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Clozapine Management Clinical Guideline

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Contents

Introduction

Clozapine, tradename Clozaril® or Clopine®, is a medication regulated by the Therapeutic Goods Administration (TGA), subsidised under the Pharmaceutical Benefits Scheme - Highly Specialised Drugs Program (PBS S100). It is intended as a third line treatment for chronic schizophrenia refractory to treatment with other antipsychotic medications. Participants may only be prescribed clozapine when mandatory blood testing, regular administration and other monitoring requirements can be achieved.

Background

Clozapine can cause serious side effects and once commenced, doses must be carefully titrated to achieve symptom control, while minimising the severity of adverse effects. The Northern Adelaide Local Health Network (NALHN), Central Adelaide Local Health Network (CALHN) and Southern Adelaide Local Health Network (SALHN) mental health services provide care for community-based clozapine participants through Clozapine Clinics, each managed by designated Clozapine Coordinators. The Women's and Children's Health Network (WCHN) co-ordinates community clozapine management through Boylan Ward, located at the Women's and Children's Hospital. The Country Health SA Local Health Network (CHSALHN) mental health service provides care for community based clozapine participants in shared care arrangements with general practice and designated Clozapine Coordinators. Clozapine is also prescribed to participants in bedded services, managed within each ward area. There are no exemptions to the monitoring criteria or other care components outlined in this document.

This guideline is to be used for the initial treatment (commencement), continued treatment (ongoing participant management) of clozapine participants and management of recommencement/treatment interruption and tobacco cessation.

This guideline has been developed inclusive of the TGA endorsed Clozaril ® Patient Monitoring System ™ Protocol 2016 version 2.17(CPMS).

For further information, copies of related documents and forms refer to the SA Health Clozapine Webpage **www.sahealth.sa.gov.au/clozapine**

Definitions

SA Health Mental Health Services (MHS)

Clozaril® Patient Monitoring System (CPMS)

Clozapine Community Pharmacy Partnership - the partnership between a prescribing team, a dispensing public hospital in the initiation phase of treatment (the first 18 weeks of clozapine treatment and as determined by the PBS), the community Clozapine Coordinator and a community pharmacy willing to be involved as a clozapine supply agent to the participant. See **Appendix 1** for registration form.

Hospital Clozapine Centre Coordinators – A person who is registered as the centre coordinator with CPMS to ensure that the hospital clozapine centre runs smoothly in accordance with the requirements of the CPMS protocol.

Community Clozapine Centre Coordinators – A nurse who is registered with CPMS, as the centre coordinator responsible for ensuring that the MHS community clozapine centre runs smoothly in accordance with the requirements of the CPMS protocol and who is responsible for the coordination of clozapine care for participants registered to the MHS community clozapine centre.

Neutropenia - a blood disorder characterized by an abnormally low number of neutrophils circulating in the blood (usually defined as a neutrophil count of less than 2 x 10^9/L). Neutrophils are the type of white blood cell most significant in the immune response to infection.

Normal reference range:

- Normal white cell count: 4.0 – 11.0 (x 10^9/L) SA Pathology reference
- Normal neutrophil count: 2.0-7.0 (x 10^9/L) SA Pathology reference
- Fasting glucose: 3.8 – 5.5 mmol/L SA Pathology reference
- Total cholesterol: <5.5 mmol/L SA Pathology reference
- Troponin T: 0-0.02 ug/L SA Pathology reference

White Cells: made up of the following cell types at the level indicated:

- Neutrophils: 2.0-7.0 x 10^9/L SA Pathology reference
- Eosinophils: 0.02-0.5 x 10^9/L SA Pathology reference
- Basophils: 0.05-0.1 x 10^9/L SA Pathology reference
- Monocytes: 0.2-1.0 x 10^9/L SA Pathology reference
- Lymphocytes: 1.0-3.0 x 10^9/L SA Pathology reference.

Therapeutic serum clozapine range - 350-600 ug/L (SA Pathology stated therapeutic range) with some participants requiring an upper range of 1000 ug/L for beneficial therapy. Participants requiring above 600 ug/L require close monitoring for concentration dependent side effects (sedation, hypotension and adverse neurological effects including myoclonus and seizure)

QT interval -The QT interval is the time from the start of the Q wave to the end of the T wave on an electrocardiograph(ECG).

QTc – QT interval shortens with faster heart rate. The corrected QT interval allows comparison of QT values at different heart rates and improves detection of patients at increased risk of arrhythmias.

Smoking – any reference to smoking in this guideline refers to the smoking of tobacco

Standards

The information in this guideline aligns with the Australian Commission on Safety and Quality in Health Care – National Safety and Quality Service Standards: Standard 1 - Governance for Safety and Quality in Health Care and Standard 4 - Medication Safety

General

1. Governance and Quality Improvement

Local Health Networks (LHN) through the Mental Health Clinical Director and Director Strategic Operations or equivalent and their quality and governance processes are responsible for implementation, monitoring and evaluation of clozapine guidelines.

The SA Health Psychotropic Drugs Committee is responsible for the oversight of Clozapine Centres to ensure compliance with this guideline including monitoring of performance indicators and protocol compliance through bi-annual clinical audit in March and October.

Within SA Health the Novartis brand of clozapine (Clozaril®) is listed as preferred brand on the SA Medicines Formulary to be used for initiating treatment. Clozapine may only be commenced by a consultant psychiatrist who is a staff specialist or visiting medical officer affiliated with the public hospital at or from which the participant is receiving treatment. After the first 18 weeks of initial treatment**,** clozapine participants may be managed under *continuing****** treatment criteria if the dose is considered stable and the treatment remains under the supervision and direction of a psychiatrist reviewing the participant at regular intervals.

The Novartis CPMS is an online database, where all participant white cell and neutrophil count blood test results and relevant information is stored. This data can be accessed by registered personnel enabling them to check compliance with the monitoring requirements. If a participant or organisation does not adhere to monitoring requirements, the information in the CMPS database will be incomplete and dispensing and dosing of the medication should cease until the required monitoring is completed as indicated by the CPMS protocol and in this clinical guideline.

Once initiated, stabilised and managed under continuing treatment by the hospital consultant psychiatrist in a specialist setting, the participant will be encouraged to move to a shared care arrangement with a general practitioner, provided the prescriber is under the supervision of a consultant psychiatrist while remaining registered to a SA Health Clozapine Centre (see Guideline 4). There is an option for the participant to be transferred to a private centre that agrees to take over the full care (see section 3.9.9).

*see PBS Authority Required continuing treatment criteria www.pbs.gov.au

2. Areas of Responsibility

Clinical Directors and the Director Strategic Operations or equivalent of Mental Health Services (MHS) are responsible for ensuring that all staff comply with the responsibilities and requirements outlined in this guideline.

All staff involved in the management of clozapine are required to comply with TGA and PBS requirements, and relevant SA Health guidelines.

SA Health currently uses the Clozaril brand in conjunction with the Clozaril Patient Monitoring System (CPMS). Where protocol compliance is breached or adverse events are reported or evident the first responding staff member is responsible for making the formal notification on the SA Health Safety Learning System (SLS) website.

All participants, medical officers, health care professionals (including those prescribing or assessing participant results and physical health status), pharmacies, pharmacists, centre co-ordinators and assistants, and treating centres or clinics involved with the distribution of clozapine must be registered with the relevant clozapine patient monitoring program.

Each Centre must have at least one Centre Coordinator, and consideration should be given to having more than one where required for continuity of service. A hospital may be one or multiple centres.

Each community nurse-led clozapine clinic requires the nomination of a Consultant Psychiatrist to act as the nurse-led clinic sponsor to support that clinic and ensure that conditions exist at each site to allow the application of these clinical guidelines. Country Clozapine Centres are supported by visiting and distance consultancy services.

Medical officers prescribing clozapine must know the indications, contra-indications, adverse effects, treatment options for these adverse effects and reporting requirements. Medical Officers must be registered to prescribe clozapine with the CPMS, and must ensure that

each participant commenced on clozapine meets CPMS criteria for the prescription and supply of clozapine including participant CPMS registration and referral to the relevant community Clozapine Centre for ongoing management. Medical Officers are also responsible for ensuring the required screening and monitoring tests are ordered at appropriate intervals, that CPMS documentation and relevant forms are completed and that prescriptions meet TGA and PBS S100 standards.

Nursing staff who administer clozapine must know the indications, safe use and screening processes for clozapine and data entry requirements. Nurses must be aware of the presentations of common and life threatening adverse effects and their management, and all other protocol and care requirements for a participant prescribed clozapine.

Each MHS Clozapine Centre requires one or more Clozapine Coordinators and may also choose to register suitably trained Centre Contacts.

Clozapine Centre Coordinators and Assistant Coordinators are responsible for facilitating the smooth running of the centre. Smooth running of a centre involves:

- ensuring centre compliance with the relevant monitoring system, SA Health guidelines, TGA and PBS Section 100 requirements;
- registering new staff and participants with CPMS and ensuring information recorded is accurate and current;
- education of medical officers, other clinical staff, participants and relevant other stakeholders on specific clozapine monitoring and documentation (electronic and paper-based) requirements;
- monitoring weekday email alerts and running the Open Architecture Clinical Information System (OACIS) and Enterprise Patient Administration System (EPAS) clozapine report each morning to identify any participants admitted to an emergency department or hospital ward and contacting the hospital treating team when appropriate to support the safe continuity of clozapine treatment;
- ensuring necessary bloods and assessments are performed, reviewed and acted upon accordingly and in a timely manner;
- liaising with hospitals, health services and pharmacies to ensure continuity of medication management at transitions of care;
- monitoring the appropriate initiation, maintenance and cessation of clozapine alerts in OACIS/ Enterprise Patient Administration System (EPAS), Client Based Information System (CBIS) and Country Consolidated CME (CCC) as appropriate; and
- all clozapine centre coordinators are responsible for providing regular feedback on centre workload, performance and outcomes as required by the SA Health Psychotropic Drugs Committee and for supporting 6 and 12 monthly audits of the processes outlined in these guidelines.

Safety Quality and Risk Managers are responsible for ensuring that 6 monthly audits of each community nurse-led clozapine clinic are completed in March and October by suitably qualified nursing or medical staff using the approved audit tools.

Public hospital Mental Health Liaison Teams (Psychiatric Consultation Liaison) are responsible for monitoring weekday email alerts or running the OACIS and EPAS Clozapine report each morning to identify all new local clozapine admissions. Liaison teams must notify the appropriate Community Clozapine Centre of the admission and ensure that the inpatient treating team has sufficient understanding of the risks of prescribing clozapine and their responsibilities under PBS Section 100, CPMS, and SA Health guidelines and provide

adequate support for the safe management of clozapine treatment. Liaison teams must ensure safe transfer of care including the completion of required documentation, Medical Record (MR) forms and electronic databases and alerts (CBIS, CCC, and EPAS).

SA Health Directors of Pharmacy are responsible for facilitating the smooth running of CPMS registered hospital pharmacies, and ensuring all hospital pharmacy staff comply with clozapine protocols, the SA Health guidelines, and SA Pharmacy business rules. Smooth running of a CPMS registered pharmacy involves**:**

- ensuring centre compliance with the relevant monitoring system, SA Health guidelines, TGA and PBS Section 100 requirements;
- ensuring new pharmacists are registered with CPMS and that information recorded is accurate and current;
- ensuring pharmacists are trained and aware of the requirements prior to dispensing clozapine;
- liaising with ward / clinical and community pharmacists as appropriate;
- liaising with hospitals / health services to ensure continuity of medication management at transitions of care; and
- liaising with SA Health staff to ensure arrangements are in place for supply in the first 18 weeks of clozapine treatment (initial treatment), including courier arrangements where necessary.

Pharmacists must be aware of PBS Highly Specialised Drugs (Section 100) rules, CPMS protocol and SA Health guideline requirements. Most clozapine participants will be maintained on treatment in the community setting and pharmacists should be familiar with the Public Sector Community Pharmacy Partnership to ensure continuity of care. Pharmacists dispensing clozapine are responsible for compliance with the CPMS protocols including assessment of mandatory blood test results and entering quantities prior to dispensing. Pharmacists are also responsible for participant counselling prior to discharge from public hospitals and for reporting drug related adverse events. SA Hospital pharmacies are responsible for the supply of clozapine during the initial 18 weeks of treatment per PBS Section 100 requirements. Arrangements for continuing supply are to be made in conjunction with the community team, GP, participant and/or carer, and others as appropriate. Pharmacists are responsible for notifying the treating Community MHS Clozapine Centre Coordinator urgently if non-compliance or significant side effects are noted, to facilitate an early medical review. Where there are problems with prescriptions pharmacists are to contact the relevant medical officer to rectify the matter.

