MANCHESTER CITY COUNCIL

Manchester Mental Health and Social Care Trust NHS

Clozapine Guideline – Community

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Document Change History

Changes to this document in different versions must be detailed below. Rationale for the change should also be given

Version Number / Name of procedural document this supersedes	Type of Change i.e. Review / Legislation / Claim / Complaint	Date	Details of Change and approving group or Executive Lead (if done outside of the formal revision process)
v1 Care Pathway for the Management of Clozapine - Community	Review of pathway and appendices	September 2013	Ratified by the Medicines Management Committee.
V1.1 Care Pathway for the Management of Clozapine - Community	Review of pathway and appendices	November 2014	Ratified by the Medicines Management Committee.

External references used in the creation of this document:
If these include monitoring duties upon the Trust for this policy the specific details should be recorded on the **Monitoring and Compliance Requirements sheet**

Privacy Impact Assessment submitted	N/a	Any issues?	Choose an item.
Fraud Proofing submitted	N/a	Any issues ?	Choose an item.
If not relevant to this procedural document give rationale:			
Policy authors are asked to consider each of the nine protected characteristics under the Equality Act 2010. We expect you to demonstrate that throughout the policy process you have had regard to the aims of the Equality Duty: 1. Eliminate unlawful discrimination, harassment and victimisation and any other conduct prohibited by the Act; 2. Advance equality of opportunity between people who share a protected characteristic and people who do not share it; and 3. Foster good relations between people who share a protected characteristic and people who do not share it. Please provide a brief account of how you have done this, further work to be completed and any support you have had in considering the aims and working in compliance with the Equality Duty. If you are unclear on how to do this or would like further advice and support then you may contact quality.admin@mhsc.nhs.uk. It is the responsibility of the approving group to ensure this statement reflects the Trusts objectives and position with compliance as set out within the NHS Equality Delivery System			

In line with the Trust values we may publish this document on our External Website. Is there any reason you would prefer this is not done?	

Monitoring and Compliance Requirements Sheet (This section MUST be completed by the Author without exception). This section demonstrates the Trust's commitment to Continuous Improvement and Lessons Learned from Incidents, Reports from the Coroner or other External Agencies and will be submitted as evidence as required.

	Minimum Requirement/Standard/Indicator to be monitored and Section of Document it appears	Process for monitoring	Responsible Individual	Frequency of Monitoring	Responsible Committee/Group/meeting for review of results / action plan approval / implementation	Comments
1	*Please state how different aspects (standards) of the effectiveness of this Procedural Document will be monitored. If more than one standard, please enter the details in the rows below (as appropriate)*	*Audit **or** review **or** reports to committees **or** meetings*	*Please enter the title of the person(s) who will be undertaking this task.*	*Please enter how often e.g. monthly or 6 monthly or annually*	*This will normally be the Integrated Risk Management and Clinical Governance Committee. If it is different specify.*	
2	*Compliance as part of the Medicines Policy*	*Annual Report*	*Chief Pharmacist*	*Annually*	*Integrated Risk Management and Clinical Governance Committee*	
3	*Incidents Reported*	*DATIX Reports*	*Chief Pharmacist*	*Quarterly*	*Medicines Management Team*	
4						

NB: If you have selected audit you should complete the required audit registration form and standards document and submit these with your expected timescales for completing the audit to quality.admin@mhsc.nhs.uk as soon as possible and no later than 4 weeks prior to the audit commencing.
The Group / Committee should also ensure the monitoring work is added to their yearly schedule of monitoring and action logs as appropriate.

Contents

1 Introduction

Evidence base for Clozapine therapy

NICE guidance for Schizophrenia states that:

For service users whose symptoms have not responded adequately to treatment the following should happen:

- Review the diagnosis
- Check that there has been adherence to antipsychotic medication, prescribed at an adequate dose and for the correct duration
- Check that psychological treatments have been offered according to NICE guidance and review engagement with these; offer CBT if family intervention has been undertaken; if CBT has been undertaken, suggest family intervention for those in close contact with their family
- Consider other causes of non-response, for example co morbid substance or alcohol misuse,
- Concurrent use of other prescribed medication, or physical illness.
- **Offer clozapine if symptoms have not responded adequately despite sequential use of at least two different antipsychotics, one of which should be a non-clozapine second-generation antipsychotic.**
- If symptoms have not responded adequately to an optimised dose of clozapine, review the diagnosis, adherence to treatment, engagement with and use of psychological treatments, other possible causes of non-response and measure therapeutic drug levels before offering a second antipsychotic to augment clozapine. The second drug should not compound the common side effects of clozapine. An adequate trial of augmentation may need to be up to 8–10 weeks.

1.1 Rationale

Due to the complex nature of Clozapine treatment in relation to physical risks, side effects and required monitoring, this guidance is intended to provide a framework to support clinicians to initiate and use Clozapine safely and effectively.

1.2 Scope

This guidance is intended to be read by all individuals who deal with Clozapine in community settings throughout Manchester Mental Health and Social Care Trust (MMHSCT). This will include prescribers, care coordinators, Treatment Suite staff and Crisis Resolution Home Treatment Teams.

1.3 Purpose of this guideline

- To ensure clozapine is prescribed, monitored and given safely
- To ensure that all staff follow standard procedures when dealing with Clozapine
- To direct staff to the appropriate policies, guidelines and Standard Operating Procedures (SOPs)
- To ensure that the all the diverse grades and bodies of staff working within the Trust are aware of their roles and limitations with respect to Clozapine.
- To ensure that service users are offered information to help them understand the risks, benefits and monitoring requirements of Clozapine

The following additional resources have been utilised in the development of this guidance and should be referred to for further information:

Bazire, S, (2012), Psychotropic Drug Directory

British National Formulary – the most recent version can be accessed via Trust intranet

ZTAS monitoring handbook

Summary of Product Characteristics for Zaponex

http://www.ztas.co.uk/pdf/Zaponex_Summary_of_Product_Characteristics_January_2012.pdf

Taylor, D, Paton, C, Kapur, S, (2012), The Maudsley Prescribing Guidelines in Psychiatry- 11th edition – this can be accessed via the Trust intranet with an Athens password

2. Decision Processes for the Initiation of Clozapine

Due to the complex nature of Clozapine treatment, it is imperative that the decision-making process is robust and thorough. To facilitate this, please refer to and use the decision making tool. This can be found in Appendix A and via the following link **Appendix A**

Please Note:

If any contraindications are identified re: the initiation of clozapine treatment, please refer to the following points:

- If Clozapine is specifically contraindicated by ZTAS the service user must not be commenced on Clozapine and must be referred back to the Consultant

- If there is a complexity issue or unlicensed use issue, then a further multidisciplinary team (MDT) meeting must be called. This meeting must involve a pharmacist

Wherever possible, service users who are being initiated in the community should have family / carer support at home. In instances where this is not the case in-patient initiation / titration should be considered. Where this is not appropriate the Team including the Consultant must ensure that risks are assessed thoroughly and decision-making documented on Amigos. This assessment must include consideration of the following:

- Is the service user able to understand the risks, potential effects and understanding of what they need to be aware of?
- Has the individual service user's history – previous initiation experience / other health and risk issues been considered?
- Is there anyone that can support them at home? – Family, friends etc. Have all options been ruled out?

If after consideration of all of the above the Team and Consultant feel that community initiation is the best option, the Team must ensure that the patient has a copy of their care plan which should include information around who to contact for advice or in an emergency

3. Prior to initiation of Clozapine Treatment

Before commencing treatment with Clozapine, it is necessary to complete both mandatory and recommended checks on physical health parameters and to ensure that all safety criteria have been assessed. To facilitate this, please refer to and use the Pre-Clozapine initiation checklist within the Multi-Disciplinary Meeting. This can be found in Appendix B and via the following link.
Appendix B

Physical investigation results must be entered onto the Pre-Clozapine initiation checklist and onto Amigos.

4. Clozapine Initiation

It is imperative that the same standards and quality of care are applied when initiating clozapine in a community setting as when initiating in an in-patient setting. It is recognized that there are differences between the settings and therefore the rate of titration and required observations are different.

