PHC Chapter 7: Family planning

The guidance contained in this chapter is currently limited to contraception and does not cover all aspects of family planning such as pre-conception care. Refer to the National guidelines for safe conception and infertility for further guidance.

INTRODUCTION TO CONTRACEPTION

For comprehensive guidance, consult the most recent National Contraception Clinical Guidelines (especially for women with medical conditions), the National Clinical Guidelines for Safe Conception and Infertility, as well as the WHO Medical eligibility criteria for contraceptive use and the WHO family planning handbook for providers.

LoE:IVb[1]

Women should decide their own family planning method in consultation with their healthcare professional, taking into account the individual considerations of safety, efficacy, acceptability, and access. Always obtain a complete medical and sexual history and perform an appropriate physical examination to ensure that there are no contra-indications to using a particular method. Provide counselling and always exclude pregnancy before commencing contraception.

Contraceptive methods

Hormonal contraception and IUCDs do not prevent sexually transmitted infections (STIs), including HIV. Dual protection, i.e. the use of a condom in combination with another contraceptive method, is recommended to reduce the risk of STIs, including HIV.

Contraceptive method	Advantages include:	Disadvantages include:
Copper IUCD (see Section 7.1)	» Suitable for most women, including nulliparous women. » Provides long-term protection, i.e. 5 years. » Convenient, does not require frequent follow up. » Works immediately upon insertion. » Non-hormonal, therefore no interaction with other medication and no hormonal side effects. » Fertility returns immediately upon removal of IUCD in women of childbearing age. » Can be used for emergency contraception (see Section 7.4). » Safe to use during breastfeeding.	» Some discomfort or cramping during, and following insertion. » IUCD must be inserted or removed by a trained healthcare professional. » Should not be used in women with menorrhagia, high risk of STIs, active STIs and active pelvic inflammatory disease (PID), purulent cervicitis, unexplained uterine bleeding, cervical and endometrial cancers or other uterine abnormalities.
Levonorgestrel Intrauterine device (LNG-IUD) (see Section 7.2.2)	» Suitable for most women, including nulliparous women. » Provides long-term protection (up to 5 years). » Convenient, does not require frequent follow-up. » Works immediately upon insertion. » Immediate return to fertility upon removal.	» Bleeding changes are common but not harmful. Typically, lighter and fewer days of bleeding, or infrequent or irregular bleeding. » LNG-IUD must be inserted or removed by a trained healthcare professional.

	» Reduces menstrual cramps, heavy menstrual bleeding, and symptoms of endometriosis. » Similar to the Copper IUCD, can be inserted at the time of a caesarean section and postpartum (within 48 hours after delivery). *LoE:IIb*[2]	» Should not be used in women with active PID. *LoE:IIIb*[3]
Hormonal subdermal: progestin-only implant (see Section 7.2.1)	» Provides long-term protection, i.e. 3 years (etonogestrel) or 5 years (levonorgestrel). » Convenient, does not require frequent follow up. » Can also be used in women >35 years who are obese, who smoke, or who have diabetes, hypertension, or a history of venous thromboembolism. » Fertility returns upon removal of the implant in women of child-bearing age.	» Frequent bleeding irregularities. » Implant must be inserted or removed by a trained health care professional under aseptic conditions to prevent infection. » Incorrect insertion and removal techniques may result in complications.
Hormonal injectable: progestin-only (see Section 7.2.3)	» Daily adherence is not required. » Long-acting, i.e. given every 8 or 12 weeks. » Interactions with other medicines do not lower the contraceptive effect. » Can be used postpartum. » Can also be used in women >35 years who are obese, who smoke, or who have diabetes, hypertension, or a history of venous thromboembolism.	» Delayed return to fertility of up to 9 months after the last injection. » Frequent bleeding irregularities (irregular, prolonged and/or heavy bleeding, or amenorrhoea). » Associated with a possible weight gain *LoE:IIIb*[4]
Hormonal oral: progestin-only (see Section 7.2.4)	» Fertility returns within 3 months of discontinuing the pill. » Can be used postpartum. » Can also be used in women >35 years who are obese, who smoke, or who have diabetes, hypertension, or a history of venous thromboembolism.	» Daily adherence is required. » Interactions with other medicines can lower contraceptive effect. » Lower efficacy compared with COC. » Frequent bleeding irregularities.
Hormonal oral: combined oral contraceptive (COC) (see Section 7.2.4)	» Non-contraceptive benefits, e.g.: alleviation of dysmenorrhoea, premenstrual syndrome, and menorrhagia. » Fertility returns after discontinuation of COC but can take upto 3 months.	» Daily adherence is required. » Interactions with other medicines can lower contraceptive effect. » Cannot be used in women with venous thrombo-embolic disease. » Cannot be used immediately postpartum.

Barrier: male and female condoms (see Section 7.3)	» Protects against STIs, including HIV.	» Possibility of breakage or slipping off. » Possible allergic reaction to latex. » Lower efficacy than other contraceptive methods therefore advised as dual contraception. » Consistent and correct use is required to prevent pregnancy

Refer to the most recent SAHPRA registered professional information for detailed information.

Effectiveness of family planning methods

Rates of unintended pregnancies per 100 women:

Contraceptive method	**Failure rate in 1st year (%)**	
	Consistent and correct use	**Typical use**
Sterilisation: male – vasectomy	0.1	0.15
Sterilisation: female - tubal ligation	0.5	0.5
Progestin-only subdermal implant	0.1	0.1
LNG-IUD	0.5	0.7
Copper IUCD	0.6	0.8
Progestin-only injectable	0.2	4
Progestin-only oral pill (during breastfeeding)	0.3	7
Combined oral contraceptive (COC) pill	0.3	7
Progestin-only oral pill (not breastfeeding)	0.3	8
Barrier: male condoms	2	13
Barrier: female condoms	5	21
No method	85	85

Key:

0-0.9: very effective	1-9: effective	
10-19: moderately effective	20+: less effective	LoE:IVb[5]

7.1 INTRAUTERINE CONTRACEPTIVE COPPER DEVICE (IUCD)

Z30.0/Z30.1/Z30.5

Dual protection with barrier methods is recommended to reduce the risk of STIs, including HIV.

The copper IUCD (also known as the Copper T) is a long-term contraceptive method that is effective, safe and reversible. It has no hormonal effects or drug interactions. It does not require daily adherence or frequent follow up.

HIV infection is NOT a contra-indication to the use of an IUCD.

IUCDs are often the most suitable contraceptive for women on enzyme-inducing medicines, because of the absence of drug interactions.

- Copper IUCD, e.g:
- Cu T380A, 380mm² copper device.
  - Devices with lower copper surface area are not recommended.

The IUCD can be inserted at any time during the menstrual cycle, once pregnancy has been excluded (by clinical history or with a pregnancy test if required). Insertion at menstruation may be easier for the woman and results in less discomfort and spotting.

Copper IUCDs may be inserted immediately postpartum, or post miscarriage and post choice termination of pregnancy (CTOP) within 48 hours, by specially trained healthcare professionals, provided that no contra-indications are present (chorioamnionitis, ruptured membranes for more than 18 hours, or postpartum haemorrhage).

Alternatively, an IUCD may be inserted at least 4 weeks postpartum. *LoE:IIb*[6]

Advise women to check the strings of the IUCD monthly to ensure that the device is still in place.

Advise women when to return:

» Expulsion of IUCD or if strings of the IUCD become visible.
» Complications (excessive bleeding, excessive pain, fever, or foul-smelling discharge). *LoE:IVb*[7]
» Routine follow-up 4–12 weeks after insertion.
» If the strings of the IUCD cannot be felt.

Copper IUCD is not recommended for women with menorrhagia, active STI, active pelvic inflammatory disease (PID), purulent cervicitis, unexplained uterine bleeding, cervical and endometrial cancers or other uterine abnormalities. If a woman has a very high individual likelihood of exposure to STIs, she should generally not have a Copper IUCD inserted unless other methods are not available or not acceptable.

For mild pain and discomfort after insertion:

- Ibuprofen, oral, 400 mg 8 hourly with or after a meal as needed for up to 3 days.

REFERRAL

» Excessive pain or bleeding after insertion.

» Signs of infection within 7 days of insertion (e.g. fever, abdominal pain and/or foul-smelling discharge).
» Abnormal or heavy menstrual bleeding for > 3 months.

7.2 CONTRACEPTION, HORMONAL

CAUTION

Before starting hormonal contraception, advise women about the expected bleeding patterns, both initially and in the longer term.

7.2.1 SUBDERMAL IMPLANT

Z30.0/Z30.4/Z30.8

Dual protection with barrier methods is recommended to reduce the risk of STIs, including HIV.

The subdermal implant is an effective, safe, reversible, and convenient long-term contraceptive method that does not require daily adherence or frequent follow-up.

- Progestin-only subdermal implant contraceptive, e.g.:
- Etonogestrel, subdermal, 68 mg, single-rod implant.

The progestin-only subdermal implant can be inserted at any time during the menstrual cycle, once pregnancy has been excluded. If the implant is inserted within day 1 to day 5 of the onset of the menstrual cycle, the contraceptive effect is achieved within 24 hours of placement.

The main reason for discontinuation of the implant is irregular bleeding. This requires good counselling before the implant is inserted to inform women that this side effect can occur and can be treated. See Section 7.6: Breakthrough bleeding with contraceptive use.

The progestin-only subdermal implant is contraindicated in certain conditions, e.g. unexplained vaginal bleeding, active liver disease. Consult the package insert in this regard.

CAUTION

Medicines that induce the metabolism of progestins could reduce contraceptive efficacy. These medicines include efavirenz, rifampicin, phenytoin, carbamazepine, and phenobarbital.

Women receiving any of the above listed hepatic enzyme-inducing medicines should be advised that the efficacy of the subdermal implant may be reduced. If it is decided to continue using the subdermal implant, women should be advised to also use a non-hormonal contraceptive method during the time of concomitant use (the subdermal implant is not contra-indicated when using the above medicines). Dolutegravir, however, can be effectively used in combination with subdermal implants.

LoE:IIIb[8]

Insertion and removal procedures

» Training on the techniques for insertion and removal of the sub-dermal implant is strongly recommended.
» Only health care professionals familiar with these procedures should insert and remove subdermal implants, under aseptic conditions.
» Insert the implant **subdermally just under the skin of the upper non-dominant arm.**
» **Important: Refer to the specific professional information for detailed guidance on the product available on the National contract**.

Insertion of etonogestrel 68 mg implant:

» Insertion should only be performed with the preloaded applicator.
» Ask the woman to lie on her back on the examination table with her non-dominant arm flexed at the elbow and externally rotated, so that her hand is underneath her head (or as close as possible).
» Identify the insertion site, which is on the inner side of the non-dominant upper arm. The insertion site overlies the triceps muscles about 8 to 10 cm from the medial epicondyle of the humerus and 3 to 5 cm posterior to the sulcus (groove between the biceps and triceps muscles). This location is intended to avoid large blood vessels and nerves lying within and surrounding the sulcus. If it is not possible to insert the implant in this location (e.g. in women with thin arms), it should be inserted as far posterior from the sulcus as possible
» Make two marks with a surgical marker: First, mark the spot where the implant will be inserted, and second, mark a spot at 5 cm proximal (toward the shoulder) to the first mark. This second mark (guiding mark) will later serve as a direction guide during insertion.
» Clean the insertion site with an antiseptic solution.
» Anaesthetise the insertion area. *LoE:IVb*[9]
» Insert the implant subdermally:
  - Hold the applicator just above the needle at the textured surface area. Remove the transparent protection cap by sliding it horizontally in the direction of the arrow away from the needle.
  - Puncture the skin with the tip of the needle slightly angled less than 30° relative to the skin surface. If you insert the needle past the bevel, withdraw it until only the bevel is beneath the skin.
  - Lower the applicator to a horizontal position. To facilitate subdermal placement, lift the skin with the needle, while sliding the needle to its full length. You should be able to see the applicator just below the skin. In a seated position, look at the applicator from the side and NOT from above to clearly see the insertion and positioning of the needle just under the skin.
  - While keeping the applicator in the same position and the needle inserted to its full length, the purple slider should be unlocked by pushing it slightly down. The slider should be moved fully back until it stops.
  - The implant is now in its final subdermal position. Remove the applicator.

» Always verify the presence of the implant in the woman's arm immediately after insertion by palpation, and allow her to feel the implant as well.
» Apply sterile gauze with a pressure bandage to minimise bruising. The woman may remove the pressure bandage in 24 hours, and the small bandage over the insertion site after 3–5 days.

Insertion of levonorgestrel 2 x 75 mg implants:

» Clean the woman's upper arm with an antiseptic solution.
» The optimal insertion area is on the medial aspect of the upper arm about 6-8 cm above the fold of the elbow.
» The implants will be inserted subdermally, in the shape of a narrow V, opening towards the armpit.
» Anesthetise two areas about 4.5 cm long, to mimic the V shape of the implantation site.
» Mark the insertion site with a marker.
» Use the scalpel to make a small incision (about 2 mm) just through the dermis of the skin. Alternatively, the trocar may be inserted directly through the skin without making an incision.
» Open the implant pouch by pulling apart the film of the pouch and let the two implants drop on a sterile cloth. Note: Always use sterile gloves or forceps when handling the implants. If an implant is contaminated (e.g. falls on the floor), leave it for later disposal, open a new package, and continue with the procedure.
» The implant is provided with a disposable trocar that is sharp enough to penetrate the skin directly. Thus, the disposable trocar can be used to puncture the skin and insert the rods, without the need for an incision.
» The trocar has two marks. One mark is close to the handle and one close to the tip. When inserting the implants, the mark closest to the handle indicates how far the trocar should be introduced under the skin before loading each implant. The mark closest to the tip indicates how much of the trocar should be left under the skin after the insertion of the first implant. When inserting the trocar, avoid touching the part of the trocar that will go under the skin.
» Once the tip of the trocar is beneath the skin it should be directed along the subdermal plane horizontally by pointing it slightly upwards and raising the skin (tenting). Failure to keep the trocar in the subdermal plane may result in deep placement of the implants, causing a more difficult removal. The trocar should be oriented with the bevel up throughout the insertion procedure.
» Advance the trocar beneath the skin, about 5.5 cm from the incision to the mark closest to the handle of the trocar. Do not force the trocar; if you feel any resistance, try another direction.
» Remove the plunger when the trocar is advanced to the correct mark.
» Load the first implant into the trocar with either tweezers or fingers.
» Push the implant gently with the plunger to the tip of the trocar until you feel resistance. Never force the plunger.

» Hold the plunger steady and pull the trocar back along it until it touches the handle of the plunger. It is important to keep the plunger steady and not to push the implant into the tissue.
» Do not completely remove the trocar until both implants have been placed. The trocar is withdrawn only to the mark closest to its tip.
» When you can see the mark near the tip of the trocar in the incision, the implant has been released and will remain in place beneath the skin. You can check this by palpation.
» Insert the second implant next to the first one, to form a V shape. Fix the position of the first implant with the left fore-finger and advance the trocar along the side of the finger. This will ensure a suitable distance between implants. To prevent expulsions, leave a distance of about 5 mm between the incision and the ends of the implants. You can check their correct position by cautious palpation of the insertion area.
» After inserting the second implant, press the edges of the incision together, close with a skin closure and dress the wound.
» Advise the woman to keep the insertion area dry for 3 days.
» The gauze and the bandage may be removed as soon as the incision has healed, usually after 3–5 days.

<u>For pain after insertion:</u>

- Ibuprofen, oral, 400 mg 8 hourly with or after a meal as needed for up to 5 days.

<u>Removal of progestin-only subdermal implants:</u>

Remove etonogestrel implants at the end of 3 years and levonorgestrel implants at the end of 5 years.

» Locate the implant/s by palpation. If impalpable, refer for ultrasound-guided removal.
» Mark the distal end (end closest to the elbow) with a surgical marker.
» Clean the removal site with an antiseptic solution.
» Anaesthetise the removal area. Inject the local anaesthetic under the implant to keep the implant close to the skin surface.
» Push down the proximal end of the implant. A bulge may appear to indicate the distal end of the implant.
» Make a longitudinal (parallel to the implant) incision of approximately 2 mm towards the elbow.
» Very gently remove the implant, using a small forceps (preferably curved mosquito forceps). Where an implant is encapsulated, dissect the tissue sheath to remove the implant with the forceps.
» Confirm that the complete implant has been removed by measuring the length (etonogestrel rod: 40 mm; levonorgestrel rods: 43 mm). Close the incision with a steristrip or plaster and dress.
» Advise the woman to keep the arm dry for a few days.

REFERRAL

» Heavy or prolonged bleeding, despite treatment with COCs.
» Infection at the insertion site, inadequately responding to an initial course of antibiotic treatment. See Section 5.4.3: Cellulitis.
» Failure to locate an implant (in the arm) by palpation.

7.2.2 LEVONORGESTREL INTRA-UTERINE DEVICE (LNG-IUD)

Z30.0/Z30.5/Z30.8

Dual protection with barrier methods is recommended to reduce the risk of STIs including HIV.

The LNG-IUD is an effective, safe, reversible, long-term contraceptive method that has minimal hormonal adverse effects and is not prone to drug interactions. It does not require daily adherence or frequent follow up.

- Progestin-only intrauterine device, e.g.:
- Levonorgestrel, intrauterine device, 52 mg. *LoE:IIb*[10]

HIV infection is NOT a contra-indication to the use of an LNG-IUD.

LoE:IIIb[11]

The LNG-IUD is a T-shaped plastic device that steadily releases a small amount of levonorgestrel every day. It has the added benefit of reducing menstrual cramping and heavy menstrual bleeding. It can be inserted by specially trained health care professionals, at any time during the menstrual cycle, once pregnancy has been excluded (by clinical history or with a pregnancy test if required). Insertion at menstruation may be easier for the woman, and results in less discomfort and spotting. It may be used by women of any age, regardless of whether they have had children before.

LNG-IUD may be inserted immediately postpartum or post miscarriage (within 48 hours), provided that no contra-indications are present (chorioamnionitis, ruptured membranes for more than 18 hours or postpartum haemorrhage). Providers require specific training in postpartum insertion by hand or using a ring forceps.

LNG-IUD may also be inserted 4 or more weeks postpartum.

Advise women when to return:
» Expulsion of LNG-IUD or if strings of the LNG-IUD protrude.
» Complications (excessive bleeding, excessive pain, fever or foul smelling discharge). *LoE:IIIb*[12]
» Routine follow-up 3–6 weeks after insertion.
» First time migraine or severe headaches during use.

LNG-IUD is not recommended for women with acute venous thromboembolism, severe liver cirrhosis, active pelvic inflammatory disease (PID), purulent cervicitis, unexplained uterine bleeding, cervical- breast- ovarian- or endometrial cancers, or other uterine abnormalities.

For mild pain and discomfort after insertion:

- Ibuprofen, oral, 400 mg 8 hourly with or after a meal as needed for up to 3 days. *LoE:IVb*

REFERRAL

» Excessive pain or bleeding after insertion.
» Signs of infection within 7 days of insertion (e.g. fever, abdominal pain and/or foul-smelling discharge).
» Abnormal or heavy menstrual bleeding for > 3 months.
» First time migraine or severe headaches.

LoE:IVb[13]

7.2.3 INJECTABLE

Z30.0/Z30.4

Dual protection with barrier methods is recommended to reduce the risk of STIs, including HIV.

- Progestin-only injectable contraceptive, e.g.:
- Medroxyprogesterone (long-acting), IM, 150 mg, 12 weekly. *LoE:IIIb*[14]

OR

- Medroxyprogesterone (long-acting), SC, 104 mg, 12 weekly.

Progestin-only hormonal contraceptives are contraindicated in certain conditions, e.g. unexplained vaginal bleeding. Consult the individual professional information in this regard.

Using the Progestin-only IM Injection

When to start the injection

» The injection can be started anytime within the menstrual cycle, provided pregnancy has been excluded. If the first injection is given within 7 days of the onset of the menstrual cycle, the contraceptive effect is achieved on the day of the first injection.
» If started after day 7, advise the woman to abstain from intercourse or use condoms for the next 7 days.
» Can be started immediately postpartum in both breastfeeding and non-breastfeeding women if no other method is acceptable or available. *LoE:IVb*[15]

Late injection

» The next injection can be as much as 4 weeks late if using the medroxyprogesterone acetate DMPA (long-acting), or 2 weeks late if using norethisterone enanthate (NET-EN).
Injectable contraceptive may be administered later than recommended (>4 weeks late for DMPA or >2 weeks late for NET-EN) if:
  - She has not had sexual intercourse since 2 weeks after the scheduled date of her injection, or

- She has used a backup method or has taken emergency contraceptive pills after any unprotected sexual intercourse since 2 weeks after the scheduled date of her injection, or
- She is fully or nearly fully breastfeeding and she gave birth less than 6 months ago.

However, in all three cases she will need a backup method for the first 7 days after the injection.

LoE:IVb[16]

Assess the need for emergency contraception in the event of a late injection (See Section 7.4: Contraception, Emergency).

Using the Progestin-only SC Injection

May be administered by a healthcare professional (HCP) or with adequate training when considered appropriate by the HCP, self-injected by the patient, with medical follow up as necessary.

When to start the injection

» The first injection of 104 mg SC should be given during the first 5 days of a normal menstrual cycle to ensure the client is not pregnant.

» The second and subsequent injections should be given at a 3 month interval (12 -14 weeks).

» Can be started immediately postpartum in both breastfeeding and non-breastfeeding women if no other method is acceptable or available.

CAUTION

» Alternative contraceptive options should be considered if the continued use of medroxyprogesterone acetate (IM or SC) is extended beyond 2 years. All effective contraceptive options should be considered, taking into account client preferences and circumstances.

» A small increased risk of meningiomas (rare, and mostly benign tumours) have been reported following long-term administration of medroxyprogesterone acetate (long-acting),

» Medroxyprogesterone (long-acting) should be discontinued if a meningioma is diagnosed.

» Caution is advised when recommending medroxyprogesterone (long-acting) to patients with a history of meningioma.

LoE:IVb[17]

REFERRAL

Heavy or prolonged bleeding, despite adequate treatment with combined oral contraceptives (See Section 7.6: Breakthrough bleeding with contraceptive use).

7.2.4 ORAL

Z30.0/Z30.4

Dual contraception with barrier methods, are recommended to reduce the risk of STIs, including HIV.

Monophasic preparations:

- Progestin only pills, e.g.:
- Levonorgestrel, oral, 30 mcg daily. *LoE:IIIa*[18]
- Progestins and estrogen, fixed combinations, e.g.:
- Ethinylestradiol/levonorgestrel, oral, 30 mcg/150 mcg:
  - 21 tablets ethinylestradiol/levonorgestrel, 30 mcg/150 mcg and
  - 7 tablets placebo. *LoE:IIIa*[19]

Triphasic preparations:

- Progestins and estrogen, sequential preparations, e.g.:
- Ethinylestradiol/levonorgestrel, oral:
  - 6 tablets ethinylestradiol/levonorgestrel, 30 mcg/50 mcg
  - 5 tablets ethinylestradiol/levonorgestrel, 40 mcg/75 mcg and
  - 10 tablets ethinylestradiol/levonorgestrel, 30 mcg/125 mcg and
  - 7 tablets placebo. *LoE:IIIa*[20]

Counselling:

» Hormonal oral pills must be taken at the same time every day without interruption.
» Taking the hormonal oral pill with food or at bedtime may alleviate nausea.
» If the woman is not using dual contraception with barrier methods and vomits within 2 hours, or has severe diarrhoea within 12 hours of taking the hormonal oral pill, repeat the dose as soon as possible. Recommend condom use.
» Women who have persistent vomiting or severe diarrhoea resulting in two or more missed pills must follow instructions for missed pills (see Section 7.2.4: Oral). Recommend condom use.

