Draft PMB definition guideline: Endometrial cancer

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Disclaimer:

The endometrial cancer 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(I) may be applied for patients who are inadequately managed by the stated benefits. The benefit definition does not describe specific in-hospital management such as theatre, anaesthetists, anaesthetist drugs and nursing care. However, these interventions form part of care and are prescribed minimum benefits. Rehabilitation interventions are also recommended as PMB level of care upon referral and when clinically indicated.

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Abbreviations

CT	Computed tomographic
FBC	Full blood count
ICD	International classification of diseases
IV	Intravenous therapy
MRI	Magnetic resonance imaging
PET	Positron emission tomography
PMB	Prescribed minimum benefit
RT	Radiation therapy
WHO	World Health Organisation

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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, 131 of 1998 (the Act). It has been noted however, that in respect of some of the diagnosis treatment pairs (DTPs), medical scheme beneficiaries sometimes find it difficult to know their entitlements in advance. Medical schemes also interpret these benefits differently, resulting in a lack of uniformity of benefit entitlements.

1.2. The benefit definition project is coordinated by the Council for Medical Schemes (CMS), and aims to define the PMB package as well as to guide the interpretation of the PMB provisions by relevant stakeholders.

2. Scope and purpose

2.1. This document serves as a recommendation for the diagnosis, treatment and care of individuals with endometrial cancer, in any clinically appropriate setting as outlined in the Act.

2.2 The purpose 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: Possible ICD10 codes for identifying endometrial cancer

ICD 10 code	WHO description
C54.1	Malignant neoplasm, endometrium
C54.3	Malignant neoplasm, fundus uteri
C54.8	Malignant neoplasm, overlapping lesion of corpus uteri
C54.9	Malignant neoplasm, corpus uteri, unspecified
C55	Malignant neoplasm of uterus part unspecified
D07.0	Carcinoma in situ, endometrium
Other applicable codes	
C57.0	Malignant neoplasm, fallopian tube
C57.1	Malignant neoplasm, broad ligament
C57.2	Malignant neoplasm, round ligament
C57.3	Malignant neoplasm, parametrium
C57.4	Malignant neoplasm, uterine adnexa, unspecified
C54.2	Malignant neoplasm, myometrium

2.3 The CMS acknowledges that some patients will not qualify for PMB entitlements under the definition of treatable cancers as outlined in explanatory note 3, annexure A of the Act. In these instances, when the treatment intent is no longer curative, DTP 260S, may be applied depending on the clinical case.

Table 2: Applicable PMB code for a non-curative setting in endometrial cancer

PMB Code	PMB Description		ICD10 Code	ICD10 Description
260S	# Imminent death regardless of diagnosis	# Comfort care; pain relief; hydration	Z51.5	Palliative care

3. Epidemiology and burden of disease

3.1 Endometrial cancer is a cancer that arises from the endometrium (the inner lining of the uterus) and is the result of the abnormal growth of cells that have the ability to invade or spread to other parts of the body (Kong, 2014).

3.2 Endometrial adenocarcinoma occurs during the reproductive and menopausal years. Most women with endometrial cancer are aged between 65-74 years with a median age of 70 years. Approximately 5% of women younger than 40 years have adenocarcinoma, and 20-25% of women are diagnosed before menopause (Creasman, 2017; NCI 2012).

3.3 In 2015, there were 455 000 incident cases of uterine cancer worldwide with 90 000 deaths. In South Africa, uterine cancer is ranked the 16th most common cancer and ranked 20th by the number of deaths.

3.4 Unlike most cancers, the number of new cases has risen in recent years, including an increase of over 40% in the United Kingdom between 1993 and 2013 [Galaal, 2014]. Some of this rise may be due to the increase in obesity rates in developed countries [Vale 2012], increasing life expectancies, and lower birth rates [Hoffman 2012].

3.5 Endometrial cancer is more common in developed countries, where the lifetime risk of endometrial cancer in people born with uteri is 1.6%, compared to 0.6% in developing countries [Galaal 2014, WCRI 2014]

3.6 Endometrial carcinoma is a less common gynaecological malignancy in the developing world, yet a significant number of individuals are diagnosed each year in South Africa [Botha 2009]. The relative frequency of endometrial carcinomas has increased over the last years in developing economies due to an increase in obesity and a decrease in fertility rate [Botha 2009].

3.7 The most common histological type is endometriod-type adenocarcinoma but other histological types include mucinous adenocarcinoma, clear cell carcinoma, uterine papillary serous carcinoma (UPSC), squamous carcinoma and also carcinosarcoma [Botha 2009, CANSA 2012, Singh 2015].