Please refer to and use the Clozapine Initiation tool to facilitate safe initiation in relation to observations. This can be found in Appendix C and via the following link. **Appendix C**

Please refer to Temperature Algorithm for advice on raised temperature. This can be found in Appendix D and via the following link. **Appendix D**

Please refer to and use the suggested Community Initiation Dose Regime to inform prescribing. This can be found in Appendix E and via the following link. **Appendix E**

When observations remain within normal range and the service user has completed titration and is stable on the dose, they will be discharged from the initiating team into the care of the Consultant Psychiatrist, care coordinator and Clozapine clinic. A clear plan must be in place for the patient to be reviewed by their normal care team.

5. Clozapine Monitoring

Advice and guidance on the mandatory and additional monitoring requirements can be found in the Clozapine Monitoring information. This can be found in Appendix F and via the following link. **Appendix F**

Clozapine serum assay guidelines can be found in **Appendix G** and via the following link http://nww.mhsc.nhs.uk/Downloads/Clozapine/Clozapine%20Serum%20Assays%20guideline.doc

6. Ongoing Prescribing Requirements

For responsibilities for prescribing of Clozapine after initiation is complete, please refer to Ongoing Prescribing Requirements (Appendix H or via the following link) **Appendix H**

7. Side Effect Monitoring and Management

Clozapine has a wide range of side effects. Many of these can be minimised at the beginning of treatment if the dose of Clozapine is titrated slowly. Please see Management of common adverse effects for advice re: management. This can be found in Appendix I and via the following link. **Appendix I**

During Clozapine titration, monitoring for side effects should occur on a daily basis and a full side effect assessment completed weekly until the end of the titration period. Identified side effects must be documented on Amigos and the prescriber should be notified immediately. Please see rating scale for Clozapine side effects. This can be found in Appendix J and via the following link. **Appendix J**

Following titration, side effects should continue to be assessed regularly. Ideally this should be done each time a service user has mandatory follow up bloods and an entry made onto Amigos to state outcome. A full side effect assessment using a validated side effect measuring tool must be completed at least every 6 months

8. Amber Results

Upon receipt of an Amber result by ZTAS, the *Amber Warning* procedure is started.
ZTAS will contact the service users healthcare providers by telephone and an "*Amber Warning"* is faxed to warn about the amber result and to advise twice weekly monitoring.

9. Red Results

Upon receipt of a Red result it is essential that Clozapine is stopped immediately and the Red Result Procedure is followed. This can be found in Appendix K and via the following link. **Appendix K**

10. Transfer of service users between services

When a service user on clozapine is transferred to a different team or ward within the Trust it is vital that all information relating to their clozapine treatment is transferred with them. Please refer to Transfer checklist – within the Trust. This can be found in Appendix L and via the following link. **Appendix L**

When a service user is transferred to a service outside the Trust please refer to Transfer of service users to external services. This can be found in Appendix M and via the following link. **Appendix M**

If transfer into Trust services from an outside organization occurs please refer to Transfer of service users into the Trust from external services. This can be found in Appendix N and via the following link. **Appendix N**

11. Re titration Procedure

Due to the severe hypotensive effects of Clozapine , the service user's usual dose cannot be taken in the event that there has been an interval of 48 hours or more between doses.
Re titration MUST commence at 12.5mg. Please refer to Re – titration procedure. This can be found in Appendix O and via the following link. **Appendix O**

12. Information to GP

Clozapine can only be prescribed under the supervision of a Consultant psychiatrist who is registered with ZTAS. GPs therefore do not prescribe clozapine but may be involved in some of the recommended physical monitoring and must be informed when their patients are taking clozapine as this will impact on other prescribing decisions.

This can be found in Appendix P and via the following link. **Appendix P**

13. Service user information

www.choiceandmedication.org.uk/mhsc/

Appendix A

Decision-making tool for the initiation of clozapine

To be completed by Responsible Consultant or Care Co-ordinator
This must be completed for all service users. If "No" is selected in answer to any of these questions, please document rationale appropriately in the comments box if initiation is to commence

	YES	NO	Signature	Comments
Diagnosis confirmed as treatment resistant schizophrenia? If not, does the service user fulfil the criteria for other indications as per the SPC? If not being used for the licensed indications above, a second opinion is required.				
Has the service user had 2 antipsychotics for a reasonable period of time at an adequate treatment dose as per NICE guidance? Please check adherence				Clozapine cannot be commenced unless two antipsychotics have been tried for an adequate time (one of these should be an atypical agent.)
Has there been a full multidisciplinary team discussion involving the Consultant Psychiatrist, Care Co-ordinator and other interested parties? Records of discussions and decision-making must be documented on Amigos.				
Service user agreeable to initiation of treatment?				
Physical health acceptable?				
Service users smoking status?				
Is there a carer at home to support initiation? If not, please refer to overarching guideline to inform decision making.				
Decision to initiate clozapine in community?				
Decision to initiate clozapine as in-patient?				
Has the service user been registered with ZTAS? Please record registration number				

Appendix B

Pre-Clozapine Initiation Checklist

This checklist must be completed by the care co-ordinator in liaison with the Responsible Clinician

		Yes/No	Comments / date completed	Signature
1.	Contraindications to clozapine are absent. Please refer to overarching policy for details or to Clozapine SPC			
2.	Cautions for Clozapine have been considered			
3.	Clozapine drug interactions have been considered			
4.	Has the G.P been contacted to complete medicines reconciliation, allergies and to request information relating to physical health concerns, investigations and treatments?			
5.	Have the service user and carer been given information about the risks and benefits of treatment and do they understand the consequences of poor adherence with treatment?			
6.	Has the service user been given the choice and medication information leaflet and had the opportunity to watch the ZTAS DVD?			
7.	Service users adherence to oral medication is likely?			
8.	Service user is aware of the need to remain with a member of staff at the initiation base for monitoring for 6 hours on day 1?			
9.	Service user is aware of physical monitoring requirements for 4 week initiation period			
10.	Service user is aware of the need for regular bloods test and is willing to undergo weekly blood tests for the first 18 weeks, then fortnightly up until 1 year and then monthly thereafter			

11.	Service user advised not to drive and not to drink alcohol			
12.	Service user has been given health living advice re: possible weight gain			
13.	Service user's GP has been informed and asked to make record on their own electronic recording system that this service user is receiving clozapine.			
14.	G.P Clozapine Support Pack sent (see appendix 1)			
15.	Service user has been registered with ZTAS and clozapine clinic and medicines management team informed			
16.	Required Baseline Monitoring have been completed		**Test Results**	
	Initial Full Blood Count and result communicated to ZTAS			
	Initial ECG			
	Baseline glucose			
	Baseline weight, BMI and waist circumference			
	Baseline Blood Pressure			
	Urea and Electrolytes			
	Liver Function Test			
	Cholesterol and lipids profile			
	CPK			
	Troponin I or T			
	CRP			
17.	Baseline measure of mental state completed (this includes suicidality)			

Appendix C

Clozapine Initiation

Titration

Dependant on tolerability and results of physical observations, it may be necessary to slow down the titration regime in some cases.

Monitoring and observations.

Complete Clozapine Initiation Observations. Trust approved physical observation NEWS recording form should be used to document results. In addition, they should be documented on Amigos.

It is imperative that observations are undertaken when initiating clozapine in a community settings as robustly as in an in-patient setting.

Agreement should be reached before initiation as to who will be responsible for staying with the service user for the 6 hours necessary to complete all observations. eg: the care co-ordinator, Treatment suite staff, CRHT.

During this period a review will be undertaken by the appropriate Medic /Advanced Practitioner or clozapine clinic nurse. If observations are stable and following review, the service user can go home with family/carer support with advice to contact CRHT Team/attend A&E/other if necessary and as appropriate.

Clozapine Initiation Observations Information

Baseline blood pressure, pulse and temperature must be measured and recorded

DAY 1

Observations should be taken:

- prior to the first dose
- 15 minutes after the dose
- and every hour up to six hours as a minimum

Please note, this is only on DAY ONE. Observations should be sitting and standing.

