then annually unless the patient's response deteriorates or troublesome side effects occur. If side effects are persistent or serious consider cautious dose reduction, but bear in mind the possible loss of response.
	Poor/ Incomplete	If clozapine treatment has continued for at least 3–6 months at the current dose, consider psychosocial intervention. Augmentation with other psychoactive drugs has been found by some to be of benefit. It is important that any such attempts should be carefully considered with respect to side effects (including the risk of neutropenia) and possible interactions.
0.51-0.99	**Good, with no clinical features of toxicity**	Review the treatment. Consider cautious dose reduction particularly if level is >0.6mg/L (e.g. 25 mg/d in week 1 and a further 25 mg/d in week 2, etc.), but balance this reduction against the risk of diminishing the patient's response to clozapine. Consider using an anticonvulsant (not carbamazepine due to neutropenia/interactions or not sodium valproate in women of child bearing potential) as prophylaxis against seizures if dose reduction is thought to be inadvisable. Monitor the patient's mental state. Repeat the assay after at least 1 week on a new dose, otherwise 3-monthly.
	Poor or incomplete or reduced and/ or with clinical features of toxicity	Consider cautious dose reduction (see above) to bring plasma clozapine below 0.6 mg/L. Monitor the patient's mental state. Repeat the assay after at least 1 week on a new dose.
1.0-1.9	**Good, with no clinical features of toxicity**	Review the treatment. Consider cautious dose reduction (see above) to bring plasma clozapine below 1.0 mg/L and possibly below 0.6 mg/L, but balance this reduction against the risk of diminishing the response to clozapine. Consider using an anticonvulsant (not carbamazepine due to neutropenia/interactions or not sodium valproate in women of child bearing potential) as prophylaxis against seizures. Monitor the patient's mental state. Repeat the assay after at least 1 week on a new dose, otherwise 3-monthly. **Bear in mind that plasma clozapine may continue to rise in the short term even after the dose has been reduced.**
	Poor, incomplete or reduced and/ or with clinical features of toxicity	Consider cautious dose reduction (see above) to bring plasma clozapine to below 1.0 mg/L and possibly below 0.6 mg/L. **Monitor the patient's mental state. Repeat the assay after at least 1 week on a new dose. Bear in mind that plasma clozapine may continue to rise in the short term even after the dose has been reduced.**
≥2	**Good, with no clinical features of toxicity**	Review the treatment urgently. Consider cautious dose reduction (see above) to bring plasma clozapine to below 1.0 mg/L and possibly below 0.6 mg/L. Consider using an anticonvulsant (not carbamazepine due to neutropenia/interactions or not sodium valproate in women of child bearing potential) as prophylaxis against seizures. Monitor the patient's mental state. Repeat the assay after at least 1 week on a new dose. **Bear in mind that plasma clozapine may continue to rise in the short term even after the dose has been reduced.**
	Poor, incomplete or reduced and/ or with clinical features of toxicity	Review the treatment urgently. If the patient is being treated in the community, consider admitting them to hospital for observation. Withhold clozapine for 24h and re-start at 75% of the last dose, and thereafter reduce the dose cautiously (see above) to bring plasma clozapine below 1.0 mg/L, and possibly below 0.6 mg/L. Consider using an anticonvulsant (not carbamazepine due to neutropenia/interactions or not sodium valproate in women of child bearing potential) as prophylaxis against seizures. Monitor the patient's mental state. Repeat the assay after at least 1 week on a new dose**. Bear in mind that plasma clozapine may continue to rise in the short term even after the dose has been reduced.**

Interpretation of clozapine and norclozapine ratios

- Results include clozapine and norclozapine (the active metabolite of clozapine) levels. The significance of norclozapine is unclear but the ratio of clozapine / norclozapine may aid the assessment of recent adherence.
- Norclozapine has a longer half-life than clozapine
- Norclozapine levels at therapeutic plasma levels are expected to be approx. two thirds of the level of clozapine. E.g. for a level of 0.6mg/L it would be approximately 0.4mg/L.
- Saturation of the enzyme (clozapine N-demethylation) can occur especially at higher doses/plasma levels. Saturation means that all available enzymes involved in processing clozapine to norclozapine are occupied. When saturation has occurred norclozapine levels would be expected to be lower than 2/3 of the clozapine level.
- The local pharmacist can help with interpretation of the results.