4. Screening of endometrial cancer

4.1 There is no evidence (Smith, 2001) nor validated tests (Leslie, 2012) to support the screening of asymptomatic women, with the exception of those who have or are at increased risk of Lynch syndrome (Smith, 2001).

4.2 The early clinical presentation and high early detection rate of 85%, make it unlikely that screening will have a successful impact on earlier detection and increased survival rate. (National Cancer Institute, 2016).

4.3 Screening for endometrial cancer is therefore not recommended as PMB level of care.

5. Diagnosis

5.1 Consultations

5.1.1 The approach to initial evaluation for suspected endometrial cancer should involve the history and physical examination, endometrial biopsy and determination of the histopathologic subtype.

5.1.2 Vaginal bleeding is the most common clinical presentation of endometrial cancer in postmenopausal women (Sorosky et al, 2012) and as such all postmenopausal bleeding should be investigated, especially if risk factors for endometrial hyperplasia or cancer are present.

Table 3: Recommended consultations for the diagnosis of endometrial cancer

Description	Frequency
General practitioner	1
Gynaecologist	1
Oncologist	1

5.2 Histopathology

5.2.1. The definitive diagnosis of endometrial cancer requires an endometrial tissue sample (Saso, 2011). Histological information obtained from the endometrial biopsy is deemed sufficient for planning definitive treatment (McCluggage, 2006 & McKenney, 2009). Persistence of symptoms following a negative initial assessment results warrants further diagnostic evaluation.

Table 4: Recommended PMB level of care histopathology for endometrial cancer

Description
Immunohistochemistry
Endometrial biopsy
Cystoscopy
Proctoscopy

5.2.2. Pathological diagnosis is standard for evaluation of the endometrial cavity. World Health Organisation (WHO) classifies endometrial carcinoma in seven different types – endometroid carcinoma, mucinous adenocarcinoma, serous carcinoma, clear cell carcinoma, neuroendocrine carcinoma, mixed carcinoma, undifferentiated and dedifferentiated carcinoma (Kurman et al, 2014)

5.2.3. Based on differences in both endocrine and metabolic factors (Bokman 1983), two distinct histological categories of adenocarcinomas of the endometrium, type I and type II are recognised (Sorosky, 2012). Type I is the most common form, representing more than 70% of cases and are associated with unopposed estrogen stimulation with high rates of K-ras and PTEN loss and defects in mismatch repair genes resulting in microsatellite instability. Type 1 generally have a favorable prognosis (Practice Bulletin, 2015).

5.2.4. Type II tumors which consist of higher grade adenocarcinomas and non-endometroid histologies, have a tendency for deep invasion of the endometrium. They carry a poor prognosis as well as having a high risk of relapse and metastasis. Although type II tumours accounts for 10% endometrial cancers, they are associated with 40% of related deaths (Sorosky, 2012).

5.2.5. Serous carcinomas as considered prototypes 2 and are characterised by the p53 mutations. However, some cases remain morphologically ambiguous, indeterminate or hybrid adenocarcinomas and require immunohistochemistry (p53, PTEN) and mutational analysis to allow for an accurate work up. Clear cell carcinomas represent a heterogeneous group of tumours with intermediate features between type I and type II.

5.2.6. As endometrial cancer is considered high-risk if it is grade 2 or 3 disease and there is evidence of clear cell or papillary serous histology, further imaging by abdominal-pelvic MRI or CT scan should therefore be reserved for women with high risk histology types (e.g. grade 3 endometrioid endometrial cancer, uterine serous cancer, clear cell cancer). (Francis et al, 2009)

5.3. Diagnostic procedures

5.3.1 For patients with abnormal or post-menopausal bleeding, work up may involve hysteroscopy combined with Dilation and curettage (D&C) to gain additional information regarding benign processes causing bleeding. Hysteroscopy may be helpful in evaluating the endometrium for lesions, such as polyp, if the patient has persistent or recurrent undiagnosed bleeding (Gimpelson, 1988)

Table 5: Diagnostic procedures recommended as PMB level of care

Description
Endometrial biopsy
Hysteroscopy

Dilation and curettage (D&C)
Cervical biopsy

5.4. Laboratory Investigations

5.4.1. Although there are no specific laboratory tests for the evaluation of endometrial cancer, preoperative investigations should include a full blood count, renal panel, urea and electrolytes and liver function tests (Baekelandt et al, 2008, Creasman et al, 2007).

