

Target product profiles for development of novel male contraceptive methods

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Declarations of interests

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Abbreviations and acronyms

Abbreviation	Term
α 1A	alpha 1 adrenoreceptor
11 β -MNTDC	11 β -methyl-19-nortestosterone dodecylcarbonate
BPH	benign prostatic hypertrophy
BRDT	bromodomain testis-specific protein
cAMP	cyclic adenosine monophosphate
CatSper	cation channel of sperm
CFC	Contraception and Fertility Care (Unit)
COC	combined oral contraceptive
CRE	(WHO Office of) Compliance, Risk Management and Ethics
DG	development group
DMAU	dimethandrolone undecanoate
DMPA	depot medroxyprogesterone acetate
DMSO	dimethyl sulfoxide
DOI	declaration of interest
EMA	European Medicines Agency
EPPIN	epididymal protease inhibitor
EU	European Union
FDA	(United States) Food and Drug Administration
FSH	follicle-stimulating hormone
GnRH	gonadotropin-releasing hormone
HPT	hypothalamic-pituitary-testis (axis)
HRP	UNDP-UNFPA-UNICEF-WHO-World Bank Special Programme of Research, Development and Research Training in Human Reproduction
ICH	International Council for Harmonization (of Technical Requirements for Pharmaceuticals for Human Use)

Abbreviation	Term
ICMC	International Consortium for Male Contraception
LH	luteinizing hormone
LHR	Life Course Health and Reproduction (WHO department)
MC	male contraceptive/male contraception
MCI	Male Contraceptive Initiative
MEC	medical eligibility criteria
NET-EN	norethisterone enanthate
NMC	novel male contraceptive
RAR α	retinoic acid receptor alpha
RFH	Research for Health (WHO Science Division)
RISUG	reversible inhibition of sperm under guidance
sAC	soluble adenylyl cyclase
SDG	Sustainable Development Goal
SLO3	slowpoke homolog 3
SMA	styrene maleic anhydride
SRH	sexual and reproductive health
T	testosterone
TPP	target product profile
TSSK	testis-specific serine/threonine kinase
UNDP	United Nations Development Programme
UNFPA	United Nations Population Fund
UNICEF	United Nations Children's Fund
WHO	World Health Organization

Glossary of terms

Term	Definition	Alternative definition
Acrosome reaction	Exocytotic release of enzymes from the acrosome (the cap-like structure on the sperm head) that allows the sperm to penetrate the outer layers of the egg. It is a required step in fertilization that some sperm-function inhibitors aim to block (1).	An exocytotic event in capacitated spermatozoa involving fusion of the plasma membrane with the outer acrosomal membrane, leading to the release of acrosomal contents required for fertilization.
Anejaculation	The absence of the emission of semen at sexual climax. It can be induced pharmacologically (for example, with $\alpha 1A$ -adrenoceptor antagonists such as silodosin) and, because no ejaculate is released, makes conception impossible (2).	The complete absence of ejaculation despite adequate sexual stimulation, resulting in failure of semen emission and/or expulsion.
Azoospermia	The complete absence of sperm in the ejaculate (3).	The complete absence of spermatozoa in the ejaculate as confirmed by examination of a centrifuged semen specimen.
Biomarker (surrogate biomarker)	A measurable indicator – such as sperm concentration or sperm motility – used as a surrogate endpoint for contraceptive efficacy before, or in place of, pregnancy prevention data (4).	A biomarker intended to substitute for a clinical endpoint and expected to predict clinical benefit, harm or lack thereof based on scientific evidence.
Capacitation	The physiological changes that sperm undergo in the female reproductive tract that confer the ability to fertilize an egg (5).	A process of biochemical and functional maturation that spermatozoa undergo after ejaculation, enabling them to acquire the ability to fertilize an oocyte. A sequence of biochemical and biophysical changes in the sperm plasma membrane that renders the cell capable of undergoing the acrosome reaction.