Protocols

1. Commencing Clozapine

The SA Health MR74D *clozapine commencement form* (or electronic equivalent where available i.e. EPAS), is the required documentation for all clozapine commencements at bedded services or community based sites. It has been designed to meet the checks and observational needs of the participant during the first 18 weeks of treatment. The full completion of the form is a minimum requirement and is a multidisciplinary responsibility within each team/unit. It must be completed if clozapine is commenced for the first time or recommenced after more than a 28 day break in treatment. Where CBIS and CCCME Clozapine Review and Physical Health Assessment screens are available, clozapine reviews and physical observations are to be recorded electronically and treatment details reflected in the service plan.

1.1 Pre–commencement: Consent and Registration

Prior to the first commencement of clozapine, the participant will have had an adequate trial of at least two other antipsychotic drugs, with documented assessment demonstrating there has been insufficient response, or unacceptable adverse effects. The participant's ability to comply is assessed preferably through a clinical review process and documented on the relevant electronic record. It is necessary to ensure that adequate compliance with oral administration and monitoring of medication can be achieved in the community.

Informed consent process: The participant and family where appropriate must be provided with verbal and written information specific to clozapine, including benefits, alternatives, required monitoring, side effects and their management. This process and the participant's decision should be documented on the MR74D *clozapine commencement form* (or electronic equivalent) and in the CBIS & CCCME medications record.

The participant must be registered with CPMS prior to commencing clozapine. Registration requires the completion of the CPMS patient registration and the patient health information storage consent forms, which must be faxed or emailed to CPMS. The participant is required to sign the patient health information storage consent form. If a participant is involuntary and does not have capacity to give consent then the doctor concerned may sign on the participant's behalf following the Local Health Network (LHN) procedure for consent for treatment. The participant must not be commenced before confirmation of registration from CPMS including the patient CPN (Clozaril® Patient Number) is received by fax or email.

1.2 Pre-commencement: Baseline Assessment

A thorough search of the participant's medical history is required to ensure that they do not have a prior history of drug induced neutropenia or bone marrow disorder before deciding to commence clozapine. A physical examination should be performed to identify other comorbidity that may contra indicate clozapine prescription. Other medication should be reviewed and consideration should be given to discontinuation or tapering where there may be significant interactions.

If the participant is pregnant further consideration and discussion with the participant and their family is required. This is due to the potential of currently unknown effects on the foetus with only limited data available.

Clozapine is contraindicated in breastfeeding therefore it is important to ensure that the participant is not breastfeeding prior to the initiation of clozapine.

A baseline white cell and neutrophil count is required, meeting the 'green range' of the guidelines (WCC >3.5 x 10^9/L, Neutrophils >2.0 x 10^9/L) – this sample must have been obtained within 10 days of the proposed start date. If the blood picture is not within this range and meets the criteria for the 'amber range' (WCC 3.0 - 3.5 x 10^9/L, Neutrophils 1.5 - 2.0 x 10^9/L), a repeat blood test and medical review is required. Stability in the white cell and neutrophil count must be achieved prior to commencing clozapine. Blood results are to be recorded on the SA Health MR75D *clozapine investigation review and prescription record form* where this is in use (or electronic equivalent).

Novartis has access to a consultant haematologist specialising in clozapine management, who can be consulted for advice in difficult cases (tel: 0404 451 327).

Due to diurnal variation and white cell count being lowest in the morning, taking blood late in the day may avoid a false low being recorded that could prevent the participant from starting (or continuing) clozapine. The decision for afternoon blood testing will be based on the participant's individual response.

Baseline fasting lipids, fasting glucose, liver and renal function and electrolyte tests prior to commencement of the medication are required, usually at the same time as the pre-treatment white cell and neutrophil tests to ensure there are no underlying comorbidities that may be exacerbated by clozapine. Baseline results are to be recorded on the SA Health MR75D *clozapine investigation review and prescription record form* where this is in use (or electronic equivalent) and the date of the observations recorded on the SA Health MR74D *clozapine commencement form (*or electronic equivalent).

The participant will have a cardiac assessment, including:

- Electrocardiograph (ECG), troponin level and high sensitivity c-reactive protein (CRP) blood tests prior to commencement of the medication;
- Where possible an echocardiogram is to be performed prior to clozapine commencement;
- If there is no history or evidence of cardiac disease and the participant is to be commenced in bedded services the echocardiogram must be completed within six months of commencement;
- The echocardiogram should always be completed prior to commencement if there is a prior cardiac history, current cardiac symptoms or the participant is being considered for a community start; and
- Echocardiograms are required annually after commencement.

Evidence of compliance with the cardiac monitoring protocol must be accessible in the participant's medical record. Cardiac monitoring results are to be recorded on the SA Health MR74D *clozapine commencement form (*or electronic equivalent*).* Where it is in use, the SA Health MR75D *clozapine investigation review and prescription record form* (or electronic equivalent) can also be used to record cardiac results.

A full medication management plan must be completed that takes into account consideration of potential drug interactions and resulting effects on clozapine levels, adverse effects and efficacy (see appendix 5). This includes assessment of current smoking, caffeine, alcohol, illicit drugs and over the counter medications. Potential interactions and their risks should be discussed with the participant.

1.3 First Time Commencement

Once a participant has been registered but prior to commencement the initiating team must enter clozapine alerts on the appropriate clinical information systems including: CBIS (Metro LHNs, CAMHS), OACIS, CCCME (CHSALHN), the iPharmacy dispensing system, EPAS and the medical record. Information should include the Clozaril® Patient Number (CPN). If at any time clozapine needs to be ceased, the status of these alerts must be updated (including a reason for cessation) on the clinical information systems by the team who ceased the medication.

For bedded services the clozapine titration doses are to be recorded on the appropriate National Inpatient Medication Chart or SA Health equivalent or electronic equivalent. All other clozapine assessment recording is to be completed on the SA Health clozapine protocol forms (or electronic equivalent).

The rate of clozapine titration will depend on symptom response, tolerability, gender, body mass index (BMI) and serum clozapine levels. Standard titration protocols are provided on the SA Health MR74D *clozapine commencement form*, in the CPMS protocol and in this Clinical Guideline (see **Table 1 Normal Dose Titration** and **Table 2 Rapid Dose Titration**). Consistent with TGA endorsed guidelines, it is recommended that the maximum dose should not exceed 900 mg per day.

Table 1: Normal dose titration example

	Day 1		Day 2		Day 3		Day 4		Day 5		Day 6		Day 7	
	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
Dose (mg)	12.5	-	25	-	25	-	25	25	25	25	25	50	25	75

	Day 8		Day 9		Day 10		Day 11		Day 12		Day 13		Day 14	
	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
Dose (mg)	25	100	50	100	50	100	50	125	50	125	50	125	50	150

The above table shows the recommended dose titration for those commencing clozapine for the first time. From day 14 the dose can be increased in 50mg intervals every 2 to 3 days depending on efficacy and side effects. Maximum dose is 900mg per day. Clozapine levels should be assessed as per commencement protocol, or if: side effects are apparent; there is evidence of infection; there are changes in medications that interact with clozapine and or; changes in the use of drugs such as tobacco smoking **(see 3.10 Tobacco Cessation**) and caffeine.

Table 2: Rapid Dose Titration Example

	Day 1		Day 2		Day 3		Day 4		Day 5		Day 6		Day 7	
	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
Dose (mg)	12.5	-	25	-	25	25	25	50	25	75	25	75	25	100

	Day 8		Day 9		Day 10		Day 11		Day 12		Day 13		Day 14	
	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
Dose (mg)	50	100	50	125	50	150	50	175	75	175	100	175	100	200

Rapid titration is optional for participants with good tolerance to previous clozapine treatment (See table above). From day 14 the dose can be increased in 50mg intervals every 2 to 3 days depending on efficacy and side effects. Maximum dose is 900mg per day. Clozapine levels should be assessed as per commencement protocol, or if clinically indicated by: side effects; evidence of infection; there are changes in medications that interact with clozapine and or; changes in the use of drugs such as tobacco smoking and caffeine.

When commencing clozapine for the first time the participant will require monitoring for a period of six (6) hours after the first dose, including vital and neurological signs as detailed on the SA Health MR74D *clozapine commencement form* (or electronic equivalent). When commenced in a community based setting a nurse special is required. All observations are to be recorded on the SA Health MR74D *clozapine commencement form* (or electronic equivalent). If there are any changes in vital signs i.e. blood pressure drop of twenty (20) mmHg systolic, increase in pulse above120 beats per minute (bpm) or pulse irregularity, chest pain, shortness of breath, syncope or altered conscious state the participant should be transported to the nearest emergency department for medical review and/or a code blue called. The medical officer responsible for commencement of the medication is to be notified.

Vital signs of participants in a bedded unit following day one of commencement are continued as per local monitoring procedures incorporating daily temperature for first 28 days or as clinically indicated.

Subsequent monitoring: Following commencement participants must have weekly monitoring including a Complete Blood Examination (CBE) and physical health assessment for the first 18 weeks of treatment. Following the first 18 weeks of continuous treatment with clozapine the participant may be eligible to move to a maintenance schedule of 4 weekly monitoring for long term management.

1.4 Interruption to clozapine therapy and recommencement:

If clozapine is stopped for more than 48 hours and then recommenced at full dosage there is a significant risk of severe side-effects similar to those that occur at initial titration including severe sedation, cardiovascular adverse effects and seizures. The CPMS protocol for recommencement of clozapine and associated monitoring requirements must be followed.

Table 3 outlines clozapine dosage requirements for recommencement after a greater than 48 hour but less than or equal to a 28 day break in treatment. Monitoring should be documented on the MR78D *clozapine recommencement form* (or electronic equivalent). When the break in treatment is longer than 28 days the full pre-commencement work up must be repeated in accordance with CPMS guidelines.

To avoid adverse events related to recommencement at full dose after a period of non-adherence, concerns regarding adherence should be discussed with the treating medical officer / consultant psychiatrist prior to dosing. Where a participant has been admitted to a non-psychiatric ward the treating team should always consult with the participant's Clozapine Coordinator or the hospital's Psychiatry Consultation Liaison team before continuing clozapine treatment. Outside of office hours the on-call psychiatry registrar should be contacted. Additional monitoring requirements may be required depending on the period of interruption (**See Table 3**).

Participants who experience an interruption in therapy are at risk of severe rebound psychosis. Treating teams should provide close monitoring of mental state during this period and consider the use of an alternative antipsychotic to control psychotic symptoms. The Psychiatry Consultation Liaison team must be contacted by non-psychiatric hospital wards for advice on the management of participants following an interruption in therapy.

Table 3: Dosage and monitoring requirements following treatment interruption

Period of interruption (time since last dose was taken)	Dosage / Monitoring Requirements
≤ 48 hours	No change to dosage or monitoring
> 48 hours to ≤ 72 hours	Start on 12.5mg and titrate up No additional monitoring requirements
> 72 hours to ≤ 28 days	Start on 12.5mg and titrate up For 4 weekly participants: Weekly monitoring for 6 weeks. If no abnormality resume 4 weekly monitoring For weekly participants: Weekly monitoring for 6 weeks or as long as needed to reach 18 weeks (126 days) (whichever is the greatest).
> 28 days	New participant registration form New pre-treatment result and monitoring same as new commencement (18 weeks): Start on 12.5mg and titrate up.

1.5 Discontinuing Therapy

If a decision has been made to cease treatment it is recommended that it occur over a period of one to two weeks with an introduction of an alternative antipsychotic if clinically indicated.

If an abrupt cessation is required or occurs the participant should be monitored for rebound psychosis and cholinergic rebound; headache, nausea, vomiting and diarrhoea with consideration for use of an anticholinergic agent.

Blood test monitoring requirement:

- Notify the monitoring provider within 24 hours via phone, fax or email using the Discontinuation of Therapy Form;
- Blood testing needs to continue for four weeks or until full recovery has occurred (whichever is greater);
- Participants on Weekly monitoring: weekly for four weeks after cessation; and
- Participants on 4 Weekly monitoring: one blood test four weeks after cessation.

*Participants who are being monitored due to an amber or red result with subsequent cessation may need additional monitoring as per clinical need or CPMS haematology advice.

If clozapine is discontinued for a red range result, CPMS requires further weekly blood tests for a total of four (4) weeks once the blood readings have returned to the green range. In this case recommencement of clozapine can only be considered after discussion with the CPMS haematologist. There must be clear evidence that clozapine did not cause the low white cell count, that is, another probable cause is identified. Due to the risk of severe infection secondary to very low neutrophil counts (febrile neutropenia), the participant must be monitored for signs and symptoms of infection. If they have an infection such as a sore throat, a further complete blood examination must occur.

2. Ongoing Participant Monitoring

Following the commencement of clozapine, mandatory participant monitoring includes assessment of test results, as well as physical health, mental state and function. The goal of these monitoring processes is to identify problems with efficacy, adverse events or comorbidity and intervene early to prevent further complications. Monitoring should be documented on the MR77D *Clozapine patient protocol 4 weekly form* (or electronic equivalent).