Contraindications and guidance to starting the hormonal oral pill

	Progestin only	**Combined estrogen/progestin**
Contra-indications	Progestin only preparations are contraindicated in certain conditions (Consult the package insert in this regard). Contraindications include: » Abnormal uterine bleeding of unknown cause. » Myocardial infarction/stroke. » Liver disease. » Cancer of the breast/ genital tract. » Known or suspected pregnancy. *LoE:IVb*[21]	Combination preparations contraindicated in certain conditions (Consult the package insert in this regard). Contraindications include: » Women >35 years of age who smoke ≥15 cigarettes a day or have risk factors for cardiovascular disease: – heart disease – liver disease – thromboembolism – certain cancers
When to start the pill	» Exclude pregnancy. » May be started anytime within the menstrual cycle, but it is advisable to start during menses.	

	» If the first pill is given between days 1 and 5 of the menstrual cycle, the contraceptive effect is achieved immediately. » If the pill is started at any other time, it needs to be taken for at least 7 days before contraceptive efficacy is established. The use of condoms is recommended during these 7 days.

Medicine interactions

Enzyme-inducing medicines interacting with oral contraceptives		Recommendation
Therapeutic class	**Examples**	
Anti-tuberculosis	Rifampicin	Use copper IUCD or alternatively use dual contraception, e.g. condoms in combination with COCs.
Anti-epileptics	Phenobarbital	
	Phenytoin	
	Carbamazepine	
Antiretrovirals	Nevirapine	
	Lopinavir/ritonavir	
	Efavirenz	

Lamotrigine:
» Lowering of contraceptive effect not expected.
» Oral contraceptives may reduce lamotrigine concentration, increasing the risk of seizures. Change to IUCD or progesterone only methods (i.e levonorgestrel implant, etonogestrel implant, or LNG-IUD), if lamotrigine is going to be used long term.

LoE:IVb[22]

Breastfeeding
» Women who are intending to breastfeed should delay initiation of COCs until cessation of breastfeeding or at 6 months postpartum, whichever occurs earlier.

REFERRAL
Abnormal vaginal bleeding for >3 months.

7.2.5 MISSED PILLS

Progestin only pills
Efficacy is rapidly lost if one pill is forgotten or taken >3 hours late. Recommend dual contraception for all scenarios for at least 7 days.

LoE:IVb[23]

Scenario	Action
One pill forgotten or pill taken >3 hours late, and unprotected sexual intercourse has not occurred in the past 5 days.	Take pill as soon as remembered and continue taking one pill daily at the usual time.
One pill forgotten or taken 3 hours late, and unprotected sexual intercourse has occurred in the past 5 days.	Give emergency contraception (see Section 7.4). Take one pill the next day and continue taking one pill daily at the usual time.

Combination of progestin and estrogen in each pill

Missing active pills and extending hormone free interval leads to decreased contraceptive efficacy. Recommend dual contraception for all scenarios for at least 7 days. *LoE:IVb*[24]

LoE:IVb[25]

Scenario	Action
One active pill forgotten.	Take pill as soon as remembered and take next one at usual time.
Two or more pills forgotten during the first 7 active pills of the pack and unprotected sexual intercourse has occurred in the past 5 days.	Give emergency contraception (see Section 7.4). Restart active pills 12 hours later.
Two or more pills forgotten during the middle 7 active pills of the pack.	Take the most recent missed pill immediately (discard the other missed pills). Continue taking remaining pills as usual. No emergency contraception required.
Two or more pills forgotten in the last 7 active pills of the pack and unprotected sexual intercourse has occurred in past 5 days.	Continue active pills of current pack. Omit the inactive pills and immediately start the active pills of the next pack.

7.3 CONTRACEPTION, BARRIER METHODS

Z30.0

Condoms (male and female) alone are the least effective contraceptive method and should be used in combination with other contraceptive methods (e.g. copper IUCD). Condoms are recommended to reduce the risk of the acquisition of HIV infection and other STIs.

Condoms (male and female) or other barrier methods may be an option for contraception where other methods are contraindicated.

7.4 CONTRACEPTION, EMERGENCY

Z30.0/Z30.4

Emergency contraception is indicated to prevent pregnancy after unprotected intercourse in women not using contraception, or where contraception is likely to be ineffective:

» Forgotten tablets (See Section 7.2.5: Missed pills)
» Slipped or broken condom
» Injectable contraception given late (>2 weeks for NET-EN, >4 weeks for DMPA)
» Sexual assault

A woman who needs emergency contraception often should be counselled to consider a longer-acting and more effective family planning method.

Emergency contraception after pregnancy is excluded

Do a pregnancy test in all women and female adolescents. Children must be tested and given emergency contraception from Breast Tanner Stage III.

- Copper IUCD inserted as soon as possible after unprotected intercourse and no later than 5 days.

OR *LoE:IIIb*[26]

- Levonorgestrel, 1.5 mg, oral, as a single dose as soon as possible after unprotected intercourse, and not later than 5 days.
  - If the client vomits within 2 hours, repeat the dose. *LoE:Ia*[27]

Advise women that their period should be on time. It is rarely delayed but it should not be more than 7 days late. If this occurs, they should come back for a pregnancy test.

If using enzyme inducing drugs or woman weighs > 80 kg / BMI ≥ 30:

» It is recommended to have a copper IUCD inserted.

» If this is not possible, double the dose of levonorgestrel administered:

- Levonorgestrel, 1.5 mg, oral, 2 tablets taken as a single dose.

» If the dedicated product is not available, use COCs containing 30 µg ethinylestradiol + 150 µg levonorgestrel (e.g. Nordette/Oralcon):

- Ethinylestradiol/levonorgestrel, oral, 30 mcg/150 mcg, 6 tablets taken as a single dose, followed by 6 tablets 12 hours later.

CAUTION

» Emergency contraceptive tablets must be taken as soon as possible, preferably within 72 hours of unprotected intercourse, and not later than 5 days.

» Enzyme inhibitors (ketoconazole, fluconazole) significantly increase the bioavailability of levonorgestrel and may increase nausea and vomiting. Women taking these medicines should preferably have copper IUCD inserted.

LoE:IIIb[28]

REFERRAL

Women in need of emergency contraception must be referred for HIV counselling and testing and PEP (See Section 21.3.6.2: Post exposure prophylaxis, rape and sexual assault).

7.5 VOLUNTARY STERILISATION, MALE AND FEMALE

Z30.2

Female sterilisation

Also known as tubal occlusion or tubal ligation. This is a permanent, surgical contraceptive method for women who do not intend to have more children.

Women who opt for sterilisation should be adequately counselled and referred.

Male sterilisation
Also known as vasectomy. This is a permanent surgical contraceptive method for men who do not intend to have more children.
Men who opt for this method should be adequately counselled and referred.

CAUTION
Sterilisation does not protect against sexually transmitted infections (STIs), including HIV. If there is a risk of STI/HIV, the correct and consistent use of condoms is recommended.

LoE:IIIb[29]

7.6 BREAKTHROUGH BLEEDING WITH CONTRACEPTIVE USE

N92.0/N92.1/N92.4

DESCRIPTION

Breakthrough bleeding refers to unscheduled or irregular vaginal bleeding, which often presents as spotting, or prolonged or frequent bleeding in women using hormonal contraception. The pattern and duration of these unscheduled bleedings vary with the contraceptive method used.

GENERAL MEASURES

Before starting hormonal contraception, counsel women regarding possible bleeding patterns, both initially and in the longer term.

Clinical assessment:

» Current method of contraception and duration of use.
» Drug interactions.
» Cervical screening history.
» Risk of sexual transmitted infections (e.g. Chlamydia trachomatis).
» Menstrual and break though bleeding history prior to current method being initiated.
» Exclude pregnancy.

Hormonal contraceptives causing breakthrough bleeding	Treatment
Progestin-only injectables	• COC containing 30 mcg ethinylestradiol, oral, for 14 days. LoE:IIIb[30]
Progestin subdermal implants	Progestins and estrogen, fixed combinations, e.g.: • Ethinylestradiol/levonorgestrel, oral, 30 mcg/150 mcg for daily for 20 days.
Progestin intrauterine devices	Refer – see Section 7.2.2.
Combined oral contraceptive pill » Unscheduled bleeding with COC usually settles with time.	• Change COC to another COC containing the lowest dose of ethinylestradiol, oral, daily.

» Changing to another COC in the first 3 months is not recommended.	<u>If bleeding persists:</u> • Change COC to a COC containing at least 30mcg ethinylestradiol, oral, daily. *LoE:IVb*

REFERRAL

» Pelvic pain.
» Pelvic mass.
» Heavy bleeding.
» Abnormal cervix on speculum examination (e.g. polyps).
» Bleeding not controlled by the treatment above.

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REPUBLIC OF SOUTH AFRICA

2030 NDP

SOUTH AFRICAN PRIMARY HEALTHCARE LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 7: FAMILY PLANNING
NEMLC RECOMMENDATIONS FOR MEDICINE AMENDMENTS (2020-2024) REVIEW CYCLE-UPDATE

Medicine amendment recommendations, with supporting evidence and rationale are listed below.
Kindly review the medicine amendments in the context of the respective standard treatment guideline (STG) and supporting medicine reviews. All reviews and costing reports may be accessed at: https://www.health.gov.za/nhi-edp-stgs-eml/

A: AMENDMENTS

SECTION	MEDICINE/ MANAGEMENT	ADDED/DELETED/AMENDED/NOT ADDED/ RETAINED
Chapter Title		Not amended, an explanatory statement added at the beginning of chapter.
Introduction to contraception	Cross references to other clinical guidelines	Editorial amendments added, references to National and other guidelines added.
Contraceptive methods (Summary table)	Copper Intrauterine contraceptive device (IUCD)	-Editorial amendments added -The duration of use retained. -Guidance on use in women at very high risk of STIs added. -Guidance on use in active STIs added. -Advantages of use as emergency contraception added. -Safety during breastfeeding added.
	Levonorgestrel Intrauterine device (LNG-IUCD)	-Editorial amendments added -The duration of use retained. -Guidance for use at the time of caesarean section added.
	Hormonal subdermal: progestin-only implant	-Editorial amendments added.
	Hormonal injectable: progestin-only	-Editorial amendments added. -Possibility of Weight gain added.
	Hormonal oral: combined oral contraceptive (COC)	-Guidance on fertility after cessation of COC amended.
	Barrier: male and female condoms	-Emphasis on consistent and correct use added.
Effectiveness of family planning methods	Rates of unintended pregnancies	-Table amended
7.1 Intrauterine contraceptive copper device (IUCD)	Post choice termination of pregnancy (CTOP)	-Guidance added.
	Return for assessment	-Guidance added.
	Routine follow-up post insertion	-4 to 12 weeks follow-up after insertion added. -Annual visit not added. -Editorial amendments added.
	STI testing for women initiating contraception	Not added.
	Exclusion of IUCD in women with active or at high risk of STI	Guidance amended
	Use of Copper IUCD for women on enzyme-inducing medicines	Guidance editorially amended for clarity

7.2.1 Subdermal implant	Timing of insertion	Amended, editorial amendments also added.
	Concomitant use with Hepatic enzyme inducing medicines	Guidance amended.
	Concomitant use with dolutegravir	Guidance added.
	Insertion of etonogestrel 68 mg implant	Guidance amended with extensive editorial amendments.
7.2.2 Levonorgestrel intra-uterine device (LNG-IUD)	Title of section	Not amended and editorial amendments added.
7.2.3 Injectable	When to start the injection	Amended.
	Risk of HIV acquisition associated with progestin injectable contraceptives	Guidance removed.
	Late injection	-Guidance amended and cross reference to Section 7.4: Contraception, Emergency added -Editorial amendments added
	Medroxyprogesterone (long acting), SC	Added outside of Progestin-only Injectable therapeutic class and administration guidance added.
	Risk of meningiomas with long term use of DMPA	Caution box added
7.2. Oral	Triphasic preparations	Classification retained.
	When to start the pill	Guidance added.
	Non-liver enzyme inducing medicines (Lamotrigine)	Guidance amended and heading removed
7.3 Contraceptive, barrier methods	ICD 10 codes	Z30.4/Z30.5 removed, editorial amendments
7.4 Contraception, emergency	Description	Clinical editorial amendments
	Ulipristal acetate	Under consideration for review.
	Frequent use of emergency contraceptive	Guidance added.
	Double dose of levonorgestrel for patients on hepatic enzyme inducing drugs	Dosing guidance added.
	Use of levonorgestrel for patients on Enzyme inhibitor drugs (such as ketoconazole, fluconazole)	Guidance added.
	Referral	Cross reference to Section 21.3.6.2: Post exposure prophylaxis, rape and sexual assault added
7.6 Breakthrough bleeding with contraceptive use	Non-steroidal anti-inflammatory drugs (NSAIDS), Tranexamic Acid and Doxycycline	Under consideration for review.
	Breakthrough bleeding with Combined oral contraceptives (COCs)	Recommended dose of COCs containing ethinylestradiol amended to 30 mcg
Therapeutic interchange database /updates		See page 21

Chapter Title: *Not amended*

The family planning chapter currently provides guidance exclusively for contraception and does not include all aspects of family planning such as pre-conception care e.g. infertility. An external comment to rename the title of the chapter was not accepted at this time. A statement has been included at the beginning of the chapter to highlight the limitations of the guidance provided in the chapter in the context of family planning. A hyperlink to the National guidelines for safe conception and infertility has been included for additional guidance.

The STG has been amended as follows:

The guidance contained in this chapter is currently limited to contraception and does not cover all aspects of family planning such as pre-conception care. Refer to the National guidelines for safe conception and infertility for further guidance.

INTRODUCTION TO CONTRACEPTION

Cross references to other clinical guidelines: *Added*

For expanded guidance to supplement the recommendations included in the family planning chapter, the updated references for the NDoH National Contraception Clinical Guidelines[1], the WHO Medical eligibility criteria for contraceptive use[2],and the WHO family planning handbook for providers[3] have been added. It is to be noted that the STG is not a comprehensive clinical practice guideline document and therefore, additional guidance should be sought from the appropriate Programmatic guidelines.

The STG has been amended as follows:

Amended from: Consult the most recent National Contraception Clinical Guidelines (especially in women with medical conditions). Women should decide their own family planning method, in consultation with their health care professional, taking into consideration safety, efficacy, acceptability, and access. Always obtain a complete medical and sexual history and perform an appropriate physical examination in order to ensure that there are no contra-indications to using a particular method. Always exclude pregnancy before commencing contraception. Amended To: For comprehensive guidance, consult the most recent National Contraception Clinical Guidelines (especially for women with medical conditions) as well as the WHO Medical eligibility criteria for contraceptive use and the WHO family planning handbook for providers. Women should decide their own family planning method in consultation with their healthcare professional, taking into account the individual considerations of safety, efficacy, acceptability, and access. Always obtain a complete medical and sexual history and perform an appropriate physical examination in order to ensure that there are no contra-indications to using a particular method. Provide counselling and always exclude pregnancy before commencing contraception.

Contraceptive methods: Summary table

Copper Intrauterine contraceptive device (IUCD):
-Editorial amendments added
-The duration of use retained.
-Guidance on use in women at very high risk of STIs added.
-Guidance on use in active STIs added.
-Advantages of use as emergency contraception added.
-Safety during breastfeeding added.

The copper IUCD currently on the state contract HP-03 (ending 30 September 2026) Nova T 380®, is indicated for removal only after 5 years[4]-[5]. It was noted by NEMLC to investigate and encourage the sourcing copper IUCDs of longer duration for up to 10 years. In addition, the contraceptive methods summary table has been amended to include safety of the copper IUCD during breast feeding and an advantage for use as emergency contraception. An external comment to provide a recommendation as to whether the copper IUCD should be recommended in women who are at high risk of STIs was reviewed and not accepted. If a woman has a very high individual likelihood of exposure to STIs, she should generally not have a copper IUCD inserted unless other methods are not available or not acceptable[1].

[1] NDoH.National Contraception Clinical Guidelines.2019. https://knowledgehub.health.gov.za/elibrary/national-contraception-clinical-guidelines-2019

[2] World Health Organization. Reproductive Health. Medical eligibility criteria for contraceptive use. World Health Organization; 2015. https://iris.who.int/bitstream/handle/10665/181468/9789241549158_eng.pdf?sequence=9

[3] Family Planning: A Global Handbook for Providers (2022 update). Baltimore and Geneva: CCP and WHO, 2022. https://www.who.int/publications/i/item/9780999203705

[4] NDoH. Master Health product list (MHPL). January 2025

[5] Bayer Healthcare. Nova T 380®.Package insert.2011

The STG has been amended as follows:

Amended From:

Contraceptive method	Advantages include:	Disadvantages include:
Copper IUCD (see Section 7.1)	» Suitable for most women, including nulliparous women. » Provides long-term protection i.e. 5 years. » Convenient, does not require frequent follow up. » Works immediately on insertion. » Non-hormonal therefore no interaction with other medication and no hormonal side effects. » Fertility returns immediately on the removal of IUCD in women of child-bearing age.	» Some discomfort or cramping during and following insertion. » IUCD must be inserted or removed by a trained health care professional. » Should not be used in women with menorrhagia, active pelvic inflammatory disease (PID), purulent cervicitis, unexplained uterine bleeding, cervical and endometrial cancers or other uterine abnormalities.

Amended To:

Contraceptive method	Advantages include:	Disadvantages include:
» Copper IUCD (see Section 7.1)	» Suitable for most women, including nulliparous women. » Provides long-term protection i.e. 5 years. » Convenient, does not require frequent follow up. » Works immediately on insertion. » Non-hormonal therefore no interaction with other medication and no hormonal side effects. » Fertility returns on the removal of IUCD in women of childbearing age. » Can be used for emergency contraception (see section 7.4). » safe to use during breastfeeding.	» Some discomfort or cramping during and following insertion. » IUCD must be inserted or removed by a trained healthcare professional. » Should not be used in women with menorrhagia, high risk of STIs, active STIs and active pelvic inflammatory disease (PID), purulent cervicitis, unexplained uterine bleeding, cervical and endometrial cancers or other uterine abnormalities.

<u>Levonorgestrel Intrauterine device (LNG-IUD):</u>

-Editorial amendments added.

-The duration of use retained.

-Guidance for use at the time of caesarean section added.

The LNG-IUD currently on the state contract HP-03 (ending 30 September 2026) Mirena® is indicated for removal only after 5 years[4-6]. It was noted by NEMLC to investigate the availability and encourage the sourcing LNG-IUDs of longer duration for up to 8 years. Similar to the copper IUCD, guidance has been added to highlight that LNG-IUD can be inserted during caesarian section as an advantage[1]. Editorial amendments also incorporated.

The STG has been amended as follows:

Amended From:

Levonorgestrel Intrauterine device (LNG-IUD) (see Section 7.2.2)	» Suitable for most women, including nulliparous women. » Provides long-term protection (up to 5 years). » Convenient, does not require frequent follow up. » Works immediately on insertion. » Immediate return to fertility on removal. » Reduces menstrual cramps, heavy menstrual bleeding, and symptoms of endometriosis.	» Bleeding changes are common but not harmful. Typically, lighter and fewer days of bleeding, or infrequent or irregular bleeding. » LNG-IUD must be inserted or removed by a trained health care professional. » Should not be used in women with active PID.

[6] Bayer Healthcare. Mirena®. Package insert.2019

	» Can be inserted postpartum (within 48 hours after delivery).	
Amended To:		
Levonorgestrel Intrauterine device (LNG-IUD) (see Section 7.2.2)	» Suitable for most women, including nulliparous women. » Provides long-term protection (up to 5 years). » Convenient, does not require frequent follow-up. » Works immediately on insertion. » Immediate return to fertility on removal. » Reduces menstrual cramps, heavy menstrual bleeding, and symptoms of endometriosis. » Similar to the Copper IUCD, can be inserted at the time of a caesarean section and postpartum (within 48 hours after delivery).	» Bleeding changes are common but not harmful. Typically, lighter and fewer days of bleeding, or infrequent or irregular bleeding. » LNG-IUD must be inserted or removed by a trained healthcare professional. » Should not be used in women with active PID.

Hormonal subdermal: progestin-only implant: *Editorial amendments added*

The STG currently recommends progestin-only subdermal implants as a therapeutic class. On the state contract HP-03 (ending 30 September 2026) Implanon NXT® containing etonogestrel; 68mg is available for use over a duration of 3 years. The NEMLC encourages the sourcing of other therapeutically equivalent alternatives with a longer duration of contraception e.g. levonorgestrel containing implants.

Minor editorial amendments have been added to the STG as follows:

Amended From:

Hormonal subdermal: progestin-only implant (see Section 7.2.1)	» Provides long-term protection i.e. 3 years (etonogestrel) or 5 years (levonorgestrel). » Convenient, does not require frequent follow up. » Can be used in women >35 years who are obese, who smoke, or who have diabetes, hypertension, or a history of venous thromboembolism. » Fertility returns on removal of implant in women of child-bearing age.	» Frequent bleeding irregularities. » Implant must be inserted or removed by a trained health care professional under aseptic conditions to prevent infection. » Incorrect insertion and removal technique may result in complications.

Amended To:

Hormonal subdermal: progestin-only implant (see Section 7.2.1)	» Provides long-term protection i.e. 3 years (etonogestrel) or 5 years (levonorgestrel). » Convenient, does not require frequent follow up. » Can also be used in women >35 years who are obese, who smoke, or who have diabetes, hypertension, or a history of venous thromboembolism. » Fertility returns on the removal of the implant in women of child-bearing age.	» Frequent bleeding irregularities. » Implant must be inserted or removed by a trained health care professional under aseptic conditions to prevent infection. » Incorrect insertion and removal techniques may result in complications.

Hormonal injectable: progestin-only:
-Editorial amendments added
-Possibility of weight gain added

Weight gain associated with the progestin-only injectable has been included as one of the undesirable effects[7]-[8]. In addition, the STG classification of progestin-only injectables as long-acting reversible contraception method has been retained.

The STG has been amended as follows with additional editorial amendments:

Amended From:

Hormonal injectable: progestin-only (see Section 7.2.2)	» Daily adherence is not required. » Long acting i.e. given every 8 or 12 weeks. » Interactions with other medicines do not lower contraceptive effect. » Can be used postpartum. » Can be used in women >35 years who are obese, who smoke, or who have diabetes, hypertension, or a history of venous thromboembolism.	» Delayed return to fertility of up to 9 months, after last injection. » Frequent bleeding irregularities (irregular, prolonged and/or heavy bleeding, or amenorrhoea).

Amended To:

Hormonal injectable: progestin-only (see Section 7.2.2)	» Daily adherence is not required. » Long acting i.e. given every 8 or 12 weeks. » Interactions with other medicines do not lower the contraceptive effect. » Can be used postpartum. » Can also be used in women >35 years who are obese, who smoke, or who have diabetes, hypertension, or a history of venous thromboembolism.	» Delayed return to fertility of up to 9 months, after the last injection. » Frequent bleeding irregularities (irregular, prolonged and/or heavy bleeding, or amenorrhoea). » Associated with a possible weight gain

Hormonal oral: combined oral contraceptive (COC): *Guidance on fertility after cessation of COC amended.*

For better clarity, the STG has been editorially amended to indicate that although fertility returns with the use of COCs, it may be delayed for up to 3 months.