Parameters		
Take action if: -		
Blood pressure (Sitting and standing)	Systolic	< 100 or > 170
	Diastolic	< 60 or > 100
	OR a postural drop of 30mmHg	
Pulse	> 100bpm	
Temperature	> 38.4 degrees C OR< 35.5 degrees C	

- Repeat the observations if outside the above parameters after 15 minutes.
- If still outside the above parameters call the doctor for advice.
- Only omit the dose if the doctor or pharmacist advises to do so as baseline observations and other factors need to be taken into consideration.
- Please see temperature advice algorithm (D) for further guidance re: temperature

Observations for subsequent doses–

DAY 2-14

Physical observations (pulse, temperature and blood pressure – sitting and standing) should be taken and recorded before every morning dose is given and then 2 hours after the morning dose.

DAY 15-28

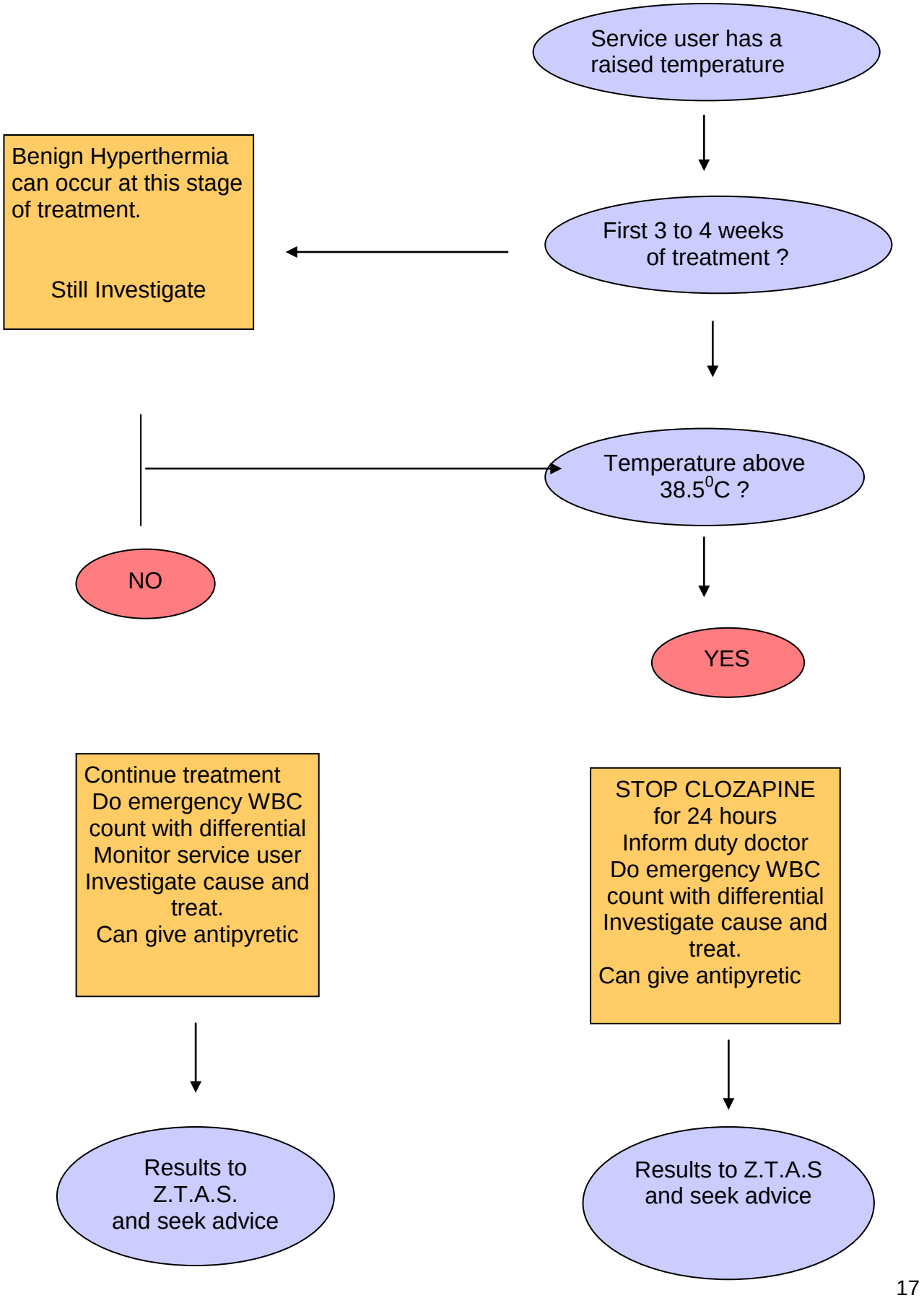
Daily physical observations (pulse, temperature and blood pressure – sitting and standing) should be taken and recorded 2 hours following the morning dose.

On- going observations and monitoring

Physical observations (pulse, temperature and blood pressure – sitting and standing) and weight should be taken and recorded at the time of routine blood testing, eg, within Clozapine clinic

Appendix D

Temperature Advice Algorithm



Appendix E

Community Initiation Dose Regime.

- Pre-initiation checks and baseline assessments should be fully completed and ready to start on first day of initiation. This should be on a Monday where possible to take weekends into account for supplies of medication.
- Ensure a green blood result is obtained from ZTAS before initiation begins.
- The first Clozapine Prescription for Day 1-7, must be completed on a medication prescription and administration record chart, and issued by pharmacy when a green result is obtained and before treatment begins. This prescription must be written by the prescriber in the CRHT if the CRHT are responsible for the administration and monitoring. This responsibility remains until initiation is completed.
- If administration and monitoring is done in the treatment suite then prescribing should be carried out by the community consultant.
- Registered nurse must review the service user prior to leaving department. If any problems / concerns are identified, please refer the service user to a Doctor or Advanced Practitioner.
- Blood tests should be taken on Days, 8, 15 and 22.

Suggested Dosing Schedule for Non in-patient initiation

Week 1

DAY	DAY OF TREATMENT	AM	PM
Monday	Day 1	12.5mg	NIL
Tuesday	Day 2	12.5mg	NIL
Wednesday	Day 3	25mg	NIL
Thursday	Day 4	25mg	NIL
Friday	Day 5	37.5mg	NIL
Saturday	Day 6	37.5mg	NIL
Sunday	Day 7	37.5mg	NIL

Week 2

DAY	DAY OF TREATMENT	AM	PM
Monday	Day 8	12.5mg	25mg
Tuesday	Day 9	12.5mg	25mg
Wednesday	Day 10	25mg	25mg
Thursday	Day 11	25mg	37.5mg
Friday	Day 12	25mg	37.5mg
Saturday	Day 13	25mg	37.5mg
Sunday	Day 14	25mg	37.5mg

Week 3

DAY	DAY OF TREATMENT	AM	PM
Monday	Day 15	37.5mg	37.5mg
Tuesday	Day 16	37.5mg	37.5mg
Wednesday	Day 17	37.5mg	50mg
Thursday	Day 18	37.5mg	50mg
Friday	Day 19	50mg	50mg
Saturday	Day 20	50mg	50mg
Sunday	Day 21	50mg	50mg

Week 4

DAY	DAY OF TREATMENT	AM	PM
Monday	Day 22	50mg	75mg
Tuesday	Day 23	50mg	75mg
Wednesday	Day 24	75mg	75mg
Thursday	Day 25	75mg	75mg
Friday	Day 26	75mg	100mg
Saturday	Day 27	75mg	100mg
Sunday	Day 28	75mg	100mg

Appendix F

Clozapine Monitoring

Risks of neutropenia and agranulocytosis

The incidence of neutropenia during treatment is approximately 3% with 0.5% of service users developing agranulocytosis.

Service users are told to report to the hospital or their GP if they develop signs of neutropenia or infection.

If a service user presents with signs of neutropenia including:

- sore throat
- temperature
- mouth ulcers
- unexplained bruising

Please send a full blood count for urgent analysis.

The result of the blood test should be telephoned through to the ZTAS telephone number..

