



PMB Benefit definition guideline for Schizophrenia  
*Version 1: 30.09.2020*

*Disclaimer:*

*The schizophrenia benefit definition has been developed for the majority of standard patients. These benefits may not be sufficient for outlier patients. Therefore Regulation 15(h) and 15(l) may be applied for patients who are inadequately managed by the stated benefits.*

## Acknowledgements <sup>1</sup>

The Council for Medical Schemes (CMS) would like to acknowledge all stakeholders who assisted in the drafting of this document, including the following general practitioners, psychiatrists, representatives from allied health professionals, patient advocacy groups, representatives from South African Medical Association (SAMA), pharmaceutical companies, different medical schemes and administrators:

Dr Kagisho Maaroganye (Psychiatrist)

Dr Lauren Hill (Nutritionist)

Dr Laurian Grace (Discovery Health)

Dr Lindiwe Mbekeni (Discovery Health)

Dr Mukesh Govind (General Practitioner)

Dr Mvuyiso Talatala (Psychiatrist)

Dr Natalie Benjamin (South African Society of Physiotherapy)

Dr Nkokone Tema (Psychiatrist)

Dr Sebolelo Seape (Psychiatrist)

Dr Selaelo Mamejja (SAMA)

Mr Brian Fafudi (Psychological Society of South Africa)

Ms Alta Kloppers (Association for Dietetics in South Africa)

Ms Cassey Chambers (South African Depression and Anxiety Group)

Ms Heidi Roth (South African Depression and Anxiety Group)

Ms Magda Fourie (South African Society of Physiotherapy)

Ms Menanda Hollands (Janssen)

Ms Rosetta Masemola (Occupational Therapist)

Ms Shelley Mc Gee (SAMA)

Ms Tryphine Zulu (Medscheme)

Prof Dana Niehaus (Psychiatrist)

Professor Daleen Casteleijn (The Occupational Therapy Association of South Africa – OTASA)

Professor Feroza Motara (Emergency Medicine – University of Witwatersrand)

The CMS would also like to acknowledge the contribution by Dr Haseena Gani in the write up of the document, as well as Dr Gerhard Grobler who was consulted prior to publishing the draft document.

---

<sup>1</sup> All affiliations indicated were at the time of the stakeholder meeting held in February 2019.

## Abbreviations

CT	Computed tomographic
FBC	Full Blood Count
ICD	International Classification of Diseases
MRI	Magnetic resonance imaging
PMB	Prescribed minimum benefit
WHO	World Health Organization
DTPs	Diagnosis Treatment Pairs
CMS	Council for Medical Schemes
DSM	Diagnostic and Statistical Manual
GP	General practitioner
ECG	Electrocardiogram
HDL	High density lipoprotein
LDL	Low density lipoprotein
Trig	Triglycerides
HIV	Human Immunodeficiency virus
EEG	Electroencephalogram
PO	Per os / by mouth
IM	Intramuscular
SGA	Second generation anti-psychotic
FGA	First generation anti-psychotic
ECT	Electro convulsive therapy
AST	Aspartate transaminase
ALT	Alanine transaminase
GGT	Gamma glutamyl transferase
U&E	Urea and electrolytes
TSH	Thyroid stimulating hormone

## Contents

1. Introduction.....	6
2. Scope of Purpose.....	6
3. Epidemiology.....	8
4. Aetiology and pathogenesis.....	8
5. DSM V – Criteria for schizophrenia.....	9
6. Diagnosis.....	10
6.1 Consultation to inform the diagnosis.....	10
6.2 Recommended baseline laboratory investigations for diagnostic work-up.....	11
6.3 Other investigations for diagnosis recommended as PMB level of care.....	12
7. Management of schizophrenia.....	13
7.1 Pharmacological management (in and out-of-hospital).....	14
7.2. Non – pharmacological treatment in and out-of-hospital.....	16
8. Laboratory and drug related investigations.....	18
9. Management of side effects (in - and out-of-hospital).....	19
10. References.....	21

## 1. Introduction

1.1. The legislation governing the provision of the Prescribed Minimum Benefits (PMBs) is contained in the Regulations enacted under the Medical Schemes Act, 1998 (Act No. 31 of 1998). With regards to some of the Diagnosis Treatment Pairs (DTPs), it has become apparent that medical scheme beneficiaries find it difficult to be fully aware of their entitlements in advance. In addition, medical schemes interpret these benefits differently, resulting in a lack of uniformity of benefit entitlements.

1.2. The benefit definition project is undertaken by the Council for Medical Schemes (CMS) with the aim of defining the PMB package, as well as to guide the interpretation of the PMB provisions by relevant stakeholders. The guidelines are based on the available evidence of clinical and cost effectiveness, taking into consideration affordability constraints and financial viability of medical schemes in South Africa.

## 2. Scope and purpose

2.1. This is a recommendation for the diagnosis, treatment and care of individuals with schizophrenia in any clinically appropriate setting as outlined in the Act.

2.2. The purpose of the guide is to improve clarity in respect of funding decisions by medical schemes, taking into consideration evidence-based medicine, affordability and in some instances, cost-effectiveness.

Table 1: Applicable PMB code for schizophrenia

PMB Code	PMB Description	Treatment Component
907T	Schizophrenic and paranoid delusional disorders	Hospital-based management up to 3 weeks / year

Table 2: Possible ICD10 codes for schizophrenia relating to DTPs

ICD10 code	WHO description
F20.0	Paranoid schizophrenia
F20.1	Hebephrenic schizophrenia
F20.2	Catatonic schizophrenia
F20.3	Undifferentiated schizophrenia
F20.4	Post-schizophrenic depression
F20.5	Residual schizophrenia
F20.6	Simple schizophrenia
F20.8	Other schizophrenia
F20.9	Schizophrenia, unspecified
F22.0	Delusional disorder
F22.8	Other persistent delusional disorders

F22.9	Persistent delusional disorder, unspecified
F23.1	Acute polymorphic psychotic disorder with symptoms of schizophrenia
F23.2	Acute schizophrenia-like psychotic disorder
F23.3	Other acute predominantly delusional psychotic disorders
F25.0	Schizoaffective disorder, manic type
F25.1	Schizoaffective disorder, depressive type
F25.2	Schizoaffective disorder, mixed type
F25.8	Other schizoaffective disorders
F25.9	Schizoaffective disorder, unspecified
F28	Other nonorganic psychotic disorders
F29	Unspecified nonorganic psychosis