The STG has been amended as follows:

Amended From:

» Non-contraceptive benefits, e.g.: alleviation of dysmenorrhoea, premenstrual syndrome, and menorrhagia.
» Fertility returns within 3 months of discontinuing COC.

Amended To:

» Non-contraceptive benefits, e.g.: alleviation of dysmenorrhoea, premenstrual syndrome, and menorrhagia.
» Fertility returns after discontinuation of COC but can take up to 3 months.

Barrier: male and female condoms: *Emphasis on consistent and correct use added.*

For emphasis, guidance has been added to the STG highlighting the importance of consistency and correct use of barrier methods to prevent pregnancies.

The STG has been amended as follows:

Amended From:

» Possibility of breakage or slipping off.
» Possible allergic reaction to latex.
» Lower efficacy than other contraceptive methods therefore advised as dual contraception.

Amended To:

» Possibility of breakage or slipping off.
» Possible allergic reaction to latex.
» Lower efficacy than other contraceptive methods therefore advised as dual contraception.

[7] Pfizer. Depo-Provera® 150mg inj. Package insert.2022

[8] Family Planning: A Global Handbook for Providers (2022 update). Baltimore and Geneva: CCP and WHO, 2022. https://www.who.int/publications/i/item/9780999203705

» Consistent and correct use is required to prevent pregnancy

Effectiveness of family planning methods: *Table amended*

Following clinical editorial review, in line with the WHO[9] guideline, the table comparing the rates of unintended pregnancies during the first year of typical vs consistent and correct use has been updated with the addition of a colour representation of the estimates of effectiveness of the various contraception methods. To make the table simpler for user interpretation, the historical column containing % of women continuing use of contraception at one year has been removed.

The STG has been amended as follows:

Contraceptive method	Failure rate in 1st year (%)		% of women continuing use at one year
	Consistent and correct use	As typically used	
Copper IUCD	0.6	0.8	78
LNG-IUD	0.2	0.2	80
Progestin-only subdermal implant	0.05	0.05	84
Progestin-only injectable	0.3	3	56
Progestin-only oral pill (not breastfeeding)	0.3	8	67
Progestin-only oral pill (during breast feeding)	0.5	1	n/a
Combined oral contraceptive (COC) pill	0.3	3	67
Barrier: female condoms	5	21	41
Barrier: male condoms	2	15	43
Sterilisation: male – vasectomy	0.1	0.15	100
Sterilisation: female - tubal ligation	0.5	0.5	100
No method	85	85	n/a

Key: 0-0.9: very effective 10-25: moderately effective
1-9: effective 26-32: less effective

Contraceptive method	Failure rate in 1st year (%)	
	Consistent and correct use	Typical use
Sterilisation: male – vasectomy	0.1	0.15
Sterilisation: female - tubal ligation	0.5	0.5
Progestin-only subdermal implant	0.1	0.1
LNG-IUD	0.5	0.7
Copper IUCD	0.6	0.8
Progestin-only injectable	0.2	4
Progestin-only oral pill (during breastfeeding)	0.3	7
Combined oral contraceptive (COC) pill	0.3	7
Progestin-only oral pill (not breastfeeding)	0.3	8
Barrier: male condoms	2	13
Barrier: female condoms	5	21
No method	85	85

Key:

0-0.9: very effective	1-9: effective
10-19: moderately effective	20+: less effective

7.1 Intrauterine contraceptive copper device (IUCD)

Routine follow-up post insertion:
-4 to 12 weeks follow-up after insertion added
-Annual visit not added
-Editorial amendments added

[9] Family Planning: A Global Handbook for Providers (2022 update). Baltimore and Geneva: CCP and WHO, 2022. https://www.who.int/publications/i/item/9780999203705

An external comment to recommend annual follow-up visits post insertion of the copper IUCD was considered but not accepted. The decision for the frequency of follow-up visits was considered in the context of programmatic implementation feasibility and capacity (National Contraception Clinical Guidelines current do not make this provision). The STG has also been amended to include re-examination at 4 to 12 weeks after insertion[10] in order to allow women to be trained on how to feel for the copper IUCD strings after each period.

Post choice termination of pregnancy (CTOP):
-Guidance added

An external comment to add post choice termination of pregnancy (CTOP) to the STG as an indication for copper IUCD insertion has been accepted.

Return for assessment:
-Guidance added

An additional criterion to return for assessment has been added to the STG, highlighting that when strings of the inserted copper IUCD cannot be felt, the woman should be advised to return for assessment. In addition, an editorial review comment to clarify that women should be advised to return for assessment if there is an expulsion of IUCD or if strings of the IUCD become visible was accepted. Furthermore, The STG advises women to return for assessment if the strings of the IUCD cannot be felt, the Committee accepted the clinical editor recommendation for guidance to be added advising women to check the strings of the IUCD monthly to ensure that the device is still in place.

STI testing for women initiating contraception:
-Not added

An external comment recommending routine STI testing for women initiating copper IUCD contraception based on the outcomes of the ECHO trial[11] was not accepted. The NEMLC noted that although the ECHO trial demonstrated a high baseline rate of STIs in African women, the authors did not specifically recommend testing before initiating the contraception method. It was felt that the decision to recommend STI testing should be pragmatically implemented from the National programme based on capacity and resource considerations.

Exclusion of IUCD in women with active or at high risk of STI
-Guidance amended

In line with the National guidelines[12], the STG has been amended to highlight that Copper IUCD is not recommended if a woman has a very high individual likelihood of exposure to STIs, unless other methods are not available or not acceptable.

Interaction of IUCD with antiretrovirals: *Caution text amended*

Following clinical editorial review, for better clarity to the reader, the caution box has been amended indicating that IUCDs are often the most suitable contraceptive for women on enzyme-inducing medicine, because of the absence of drug interactions.

The STG has been amended including editorial amendments as follows:

Amended From:	Amended To:

[10] Bayer. Nova-T 380®. Package insert.2011

[11] Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial Consortium. HIV incidence among women using intramuscular depot medroxyprogesterone acetate, a copper intrauterine device, or a levonorgestrel implant for contraception: a randomised, multicentre, open-label trial. Lancet. 2019;394(10195):303–13. doi: 10.1016/S0140-6736(19)31288-7.

[12] NDoH.National Contraception Clinical Guidelines.2019. https://knowledgehub.health.gov.za/elibrary/national-contraception-clinical-guidelines-2019

Dual protection with barrier methods is recommended to reduce the risk of STIs including HIV. The IUCD is a long-term contraceptive method that is effective, safe and reversible. It has no hormonal effects or drug interactions..It does not require daily adherence or frequent follow up.	Dual protection with barrier methods is recommended to reduce the risk of STIs including HIV. The copper IUCD (also known as the Copper T) is a long-term contraceptive method that is effective, safe and reversible. It has no hormonal effects or drug interactions. It does not require daily adherence or frequent follow up.
HIV infection is NOT a contra-indication to the use of an IUCD. **IUCDs are often the most suitable contraceptive for women on antiretrovirals and other enzyme-inducing medicines, because of the absence of drug interactions.**	**HIV infection is NOT a contra-indication to the use of an IUCD.** **IUCDs are often the most suitable contraceptive for women on enzyme-inducing medicines, because of the absence of drug interactions.**
Copper IUCD, e.g.: Cu T380A, 380mm² copper device. Devices with lower copper surface area are not recommended. The IUCD can be inserted at any time during the menstrual cycle, once pregnancy has been excluded (by clinical history or with a pregnancy test if required). Insertion at menstruation may be easier for the woman and results in less discomfort and spotting. Copper IUCDs may be inserted immediately postpartum or post miscarriage (within 48 hours) by specially trained health care professionals, provided that no contra-indications are present (chorioamnionitis, ruptured membranes for more than 18 hours, or postpartum haemorrhage). Alternatively, an IUCD may be inserted at least 4 weeks postpartum. *LoE:IIb*[i] Advise women when to return: Expulsion of IUCD or if strings of the IUCD protrude. Complications (excessive bleeding, excessive pain, fever, or foul-smelling discharge). Routine follow-up after 3–6 weeks. *LoE:IVb*[ii] Copper IUCD is not recommended for women with menorrhagia, active pelvic inflammatory disease (PID), purulent cervicitis, unexplained uterine bleeding, cervical and endometrial cancers or other uterine abnormalities. <u>For mild pain and discomfort after insertion:</u> Ibuprofen, oral, 400 mg 8 hourly with or after a meal as needed for up to 3 days. **REFERRAL** Excessive pain or bleeding after insertion. Signs of infection within 7 days of insertion (e.g. fever, abdominal pain and/or foul-smelling discharge). Abnormal bleeding for > 3 months.	Copper IUCD, e.g.: Cu T380A, 380mm² copper device. Devices with lower copper surface area are not recommended. The IUCD can be inserted at any time during the menstrual cycle, once pregnancy has been excluded (by clinical history or with a pregnancy test if required). Insertion at menstruation may be easier for the woman and results in less discomfort and spotting. Copper IUCDs may be inserted immediately postpartum or post miscarriage and post choice termination of pregnancy (CTOP) (within 48 hours) by specially trained healthcare professionals, provided that no contra-indications are present (chorioamnionitis, ruptured membranes for more than 18 hours, or postpartum haemorrhage). Alternatively, an IUCD may be inserted at least 4 weeks postpartum. *LoE:IIb*[iii] Advise women to check the strings of the IUCD monthly to ensure that the device is still in place. Advise women when to return: Expulsion of IUCD or if strings of the IUCD become visible. Complications (excessive bleeding, excessive pain, fever, or foul-smelling discharge). Routine follow-up at 4–12 weeks after insertion. *LoE:IVb*[iv] If the strings of the IUCD cannot be felt. Copper IUCD is not recommended for women with menorrhagia, active STI, active pelvic inflammatory disease (PID), purulent cervicitis, unexplained uterine bleeding, cervical and endometrial cancers or other uterine abnormalities. If a woman has a very high individual likelihood of exposure to STIs, she should generally not have a Copper IUCD inserted unless other methods are not available or not acceptable. <u>For mild pain and discomfort after insertion:</u> Ibuprofen, oral, 400 mg 8 hourly with or after a meal as needed for up to 3 days. **REFERRAL** Excessive pain or bleeding after insertion. Signs of infection within 7 days of insertion (e.g. fever, abdominal pain and/or foul-smelling discharge). Abnormal; or heavy menstrual bleeding for > 3 months.

7.2.1 Subdermal implant

<u>Timing of insertion:</u>

-Amended

<u>Concomitant use with Hepatic enzyme inducing medicines:</u>

-Guidance amended

<u>Concomitant use with dolutegravir:</u>

Guidance added

<u>Insertion of etonogestrel 68 mg implant:</u>

Guidance amended with extensive editorial amendments

The timing of insertion of the subdermal implant has been revised. The implant should be inserted between Day 1 (first day of menstrual bleeding) and Day 5 of the menstrual cycle[13] with the contraceptive effect being achieved within 24 hours of placement.
For better clarity, the STG has also been amended to highlight that subdermal implants are not contraindicated when using drugs which induce the metabolism of progestins[14]-[15]. However, it is emphasised that patients should be advised to use non-hormonal contraceptive methods during the time of concomitant use.
Additionally, the STG has been amended to highlight that subdermal implants may effectively be combined with dolutegravir-based ART regimens[16].
In line with the revised package insert[17] of the product currently on the state contract, the guidance for the safe insertion and removal of the etonogestrel implant has been revised extensively with editorial amendments. In addition, an editorial comment to consider revising the product specific guidance included in the STG in the event that a different product is procured was reviewed, the STG text has been amended to indicate that readers should refer to the specific professional information for detailed guidance on the product available on the National contract.

The STG has been amended as follows:

Amended From:	Amended To:
SUBDERMAL IMPLANT Z30.0/Z30.4/Z30.8	**SUBDERMAL IMPLANT** Z30.0/Z30.4/Z30.8
Dual protection with barrier methods is recommended to reduce the risk of STIs, including HIV.	Dual protection with barrier methods is recommended to reduce the risk of STIs, including HIV.
The subdermal implant is an effective, safe, reversible, and convenient long-term contraceptive method that does not require daily adherence or frequent follow-up.	The subdermal implant is an effective, safe, reversible, and convenient long-term contraceptive method that does not require daily adherence or frequent follow-up.
Progestin-only subdermal implant contraceptive, e.g.: Etonogestrel, subdermal, 68 mg, single-rod implant.	Progestin-only subdermal implant contraceptive, e.g.: Etonogestrel, subdermal, 68 mg, single-rod implant.
The progestin-only subdermal implant can be inserted at any time during the menstrual cycle, once pregnancy has been excluded. If the implant is inserted within 7 days of the onset of the menstrual cycle the contraceptive effect is achieved on the day of insertion.	The progestin-only subdermal implant can be inserted at any time during the menstrual cycle, once pregnancy has been excluded. If the implant is inserted within day 1 and day 5 of the onset of the menstrual cycle the contraceptive effect is achieved within 24 hours of placement.
The main reason for discontinuation of the implant is irregular bleeding. This requires good counselling before the implant is inserted to inform women that this side effect can occur and can be treated. See Section 7.6: Breakthrough bleeding with contraceptive use.	The main reason for discontinuation of the implant is irregular bleeding. This requires good counselling before the implant is inserted to inform women that this side effect can occur and can be treated. See Section 7.6: Breakthrough bleeding with contraceptive use.
Progestin-only hormonal contraceptives are contraindicated in certain conditions e.g. unexplained vaginal bleeding, active liver disease. Consult the package insert in this regard.	The progestin-only subdermal implant is contraindicated in certain conditions e.g. unexplained vaginal bleeding, active liver disease. Consult the package insert in this regard.
LoE:IIIb[v]	*LoE:IIIb*[vi]
CAUTION Medicines that induce the metabolism of progestins could reduce contraceptive efficacy. These medicines include efavirenz, rifampicin, phenytoin, carbamazepine, and phenobarbital. Women on these medicines should be advised to use alternate contraceptive methods such as the copper IUCD or DMPA. If the client chooses to use the implant, then she should be advised to use dual contraception.	**CAUTION** Medicines that induce the metabolism of progestins could reduce contraceptive efficacy. These medicines include efavirenz, rifampicin, phenytoin, carbamazepine, and phenobarbital. Women receiving any of the above listed hepatic enzyme-inducing medicines should be advised that the efficacy of the subdermal implant may be reduced. If it is decided to continue using the subdermal implant, women should be advised to also use a non-hormonal contraceptive method dur-

[13] Organon SA. Implanon NXT® 68 mg Implant ®. Package insert.2019

[14] Stalter RM, Amorim G, Mocello AR, Jakait B, Shepherd BE, Musick B, Bernard C, Bukusi EA, Wools-Kaloustian K, Cohen CR, Yiannoutsos CT, Patel RC; Implant/Efavirenz Study Group and the East Africa IeDEA regional consortium. Contraceptive implant use duration is not associated with breakthrough pregnancy among women living with HIV and using efavirenz: a retrospective, longitudinal analysis. J Int AIDS Soc. 2022 Sep;25(9):e26001. doi: 10.1002/jia2.26001. PMID: 36073977; PMCID: PMC9454412.

[15] Todd CS, Lorenzetti L, Mussa A, Ridgeway K, Morroni C, Nanda K. Drug-drug interactions between antiretrovirals and hormonal contraception: An updated systematic review. Contraception. 2024 Oct;138:110490. doi: 10.1016/j.contraception.2024.110490. Epub 2024 May 16. PMID: 38762199.

[16] Bishop IJ, Gertz AM, Simon B, Tawe L, Lechiile K, Liu S, Teodoro N, Mussa A, Avalos A, Malima S, Maotwe T, Mokganya L, Westhoff CL, Morroni C. Etonogestrel concentrations among contraceptive implant users in Botswana using and not using dolutegravir-based antiretroviral therapy. Contraception. 2020 Sep;102(3):174-179. doi: 10.1016/j.contraception.2020.04.019. Epub 2020 May 7. PMID: 32387328.

[17] Implanon NXT® 68mg Implant.Package insert.South Africa.Revision:27 August 2019

Insertion and removal procedures Participation in a training session is strongly recommended to become familiar with the use of the subdermal implants and techniques for insertion and removal. Only health care professionals familiar with these procedures should insert and remove subdermal implants, under aseptic conditions. Insert the implant **subdermally just under the skin of the upper non-dominant arm.** **Important: Refer to the package inserts for detailed information**. <u>Insertion of etonogestrel 68 mg implant:</u> Insertion should only be performed with the preloaded applicator. Have the woman lie on her back on the examination table with her non-dominant arm flexed at the elbow and externally rotated so that her wrist is parallel to her ear and her hand is positioned next to her head. Identify anatomical surface markings to establish the area of insertion, which is the inner side of the non-dominant upper arm about 8–10 cm above the medial epicondyle of the humerus, avoiding the sulcus (groove) between the biceps and triceps muscle and the large blood vessels and nerves situated in the neurovascular bundle deeper in the subcutaneous tissue. Clean the insertion site with an antiseptic solution. Anaesthetise the insertion area. Mark the insertion site with a marker. Insert the implant subdermally:. Remove the transparent protection cap by sliding it horizontally in the direction of the arrow, away from the needle. Puncture the skin with the tip of the needle slightly angled less than 30° relative to the skin surface. Lower the applicator to a horizontal position. While lifting the skin with the tip of the needle, slide the needle to its full length. You should be able to see the applicator just below the skin. Be seated, looking at the applicator from the side and NOT from above to clearly see the insertion and positioning of the needle just under the skin. While keeping the applicator in the same position and the needle inserted to its full length, unlock the purple slider by pushing it slightly down. Move the slider fully back until it stops. The implant is now in its final subdermal position. Remove the applicator. Always verify the presence of the implant in the woman's arm immediately after insertion by palpation and allow her to feel the implant as well. Apply sterile gauze with a pressure bandage to minimise bruising. The woman may remove the pressure bandage in 24 hours and the small bandage over the insertion site after 3–5 days. <u>Insertion of levonorgestrel 2 x 75 mg implants:</u> Clean the woman's upper arm with an antiseptic solution. The optimal insertion area is in the medial aspect of the upper arm about 6-8 cm above the fold of the elbow. Use the scalpel to make a small incision (about 2 mm) just through the dermis of the skin. Alternatively, the trocar may be inserted directly through the skin without making an incision. The implants will be inserted subdermally, in the shape of a narrow V, opening towards the armpit. Anesthetise two areas about 4.5 cm long, to mimic the V shape of the implantation site. Mark the insertion site with a marker. Open the implant pouch by pulling apart the film of the pouch and let the two implants drop on a sterile cloth. Note: Always use sterile gloves or forceps when handling the implants. If an implant is contaminated, e.g. falls on the floor leave it for later disposal. Open a new package and continue with the procedure. The implant is provided with a disposable trocar that is sharp enough to penetrate the skin directly. Thus the disposable trocar can be used to puncture the skin and insert the rods, without the need for an incision. The trocar has two marks. One mark is close to the handle and one close to the tip. When inserting the implants, the mark closest to the handle indicates how far the trocar should be introduced under the skin before loading each implant. The mark closest to the tip indicates how much of the trocar should be left under the skin after the insertion of the first implant. When inserting the trocar, avoid touching the part of the trocar that will go under the skin. Once the tip of the trocar is beneath the skin it should be directed along the subdermal plane horizontally by pointing it slightly upwards and raising the skin (tenting). Failure to keep the trocar in the subdermal plane may	ing the time of concomitant use (the subdermal implant is not contra-indicated when using the above medicines). Dolutegravir, however, can be effectively be used in combination with subdermal implants. **Insertion and removal procedures** Participation in a training session is strongly recommended to become familiar with the use of the subdermal implants and techniques for insertion and removal. Only health care professionals familiar with these procedures should insert and remove subdermal implants, under aseptic conditions. Insert the implant **subdermally just under the skin of the upper non-dominant arm.** **Important: Refer to the specific professional information for detailed guidance on the product available on the National contra** <u>Insertion of etonogestrel 68 mg implant:</u> Insertion should only be performed with the preloaded applicator. Have the woman lie on her back on the examination table with her non-dominant arm flexed at the elbow and externally rotated, so that her hand is underneath her head (or as close as possible). Identify the insertion site, which is at the inner side of the non-dominant upper arm. The insertion site is overlying the triceps muscles about 8 to10 cm from the medial epicondyle of the humerus and 3 to 5 cm posterior to the sulcus (groove) between the biceps and triceps muscles). This location is intended to avoid the large blood vessels and nerves lying within and surrounding the sulcus. If it is not possible to insert the implant in this location (e.g. in women with thin arms), it should be inserted as far posterior from the sulcus as possible Make two marks with a surgical marker: First, mark the spot where the implant will be inserted, and second, mark a spot at 5 centimetres proximal (toward the shoulder) to the first mark This second mark (guiding mark) will later serve as a direction guide during insertion (guiding mark). *LoE:IVb*[vii] Clean the insertion site with an antiseptic solution. Anaesthetise the insertion area. Insert the implant subdermally:. - Hold the applicator just above the needle at the textured surface area. Remove the transparent protection cap by sliding it horizontally in the direction of the arrow away from the needle Puncture the skin with the tip of the needle slightly angled less than 30° relative to the skin surface. If you insert the needle past the bevel, withdraw it until only the bevel is beneath the skin. Lower the applicator to a horizontal position. To facilitate subdermal placement, lift the skin with the needle, while sliding the needle to its full length. You should be able to see the applicator just below the skin. Be seated, looking at the applicator from the side and NOT from above to clearly see the insertion and positioning of the needle just under the skin. While keeping the applicator in the same position and the needle inserted to its full length. The purple slider should be unlocked by pushing it slightly down). The slider should be moved fully back until it stops. The implant is now in its final subdermal position. Remove the applicator. Always verify the presence of the implant in the woman's arm immediately after insertion by palpation and allow her to feel the implant as well. Apply sterile gauze with a pressure bandage to minimise bruising. The woman may remove the pressure bandage in 24 hours and the small bandage over the insertion site after 3–5 days. <u>Insertion of levonorgestrel 2 x 75 mg implants:</u> Clean the woman's upper arm with an antiseptic solution. The optimal insertion area is in the medial aspect of the upper arm about 6-8 cm above the fold of the elbow. The implants will be inserted subdermally, in the shape of a narrow V, opening towards the armpit. Anesthetise two areas about 4.5 cm long, to mimic the V shape of the implantation site. Mark the insertion site with a marker.