Clozapine: norclozapine ratio

Norclozapine levels	Comments
Approximately 2/3 of the clozapine level	This is normally expected when doses are within therapeutic range.
More than 2/3 of the clozapine level (i.e. clozapine 0.6mg/L = norclozapine more than 0.4mg/L)	Suggests • Erratic adherence in the preceding days • Rapid metaboliser of clozapine • Started smoking • Enzyme-inducing drug has started • Saturation of the enzyme (especially with high clozapine levels)
Less than 2/3 of the clozapine level. (i.e. clozapine 0.6mg/L = norclozapine less than 0.4mg/L)	Suggests • Sample was not a trough • Slow metaboliser of clozapine • Enzyme inhibiting drug has started • Smoking reduced significantly or stopped. (NB NRT has no effect on clozapine metabolism)

Sussex Partnership NHS
NHS Foundation Trust

Appendix 12

Patient Name

Date of birth

Address

Important information about clozapine and potentially fatal side effects

Dear Dr

Two potentially serious side effects of clozapine that are sometimes overlooked are constipation and bowel obstruction (occasionally fatal).

The above patient is to be started on **clozapine** at home on_____ under the supervision of team.

All patients initiated on clozapine will be given information about following a high fibre diet and advised to seek help from their G.P or pharmacist if they become constipated. If the patient presents to you with symptoms of constipation please ensure:

- A full history including an abdominal examination is carried out.
- Regular laxatives are prescribed. Stimulant laxatives must be prescribed for clozapine induced constipation e.g. docusate, senna or an enema preparation. **Bulk forming laxatives are NOT effective at managing this type of constipation**.
- The mental health team are informed if constipation persists.
- Prescribing of any other medication that may cause constipation as a side effect, (e.g. antimuscarinic medicines) is avoided.

Certain medicines are contra-indicated with the use of clozapine; a table of those more commonly prescribed can be found on the reverse of this letter. The manufacturer's SmPC for clozapine at www.medicines.org.uk should be referred to for a full list of contraindicated medication and additional cautions.

If this patient either starts smoking or decides to stop, please inform the mental health team. When smoking status changes, this can significantly affect plasma levels of clozapine and clozapine plasma level monitoring may be needed to ascertain if any changes to the dose are required. Dose increases for smokers of up to 70% are sometimes needed, whilst the average patient who stops smoking needs to reduce their dose by at least one quarter to avoid serious side-effects developing.

Whilst clozapine is being titrated the patient will be supervised closely at home. They have been given an emergency number to contact out-of-hours and at weekends if they have any side-effects or feel unwell.

Please update your records, including the prescribing system, even though secondary care will do all the prescribing, to indicate that this patient has started clozapine and to monitor for constipation. We will keep you informed of their progress. Once the patient is stabilised, if appropriate, (and with the agreement of your practice), ongoing clozapine blood tests may be undertaken at your surgery. In this event, we will advise you how this may be facilitated.