Mandatory Monitoring

Regular blood monitoring is a mandatory requirement for continuing Clozapine Therapy. This is due to its association with serious haematological side effects such as neutropenia and agranulocytosis. The purpose of blood monitoring is early detection of haematological side effects and the prevention of exacerbation of such side effects, which might put service users at serious health risk. **The service user must have a weekly blood test for 18 weeks, then 2 weekly until the service user has been on Clozapine for 1 year, then 4 weekly thereafter.**

Additional Monitoring Requirements

Along with the mandatory blood monitoring detailed above, the table below shows additional monitoring requirements.

	Initial visit*	4 weeks*	8 weeks*	12 weeks	6 months	9 months	12 months	6 monthly thereafter	Annually thereafter
U&Es, including eGFR	X						X		X
Blood lipids (ideally fasting)	X			X	X	X	X		X
BMI = Weight/†Height	X	X	X	X	X	X	X		X
Waist circumference (cm)	X	X	X	X	X	X	X		X
Fasting blood glucose‡ (repeat if abnormal)	X	X			X		X	X	
ECG	X						X		X
Blood Pressure (sitting & standing)	X	X	X	X	X		X		X
LFTs	X						X		X
Troponin T or I	X weekly	X							
CRP	X weekly	X							
Creatine Phosphokinase (CPK)	X								

As part of the initiation process, MMHSCT will be responsible for the blood monitoring required at baseline and 1 month. It is essential that results are shared with the G.P in writing (this excludes mandatory ZTAS bloods discussed in section above).
Future arrangements relating to monitoring must be communicated to G.Ps clearly and in writing. This should be done by the prescriber and must include information as to exactly what monitoring is required with the request that they share results with the prescriber.

In the case that additional monitoring (as per table above) is managed via the G.P, The Clozapine Clinic Team should contact the G.P at the required times to ensure that service users are receiving the required monitoring and that results are shared with the prescriber.
In cases whereby the service user has not received additional monitoring via the G.P, the Clozapine clinic team should arrange for this to be completed or undertake monitoring as appropriate ensuring results are communicated to the G.P and prescriber.

Substance use and misuse

Smoking cessation has been reported to increase clozapine levels by up to 73% (Thompson, 2007), since cigarette smoke is an inducer of the cytochrome P450 system. If your service user wants to quit/ reduce smoking then inform the mental health team. A dose reduction may be appropriate when stopping smoking. Side effects should be reviewed regularly during the period of cutting down.
Plasma clozapine concentration is increased by caffeine intake and decreased by 50% following a 5-day caffeine free period (Novartis, 2007). Advise service user to maintain a stable caffeine intake and inform mental health team of any changes.
The effect of drinking alcohol when taking clozapine is known to be increased levels of sedation

Appendix G

Guideline for the Monitoring and Management of Clozapine Plasma Levels

Medicines Management Committee July 2008
Reviewed: July 2010, October 2012
For Review: October 2014

Lay summary

Clozapine is an antipsychotic medication that works better than other drugs for “treatment resistant schizophrenia”, which is schizophrenia that does not improve much after at least two other antipsychotic medications have been tried. Unfortunately it has many side effects and some can be serious. The dose needs to be high enough for the drug to work but not so high it causes too many side effects. Checking the level of clozapine in the blood can help doctors get this right. This guideline talks about how to get the dose right, when to do clozapine blood levels and how to use the information.

Sometimes, but not always, it can be useful to check levels when treatment is started; if people do not get better; if the team starts another drug as well; if a clinical team is not sure how regularly somebody takes the medicine; if the person taking clozapine stop smoking, has lots of side effects or gets physically ill.

Clinicians’ summary

This guideline covers these topics:

1. the threshold for response and for toxicity
2. how monitoring can be used in relation to initial titration and a scheme for determining the target dose for titration
3. situations during maintenance when monitoring might be appropriate.
4. Briefly: prescribing for the elderly and in special situations
5. Actual serum level-dose nomograms (from Rostami-Hodjegan et al., 2004)
6. Some relevant references

In turn, point 3 above covers these situations:

1. When to check levels for the first time (when increasing the dose)
2. When to do levels during dose escalation or reduction where previous levels are available
3. When there is evidence of acute (perhaps severe) or chronic (mild) toxicity
4. When adherence is uncertain
5. Smoking: stopping and starting
6. Other drugs that potentially interact
7. Intercurrent inflammation

The following is not intended as an exhaustive list or to replace clinical judgement. A relevant review of clozapine prescribing is Nielsen, J. et al. (2011).

Possible thresholds for response and side effects

Serum threshold for response has been identified as between 0.35 and 0.42mg/l in different studies (most near 0.35mg/l); apart from in people of Chinese or Korean descent who are often more sensitive - levels necessary for response of the order of 0.2mg/l have been suggested but this is uncertain.

Likelihood ratios (a measure of the usefulness of the threshold) are not high enough to make serum level a very good predictor of response: response is only 3 times more likely above the threshold than below it. This implies some patients may not respond above 0.35-0.4mg/l and some will respond to lower doses (e.g. possibly 0.15 or 0.2mg/l or about 200mg/day). Moreover, patients often relapse with serum levels >0.45mg/l, though this group may have more variable levels.

However, serum Clozapine level does predict side effects, correlating weakly (**r** about 0.26). Twice as many suffer side effects above a threshold of about 0.35mg/l in mainly Caucasian samples.

There is no evidence of efficacy being better above 0.6mg/l but side effects are definitely increased in this group. The risk of seizure is believed to increase above 600mg/day dose, which implies this sort of plasma level. There is a clearer link between seizures and plasma levels over 1.0mg/l, and other types of toxicity and levels over 0.75mg/l. Although some clinicians advocate trials of high levels in certain situations, there is not yet evidence to support this. There have been countervailing suggestions that above 0.75mg/l anticholinergics effects may increase, leading to delirium-like side effects in sensitive individuals.

The ratio of plasma level to dose in a London sample of 103 (Yusufi, B. et al., 2007) had a mean of 1.03 (SD 0.63) microgr/l per mg/day for men and 1.78 (SD 1.05) microgr/l per mg/day for women. This is consistent with the dose and concentration figures for seizure risk above, though women are therefore at higher risk than men.

There is data that suggests plasma levels are up to 50% higher in non-smokers (Rostami-Hodjegan et al, 2004; below). There are also effects of age and weight (see tables and explanatory notes below).

Starting clozapine: suggested initial target doses
The aim of these suggested initial target doses is to give a guide to what dose a patient of a given smoking history, sex, age and weight might need to achieve a serum level above about 0.35mg/l without an unacceptable risk of toxicity, once they have titrated up to a stable clozapine dose.

To calculate an appropriate suggested dose first select one of the initial 4 values adjusted for sex and smoking history immediately below. [*At these doses the chance of plasma levels over 1.0mg/l is approximately 5% or less but there is about 50% chance of plasma level under 0.35mg/l.*] Then add or subtract according to the weight and age tables to give a **rough** guide to the correct threshold. [*These tables are estimated from Rostami-Hodjegan et al.'s nomograms to approximations of 25mg for convenience.*]

425 mg/day in male smokers;
250 mg/day in male non-smokers;
325 mg/day in women smokers; or
225 mg/day in female non-smokers
(depending on side effects, weight and age: see below).

Weight
This decreases expected concentration at 5% every 10kg over 80kg.
Suggested difference from reference threshold dose (mg/d) by weight (kg).

Weight	***Male smoker***	***Female smoker***	***Male non-smoker***	***Female non-smoker***
60kg	**-50**	**-25**	**-50**	**-25**
80kg	reference	reference	reference	reference
100kg	**+75**	**+50**	**+50**	**+0**

Table constrained by population limits of original study..

Age
This increases expected concentration by 4% per 5 years over 40.
Suggested difference from reference threshold dose (mg/d) by age.

Age	***Male smoker***	***Female smoker***	***Male non-smoker***	***Female non-smoker***
20	**+100**	**+100**	**+50**	**+25**
40	reference	reference	reference	reference
50	**-50**	**-25**	**-25**	**-25**

Table constrained by population limits of original study..

The suggested initial dose thresholds thus vary from under 200mg for a 10 stone female non-smoker of 50 to 600mg for a 16 stone 20 year old male smoker.