Term	Definition	Alternative definition
Contraceptive effectiveness	Contraceptive effectiveness refers to the ability of a contraceptive method to prevent pregnancy, usually measured as the percentage of users who avoid pregnancy during the first year of use or, conversely, by the contraceptive failure rate (the proportion of users who become pregnant within the first 12 months after initiating method use). Effectiveness may be reported as perfect use (consistent and correct use) or typical use (how the method is actually used in real-life settings, including the experience of those who use it inconsistently or incorrectly) (6).	Contraceptive effectiveness is determined by a combination of drug or device efficacy, individual fecundity, frequency of intercourse and user adherence and continuation (7).
Contraceptive efficacy (failure rate)	The ability of a method to prevent pregnancy, commonly expressed as the number of unintended pregnancies per year of use, for example as a 12-month cumulative pregnancy rate (8).	The ability of a contraceptive method to prevent pregnancy, typically expressed as the rate of pregnancy occurrence among users over a defined period. It is commonly quantified using the Pearl Index or life-table (Kaplan–Meier) analysis and reflects the capacity of a contraceptive method to prevent pregnancy during use (9).
Contraceptive efficacy versus contraceptive effectiveness	Contraceptive efficacy measures how well the contraceptive works under ideal, controlled conditions, that is, in research or clinical trials, while contraceptive effectiveness measures how well a contraceptive method works in everyday, real-world clinical practice and is typically evaluated through two main standards: perfect use and typical use (10).	
Contraceptive safety	The extent to which a contraceptive method can be used without causing unacceptable health risks or adverse effects, taking into account an individual's medical condition, characteristics and circumstances of use (11).	
Couple-year of protection	The estimated protection provided by family planning (FP) methods during a one-year period, based upon the volume of all contraceptives sold or distributed free of charge to clients during that period (12).	An estimate of the protection against pregnancy provided by contraceptive methods during one year of use, calculated using method-specific conversion factors applied to the quantity of contraceptives distributed (12).
Hyperactivated motility (hyperactivation)	A vigorous, high-amplitude, whip-like pattern of sperm movement acquired during capacitation that is required to reach and fertilize the egg (13).	A specialized pattern of sperm movement characterized by high-amplitude, asymmetrical flagellar beating and vigorous, nonlinear swimming trajectories that facilitate fertilization.

Term	Definition	Alternative definition
Investigational product	A drug, biologic, placebo or other pharmaceutical product being tested or used as a reference in a clinical trial (14).	
Kaplan–Meier analysis	A statistical method for estimating the probability of an event – here, pregnancy – occurring over time, used to derive the 12-month cumulative pregnancy rate (15).	A nonparametric method for estimating the probability of survival or remaining free of an event over time while accounting for censored observations.
Minimal criteria	The essential, minimally acceptable performance characteristics that a product must attain; effectively a “go/no-go” threshold for development (16).	The minimum requirements that a contraceptive method must meet in terms of efficacy, safety, reversibility and acceptability to be considered suitable for development or use.
Optimal criteria	The preferred performance characteristics that would maximize the public health impact and clinical utility of a product (16).	The ideal characteristics that would provide the greatest benefit and public health impact.
Oligozoospermia (severe)	A low concentration of sperm in the ejaculate. In this document “severe oligozoospermia” is defined as ≤ 1 million sperm/mL ejaculate, the target threshold used for agents that suppress spermatoreversible hormonal genesis (17).	A severe reduction in sperm concentration, typically defined as fewer than 5×10^6 spermatozoa/mL of semen.
Perfect use	Contraceptive effectiveness measured when a method is used consistently and correctly on every occasion.	The effectiveness of a contraceptive method when it is used consistently and correctly at all times according to the prescribed instructions, without errors or omissions by the user. Perfect-use effectiveness reflects the intrinsic efficacy of the method under ideal conditions and is higher than effectiveness observed under typical-use conditions (18).
Reversibility (reversible contraception)	The return of normal fertility – for example, sperm production, motility or transport – after the method is discontinued.	Contraception in which suppression of fertility is temporary, and normal reproductive capacity is expected to recover after discontinuation of treatment (18).
Safety profile	The characterization of the adverse effects, risks, tolerability and overall safety of a medical product or intervention based on available clinical and nonclinical evidence (19).	