result in deep placement of the implants, causing a more difficult removal. Throughout the insertion procedure, the trocar should be oriented with the bevel up. Advance the trocar beneath the skin about 5.5 cm from the incision to the mark closest to the handle of the trocar. Do not force the trocar, and if you feel any resistance, try another direction. Remove the plunger when the trocar is advanced to the correct mark. Load the first implant into the trocar with either tweezers or fingers. Push the implant gently with the plunger to the tip of the trocar until you feel resistance. Never force the plunger. Hold the plunger steady and pull the trocar back along it until it touches the handle of the plunger. It is important to keep the plunger steady and not to push the implant into the tissue. Do not completely remove the trocar until both implants have been placed. The trocar is withdrawn only to the mark closest to its tip. When you can see the mark near the tip of the trocar in the incision, the implant has been released and will remain in place beneath the skin. You can check this by palpation. Insert the second implant next to the first one, to form a V shape. Fix the position of the first implant with the left fore-finger and advance the trocar along the side of the finger. This will ensure a suitable distance between implants. To prevent expulsions, leave a distance of about 5 mm between the incision and the ends of the implants. You can check their correct position by cautious palpation of the insertion area. After inserting the second implant, press the edges of the incision together, close with a skin closure and dress the wound. Advise the woman to keep the insertion area dry for 3 days. The gauze and the bandage may be removed as soon as the incision has healed, usually after 3–5 days. <u>For pain after insertion:</u> Ibuprofen, oral, 400 mg 8 hourly with or after a meal as needed for up to 5 days. <u>Removal of progestin-only subdermal implants:</u> Remove etonogestrel implants at the end of 3 years and levonorgestrel implants at the end of 5 years. Locate the implant/s by palpation. If impalpable refer for ultrasound removal. Clean the removal site with an antiseptic solution. Anaesthetise the removal area. Push down the proximal end of the implant and a bulge may appear to indicate the distal end of the implant. Make a 2-4 mm vertical incision with the scalpel close to the distal end of the implant, towards the elbow. Remove the implant very gently, using a small forceps (preferably curved mosquito forceps). Where an implant is encapsulated, dissect the tissue sheath to remove the implant with the forceps. Confirm that the complete implant has been removed by measuring the length (etonogestrel rod: 40 mm; levonorgestrel rods: 43 mm). Close the incision with a steristrip or plaster and dress. Advise the woman to keep the arm dry for a few days. **REFERRAL** Heavy or prolonged bleeding, despite treatment with COCs. Infection at insertion site, inadequately responding to initial course of antibiotic treatment. See Section 5.4.3: Cellulitis. Failure to locate an implant (in the arm) by palpation.	Use the scalpel to make a small incision (about 2 mm) just through the dermis of the skin. Alternatively, the trocar may be inserted directly through the skin without making an incision. Open the implant pouch by pulling apart the film of the pouch and let the two implants drop on a sterile cloth. Note: Always use sterile gloves or forceps when handling the implants. If an implant is contaminated, e.g. falls on the floor leave it for later disposal. Open a new package and continue with the procedure. The implant is provided with a disposable trocar that is sharp enough to penetrate the skin directly. Thus, the disposable trocar can be used to puncture the skin and insert the rods, without the need for an incision. The trocar has two marks. One mark is close to the handle and one close to the tip. When inserting the implants, the mark closest to the handle indicates how far the trocar should be introduced under the skin before loading each implant. The mark closest to the tip indicates how much of the trocar should be left under the skin after the insertion of the first implant. When inserting the trocar, avoid touching the part of the trocar that will go under the skin. Once the tip of the trocar is beneath the skin it should be directed along the subdermal plane horizontally by pointing it slightly upwards and raising the skin (tenting). Failure to keep the trocar in the subdermal plane may result in deep placement of the implants, causing a more difficult removal. The trocar should be oriented with the bevel up throughout the insertion procedure.. Advance the trocar beneath the skin about 5.5 cm from the incision to the mark closest to the handle of the trocar. Do not force the trocar; if you feel any resistance, try another direction. Remove the plunger when the trocar is advanced to the correct mark. Load the first implant into the trocar with either tweezers or fingers. Push the implant gently with the plunger to the tip of the trocar until you feel resistance. Never force the plunger. Hold the plunger steady and pull the trocar back along it until it touches the handle of the plunger. It is important to keep the plunger steady and not to push the implant into the tissue. Do not completely remove the trocar until both implants have been placed. The trocar is withdrawn only to the mark closest to its tip. When you can see the mark near the tip of the trocar in the incision, the implant has been released and will remain in place beneath the skin. You can check this by palpation. Insert the second implant next to the first one, to form a V shape. Fix the position of the first implant with the left fore-finger and advance the trocar along the side of the finger. This will ensure a suitable distance between implants. To prevent expulsions, leave a distance of about 5 mm between the incision and the ends of the implants. You can check their correct position by cautious palpation of the insertion area. After inserting the second implant, press the edges of the incision together, close with a skin closure and dress the wound. Advise the woman to keep the insertion area dry for 3 days. The gauze and the bandage may be removed as soon as the incision has healed, usually after 3–5 days. <u>For pain after insertion:</u> Ibuprofen, oral, 400 mg 8 hourly with or after a meal as needed for up to 5 days. <u>Removal of progestin-only subdermal implants:</u> Remove etonogestrel implants at the end of 3 years and levonorgestrel implants at the end of 5 years. Locate the implant/s by palpation. If impalpable refer for ultrasound guided removal. Mark the distal end (end closest to the elbow) e.g. with a surgical marker Clean the removal site with an antiseptic solution. Anaesthetise the removal area. Inject the local anaesthetic under the implant to keep the implant close to the skin surface Push down the proximal end of the implant and a bulge may appear to indicate the distal end of the implant. Make a longitudinal (parallel to the implant) incision of approximately 2 mm towards the elbow . Very gently remove the implant, using a small forceps (preferably curved mosquito forceps). Where an implant is encapsulated, dissect the tissue sheath to remove the implant with the forceps. Confirm that the complete implant has been removed by measuring the length (etonogestrel rod: 40 mm; levonorgestrel rods: 43 mm). Close the incision with a steristrip or plaster and dress. Advise the woman to keep the arm dry for a few days.

	REFERRAL Heavy or prolonged bleeding, despite treatment with COCs. Infection at the insertion site, inadequately responding to an initial course of antibiotic treatment. See Section 5.4.3: Cellulitis. Failure to locate an implant (in the arm) by palpation.

7.2.2 LEVONORGESTREL INTRA-UTERINE DEVICE (LNG-IUD)

Title of section: *Not amended and editorial amendments added.*

An external comment to rename this section Levonorgestrel containing intra-uterine device (LNG-IUD) to allow for other progestin-containing devices that may be used in future was considered but not accepted at this stage. Minor editorial amendments to the referral criteria have also been made to include heavy menstrual bleeding as an indication for referral. ICD 10 code Z30.5 (Z30.5 - Surveillance of (intrauterine) contraceptive device) has been added and ICD 10 code Z30.4 (Surveillance of contraceptive drugs) removed.

The STG has been amended as follows:

Amended From:

REFERRAL
Excessive pain or bleeding after insertion.
Signs of infection within 7 days of insertion (e.g. fever, abdominal pain and/or foul-smelling discharge).
Abnormal bleeding for > 3 months.
First time migraine or severe headaches.

Amended To:

REFERRAL
Excessive pain or bleeding after insertion.
Signs of infection within 7 days of insertion (e.g. fever, abdominal pain and/or foul-smelling discharge).
Abnormal or heavy menstrual bleeding for > 3 months.
First time migraine or severe headaches.

7.2.3 INJECTABLE

When to start the injection: *Amended*

The STG guidance for initiation of the progestin-only injectable contraceptive has been amended, recommending treatment to be started immediately postpartum in both breastfeeding and non-breastfeeding women if no other method is acceptable or available. It was noted that progestin-only injectable are classified as WHO Medical eligibility criteria for contraceptive use (MEC) category 3[18], whereas classified as MEC category 2 under the National contraceptive guidelines[19].

Risk of HIV acquisition associated with progestin injectable contraceptives: *Removed*

The previous STG recommendation advised for dual contraception with barrier methods in view of the uncertainty of the risk of HIV acquisition associated with using the progestin injectable contraceptives at the time of chapter review. This recommendation has been removed. In line with the ECHO trial results, there is no substantial difference in HIV acquisition among the various contraceptive methods evaluated (DMPA-IM, a copper IUD, or a LNG implant) in the trial, all methods were safe and highly effective[20].

[18] World Health Organization. Reproductive Health. Medical eligibility criteria for contraceptive use. World Health Organization; 2015.

[19] NDoH.National Contraception Clinical Guidelines.2019. https://knowledgehub.health.gov.za/elibrary/national-contraception-clinical-guidelines-2019

[20] Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial Consortium. HIV incidence among women using intramuscular depot medroxyprogesterone acetate, a copper intrauterine device, or a levonorgestrel implant for contraception: a randomised, multicentre, open-label trial. Lancet. 2019 Jul 27;394(10195):303-313. doi: 10.1016/S0140-6736(19)31288-7. Epub 2019 Jun 13. Erratum in: Lancet. 2019 Jul 27;394(10195):302. doi: 10.1016/S0140-6736(19)31408-4. PMID: 31204114; PMCID: PMC6675739.

Late injection:

-Guidance amended and cross reference to Section 7.4: Contraception, Emergency added

-Editorial amendments added

The STG has been amended, allowing for a late reinjection grace period for up to 4 weeks for Depot medroxyprogesterone acetate (DMPA) and 2 weeks late reinjection grace period for norethisterone enanthate (NET-EN). Delayed reinjection for 4 weeks with DMPA and 2 weeks with NET-EN does not increase pregnancy risk and could increase contraceptive continuation[21] .This recommendation is also In line with the updated WHO Family planning handbook for providers[22]. In addition, an editorial review comment adding a cross reference to Section 7.4: Contraception, emergency in the event of a late injection was accepted.

An editorial review comment to incorporate the SAHPRA professional information for depot medroxyprogesterone SC, Sayana® 104 mg/0.65 ml, which recommends administration no later than 14 weeks after last injection was not accepted. For pragmatism, the Committee felt that the updated STG recommendation allowing up to 4 weeks late injection applies to both DMPA (long-acting) IM and SC formulations.

The STG has been amended as follows:

<table>
<tr>
<td>Amended From:
Late injection
If it has been <2 weeks since the missed injection, the next injection can be given without loss of protection. Continue with dual contraceptive method, i.e. condom in combination with the injection.
If it has been >2 weeks since the missed injection, exclude pregnancy:
<table>
<tr><th>Pregnancy test positive</th><th>Pregnancy test negative or unavailable</th></tr>
<tr><td>Refer for ante-natal care (See Section 6.4: Antenatal care).
or
TOP, see Section 6.3: Termination of pregnancy (TOP).</td><td>Provide emergency contraception, if indicated (see Section: 7.4 Contraception, emergency).
Administer the next injection.
Advise the woman to abstain from intercourse or use condoms to prevent pregnancy for the next 7 days.</td></tr>
</table>
</td>
<td>Amended To:
Late injection
The next injection can be as much as 4 weeks late if using the medroxyprogesterone acetate DMPA (long-acting),or 2 weeks late if using norethisterone enanthate (NET-EN).
» Injectable contraceptive may be administered later than recommended if more >4 weeks late for DMPA or >2 weeks late for NET-EN the next injection can receive, if:
• She has not had sex since 2 weeks after the scheduled date of her injection, or
• She has used a backup method or has taken emergency contraceptive pills after any unprotected sex since 2 weeks after the scheduled date of her injection, or
• She is fully or nearly fully breastfeeding and she gave birth less than 6 months ago.
However, in all three cases she will need a backup method for the first 7 days after the injection
» Assess the need for emergency contraception in the event of a late injection (See Section 7.4: Contraception, Emergency).</td>
</tr>
</table>

Depot medroxyprogesterone (long acting), SC: *Added outside of therapeutic class.*

Following the 2020 NEMLC review[23] conditionally recommending depot medroxyprogesterone acetate SC (DMPA-SC) as a therapeutic alternative in the progestin-only injectable contraceptive therapeutic class. The NEMLC felt at the time that there is no preference for either formulation as they seem to have similar therapeutic efficacy and safety profile. The recommendation was ratified by NEMLC pending the registration of a product by South African Health Products Authority (SAHPRA) which includes the self-injection label and additional local feasibility and acceptability studies to determine if the self-administration option is a viable option in the South African context. In 2024, a follow-up review was submitted and adjudicated by NEMLC providing further evidence on the SAHPRA registration, pricing and user acceptability studies for the consideration of DMPA-SC as an alternative choice of contraception method outside of the progestin-only injectable therapeutic class. NEMLC has recommended DMPA-SC as an EML

[21] Steiner MJ, Kwok C, Stanback J, Byamugisha JK, Chipato T, Magwali T, Mmiro F, Rugpao S, Sriplienchan S, Morrison C. Injectable contraception: what should the longest interval be for reinjections? Contraception. 2008 Jun;77(6):410-4. doi: 10.1016/j.contraception.2008.01.017. Epub 2008 Apr 10. PMID: 18477489

[22] Family Planning: A Global Handbook for Providers (2022 update). Baltimore and Geneva: CCP and WHO, 2022. https://www.who.int/publications/i/item/9780999203705

[23] NDoH Review. Medroxyprogesterone 104mg SC for prevention of pregnancy.2020

item in view of the updated approval by SAHPRA of DMPA-SC for self-administration along with updated evidence of feasibility, acceptability and affordability.

See NEMLC recommendation as tabulated below. A copy of the full review may be accessed on the NHI webpage.

	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
Type of recommendation				**X**	

NEMLC Recommendation: NEMLC suggests that either low dose DMPA-SC or intramuscular progestogen injectables may be used by women for preventing pregnancy. (Conditional recommendation, moderate certainty evidence).

Remarks:
This marks a change of DMPA-SC from a therapeutic interchange option to an EML item and is based on available evidence of efficacy and safety, the change in access given the updated approval of DMPA-SC by the South African Health Products Authority (SAHPRA) for self-administration, along with updated evidence of feasibility, acceptability and affordability.

Rationale: The current review found that there is evidence that DMPA-SC is acceptable to stakeholders, feasible to implement and access, and cost-effective. This is in addition to the previously appraised evidence of safety and efficacy which has not changed since first reviewed in 2020. NEMLC noted that the option for self-administration and expansion of contraceptive options may have important equity implications and public health benefit for women in the South African setting. This recommendation is conditional on the product being available at the indicative price provided herein (R29.63 incl VAT) or less.

Level of Evidence: Review indicator: *Increase in product price*

Monitoring and evaluation considerations:
Patients switching from another contraceptive option to DMPS-SC – has implications for forecasting.

Research priorities:
Acceptability and contraceptive adherence using self-administration in South Africa.

The STG has been amended as follows:

Amended From:	Amended To:
Dual protection with barrier methods is recommended to reduce the risk of STIs, including HIV. □ Progestin-only injectable contraceptive, e.g.: • Medroxyprogesterone (long-acting), IM, 150 mg, 12 weekly. Progestin-only hormonal contraceptives are contraindicated in certain conditions e.g. unexplained vaginal bleeding. Consult the package insert in this regard. When to start the injection » The injection can be started anytime within the menstrual cycle, provided pregnancy has been excluded. If the first injection is given within 7 days of the onset of the menstrual cycle, the contraceptive effect is achieved on the day of the first injection. » If started after day 7,advise the woman to abstain from intercourse or use condoms for the next 7 days. » Can be used postpartum. Late injection » If it has been <2 weeks since the missed injection, the next injection can be given without loss of protection. Continue with dual contraceptive method, i.e. condom in combination with the injection.	Dual protection with barrier methods is recommended to reduce the risk of STIs, including HIV. Progestin-only injectable contraceptive, e.g.: Medroxyprogesterone (long-acting), IM, 150 mg, 12 weekly. OR • Medroxyprogesterone (long-acting), SC,104mg, 12 weekly Progestin-only hormonal contraceptives are contraindicated in certain conditions e.g. unexplained vaginal bleeding. Consult the individual professional information in this regard. **Using the Progestin-only IM Injection** When to start the injection The injection can be started anytime within the menstrual cycle, provided pregnancy has been excluded. If the first injection is given within 7 days of the onset of the menstrual cycle, the contraceptive effect is achieved on the day of the first injection. If started after day 7, advise the woman to abstain from intercourse or use condoms for the next 7 days. Can be started immediately postpartum in both breastfeeding and non-breastfeeding women if no other method is acceptable or available.

» If it has been >2 weeks since the missed injection, exclude pregnancy

Pregnancy test positive	Pregnancy test negative or unavailable
Refer for ante-natal care (See Section 6.4: Antenatal care). ***or*** TOP, see Section 6.3: Termination of pregnancy (TOP).	Provide emergency contraception, if indicated (see Section: 7.4 Contraception, emergency). Administer the next injection. Advise the woman to abstain from intercourse or use condoms to prevent pregnancy for the next 7 days.

There is uncertainty of the risk of HIV acquisition associated with progestin injectable contraceptives (Refer to the WHO MEC 2017 guidelines). Dual protection is recommended.

Late injection

The next injection can be as much as 4 weeks late if using the medroxyprogesterone acetate DMPA (long-acting),or 2 weeks late if using norethisterone enanthate (NET-EN).

If more >4 weeks late for DMPA or >2 weeks late for NET-EN the next injection can receive, if:

- She has not had sex since 2 weeks after the scheduled date of her injection, or
- She has used a backup method or has taken emergency contraceptive pills after any unprotected sex since 2 weeks after the scheduled date of her injection, or
- She is fully or nearly fully breastfeeding and she gave birth less than 6 months ago.

However, in all three cases she will need a backup method for the first 7 days after the injection

Using the Progestin-only SC Injection

May be administered by a healthcare professional (HCP) or with adequate training when considered appropriate by the HCP, self-injected by the patient, with medical follow up as necessary.

When to start the injection

» The first injection of 104 mg SC should be given during the first 5 days of a normal menstrual cycle to ensure the client is not pregnant.

» The second and subsequent injections should be given at a 3 month interval (12 -14 weeks).

» Can be started immediately postpartum in both breastfeeding and non-breastfeeding women if no other method is acceptable or available

-Risk of meningiomas with long term use of DMPA: *Caution box added*

In line with the revised SAHPRA professional information for DMPA containing products[24], citing an observational case control study which showed an excess risk of meningioma with use of medroxyprogesterone acetate and other selected progestogens. (injectable medroxyprogesterone acetate, 9/18 061 (0.05%) vs 11/90 305 (0.01%) exposed controls, odds ratio 5.55 (95% confidence interval 2.27 to 13.56))[25]. The STG has thus been amended, adding a caution box to address this signal. In addition, the STG has been amended with guidance for the consideration of alternative contraceptive methods instead of the DMPA- injectable (taking into account client preferences and circumstances) when contraception is required for long term use (e.g., longer than 2 years).

The STG has been amended as follows:

CAUTION

» Alternative contraceptive options should be considered if the continued use of medroxyprogesterone acetate (IM or SC) is extended beyond 2 years. All effective contraceptive options should be considered, taking into account client preferences and circumstances.
» A small increased risk of meningiomas (rare, and mostly benign tumours) have been reported following long-term administration of Medroxyprogesterone acetate (long-acting),
» Medroxyprogesterone (long-acting) should be discontinued if a meningioma is diagnosed.
» Caution is advised when recommending Medroxyprogesterone (long-acting) to patients with a history of meningioma.

7.2.4 ORAL

[24] Depo-Provera®.Professional Information.South Africa.Revision:21 January 2025

[25] Roland N, Neumann A, Hoisnard L, Duranteau L, Froelich S, Zureik M, Weill A. Use of progestogens and the risk of intracranial meningioma: national case-control study. BMJ. 2024 Mar 27;384:e078078. doi: 10.1136/bmj-2023-078078. Erratum in: BMJ. 2024 Mar 28;384:q776. doi: 10.1136/bmj.q776. PMID: 38537944; PMCID: PMC10966896.

Triphasic preparations: *Classification retained*

An external comment to rename triphasic oral preparations to multiphasic preparation as triphasic preparations a generally considered as old generation was not accepted. The WHO still classifies oral contraceptives as monophasic, biphasic, and triphasic and in line, the STG has remained unchanged.

When to start the pill: *Guidance added*

The STG currently recommends that the pill, if started at any other time outside the menstrual cycle, has to be taken for at least 7 days to protect against pregnancy. Guidance has now been added recommending condom use during this time.

Non-liver enzyme inducing medicines (Lamotrigine): *Guidance amended, and heading removed*

The interaction between oral contraceptives and lamotrigine has been highlighted, recommending the use of a backup method (e.g. barrier contraception) if short term lamotrigine is required, or a change to IUCD or progesterone only methods if long term use of lamotrigine is required. A an external comment to include in the STG that the contraceptive effectiveness of COCs might be compromised when lamotrigine is taken concurrently has not be accepted due to insufficient supportive evidence. The lowering of contraceptive effect by the concurrent use of lamotrigine and oral contraceptives is not expected[26]-[27]. In addition, The Committee accepted an editorial review comment to remove the heading "*non-liver enzyme inducing medicines"* as the purported mechanism of the interaction between lamotrigine and COCs is that of liver enzyme induction.

The STG has been amended as follows:

Amended From:
» Exclude pregnancy.
» Start anytime within the menstrual cycle, but it is advisable to start during menses.
» If the first pill is given between days 1 and 5 of the menstrual cycle the contraceptive effect is achieved immediately.
» If the pill is started at any other time, it needs to be taken for at least 7 days before it protects against pregnancy.

Non-liver enzyme inducing medicines
Lamotrigine:
» Lowering of contraceptive effect not expected.
» Oral contraceptives may reduce lamotrigine concentration by 50%, increasing the risk of seizures. Consider alternative dual contraception method.

Amended To:
» Exclude pregnancy.
» Start anytime within the menstrual cycle, but it is advisable to start during menses.
» If the first pill is given between days 1 and 5 of the menstrual cycle the contraceptive effect is achieved immediately.
» If the pill is started at any other time, it needs to be taken for at least 7 days before it protects against pregnancy. The use of condoms is recommended

Lamotrigine:
» Lowering of contraceptive effect not expected.
» Oral contraceptives may reduce lamotrigine concentration, increasing the risk of seizures. Change to IUCD or progesterone only methods i.e (levonorgestrel implant or etonogestrel implant or LNG-IUD) if lamotrigine is going to be used long term.

7.3 CONTRACEPTION, BARRIER METHODS

ICD 10 codes Z30.4/Z30.5 removed, editorial amendments

Following clinical editorial review, the following ICD 10 codes were removed:
Z30.4 - Surveillance of contraceptive drugs

[26] Gaffield ME, Culwell KR, Lee CR. The use of hormonal contraception among women taking anticonvulsant therapy. Contraception. 2011 Jan;83(1):16-29. doi: 10.1016/j.contraception.2010.06.013. Epub 2010 Sep 15. PMID: 21134499.

[27] Family Planning: A Global Handbook for Providers (2022 update). Baltimore and Geneva: CCP and WHO, 2022. https://www.who.int/publications/i/item/9780999203705

Z30.5 - Surveillance of (intrauterine) contraceptive drugs

Including some editorial amendments, the STG Has been amended as follows:

Amended From	Amended To
Z30.0/Z30.4/Z30.5 Condoms (male and female) alone are not the most effective contraceptive method and should be used in combination with other contraceptive methods (e.g. copper IUCD). Condoms are recommended to reduce the risk of the acquisition of STIs and HIV infection. Condoms (male and female) or other barrier methods may be an option for contraception where other methods are contraindicated.	Z30.0 Condoms (male and female) alone are the least effective contraceptive method and should be used in combination with other contraceptive methods (e.g. copper IUCD). Condoms are recommended to reduce the risk of the acquisition of HIV infection and other STIs. Condoms (male and female) or other barrier methods may be an option for contraception where other methods are contraindicated.

7.4 CONTRACEPTION, EMERGENCY

Ulipristal acetate: *Under consideration for review*

Ulipristal acetate is currently proposed for consideration for NEMLC review in the next review cycle as an alternative for levonorgestrel for the management of emergency contraception.

Frequent use of emergency contraceptive: *Guidance added*

An external comment to include guidance for women who use emergency contraceptive frequently was accepted. Guidance to provide counselling for consideration of a longer acting and more effective family planning method has been added.