Table 3: Possible ICD10 codes for identifying schizophrenia as a chronic disease

ICD10 code	WHO description
F20.0	Paranoid schizophrenia
F20.1	Hebephrenic schizophrenia
F20.2	Catatonic schizophrenia
F20.3	Undifferentiated schizophrenia
F20.4	Post-schizophrenic depression
F20.5	Residual schizophrenia
F20.6	Simple schizophrenia
F20.8	Other schizophrenia
F20.9	Schizophrenia, unspecified

3. Epidemiology and burden of disease
  - 3.1. Schizophrenia is a complex mental illness that has a significant impact on the affected individuals and their families. The lifetime risk of schizophrenia is approximately 1% and typically manifests in early adulthood (Owen, Sawa & Mortensen, 2016).
  - 3.2. Schizophrenia affects more than 23 million people worldwide but is not as common as many other mental disorders. It is more common among males (12 million), than females (9 million). Schizophrenia also commonly starts earlier among men (WHO, 2018).
  - 3.3. Literature on the current prevalence rate of schizophrenia in South Africa is lacking, but it is estimated that 1% of the South African population suffers from schizophrenia, amounting to a figure of roughly 500 000 people (following census estimates of population size) suffering from this disorder at any given time (Trump & Hugo 2006).
  - 3.4. The CMS Annual Report 2017-2018 indicates that mental health coverage for psychosis was 8.3 / 1000 beneficiaries (consolidated for the open and restricted private schemes) (CMS, 2017).
  - 3.5. Variation in the incidence and prevalence of schizophrenia between populations is greater than was once believed (Simeone, Ward, Rotella, Collins & Windisch, 2015). As many as 1% of people meet diagnostic criteria for the disorder over their lifetime. Schizophrenia often has profound effects on people with the disorder and their families. In terms of the global burden of disease and disability, schizophrenia ranks among the top 10 disorders worldwide (Mathers & Loncar, 2006).
  - 3.6. Approximately three-quarters of people who have been diagnosed with schizophrenia will experience a relapse with about one-fifth going on to have long-term symptoms and disability (Owen, Sawa & Mortensen, 2016).
  - 3.7. Schizophrenia is associated with excess mortality, which has been well documented by epidemiological studies on large cohorts over extended periods. Laursen (2011) found a reduction in life expectancy of 18.7 years for men and 16.3 years for women with schizophrenia. The leading causes of premature death among people with schizophrenia are cardiometabolic diseases, suicide and accidents (Laursen, 2011). In recent years there has been a growing emphasis on early detection and intervention in order to delay or possibly prevent the onset of psychosis and schizophrenia. This focus on very early intervention and prevention has stimulated an interest in identifying, and potentially intervening in, the so-called 'at risk mental states' (or prodrome) which may precede the onset of the disorder (NICE, 2014).
  - 3.8. Integrating mental health into current health systems with treatment, prevention, and screening to people with HIV and other chronic health conditions who are at high risk for mental disorders may be the most effective and cost-efficient approach to increase access to mental health services in South Africa (Jack, et al., 2014).



#### 4. Aetiology and pathogenesis

4.1. Schizophrenia is a complex, multifactorial disorder. Its aetiology has a major genetic component involving multiple genes of small effect, individual assortments of rare mutations (copy number variations) and molecular pathways that are likely to be heterogeneous, both within and across populations (Sullivan, Daly & O'Donovan, 2012). Environmental factors, ranging from neurodevelopmental insults (e.g. maternal pregnancy complications and birth complications) to psychosocial adversity and substance misuse, interact with genetic susceptibility to produce widespread phenotypic variation (Demjaha, MacCabe & Murray, 2012). The 'social defeat' hypothesis draws together various environmental risk factors to explain how they might lead to schizophrenia (Selten et al., 2013).

4.2. Precursors of schizophrenia, including developmental delays, cognitive abnormalities, attenuated symptoms and odd behaviour, may appear very early in life. However, such developmental precursors – if they occur – are usually subtle and are not specific indicators of subsequent psychosis (Thibaut et al., 2015).

4.3. Most research into schizophrenia is based on the highly unlikely assumption that schizophrenia is a single, uniform disorder. Research into the various forms of schizophrenia has been assisted by the conceptual tool of endophenotypes, which are heritable, objectively measurable biological traits that co-segregate with clinical illness in pedigrees and may also be expressed in unaffected members. Endophenotypes include distinct patterns on neuropsychological tests of cognitive function, brain electrophysiological measures and neuroimaging variables (Thibaut et al., 2015).

#### 5. Diagnostic and Statistical Manual-5 (DSM-5) – Criteria for schizophrenia

DSM-5 Criteria for the diagnosis of schizophrenia must be met (American Psychiatric Association, 2013; Tandon et al., 2013). Diagnosis must be made by a registered psychiatrist.

##### A.

Two or more symptoms must be present for at least 1 month. One of the two symptoms must include

- a) Delusions
- b) Hallucinations
- c) Disorganized speech (e.g., frequent derailment or incoherence)
- d) Grossly disorganized or catatonic behaviour
- e) Negative symptoms (i.e., diminished emotional expression or avolition)

##### B.

For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning, such as work, interpersonal relations, or self-care, are markedly below the level achieved prior to

the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement).

C.

Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed in Criterion A, present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).

D.

Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either

(1) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms; or  
(2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.

E.

The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

F.

If there is a history of autism spectrum disorder or a communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated).

Specifiers:

- First episode, currently in acute episode
- First episode, currently in partial remission
- First episode, currently in full remission
- Multiple episodes, currently in acute episode
- Multiple episodes, currently in partial remission,
- Multiple episodes, currently in full remission
- Continuous
- Unspecified
- With catatonia
- Severity score

## 6. Diagnosis

### 6.1. Consultations to inform the diagnosis

6.1.1. According to the Mental Health Care Act, 2002 (Act No. 17 of 2002), “a mental health care practitioner” means a psychiatrist or registered medical practitioner or a nurse, occupational therapist, psychologist or social worker who has been trained to provide prescribed mental health care, treatment and rehabilitation services. A “mental health care provider” means a person providing mental health services to mental health care users and includes mental health care practitioners.