2.1 White cell count monitoring:

Neutropenia occurs in 2-3% of participants treated with clozapine. It should be noted that 85% of neutropenia cases occur during the first 18 weeks of treatment. Blood tests for white cell count and neutrophil counts are taken at least each 7 days for the first 18 weeks and then every 28 days if there are no complications during the initiation period. **Table 4** shows that white cells and neutrophils are stratified into ranges indicating level of risk to the participant.

Table 4: White Cell Count Monitoring Ranges

White Blood Cell (WBC) & Neutrophil Count (NC) Results	**Range**	**Action**
WBC >3·5 x10^9/L and NC >2·0 x10^9/L	**Green**	Clozapine therapy can continue or be titrated upwards as required
WBC 3·0 - 3·5 x10^9/L and/or NC 1·5 - 2·0 x10^9/L	**Amber**	Requires increasing frequency of monitoring, to twice weekly
WBC <3·0 x10^9/L and/or NC <1·5 x10^9/L	**Red**	STOP clozapine immediately and repeat blood test within 24 hours. Contact Consultant Psychiatrist and arrange urgent medical review

When in the amber range blood tests must be completed twice weekly until the participant blood result returns to the green range. Once in the green range regular monitoring is recommenced. During the time the participant is in the amber range only 3-4 days' of medication can be dispensed at a time.

When in the red range, clozapine must be ceased and telephone contact with the CPMS haematologist (tel: 0404 451 327) is mandatory. Contact the Consultant Psychiatrist and arrange an urgent medical review. Blood tests need to be repeated daily until out of the red range, then twice weekly until back into the normal (green) range.

NOTE: If the participant is in the amber or red range, immediately contact a senior psychiatrist with experience in the use of clozapine to discuss a management plan.

2.2 Clozapine Level Monitoring:

During commencement, blood testing for serum clozapine levels will occur at least on week four (4), week nine (9), and prior to discharge from hospital. Once the participant has moved to 4 weekly monitoring, levels are recommended at least 6 monthly . More regular levels may be indicated if there are concerns regarding efficacy, compliance, changes in concomitant medications or substance use (e.g. tobacco). Clozapine level testing on admission should be considered as part of the assessment.

If efficacy is incomplete and there are no significant side effects then levels should be titrated above 350 ug/L (literature evidence of best efficacy). Clozapine levels above 600 ug/L are associated with an increased risk of severe side effects including seizures and sedation. Where possible participants should be maintained at levels below 600 ug/L, however a percentage of participants will respond only at higher levels. The consensus maximum serum level is 1000 ug/L. Where participants record serum levels above 1000 ug/L, or above 600 ug/L where response is known below this value, a review of treatment should occur, to identify drug interactions, changes in substance use (e.g. tobacco), timing of clozapine level in respect to dose, or comorbid infection, liver or renal dysfunction.

The rate of dose reduction will depend on the risk as determined by the clozapine level, the presence of dose related side effects, the stability of the participant, the clozapine level at which the participant is known to respond and the management of the cause of the level increase (e.g. drug interaction). Where risk is high due to severe side effects and/or very high levels, the dose can be held for up to 48 hours without interruption of therapy (see section 1.4 and CPMS guidelines). If there are no contraindications, recommencement at a reduced dose should be considered before 48 hours to avoid an interruption in therapy. Where interruption in therapy is unavoidable, CPMS guidelines for recommencement must be followed (see section 1.4).

Where the risk from clozapine levels or side effects is low, then a gradual down titration at 25-50mg increments until a safe tolerable level is achieved will reduce the risk of relapse. Mental state should be monitored as clinically indicated during this period and clozapine levels can be reviewed from 5 days after the adjustment in dose.

Participants whose clozapine level provides adequate therapeutic effect below 350 ug/L or above 600 ug/L should have this reflected in the care plan documentation.

If a level less than 50 ug/L is recorded it indicates a break in therapy which is likely to be longer than 48 hours. An urgent assessment of compliance is required to determine the likely length of non-compliance. Recommencement at full dose may result in severe sedation, cardiovascular adverse effects and seizures, and contra-indicated. CPMS recommencement guidelines must be followed (see section 1.4).

A serum clozapine level should be taken on hospital admission as a part of routine participant assessment.

NOTE: Blood testing samples for serum trough levels should be taken 12 hours after the last dose

Clozapine levels during infection
There is emerging evidence that a normal response to infection inhibits cytochrome P450 enzymes resulting in significantly elevated serum clozapine concentration which can lead to increased side effects including sedation and seizure activity. If there is evidence of an infection, the participant should be assessed for signs of clozapine toxicity and if indicated a serum clozapine concentration taken and reviewed by a medical officer. In the event of a raised serum clozapine concentration or clinical signs of clozapine toxicity then a medical review is required with consideration given to dose reduction if indicated. If the serum clozapine concentration is raised, consideration should be given to monitoring the serum clozapine concentration weekly during the period of infection. Treatment with antibiotics that inhibit CYP enzymes associated with clozapine metabolism (e.g. CYP 1A2 - quinolones such as ciprofloxacin) will also increase the risk of toxicity (see **Appendix 5** "Clozapine Potential Drug Interactions").

Clozapine levels and tobacco use during clozapine treatment
Changes in tobacco use can effect clozapine concentrations. Commencement of tobacco smoking (or an increase in smoking) may reduce clozapine concentration, while tobacco smoking cessation may increase serum clozapine concentration, with potential for clozapine toxicity and its associated adverse effects, including death.

Polycyclic aromatic hydrocarbons in tobacco smoke induce the CYP1A2 enzyme responsible for clozapine metabolism. On cessation of smoking, serum clozapine concentration may rise significantly over the next 7-10 days, regardless of the use of nicotine replacement therapy.

The potential for increased serum concentration of clozapine is NOT a reason to discourage participants from stopping smoking, as smoking is one of the most serious risk factors for poor physical health and reduced life expectancy among people living with mental illness.

Factors to consider when determining impact of smoking cessation on clozapine levels include:

1. how much a person smokes: light (5-12 cigarettes per day);moderate (13-24 cigarettes per day), heavy (≥ 25 cigarettes per day);
2. the expected change in smoking on admission (e.g. complete cessation on closed wards) and on discharge (e.g. return to pre-admission levels, an increase from baseline);
3. the participant's normal compliance with the medication and clozapine compliance preadmission;
4. the participant's rate of clozapine metabolism, as measured by dose versus serum clozapine concentration;
5. history of side effects on clozapine and the approximate serum clozapine concentration at which these occurred; and
6. changes in caffeine intake, an increase in caffeine can result in increasing serum clozapine concentrations.

Participants should be encouraged to reduce their caffeine intake when stopping smoking. Caffeine toxicity may result as caffeine is also a substrate for CYP1A2. Caffeine toxicity may cause agitation, sleep disturbance and gastrointestinal symptoms all of which may be misinterpreted as nicotine withdrawal. It must be noted that nicotine replacement therapy (NRT) will not mitigate these effects.

Tobacco use in community settings

The participant's smoking habits are to be recorded at each clozapine review. Participants should be actively encouraged to cease smoking and advise staff if they do cease, reduce or otherwise change their smoking habit. See SA Health Smoke-free Policy. The potential effects of smoking and smoking cessation are to be explained to the participant and their carers.

If a participant reports the commencement/recommencement of regular smoking for longer than 1 week then a clozapine level should be considered, particularly for participants with break through symptoms, unstable illness or those with dosing adjusted close to threshold of efficacy. Where clozapine levels are significantly reduced, then upward titration of dose should be considered to return to therapeutic levels. This can occur at 25 to 50mg increments depending on the severity of illness and drop in clozapine level.

When the participant has made the decision to stop smoking, measure serum clozapine concentration prior to smoking cessation.

Consider the participant's likely adherence to smoking cessation, establishing good communication to ensure that, if the Quit program fails the clozapine dose is adequate to maintain therapeutic serum clozapine concentration for that participant. Participants with irregular smoking patterns will require closer monitoring of their serum clozapine concentrations.

It is recommended that serum clozapine concentration following smoking cessation or reduction is taken at day 7, day 14, day 21 and day 28 or until stable. Ensure the test includes time of last dose and the time that the blood is taken. An early morning blood sample 12 hours after the last dose is required (this can be synchronised with routine blood tests).

An action management plan is to be documented in the medical record to ensure the participant receives appropriate smoking cessation assistance and counselling. The plan is to include a timeline for blood monitoring, the education required to ensure that the participant/carer has an ongoing understanding of symptoms that may indicate clozapine toxicity and the contact details for medical support.

All participants that cease smoking should be monitored closely for clinical side effects of raised serum clozapine concentration. The risk of sedation, hypotension and adverse neurological effects including myoclonus and seizures will be greater when serum clozapine concentrations are higher; however the occurrence of clozapine-induced agranulocytosis and many other adverse effects are not dose dependent.

The clozapine dose may need to be reduced if the serum clozapine concentration rises outside of the participant's base range, or above 1000 ug/L, during smoking cessation.

Tobacco Use in bedded units

Participants who are admitted to a non-smoking bedded service are to have their serum clozapine concentration taken as soon as possible following admission.

It is recommended that serum clozapine concentrations are taken at day 1, day 7 then weekly for the duration of the admission or until stable and then on discharge. Ensure the test includes time of last dose and the time that the blood is taken. An early morning fasting blood sample, 12 hours after the last dose, is required (this can be synchronised with routine blood picture tests).

All participants should be monitored closely for clinical side effects of raised serum clozapine concentration and have their dose adjusted accordingly as per the management described for community teams as described above.

The participant's smoking status should be assessed on a regular basis and education provided to the participant regarding notifying staff of any change in their smoking status.

On discharge from a bedded service the Transfer of Care (MR76D) form is to be completed with the current serum clozapine concentration and documentation of the participant's smoking status and smoking plans post-discharge.

2.3 Cardiac Monitoring:

Cardiac monitoring is designed to assess for complications such as arrhythmias, long QT interval, myocarditis and cardiomyopathy. Required investigations include: ECG, Troponin and CRP and echocardiogram.

Week 1 (day 7) - ECG, Troponin and CRP blood tests
Week 2 (day 14) - ECG, Troponin and CRP blood tests
Week 3 (day 21) - Troponin and CRP blood tests
Week 4 (day 28) - ECG, Troponin and CRP blood tests
Week 12 - ECG, Troponin and CRP blood tests
Annual: - ECG, Troponin and CRP blood tests, echocardiogram

Myocarditis

- Myocarditis is most common in the first month of clozapine treatment and is associated with fever, flu-like illness, gastrointestinal and cardiorespiratory symptoms.
- Participants and their carers should be encouraged to report flu-like symptoms, GI upsets, dizziness or chest pain to their treating team.
- Body temperature should be monitored daily (at the same time) to assess for fever. A temperature above 38 degrees centigrade may indicate the onset of myocarditis or of febrile neutropenia, requiring urgent medical intervention.
- To support daily monitoring during the first 28 days, thermometers will be supplied to participants commencing clozapine. Participants should be trained in the use of thermometers and should understand the urgency of seeking medical intervention in the event of a febrile reading.
- If at any time participants report a flu-like illness or a fever of 38 degrees centigrade or greater then clozapine may continue but an urgent Troponin and CRP and CBE measurement is required in accordance with CPMS guidelines.

Troponin

- If Troponin is more than 2 times the upper level of normal and CRP is elevated then an urgent echocardiogram and cardiology review is required to assess for myocarditis and the clozapine should be withheld. Participants should be transported to the nearest emergency department;
- If Troponin is more than 2 times the upper level of normal and CRP is normal then an urgent cardiology review is required to exclude an acute coronary syndrome/ myocardial infarction and consideration should be given to withholding the clozapine. Participants should be transported to the nearest emergency department;
- If Troponin is 1-2 times the upper level of normal then clozapine treatment can continue but a cardiology consult should be obtained and daily assessment of Troponin, CRP and symptoms are indicated to assess for progressive elevation. This may involve transfer to a local emergency department.

Abnormal Echocardiography

- Abnormal ECGs or echocardiography should be discussed with a cardiologist. Any evidence of acute myocardial infarction, severe heart failure or significant arrhythmia should be referred for urgent medical review. When this occurs as an outpatient, urgent transport to an Emergency Department is required. Clozapine has the potential to increase QT interval and increase the risk of arrhythmia. A finding of abnormal QT interval on ECG should be discussed with a cardiologist. QTc is prolonged if > 440ms in men or > 460ms in women. QTc> 500 is associated with increased risk of life threatening arrhythmias (torsades de pointes). QTc is abnormally short if < 350ms.

2.4 Annual blood pathology review:

At yearly intervals following transition to 4 weekly monitoring as indicated on the SA Health MR77D *Clozapine patient 4 weekly protocol form* (or electronic equivalent), the following blood testing will occur in addition to the CBE:

- Clozapine level
- Fasting blood glucose level
- Fasting full lipid studies
- Electrolytes / Liver function test
- C - reactive protein (CRP)
- Troponin I or T

All results will be documented on the SA Health MR75D *clozapine investigation review and prescription record form* (or electronic equivalent) where this is in use. Abnormal clozapine levels or cardiac blood test results must be managed by medical officers according to guidelines. Abnormal glucose, lipids and electrolyte /liver function tests should be reviewed and managed by medical officers. Where appropriate this may involve liaison with GP shared care or may involve the use of emergency medical services.