The STG has been amended as follows:

A woman who needs emergency contraception often should be counselled to consider a longer acting and more effective family planning method.

Double dose of levonorgestrel for patients on hepatic enzyme inducer drugs: *Guidance added*

Dosing guidance on doubling the dose of levonorgestrel in patients using hepatic enzyme inducer drugs has been added. To be taken as two x 1.5 mg tablets taken as a single dose, or if the dedicated product is not available, use COCs containing 30 µg ethinylestradiol + 150 µg levonorgestrel (e.g. Nordette/Oralcon). Six tablets followed by six tablets 12 hours later. A clinical editorial comment that the guidance for this section be incorporated outside of the caution box to avoid being missed by the reader which was accepted by the Committee.

Use of levonorgestrel for patients on Enzyme inhibitor drugs (such as ketoconazole, fluconazole): *Guidance added*

A recommendation to have a copper IUCD inserted or reduce the dose of levonorgestrel in patients on Enzyme inhibitor drugs requiring emergency contraception has been added. Enzyme inhibitors (such as ketoconazole, fluconazole) significantly increase the bioavailability of levonorgestrel thus potentiating nausea and vomiting.

Cross referral to Section 21.3.6.2: Post exposure prophylaxis, rape and sexual assault added

The STG has been amended, adding a cross referral to Section 21.3.6.2: Post exposure prophylaxis, rape and sexual assault for women who need of emergency contraception.Editorial amendments have been added and the STG amended as follows:

Amended From:

Emergency contraception is indicated to prevent pregnancy after unprotected intercourse in women not using contraception or where contraception is likely to be ineffective:

forgotten tablets (See Section 7.2.4: Missed pills)
slipped or broken condom
injectable contraception given >2 weeks late
sexual assault

Emergency contraception after pregnancy is excluded

Do a pregnancy test in all women and female adolescents. Children must be tested and given Emergency contraception from Breast Tanner Stage III.

Copper IUCD, e.g.:
Cu T380A, inserted as soon as possible after unprotected intercourse and not later than 5 days.

OR

Levonorgestrel 1.5 mg, oral, as a single dose as soon as possible after unprotected intercourse, and not later than 5 days.
If the client vomits within 2 hours, repeat the dose.

Advise women that their period should be on time; very rarely is it delayed but it should not be more than 7 days late. If this occurs, they should come back for a pregnancy test.

CAUTION

Emergency contraceptive tablets must be taken as soon as possible, preferably within 72 hours of unprotected intercourse, and not later than 5 days.

Enzyme inducers (including efavirenz and carbamazepine) cause a significant reduction in levonorgestrel concentrations. Women on these medicines should preferably have copper IUCD inserted ***or*** alternatively double the dose of levonorgestrel.

Women > 80 kg or BMI ≥ 30 should also preferably have copper IUCD inserted ***or*** alternatively double the dose of levonorgestrel.

REFERRAL
Women in need of emergency contraception must be referred for HIV counselling and testing and PEP

Amended To:

Emergency contraception is indicated to prevent pregnancy after unprotected intercourse in women not using contraception or where contraception is likely to be ineffective:

Forgotten tablets (See Section 7.2.45: Missed pills)
Slipped or broken condom
Injectable contraception given late (>2 weeks for NET-EN, >4 weeks for DMPA)
Sexual assault

A woman who needs emergency contraception often should be counselled to consider a longer acting and more effective family planning method.

Emergency contraception after pregnancy is excluded

Do a pregnancy test in all women and female adolescents. Children must be tested and given emergency contraception from Breast Tanner Stage III.

Copper IUCD, e.g.:
Cu T380A, inserted as soon as possible after unprotected intercourse and no later than 5 days.

OR

Levonorgestrel 1.5 mg, oral, as a single dose as soon as possible after ~~unprotected intercourse, and not later than 5 days~~.
If the client vomits within 2 hours, repeat the dose.

Advise women that their period should be on time. It is rarely delayed but it should not be more than 7 days late. If this occurs, they should come back for a pregnancy test.

If using enzyme inducing drugs or woman weighs > 80 kg / BMI ≥ 30:

- » It is recommended to have a copper IUCD inserted.
- » If this is not possible, double the dose of levonorgestrel administered:
  - Levonorgestrel, 1.5 mg, oral, 2 tablets taken as a single dose.
- » If the dedicated product is not available, use COCs containing 30 µg ethinylestradiol + 150 µg levonorgestrel (e.g. Nordette/Oralcon):
  - Ethinylestradiol/levonorgestrel, oral, 30 mcg/150 mcg, 6 tablets taken as a single dose, followed by 6 tablets 12 hours later.

CAUTION

- » Emergency contraceptive tablets must be taken as soon as possible, preferably within 72 hours of unprotected intercourse, and not later than 5 days.
- » Enzyme inhibitors (ketoconazole, fluconazole) significantly increase the bioavailability of levonorgestrel and may increase nausea and vomiting. Women taking these medicines should preferably have copper IUCD inserted or reduce the dose of levonorgestrel

REFERRAL
Women in need of emergency contraception must be referred for HIV counselling and testing and PEP (See Section 21.3.6.2: Post exposure prophylaxis, rape and sexual assault).

7.6 BREAKTHROUGH BLEEDING WITH CONTRACEPTIVE USE

Non-steroidal anti-inflammatory drugs (NSAIDS), tranexamic acid and doxycycline: *Under consideration for review*

The STG currently recommends combined oral contraceptives for the management of breakthrough bleeding with hormonal contraception. External comments to consider the addition of other treatment options such as NSAIDS, tranexamic acid and doxycycline in line with other clinical practice recommendations[28]-[29] were not considered at this stage. The requests have been proposed for consideration by NEMLC in the next review cycle.

Breakthrough bleeding with Combined Oral Contraceptives (COC)- *Recommended dose of COCs containing ethinylestradiol amended*

The STG currently recommends changing to a COC containing 35mcg ethinylestradiol if breakthrough bleeding on COC persists. Following market intelligence, it was confirmed that there is currently no commercially available product containing COC with 35mcg ethinylestradiol but only combinations containing 30 mcg ethinylestradiol. It was recommended for the STG to be amended, to recommend COC containing ethinylestradiol 30mcg for the management of breakthrough bleeding on COCs.

The STG has been amended as follows:

Amended From:		Amended To:	
Combined oral contraceptive pill **Unscheduled bleeding with COC usually settles with time.** **Changing to another COC in the first 3 months is not recommended.**	• **Change COC to another COC containing the lowest dose of ethinylestradiol, oral, daily.** **If bleeding persists:** • **Change COC to a COC containing 35 mcg ethinylestradiol, oral, daily.**	**Combined oral contraceptive pill** **Unscheduled bleeding with COC usually settles with time.** **Changing to another COC in the first 3 months is not recommended.**	• **Change COC to another COC containing the lowest dose of ethinylestradiol, oral, daily.** **If bleeding persists:** • **Change COC to a COC containing 30 mcg ethinylestradiol, oral, daily.**

[28] Abdel-Aleem H, d'Arcangues C, Vogelsong KM, Gaffield ML, Gülmezoglu AM. Treatment of vaginal bleeding irregularities induced by progestin only contraceptives. Cochrane Database Syst Rev. 2013 Oct 21;(10):CD003449. doi: 10.1002/14651858.CD003449.pub5. PMID: 24146298.

[29] Australia FP. Guidance for management of troublesome vaginal bleeding with progestogen-only long-acting reversible contraception (LARC). Manly, Qld: Family Planning Alliance Australia, 2015 [Internet].

B: Therapeutic interchange database

Section	Indication	Therapeutic class	INN	strength	unit	NEMLC Recommendation
Intrauterine contraceptive copper device (IUCD)						
7.1	Contraception	Intrauterine contraceptive copper device (IUCD)	IUCD	Cu T380A, 380mm² copper device	1	27 March 2025 Non-hormonal device. Not listed on the therapeutic Interchange database in a class. Market intelligence required for other similar devices and duration of insertion for competitive prices. The chapter has not been updated.
CONTRACEPTION, HORMONAL						
Progestin-only subdermal implant contraceptive						
7.2.1	Contraception	Progestin-only subdermal implant contraceptive	Etonorgestrel	68 mg	1	
7.2.1	Contraception	Progestin-only subdermal implant contraceptive	Levonorgestrel	75 x 2 mg	1	
Progestin-only intrauterine device						
7.2.2	Contraception	Progestin-only intrauterine device	Levonorgestrel	52 mg	1	
		Progestin-only intrauterine device	Levonorgestrel	19.5 mg	1	
Progestin-only injectable contraceptive						
7.2.3	Contraception	Progestin-only injectable contraceptive	Medroxyprogesterone	150mg	1 x IM inj	
7.2.3	Contraception	Progestin-only injectable contraceptive	Norethisterone	200mg	1X IM inj	
ORAL						
Progestin-only: Monophasic preparations (low VTE risk)						
7.2.4	Contraception	Monophasic-progestin only pills - low VTE risk	Levonorgestrel	30mcg	28 tabs	
7.2.4	Contraception	Monophasic-progestin only pills - low VTE risk	Norethisterone	350 mcg	28 tabs	
Monophasic preparations: combination of estrogen and progestin (low to moderate VTE risk)						
7.2.4	Contraception	Monophasic preparations: combination of estrogen and progestin in each pill - low to moderate VTE risk	Levonorgestrel and ethinylestradiol	150/30 mcg	28 Tabs	
7.2.4	Contraception	Monophasic preparations:	Gestodene and ethinylestradiol	75/30 mcg	28 Tabs	

		combination of estrogen and progestin in each pill - low to moderate VTE risk				
7.2.4	Contraceptio n	Monophasic preparations: combination of estrogen and progestin in each pill - low to moderate VTE risk	Desogestrel and Ethinylestradiol	150/30 mcg	28 Tabs	
7.2.4	Contraceptio n	Monophasic preparations: combination of estrogen and progestin in each pill - low to moderate VTE risk	Drospirenone and ethinylestradiol	3/30 mcg	28 Tabs	
Triphasic preparation: combination of estrogen and progestin - low to moderate VTE risk						
7.2.4	Contraceptio n	Triphasic preparation: combination of estrogen and progestin - low to moderate VTE risk	Levonorgestrel and ethinylestradiol	0.05/0.03mg (6); 0.075/0.04 mg (5); 0.125/0.03 mg (10)	28 Tabs	24 April 2025 Retained as the example of class item in the chapter.
7.2.4	Contraceptio n	Triphasic preparation: combination of estrogen and progestin - low to moderate VTE risk	Norethisterone/Norethinderone and ethinylestradiol	0.5/0.035mg (7); 0.75/0.035 mg (7); 1/0.035mg (7)	28 tabs	24 April 2025 No product identified in the SA market
7.2.4	Contraceptio n	Triphasic preparation: combination of estrogen and progestin - low to moderate VTE risk	Norgestimate and ethinylestradiol	0.18/0.035 mg (7); 0.215/0.035 mg (7); 0.25/0.035 mg (7)	28 tabs	24 April 2025 No product identified in the SA market
7.2.4	Contraceptio n	Triphasic preparation: combination of estrogen and progestin - low to moderate VTE risk	Gestodene and ethinylestradiol	0.05/0.03 mg	28 tabs	24 April 2025 No product identified in the SA market
Monophasic preparations: combination of estrogen and progestin (low to moderate VTE risk)						
7.6	Breakthrough bleeding with Progestin subdermal implants	Monophasic preparations: combination of estrogen and progestin in each pill - low to moderate VTE risk	Levonorgestrel and ethinylestradiol	150/30 mcg	28 Tabs	27 March 2025 Updated the chapter to include Ethinylestradiol/ levonorgestrel 150/30 mcg as a therapeutic class recommendation.
7.6	Breakthrough bleeding with Progestin subdermal implants	Monophasic preparations: combination of estrogen and progestin in each pill - low to	Gestodene and ethinylestradiol	75/30 mcg	28 Tabs	

		moderate VTE risk				
7.6	Breakthrough bleeding with Progestin subdermal implants	Monophasic preparations: combination of estrogen and progestin in each pill - low to moderate VTE risk	Desogestrel and Ethinylestradiol	150/30 mcg	28 Tabs	
7.6	Breakthrough bleeding with Progestin subdermal implants	Monophasic preparations: combination of estrogen and progestin in each pill - low to moderate VTE risk	Drospirenone and ethinylestradiol	3/30 mcg	28 Tabs	

Updates after NEMLC meeting 27 March 2025.

Amendments April 2025

Triphasic preparation: combination of estrogen and progestin - low to moderate VTE risk class- *Amendments to class*

Following market intelligence of available products recommended in this class, it was found that only the class example containing Levonorgestrel and ethinylestradiol 0.05/0.03mg is commercially available in the SA market. On the 24 April 2025, NEMLC electronically ratified to retain the oral Triphasic preparations as a class in the chapter pending the availably of the suggested alternative product in future.

South African National Essential Medicine List
Primary Healthcare Medication Review Process
Component: Family Planning

MEDICINE REVIEW

1. Executive Summary

Date: 27 February 2025
Medicine (INN): Subcutaneous (SC) depot medroxyprogesterone acetate (DMPA-SC) (104 mg)
Medicine (ATC): G03AC06
Indication (ICD10 code): Z30.0/Z30.4/Z30.8
Patient population: Women of child-bearing potential (WOCP)
Prevalence of condition: This is for prevention of pregnancy.
Level of Care: Primary Health Care
Prescriber Level: Nurse
Motivator/reviewer name(s): Olawale Ajose (Market Access Africa), Lesley Bamford (NDOH), Megan Christofield (Jhpiego), Naoko Doi (Jhpiego), Sam Lee (Bill & Melinda Gates Foundation), Phatheka Mathola (Jhpiego), Boitumelo Molongoana (Market Access Africa Consultant), Tendai Mvuvu (Market Access Africa), Wandile Ntshangase (Jhpiego), Sibusiso Simelane (Jhpiego), Nicole Young (Bill & Melinda Gates Foundation), Maiyuran Vethakuddikurukkal (Jhpiego), and Thembi Zulu (NDOH).
PTC affiliation: N/A

2. Key findings

- In 2020 the Adult Hospital Level Committee recommended that subcutaneous DMPA should be considered as a therapeutic alternative of the progestogen injectable therapeutic group and there was no preference for either formulation as they seemed to have similar therapeutic efficacy and safety profile.
- NEMLC indicated that the decision to include the product in the EML and STGs for PHC/Adult Hospital STG may be reconsidered upon submission of additional data including, updates regarding SAHPRA registration of the self-injection label, DMPA-SC pricing, and additional user acceptability studies.
- The objective of this medicine review was to appraise evidence on affordability, cost effectiveness and user acceptability of the low dose (104mg) subcutaneous DMPA (DMPA-SC) formulations of injectable contraception compared to the current intramuscular 150mg DMPA formulation,
- In addition to the eight acceptability and continuation studies described in the 2020 submission, 15 additional studies were included in the current review which provide supplementary evidence required to address the insufficiency of data provided in the previous review on price, user acceptability and cost-effectiveness. While no user acceptability studies have been conducted within the South African context, evidence on acceptability is available from other low- and middle-income countries (LMICs) in sub-Saharan African and other regions (including Malawi, Nigeria, Uganda, Ghana, DRC, Nepal, Brazil, Chile, Dominican Republic). The data demonstrates high acceptability rates for DMPA-SC as compared to other contraceptive methods, including the intramuscular (IM) route.
- Self-administration of DMPA-SC is an acceptable option for women and cost-effective strategy from a health systems perspective especially in LMIC settings. This option provides both economic and health benefits by reducing unintended pregnancies, improving maternal health outcomes, and lowering delivery costs. The method of training impacts cost effectiveness, and the learnings from the Senegal and Ugandan studies can be applied in the South

African context to inform best practices for introduction and scale-up. Community-based distribution also shows promise for reducing costs of injectable contraception delivery, self-administration potentially prevents a substantial number of unintended pregnancies and maternal DALYs, leading to significant societal savings.

3. NEMLC Recommendation

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITTEE RECOMMENDATION:					
	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
Type of recommendation				**X**	

NEMLC Recommendation: NEMLC suggests that either low dose DMPA-SC or intramuscular progestogen injectables may be used by women for preventing pregnancy. (Conditional recommendation, moderate certainty evidence).

Remarks:
This marks a change of DMPA-SC from a therapeutic interchange option to an EML item and is based on available evidence of efficacy and safety, the change in access given the updated approval of DMPA-SC by the South African Health Products Authority (SAHPRA) for self-administration, along with updated evidence of feasibility, acceptability and affordability.

Rationale: The current review found that there is evidence that DMPA-SC is acceptable to stakeholders, feasible to implement and access, and cost-effective. This is in addition to the previously appraised evidence of safety and efficacy which has not changed since first reviewed in 2020. NEMLC noted that the option for self-administration and expansion of contraceptive options may have important equity implications and public health benefit for women in the South African setting. This recommendation is conditional on the product being available at the indicative price provided herein (R29.63 incl VAT) or less.

Level of Evidence: Review indicator: *Increase in product price*

Monitoring and evaluation considerations:
Patients switching from another contraceptive option to DMPS-SC – has implications for forecasting.

Research priorities:
Acceptability and contraceptive adherence using self-administration in South Africa.

4. Author Names and Affliations

Name of author(s)/motivator(s)

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No conflicts of interest to declare.

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No conflicts of interest to declare.

Support and affiliation:

- B. Molongoana (Market Access Africa Consultant)

Conflict of interest to declare. NEMLC Member. Ms Molongoana recused herself from all NEMLC discussions related to the review and was not involved in NEMLC decision making regarding DMPA-SC due to her declared conflict of interest as a Market Access Africa Consultant.

National Essential Medicine List Committee Secretariat Support:

- Derusha Frank (Clinton Health Access Initiative)
- Maropeng Rapetsoa (National Department of Health, Essential Drugs Programme)
- Millidhashni Reddy (Supply Chain Technical Assistance)

No conflicts of interest to declare.

5. Introduction/ Background

In South Africa, about one in five women of reproductive age (15–49 years) have an unmet need for contraception, and among adolescent girls and young women (AGYW), there is an even higher unmet need (31% among adolescent girls aged 15-19 and 28% among young women aged 20–24 years) [Jonas et al., 2022] (1). In fact, the country is seeing an unhealthy surge in adolescent and teen pregnancy rates with just less than 125,000 girls aged from 10-19 years giving birth in public sector health facilities during 2023 (2). As a self-care intervention that is also recommended by the World Health Organisation, the introduction of depot medroxyprogesterone acetate subcutaneous, (DMPA-SC), is likely to increase options and autonomy for girls and young women, especially as studies have shown that DMPA-SC uptake in other

countries, is often higher amongst younger women (3). For example, of the 300,000 doses of DMPA-SC provided during pilots conducted in Senegal, Niger and Uganda in 2014 – 2016, 44% were amongst women who were 25 years or younger, whilst 12% were administered to women 20 years or younger (4) (Stout et al., 2018). Research with women in Kenya, Malawi, Nigeria, and Uganda who are potential users of DMPA-SC show that the option to take home doses for self-administration has unique potential to decrease barriers to contraception and promote women's agency compared to provider-administered injectables, particularly among adolescents (5) (Ali et al., 2023).This is particularly critical as AGYW in South Africa face negative attitudes and social practices, such as rampant gender-based violence; partner, family, and community expectations around fertility; stigma and discrimination of sexually active single AGYW; and poor knowledge on contraception options that jeopardize efforts to support informed contraceptive use.

South Africa has the largest HIV epidemic in the world with 7.8 million people living with HIV (PLHIV) (6). Preventing unintended pregnancies among HIV-positive women is a key strategy in the elimination of mother-to-child HIV transmission and helps reduce a range of other adverse maternal and child health outcomes. Many HIV-positive women receive antiretroviral therapy (ART) refills through less-intensive differentiated service delivery (DSD) models like Central Chronic Medicines Dispensing and Distribution (CCMDD). Providing DMPA-SC take-home units for self-injection can reduce clinic visits for contraception, aligning with DSD models and improving convenience. Urgent investment is needed to diversify contraceptive methods and enhance the integration of family planning and HIV services at national and subnational levels.

The initial submissions to the NEMLC were made in 2019 and August 2020 respectively, to support inclusion of the self-injection and healthcare provide administered DMPA-SC in the Essential Medicines List (EML) and Standard Treatment Guidelines (STGs) for Primary Health Level. Annexed to this document is the previous submission reviewed in August 2020 that demonstrated the evidence for efficacy and safety (See Annex A). In 2020, the PHC/Adult Hospital Level Expert Review Committee recommended DMPA-SC as a therapeutic alternative in the progestogen injectable group, noting no preference between formulations due to similar efficacy and safety. However, DMPA-SC was not included in the EML because the submission lacked sufficient data regarding an updated self-injection label, pricing, cost-effectiveness, and user acceptability. The NEMLC indicated that they may review and reconsider the decision to include the product in the EML and STGs for PHC/Adult Hospital STG upon submission of additional data including, updates regarding SAHPRA registration on the self-injection label, DMPA-SC pricing, and additional user acceptability studies.

6. Purpose/Objective

The objective of this medicine review is to appraise the evidence on affordability, cost effectiveness and user acceptability of the low dose (104mg) subcutaneous DMPA (DMPA-SC) formulations of injectable contraception compared to the current intramuscular 150mg DMPA formulation. The inclusion of DMPA-SC in the EML is not intended to replace the injectable contraceptives used as standard of care. On the contrary, it is meant to expand the current "basket of products" to increase access to contraceptives and expand choices available to end users, thereby taking forward the department's commitment to increase method choice as outlined in the National Integrated Sexual Reproductive Health Rights (SRHR) policy of 2019, and the National Contraception Clinical Guidelines of 2019 (which include DMPA-SC) (7) (8). Furthermore, having alternative products also increases supplier diversification, reducing the risk of supply security and disruption which can have dire consequences such as unwanted and unplanned pregnancies.

The review provides supplementary evidence required to address the insufficiency of data provided in the previous review on price, user acceptability and cost-effectiveness. The additional materials include:

- **Self-administration label:** In May 2024 the South African Health Products Authority (SAHPRA) approved the self-administration label for DMPA-SC, establishing DMPA-SC as a contraceptive choice that can be delivered differently (i.e. via self-injection) compared to other available injectables.
- **Indicative price from manufacturer:** Numerous consultations and concerted efforts have gone into encouraging the manufacturer to provide the unit cost of the product to enable determination for the affordability of the product within a resource constrained environment. DMPA-SC generics are projected to be available in the market in 2026, a factor that is expected to influence product price. The additional evidence and data reinforce the product's potential to improve uptake and use of self-injection formulations where self-care is acceptable.
- **Cost effectiveness:** Using learnings from other countries such as Senegal and Uganda, the data presented herein demonstrates that under reasonable programmatic scenarios, self-injected DMPA-SC could be cost saving or cost effective compared to provider administered DMPA-IM from both societal and health systems perspectives.
- **Acceptability and feasibility:** In addition to the 8 acceptability and continuation studies described in the 2020 submission, 15 additional studies have been included in this review. While no user acceptability studies have been conducted within the South African context, comparative evidence is presented from other low- and middle-income countries in sub-Saharan African and other regions (including Malawi, Nigeria, Uganda, Ghana, DRC, Nepal, Brazil, Chile, Dominican Republic), a significant volume of which has been produced and published since the prior NEMLC submission. The data demonstrates high acceptability rates for DMPA-SC as compared to other contraceptive methods, including the intramuscular (IM) route.