5.4.2. Prothrombin time and partial thromboplastin time may also be considered for patients with heavy bleeding.

Table 6: Recommended PMB level of care laboratory investigations for endometrial cancer

Description	Comment
Full Blood Count (FBC) including platelets	Initial preoperative evaluation.
Urea, electrolytes and creatinine (UEC)	Initial preoperative evaluation.
Liver function test (LFT)	Initial preoperative evaluation.
Prothrombin time (PT) and partial thromboplastin time (PTT)	May be required for patients with heavy bleeding
CA125	Helpful in monitoring clinical response in patients with extrauterine disease.

5.5. Imaging

5.5.1. Depending on access, histologic endometrial evaluation and transvaginal ultrasound are the preferred initial diagnostic evaluations for patients with suspected endometrial cancer. The recommendation of either transvaginal ultrasonography or endometrial biopsy being performed as the initial work-up for the evaluation of endometrial cancer is reflected in most guidelines (Saso, 2011).

5.5.2. Transvaginal ultrasound measures the endometrial thickness and discriminates between benign and malignant endometrium. Because of its high sensitivity, a transvaginal ultrasound (TVS) is often the diagnostic tool of choice when evaluating for endometrial cancer (Khathi, 2014). Persistence of bleeding despite a normal transvaginal ultrasonography result, warrants a tissue biopsy (Sorosky, 2012).

5.5.3. Imaging tools such as CT, MRI, and/or PET/CT are not recommended as PMB level of care in the diagnostic stage but have a role in the staging and risk assessment of endometrial cancer. These may be used to assess disease extent and to evaluate for metastatic disease as indicated based on clinical symptoms, physical findings, or abnormal laboratory findings (Lee et al, 2011, Ortesh et al, 2008, Antonsen et al, 2013).

5.5.4. Chest X-ray is recommended as a tool to rule out pulmonary metastasis and should be the work up package for initiation assessment (Pecorelli, 1999).

Table 7: Recommended PMB level of care imaging radiology for diagnosis and work-up of endometrial cancer

Description	Comment
Ultrasound: abdominal / pelvic	Transabdominal sonography is the preferred technique for evaluation of endometrial disorders and is especially useful in the workup of abnormal uterine bleeding.
Transvaginal ultrasound	Initial study for the evaluation of endometrial cancer.
Chest x-ray	If abnormality is detected, then chest imaging is recommended.
Ultrasound abdomen and chest	
Exclusions for diagnosis	
MRI	Recommended for disease staging
PET – CT	
CT chest	
CT abdomen and pelvis	

6. Staging and risk assessment

6.1 Consultations

Table 8: Recommended consultations for staging and risk assessment of endometrial cancer

Description	Frequency
Oncologist	3
Gynaecologist	3

6.1.1 Endometrial carcinoma is surgically staged according to the joint 2010 International Federation of Gynecology and Obstetrics (FIGO)/TNM classification system (Creasman, 2009) This staging system has been found to be highly prognostic in the case of endometrioid tumors (Lewis, 2009) The most important prognostic factors identified in endometrial carcinoma are the FIGO stage, histological subtype, grade, depth of myometrial invasion, lymphovascular space invasion (LVSI), and age (Colombo, 2016).

6.1.2 The staging streamlines stages I and II of endometrial cancer. Stage I is now less than 50% of myometrial invasion and stages IB being 50% of more of myometrial invasion. (Creasman, 2009) Stage II only involves patients with cervical stromal invasion whilst stages IIIC is divided into IIIC1 and IIIC2 given worse survival with paraortic nodes. (Creasman, 2009)

6.1.3 Traditionally surgical staging has been accomplished with open laparotomy, but minimally invasive techniques are increasingly getting widely accepted. A number of studies have demonstrated feasibility of a laparoscopic approach (Walker, 2006, Humprey, 2009 & Palamba 2009).

6.2 Imaging radiology for staging endometrial cancer

6.2.1. CT although not routinely recommended for evaluation of most endometrial carcinoma, could be useful in further preoperative work up of papillary serous tumours or more aggressive histological types (Spencer et al, 2008).

6.2.2 Contrast enhanced MRI can be of use in assessment if locoregional extension in the pelvis is clinically indicated (Baekelandt et al, 2008). MRI can identify patients at highest risk of metastatic disease (Spencer et al, 2008, Frei et al, 2000).