6.1.2. In view of the definitions of a mental health care provider and / or practitioners, table 4 gives the recommended providers for diagnosis and the supportive allied providers.

Table 4: Recommended PMB level of care - consultations for the diagnosis of schizophrenia

Discipline	Comment
General Practitioner	A GP can do the initial diagnosis and can initiate treatment. However, the patient should be referred to a psychiatrist within 6 months to confirm the diagnosis. Stable patients can be managed by the GP.
Psychiatrist	Preferred provider for diagnosis
Other supportive providers only upon referral from GP or psychiatrist	
Clinical psychologist Occupational therapist Social worker	

6.1.3. The latest SASOP Guidelines (2017) suggest that the assessment of disability in mental health has become increasingly difficult due to, amongst others, inadequate treatment in terms of lack of referral to rehabilitation specialists including occupational therapists. The occupational therapist in mental health assess the individuals on two levels:

- a) Mental health status: which includes a comprehensive assessment considering all details of the injury, the diagnosis, history and treatment to date. He/she may also use recognised and standardised mental health assessment tools to help gain the best understanding of the current health status.
- b) Function: This component looks at habits, routines, roles, values, interests, environment, attitudes,

motivation, activities of daily living (ADL), family and relationships.

- 6.1.4. This two-part assessment provides the Occupational Therapist with a comprehensive picture of the individual's health status and how it is impacting their ability to perform skills and tasks that are important in daily life. A comprehensive and targeted rehabilitation program can then be developed and implemented together with the other providers (Back on Track Mental Health Occupational Therapy, 2019).
  - 6.1.5. A systematic review to evaluate evidence for the effectiveness of interventions within the scope of occupational therapy to improve and maintain performance and participation for people with serious mental illness concluded that there was support for the use of evidence-based practice within the scope of occupational therapy, inclusion of occupational therapy practitioners as mental health service providers, and continued research. Areas covered by the review included activities of daily living, instrumental activities of daily living, leisure, social participation, and rest and sleep (D'Amico, Jaffe, Gardner JA, 2018). All these areas are applicable to schizophrenia, based on the assertion by Bromley & Brekke (2010) that the diagnosis of schizophrenia can only be made in the presence of a loss of functioning in domains such as employment, independent living, and social functioning.
- 6.2. Recommended baseline laboratory investigations for diagnostic work-up
- 6.2.1. Full blood count (FBC) should be conducted at baseline and where clozapine is used in the management, the absolute neutrophil count should be monitored as recommended below in the chronic management section (Galletly et al., 2016; SASOP, 2013).
  - 6.2.2. Electrolytes (Sodium + potassium + chloride + CO<sub>2</sub> + urea+ creatinine)<sup>21</sup> should be measured to obtain a baseline and to exclude co-morbidities.
  - 6.2.3. Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Gamma glutamyl transferase (GGT) (Atasoya et al., 2007) should be measured initially and any abnormalities would warrant a full liver function test.
  - 6.2.4. Thyrotropin (TSH) must be requested initially and any abnormalities may warrant further thyroid function tests, as clinically indicated (Galletly et al., 2016; Saleem et al., 2015).
  - 6.2.5. Random or fasting glucose should be done at diagnosis and at 6-monthly intervals thereafter (De Hert et al. 2011). This informs the choice of therapy and monitor the risk of developing diabetes with anti-psychotic therapy.
  - 6.2.6. Fasting Lipogram (cholesterol / HDL/ LDL/ Trig (Galletly et al., 2016; Delacretaz et al., 2018) should be requested at diagnosis and annually thereafter, unless clinically indicated to test at other times.
  - 6.2.7. Pregnancy test (Galletly et al., 2016; Barnes & Paton, 2011) must be requested in all females

with child-bearing potential and more especially if valproate or carbamazepine are part of the treatment plan.

- 6.2.8. Treponema pallidum hemagglutination and HIV tests are recommended as PMB level of care (Galletly et al; SASOP, 2013).
- 6.2.9. Vitamin B12 serum level (Galletly et al., 2016; Zhang et al., 2016) is recommended in all patients above 60 years old or if clinically indicated.
- 6.2.10. Toxic drug screen, urine and blood should be requested at diagnosis and when there is reason for clinical suspicion (Galletly et al., 2016; SASOP, 2013).

Table 5: Laboratory/ point of care baseline investigations for diagnostic work-up of schizophrenia recommended as PMB level of care

Description	Frequency	Comment (if any)
Full blood counts	1	As a baseline and to exclude other conditions
Electrolytes (Sodium + potassium + chloride + CO2 + urea+ creatinine)	At diagnosis	For exclusion of other illness and as a baseline
Liver function - Aspartate aminotransferase (AST) - Alanine aminotransferase (ALT) - Gamma glutamyl transferase (GGT)	At diagnosis  Once unless clinically indicated	No additional benefit for a full LFT unless clinically indicated  Any abnormalities should trigger a full LFT
Thyroid stimulating hormone (TSH)	1	Abnormalities will require more thyroid tests
Random or fasting glucose	At diagnosis and at 4 months then annually thereafter  when a patient has initiated treatment e.g. atypical antipsychotic	assists to determine the risk of developing diabetes while on treatment

Fasting Lipogram (Chol/ HDL/ LDL/ Trig)	At diagnosis & annual unless clinically indicated	
Treponema pallidum hemagglutination	1	
HIV	1	
Pregnancy test	When indicated	
Toxic drug screen (urine and blood)	At diagnosis and when there are any clinical suspicions	