7. Methods

Data sources
PUBMED, expert opinion

Search strategy We searched PUBMED using the same search strategy from the original NEMLC application in 2020 (see search strategy below), with a focus on acceptability and cost-effectiveness. We also contacted experts in the field, searched the grey literature, and carried out reference checking and citation searching to identify additional studies. There were no language restrictions.

Search period: 2019 to 2024.

Selection criteria: New studies not captured in the original NEMLC submission, were included, which focused on cost effectiveness and acceptance of DMPA-SC by users, service providers, and healthcare professionals.

Search keywords:

("Sayana Press" [tiab] OR "depot medroxyprogesterone acetate" [tiab] OR "depo-medroxyprogesterone acetate" [tiab] OR "Depo Medroxyprogesterone Acetate" [tiab]

OR "Medroxyprogesterone" [tiab] OR "Medroxyprogesterone Acetate" [tiab] OR DMPA [tiab] OR DMPA- SC[tiab] OR Uniject [tiab] OR Depo-Provera [tiab] OR "Depo Provera" [tiab] OR "Depo-Subq Provera" [tiab] OR "Long-Acting Reversible Contraception" [Mesh])

AND (self-administration [tiab] OR self-administer [tiab] OR self-administered [tiab] OR self-injection [tiab] OR self-inject [tiab] OR self-injected [tiab] OR "home use" [tiab] OR "home administration" [tiab] OR "home injection" [tiab] OR "self- vs

provider-administered" [tiab] OR "self- and provider-administered" [tiab] OR "self- vs physician- administered" [tiab] OR "self- and physician-administered" [tiab] OR "self and clinical administration" [tiab] OR "self- vs clinician-administered" [tiab] OR "self and clinician administered" [tiab] OR "self-care" [Mesh] OR self-administration [Mesh] OR self-assessment [Mesh])

8. Results

i. The evidence synthesis comprises four sections, namely: (i) Updates to acceptability and continuation of DMPS-SC self-administration, (ii) Updates on Cost-effectiveness, (iii) Updates on pricing, (iv) Feasibility and (iv) Added, in the EtD summary of evidence for efficacy and safety (covered in the NEMLC 2020 review). There is no new evidence from randomized controlled trials on safety and efficacy of DMPA, hence an update on safety and efficacy has not been undertaken in this review.

8.1 Updates to acceptability and continuation of DMPA-SC self-administration

Summary and overall conclusion from new evidence provided (2019-2024)

The new evidence from 15 recently published studies provided illustrates that self-administration of DMPA-SC is highly acceptable among women, improves continuation when self-injected, especially when women are provided with sufficient counselling and training, with variation across different demographic groups and contexts. In Malawi, the majority of client respondents stated a preference for DMPA-SC over intramuscular DMPA (DMPA-IM) in the future, primarily due to cost and time savings, as well as the proposition of privacy (51)[Burke 2018]. Acceptability studies found that of women who received DMPA-SC, 80% in Senegal and 84% in Uganda said they would select DMPA-SC over DMPA-IM if both products were available (52)[Burke 2014]. In Nepal, more than two-thirds of women selected DMPA-SC over DMPA-IM when given the option. Additionally, the study found that the continuation rate for DMPA-SC (47%) was higher than for DMPA-IM (34%) at six months (23) [Sherpa 2021]. This is further supported by a systematic review which found that contraceptive continuation was higher with DMPA-SC self-injection compared to facility-based administration (49) [Millogo 2023]. The convenience, personal agency, and effectiveness of self-administration contribute to DMPS-SC's acceptability and improved continuation rates, especially among younger women. In Niger, Senegal, and Uganda, 44% of women who chose to use DMPA-SC were aged 25 years or younger and 12% were aged 20 years or younger (48) [Stout 2018] (4). Evidence from Uganda suggests that younger women who self-inject showed improved continuation relative to their age peers who received DMPA-IM from a provider (50) [Cover 2018]. Expanding self-administration programs, particularly in LMICs and among younger women, can lead to increased contraceptive use. Data from Burkina Faso, the Democratic Republic of Congo, and Uganda show that DMPA-SC reaches new populations of women and is appealing to new users of family planning, rather than inspiring current users to switch to DMPA-SC from other methods of contraception (37) [Anglewicz 2021]. While barriers such as initial anxiety and fear to self-inject exist, these however, can be mitigated through proper education and support (18) [Liu 2018]. The ability of DMPA-SC to reach those who have never used contraception at all ages, and to meet the needs of adolescents and young people, demonstrates its potential to advance equity in contraceptive access and use.

Author, date	*Type of study*	n	Population	Comparators	Primary outcome	Effect sizes	Comments
Bertrand et al., (2018) (9)	An **observational study** which included surveys	850 clients at baseline	• DMPA-SC clients • Medical and Nursing (M/N) students • Ministry of Health and health zone personnel	None	Of 850 clients selecting DMPA-SC at baseline, 640 (**75.3%**) **opted for self-injection** over being injected by the M/N students for reasons of convenience and personal agency. Among these 640 self-injectors, **47.5%** were **anxious at baseline** (for fear of needles or injecting incorrectly). Over **80%** reported feeling very ready after training, **confident** that they knew how to self-inject and confident that they would remember the next injection date. By 3 months, **97%** described it as **easy**. Half (**54%**) experienced **side effects**, mainly menstrual irregularities, the main reason for discontinuation. At 6-month follow-up, self-injectors cited effectiveness and ease of use as positive elements, though one quarter reported side effects. Their impressions of M/N students as instructors were highly positive. **Where DMPA-SC was free and easily accessible, the majority of women interested in DMPA-SC opted to learn self-injection.** The M/N students performed well in instructing women to self-inject. Clients were highly satisfied with the services received.		Study conducted in a community context, without the benefit of client records available through fixed health facilities. Severe loss to follow-up between surveys. Due to logistical problems, the student providers and interviewers returned 1 week late for the designated 3-month follow-up/campaign days (potentially affecting an estimated 15% of DMPA-SC acceptors interviewed at baseline).

Burke et al., (2019) (10)	**Secondary analysis** of a 12-month randomized control trial	731	Women receiving DMPA-SC from clinic-based providers at 6 public clinics or from community health workers.	None	The type of provider with whom the client interacted and was trained to self-inject (ie clinic-based vs community health worker) did not seem to influence continuation, pregnancy, or safety. The risk for discontinuation was also different among health facility catchment sites (P<.001). No other assessed sociodemographic factors were found to significantly influence the risk for discontinuation. This drove authors to the conclusion that **Public-sector CHWs can safely and effectively provide DMPA-SC and train women to self-inject DMPA-SC in low-resource settings.**		The RCT affiliated with this secondary analysis is included in the Kennedy et al, meta-analysis which was submitted for review in earlier EML application. This particular secondary analysis is included given the increased focus on acceptability amongst young people. Additionally, this study has limitations including that women's reported outcomes may have been influenced by social desirability bias. These are non-randomized comparisons and therefore may be affected by selection biases. Lastly, there are numerous other variables and combinations of variables that were not explored, but which may influence continuation.
Burke et al., 2020) (11)	**Secondary analysis** of a 12-month randomized control trial.	731 women were included in the RCT	Women receiving DMPA-SC	None	Among self-injectors, there were no significant differences found in continuation by age (p = 0.345) with **continuation rates** at 12 months of **79% for young women** (18-24 years) and **69% for older women** (≥25 years). Continuation rates were lower for both age groups with provider-administered injections. In the provider-administered group, continuation rates among young women (39%) were lower than among older women (49%) (p = 0.047). The distribution of reasons for discontinuation did not differ significantly by age for those receiving provider injections (p = 0.698). However, younger self-injectors were less likely to miss the reinjection window than older self-injectors (p = 0.011). Age did not		The RCT affiliated with this secondary analysis is included in the *Kennedy et al*, meta-analysis which was submitted for review in earlier EML application. This particular secondary analysis is included given the increased focus on acceptability. The original study was not designed to assess whether clients' age had different risks of discontinuation or other outcomes, so the sample size for some of the comparisons may be too small to be conclusive. Additionally, these were non-randomized comparisons and may be affected by selection biases. Women's reported outcomes may also have been influenced by social desirability bias. In this secondary analysis, the authors were limited by the data available, for example they were not able to include younger adolescents in this study.

					significantly influence pregnancy or safety.		With evidence of potential higher impact on continuation and no safety concerns, the authors recommend self-injection be added to the contraception options available to young women in low-resource settings.
Burke et al., (2022) (12)	An acceptability study using questionnaires within a clinical trial to evaluate contraceptive effectiveness of Sayana® Press when the reinjection interval was extended from 3 to 4 months.	750	Women aged 18 to 35 years and at risk of pregnancy. Women enrolled in the trial were not pregnant or lactating and did not desire pregnancy for the next 18 months; had not been pregnant in the prior month; had regular menstrual cycles; and had not received an injection of a combined injectable contraceptive or DMPA in the prior 6 months.		Satisfaction with DMPA-SC when injected every 4 months was high across the centers despite center-level differences among participants on age, cohabitation status, years of schooling, and race. At the final study visit, **90.2%** of all participants reported that they were **satisfied or very satisfied**; **97.3%** would **recommend it to a friend or family member**; and **93% would use it in the future**. When asked at the final visit if participants would be willing to self-inject, about three-quarters (**74.5%**) of participants said they were **willing to self-inject**.		
Corneliess et al., (2023) (13)	Cross-sectional, mixed methods study conducted within implementation context of DMPA-SC introduction.	Structured surveys (n = 1,060) and in-depth interviews (n = 36)	randomly selected adolescent and adult participants in the DMPA-SC self-injection program. Adolescents aged 15-19 years (n=208), young adults aged 20-24 (n=302), and adult women		The study found no significant difference in self-injection proficiency or continuation between adolescents and adult women; **86.1%** of adolescents **self-injected independently** when due for reinjection. Adolescents were significantly less likely than adults to report first hearing about self-injection from a community health worker. More adolescents expressed concern over discovery when seeking contraception at a clinic		Adolescents were only followed for one follow-up injection. Additionally, to be eligible to participate in the evaluation, adolescents under the age of 18 had to be emancipated, thus the views and experiences of adolescents who are under the age of 18 but not emancipated are not represented in the data. This group of adolescents may differ in their views of and experiences with contraceptive self-injection. Qualitative participants were selected purposively based on how forthcoming

			aged 25-55 (n=550) receiving self-injection training from a provider affiliated with a study site were included.		and fear of their DMPA-SC units being discovered at home. Adolescents were significantly less likely than adult women to mention convenience as a rationale for self-injecting, and more likely to mention wanting to learn a new skill and/or that friends recommended self-injection. From this, the authors concluded that self-injection is a promising contraceptive for adolescents in Uganda, given comparable proficiency and continuation relative to adult women.		they were with their opinions during the interview. The authors state that "favorability toward the program did not influence participant selection;" however, those that had more favorable opinions or positive experiences might have been more forthcoming during the interview, which would have increased their likelihood of being selected for the qualitative interview, and/or they may have been more willing to agree to participate in the in-depth interview. Provider bias, a barrier to adolescent contraceptive self-injection use that has been reported in other studies, was not measured in this study. This omission was noted as a study limitation by the authors.
Cover et al., (2017) (14)	Prospective cohort study to assess, via interviews and observation of injections, the feasibility and acceptability of self-injection among women in Senegal.	380	18–49-year-old women		Outcomes included injection proficiency, timely reinjection and acceptability (desire to continue). Out of 337 participants followed up at 3 months post-training, **80% demonstrated injection competence**, and **84% reinjected on time**. **93% expressed a desire to continue self-injection**.		
Cover et al., (2017) (15)	Prospective cohort study	380	18–45-year-old women		Out of 368 participants followed up at 3 months post-training, **88% demonstrated injection competence**, and **95% reinjected on time**. Nearly all (**98%**) expressed a **desire to continue self-injection.**		
Cover et al., 2022. (16)	Cross sectional survey (interviews) and injection observations	958	Women trained to self inject DMPA-SC via routine service delivery.		Nearly three quarters (**73%**) demonstrated **injection proficiency** (training quality, education, and use of job aids significantly affect proficiency); **93%** of women **continued** with		

					the second self-injection and satisfaction was high; Just 62 out of 1859 units given out (**3%**) were **unaccounted for** and may have been wasted; Three quarters (75%) of units given for home use to CHW clients were returned to the CHW. **Less than 1%** of units were **disposed in the household garbage**; a substantial share of women declined to adopt SI post-training and factors associated with SI uptake include training with a job aid, practicing, witnessing a demonstration, exposure to a complete training, being single and having a supportive partner.		
Katz et al., (2020) (17)	Observational cohort study.	70	Non-pregnant patients at an urban, safety-net hospital-based primary care clinic who had been prescribed DMPA-IM in the past year were contacted to gauge interest in self-administered DMPA-SC. Interested patients received a prescription for DMPA-SC and a telehealth appointment with a clinic provider to learn self-injection.		Twenty-six (**37%**) patients **expressed interest** in DMPA-SC and scheduled telehealth appointments to learn to self-administer the medication. Fifteen (**58%**) of those interested (21% of the total) **successfully self-injected DMPA-SC**. Of the 44 (63%) patients not interested in DMPA-SC, the three most common reasons were **fear of self-injection** (n = 23 [52%]), **wanting to stop DMPA** (n = 11 [25%]), and **satisfaction with DMPA-IM** (n = 6 [14%]).		USA based study. Study done during the COVID-19 pandemic. Data provides evidence for the interest and successful first injection rate after offering self-administered DMPA-SC to patients on DMPA-IM. Expanding coverage of self-administered DMPA-SC could increase patient-centeredness and accessibility of contraception as well as reduce patient anxiety around COVID-19 transmission without losing contraceptive access.

			Study participants were aged 17-54 years.				
Liu et al., (2018) (18)	Telephone survey from March to August 2016, with a convenience sample	311	DMPA-SC users (N=311) was reached.		Multivariate results for sociodemographic predictors of continued DMPA-SC use show that those with some college education or more (OR=2.79; 95% CI: 1.09–7.14), and those with four or more children (OR=2.89; 95% CI: 1.09 0 7.67) were more likely to obtain another dose. The summary quality measure showed that women overall rated the quality of their initial counselling session high. Logistic regressions indicated that higher quality during the initial counselling session is related to the likelihood of getting another dose of DMPA-SC (OR=2.04; 95% CI: 1.12–3.47) whereas those experiencing more bleeding reduced the likelihood of continuation after 3 months (OR=0.15; 95% CI: 0.07–0.34).		The sample was predominantly urban, from seven South West states, and likely wealthier and more educated than the national average. The examination of continuation is limited to women who completed both surveys, who were generally older and married. While quality analysis showed no significant differences between follow-up and lost-to-follow-up groups, younger, unmarried women often experience worse quality. Only a few questions related to quality were asked, potentially not reflecting women's perceptions of contraceptive service quality. Participant responses could be biased due to poor recall or social desirability, and there is a low risk that providers selected certain clients for the survey. The current analysis only covers a short period after the initial dose, and resource constraints prevented extended follow-up.
Miles et al., (2022) (19)	Implementation study using medical chart review to identify current DMPA-IM users and offer DMPA-SC as a replacement. Phone surveys collected information on injection behaviour	38	Women using DMPA		Four physicians telephoned patients with DMPA-IM on their medication list in two urban primary care clinics and offered counselling and prescriptions to patients interested in transitioning to DMPA-SC. Over half of patients (**20/38**) contacted were **interested in DMPA-SC** and 10 of 20 (**50%**) of those interested **successfully injected**, with 9 of 10 (**90%**) **continuing at three months**.		USA based study, small sample. Intervention took place during the first year of the COVID pandemic.

Morozoff et al., (2022) (20)	Mixed methods survey and in-depth interviews	120	Health workers in Uganda, both clinic and community based, offering self-injection services.		Providers expressed moderately high satisfaction with the self-injection program, indicating it was moderately easy to integrate self-injection training. Lack of time to train and shortage of materials present feasibility challenges; client fear of needles slows uptake of self-injection. CHWs reported fewer challenges offering self-injection to their repertoire of services offered.		
Nabhan et al., (2021) (21)	Systematic review and meta-analysis [3 randomized trials (9 reports)	1264	Women in their reproductive age, receiving DMPA-SC for contraception, randomized to self-administration (651 women) versus a provider administration (613 women)		The risk of bias in the included studies was low except for performance bias and detection bias of participant-reported outcomes in unmasked trials. **Self-administration**, compared to provider-administration, **increased continuation of contraceptive use** (risk ratio 1.35; 95% confidence intervals 1.10–1.66); moderate-certainty evidence).		Only one study out of the three was conducted in Sub-Saharan Africa, in Malawi in 2018. The study by *Burke et al.,* and was already included in the *Kennedy et al*, meta-analysis which was submitted for review in earlier EML application. Self-injection appears to be making more of an impact on continuation for younger women compared to women 25 years and older and on women living in low and middle income compared to high income countries. There was no subgroup difference by the type of care provider (community health worker vs. clinic-based provider).
Nai et al., (2022) (22)	Prospective cohort study	378	Women aged 18– 49 years who sought family planning services from 1 of the 8 study facilities, were not planning on becoming pregnant in the next 6 months and were more than 6 weeks postpartum or breastfeeding.		At their third injection, or 6 months into using DMPA-SC, **73%** of these users **chose self-injection**, an increase from 42% who chose self- injection at the first injection. Clients who were new family planning users, never married, or attended high school/attained higher education were significantly more likely to self-inject by the third injection compared to their respective counterpart.		Attrition: The study excluded 68 women who discontinued DMPA-SC and 122 women who were lost to follow-up. Women who were lost to follow-up were significantly more likely to be younger, unmarried, and have fewer children. Of those included in the follow-up survey, 49.7% of women had obtained another dose of DMPA-SC.

Sherpa et al., (2021) (23)	Prospective cohort study.	1112	Women between 18- 49 years seeking injectable contraception at 14 public health facilities in Nepal were enrolled and self-selected either Sayana Press (DMPA-SC) or DMPA-IM.	DMPA-IM	794 women (**71%**) selected and received **DPMA-SC**, while 318 women (28.6%) selected and received DMPA-IM. 178 (48%) women continuing DMPA-SC injection reported that they experienced "no possible side effects" compared to 29 (22%) among DMPA-IM selectors during the previous 6 months. The **continuation rate** of DMPA-SC at 6 months was higher than DMPA-IM (**DMPA-SC 46.5% vs DMPA-IM 34.4%**; p < 0.001). Selection of DMPA-SC method (OR adj. 1.74; 95% CI 1.32–2.3) and approval from husband (OR adj. 1.59; 95% CI 1.21–2.09) were associated with injection continuation.		Random sampling methods were not employed when selecting public health facilities for inclusion in the study. Measures of independent variables, such as the characteristics of counselling, relied on recall and self-report by the participant. Furthermore, the measure of husband/partner's approval relied on proxy reporting by the contraceptive user. The adjusted logistic regression model used to identify predicators of injection continuation included a select set of variables. It is unclear why some variables were not included in the models such as experience of side effects, user type (new, continuing, switching), and method satisfaction. The study was conducted during the COVID-19 lockdown, which was reported as one of the main reasons for contraceptive discontinuation. Conducting the study during this time limits the generalizability of the findings.
Author, date	***Type of study***	**n**	**Population**	**Comparators**	**Primary outcome**	**Effect sizes**	**Comments**
Himes et al 2024 (24)	Qualitative (semi-structured interviews)	241	Women were purposively sampled to ensure representation of two age groups (ages 15– 19 years and ages 20–45 years) and diversity of contraceptive use experience (users and		There were three main domains- privacy, eased access barriers, and self-management. These findings were based on both real experiences of SC users and perceptions of those not using SC on the role it could play in their lives. Across all study contexts and regardless of experience with contraception, participants viewed		In this study, women themselves see value in the potential of SC contraception to give women control over who knows about their contraceptive use, either at home or in the community, making it easier to use for those with disapproving or controlling family members. Programmatic solutions are needed to address women's fear of SC contraception.

			non-users of SC contraception). The study was done in four sub-Saharan African countries (Kenya, Malawi, Nigeria, Uganda)		SC as an option that could make contraception more accessible. A noteworthy theme specific to SC users' experiences was that self-injecting led to increased self-assuredness over time. After being trained and successfully self-injecting, in many cases, SC users expressed a boost in confidence		

8.2 Updates on cost-effectiveness

Summary and overall conclusion from new evidence on cost effectiveness

Studies from Uganda and Senegal suggest that self-injection of DMPA-SC is more cost-effective compared to facility-based administration of DMPA-IM (28) (Mvundura, 2019); (25)(DiGiorgio, 2018); (29)DiGiorgio, 2018). Both studies, in Uganda and Senegal, were done under research settings but they evaluated alternative scenarios with realistic implementation conditions. Under the realistic program implementation conditions, self-injection programs are cost effective under societal and health systems perspectives when compared to both conservative and traditional cost effectiveness thresholds (27)(Marseille, 2015); (26)(Woods, 2016). In both countries, improved continuation using DMPA-SC compared to DMPA-IM was the key driver of effectiveness (i.e., DMPA-SC: 81% (Uganda), 80% (Senegal) vs. DMPA-IM: 65% (Uganda), 70% (Senegal). From a health system perspective, self-injection may be cost effective, or cost saving compared to provider administered doses (See Table Below). Reduction in training costs through simplified client instructions and/or limiting the number of DMPA-SC units for practice can reduce costs of self-injection provision thereby improving cost effectiveness of self-injection. Considering a societal perspective, in both Uganda and Senegal, self-injection costs less than facility-based administration due to savings to women in transportation and time. Overall, self-injection of DMPA-SC is shown to be a cost-effective strategy across the studies, providing significant health and economic benefits compared to health-worker administered DMPA-IM, whether considered from a societal or health system perspective.