Table 9: Recommended PMB level of care imaging radiology for staging and risk assessment of endometrial cancer

Description	Comment
CT chest	Chest imaging without contrast is recommended for staging
CT abdomen and pelvis	For high grade carcinoma, may be used to assess disease extent and evaluate metastatic disease based on clinical symptoms or pathology findings. (Ortashi et al, 2008, Kitajima et al, 2011)
MRI abdomen and pelvis	In patients who are inoperable to plan radiotherapy. Clinical criteria to be defined
PET – CT	On motivation for patients who are undergoing surgery

7. Treatment options for endometrial cancer

7.1 Surgical management

7.1.1 Endometrial cancer is treated primarily with a comprehensive surgical staging operation, which is usually curative and includes hysterectomy (abdominal, vaginal, or minimally invasive), bilateral salpingo-oophorectomy, abdominopelvic

washings, lymph node evaluation and pelvic and para-aortitic lymph nodes dissection (Kong et al, 2010; Creasman, 2015; Lachance et al, 2008; Sonoda, 2014, Volpi et al., 2005, Zullo et al., 2005).

7.1.2 It is sometimes difficult to distinguish primary cervical cancer from endometrial cancer with cervical involvement. A radical hysterectomy is recommended as PMB level of care and should be considered for the cases with stage II endometrial cancers (Takano et al, 2013).

7.1.3 With increasing surgeon experience and a corresponding increase in detection rate of 90% or greater, combined with a decrease in false-negative rates, sentinel lymph node mapping can play a more prominent role in lymph node assessment and staging in early-stage of endometrial cancer (Nadeem & Abu-Rustum, 2014)

7.1.4 Patients with high-risk histological subtypes of endometrial cancer such as clear cell and papillary serous adenocarcinomas should receive full staging surgery that includes pelvic and/ or para-aortic lymphadenectomy and omentectomy (Giede et al, 2013).

7.1.5 If the cancer has spread throughout the pelvis and abdomen, a debulking procedure (removal of as much cancer as possible) may be done (American Cancer Society, 2016).

7.1.6 Advanced disease patients may be treated with maximal surgical cytoreduction (Creasman, 2015).

7.1.7 Multiple studies have addressed the potential benefits of the excision of secondary lesions on overall survival in patients with recurrent endometrial cancer (William et al, 2014).

7.1.8 Laparoscopic hysterectomy is recommended as PMB level of care subject to the use of the following surgical equipment. This is to ensure that the costs of disposables used for the procedure make this procedure cost effective and affordable.

Table 10: Recommended basket for laparoscopic hysterectomy

Disposable instruments
1xoptic standard port 5/10/11/12 3x5mm ports Sutures: PDS/Vicryl/V-lock/J-needle/ Vicryl Rapid skin/Monocril Ligasure/harmonic scalpel/Thunderbeat/or other Bipolar Device Foleys catheter
Reusable instruments
Suction and irrigation Graspers and needle holders Bipolar forceps and cable Monopolar cable Uterine manipulator with colpotomy cuff / VCare Plus

Table 11: PMB Level of care for surgical management of Endometrial Cancer

Description
Primary surgery remains the preferred approach which may include:
Salpingo-oophorectomy (unilateral or bilateral)
Total abdominal hysterectomy
Total laparoscopic hysterectomy
Hysterectomy (vaginal or radical)
Omentectomy
Sentinel lymph node mapping
Pelvic and para-aortic lymph node dissection
Debulking surgery
Excision of secondary lesion(s)
Peritoneal lavage

7.2 Chemotherapy

There is no general agreement as to what constitutes the best chemotherapy, as very few phase III studies have been done comparing different chemotherapy regimens (Creasman, 2017). As a result, cytotoxic chemotherapy has a limited place in the management of advanced or recurrent endometrial cancer (Humber et al, 2007). Multi-agent chemotherapy regimens are preferred over single agents, if tolerated (NCCN, 2016).

7.2.1 Adjuvant

7.2.1.1 For patients with stage III or stage IV disease and for those with recurrent endometrial cancer, the prognosis remains poor and the optimal adjuvant therapy is yet to be established. However, a subset of these patients may benefit from hormonal manipulation, systemic chemotherapies, or combination treatment with volume-directed radiotherapy and systemic chemotherapy.

7.2.1.2 Docetaxel may be considered for patients in whom paclitaxel is contraindicated (NCCN, 2016).

7.2.1.3 Salvage agents such as paclitaxel may be an option for second-line therapy in patients who have disease recurrence even after first-line chemotherapy (Creasman, 2017).

7.2.2 Metastatic

7.2.2.1 For patients with recurrent or metastatic disease, rates of response to multi-agent chemotherapy are as high as 50% to 60%. However, cures with chemotherapy alone are rare (Eifel, 2013).

7.2.2.2 Adjuvant postoperative treatment recommendations in advanced stage disease are widely disparate and an area of active research (Kumar, 2015).