6.3. Other investigations for diagnostic workup recommended as PMB level of care

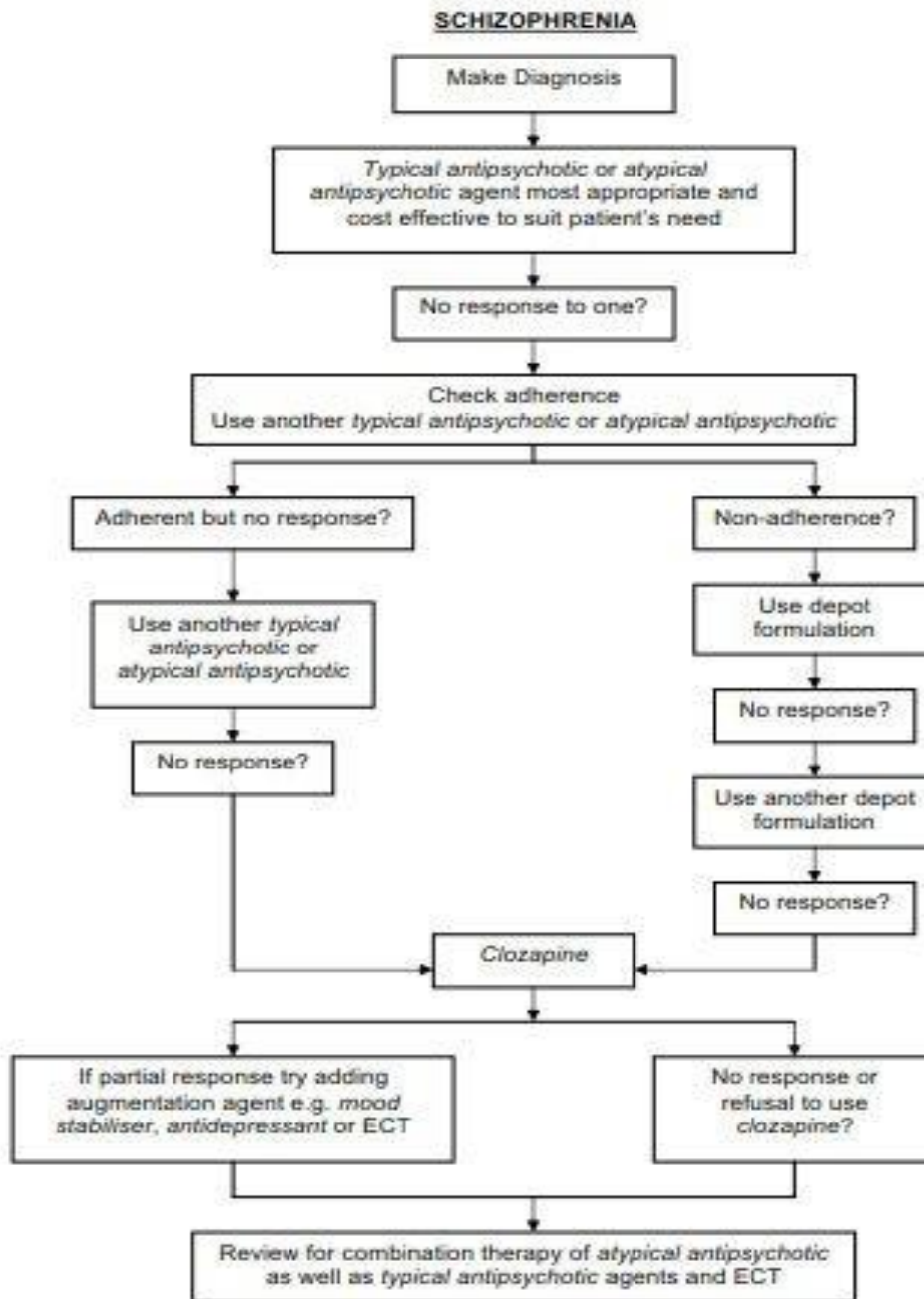
- 6.3.1. 24-hour EEG (Galletly et al., 2016) is recommended as PMB level of care when there is any clinical suspicion or to exclude temporary lobe epilepsy (TLE).
- 6.3.2. A baseline ECG with QTc calculation (Yuan, Chai & Wei, 2017; Galletly et al., 2016) is PMB level of care as anti- psychotic therapy may prolong QT interval
- 6.3.3. While neuroimaging and cognitive testing may help to rule out alternatives such as schizophrenia-like manifestations of other disorders affecting brain function, schizophrenia is essentially a clinical diagnosis (Galletly et al., 2016). Neuroimaging is recommended for 1<sup>st</sup> episode, when the clinical picture is atypical, when there are abnormal findings on routine examination and for all cases of late onset disease (SASOP, 2013).
- 6.3.4. A CT scan of the brain is PMB level of care whilst a motivation would be required for a Brain MRI (Galletly et al., 2016; SASOP, 2013).

Table 6: Other baseline investigations for diagnostic work up of schizophrenia

Description	Comment
24-hour EEG	Only if there is any clinical suspicion or temporary lobe epilepsy
ECG with QTc calculation	Most medication prolongs the QT interval
CT scan brain	When clinically indicated for 1 <sup>st</sup> episode, ALL late onset
Brain MRI	On motivation. Not for all patients

## 7. Management of schizophrenia

Figure 1: The treatment algorithms for schizophrenia as outlined in the Medical Schemes Act Chronic Disease List



### 7.1. Pharmacological management of schizophrenia (in and out-of-hospital)

- 7.1.1. Patients may be managed in hospital either as voluntary, assisted, involuntary mental health care users or even be secluded in accordance with the Mental Health Care Act.