Table summarizing results of health economics studies

Titles	Health System Perspective	Societal Perspective
Is contraceptive self-injection cost-effective compared to contraceptive injections from facility-based health workers? **Evidence from Uganda** (25)	• **$15 per pregnancy averted.** • **$98 per maternal DALY averted.** Note: the study references two cost effectiveness thresholds: 1) $293 per DALY averted (26) and 2) $615 to $1845 per DALY averted (WHO threshold) (27)	DMPA-SC self-injection is **dominant** compared to DMPA-IM provider administration
Cost-effectiveness of self-injected DMPA-SC compared with health-worker-injected DMPA-IM in **Senegal** (28)	• If 1 DMPA-SC unit used for training, **DMPA-SC self-injection is dominant**. • If 2 DMPA-SC units are used: **$208 per DALY averted.** • If 3 DMPA-SC units are used: **$664 per DALY averted.** • If 4 DMPA-SC units are used: **$1080 per DALY averted.** • If 4 water-filled Uniject devices are used for training: **$18 per DALY averted.** Note: the study references a cost effectiveness threshold range of $544 (conservative) to $958 (traditional) per DALY averted	DMPA-SC self-injection is **dominant** compared to DMPA-IM provider administration
Costs of administering injectable contraceptives through health workers and	<u>Uganda</u> • DMPA-SC self-injection: $6.23	<u>Uganda</u> • DMPA-SC self-injection: $7.83

self-injection: evidence from **Burkina Faso, Uganda, and Senegal** (29)	• DMPA-IM facility-based provider administration: $5.45 • DMPA-SC community-based distribution: $4.95 • DMPA-IM community-based distribution: $4.97 <u>Senegal</u> • DMPA-SC self-injection: $7.41 • DMPA-IM facility-based provider administration: $6.44 <u>Burkina Faso</u> • DMPA-SC facility-based provider administration: $7.92 • DMPA-IM facility-based provider administration: $7.38	• DMPA-IM facility-based provider administration: $10.12 • DMPA-SC community-based distribution: $$7.69 • DMPA-IM community-based distribution: $7.71 <u>Senegal</u> • DMPA-SC self-injection: $8.38 • DMPA-IM facility-based provider administration: $9.46 <u>Burkina Faso</u> • DMPA-SC facility-based provider administration: $12.14 • DMPA-IM facility-based provider administration: $11.60

Author, date	Type of study	n	Population	Comparators	Primary outcome	Effect sizes	Comments
Di Giorgio et al., (2018) (29)	Four cross-sectional micro-costing studies in three countries.	N/A	N/A	DMPA-IM vs DMPA-SC, when DMPA-SC is delivered under three strategies (facility-based, community-based, and self-injection) and DMPA-IM is delivered under two strategies (facility-based and community-based).	Direct medical costs overall were lowest for community-based distribution of DMPA-SC in Uganda (US$4.95). This was followed by DMPA-IM community-based distribution ($4.97), DMPA-IM facility-based distribution ($5.45), and DMPA-SC self-injection ($6.23, adjusted) also all from Uganda. With non-medical costs included (ie women's time and travel), total costs were lowest for community-based distribution of DMPA-SC (US$7.69) and DMPA-IM ($7.71) in Uganda. Total costs for self-injection in Uganda were $7.83 and in Senegal $8.38 upon adjustment to a simplified, scalable job aid and were lower than the costs of facility-based administration of DMPA-IM ($10.12 Uganda, $9.46 Senegal). Total costs including nonmedical were highest for facility-based administration of DMPA-SC ($12.14) and DMPA-IM ($11.60) in Burkina Faso. Across all studies, direct nonmedical costs were lowest for self-injecting women. Community-based distribution and self-injection may be promising channels for reducing injectable contraception delivery costs. We observed no major differences in costs when administering DMPA-SC and		Commodity costs accounted for the largest share of the direct medical costs, except under the self-injection research intervention before adjustment, for which client training aid represented the largest costs. Variation in self-reported duration of client visit times, health workers' salaries, and reported side effects and treatment practices drove differences in the estimated direct medical costs across countries. Costs were drawn from experiences of facilities involved in pilot introduction of DMPA-SC or research studies and may not be representative of costs when product is taken to scale. Self-reported estimates of health worker and client resources may be inaccurate due to recall bias. Some delivery or programmatic costs were not included, such as costs for training and supervising health workers to deliver injectables, facility operational and management costs, and supply chain costs, which may further impact estimates.

					DMPA-IM under the same strategy.		
Di Giorgio et al., (2018) (25)	Decision-tree model with a 12-month time horizon to estimate the incremental costs per pregnancy averted and per disability-adjusted life year (DALY) averted. The study design derived model inputs from DMPA-SC self-injection continuation and costing research studies and peer-reviewed literature.	Approximately 1 million	A hypothetical cohort of approximately 1 million injectable contraceptive users in Uganda to estimate the incremental costs per pregnancy averted and per disability-adjusted life year (DALY) averted.	DMPA-IM	Self-injected DMPA-SC could prevent 10,827 additional unintended pregnancies and 1620 maternal DALYs per year for this hypothetical cohort compared to DMPA-IM administered by facility-based health workers. Due to savings in women's time and travel costs, under a societal perspective, self-injection could save approximately US$1 million or $84,000 per year, depending on the self-injection training aid used. From a health system perspective, self-injection would avert more pregnancies but incur additional costs. A training approach using a one-page client instruction sheet would make self-injection cost-effective compared to DMPA-IM, with incremental costs per pregnancy averted of $15 and per maternal DALY averted of $98.		Sensitivity analysis showed that the estimates were robust. The one-way and probabilistic sensitivity analyses showed that the costs of the first visit for self-injection (which include training costs) were an important variable impacting the cost-effectiveness estimates. Under a societal perspective, self-injected DMPA-SC averted more pregnancies and cost less compared to health-worker-administered DMPA-IM. Under a health system perspective, self-injected DMPA-SC can be cost-effective relative to DMPA-IM when a lower-cost visual aid for client training is used.
Mvundura et al., (2019) (28)	A decision-tree model with a 12-month time horizon.	100,000	Hypothetical cohort of 100,000 injectable contraceptive users in Senegal.	Health worker administered DMPA -IM vs DMPA-SC	The incremental cost-effectiveness ratios of self-injection of DMPA-SC versus health-worker-administration of DMPA-IM were estimated at $18 per DALY averted. Whether using the upper end of the conservative cost-effectiveness threshold for Senegal ($544) or the traditional threshold ($958), self-injection of DMPA-SC at $18 per DALY averted would be cost-effective compared to		Researchers conducted this study in concert with the [Cover et al., (2019)] Senegal injectable contraceptive continuation study, where women who visited a clinic to receive an injectable contraceptive could choose to be trained to self-inject DMPA-SC or receive a DMPA-IM injection from a health worker. – To facilitate cross-country comparisons, the researchers replicated methods used in their Uganda study *[Giorgio et al., 2019]*. They developed a static decision-tree

					health worker administration of DMPA-IM. Compared to health-worker-administered DMPA-IM, self-injected DMPA-SC could prevent 1402 additional unintended pregnancies and avert 204 maternal DALYs per year for this hypothetical cohort. From a societal perspective, self-injection costs less than health worker administration regardless of the training approach and is therefore dominant. From the health system perspective, self-injection is dominant compared to health worker administration if a one-page instruction sheet is used and one additional DMPA-SC unit is used for training and is cost-effective at $208 per DALY averted when two additional DMPA-SC units are used.		model for a hypothetical cohort of 100,000 women in Senegal who self-injected DMPA-SC or received DMPA-IM from a health worker. – The cohort size was based on the estimated number of women of reproductive age in Senegal who used injectable contraceptives in 2017. The researchers used a 1-year time horizon, as this was used in the Senegal continuation study [Cover et al., 2019) We assumed that, at the beginning of this 12-month period, women were using these contraceptives due to a desire to prevent pregnancy. – The cost-effectiveness analysis considered both health system and societal perspectives. For the health system perspective, costs for health-worker-administered DMPA-IM included commodity costs (injectable contraceptive, syringes and safety box), time cost for health workers to administer the contraceptive and treat side effects (if applicable), and drugs used for treatment of side effects (such as ibuprofen and oral contraceptives). For self-injection, commodity costs and drug costs were included, as were the time costs for health workers to train women to self-inject and treat side effects and the cost of self-injection training supplies. We assumed that women who continued for the year would use four units of DMPA. Key cost estimates used in this analysis were informed by a costing study conducted in Senegal *(Giorgio et al., 2018)*

8.3. Updates on pricing

The proposed price is **R25.76 ex VAT (R29.63 incl VAT) per Sayana Press Uniject,** (written communication from supplier to NDOH refers) These will be presented as a 200 Unijects per pack. It is understood that requests for price adjustments may be submitted to the NDoH Affordable Medicines Directorate's Contract Management Unit, as and when required in response to fluctuations in the rand/dollar exchange rates.

The supplier is yet to submit application to the Pricing Committee for the reference Single Exit Price (SEP). However, their intention is to submit parallel application to the Pricing Committee as the NEMLC review is underway.

Additionally, additional manufacturers are developing generic versions of DMPA-SC and are expected to begin global production by 2026, which may further impact product pricing.

Projected Target Patient Populations Size over 4 years

The estimated number of DMPA-SC users was developed based on the estimated number of DMPA users (both IM and SC presentations) and the market share of the SC presentation over a 4-year period.

The number of DMPA users (both IM and SC presentations)

The total DMPA doses dispensed per province for FY 2022/2023 were extracted from the 2022/23 District Health Barometer (30). These volumes were divided by 4, the number of doses a single client requires per year, to arrive at the estimated number of DMPA users for FY 2023/24.

The projection for the number of DMPA users was developed for 2023/2024 (Year 1) through 2026/2027 (Year 4).

- The number of DMPA users in Year 1 was assumed to grow by the same number of DMPA users compared to the previous year.
- The total numbers of DMPA users for Year 2-4 were maintained at the same level as Year 1, as there is no foundation to assume the same growth will continue in multiple years.

The share of DMPA-SC users

The share of SC presentation of DMPA users seen in the literature ((5)Porter et al., 2023 and Wood et al, 2022) on the DMPA-SC introduction in other sub-Saharan African countries was used to estimate the number of DMPA-SC users.

- Year 1
  - 15% of the new DMPA users will use DMPA-SC
  - 25% of continuing DMPA users will switch to DMPA-SC
- Year 2
  - 35% of total DMPA users will use DMPA-SC
- Year 3
  - 50% of total DMPA users will use DMPA-SC
- Year 4
  - 65% of total DMPA users will use DMPA-SC

8.4. Feasibility

To date, there are 59 countries with DMPA-SC and self-injection regulatory approval (including South Africa) and 20 sub-Saharan African countries have DMPA-SC on their respective national essential medicine lists. There have been 5.3 million DMPA-SC visits recorded between Q2 2023 and Q1 2024, among 14 countries with data reporting tracked by the

Injectables Access Collaborative (Benin, Burkina Faso, Côte d'Ivoire, DRC, Ghana, Guinea, Malawi, Mali, Mauritania, Nigeria, Senegal, Togo, Uganda, and Zambia) (Report available upon request) (31). Among DMPA-SC visits in these countries, 22% were for self-injection. Notably, the DMPA-SC visit indicator tracks the number of family planning visits where clients received DMPA-SC and self-administered the injection after being taught by the provider; these women would then be given units to take home according to each country's prescribing protocol. Hence the use of DMPA-SC may be 2-3x higher than number of visits recorded, depending on the number of units given for home use (which reduces future visits) (32)

It has been demonstrated through numerous studies that women can safely and effectively self-administer DMPA-SC with training and support and consider self-injection acceptable. In separate studies in Senegal and Uganda, research found that women could self-inject competently and on time three months after being trained (80% and 87%, respectively), and almost all women who tried self-injection expressed the desire to continue (93% and 98%, respectively), (14)[Cover et al., 2017], (15)Cover et al, 2017) A subsequent evaluation of the self-injection pilot program in Uganda found positive results for self-injection offered outside of a research study (16) (Cover, 2022). That evaluation found good injection proficiency (73%) and identified training quality as a key determinant of both injection proficiency and adoption of self-injection. Client satisfaction was high, as was continuation (93% self-injected a second time and 74% self-injected through four injections).

Small-scale introduction to inform scale-up in South Africa

National Department of Health (NDOH), Women's Health and Genetics Directorate, is considering small-scale introduction of DMPA-SC in two provinces (Eastern Cape and KwaZulu-Natal) to inform operational guidance for further scale-up. This intervention is expected to last a period of 6 months, after which DMPA-SC will be introduced into the remaining provinces. Thus, the demand estimates for Year 1 includes 12-month demand in 2 provinces and 6-month demand in other provinces.

Finally, the estimated numbers of DMPA-SC users were rounded up.

YEAR 1	269,000	15% of new DMPA users + 25% of existing DMPA users
YEAR 2	595,000	35% of existing DMPA users
YEAR 3	850,000	50% of existing DMPA users
YEAR 4	1,105,000	65% of existing DMPA users

9. Conclusion

The introduction of DMPA-SC, a self-care intervention recommended by WHO, could increase contraceptive options and autonomy for young women, as seen in other countries where uptake is higher among younger women and the method attracts new users of contraception. This is crucial as South African AGYW face challenges like gender-based violence, societal expectations around fertility, stigma, and poor contraception knowledge. Key benefits of DMPA-SC include 99% efficacy, quarterly administration with self-administration option, reduced travel and waiting times, higher contraceptive maintenance rates, ease of use, and suitability for community health workers and self-administration.

In 2020, the Adult Hospital Level Committee recommended DMPA-SC as a therapeutic alternative in the progestogen injectable group, noting no preference between formulations due to similar efficacy and safety. Updated SAPHRA approval for the self-injection label, distinguishing DMPA-SC from DMPA-IM through method of administration is now available. Additionally, this resubmission addresses the gaps identified by previous reviewers with new evidence including 1) SAPHRA newly approved self-injection label, 2) an indicative price from Pfizer; 3) cost-effectiveness studies; and 4) new evidence on acceptability.

Self-administration of DMPA-SC is a cost-effective strategy from a health systems perspective, for contraceptive delivery, especially in LMIC settings, providing substantial economic and health benefits by reducing unintended pregnancies, improving maternal health outcomes, and lowering delivery costs. The method of training impacts cost effectiveness, and the learnings from the Senegal and Ugandan studies can be applied in the South African context to inform best practices for introduction and scale-up. Community-based distribution also shows promise for reducing costs of injectable contraception delivery, self-administration potentially prevents a substantial number of unintended pregnancies and maternal DALYs, leading to significant societal savings.

Although there are no current studies on DMPA-SC conducted in South Africa, the option of self-administration has been shown to be feasible and acceptable in comparable countries in Sub-Saharan Africa (Malawi, Uganda, and Senegal), where training and support are available to women. We believe that countries within the same region often have similar health challenges and health system structures. In this case, Senegal, Uganda, Burkina Faso where DMPA-SC has been introduced share similar challenges with South Africa such as high rate of unmet needs and limited access to services. The experiences of these peer countries can assist in predicting the performance of DMPA-SC in a comparable setting like South Africa.

10. Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High [X] Moderate [ ] Low [ ] Very low [ ] *High quality:* confident in the evidence • *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	Based on the previous review (2019, Updated in August 2020) which appraised the efficacy and safety of low dose subcutaneous DMPA formulations compared to the current intramuscular 150mg dose, NEMLC was confident in the overall evidence of effectiveness. **Jain et al, 2004:** • Two Phase 3, open label multi-center trials • **Population and N:** o 722 for North and South American population (total 7,209 woman-cycles of exposure). o 1,065 for European and Asian population (total 11,472 woman-cycles of exposure). • **Comparators:** o DMPA-SC (104 mg/0.65 mL) every 3 months was the intervention. Non-comparator trial • **Outcomes:** o Contraceptive efficacy at 1 year: No pregnancies observed. Also, No pregnancies across all BMIs. DMPA-SC provides highly reliable (99.9%) contraceptive efficacy that is uncompromised by BMI o Safety: DMPA-SC tolerability profile was similar to or better than that of DMPA-IM. **Jain J et al., (2004)** (33) **Author: Kaunitz et al, 2009** • Randomized, evaluator-blinded study • **Population and N**: o DMPA-SC (n=266) or DMPA-IM (n=268) for 2 years with an option to continue for a third year. • **Comparators:** o Subcutaneous injection (104 mg/0.65 mL; DMPA-SC) vs. intramuscular DMPA (150 mg/mL; DMPA-IM). • **Outcomes**: o Contraceptive efficacy at 2 years: The 2-year treatment-failure cumulative pregnancy rate was 0% in the DMPA-SC group and 0.8% (95% CI, 0.00–2.37%) in the DMPA-IM group (life-table method). **(Kaunitz A et al.,2009)** (34) No new RCT evidence of efficacy available since the August 2020 review update.
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large [ ] Moderate [X] Small [ ] None [ ]	Based on the previous review (2019, Updated in August 2020) which appraised the efficacy and safety of low dose subcutaneous DMPA formulations compared to the current intramuscular 150mg dose - Moderate quality. High rates of drop out. The size of the beneficial effect may be large when considering self-injection. Self-injection of DMPA reduces drop-out rates, and self-injection is only possible with sub-cutaneous DMPA -SC). Significant differences in continuation have been found across different contexts, all pointing to the same effect - higher continuation with self-injected SC relative to provider administered IM Evidence demonstrates that self-injection leads to higher continuation with self-injectors 38% less likely to discontinue at 12 months in the 2 NRCTs (RR: 0.62; 95% CI: 0.47-0.82; p = 0.001, moderate certainty evidence) and 44% less likely to discontinue at 12 months in the 3 RCTs (RR: 0.56; 95% CI: 0.37-0.86; p < 0.01, moderate certainty evidence) (Millogo T et al.,2023) (35)

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
		See summary of outcomes for Jain et al, 2004 and Kaunitz et al, 2009 listed above.
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High [ ] Moderate [X] Low [ ] Very low [ ] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	Based on the previous review (2019, Updated in August 2020) which appraised the efficacy and safety of low dose subcutaneous DMPA formulations compared to the current intramuscular 150mg dose - Moderate quality. **Dragoman et al - systematic review (2016):** Evaluated the published peer-reviewed literature regarding the safety of DMPA-SC among women with various characteristics/medical conditions. • No clinical safety concerns unique to DMPA-SC were reported. • Safety profiles of the SC and IM largely similar. • Weight change in obese women: Data suggested safety of DMPA-SC use among obese women is like nonobese women. Obese users of DMPA-SC and DMPA-IM experience similar adverse effects. • Weight change in non-obese women across different age-groups: All women experienced similar weight gain during use of either method over time. However, in the DMPA-SC/IM Phase 3 trial including women aged 18–35 years, weight gain was significantly higher among women < 25 years using DMPA-SC vs women aged 25 to 35 years at month 9 (p = 0.025) and 12 (p = 0.003). • Changes in bone mineral density (BMD): Over 2 and 3 years, non-statistically different median % changes in BMD among DMPA-SC vs DMPA-IM users. • Endometriosis: No evidence that DMPA-SC contributed to a worsening condition or increased frequency of any other serious adverse events. • HIV acquisition risk: The ECHO trial: In the modified intention-to-treat analysis, the hazard ratios for HIV acquisition were 1·04 (96% CI 0·82–1·33, p=0·72) for DMPA-IM vs with copper IUD, 1·23 (0·95–1·59, p=0·097) for DMPA-IM vs with LNG implant, and 1·18 (0·91–1·53, p=0·19) for copper IUD compared with LNG implant. Overall, there was no substantial difference in HIV risk among the methods evaluated, and all methods were safe and highly effective. • Injection site reactions: Users of DMPA-SC may experience injection site reactions more frequently, but these are rare, typically mild to moderate in severity and generally resolve without further intervention. **(Dragoman M et al.,2016)** (36)
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large [ ] Moderate [ ] Small [X] None [ ]	DMPA-IM has been appraised as safe, with low risk of harms. There is no evidence to suggest a higher risk with the sub-cutaneous formulation. ***See summary of Dragoman et al (2016) listed above.***
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention [X] Favours control [ ] Intervention = Control *or* Uncertain [ ]	Based on the previous review (2019, Updated in August 2020) which appraised the efficacy and safety of low dose subcutaneous DMPA formulations compared to the current intramuscular 150mg dose - benefits outweigh potential harms. ***See summary of measures of effect, safety and harms listed above. From previous review (August 2020).***

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes ☐ No ☒ List the members of the group. N/A List specific exclusion from the group:	A direct comparison of DMPA-SC to DMPA-IM or the range of oral contraceptives on the EML might not be useful as there are advantages and disadvantages to each type of formulation. DMPA-SC for example offers the benefit of self-administration compared to DMPA-IM and longer coverage compared to oral contraceptive alternatives i.e. the preference and advantages applies to different population groups. There are no therapeutic alternatives to DMPA-SC for self-injection. While both DMPA products are effective at preventing pregnancy, only the sub cutaneous version can be self-injected. There is no therapeutic alternative when self-injection is also taken into account. Evidence demonstrates that self-injection leads to higher continuation with self-injectors 38% less likely to discontinue at 12 months in the 2 NRCTs (RR: 0.62; 95% CI: 0.47-0.82; p = 0.001, moderate certainty evidence) and 44% less likely to discontinue at 12 months in the 3 RCTs (RR: 0.56; 95% CI: 0.37-0.86; p < 0.01, moderate certainty evidence) (Millogo T et al., 2023) (35)
FEASIBILITY	**Is implementation of this recommendation feasible?** Yes ☒ No ☐ Uncertain ☐	No user acceptability studies have been conducted within the South African context; however, comparative evidence is available from other low- and middle-income countries in sub-Saharan African and other regions (including Malawi, Nigeria, Uganda, Ghana, Democratic Republic of the Congo, Nepal, Brazil, Chile, Dominican Republic). A significant volume of which has been produced and published since the prior EML submission. The data demonstrates high acceptability and continuation (with the option of self-injection) rates for DMPA-SC as compared to other contraceptive methods, including the Intramuscular (IM) route.
RESOURCE USE	**How large are the resource requirements?** More intensive ☐ Less intensive ☐ Uncertain ☒	**Price of medicines available for state procurement/ treatment course**

Medicine	Price (ZAR) Per Pack (Master Health Product List – November 2024)	Price/84 days (ZAR)
Medroxyprogesterone, 104mg/0.65mL, SC – SAHPRA registered but no SEP. indicative price = R29.63 (incl. VAT) for 1 self-inject vial∞	N/A	N/A
Copper IUCD*	248	11.41
Levonorgestrel Intra-uterine device* x 1	720.36	33.16
Levonorgestrel/ethinyl estradiol, triphasic 28 tablets	6.54	19.62
Levonorgestrel/ethinyl estradiol, 0.15mg/ 0.03mg monophasic 28 tablets	6.66	19.98
Levonorgestrel tablets (progestin only), 0.03 mg 28 tablets	6.08	18.24
Norethisterone enanthate 200mg/ml injection** x1	23.92	35.88
Etonorgestrel 68mg implant x 1	385.25	29.55
Medroxy progesterone acetate IM 150mg injection∞ x 1	****17.40	17.40

∞ Administered every 84 days
* Provides long-term protection - 5 years
** Administered every 8 weeks
*** Provides long-term protection - 3 years
**** Weighted average (Supplier 1 (40% split) = R15.83 & Supplier 2(60% split) = R18.45)

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
		To note: Although the Progestin-only injectables are listed as a therapeutic class in the STG, for security of supply, the available members of the class (Medroxyprogesterone and Norethisterone Enanthate) have been awarded as a split award and are both available. With adequate user training, the introduction of DMPA-SC will likely reduce the number of facility visits (2 visits per year) leading to Health care efficiency gains as compared to other facility-based administration contraceptive options. Refer to updates on pricing outlined in the review above.
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [X] Major [ ] Uncertain [ ] **Is the option acceptable to key stakeholders?** Yes [X] No [ ] Uncertain [ ]	There is a possibility of self-administration which may increase the way people value the option. -It is very likely this option will be acceptable to stakeholders as it has non-inferior efficacy and safety profile to DMPA-IM and will allow healthcare workers to dedicate more time to other critical areas of need as DMPA-SC is licenced for self-administration. In addition, studies in other countries have demonstrated high continuation rates with an option of self-injection.
EQUITY	**Would there be an impact on health inequity?** Yes [X] No [ ] Uncertain [ ]	Expanding self-administration programs, particularly in LMICs and among younger women, can lead to increased contraceptive use. Data from Burkina Faso, the Democratic Republic of Congo, and Uganda show that DMPA-SC reaches new populations of women and is appealing to new users of family planning, rather than inspiring current users to switch to DMPA-SC from other methods of contraception3. While barriers such as initial anxiety and fear to self-inject exist, these however, can be mitigated through proper education and support4. The ability of DMPA-SC to reach those who've never used contraception at all ages, and to meet the needs of adolescents and young people, demonstrates its potential to advance equity in contraceptive access and use. Additionally, women with physical disabilities making it difficult to travel to clinics would particularly benefit from learning self-injection. In this sense, DMPA-SC could reduce health inequities for marginalized populations

Version	Date	Reviewer(s)	Recommendation and Rationale
1	28 November 2024	1. Thembi Zulu (NDOH), 2. Lesley Bamford (NDOH), 3. Tendai Mvuvu (Market Access Africa), 4. am Lee (Bill & Melinda Gates Foundation), 5. Nicole Young (Bill & Melinda Gates Foundation), 6. Naoko Doi (Jhpiego), 7. Phatheka Mathola (Jhpiego), 8. Maiyuran Vethakuddikurukkal (Jhpiego).	DMPA-SC recommended as an EML item conditional on the product being available at the indicative price provided herein (R29.63 incl VAT) or less. DMPA-SC is acceptable to stakeholders, feasible to implement and accessible.