7.2.2.3 Advanced, metastatic or recurrent endometrial carcinoma presents a difficult management problem (Humber et al, 2007; Moxley, KM & McMeekin, 2010). The platinum and anthracycline compounds have been widely used for many years, but their impact on progression-free survival (PFS) and overall survival (OS) is not clear. The addition of anthracyclines (e.g. doxorubicin) or the taxanes [e.g. paclitaxel] to cisplatin increases the response rate. However, while more intensive regimens are associated with the gain in survival, grade 3 and 4 myelosuppression and gastrointestinal toxicity are also increased (Humber et al, 2007, Tirmazy et al., 2014).

7.2.2.4 The effectiveness of progestational agents has been theorised to increase with the use of estrogenic compounds, such as tamoxifen, which have been documented to increase progesterone receptors (PgRs) in human endometrial cancers. While hormone therapy as an adjuvant treatment is not recommended, for advanced or recurrent disease, oral medroxyprogesterone acetate showed an overall response rate of 25%, and patients with well-differentiated tumours and positive progesterone receptor status had an even higher response rate, particularly with tamoxifen combined with medroxyprogesterone acetate (Plataniotis, G. & Castiglione, M. 2010).

Table 12: Recommended chemotherapy for endometrial cancer

Indication	Active ingredient/s	Comment (when necessary)
Adjuvant	Doxorubicin Cisplatin Carboplatin Paclitaxel	Docetaxel may be considered for patients in whom paclitaxel is contraindicated
Metastatic ER/PR +:	Doxorubicin Cisplatin Carboplatin Paclitaxel Tamoxifen; Medoxyprogesterone	

7.3 Radiation therapy

Women with recurrent endometrial cancer following primary surgical treatment alone may be appropriate candidates for radiation therapy. For a select group of patients not previously radiated and with small vaginal recurrences, radiation therapy may be curative, since primary radiation therapy influences sites of recurrence and survival after relapse in these cases (Rauh-Hain & del Carmen, 2010).

7.3.1 Adjuvant Radiation therapy:

7.3.1.1 Adjuvant radiotherapy is given depending on the stratified risk. For high-risk patients, the alternative or additional administration of chemotherapy should be considered (Denschlag et al, 2011).

7.3.1.2 Adjuvant radiotherapy decreases loco-regional recurrence and has good local control in FIGO stage IIIC endometrial carcinoma. There is uncertainty as to whether adjuvant radiotherapy improves overall survival (Colombo et al, 2013; Hsieh H-Y, et al., 2017).

7.3.1.3 However, three large randomised studies failed to demonstrate that radiation improves overall or disease-specific survival (Colombo et al, 2013).

7.3.1.4 Studies have shown that 3DCRT improves patient tolerance to curative treatment and allows for dose escalation (Hsieh et al, 2013; Hanks et al, 1996), as well as decreases the dose to the small bowel up to 33% in postoperative node-positive cervical cancer patients.

7.3.1.5 Recommended PMB level of care for adjuvant radiotherapy in endometrial cancer includes 3DCRT, in the form of both conventional single volume and multiple volumes of 45Gy to 50.4Gy.

7.3.1.6 External beam radiotherapy pelvic doses of 45 Gy in 25 fractions or 50.4 Gy in 28 fractions are both considered as standard prescriptions (Mazeron R et al, 2016). However, these authors, following a study to compare the ability of reaching different planning aims after each of these doses, they concluded that the delivery of 45 Gy in 25 fractions to the pelvis before brachytherapy warrants a higher probability to reach brachytherapy planning aims, in comparison with 50.4 Gy in 28 fractions.

7.3.1.7 Vaginal brachytherapy has shown a survival effect in patients with an intermediate and high risk of recurrence of endometrial cancer (Hass et al., 2018).

7.3.2 Palliative therapy

7.3.2.1 Palliative RT can be used in symptomatic management of metastatic sites. Palliative radiation doses of 3 Gy - 30 Gy have been prescribed and are recommended as PMB level of care (Elshaikh, 2016; Lutz, 2014).

7.3.3 Exclusions from PMB benefit:

7.3.3.1 . Intensity-Modulated Radiation Therapy (IMRT) is substantially more costly than conformal radiation and, to date, the benefits of IMRT for uterine cancer are not well defined (Wright et al, 2013).

7.3.3.2 Stereotactic body radiation is also not recommended as PMB level of care for endometrial cancer.

Table 13: Recommended PMB level of care for radiation therapy in endometrial cancer

Description
Adjuvant Radiation therapy: Conventional single volume / multiple volumes including 3D CRT: 45Gy to 50.4Gy Brachytherapy
Palliative Radiation therapy: Conventional single volume / multiple volumes including 3D CRT: 3Gy – 30Gy
Exclusions
Intensity-Modulated Radiation Therapy (IMRT)
Stereotactic body radiation therapy (SBRT)

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