- 7.1.2. The DTP in the regulations of the Medical Schemes Act states that hospital-based medical management is up to 3 weeks /year only (i.e. 21 days) for schizophrenia.
- 7.1.3. The CMS recommends that a case coordinator be assigned for all mental health patients diagnosed with schizophrenia. A detailed care plan should be submitted to the case coordinator at the funder / administrator to coordinate optimal care for the patient both in and out-of-hospital.
- 7.1.4. As per the Medical Schemes Act, there is provision for schemes to develop their own formularies. Table 7 below includes at least one medicine for each drug class and medical schemes are entitled to apply treatment protocols and formularies. Although managed care protocols might not include all the medicines below, all the medicine classes should be included.
- 7.1.5. Out-of-hospital pharmacological treatment will include all medications used in hospital (SASOP, 2013).
- 7.1.6. The evidence base has shown that slow release depot or long acting anti-psychotic injections are recommended for patients for whom adherence with oral medication is inconsistent and unreliable or where the patient chooses this formulation. Non-adherence in schizophrenia is common with only 25% of patients fully adherent with oral medication at 2 years of treatment. The consequence is relapse and rehospitalization.
- 7.1.7. According to Tempest et al, (2015), schizophrenia is a severe and debilitating psychiatric disorder and pharmacological interventions aim to ameliorate symptoms and reduce the risk of relapse and hospitalization. Tempest et al, warns that, despite the established efficacy of antipsychotic medication, compliance to treatment is poor, particularly with oral formulation.
- 7.1.8. The emergence of long acting injectable (LAI) antipsychotic formulations in recent years has aimed to counteract the poor compliance rates observed, and optimise long term patient outcomes. Olivares, Pinal & Cinos (2011) assert that nonadherence to treatment in patients with schizophrenia has been estimated in 40–60% of patients, and it has important clinical and social consequences for patients and carers, accounting for 40% of health spending for the disease.
- 7.1.9. Another perspective is from Brissos et al (2014) who, in describing the bioavailability and dosing of long acting injectable antipsychotics, stated that while oral antipsychotics are converted to active and inactive metabolites and only a relatively small portion reaches the brain, long acting injectables bypass the initial deactivating process by avoiding first-pass metabolism in the liver; and in that way a higher proportion of the drug is available centrally, which arguably can allow the use of the lowest effective dose.
- 7.1.10. The advantages and disadvantages of long acting injectable antipsychotics compared to oral antipsychotics is summarized in the table below.



Table 7. Summary of potential advantages and disadvantages of long-acting injectable antipsychotics as compared to oral antipsychotics.

Advantages
<ul style="list-style-type: none"> <li>• No need for daily administration</li> <li>• Guaranteed administration and transparency of adherence [Gerlach, 1995; Remington and Adams, 1995]</li> <li>• Allows healthcare professionals to be alerted and to intervene appropriately if patients fail to take their medication [NICE, 2009]</li> <li>• Less probability for rebound symptoms and rapidly occurring/abrupt relapses</li> <li>• Overcomes partial adherence or overt nonadherence</li> <li>• If a relapse occurs, it is due to other reasons beyond noncompliance [Waddell and Taylor, 2009]</li> <li>• Reduced risk of unintentional or deliberate overdose [Gerlach, 1995; Remington and Adams, 1995]</li> <li>• Lower relapse rates [Walburn <i>et al.</i> 2001; De la Gandara <i>et al.</i> 2001; Kane <i>et al.</i> 2001]</li> <li>• Minimal gastrointestinal absorption problems, circumventing first-pass metabolism [Dencker, 1984; Marder <i>et al.</i> 1989]</li> <li>• More consistent bioavailability [Waddell and Taylor, 2009]</li> <li>• More predictable correlation between dosage and plasma levels [Rocca <i>et al.</i> 2013]</li> <li>• Reduced peak-trough plasma levels [McEnvoy, 2006]</li> <li>• Improved patient outcomes [Olfson <i>et al.</i> 1999]</li> <li>• Improved patients and physicians satisfaction [Peuskens <i>et al.</i> 2010]</li> <li>• Regular contact between the patients and mental healthcare team [Pandarakalam, 2003]</li> </ul>
Disadvantages
<ul style="list-style-type: none"> <li>• Slow dose titration [Heres <i>et al.</i> 2007]</li> <li>• Longer time to achieve steady state levels [Heres <i>et al.</i> 2007; Remington and Adams, 1995; Knox <i>et al.</i> 2004]</li> <li>• Delayed disappearance of distressing and/or severe side effects</li> <li>• Pain at the injections site can occur, and leakage into the subcutaneous tissue/and or the skin may cause irritation and lesions (especially for oily long-acting injectable)</li> <li>• Burden of frequent travel to outpatient clinics or home visits by community nurses for their administration</li> <li>• Risperidone long-acting injectable needs refrigeration, which may be cumbersome in some latitudes</li> <li>• Perception of stigma</li> </ul>

7.1.11. Several of the guidelines recommend LAI only for patients with recurrent relapses related to partial or full nonadherence, or patients with persistent positive symptoms (Lehman *et al.* 2004; Canadian Psychiatric Association, 2005), but more recent guidelines have introduced subtle changes, with guidance from the National Institute for Clinical Excellence (NICE) (2009) stating that clinicians should consider offering LAI to patients who would 'prefer such treatment after an acute episode.

7.1.12. Several authors propose that LAI should not be restricted to patients with adherence

problems, but instead should be more widely prescribed (Altamura et al. 2012), and systematically offered to all patients through shared decision-making (Llorca et al. 2013).

7.1.13. An electronic database search and critical review of all studies in which a long acting injectable antipsychotic was evaluated in early psychosis patients in South Africa, (Emsley et al, 2013), also found that the available evidence suggests that long-acting injectable antipsychotics can be used safely and effectively in early stages of the illness, and that they may be associated with better outcomes than with oral medications.

Table 8: Recommended PMB level of pharmacological treatment of schizophrenia

Medicine class	Medicine name and/ or comment
1 <sup>st</sup> line for Acute and/ or 1 <sup>st</sup> episode	
Atypical/ Second generation antipsychotics (SGA)	Quetiapine
	Olanzapine (PO and IMI)
	Risperidone
	Ziprasidone (PO and IMI)
	Paliperidone
Benzodiazepine	Adjunct – Benzodiazepine (PO and IM) Adjunctive benzodiazepines (the evidence supports lorazepam can be used liberally to attenuate disruptive behaviour in the acute setting (NICE, 2014).
Typical / First generation antipsychotics (FGA)	Chlorpromazine
	Haloperidol
	Pimozide
2 <sup>nd</sup> line for Acute and/ or 1 <sup>st</sup> episode	

Amisulpride – as an alternative in patients failing 1 <sup>st</sup> and 2 <sup>nd</sup> generation antipsychotics	
3 <sup>rd</sup> line f or acute and/ or 1 <sup>st</sup> episode and/ or relapse	
Clozapine	
Multi episode/ relapse	
Drug of choice will be influenced by any prior agents' efficacy and tolerability (SASOP, 2013)	
SGA given above are recommended	
Haloperidol	
Chlorpromazine	
Maintenance (to prevent relapse)	
Antipsychotics	Continuation of pharmacological treatment that was effective in the acute and stabilisation phases is advised. (SASOP, 2013)
	Long acting second generation antipsychotics
	Flupentixol depot (IMI)
	Zuclopenthixol depot (IMI)
	Fluphenazine depot (IMI)
Mood stabilisers added to antipsychotics	Lithium
	Carbamazepine
	Sodium valproate
	Lamotrigine
Second-trial agent can be another SGA or an FGA but should be an SGA if there was a failed response to an FGA in the first trial.	