2.5 Six (6) monthly pathology review:

This will be conducted as noted on the SA Health MR77D *Clozapine patient 4 weekly protocol* form. The review will consist of the usual physical health assessment and complete pathology testing as indicated on the annual review minus the cardiac screening which occurs annually. All results will be documented on the SA Health MR75D *clozapine investigation review and prescription record form* (or electronic equivalent) where this is in use. Abnormal clozapine levels must be managed by medical officers according to guidelines. Abnormal glucose, lipids, and electrolyte / liver function tests should be reviewed and managed by medical officers. Where appropriate, this may involve liaison with GP shared care or may involve the use of emergency medical services.

2.6 The Physical Health Assessment

All reviews are to be conducted face to face within 48 hours of the CBE blood test and include:

1. physical health assessment:
    - weight and waist measurement;
    - Body Mass Index (BMI);
    - blood pressure;
    - temperature;
    - manual Pulse;
    - number of cigarettes smoked per day; and

- recording of any other relevant clinical information as indicated by review of the self-report questionnaire (Appendix 3) including surplus tablets from the last cycle of care.

2. clinical response to the medication;
3. review for constipation;
4. review for signs of toxicity (including seizure activity that may be related to clozapine serum levels);
5. an assessment for signs and symptoms of infection;
6. review of the CBE result by a medical officer;
7. finger prick random blood glucose level (three monthly) to monitor for type two diabetes mellitus and hyperglycaemia;
8. assessment of changes in medications:
   Drugs that inhibit or enhance clozapine metabolism may affect serum clozapine levels and either decrease efficacy or increase risk of clozapine toxicity. Changes in medications can exacerbate known side effects e.g. sedation, agranulocytosis, and constipation; and
9. participants are encouraged to actively participate in the clozapine review by completing the self-report participant questionnaire and discussing clozapine adherence, response and side effects. This assessment will also cover changes in concurrent medications, smoking habit, caffeine consumption, and illicit drug use.

All observations will be recorded by the person completing the assessment on the clinically indicated form (or electronic equivalent):

- SA Health MR74D *Clozapine commencement form* or the
- SA Health MR78D *Clozapine recommencement form* or the
- SA Health MR77D *Clozapine patient 4 weekly protocol* form

Clozapine reviews and physical observations are to be recorded electronically into the CBIS, CCCME and EPAS physical health and clozapine-specific screens where available.

Abnormal physical findings should be referred for medical review and this process should be documented in the participant's record/care plan. In some cases the care process will involve liaison with the participant's GP or medical specialists. Cardiometabolic syndrome and related physical health issues can be managed using the Positive Cardiometabolic Algorithm found here and **Appendix 6**: http://www.heti.nsw.gov.au/Resources-Library/Positive-Cardio-Metabolic-Algorithm-2011/

Clozapine treatment is associated with an increased risk of pneumonia. Due to clozapine's effect on the immune system pneumonia may not present with elevated WCC or with the absence of classical clinical signs and symptoms. Due to elevated clozapine levels during infection consumers treated with clozapine may be sedated and confused and therefore present late for treatment with worse prognosis. Respiratory infection should be considered in consumers with high white cells counts. Where respiratory infection is suspected then an appropriate physical exam must be performed. When this exam is abnormal (i.e. abnormal findings on auscultation, reduced oxygen saturation, increased confusion) there should be a low threshold for urgent chest X-ray examination to identify possible pneumonia. Urgent antibiotic treatment may prevent further deterioration and risk of mortality. Please note there is a potential for interactions between clozapine treatment and antibiotics. For more information, refer to 'Clozapine levels during infection' on p.13.

2.7 Frequency and Monitoring Plan:

When commencing clozapine for the first time or when recommencing after a break of more than 28 days, weekly for eighteen weeks from commencement, the participant will receive a CBE and physical health assessment within 48 hours by a qualified health practitioner. This will be accompanied by a clozapine review performed by a medical officer. Medical reviews

during this period may only be completed by a Consultant Psychiatrist or medical officers under the direct supervision of a Psychiatrist. In remote country areas this can be achieved through the use of Tele-health if face to face appointments are not possible. *This is mandatory and in the event of Did Not Attend(DNA) or appointment cancellation, then an appointment will need to be re-allocated for medical review within 48 hours of the CBE*. The medical officer will only prescribe medication once they have reviewed a satisfactory WCC and NC and performed a medical review. Each prescription for clozapine in the initial eighteen weeks for participants undergoing weekly monitoring must not exceed seven (7) days' supply unless dispensation has been approved by CPMS.

After 18 weeks of continuous weekly monitoring, and if clinically stable, the participant will progress to 4 weekly monitoring within a community mental health Clozapine Clinic or in shared care with general practice. The participant will receive a full review that will be considered as the first annual review at transition to 4 weekly monitoring. There after annual reviews will be conducted at the completion of 12 four weekly review cycles. During these cycles, participants are reviewed by a medical officer or a nurse every 28 days within 48 hours of the CBE at a Community Clozapine Clinic or at a GP clinic or by local medical or nursing staff in bedded services. *This is mandatory and cannot be cancelled. If the participant cancels, he/she will need to be re-allocated an appointment for clinical review within 48 hours of the CBE.*

2.8 Medical / Psychiatric Review

Participants seen within nurse-led clinics or general practice must have a psychiatric review a minimum of every 6 months or earlier as clinically indicated. This is facilitated by the use of Tele-health in rural areas if face to face appointments are not possible.

If there are significant concerns during the nurse-led clinic or GP review assessment a senior medical officer is to be contacted to assess the participant. This may occur on the day of the review if urgent or the participant can be scheduled for an early psychiatric review appointment. When the risk is considered to be high transfer to an emergency department for review should occur.

Metropolitan mental health service participants whose mental state and clozapine management is considered unstable must continue to be seen in public medical clinics.

Country mental health service participants whose mental state and clozapine management is considered unstable must have a regular psychiatric review as clinically indicated. This is facilitated by the use of Tele-health in rural areas if face to face appointments are not possible.

All prescriptions must be compliant with PBS and CPMS Protocol guidelines and are to be written following medical officer review of satisfactory blood results and given to the participant or forwarded to pharmacy following the satisfactory completion of the physical health assessment. It is desirable that the prescription details will be recorded on the SA Health MR75D *clozapine investigation review and prescription record* (or electronic equivalent) where this is in use, by the medical officer writing the prescription for bedded and community services.

NOTE: Medical officers, General Practitioners and consultant psychiatrists directly involved in clozapine management are required to be registered with the relevant CPMS Clozapine Centre.

3. Nurse-led Clinic Model

Nurse-led clinics are to be supported by a designated consultant psychiatrist as the clinic sponsor.

Stable participants requiring 4 weekly monitoring are seen by nursing staff in the SA Health Nurse-led clinics or in partnership with a GP.

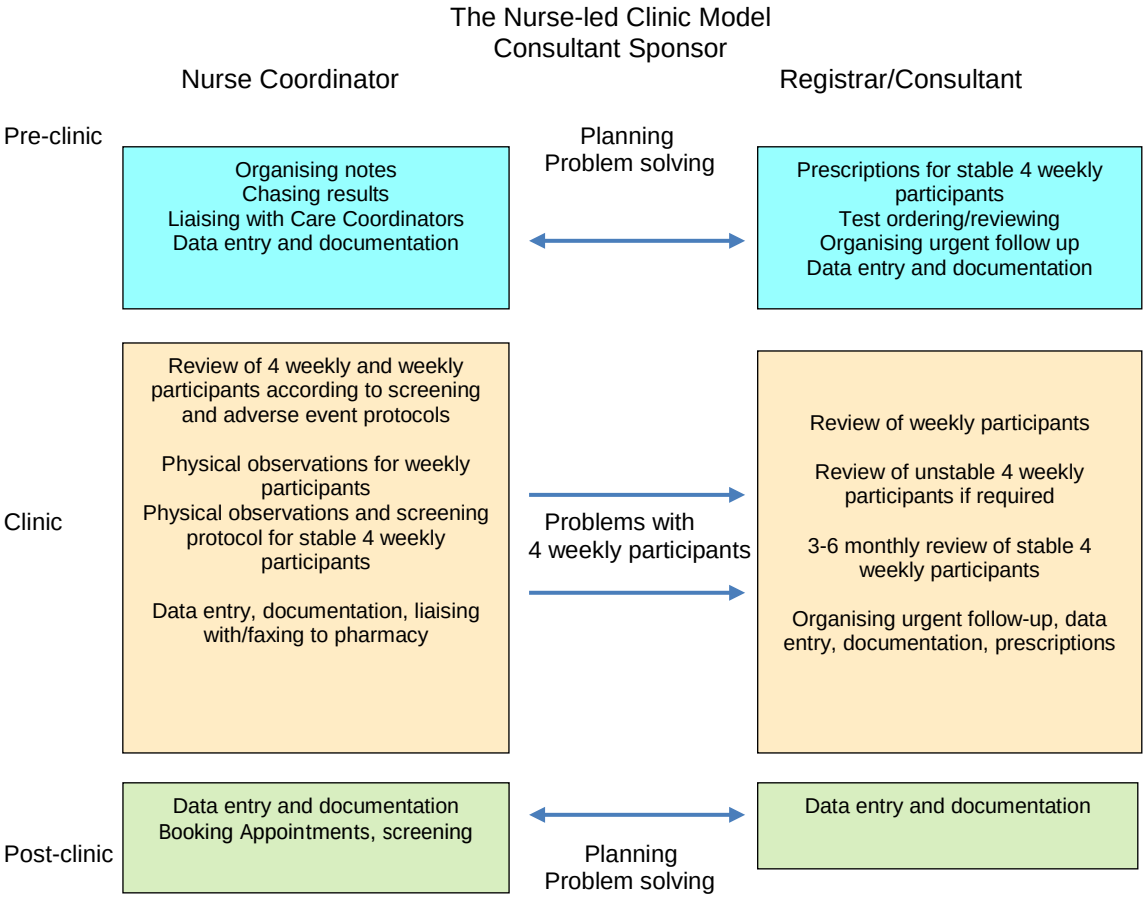
A medical officer is to be allocated to review the blood test and write the clozapine prescription within 48 hours of the blood test.

Nurses are to encourage participants to complete a self-report '*Clozapine questionnaire'* (see **Appendix 3**) to assist in the assessment of side effects, compliance, mental state and changes in other medication, tobacco or substance use.

If the nurse has significant concerns, a medical officer is to be contacted to discuss the review and if required assess the participant. Otherwise medical officers review participants as determined by clinical need or a minimum of 6 monthly.

If the nurse feels that the community clozapine clinic is unable to meet the requirements of the TGA endorsed CPMS protocol or the SA Health Clinical Guidelines, this should be raised through local management structures and the consultant sponsor and further to the SA Health Psychotropic Drugs Committee if local processes are not able to rectify the situation.

The complete set of nurse-led clinic tools for use including the adverse event protocols can be found on the SA Health Clozapine web page at www.sahealth.sa.gov.au/clozapine



4. General Practice Shared Care

The SA Health Clozapine Pathways (see **Appendix 2**) are to be followed when managing the care of clozapine participants between SA Heath clozapine clinics and General Practitioners (GPs).

Participants who are considered stable and who are on a maintenance dose of clozapine can be moved into shared care with GPs guided by **Appendix 4**.

Participants in shared care must be registered to a SA Health clozapine centre and be registered with the SA Health mental health service until they are eligible for transfer to a private centre.

GPs registered with CPMS are able to prescribe maintenance doses of clozapine under the supervision of a consultant psychiatrist. Dosage changes may only occur under the guidance of a psychiatrist.

Clozapine participants will attend the GP practice every 28 days for a face to face clozapine review including mental state assessment, physical health assessment, assessment and management of side effects, monitoring of metabolic changes and prescription management. While GPs have their own data record systems it is best practice to use a system of liaison with the Clozapine Coordinator to facilitate review and support.

SA Health Clozapine Coordinators are to ensure that they review the blood results of participants in shared care.

SA Health Clozapine Coordinators or Pharmacists are to enter the blood results into the CPMS data base or where other systems are in place, ensure the blood results have been entered in a timely manner (e.g. Country SA Health Clozapine Coordinators ensure that dispensing pharmacists have entered the blood results and dispensing data into the CPMS database).

SA Health Clozapine Coordinators are to enter the GP clozapine review into the CBIS or CCCME GP clozapine review screen. SA Health Clozapine Coordinators are to communicate regularly, (minimum of three monthly), with GPs providing shared care. At this time the Clozapine Coordinators are to collect the physical health review information from GPs if it hasn't already been sent to the MHS. Clozapine Coordinators are to advise the GP of any 6 monthly or annual testing requirements to ensure the protocols are met.