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Annex A

health
Department:
Health
REPUBLIC OF SOUTH AFRICA

South African National Essential Medicine List
Primary Health Care Medication Review Process
Component: Family planning

MEDICINE REVIEW:

1. **Executive Summary**

Date: 26 August 2020 (Update of August 2019 review)
Medicine (INN): Medroxyprogesterone (104 mg), SC injection
Medicine (ATC): G03AC06
Indication (ICD10 code): Z30.0/Z30.4/Z30.8
Patient population: Women of childbearing potential (WOCP)
Prevalence of condition: n/a - This is for prevention of pregnancy
Level of Care: Primary health care
Prescriber Level: Nurse prescriber
Current standard of Care: IM – DMPA, 150 mg
Efficacy estimates: (preferably NNT): n/a
Motivator/reviewer name(s): S Takuva, E Bera
PTC affiliation: n/a

2. **Name of author(s)/motivator(s):** Dr Simbarashe Takuva; Dr Ebrahim Bera; supported by Trudy D Leong for comparative costing analysis.

3. **Author affiliation and conflict of interest details:**

Primary reviewer – S Takuva

a. Affiliation: Perinatal HIV Research Unit, Faculty of Health Sciences, University of the Witwatersrand; School of Health Systems and Public Health, Faculty of Health Sciences, University of Pretoria; Adult Hospital Level Committee member (2017-2020).
b. No conflicts of interest to declare.

Secondary reviewer – E Bera

a. Affiliation: Department of Obstetrics & Gynaecology, University of the Witwatersrand; Adult Hospital Level Committee member (2017-2020).
b. No conflicts of interest to declare.

Support – TD Leong

a. Affiliation: Essential Drugs Programme, National Department of Health; Secretariat to the Primary Health Care and Adult Hospital Level Expert Review Committees.
b. No conflicts of interest to declare.

4. **Introduction/ Background:**

Contraception is one of the World Health Organization's four strategic prongs for the prevention of mother-to-child transmission of HIV. Contraception and planning for conception contribute to the reduction of HIV transmission, thereby supporting the National Strategic Plan on HIV, STIs and TB (2017-2022). (1) There has been increasing focus on LARC (long-acting reversible contraception), which are among the most effective contraceptive methods and have the greatest potential to reduce unintended pregnancies. There are two available and widely used progestogen-only injectables in South Africa: depot medroxyprogesterone acetate (DMPA), 150mg formulation once every 12 weeks, and norethisterone

enanthate (NET-EN), once every 8 weeks.(2) Injectables are popular among clients because they are highly effective, easy to comply with, require only periodic clinic visits, are private and no supplies need to be kept at home. (3)

DMPA works as a contraceptive by inhibiting the secretion of gonadotropins which, in turn, prevents follicular maturation and ovulation and results in endometrial thinning. DMPA at its current 150 mg IM dose has visible metabolic effects: Weight gain is common and may be a problem for some clients and tends to increase with duration of use. This is mainly mediated through increased appetite.(4) Also, glucose tolerance is impaired thereby reducing the threshold for diabetes onset among women with borderline glucose tolerance. Other common side-effects include changes in menstrual bleeding (irregular, prolonged or/and heavy bleeding, amenorrhoea), headaches, dizziness, acne, mood changes and decrease in sex drive These metabolic effects are postulated to be due to its initial very high peak levels after administration, these stay relatively high over 3 months. It has however been demonstrated that the current IM formulation when administered SC at lower doses achieves 5-6 times much lower initial peak levels and these levels remain much lower but still above the presumptive contraceptive threshold over 3 months than the IM formulation. This then points to alternative potential dosing and route of administration of DMPA. Studies indicate that the 100 mg/0.5 mL dose is the lowest subcutaneous DMPA dose that consistently suppressed ovulation for at least 3 months. See Figure 1 and Figure 2 (Source: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/076553_S000_Medroxyprogesterone_BIOPHARMR.pdf). The slower rate of absorption observed with DMPA-SC relative to the IM formulation allows for a lower peak serum concentration and a long duration of effect; thus, serum concentrations are maintained above the required minimum concentration for ovulation suppression over a targeted period of 3 months with a 30% lower subcutaneous dose.

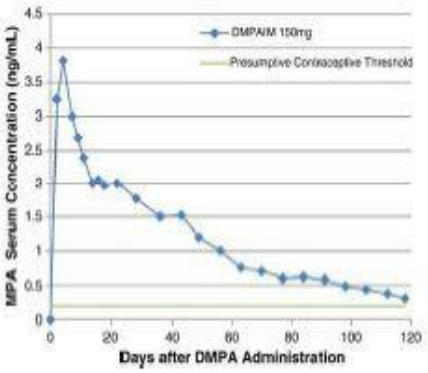

Figure 1: MPA blood levels after a single injection of DMPA IM 150 mg.

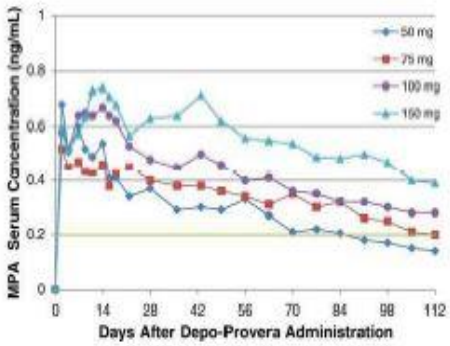

Figure 2: MPA blood levels after single injection SC of various doses of current DMPA IM formulation.

As the dose ...uscular ...ally lower ...ewer side a small but growing evidence base provides consistent evidence to suggest that self-administration of depot medroxyprogesterone acetate subcutaneous injectable contraception can lead to improved contraceptive continuation rates and equivalent pregnancy prevention compared with healthcare provider administration.(5) . Therefore DMPA-SC potentially offers women a new, highly effective and convenient long-acting contraceptive option.

5. Purpose/Objective

The objective of this medicine review is to appraise the efficacy and safety of low dose subcutaneous DMPA formulations compared to the current intramuscular 150mg dose. This review followed the PICO (population, intervention, comparison and outcomes) question: Is DMPA-SC of similar therapeutic efficacy and safety profile as DMPA-IM? Additionally, the evidence on acceptability of self-administration of low dose SC DMPA was reviewed.

Population	Individuals of reproductive age
Intervention	Low dose DMPA subcutaneous formulations (class) — DMPA S.C. 104mg every 3 months
Comparison	DMPA 150 mg intramuscular formulation given every 3 months
Outcomes	Efficacy – prevention of pregnancy Safety – weight gain, bleeding patterns, endometriosis, HIV acquisition, other adverse events

6. **Methods:**

   a. **Data sources: PubMed and EMBASE**

   b. **Search strategy** Search strategy adapted from Drogoman et al, 2016 (6). PubMed database searched to identify all relevant evidence published in peer-reviewed journals in any language from inception through June 2019 regarding the safety and efficacy of DMPA-SC in women of reproductive age: ("contraceptive agents, female"[MeSH] AND ("injections"[MeSH] OR ("injections"[MeSH] OR "injections"[All Fields] OR "injection"[All Fields])) AND (subcutaneous[All Fields] OR ("sc"[All Fields]) OR SQ[All Fields])) OR ("dmpa"[All Fields] OR (depot[All Fields] AND ("medroxyprogesterone"[MeSH] OR "medroxyprogesterone"[All Fields])) OR ("medroxyprogesterone acetate"[MeSH] OR ("medroxyprogesterone"[All Fields] AND "acetate"[All Fields]) OR "medroxyprogesterone acetate"[All Fields] OR ("depo"[All Fields] AND "provera"[All Fields]) OR "depo provera"[All Fields])) AND (subcutaneous[All Fields] OR ("sc"[All Fields]) OR "SQ"[All Fields] OR "subQ"[All Fields]")). We also searched the Cochrane Library database for any existing systematic reviews on the method using the search terms "depot medroxyprogesterone SC or SQ or subcutaneous." Additionally, we hand-searched reference lists of identified articles for further citations of interest. For efficacy only studies designed with efficacy as the outcome/primary outcome were considered.

   To extract studies comparing self-administration versus provider administration of injectable contraception on outcomes of pregnancy, side effects/adverse events, contraceptive uptake, contraceptive continuation, self-efficacy/empowerment and social harms, we adapted the search strategy from the systematic review and meta-analysis by Kennedy et al (2019).
   ("Sayana Press" [tiab] OR "depot medroxyprogesterone acetate" [tiab] OR "depo-medroxyprogesterone acetate" [tiab] OR "Depo Medroxyprogesterone Acetate" [tiab]
   OR "Medroxyprogesterone" [tiab] OR "Medroxyprogesterone Acetate" [tiab] OR DMPA [tiab] OR DMPA-SC[tiab] OR Uniject [tiab] OR Depo-Provera [tiab] OR "Depo Provera" [tiab] OR "Depo-Subq Provera" [tiab] OR "Long-Acting Reversible Contraception" [Mesh])
   AND (self-administration [tiab] OR self-administer [tiab] OR self-administered [tiab] OR self-injection [tiab] OR self-inject [tiab] OR self-injected [tiab] OR "home use" [tiab] OR "home administration" [tiab] OR "home injection" [tiab] OR "self- vs provider-administered" [tiab] OR "self- and provider-administered" [tiab] OR "self- vs physician- administered" [tiab] OR "self- and physician-administered" [tiab] OR "self and clinical administration" [tiab] OR "self- vs clinician-administered" [tiab] OR "self and clinician administered" [tiab] OR "self-care" [Mesh] OR self-administration [Mesh] OR self-assessment [Mesh]).

c. **Evidence synthesis**

- **EFFICACY**

Author: Jain et al, 2004 (6)
Type of study: 2 Phase 3, open label multi-center trials
Population and N: 722 for North and South American popn (total 7,209 woman-cycles of exposure). 44% were overweight or obese at baseline.
1,065 for European and Asian popn (total 11,472 woman-cycles of exposure). 27% were overweight or obese at baseline.
Comparators: DMPA-SC (104 mg/0.65 mL) every 3 months was the intervention. Non-comparator trial
Outcomes:

Contraceptive efficacy at 1 year: No pregnancies observed. Also, No pregnancies across all BMIs. DMPA-SC provides highly reliable (99.9%) contraceptive efficacy that is uncompromised by BMI
Patient satisfaction: Very high level of satisfaction. In both trials, subjects reported a very high level of satisfaction with DMPA-SC in three of the PSQ and EOTQ measures: preferring it with respect to other contraceptive methods, being willing to continue treatment and willingness to recommend it to a friend.
Safety: DMPA-SC tolerability profile was similar to or better than that of DMPA-IM. See safety section of this review.

Comments:
- These were industry sponsored studies (funding, statistical expertise, etc.).
- Study drop-out rates were high (>20%) especially in the Americas study. 489 (67.7%) completed the study and in the Europe and Asia study, 856 (80.4%) completed the study.
- While these studies do include women from study sites around the world, supporting some generalizability of the results, most studies did not include women from sub-Saharan Africa.
- The open-label, non-comparator study design (rather than placebo-controlled) was considered suitable and ethical for these trials because Depo-Provera IM® is used as a contraceptive in many countries and has proven efficacy.
- Efficacy outcome: Pearl Index (number of pregnancies per 100 woman-years of use) was 0, as was the cumulative pregnancy rate at 1 year (the primary efficacy endpoint), based on the life-table method (percentage of women whose method of contraception failed within the specified time period) in each study.
    - Excluding months during which barrier contraception was used at least sometimes or no intercourse occurred, DMPA-SC was a highly effective (99.9%) contraceptive in these studies, as evidenced by the absence of pregnancies in the 720 women in the Americas trial or the 1059 women in the European/Asian trial for whom data were available.
- Participant satisfaction with treatment results was evaluated using a patient satisfaction questionnaire (PSQ) and end-of-treatment questionnaire (EOTQ). It collected data regarding the respondent's experience with the study, the aspects of treatment that were liked and disliked and the likelihood of selecting that method for future contraceptive purposes.

Author: Kaunitz et al, 2009 (7)
Type of study: Randomized, evaluator-blinded study
Population and N: DMPA-SC (n=266) or DMPA-IM (n=268) for 2 years with an option to continue for a third year.
Comparators: Subcutaneous injection (104 mg/0.65 mL; DMPA-SC) vs. intramuscular DMPA (150 mg/mL; DMPA-IM).
Outcomes:

Contraceptive efficacy at 2 years: The 2-year treatment-failure cumulative pregnancy rate was 0% in the DMPA-SC group and 0.8% (95% CI, 0.00–2.37%) in the DMPA-IM group (life-table method). The Pearl Index was 0 for DMPA-SC and 0.24 (95% CI, 0.00–0.70) for DMPA-IM at 3 years.
Bone mineral density (BMD) changes: There were no statistically significant differences in BMD loss between DMPA-SC and DMPA-IM groups at the end of Year 3.
Patient satisfaction: In both study groups, participants reported being very satisfied with their contraceptives; no statistically significant differences were noted between the two study groups with regard to treatment satisfaction.

Comments:

- This industry sponsored study was an extension of the studies published by *Jain et al*.
- A total of 225 women completed the first 2 years of this study (DMPA-SC, n=116; DMPA-IM, n=109).

- **SAFETY**

Dragoman et al published a systematic review in 2016 that evaluated the published peer-reviewed literature regarding the safety of DMPA-SC among women with various characteristics or medical conditions. Results of this review informed the decision-making of a WHO Guideline Development Group. The search strategy for this technical review was adopted from this SR. Post the 2016 review, the ECHO trial was published, and their findings are added to the summaries below.(8,9)

  - Due to heterogeneity of study designs, study populations, and outcome measures collected, the authors did not compute summary measures of associations.
  - No clinical safety concerns unique to DMPA-SC have been reported in any of these studies. The safety profiles of the SC and IM are largely similar.

- **Weight change in obese women:** Data suggests that the safety of DMPA-SC use among obese women is like nonobese women; and, obese users of DMPA-SC and DMPA-IM experience similar adverse effects. No studies reported on adverse outcomes among adolescents.
- **Weight change in non-obese women across different age-groups**: All women experienced weight gain during use of either method over time that was similar, there were no consistent differences in the distribution of weight change across age groups (< 25, 25–35, > 35 years). There was a trend toward higher weight gains among women > 35 years in the North/South American noncomparative Phase 3 trial (not statistically significant, p = .076). However, in the DMPA-SC/IM Phase 3 trial including among women aged 18–35 years, weight gain was significantly higher among women < 25 years using DMPA-SC compared to women ages 25 to 35 years at month 9 (p = .025) and 12 (p = .003).
- **Changes in bone mineral density**: Over two and three years, the median percent changes in BMD among DMPA-SC compared to DMPA-IM users were not statistically different.
- **Endometriosis:** There was no evidence that DMPA-SC contributed to a worsening of their condition or an increased frequency of any other serious adverse events.
- **HIV acquisition risk:** The ECHO trial was a randomized, multicenter, open-label trial across 12 research sites in eSwatini, Kenya, South Africa, and Zambia. It included 7829 HIV-seronegative women aged 16–35 years who were seeking effective contraception and were randomly assigned to receive an injection of 150 mg/mL **DMPA-IM** every 3 months, a copper IUD, or an LNG implant. In the modified intention-to-treat analysis, the hazard ratios for HIV acquisition were 1·04 (96% CI 0·82–1·33, p=0·72) for DMPA-IM compared with copper IUD, 1·23 (0·95–1·59, p=0·097) for DMPA-IM compared with LNG implant, and 1·18 (0·91–1·53, p=0·19) for copper IUD compared with LNG implant. Depo-Provera appeared to pose a marginally higher risk of H.I.V. infection than contraceptive implants? Overall, there was no substantial difference in HIV risk among the methods evaluated, and all methods were safe and highly effective. (10)
- **Injection site reactions:** Users of DMPA-SC may experience injection site reactions more frequently, but these are rare, typically mild to moderate in severity and generally resolve without further intervention.

- **Changes in bleeding patterns and other adverse effects:** No consistent differences reported in bleeding patterns across age groups (≤ 25, 25–35, > 35 years) among DMPA-SC users in Phase 3 trials. No differences in AEs, most mild or moderate in severity and SAEs rare.

Comments:
- These were industry sponsored studies (funding, statistical expertise, etc.).
- Study drop-out rates were high (>20%) in many of the trials
- While these studies do include women from study sites around the world, supporting some generalizability of the results, most studies did not include women from sub-Saharan Africa
- Safety outcomes measured – many used surrogate markers and many outcomes are heterogenous hence difficult to combine into single estimates.

- **ACCEPTABILITY OF SELF-ADMINISTRATION**

As no new studies focusing on sub-Saharan Africa were identified after publication of the Kennedy et al 2019 systematic review and meta-analysis (5) we review below this synopsis of published studies.

Summary of results (Kennedy et al, 2019): Six studies with 3851 total participants met the inclusion criteria: three RCTs and three controlled cohort studies. All studies examined self-injection of DMPA-SC;
comparison groups were either provider-administered DMPA-SC or provider-administered intramuscular DMPA. All studies followed women through 12 months of contraceptive coverage and measured (dis)continuation of injectable contraception.
Three studies were conducted in SSA:

- *Burke et al*(11) - Mangochi District, Malawi: Women aged 18–40 years old receiving family planning services. Mean age: 26.9 years (SD: 5.21). Randomised controlled trial, 731 participants (364 self administration, 367 provider administration) and 12-month follow-up;
- *Cover et al* (12)- 5 districts in Uganda: Women aged 18–45 years old attending participating health facilities for routine FP visits who expressed an interest in using injectable contraception, Mean age: (Intervention) 26.9 (SD: 6.4); (Control) 26.5 (SD: 6.2).Controlled cohort study. 1161 participants (561 self administration, 600 provider administration). 12-month follow-up;
- *Cover et al*(13) - Dakar and Thiés regions of Senegal: Women aged 18–45 years old attending participating health facilities for routine FP visits who expressed an interest in using injectable contraception, Mean age: (Intervention) 26.9 (SD: 6.4); (Control) 26.5 (SD: 6.2). Controlled cohort study. 1299 participants (650 self administration, 649 provider administration). 12-month follow-up.

Meta-analysis found higher rates of continuation with self-administration compared with provider administration in three RCTs (RR: 1.27, 95% CI 1.16 to 1.39) and three controlled cohort studies (RR: 1.18, 95% CI 1.10 to 1.26). Four studies reported pregnancies; all showed no difference across study arms. Four studies reported side effects/adverse events; while two controlled cohort studies showed increased injection site reactions with self-administration, no other side effects increased with self-administration. One study found no difference in social harms. No studies reported measuring uptake or self-efficacy/empowerment.

- In the meta-analysis, the relative risk of contraceptive continuation was higher with self-administration of injectable contraception compared with provider administration.
- There were no major differences in pregnancy or side effects/adverse events, except that the two controlled cohort studies showed increased injection site reactions with self-administration.

d. Evidence quality: Moderate quality. High rates of drop out.

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE	**What is the overall confidence in the evidence of effectiveness?** Confident: x Not confident: Uncertain:	Clinical trial data
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms: x Harms outweigh benefits: Benefits = harms or Uncertain:	Benefits outweigh potential harms
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes: x No: All other *available* contraceptive modalities, as women's choice is a prerogative. List the members of the group: see above List specific exclusion from the group: n/a	Rationale for therapeutic alternatives included: All other *available* contraceptive modalities, as women's choice is a prerogative. References: n/a Rationale for exclusion from the group: n/a References: n/a
VALUES & PREFERENCES / ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor: x Major: Uncertain: **Is the option acceptable to key stakeholders?** Yes: x No: Uncertain:	-There is a possibility of self-administration which may even increase the way people value the option. -Its very likely this option will be acceptable to stakeholders as it has non-inferior efficacy and safety profile. **Note:** Please see evidence described in the narrative above.
RESOURCE USE	**How large are the resource requirements?** More intensive: Less intensive: Uncertain: X	**Price of medicines/3 months (84 days):** Medroxyprogesterone,104 mg/0.65 mL, SC – SAHPRA registered but no SEP available: Pack size Price (ZAR)*: n/a; Price/ 84 days (ZAR): n/a Copper IUCD: 159,99; 7,36 Levonorgestrel/ethinyl estradiol, triphasic tablets: 6,28; 18,84 Levonorgestrel/ethinyl estradiol, monophasic tablets: 2,90; 8,70 Norethisterone enanthate injection: 24,01; 36,02 Etonogestrel implant: 224,58; 17,23 DMPA injection: 15,40; 15,40 * Contract circulars RT283-2017, HP03-2017CHM/01 **Additional resources:** Could not source other international prices (including Canada; Australia; Netherlands; Spain; Turkey).
EQUITY	**Would there be an impact on health inequity?** Yes: No: X Uncertain:	
FEASIBILITY	**Is the implementation of this recommendation feasible?** Yes: No: Uncertain: X	While the product is now SAHPRA registered, the price to the market is not yet available.

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	[x]	☐	☐	☐	☐

Recommendation: Based on the evidence reviewed, the Adult Hospital Level Committee recomends that subcutaneous DMPA should be considered as a therapeutic alternative of the progestogen injectable therapeutic group. There is no preference for either formulation as they seem to have similar therapeutic efficacy and safety profile. The option of self-administration has been shown to be feasible and acceptable in Sub-Saharan Africa (Malawi, Uganda and Senegal); where training and support is available to women.

Rationale: Available evidence among healthy women suggests that DMPA-SC and DMPA-IM appears to be therapeutically equivalent interms of safety and efficacy. Satisfication rate for DMPA-SC is similar to that of the IM formulation. Data from other countries in sub-Saharan Africa supports the option of self administration of DMPA -SC. A local acceptability and feasibility study may be required to determine if the self-administration option is a viable option for South Africa.

Low dose DMPA- SC:

Level of Evidence: I Systematic review, RCT

Self administration of low dose DMPA-SC:

Level of Evidence: II Systematic Review (moderate quality RCTs); cohort studies

Review indicator: *Availability of SAHPRA registered product on the South African market, affordable price*

Evidence of efficacy	Evidence of harm	Price reduction
x		

VEN status:

Vital	Essential	Necessary
	x	

NEMLC MEETING OF 26 SEPTEMBER 2019:

NEMLC accepted the proposal as recommended by the Adult Hospital Level Committee, noting that SAHPRA registration and a reasonable price is required for consideration for inclusion in the national EML.

NEMLC MEETING OF 17 SEPTEMBER 2020:

NEMLC accepted the updated medicine review that now includes comparative pricing.

Monitoring and evaluation considerations

Research priorities

- Feasibility of self administration
- Long term safety profile
- Acceptability studies for self-administration of subcutaneous low-dose DMPA in South Africa

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