## 7.2. Non – pharmacological treatment in and out-of-hospital

- 7.2.1. 1 session / month of maintenance ECT is recommended as clinically indicated (SASOP, 2013). Prolonged courses of ECT without measured improvement are not recommended for people with schizophrenia because most research suggests that response occurs within 12 treatments. For a minority of individuals, longer courses may be required if progressive improvement occurs with each treatment (Galletly, 2016).
- 7.2.2. Electro convulsive therapy (ECT) (SASOP, 2013) may be considered should the following criteria be met:
- extreme psychomotor agitation
  - catatonia
  - pregnancy
  - life is at risk
- 7.2.3. The sessions of ECT may be provided as clinically indicated.
- 7.2.4. The role of the multi-professional team is critical in the management of the patient with schizophrenia.
- 7.2.5. The CMS recommends that a care plan must be submitted to the funder/ administrator when a patient is diagnosed with schizophrenia. The case coordinator will be able to assist and ensure the optimal utilisation of the allied health professionals. It is also important that all benefits, especially for allied health professionals, are individualised and not bundled as family benefits. All health providers shown below should be referred to by the treating doctor.

Table 9: Recommended providers for patient with schizophrenia

Discipline	Frequency	
	In hospital	Out-of-hospital
Psychiatrist	1 contact session daily	Max of 6 based on the treatment algorithm – depends on treatment response
Primary treating physician / GP	1 per day [if primary treating provider]	
All allied listed below are only on referral based on a therapeutic programme		
Psychologist	1 individual / group session daily	12 per annum
Occupational therapist	2 contact sessions daily (10 sessions / week)	10 – 12 per annum
Social worker	3 contact sessions / week as individual / group sessions on referral from the psychiatrist	4 per annum

Physiotherapists, Dietician and/or Speech therapist	Maximum 3 contact sessions / week individual or group	Maximum 12 per annum individual or group
---	---	--

## 8. Laboratory and drug related investigations

Table 10: Recommended PMB level of care laboratory and drug related investigations

Patient Is Maintained on:	Check	Monitor for:
Lithium	Drug serum level: once therapeutic level is achieved, every 3–6 months	Sub-therapeutic or toxic level
	Electrolytes, urea and creatinine (EUC): every 3–6 months	Renal insufficiency, nephrogenic diabetes insipidus
	Calcium, TSH, weight: after 6 months and then annually	Thyroid/parathyroid dysfunction
Valproate	Serum level: during initial therapy and then as clinically indicated	Sub therapeutic or toxic level
	Weight, full blood count, menstrual history, liver function tests every 3 months for the first year and then annually	Weight gain, thrombocytopenia, dysmenorrhea, liver failure
	Blood pressure, fasting blood glucose, lipid profile, bone densitometry (if risk factors)	Metabolic syndrome, anticonvulsant-related osteopenia
Carbamazepine	Serum level: during initial therapy, then as clinically indicated	Sub therapeutic or toxic level
	Full blood count, liver function tests, EUC monthly for 3 months then annually	Blood dyscrasias, hyponatremia
	Bone densitometry	Anticonvulsant-related osteopenia,
	Monitor for rash	Stevens-Johnson Syndrome
Lamotrigine	Monitor for rash	Stevens-Johnson Syndrome
Second-generation antipsychotics	Weight monthly for 3 months and then every 3 months	Weight gain
	Blood pressure, fasting blood glucose, lipid profile every 3 months and then annually	Metabolic syndrome
	Monitor for abnormal movements	Acute dystonias, drug-induced parkinsonism, tardive dyskinesia

Table 11: Other lab investigations recommended as PMB level of care for patients with schizophrenia

Investigation	Frequency	Comment
Glucose	Twice yearly and thereafter annually	Co-morbid diabetes may be exacerbated by antipsychotic medication, hence medical monitoring is advocated in addition to education about lifestyle modification (Owen, Sawa & Mortensen, 2016; De Hert et al., 2011).
Lipogram	Annually	All individuals with schizophrenia should be under active care and be screened for cardiometabolic risk at least annually if they have normal baseline values. Those who already present with cardiovascular risk factors should be monitored more frequently (Owen, Sawa & Mortensen, 2016; De Hert et al., 2011).
AST, ALT and GGT	Annually	Asymptomatic increases in ALT, AST, GGT and serum bilirubin levels in the first month of the study. These results were in accordance with previous studies that asymptomatic increase of liver enzymes are common but significant liver enzyme elevations are rare during atypical antipsychotic treatment. We suggest that obtaining baseline liver enzyme tests before atypical antipsychotic therapy and monitoring regularly specifically in patients with risk factors for liver damage during therapy (Atasoy et al., 2007).
Prolactin	Annually	Antipsychotic-induced hyperprolactinaemia has been estimated to occur in up to 70% of patients with schizophrenia, depending on the choice of antipsychotic agent (Barnes & Paton, 2011).

## 9. Management of side effects (in - and out - of hospital)

9.1. Emergent extrapyramidal symptoms that may be iatrogenic should be managed on an individualised basis. The patient's history of e.g. Parkinsonism and acute dystonias should be considered together with the side effects of anticholinergic medication. PMB level of care for extrapyramidal symptoms includes biperidin and orphenadrine (Barnes & Paton, 2011).

9.2. If anticholinergic drugs are required to treat extrapyramidal side effects, their use should be reviewed after 3 months. It is sometimes possible to gradually withdraw the anticholinergics without changing the dose of the antipsychotic. Cessation of anticholinergics can be associated with improvement in cognition and in tardive dyskinesia (Desmarais et al., 2014).