Participants under shared care are to have a psychiatric assessment by a private or public mental health psychiatrist a minimum of every 6 months or more frequently as clinically required. GPs are to be encouraged to provide a summary of efficacy, side effects and metabolic data when referring participants for assessment.

Participants who return an amber reading can still be maintained in shared care with in-reach and support to the GP from the SA Health Clozapine Coordinator and treating psychiatrist and monitored according to protocol.

The care of participants in shared care who return a red result are to be returned to the public mental health service for urgent follow up with a consultant psychiatrist and haematologist.

The care of participants in shared care with a significant clinical or functional instability, partial/non-adherence or significant clozapine side effects are to be returned to the public mental health service for review and follow up.

5. Prescriptions and Pharmacy

All prescriptions must be written in accordance with PBS and Section 100 requirements and the CPMS Protocol guidelines following the medical officer review of satisfactory blood results and given to the participant or forwarded to pharmacy after the satisfactory completion of the physical health assessment.

Prescriptions are to be written on an authority or hospital prescription pad or paper and must contain the following (see **Appendix 5**):

- participant name and address;
- Medicare number;
- PBS box ticked;
- CPN (Clozaril Patient Number) of the participant;
- hospital provider number of the consultant psychiatrist (initiation);
- must use the brand name “Clozaril” (only private psychiatrists may use Clopine);
- Clozaril tablet strength in mg (a separate script is required for each strength);
- exact number of tablets;
- Clozaril dose regimen (e.g. 300mg nocte oral);
- streamlined code for quantities less than 200 tablets/strength or authority approval number for quantities more than 200 tablets/strength;
- white cell count (WCC) and neutrophil count (NC) and the date that the blood test was taken; and
- no brand substitution box must be ticked for all community prescriptions.

A prescription must not be issued if a clinical assessment has not been undertaken. Completed prescription(s) for maintenance treatment can either be given to the participant, carer or support person to take to the community pharmacy.

The quantity prescribed must not exceed 3 to 4 days treatment for twice weekly monitored participants, 7 days treatment for weekly monitored participants or 28 days treatment for 4 weekly monitored participants, unless dispensation has been applied for and approved by the CPMS.

It is desirable that the prescription details are recorded on the SA Health *MR75D clozapine investigation review and prescription record* (or electronic equivalent) where this is in use, by the medical officer writing the prescription for bedded and community services.

During the initiation phase of treatment, a SA Health Hospital Pharmacy is required to supply clozapine either directly to the participant or via the participant’s chosen designated community pharmacy, as per the public sector clozapine commencement partnership (see **Appendix 1**). This needs to be negotiated via team consultation and specified in the care plan.

6. Transfer of Care

Clear communication of the participant details, CPMS registration, monitoring results and documentation surrounding clozapine treatment progress and any history of adverse events, side effects or risk factors in treatment including compliance is essential to ensure the safe management of clozapine during the transition of care. The transition process is potentially a high risk period for breaks in treatment or other adverse events occurring due to poor communication.

Every transfer between treating sites requires the completed SA Health MR76D *Clozapine transfer of care form* (or electronic equivalent) to be provided to the subsequent treating team as early as possible (must be prior to the first community clozapine assessment appointment for transfer from bedded units) to allow seamless transition of the participant's care. This includes transfer between community sites, transfer from the community to bedded services, transfer between bedded services and transfer from bedded services back in to the community.

The transferring team are responsible for ensuring that monitoring requirements can be met during the transition of care through discussion and planning with the participant and receiving team.

If the participant has been commenced on clozapine for the first time then the referring team needs to complete the Clozapine Community Pharmacy Partnership registration form (see **Appendix 1**) in collaboration with the hospital pharmacy that will provide dispensing services and help facilitate courier services to the identified community pharmacy as the collection point.

Clozapine Coordinators are to be notified as soon as discharge planning commences from bedded services. Timely information exchange and direct liaison to set up appointments either with the Clozapine Clinic or GP service within 48 hours of the Complete Blood Examination (CBE) should be reflected in the Mental Health Care Plan and electronic Clinical Review documentation.

The discharge team in collaboration with the receiving team must organise a CBE to occur at the appropriate interval post discharge as per the CPMS protocol (e.g. within a week of the last CBE if weekly monitoring or within 4 weeks of the last CBE if on maintenance monitoring) and provide the participant with a pathology form and instructions. CPMS may be contacted to provide dispensation to extend the time to the next follow up CBE/assessment if there is a delay in community clozapine clinic appointments (up to 2 days for weekly participants, up to 2 weeks for monthly participants). Alternatively, an early blood test can be performed on discharge to ensure monitoring requirements are met until the next CBE/assessment.

Participants still in the first 28 days of the initiation phase require a thermometer on discharge so they can self-monitor their temperature on a daily basis to screen for possible myocarditis or febrile neutropenia. They are to be given instructions on how to monitor temperature and how to respond to an elevated result:

- measure oral temperature under your tongue at same time every day;
- do not measure your temperature immediately after hot drinks food or a cigarette;
- if the temperature is above 38 degrees centigrade repeat it after 15 minutes;
- if temperature remains above 38 degrees centigrade then seek medical review either by contacting your Clozapine Coordinator, care coordinator or visiting your GP or local hospital emergency department; and
- if your fever is persistent you will need blood tests to rule out low white cells or inflammation of the heart (myocarditis), you may require urgent treatment for these conditions.

On discharge from an inpatient service participants are to be supplied with enough clozapine to last up to their next clozapine review. CPMS can be contacted for an extra 2 day dispensation so that supply is maintained in the event of a delayed appointment.

Transfer of care paperwork for the receiving clozapine centre and GP if applicable typically consists of the following information:

- copy of the current SA Health monitoring protocol form (MR74D *Clozapine commencement form,* MR78D *Clozapine recommencement form,* MR77D *Clozapine patient 4 weekly protocol* form);
- copy of the SA Health MR75D *Clozapine investigation review and prescription record form* (where used and no electronic equivalent is available);
- copy of the SA Health MR 76D *Clozapine Transfer of Care form* (or electronic equivalent);
- a copy of the current medication record (or electronic equivalent);
- a copy of recent blood results, ECGs and echocardiograms; and
- a discharge summary if transferred from a bedded service.

If a participant arrives unexpectedly from out of region or interstate the new treating team should urgently establish the following:

- the contact details of their usual prescriber/ Clozapine Coordinator;
- has there been an interruption to treatment;
- how many tablets/ days of clozapine supply does the participant have access to;
- the contact details of their usual dispensing pharmacy;
- when are the next blood results due; and
- are they taking Clozaril® or Clopine®?

If a participant is taking Clopine®, contact should be made with the ClopineCentral™Team on 1800 656 403 to establish current treatment, blood test monitoring results, and plans for ongoing monitoring and dispensing. If you require further information or support, contact your pharmacy department. If the participant requires long term treatment in the South Australian public health system, consideration should be given to switching to Clozaril and monitoring via the CPMS system.

While Clozaril is the formulary-preferred brand of clozapine, SA Health maintains a supply of Clopine to public hospitals allowing continuity of monitoring via Clopine Central for patients maintained on Clopine.

NOTE: CPMS and ClopineCentral have a memorandum of understanding whereby they exchange the blood test results history and transfer to the current monitoring system.

Within South Australia a request should be made to the previous treating team for an SA Health MR76D *Clozapine transfer of care form.* Interstate prescribers should be asked for equivalent information.

6.1 Transfer to a private Clozapine Centre

Consideration can be given to transferring care to a private Clozapine Centre if the following has been achieved and a transfer plan has been developed via clinical review involving the participant and their family/ carers, the treating and receiving psychiatrists and the GP service:

1. 12 months of maintenance therapy in a public clinic or GP Shared Care with no exacerbations. It is recommended that a partnership of 2 GPs cover each other to avoid interruptions to treatment;
2. regular attendance of blood tests and appointments;
3. stable and steady blood tests including therapeutic clozapine levels with no known complications;
4. a private psychiatrist has been reviewing the participant's care 6 monthly and is willing to take over responsibility under their own Clozapine Centre with a partnership of the GP and nominated pharmacy taking full responsibility for the CPMS data entry and management;

5. a full handover and transfer of care would formalise the closure of the episode with the MHS; and
6. assuring immediate re-entry to the MHS would be facilitated should there be an exacerbation /relapse or if there are concerns with compliance, abnormal results or should any part of the arrangement be unsustainable.

7. Bedded Units Including Non-Mental Health Unit Admissions

All SA Health bedded services need to have a plan for clozapine management supported by their pharmacy department, medical staff and managers. A designated nurse(s) Clozapine Coordinator assists with oversight and liaison with community based Clozapine Coordinators, medical staff, pharmacies, care coordinators and other relevant stakeholders.

Ward nursing staff are responsible for the completion or coordination of the following tasks upon admission:

- request SA Health MR76D *Clozapine transfer of care form* with referral;
- select appropriate SA Health forms or admission pack;
- complete baseline observations and record on appropriate form;
- utilise the clozapine questionnaire to cover all assessment domains and record in electronic data system checking compliance, efficacy and side-effects;
- obtain patient's own clozapine supply if possible and contact the relevant pharmacist / pharmacy department for review;
- check frequency of monitoring and when next blood test due (if this information is not freely available call CPMS on 1800 501 768 for patients taking Clozaril, or call ClopineCentral on 1800 656 403 for patients taking Clopine);
- manage changes to smoking in conjunction with medical staff, including arranging for a clozapine level to provide an assessment of compliance and to exclude high levels associated with infection or inflammation and to identify the need for preventative dose adjustment prior to smoking cessation (see in Section 2 - smoking cessation);
- notify the hospital pharmacy, community Clozapine Coordinator, GP/psychiatrist of admission;
- review clozapine alerts and the care plan;
- ensure blood test and physical health review due dates are added to the local Journey Board system or equivalent;
- ensure timely liaison with the hospital pharmacy, community Clozapine Coordinators regarding discharge planning, continuity of clozapine monitoring, discharge medications and transfer of care; and
- the quantity of clozapine provided at discharge must not exceed 3 to 4 days treatment for twice weekly monitored participants, 7 days treatment for weekly monitored participants or 28 days treatment for 4 weekly monitored participants, unless dispensation has been applied for and approved by the CPMS. Smaller quantities may be supplied if there is a risk associated with the participant having large quantities but continuity of supply must be organised in the community.

Psychiatry Consultation Liaison:

- run the OACIS/EPAS Clozapine report each morning to identify all new local admissions of participants who are treated with clozapine;
- notify the hospital pharmacy and the appropriate Community Clozapine Centre of the admission;
- ensure that the inpatient treating team has sufficient understanding of the risks of prescribing clozapine and their responsibilities under PBS, CPMS, and SA Health guidelines and provide adequate support for the safe management of clozapine treatment;

- assist with safe transfer of care including the completion of required documentation such as MR forms and electronic databases (CBIS, CCCME, EPAS), timely liaison with the hospital pharmacy, community Clozapine Coordinators regarding discharge planning, continuity of clozapine monitoring and discharge medications; and
- the quantity of clozapine provided at discharge must not exceed 3 to 4 days treatment for twice weekly monitored participants, 7 days treatment for weekly monitored participants or 28 days treatment for 4 weekly monitored participants, unless dispensation has been applied for and approved by the CPMS. Smaller quantities may be supplied if there is a risk associated with the participant having large quantities of medication but continuity of supply must be organised in the community.

8. Evaluation

Bi-annual audits which monitor the key performance indicators related to compliance with TGA endorsed protocol requirements. These audits are mandatory and each LHN is responsible for administering the audit at set intervals twice a year (March and October), managing these results and reporting them to the SA Health Psychotropic Drugs Committee.

The audit of the medical records of participants who have ceased smoking for evidence that serum clozapine concentrations were tested as per procedure, and toxic levels were not reached.

Adverse events such as amber and red blood results are reported according to SLS and CPMS notification requirements which are monitored and reviewed by each LHN.

Appendix 1 – Clozapine Pharmacy Partnership Registration Form

SA Clozapine Community Pharmacy Partnership Registration form		Affix patient identification label in this box UR No: (**for DISPENSING hospital**)…… Surname: ……..…… Given names: …… DOB: …….. Sex: …… Address: …… …… ……
CPN:	Clozapine Commencement date:	
Medicare No:		

Concession card Type / No:	CTO: **Y / N**	Expires:
Safety Net Card No:	Initiating Consultant:	

BEFORE COMMENCEMENT OF CLOZAPINE PLEASE IDENTIFY:		
Community Mental Health Team:	Phone:	Email/ Fax:
Community Clozapine Coordinator:	Phone:	Email/ Fax:
Community Care Coordinator:	Phone:	Email/ Fax:
Community Consultant Psychiatrist:	Phone:	Email/ Fax:

Commonwealth Government requirements stipulate that a Public Hospital Pharmacy must dispense clozapine during the 18 week initiation phase. This form enables transfer of information between hospital and outpatient services, and must be completed **BEFORE** discharge to community services.