Continuing clozapine: situations in which to perform serum assays

1. If increasing Clozapine dose blind (i.e. without a previous level) above the thresholds suggested on the previous page

For instance, when trying to find the maintenance dose after initiating clozapine. This will of course depend on whether the patient has tolerated this dose before, their current level of side effects, whether there are previous serum levels to act as a guide etc.

Incidentally, even patients with adequate serum levels and poor initial responses (less than 20% reduction in symptoms after 6 weeks) can respond to clozapine by 4-6 months, with some evidence that in these cases slow increases in levels occur. If there is very little response within 6 weeks there is less chance of eventual response, so checking levels if target dose has been reached (see above) or adverse effects limit dose is sensible. However, it is reasonable to continue clozapine monotherapy at a serum level >0.35mg/l (or even 0.42mg/l) for at least 4 months before considering augmentation or switching.

2. If increasing doses from an already high dose, after previous levels

This depends on what the previous level was, the dose increase envisaged and the nature of the patient (see above). It will often be in a patient with a low serum level but a high dose (i.e. they metabolise clozapine unusually effectively). In general, clozapine's levels change in a linear way: so increasing dose by 30% increases levels by about 30%, provided other factors affecting metabolism (other drugs, smoking etc) are unchanged. However, there is evidence that clozapine's kinetics can saturate at clinical levels, usually at high doses or serum levels. That is, serum levels can suddenly increase as the dose goes up and the metabolising enzymes' capacity saturates. The serum level suddenly shoots up at that point and can go from clinically appropriate (e.g. 0.35-0.6mg/l) to toxic (e.g. >1mg/l).

3. If side effects suggest a high serum level

a. Sudden onset of side effects suggests irregular compliance. This can be a dangerous, even fatal situation so patient, dose and administration regime need reviewing. Myoclonus has been identified as a particular warning sign of seizure (patients are often jittery too) but sedation and clouding of consciousness can occur, plus the full range of other side effects. Acute onset may be dealt with by omitting doses (clozapine has a short half life so this can fix the problem in hours) and then restarting at lower dose for a period (e.g. a few days). Covering seizure risk with valproate and checking ECG are often prudent; sometimes benzodiazepines are used but they can worsen sedation and risk more serious side effects. They and valproate can theoretically slow the drop in serum levels but this is probably usually a minor effect.

b. Chronic adverse effects are a different problem. Reducing dose can alleviate adverse effects that might otherwise threaten therapy and reduce quality of life (or even risk mortality) but it may be appropriate to establish serum levels afterwards, particularly if previous levels offer a guide to the risk of relapse. Reviewing co-prescription is also wise (e.g. anticholinergics treat sialorrhoea but increase risk of urinary side effects, constipation and even ileus).

4. To monitor compliance

This is best done in conjunction with the nomograms. The Clozapine/norclozapine ratio can be informative. Since norclozapine has a longer half life, a high ratio suggests the patient only took Clozapine recently. The median ratio is 1.3 but the range is wide, commonly 0.3-3. An individual patient often has a stable ratio, provided other drugs, smoking etc have not changed, so previous CLZ/NCLZ is a guide.

5. Stopping smoking
Clozapine levels can change substantially when patients start (reducing levels) or stop (increasing levels) smoking: see the nomograms. Occasionally levels can shoot up (possibly as a result of saturation, see above). Unfortunately, changes can start quickly and continue for a couple of weeks; changes in cytochromes (especially P450 1A2) that metabolise both clozapine and the hydrocarbons in tobacco smoke often take about a week and changes in clozapine levels lag after that (depending on half life). Starting smoking is a less urgent problem because the risk of toxicity is low.

A logical approach is to decrease the dose blind (either using the nomograms or a rule of thumb of a 30-40% decrease in dose) immediately after smoking stops and then check serum levels after 2 weeks when they have probably re-stabilised.

6. If adding another drug likely to interact
These include some antidepressants: tricyclics, SSRIs (to varying extents) and others. Reboxetine seems the least prone to increase levels; with fluvoxamine the most reliable and dramatic interaction; modest effects for low dose paroxetine; and only case reports of problems for sertraline, citalopram and escitalopram despite studies showing their usual effects are minimal. Citalopram, like venlafaxine (which also can occasionally increase levels) has the risk of QTc prolongation. The little data on mirtazapine are consistent with little effect.

Benzodiazepines do not much affect clozapine's kinetics. There is a potential for respiratory suppression as well as the risk of bone marrow suppression common to psychotropics.

Carbamazepine, phenytoin and phenobarbital all decrease levels; valproate and lamotrigine can increase levels but this is often not clinically significant. .

There is little evidence of major effects with quetiapine, risperidone, sulpiride, amisulpride; or perhaps aripiprazole and olanzapine.

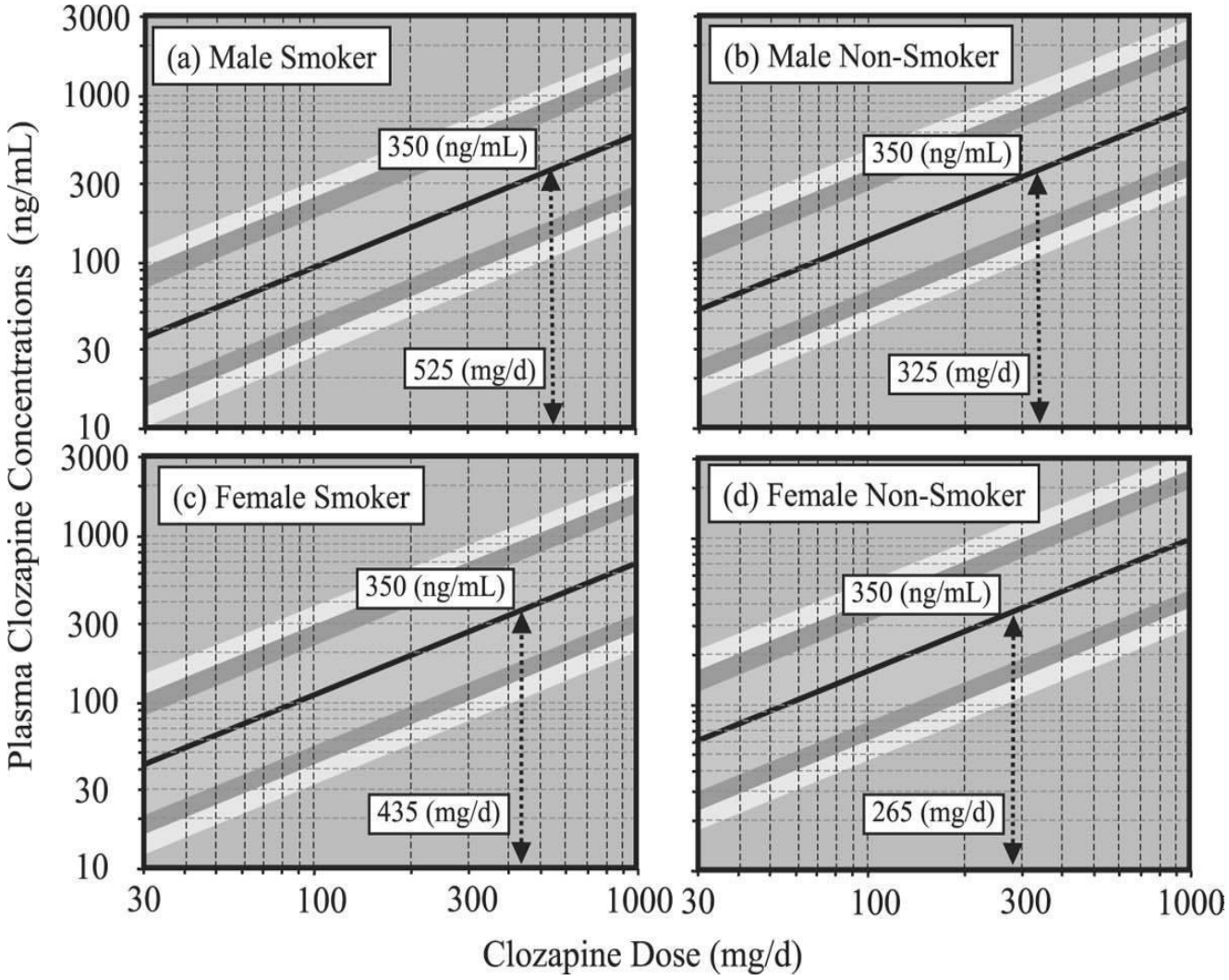
However, like anticonvulsants these drugs can have effects on serum levels and if there is evidence of toxicity they should be checked. Any drugs that affect the major metabolising enzymes (e.g. cytochrome P450 1A2 & 3A4, perhaps 2D6) or reduces plasma proteins' carrying capacity risks increasing levels (e.g. warfarin etc.). There are reports of toxicity with pregabalin.