9.3. Any other emergent side effects should be managed as clinically indicated and funded as part of PMB level of care.

## 10. References

- Altamura, A., Aguglia, E., Bassi, M., Bogetto, F., Cappellari, L., De Giorgi, S. *et al.* (2012). Rethinking the role of long-acting atypical antipsychotics in the community setting. *Int Clin Psychopharmacol*, 27: 336–349.
- American Psychiatric Association, 2013. *Diagnostic and statistical manual of mental disorders (DSM-5®)*. American Psychiatric Pub.
- Atasoy, N., Erdogan, A., Yalug, I., Ozturk, U., Konuk, N., Atik, L. and Ustundag, Y. (2007). A review of liver function tests during treatment with atypical antipsychotic drugs: a chart review study. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 31(6): pp.1255-1260.
- Back on Track Mental Health Occupational Therapy. (2019). The Back on Track Assessment is completed in two stages. <http://backontrackmhot.com.au/Mental-Health-Occupational-Therapy-Assessment>. Accessed on 24 September 2019.
- Barnes, T. R. and Paton, C. (2011). Do antidepressants improve negative symptoms in schizophrenia?. *Bmj*, 342: p.d3371.
- Birken, M., Henderson, C., & Slade, M. (2018). The development of an occupational therapy intervention for adults with a diagnosed psychotic disorder following discharge from hospital. *Pilot and feasibility studies*, 4, 81. doi:10.1186/s40814-018-0267-7.
- Brissos S., Veguilla M. R., Taylor D and Balanzá-Martinez V. (2014). The role of long-acting injectable antipsychotics in schizophrenia: a critical appraisal.
- Bromley, E. & Brekke, J. (2010). Assessing Function and Functional Outcome in Schizophrenia. *Current topics in behavioral neurosciences*, 4: 3-21. 10.1007/7854\_2010\_40.
- Canadian Psychiatric Association. (2005). Clinical practice guidelines. Treatment of schizophrenia. *Can J Psychiatry*, 50(13 Suppl. 1): 7–57.
- CMS Annual Report 2017 – 2018. Available at [http://www.medicalschemes.com/files/Annual%20Reports/CMS\\_AnnualReport2017-2018.pdf](http://www.medicalschemes.com/files/Annual%20Reports/CMS_AnnualReport2017-2018.pdf). Accessed 10 September 2019
- D'Amico M. L., Jaffe L. E., and Gardner J. A. (2018). Evidence for Interventions to Improve and Maintain Occupational Performance and Participation for People With Serious Mental Illness: A Systematic Review. *Am J Occup Ther*. 72(5):7205190020p1-7205190020p11. doi: 10.5014/ajot.2018.033332.
- De Hert, M., Vancampfort, D., Correll, C. U., Mercken, V., Peuskens, J., Smeets, K., van Winkel, R and Mitchell, A. J. (2011). Guidelines for screening and monitoring of cardiometabolic risk in schizophrenia: systematic evaluation. *The British Journal of Psychiatry*, 199(2): pp.99-105.
- Delacrétaz, A., Vandenberghe, F., Gholam-Rezaee, M., Morgui, N. S., Glatard, A., Thonney, J., Solida-Tozzi, A., Kolly, S., Gallo, S. F., Baumann, P and Berney, S. (2018). Early changes of blood lipid levels during psychotropic drug treatment as predictors of long- term lipid changes and of new onset dyslipidemia. *Journal of clinical lipidology*, 12(1): pp.219-229.
- Demjaha, A., MacCabe, J. H and Murray, R. M. (2011). How genes and environmental factors determine the different neurodevelopmental trajectories of schizophrenia and bipolar disorder. *Schizophrenia bulletin*, 38(2): pp.209-214.
- Desmarais, J. E., Beauclair, L., Annable, L., Bélanger, M. C., Kolivakis, T. T., Margolese, H. C. (2014). Effects of discontinuing anticholinergic treatment on movement disorders, cognition and psychopathology in patients with schizophrenia. *Therapeutic advances in psychopharmacology*, 4(6): 257-67.
- Furiak, N. M., Gahn, J. C., Klein, R. W., Camper, S. B., Summers, K. H. (2012). Estimated economic benefits from low-frequency administration of atypical antipsychotics in treatment of schizophrenia: a decision model. *Ann Gen Psychiatry*, 11(1): 29.

Galletly, C., Castle, D., Dark, F., Humberstone, V., Jablensky, A., Killackey, E., Kulkarni, J., McGorry, P., Nielssen, O and Tran, N. (2016). Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the management of schizophrenia and related disorders. *Australian & New Zealand Journal of Psychiatry*, 50(5): pp.410-472.

General Regulations Relating to the Mental Health Care Act. (2002): AMENDMENT. 6 Nov 2014. No. 38182. [https://www.sasop.co.za/Content/Docs/Mental\\_Health\\_Act.pdf](https://www.sasop.co.za/Content/Docs/Mental_Health_Act.pdf)

Hetlevik Ø., Bjørnå C. H., Lundring I. T., and Gjesdal S, 2019. Adolescents consulting general practitioners for psychological problems-a nationwide, register-based study in Norway. *Fam Pract*. 2019 Jan 25;36(1):77-83. doi: 10.1093/fampra/cmz066.

Jack, H., Wagner, R. G., Petersen, I., Thom, R., Newton, C. R., Stein, A., Kahn, K., Tollman, S. and Hofman, K. J. (2014). Closing the mental health treatment gap in South Africa: a review of costs and cost-effectiveness. *Global health action*, 7(1): p.23431.

Kane, J., Aguglia, E., Altamura, A., Ayuso Gutierrez, J., Brunello, N. and Fleischhacker, W. (1998). Guidelines for depot antipsychotic treatment in schizophrenia. European Neuropsychopharmacology Consensus Conference in Siena, Italy. *EurNeuropsychopharmacol*, 8: 55–66.

Keating, D., McWilliams, S., Schneider, I., Hynes, C., Cousins, G., Strawbridge, J. and Clarke, M. (2017). Pharmacological guidelines for schizophrenia: a systematic review and comparison of recommendations for the first episode. *BMJ open*, 7(1): p.e013881.