Following prior agreement, this completed form should be sent to **both** the dispensing hospital pharmacy **and** the relevant community clozapine clinic. It is the responsibility of the commencing team's Clozapine Coordinator (Nursing or Pharmacy) with the support of the treating team to ensure that communication occurs prior to transfer.

INPATIENT CONTACTS:	PUBLIC HOSPITAL SITE:	
Responsible Medical Officer:	Phone:	Email/ Fax:
Initial public hospital pharmacy contact: ***(dispensary or clinical pharmacist)***	Phone:	Email/ Fax:

Estimated date of discharge from inpatient unit:

SA PUBLIC HOSPITAL DISPENSING PHARMACY *(to supply balance of first 18 weeks of clozapine)*:

NB: Referring team must acquire new hospital UR No. if required BEFORE dispensing can occur (enter above)

Hospital pharmacy contact:	Phone:	Email/ Fax:
Is patient going to ICC, CRC prior to home :**Y / N**	If **YES**, discharge destination:	

If **YES**, initial clozapine delivery destination *(NB – must not be a P.O. Box):*

Is dose administration aid required? **Y / N**	If **YES**, liaise with preferred pharmacy re requirements **DONE** ☐

Expected date of discharge to home address:
(NB – must inform Public Hospital Pharmacy to ensure delivery of clozapine to preferred community pharmacy below)

NEGOTIATED PREFERRED COMMUNITY PHARMACY DETAILS:		
Community pharmacy:	Phone:	Email/ Fax:
Address:		
Is pharmacy CPMS registered? **Y / N**	If **NO**, community pharmacy to register prior to dispensing maintenance therapy	

GP DETAILS (IF APPLICABLE):		
GP Name / GP Centre :	Phone:	Email/ Fax:
Address:		
Is GP CPMS registered? **Y / N**	If **NO**, MUST be arranged by initiating coordinator: **DONE** ☐	

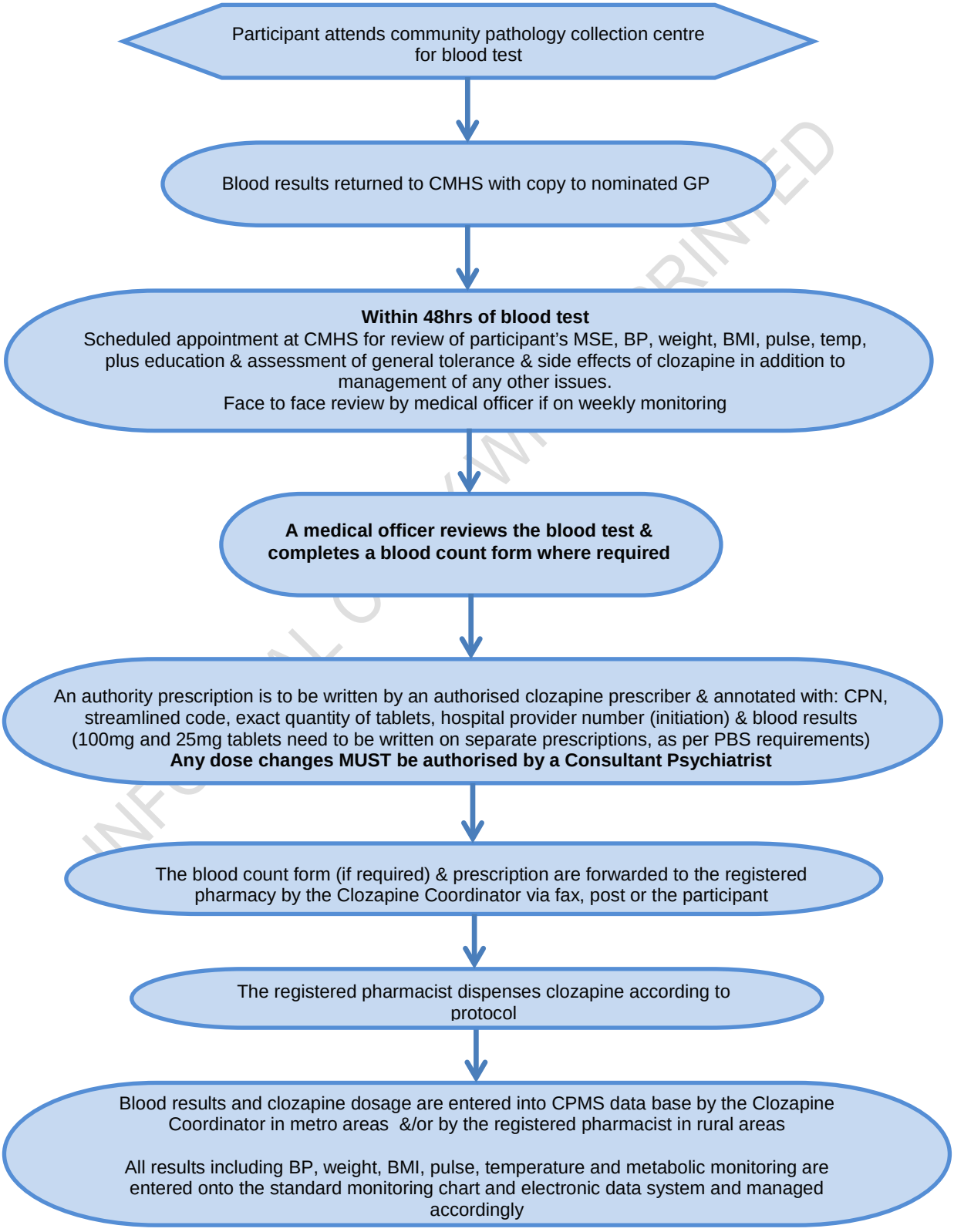
NOTES:

Appendix 2 – SA Health Clozapine Pathways

SA Health CLOZAPINE PATHWAYS

Community Mental Health Services (CMHS)

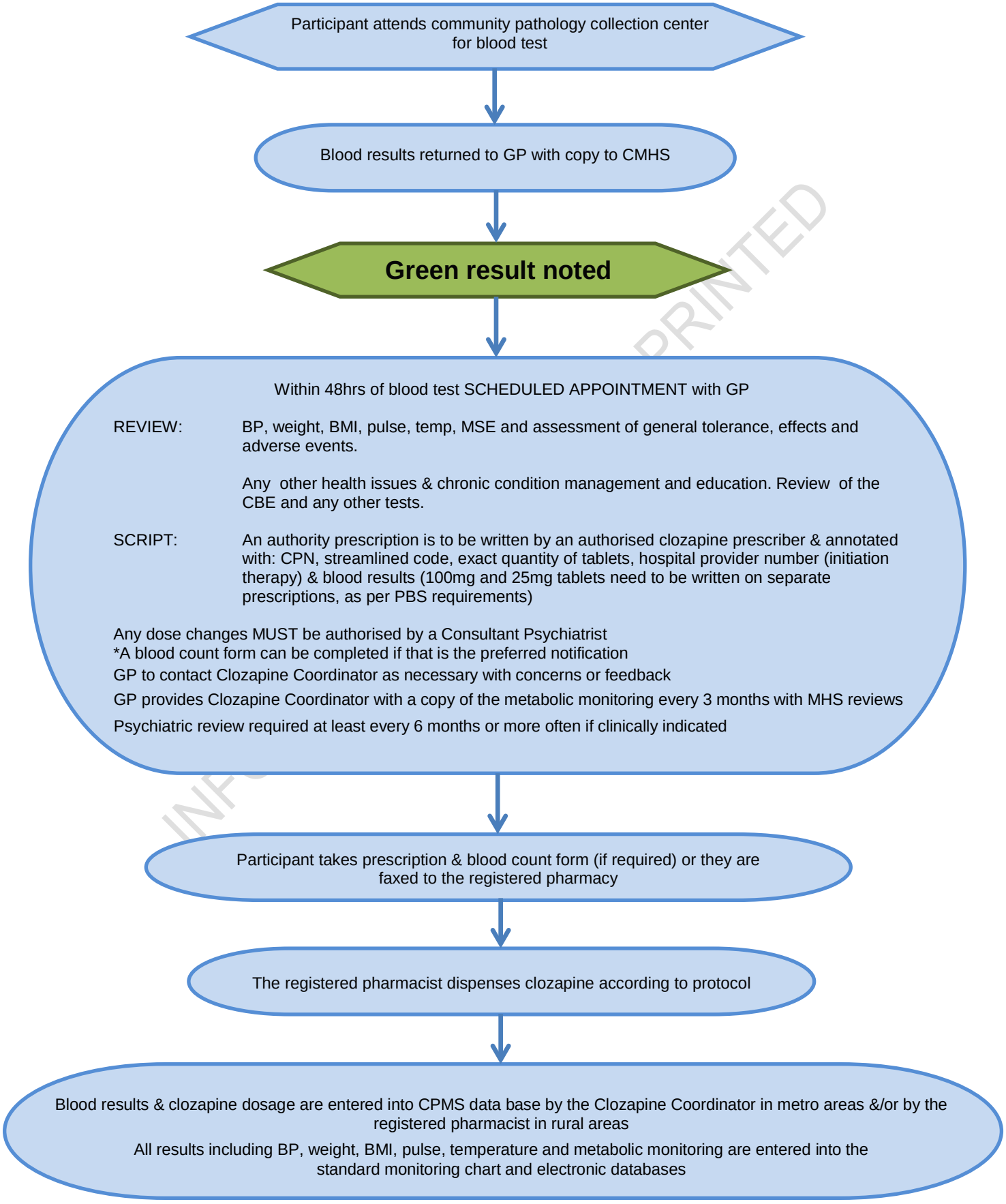
As per TGA endorsed clozapine management of protocols the participant is to be seen every 7 or 28 days (depending on whether they are on weekly or 4 weekly monitoring) for clinic assessment of signs and symptoms of infection



SA Health Clozapine GP Shared Care Arrangements

As per TGA endorsed clozapine management of protocols the participant is to be seen every 7 or 28 days (depending on whether they are on weekly or 4 weekly monitoring) for clinic assessment of signs and symptoms of infection

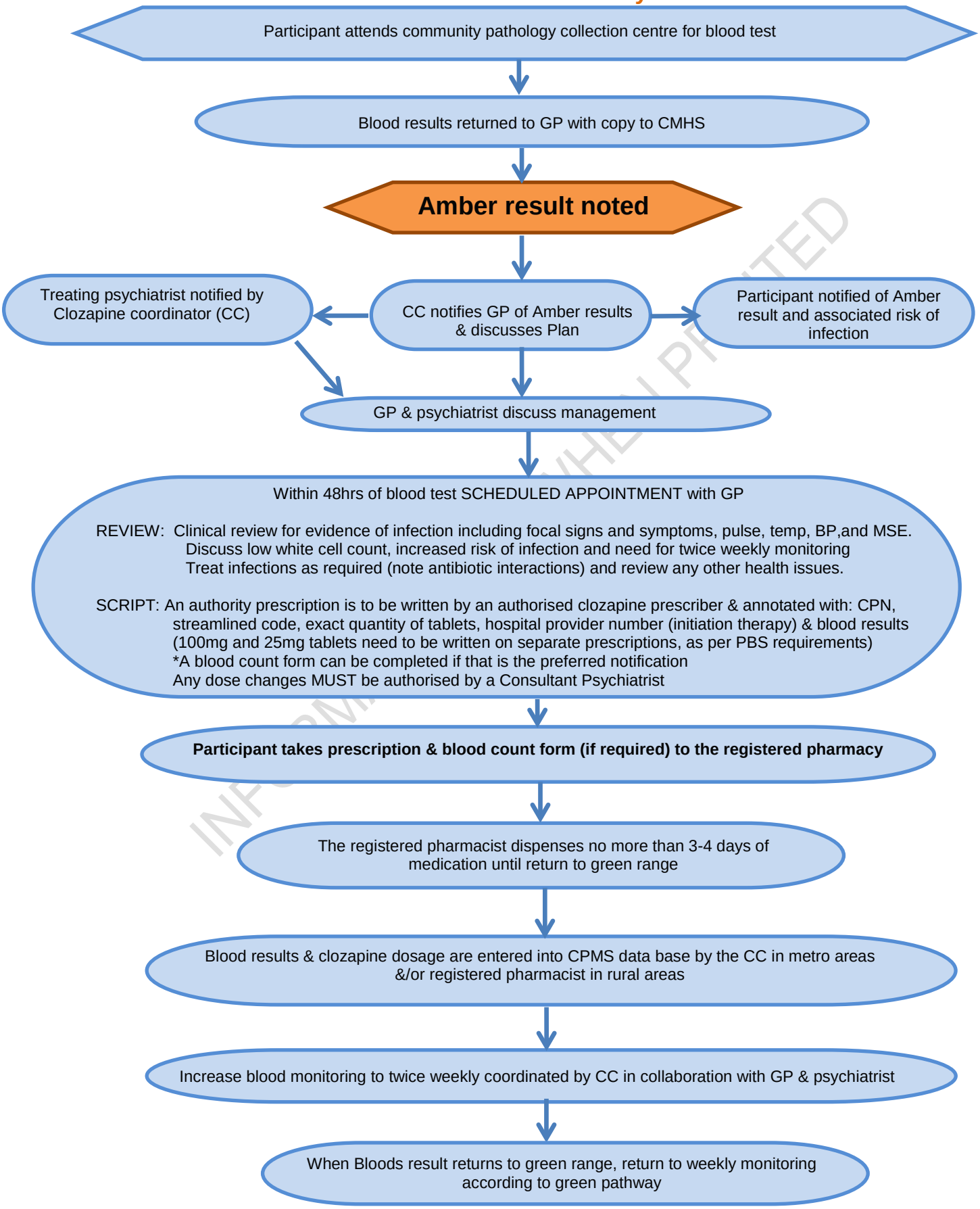
Green Result Pathway



SA Health Clozapine GP Shared Care Arrangements

As per TGA endorsed clozapine management of protocols the participant is to be seen every 7 or 28 days (depending on whether they are on weekly or 4 weekly monitoring) for clinic assessment of signs and symptoms of infection