7. In the presence of systemic inflammation
There is no good evidence on this topic but there are case series suggesting that clozapine levels may increase significantly with intercurrent inflammation (e.g. Pfuhlman, B. et al., 2009) and perhaps alterations in immune function, either during infection, autoimmune processes or cancer. Interactions of clozapine with cytokines, down-regulated cytochrome P450 activity or changes in plasma protein carrying capacity have been proposed as the reason, though often other medication is being initiated at the same time. In any case levels should be carefully monitored during these periods and extra vigilance for evidence of toxicity, which can resemble symptoms of the physical illness. One survey (Taylor D. et al., 2009) found an incidental association between clozapine use and risk of death from pneumonia (though quite possibly a chance finding or confounded by patient characteristics).

Age over 50
Serum thresholds are uncertain: there is no reason to expect efficacy threshold to be different but sensitivity might well be greater and metabolism slower in the elderly. Very few data exist for this group (reviewed by Suzuki et al., 2011). Trials have been too small to test efficacy realistically, though there are suggestions that it may be reduced over 65. Low doses (at least 30% lower over 65 according to models) e.g. 50% or lower are often used (300mg a day was tolerated reasonably in one trial of >55 year olds).

Further limitations of serum assays
In patients with a predisposition to adverse effects, e.g. seizures, the usual thresholds are unlikely to apply. Serum monitoring may only be useful here in achieving a plausible therapeutic concentration while minimising the risk of a high serum level. Further, where anticonvulsants are co-prescribed to minimise seizure risk, it important to dose them accordingly, monitoring their serum levels if appropriate, without confusion arising about their possible use as mood stabilisers

Concentration-Dose Nomograms from Rostami-Hodjegan et al. (2004)



Key References

Nielsen J, Damkier P, Lublin H, Taylor D (2011) Optimizing clozapine treatment. *Acta Psych Scand* 123; 411-22.

Pfuhlmann, B., Hiemke, C., Unterecker, S. et al. (2009). Toxic clozapine serum levels during inflammatory reactions. *J Clin Psychopharmacol*. 29(4); 392-4, 2009.

Rostami-Hodjegan, A, Amin, AM, Spencer, EP, et al. (2004) Influence of dose, cigarette smoking, age, sex, and metabolic activity on plasma clozapine concentrations: a predictive model and nomograms to aid clozapine dose adjustment and to assess compliance in individual patients *J Clin Psychopharmacol* 24 (1), 70-78

Suzuki, T., Remington, G., Uchida, H. et al. (2011). Mangement of schizophrenia in late life with antipsychotic medications A qualitative review. *Drugs Aging* 28 (12); 961-80

Taylor ,DM,, Douglas-Hall, P,, Olofinjana, B, et al. (2009). Reasons for discontinuing clozapine: matched, case-control comparison with risperidone long-acting injection. *Br J Psychiatry*. 194; 165-167.

Yusufi B, Mukherjee S, Flanagan R et al. (2007) Prevalence and nature of side effects during clozapine maintenance treatment and the relationship with clozapine dose and plasma concentration. *Int J Psychopharmacol* 22; 238-43.

Summary of Clozapine plasma level interpretation

Trough Clozapine plasma level (micrograms / L)	Clinical Response	Comment
<10 micrograms / L or not detected	Any	Clozapine unlikely to have been taken for at least a week unless in the very early stages of initiation.
<350 micrograms / L	Good	Continue current dose, repeat levels annually or sooner if response deteriorates, or adverse reactions become troublesome.
	Poor or incomplete	If poor adherence is suspected, consider education, supervised consumption, reminder cards, compliance aids or using crushed tablets. If no improvement, consider a cautious dose increase , monitoring response and tolerability. Repeat level after 1 week at new dose.
350 – 600 micrograms / L (Target range for good clinical response vs minimal toxic effects)	Good	Continue current dose, review regularly for continuing response and tolerability. Consider repeating levels annually
	Poor or incomplete	If clozapine has continued for at least 3 to 6 months and still incomplete response, consider augmentation with another suitable psychotropic.
601 – 999 micrograms /L	Good with no features of toxicity	Consider a cautious dose reduction, weighing against response, risk and tolerability. If considered essential to maintain at current dose , consider using a prophylactic anticonvulsant to protect against seizures (usually lamotrigine or valproate) Monitor closely for tolerability and response.
	Poor, incomplete or features of toxicity	Consider a cautious dose reduction, weighing against response, risk and tolerability. Repeat levels once stabilized on new dose.

>1000 micrograms /L (upper limit not well defined)	Any	Review urgently. Consider a dose reduction to bring levels down below 1000 micrograms /L and ideally below 600 micrograms/L, weighing against risk, response and tolerability. If clinical signs of toxicity (severe sedation, delirium, falls, seizures) consider withholding clozapine for 24 hours and re introducing at a lower dose. Consider initiating an anticonvulsant to protect against seizures. Repeat levels once the lower dose is stabilized.

Ensure all plasma levels are taken at trough level (approx 12 hours after previous dose) before interpreting the result

A plasma level is recommended after the initial titration stage once the target dose has been reached and has been stable for at least a week.

Undetectable plasma levels indicate non adherence over at least the preceding week. Clozapine tablets should be removed and re-titration considered if appropriate.

Partial adherence will result in unpredictable plasma levels which are difficult to interpret.

In suspected poor adherence repeating levels at regular intervals may be useful to detect trends.

Ref: Bleakley,S.,Taylor,D. *(*Aug 2013). *Clozapine Handbook* :*First edition.* Dorsington: Lloyd-Reinhold

Appendix H

Ongoing Prescribing of Clozapine

The maximum validity of any prescription (excluding controlled drugs) is 6 months, therefore a new prescription for clozapine must be written at least every 6 months in accordance with legal requirements. Therefore, all patients on clozapine will require a review of their treatment at least every 6 months. Following this review, a new prescription must be supplied to the dispensing pharmacy.
If prior to this 6 monthly review, changes are made to treatment including dose, frequency, times of administration, a new prescription must be supplied to the dispensing pharmacy. This new prescription will then invalidate and replace the previous prescription. Failing to supply a prescription reflecting the changes, will lead to patients continuing to receive the medication prescribed previously.
Following any changes to a service users clozapine treatment regime, the G.P must be informed and asked to update their records accordingly.

Please see SOP 1 Prescribing of medicines for further information. This can be accessed via the following link: http://nww.mhsc.nhs.uk/Downloads/Medicine%20Management/Sop%20Documents/SOP%2001%20Prescribing%20of%20Medicines.pdf

Appendix I

Management of common adverse effects

Adverse Effect	Time Course	Action
Sedation	First few months. May persist, but usually wears off	Give smaller dose in the morning. Reduce dose if necessary – check plasma level.
Hypersalivation	First few months. May persist, but sometimes wears off. Often more troublesome at night.	Consider prescribing of hyoscine at night
Constipation	Usually persists	Recommend high fibre diet. Bulk forming laxatives and stimulants should be used. Effective prevention or treatment is essential as death may result.
Hypotension	First 4 weeks	Advise service user to take time when standing up. Reduce dose or slow down rate of increase. If severe consider meclobemide and Bovril, or fludrocortisone
Hypertension	First 4 weeks, sometimes longer	Monitor closely and increase dose as slowly as is necessary. Hypotensive therapy (eg, atenalol 25mg / day is sometimes necessary)
Tachycardia	First 4 weeks, but sometimes persists	Very common in early stages of treatment, but usually benign. Tachycardia, if persistent at rest and associated with fever, hypotension or chest pain, may indicate myocarditis. Referral to cardiologist advised. Clozapine should be stopped if tachycardia occurs in the context of chest pain or heart failure. Benign sinus tachycardia can be treated with atenalol.
Weight Gain	Usually during the first year of treatment.	Dietary counselling is essential. Advice may be more effective if given before weight gain occurs. Weight gain is common and often profound (>10lbs)
Fever	First 3 weeks	Clozapine induces increased inflammatory response. Give anti-pyretic but check FBC. Reduce rate of titration. This fever is not usually related to blood dyscrasias, but beware myocarditis.