Kramer T., Als L. C., & Garralda M. E. (2015). Practice Guidelines: Diagnosis and management of depression in children and young people: summary of updated NICE guidance. *BMJ*, 2015: 350.

Laursen, T. M., 2011. Life expectancy among persons with schizophrenia or bipolar affective disorder. *Schizophrenia research*, 131(1-3): pp.101-104.

Lehman, A., Lieberman, J., Dixon, L., McGlashan, T., Miller, A., Perkins, D. et al. (2004). American Psychiatric Association; Steering Committee on Practice Guidelines: Practice guideline for the treatment of patients with schizophrenia, second edition. *Am J Psychiatry*, 161(2.): 1–56.

Lin, J., Wong, B., Offord, S. and Mirski, D. (2013). Healthcare cost reductions associated with the use of LAI formulations of antipsychotic medications versus oral among patients with schizophrenia. *J Behav Health Serv Res*, 40: 355–366.

Llorca, P., Abbar, M., Courtet, P., Guillaume, S., Lancrenon, S. and Samalin, L. (2013) Guidelines for the use and management of long-acting injectable antipsychotics in serious mental illness. *BMC Psychiatry*, 13: article 340.

Mathers, C. D. and Loncar, D. (2006). Projections of global mortality and burden of disease from 2002 to 2030. *PLoS medicine*, 3(11): p.e442.

Medical Schemes Act, No. 131 of 1998. Available at <https://www.medicalschemes.com/files/Acts%20and%20Regulations/MSACT19July2004.pdf>

Medical Schemes Act, 131 of 1998: Regulations. GNR.1262 – 20 October 1999

Mental Health Care Act 17 OF 2002 as amended by: Judicial Matters Amendment Act 55 of 2002. Available at [https://www.gov.za/sites/default/files/gcis\\_document/201409/a17-02.pdf](https://www.gov.za/sites/default/files/gcis_document/201409/a17-02.pdf)

NICE. (2009). *Schizophrenia: Core Interventions in the Treatment and Management of Schizophrenia in Primary and Secondary Care (update)*. NICE Clinical Guidelines No. 82. London: National Institute for Health and Care Excellence.

Olivares, J. M., Pinal, B & Carmen C. C. (2011). Comparison of long-acting antipsychotic injection and oral antipsychotics in schizophrenia. Olivares, J., Pinal, B. and Cinos, C. (2011). *Neuropsychiatry*, 1: 275–289.

Psychosis and Schizophrenia in adults, A NICE guideline on treatment and management, Updated edition. 2014. NCG 178.

Regulations to the Act [https://www.gov.za/sites/default/files/gcis\\_document/201409/25537b0.pdf](https://www.gov.za/sites/default/files/gcis_document/201409/25537b0.pdf)



Saleem, S., Arooj, M., Basit, A., Parveen, G., Rasool, R., Ahmad, S., Waquar, S., Qazi, M. H., Ali, S. S. and Malik, A. (2015). Inter- Relationship of Thyroid Disorders and Schizophrenia: An Extended Review. *Pakistan J. Mol. Med*, 1(1-2): pp.49-62

SASOP. (2017). Guidelines to the Management of Impairment Claims On Psychiatric Grounds, Third Edition.

Selten, J. P., van der Ven, E., Rutten, B. P. and Cantor-Graae, E. (2013). The social defeat hypothesis of schizophrenia: an update. *Schizophrenia bulletin*, 39(6): pp.1180-1186.

Simeone, J. C., Ward, A. J., Rotella, P., Collins, J. and Windisch, R. (2015). An evaluation of variation in published estimates of schizophrenia prevalence from 1990– 2013: a systematic literature review. *BMC psychiatry*, 15(1): p.193.

Sullivan, P. F., Daly, M. J. and O'donovan, M. (2012). Genetic architectures of psychiatric disorders: the emerging picture and its implications. *Nature Reviews Genetics*, 13(8): p.537.

Tandon, R., Gaebel, W., Barch, D. M., Bustillo, J., Gur, R. E., Heckers, S., Malaspina, D., Owen, M. J., Schultz, S., Tsuang, M. and Van Os, J. (2013). Definition and description of schizophrenia in the DSM-5. *Schizophrenia research*, 150(1): pp.3-10.

The South African Society of Psychiatrists (SASOP) Treatment Guidelines for Psychiatric Disorders. 2013. [Online] Available at: [https://www.sasop.co.za/Content/Docs/474-2366-1-PB\\_SASOP\\_TREATMENT\\_GUIDELINES.pdf/](https://www.sasop.co.za/Content/Docs/474-2366-1-PB_SASOP_TREATMENT_GUIDELINES.pdf/) [Accessed 2 February 2019].

Thibaut, F., Boutros, N., Jarema, M. et al. (2015) Consensus paper of the WFSBP Task Force on Biological Markers: Criteria for biomarkers and endophenotypes of schizophrenia. Part I: Neurophysiology. *World Journal of Biological Psychiatry*, 16: 280–290.

Trump, L. and Hugo, C. (2006). The barriers preventing effective treatment of South African patients with mental health problems. *African Journal of Psychiatry*, 9(4): pp.249-260.

Verhaak, F. P., van Dijk, M., Walstock M. D., and Zwaanswijk, M., 2015. A new approach to child mental healthcare within general practice. *BMC Fam Pract*. 2015; 16: 132.

World Health Organisation (WHO) International Classification of Diseases. <https://icd.who.int/browse10/2016/en>

World Health Organisation (WHO). 2019. Schizophrenia. <https://www.who.int/news-room/fact-sheets/detail/schizophrenia>.

Yuan Ng, P. M. Chai, S. B and Wei, K. C. (2017). Antipsychotics and Electrocardiographic monitoring in patients with Schizophrenia.

Zhang, Y., Hodgson, N. W., Trivedi, M. S., Abdolmaleky, H. M., Fournier, M., Cuenod, M., Do, K. Q. and Deth, R. C. (2016). Decreased brain levels of vitamin B12 in aging, autism and schizophrenia. *PLoS One*, 11(1): p.e0146797.