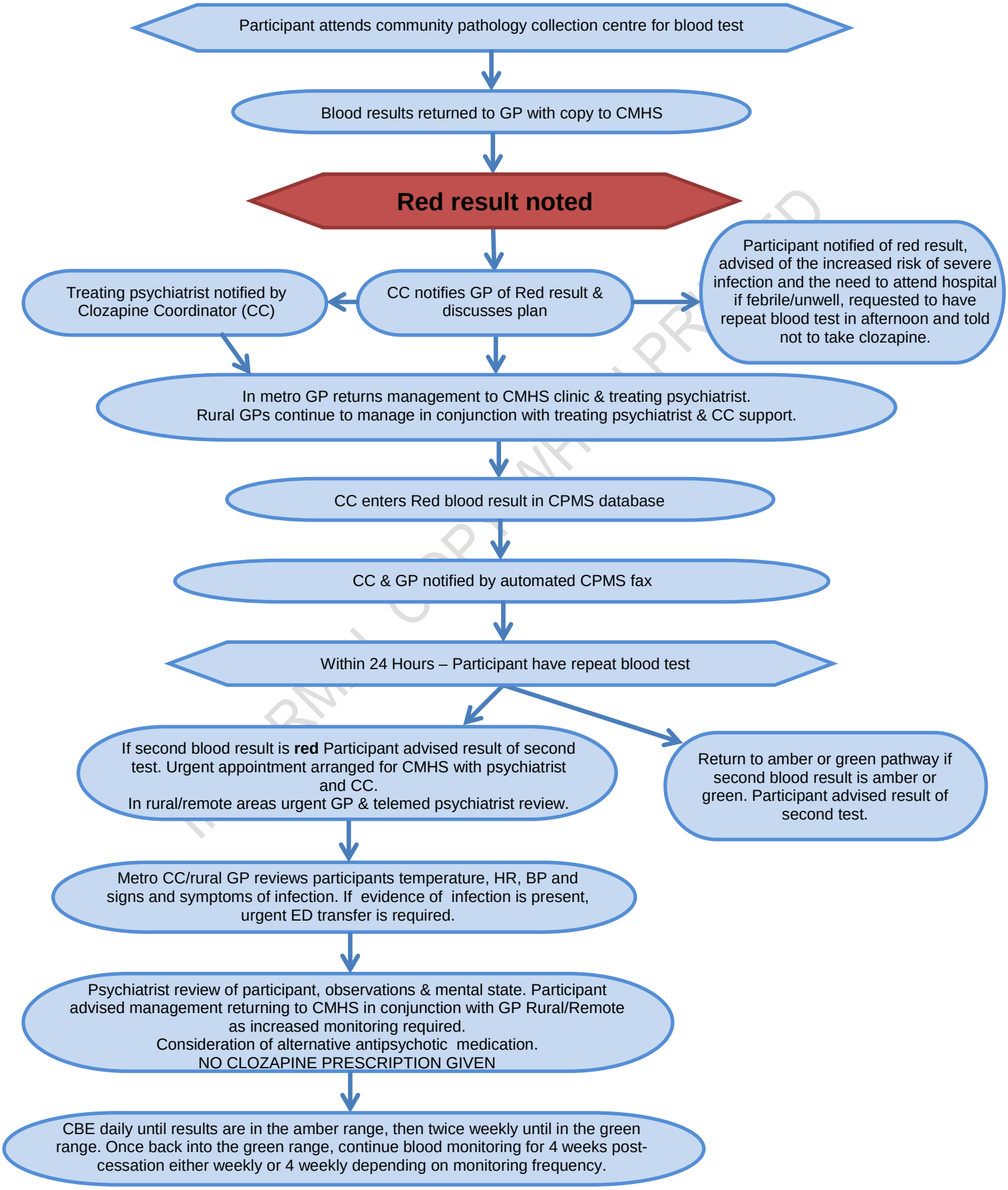
Amber Result Pathway



SA Health Clozapine GP Shared Care Arrangements

As per TGA endorsed clozapine management of protocols the participant is to be seen every 7 or 28 days (depending on whether they are on weekly or 4 weekly monitoring) for clinic assessment of signs and symptoms of infection

RED Result Pathway



Appendix 3 – Clozapine Questionnaire

Name:_____ **Date**_____

We hope that the last week/month has been a positive one for you.
The questions below cover possible side effects or health problems that are important to manage.
Answering honestly can help others understand how clozapine is working for you.

	Please circle yes or no		
1	Have your thoughts been as clear as usual this week/month?		Yes No
2	Have you been able to manage your home and/or finances this week/month?		Yes No
3	Have you had any thoughts that have worried you this week/month?		Yes No
4	Have you attended	an emergency department?	Yes No
		been admitted to hospital?	
		had extra visits to your GP or outpatients?	Yes No
5	Have you started or stopped any medications this week/month including any pain relief or anything purchased over the counter from the pharmacy?		Yes No
6	This week/month have you changed how much you use	cigarettes or tobacco?	Yes No
		cannabis?	Yes No
		alcohol?	Yes No
		other drugs?	Yes No
7	Have you made any changes to how much coffee, cola or high energy drinks you use?		Yes No
8	This week/month have you	missed clozapine doses?	Yes No
		decreased or increased your dose of clozapine?	Yes No
	How many tablets do you have left at home?		
9	Have you missed, decreased or increased your dose of any other medications this week/month?		Yes No
10	Have you been unwell this week/month?	fever or increased sweating?	Yes No
		cough or cold?	Yes No
		nausea or vomiting?	Yes No
11	Have you had any dizziness, chest pain or shortness of breath this week/month?		Yes No
12	Has there been any change in the frequency in which you pass urine this week/month?		Yes No
13	Have you had any unexplained wetting (day or night) this week/month?		Yes No
14	Have you had any muscle stiffness or tremors this week/month?		Yes No
15	Have you felt more drowsy than usual this week/month?		Yes No
16	Have you had an increase or decrease in dribbling this week/month?		Yes No
17	Have you had any change in your bowel movements such as constipation or diarrhoea?		Yes No
	If yes what did do you do to try to fix this?		
18	This week/month have you had any changes to your sleeping pattern or have your dreams become upsetting?		Yes No

Do you have any other comments or questions? Please turn over if you need extra space to write.

This questionnaire can be used by anyone taking clozapine or clinicians involved in support or management

Appendix 4 – GP Information

CLOZAPINE Shared Care for General Practice

Use in conjunction with the Clozaril® Patient Monitoring Service (CPMS) protocol book 2016

CBE: blood test usually every 7 days (initiation) or 28 days (maintenance):

- Full blood count (White blood cell count & neutrophil count) prior to appointment

6 monthly in addition to CBE	12 monthly in addition to CBE
Clozapine level	ECHO
Fasting glucose	ECG
Fasting full lipid studies	Troponin I or T
LFT and electrolytes	CRP
Psychiatrist referral / review	

Review: GP or trained Practice Nurse to complete assessment within the 48 hour window post blood test

- Assess mental state and medication compliance, check number of tablets remaining
- Change to smoking status may significantly affect clozapine levels requiring increased monitoring to detect toxicity or reduced effectiveness. Discuss concerns with Psychiatrist.
- Changes to other prescribed or use of over-the-counter medications
- Assess substance use including caffeine that may affect clozapine levels
- Physical health assessment check for: signs of infection, temperature, girth, weight, BMI
- Cardiovascular dysfunction: chest pain, shortness of breath, manual pulse & BP
- Seizure activity: consider clozapine level (discuss with psychiatrist)
- Side effects: constipation, hypersalivation, sedation, extra pyramidal side effects (EPSE)
- Notify coordinator if clozapine dose is changed by the treating psychiatrist

White Blood Cell and neutrophil count results	Range	Action
WBC >3·5 x 10^9 /L and NC > 2.0 x 10^9 /L	**Green**	Continue with clozapine
WBC 3·0 – 3.5 x 10^9 /L and / or NC 1.5 – 2.0 x 10^9 /L	**Amber**	Inform coordinator & psychiatrist Can continue clozapine with twice weekly CBE until green
WBC < 3·0 x 10^9 /L and / or NC < 1.5 x 10^9 /L	**Red**	STOP clozapine immediately! Repeat blood test within 24 hours. Inform coordinator & psychiatrist.

Authority Prescription: written by clozapine registered Medical Officer

NB The clozapine dose can only be changed in consultation with the psychiatrist

When quantity prescribed is ≤ 200 tablets/strength for a 28 day supply (dose ≤ 700mg/day)	When quantity prescribed is >200 tablets/strength for a 28 day supply (dose >700mg/day)
MO must endorse authority prescription with: 1. STREAMLINED authority code: **4998 maintenance therapy 5015 Initiation therapy**	MO must endorse authority prescription with: • Authority approval number obtained from PBS authorities line (Tel: 1800 888 333)
For initiation treatment only add: **Public hospital provider number**: (clozapine coordinator will provide appropriate provider number)	
All prescriptions must be endorsed with: 2. **Clozaril Patient Number** (CPN) to assist pharmacy ID for required data entry 3. Exact **quantity** of tablets (Clozaril comes in 25mg and 100mg tablet strengths) 4. **CBE** Date and result of test: e.g. 1/07/2015 WCC 3.6 NC 2.2	

- Complete the blood pathology request form for next CBE; cc treating psychiatrist
- Provide the patient with the prescription and the pathology form

Contact Clozapine Coordinator to Advise:

- Metabolic health data – minimum every 3 months
- Non-attendance of the patient to an appointment
- There has been an interruption of therapy
- Inability to review the patient due to leave / no other doctor registered at your practice
- You have concerns or feedback

CLOZAPINE

Clozapine, tradename Clozaril® or Clopine®, is an antipsychotic medication regulated by the Therapeutic Goods Administration (TGA) subsidised under the Highly Specialised Drugs Program. It is a third line treatment for chronic schizophrenia refractory to treatment with other medications. Clozapine availability is tightly controlled; patients may only be prescribed clozapine when mandatory blood testing and other monitoring can be achieved at the required intervals. SA Health uses the Clozaril brand of clozapine, which comes in 25mg and 100mg tablet strengths. Standard PBS co-payments apply.

The Clozapine Coordinators are central to ensuring compliance by all registered personnel with the CPMS protocol thereby maintaining patients safely on clozapine.