Seizures	May occur at any time	Dose -/ dose increase related . Consider prophylactic valproate * if on high dose or with high plasma level. After a seizure: withhold Clozapine for 1 day; restart at reduced dose; give sodium valproate. EEG abnormalities are common in those on Clozapine.
Nausea	First 6 weeks	May give ant-emetic. Avoid prochlorperazine and metclopramide if previous EPSEs.
Nocturnal enurisis	May occur at any time	Try manipulating dose schedule. Avoid fluids before bedtime. May resolve spontaneously, but may persist for months or years. In severe cases, desmopressin is usually effective but it is not without risk: hyponatraemia may result. Anticholinergic agents may be effective but support for this approach is weak.
Neutropenia / agranulocytosis	First 18 weeks (but may occur any time)	Stop Clozapine; admit to hospital if agranulocytosis confirmed.
*Usual dose of Sodium Valproate is 1000-2000mg/day. Plasma levels may be useful as a rough guide to dosing – aim for 50-100mg/l. Use of modified-release preparation (Epilim Chrono) may aid compliance: can be given once daily and may be better tolerated.		

Appendix J

Rating Scale to Assess the Side-Effects of Clozapine

Service User Details:

NAME..... DATE..... AGE..... SEX: M / F

CURRENT MEDICATION.....

(+ TOTAL DAILY DOSE).....

CODE:

0 = None; **1** = Mild; **2** = Moderate; **3** = Severe

Since starting your medication, have you experienced:

1) Any dizziness?	**0 1 2 3**
2) Problems with constipation?	**0 1 2 3**
3) Problems with urinary retention or incontinence?	**0 1 2 3**
4) Twitching of your face or lips?	**0 1 2 3**
5) Low energy or sleepiness?	**0 1 2 3**
6) Difficulty concentrating or remembering things?	**0 1 2 3**
7) Low mood?	**0 1 2 3**
8) Problems with sexual drive or function?	**0 1 2 3**
9) Problems with drooling / lot's of saliva?	**0 1 2 3**
10) Any weight gain?	**0 1 2 3**
11) Any blackouts or fainting?	**0 1 2 3**
12) Have you been feeling nauseous?	**0 1 2 3**

Appendix K

Red Result Procedure

As soon as a RED result is recorded **Clozapine must be stopped immediately and all clozapine tablets withdrawn.**

The patient and RC must be informed immediately. If RC is not available, the covering Consultant / duty consultant should be contacted. If the patient is not present, they must be recalled and all Clozapine tablets taken from them. The patient must be reviewed by the medical team immediately **as they will require close clinical and haematological monitoring.**

The Infection Prevention and Control Team must also be informed.

Medical cover for the patient will stay with usual RC during normal working hours During 5pm – 9am medical cover will be provided by on-call RC. It is the responsibility of the RC to ensure that there is a detailed clinical management plan documented on Amigos.

ZTAS will generate a fax which will be sent to the RC, the clozapine pharmacist and the dispensing pharmacy outlining details of the emergency procedure.

Obtain the faxed copy of the RED alert guideline from ZTAS and follow this procedure. Physical observations (blood pressure, pulse, temperature) should be commenced as per ZTAS guidance.

The patient should be kept under close clinical surveillance and daily blood monitoring.

The patient's status will be checked by ZTAS on a daily basis and they must receive a follow up blood result within 24hours of the initial red result

The results following the initial RED result will determine the course of further action with regards to clozapine treatment.

Follow the ZTAS RED alert guidelines and contact ZTAS for advice before re-starting clozapine treatment following a RED result.

Immediate actions to be taken

- Stop clozapine administration immediately
- Arrange for daily blood testing
- Identify other medications which could be contributing to a red result
- Perform blood pressure and pulse measurements at least once daily
- Perform oral temperature measurements at least once daily
- Instruct patient to take additional temperatures at home if patient is feeling warm or unwell
- Instruct patient to report immediately if any signs of infection develop, for example; sore throat, fever, or other flu-like symptoms

Febrile neutropenia (FN) and/or agranulocytosis

- High risk patients for FN are: patients > 60 years, patients with co-morbidities (e.g. diabetes, poor nutritional status), patients who are unwell (e.g. hypotensive, oliguric) or patients with a rapidly

- falling neutrophil count.
- If the neutrophil count falls below **0.5 x 10**9**/L**, or if a patient with neutrophil count below 1.0 x 109/L
- develops a fever (38.5°C), it is extremely important to contact the hospital haematologist or general
- medical physician for an appropriate assessment and treatment regimen for the patient*.
- If the oral temperature rises **above 38.5°C** at any time, or >38.0°C on two consecutive readings
- (with an interval of > 2 hours between the readings), or if the patient develops systemic symptoms
- of infection or septic shock (unwell, hypotensive), the following should be done:
- Take blood cultures.
- Identify focus of infection and take appropriate swabs or Mid-Stream Urine (MSU) specimens
- etc., for culture analysis.
- Start immediate intravenous broad spectrum antibiotics** such as gentamicin plus piperacillin,
- or vancomycin plus ceftazidime. Alternative antibiotics for allergic patients or those with renal
- impairment may be considered after discussion with a haematologist.
- Assess vital signs every 4 hours, or even more frequently if
- Oral temperature > 38°C or < 36°C
- Systolic Blood Pressure < 90 mm Hg or a drop of > 40 mm Hg
- Pulse rate > 90 beats per minute
- Respiratory rate > 20 per minute
- Oxygen saturation < 90%

Appendix L

Transfer Checklist – within Trust

	Signed	Date
1. Clozapine pathway must be transferred with the service-user. This must be up to date and reflect where a service user is currently on the pathway thereby enabling appropriate continuation of care		
2. Transfer of prescription card/ community prescription as appropriate.		
3. Transferring Consultant must notify ZTAS of change of Consultant and ensure the prescription is completed to ensure smooth transition between responsible Consultants.		
4. Care plan must contain up to date information relating to arrangements for mandatory blood monitoring follow up, including date this is due and where it will be undertaken.		
5. Handover of care must include specific information relating to: • Prescribing arrangements, including the name of the responsible Consultant who will be taking over prescribing. • Current dose of Clozapine and other medication including who prescribes these. • Name and contact details of Care Co-ordinator • Supply of Clozapine – where service-users obtain their Clozapine including where and when they can collect and out of hours arrangements.		
6. G.P must be informed of transfer details		

Appendix M

Transfer of service users to external services

	Signed	Date
1. Transferring Consultant must notify ZTAS of change of Consultant where relevant.		
2. Copy of current prescription to be sent by transferring Consultant.		
3. Handover of care must include specific information where appropriate relating to: Prescribing arrangements, including the name of the responsible Consultant who will be prescribing. Current dose of Clozapine and other medication including who prescribes these. Name and contact details of Care Co-ordinator Supply of Clozapine – where service-users obtain their Clozapine if appropriate, including where and when they can collect and out of hours arrangements.		
4. Inform G.P of transfer details		

Appendix N

Transfer of Service Users Into the Trust from external services

In addition to normal Trust transfer procedures, the following must be completed.