Yours sincerely,

Appendix 13 The most common drug interactions with clozapine

Drug	Interactions	Comments
Bone marrow suppressants (e.g. carbamazapine, chloramphenicol), sulphonamides (e.g. co-trimoxazole), pyrazolone analgesics (e.g. phenylbutazone), penicillamine, cytotoxic agents and long-acting depot injections of antipsychotics	Interact to increase the risk and/or severity of bone marrow suppression.	Clozapine **must not be used** concomitantly with other agents having a well known potential to suppress bone marrow function.
Anticholinergics	Clozapine potentiates action of these agents through additive anticholinergic activity.	Observe patients for anticholinergic side-effects, e.g. constipation, especially when using to help control hypersalivation.
Antihypertensives	Clozapine can potentiate hypotensive effects of these agents due to sympathomimetic antagonistic effects.	Caution is advised. Patients should be advised of the risk of hypotension, especially during the period of initial dose titration.
Alcohol, MAOIs, CNS depressants, including narcotics and benzodiazepines	Enhanced central effects. Additive CNS depression and cognitive and motor performance interference when used in combination with these drugs.	Caution is advised if clozapine is used concomitantly with other CNS active agents. Advise patients of the possible additive sedative effects and caution them not to drive or operate machinery. Monitor for respiratory depression especially with benzodiazepines.
Highly protein bound substances (e.g. warfarin and digoxin)	Clozapine may cause increase in plasma concentration of these substances due to displacement from plasma proteins.	Patients should be monitored for the occurrence of side effects associated with these drugs, and doses of the protein bound substance adjusted, if necessary.
Phenytoin	Addition of phenytoin to clozapine regimen may cause a decrease in the clozapine plasma concentrations.	If phenytoin must be used, the patient should be monitored closely for a worsening or recurrence of psychotic symptoms.
Lithium	Concomitant use can increase the risk of development of neuroleptic malignant syndrome (NMS).	Observe for signs and symptoms of NMS.
CYP1A2 inducing substances (e.g. **Smoking** and omeprazole)	Concomitant use may decrease clozapine levels	Potential for reduced efficacy of clozapine should be considered. Hydrocarbons not nicotine.
CYP2D6 inducing substances (e.g. paroxetine and fluoxetine)	Concomitant use may decrease clozapine levels	Potential for reduced efficacy of clozapine should be considered.
CYP1A2 inhibiting substances (e.g. fluvoxamine, caffeine, ciprofloxacin)	Concomitant use may increase clozapine levels	Potential for increase in adverse effects. Care is also required upon cessation of concomitant CYP1A2 inhibiting medications as there will be a decrease in clozapine levels. If caffeine is abstained from for a significant period levels may decrease.

Taken and abridged from SmPC for Denzapine last revised 15/11/2019

Appendix 14 **Red alert with clozapine flowchart**

DMS detects a red result. The registered contact (consultant psychiatrist or nominated deputy) and the clozapine supply service is contacted.

STOP CLOZAPINE IMMEDIATELY and advise the patient to stop taking clozapine until further notice. **Document** the clinical plan in care notes

Monitor the patient's physical health especially for signs of infection and give advice on what signs of infections need immediate medical advice.
Monitor mental state.

Arrange an emergency blood test. Two green results are required before restarting.
If blood tests are required out of hours liaise with the **CRHT team**.

Send the emergency blood test to the local pathology lab or Yumizen machine.
Document in care notes and inform the local pharmacist, clozapine supply service or the on-call pharmacist (out of hours) where the blood test has been sent.

The clozapine supply service or the on-call pharmacist will obtain the blood test results and **enter** the results on DMS to receive a result.

When two **green results** have been given the supply service or on call pharmacist will inform the team or ward that the clozapine can be **restarted**.
If this is longer than **48 hours** the clozapine must be **retitrated**

If it is a confirmed **red result** the clozapine will be contraindicated**.**
Clozapine can only be **re-challenged** with the full MDT approval including pharmacy and haematology. An **off label** form must be completed.

Physical observations
Daily checks - temperature, BP, pulse rate and respiratory rate.
Monitor for clinical signs and symptoms of infection (e.g. fever, sore throat, mouth ulcers etc.).
The medical team should be updated on the patient's progress and informed if any physical health concerns occur.

Mental state examinations
Monitor mental state on an on-going basis as a psychotic relapse

Appendix 15 **Amber alert with clozapine flowchart**