Side Effects:

- Weight gain
- Metabolic syndrome
- Diabetes
- Hypersalivation – more often at night
- Nausea
- Sedation
- Severe constipation
- Increased heart rate
- Myoclonic jerks
- Obsessional traits
- Nocturnal enuresis

Serious Adverse Effects: (Medical Emergency)

- Agranulocytosis / neutropenia
- Severe infections, fever
- Seizures
- Hypertension / hypotension
- Myocarditis
- Cardiomyopathy
- Pulmonary embolus
- Acute renal failure

When to liaise with the Clozapine Coordinator or psychiatrist:

- Concerns regarding compliance
- **Treatment interruptions of greater than 48 hours (refer to protocol)**
- Infection, fever, rigors, temperature greater than 38°
- Chest pain, pale, sweaty symptoms
- Increased heart rate, marked changes to blood pressure
- Deterioration in mental state
- Queries about when the blood test is due
- Monitoring frequency questions
- Transfer to another region and discharge planning
- Introduction of new medication
- Care plan and clinical review

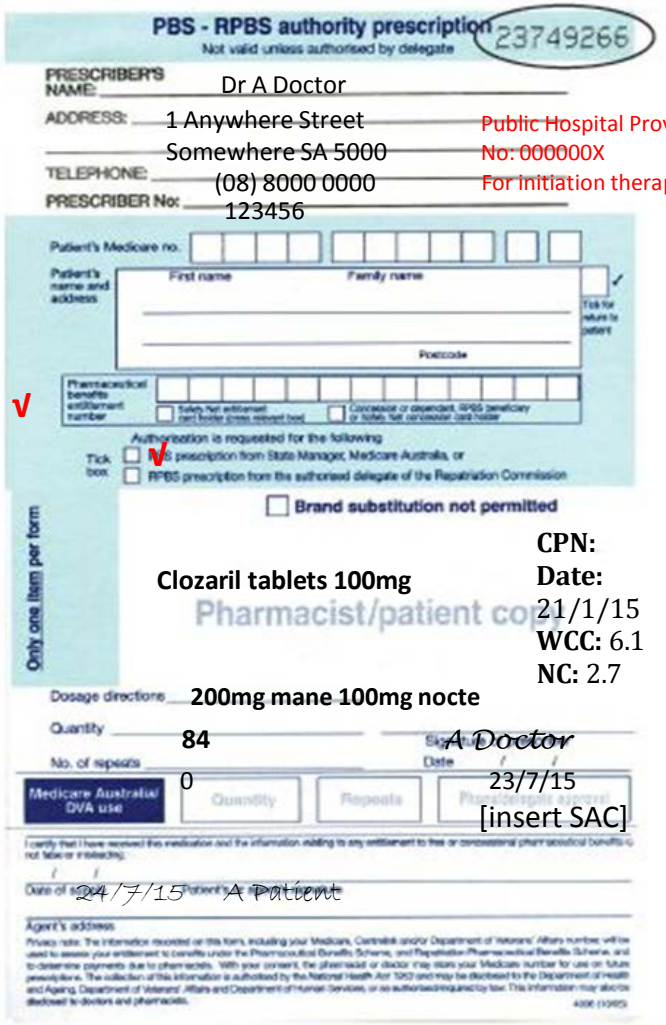
The patient will remain registered with the Mental Health Service while on clozapine

Contacts:

Local Clozapine Coordinator:……	**……**
Clozaril® Patient Monitoring Service (CPMS): For monitoring enquiries	**1800 501 768**
Mental Health Triage & Emergency Triage and Liaison Service (ETLS)	**13 14 65**
SA Health Web Page www.sahealth.sa.gov.au/clozapine	

Community ClozarilPrescription Guide

Authority prescription



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PBS & safety reminders

- ❖ Use an authority pad or paper
- ❖ A separate script is required for each strength

Annotate with:

- **CPN**
- **CBE Date & result**
- **Streamlined Authority Code (SAC):**

5015 initiation

4998 maintenance

Or

Authority Approval No

for increased quantities of >200 tabs

- **Exact tablet quantity**

✓ **PBS box and**
✓ **No brand substitution**

TABLET CALCULATOR

28 day supply

Dose (mgs)	Days	No of tablets
PBS Prescription		
25	28	28
50	28	56
75	28	84
100	28	28
200	28	56
300	28	84
400	28	112
500	28	140
600	28	168
700	28	196
Telephone Authority required		
800	28	224
900	28	252
Limit of prescription		

7 day supply

Dose (mgs)	Days	No of tablets
PBS Prescription		
25	7	7
50	7	14
75	7	21
100	7	7
200	7	14
300	7	21
400	7	28
500	7	35
600	7	42
700	7	49
800	7	56
900	7	63
Limit of prescription		

Pharmacists check PBS compliance ->	**Check with consumer how many surplus tablets remaining & dispense balance req. ->**	
Endorse prescription with amount supplied and complete CPMS data entry ->	Dispense as PBS and charge relevant co-payment ->	Claim reimbursement as for other PBS scripts

CLOZAPINE Potential Drug Interactions

Clozapine prescribing information for health professionals

This information is general in nature and is not an exhaustive list. Health practitioners should review and assess individual patients and refer to up to date resources, e.g. Australian Medicines Handbook, MIMS and the SA Health website, or contact your pharmacist for advice.

Potential to Increase Clozapine Levels (enzyme inhibitors)

- SSRIs e.g. fluvoxamine (very large effect), fluoxetine, paroxetine, sertraline (large doses)
- Caffeine (3-4 cups/ day, especially in non- smokers)
- Some antibiotics such as macrolides (e.g. erythromycin), ciprofloxacin
- Cimetidine
- Oral contraceptives
- Ritonavir

Potential to Decrease Clozapine Levels (enzyme inducers)

- Carbamazepine
- Omeprazole
- Phenobarbitone
- Phenytoin
- Rifampicin
- St John's Wort
- Tobacco smoking

Potential to Depress Bone Marrow

- Carbamazepine
- Cytotoxic medication
- Immunosuppressant medication
- Nitrofurantoin
- Trimethoprim/sulfamethoxazole

Potential to Depress Respiration

- Benzodiazepines (especially large parenteral doses or at start of therapy)

Potential for Anticholinergic Side Effects (e.g. constipation, urinary retention, delirium)

- Anticholinergic tricyclic antidepressants (TCAs) e.g. amitriptyline, dothiepin
- Anticholinergic antipsychotics e.g. chlorpromazine, pericyazine, olanzapine
- EPSE medication e.g. benzhexol, benztropine, biperiden
- Sedating antihistamines e.g. diphenhydramine, cyproheptadine, promethazine, trimeprazine
- Other anticholinergic agents e.g. atropine, hyoscine

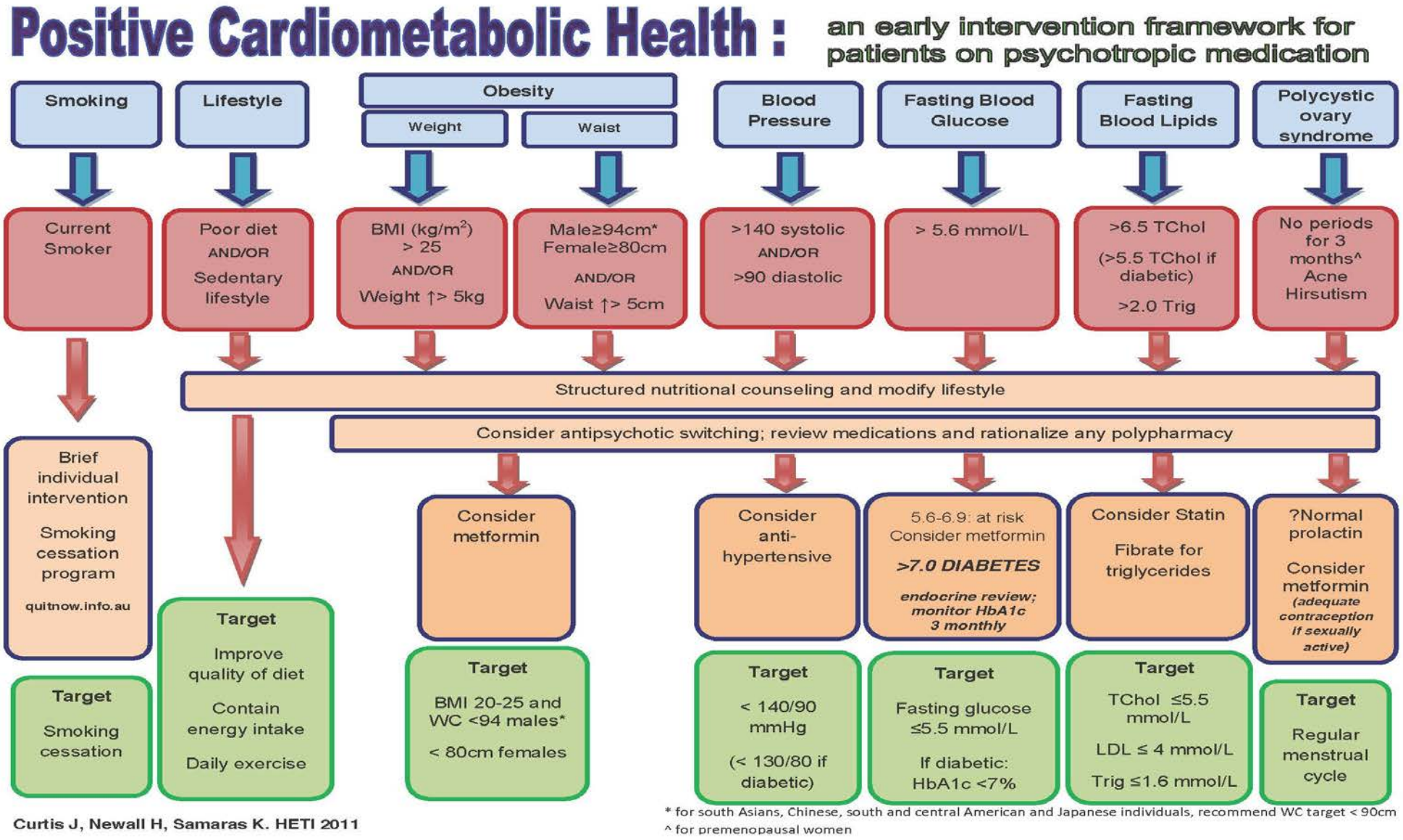
Potential for Hypotension (both postural and non- postural)

- Antihypertensives
- TCAs
- Some antipsychotics e.g. chlorpromazine, pericyazine, trifluoperazine, risperidone (initially), quetiapine (initially)

Potential for changes due to tobacco smoking (enzyme inducer)

- Starting or stopping smoking can cause dramatic changes in clozapine levels
- Prescription medications used for smoking cessation have been associated with destabilisation of mental state in some patients. Consider a strategic approach in consultation with the psychiatrist.

Appendix 6 – Positive Cardiometabolic Algorithm



History: smoking, exercise, diet, FHx (diabetes, obesity, CVD), gestational diabetes, ethnicity, Polycystic ovary syndrome

Then at least 3 monthly

Examination: weight, BMI, waist circumference, BP

Investigations: Fasting blood glucose and lipids: total cholesterol (TChol); LDL, HDL, triglycerides (Trig);

Vitamin D (twice per year).

Interventions:

Nutritional counseling: reduce take away and junk food, reduce energy intake to prevent weight gain, stop soft drinks and juices, increase fibre intake.

Physical activity: structured education-lifestyle intervention. Advise daily physical activity: eg 30 minutes of walking.

If unsuccessful after 3 months in reaching targets, then consider switching and medication interventions below

Switching: Consider switching to a more weight neutral medication. Review diagnosis and ensure ongoing need for all psychotropic medications.

Don't just SCREEN → INTERVENE

for all patients in the "red zone"

Screen cardiometabolic risk factors using screening tool (eg Waterreus, et al 2009, Curtis et al 2009 SESLHD); examine and investigate 3 monthly on all clients on psychotropic medications.

NB additional considerations for those on mood stabilizers & clozapine not included here and need to be performed (eg medication plasma levels, TFT's UEC's, ECHO, etc)

Always involve general practitioner, and, where appropriate and possible refer to specialist (eg dietitian/ physician/ diabetic clinic/ exercise physiologist).

NB: Some drugs used in metabolic disease treatment are contraindicated in pregnancy (eg some antihypertensives and lipid lowering drugs). If your patient on any metabolic medications is considering pregnancy, please discuss with their GP

Specific Pharmacological Interventions:

Consider metformin if:

- impaired glucose
- PCOS
- obesity or rapid weight gain

Metformin therapy: start at 500mg x ½ tablet before breakfast and dinner for two weeks then increase to 500mg bd. Dose can be increased to a maximum of 3 grams daily, though as this is off label treatment, no adverse effects should be tolerated. If side-effects of nausea, abdominal cramping, shift to after meal.

Lipid lowering therapy: (use PBS guidelines)

Statin initiation doses for cholesterol lowering:

simvastatin 10 mg nocte — atorvastatin 10mg nocte
pravastatin 10mg nocte — rosuvastatin 10 mg nocte

Fibrate therapy for triglyceride lowering:

gemfibrozil 600 mg bd — fenofibrate 145 mg mane

Anti hypertensive therapy: Multiple agents are available. Liaise with the GP who can monitor.

Vitamin D:

- <50 nmol/L: replenish stores: cholecalciferol 4,000 IU per day for one month;
- maintenance: 1,000 IU daily. Target >80nmol/L.

Authors: Curtis J, Newall H, Samaras K. © HETI 2011

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For online access to this fact sheet, please visit http://www.heti.nsw.gov.au/cmalgorithm

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Does this policy amend or update and existing policy? **N**
Does this policy replace another policy with a different title? **Y**

- Clinical Guideline for Clozapine Monitoring with Cessation of Tobacco Use
- Clinical Guideline for the Commencement of Clozapine

Approval Date	Version	Who approved New/Revised Version	Reason for Change
05/09/17	V1	SA Health Policy Committee	Original SA Health Policy Committee approved version.

For more information

For further information please contact the Office of the Chief Psychiatrist:
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Government of South Australia
SA Health