	Signed	Date
1.If service user is currently registered with ZTAS, responsible Consultant must contact ZTAS to inform of transfer. In the event that the service user is not registered with ZTAS (ie, service user was taking alternative brand, eg, Clozaril), the appropriate forms must be completed in order to register the service user so that they can continue to receive their treatment. **Please note that if this is not completed in a timely manner, the service user will not be able to receive their Clozapine**		
2. Service user **must** have a valid blood result. If not, this will need to be arranged as per local protocols		
2. Copy of current prescription to be sent by transferring Consultant.		
3. Handover of care from the transferring Trust must include specific information where appropriate relating to: • Current dose of Clozapine and other medication including who prescribes these along with the most recent copy of prescription. • Name and contact details of Care Co-ordinator		
4. Inform G.P of transfer details		

Appendix O

Re-titration monitoring

Rate of titration

In service users in whom the interval since the last dose of clozapine exceeds 48 hours, treatment should be re-initiated with 12.5mg given once or twice daily on the first day.
If this dose is well tolerated, it may be feasible to titrate the dose to a therapeutic level more quickly than is recommended for initial treatment (BNF / SPC).
The maximum rate of increase according to the BNF and SPC after the first day is by 25 – 50mg per day.
In cases where it is not possible to view the physical observations from previous titrations, the standard Community titration dosing schedule should be followed to minimise the risk associated with increasing doses of clozapine.

Monitoring of Physical Obs

On Day 1 Physical observations (Pulse , Temp , BP) should be taken:
before first 12.5mg dose and hourly for 6 hours post dose

Subsequent monitoring will depend on the daily dose and the rate of increase of dose.
If the suggested community dosing regime is followed then physical obs may be monitored in accordance with the community initiation pathway.
If a faster rate of titration and higher daily doses are used then physical obs should be monitored in accordance with the in-patient initiation pathway.
Deviation from this monitoring schedule must be based on clinical decision of the RC and must be clearly documented.
Any service users who complain of dizziness, falls, shortness of breath, chest pains or other potential ADRs should be referred to a medic for immediate review.

Monitoring of bloods

Where a treatment break is thought to have occurred, ZTAS should be contacted so that the required blood monitoring status of the service user can be determined and their records kept up to date. The telephone number for this is; 02073655842.
Regarding changes in blood monitoring frequency, the ZTAS manual states;
'*To determine the appropriate monitoring frequency after a treatment break, the duration of the treatment break and the monitoring frequency before the treatment break should be considered'*.

Monitoring frequency	Duration of treatment break	Monitoring frequency after treatment break
Weekly	3 days or less	Weekly, continue 18 weeks period
Weekly	>3days but less than 1 week	Weekly, continuing the 18 weeks period: it will be ensured that the service user has at least 6 weeks of weekly monitoring prior to going to fortnightly bloods
Weekly	>1 week	Weekly, restart 18 weeks period
Fortnightly	3 days or less	Fortnightly continue
Fortnightly	>3days but less than 1 week	Weekly monitoring for 6 weeks, then continue fortnightly
Fortnightly	>1week	Weekly, restart 18 weeks period
4-weekly	3 days or less	4-weekly, continue
4-weekly	>3days but less than 1 week	Weekly monitoring for 6 weeks, then continue 4-weekly
4-weekly	>1 week	Weekly, restart 18 weeks period, after 18 weeks, switch straight to 4-weekly

Appendix P

Our ref

Your ref

Date

Department/service/ward name
Service area
Manchester Mental Health & Social Care NHS Trust
Address 1
Address 2
Postcode
Tel: 0161 direct telephone
Fax: 0161 direct fax number
E-mail:
www.mhsc.nhs.uk

Dear Doctor,

Clozapine information for GPs

Re.: Patient Name (DoB)
Address
NHS Number

Your patient is about to be commenced on clozapine and this leaflet is provided for your information. If you have any questions about the contents of the leaflet, or about the decision to start your patient in clozapine, please contact their consultant psychiatrist, who is:

Dr.
CMHT
Telephone no.

The team managing your patient's clozapine initiation is:

Team
Telephone no.:

Please ensure your records are updated to highlight that this service user is prescribed clozapine.

About clozapine:

- Clozapine is an atypical antipsychotic that is licensed for the treatment of treatment resistant schizophrenia and psychosis in Parkinson's disease. Treatment resistant schizophrenia is diagnosed when a patient has ongoing symptoms despite an adequate trial of at least two other antipsychotics.
- Clozapine can cause a range of side effects, but probably most importantly, it can cause agranulocytosis, and therefore patients receiving this treatment are subject to a mandatory regime of FBC testing whilst they remain on treatment. The FBC programme is organised by a monitoring service.
- Clozapine is a red drug and will always be prescribed by, dispensed by and monitored by the mental health trust.

- If a patient has a break in treatment (for whatever reason) of greater than 48 hours, they must be retitrated; they **must not** simply take their usual dose.
- There are three brands of clozapine, Zaponex (used in Manchester), Clozaril and Denzapine; each manufacturer runs a monitoring service, and there is a central database of red results (see below).

Before starting:

- In order to make sure that the initiation of this treatment is as safe as possible, your patient will be assessed before treatment commences and blood tests and an ECG will be performed. You can help us by providing a summary of your patient's medical history, and ensuring that they are on your SMI register so that they will receive an annual health check at the practice.

Clozapine initiation:

- Clozapine will be started using a titration regime to minimise the risk of side effects. Inpatient titration can be faster as it possible to monitor patients more closely. A significant number of patients in Manchester start on their treatment in the community, supported by the Treatment Suite and/or Crisis Resolution and Home Treatment teams.
- We will advise you of the regular dose of clozapine when the titration is completed.

Agranulocytosis:

- Agranulocytosis is an important and potentially life threatening side effect of treatment with clozapine.
- There is a standard FBC testing regime – initially weekly, then two weekly, then monthly. Routine tests are undertaken in clozapine clinics at each of the three hospital sites. Each result is assigned a RED, AMBER or GREEN result. Green results enable the pharmacist to dispense the medication without any further action, AMBER results allow dispensing but necessitate closer monitoring and RED results mean that the patient must stop treatment.
- Patients are advised to seek medical advice if they develop symptoms of neutropenia (cough, cold, flu-like symptoms, fever) and an urgent FBC should be arranged. If the WBC/ neutrophil count are low, seek the advice of the on call psychiatrist.

Other side effects to be aware of:

Postural hypotension	Sedation
Increased heart rate and cardiac symptoms – **may be symptomatic of myocarditis and heart failure**	Hypersalivation
Weight gain	Seizures
Constipation	Neuroleptic malignant syndrome
Urinary incontinence	

Drug interactions:

- Clozapine can interact with a number of agents.
- Please ensure that you record the prescription of clozapine in your primary care record (even though you are not issuing prescriptions) so that important interactions are flagged up.

Important interactions to be aware of:

Bone marrow suppressants	Benzodiazepines
Highly protein bound drugs (eg digoxin, warfarin)	Cimetidine and omeprazole
Lithium	SSRIs
Antibiotics may increase the risk of blood dyscrasias (including chloramphenicol eye drops) and increased FBC monitoring may be necessary. They may also affect drug levels.	Antihypertensives
Anticholinergic agents	Centrally acting drugs

Caffeine, alcohol, tobacco:

- Caffeine can increase clozapine levels.
- Tobacco can decrease clozapine levels. **If the patient approaches you for stop smoking advice, or tells you they have stopped smoking, consider informing the prescriber**.
- Alcohol can increase the sedative effect of clozapine.

Ongoing care:

- Your patient will remain under the care of mental health services whilst they remain on clozapine and we will continue to arrange routine monitoring, prescribing and dispensing.
- We advise that the patient is placed on your SMI register so that they can access an annual health check in your practice; **if the patient fails to attend for annual health monitoring, please contact their consultant psychiatrist, or care coordinator to let them know so that they can facilitate the patient in attending for this important appointment with you.**
- Please be aware of the potential for side effects and interactions with this treatment.

Further information:

- Further information may be obtained from your patient's consultant psychiatrist, or care coordinator.
- The MMHSCT mental health pharmacy team can be contacted during working hours on 0161 882 2115
- BNF: http://www.bnf.org/bnf/search.htm?source=bnf&q=clozapine
- Choice and Medication website (for patients, but useful for professionals as well): http://www.choiceandmedication.org/mhsc/medications/10/
- The initiation pathway, atypical shared care guidelines and this information leaflet are available on our website: www.mhsc.nhs.uk

Contact details:
For up to date contact details for teams, and consultants, please consult our directory at www.mhsc.nhs.uk

Yours sincerely