Term	Definition	Alternative definition
Sperm function	The set of properties – including motility, morphology, capacitation, hyperactivation and the acrosome reaction – that together determine the fertilizing capacity of sperm (3).	The set of biological properties and activities of spermatozoa that are required for successful fertilization, including motility, capacitation, acrosome reaction, interaction with the female reproductive tract, oocyte recognition and gamete fusion.
Sperm morphology	The structural characteristics of spermatozoa, including the head, midpiece and tail, reported as the percentage of spermatozoa exhibiting normal form according to standardized criteria (3).	
Sperm motility	Movement of spermatozoa, usually expressed as a percentage relative to the total number of spermatozoa. There are several types of sperm motility (for example, nonprogressive, progressive, hyperactivated) (20).	
Sperm transmission/transport	The movement of spermatozoa through the reproductive tracts to the site of fertilization, facilitated by both sperm motility and tract-derived mechanisms.	The process by which spermatozoa move from their site of origin in the testis to the female reproductive tract. It includes release into the seminiferous tubules and epididymis; ejaculation, which propels sperm through the vas deferens and expulsion through the urethra into the female genital tract; and on to the fertilization site (21). The movement of sperm along the vas deferens can be interrupted by vasectomy or by vas occlusion methods.
Spermiogenesis	The final stage of spermatogenesis, in which round spermatids elongate, condense chromatin and differentiate into mature, motile spermatozoa (22).	The differentiation process by which haploid spermatids are transformed into structurally mature spermatozoa without further cell division (23).
Typical use	Contraceptive effectiveness as it occurs in real-world conditions, including inconsistent or incorrect use.	The effectiveness of a contraceptive method under real-life conditions, including inconsistent or incorrect use by individuals. Therefore, it reflects the pregnancy rates experienced by average users (24).
Vas occlusion	Blockage of the lumen of the vas deferens – for example, with an injectable hydrogel – to prevent sperm transport, with the potential to be reversed by dissolving or flushing the occluding agent (25).	Deliberate blockage of the vas deferens to prevent sperm passage into the ejaculate, thereby producing contraception.

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1 Background

1.1 Introduction

This publication, the *Target product profiles for novel male contraceptives* (TPP NMC), provides important information on key parameters and values to be used for research and development of high-quality, effective, safe, acceptable and affordable male contraceptives. Male contraceptives are intended to improve sexual and reproductive health (26). This TPP NMC is a reference document that guides the development, introduction, regulation and monitoring of reversible male contraceptive use.

Globally, 48% of pregnancies are unplanned or unintended, and 60% of these unplanned pregnancies end in an abortion (27). In the USA, even with relatively easy access to modern contraceptives, rates of unintended pregnancy are approximately 45% (28, 29). Unintended pregnancies occur when contraceptives are not used, are used inconsistently or are used consistently but fail (30). The correct use of a highly effective contraceptive results in significant reductions in maternal, neonatal and infant mortality; improvements in women's health and well-being; and dramatically reduced abortion rates (31–34). Therefore, there is a great need for improved access to contraceptives and more contraceptive options for people at risk of unintended pregnancy.

Men are significant users of contraception; about 30% of couples rely on male methods of contraception. Globally, 21.8% of women of reproductive age (aged 15–49 years) rely on male condoms for contraception, while only 1.8% rely on vasectomy (35). Survey studies from the early 2000s consistently indicate that men are willing to use male contraceptive methods and that women

would trust their male partner to use male methods of contraception (36–38). The willingness to use NMC is corroborated by a WHO global survey on male contraception (39). Results from four low- to medium-income countries (LMICs) show that over 75% of all respondents (male and female) are willing to use NMC, and over 85% of women report that they would trust their male partners to consistently use NMC (39).

A recent survey of 12 000 men and more than 9000 women in six LMICs indicated that, overall, 61% of men would try a new male contraceptive (MC) method within a year of availability (compared with 39% in the USA). The men preferred daily transdermal patches or gels or pills over injections and implants. Female partners had high trust and interest in their male partners using male contraceptives (40). These studies provide evidence that the demand for novel male contraception is high and lend support to the current efforts to develop reversible hormonal contraception, including targeted approaches to suppress sperm output and function and new methods to block sperm

transmission (anejaculation) and transport with hydrogels for vas occlusion (41–43).

This first edition of the WHO TPP NMC seeks to contribute to improving sexual and reproductive health (26), as well as to enhance access to family planning and contraception services. With its focus on contraceptive developments for men, the TPP NMC supports the attainment of Sustainable Development Goal (SDG) target 3.7: By 2030, ensure universal access to sexual and reproductive health care services, including for family planning, information and education, and the integration of reproductive health into national strategies and programmes; and SDG indicator 3.7.1: Proportion of women of reproductive age (aged 15–49 years) who have their need for family planning satisfied with modern methods. This publication is also in line with global efforts to accomplish SDG target 3.8, which addresses achieving universal health coverage, including financial risk protection, and access to essential health care services. As a regulatory document, this TPP supports SDG 5.6: Ensuring universal access to sexual and reproductive health and reproductive rights, and specifically SDG indicator 5.6.2: Number of countries with laws and regulations that guarantee full and equal access to women and men aged 15 years and older to sexual and reproductive health care, information and education (44).

1.2 WHO's work to support male contraceptive development

WHO has been involved in male contraceptive development for over 50 years, initially providing technical leadership, supporting early research, building research capacity and standardizing semen analysis procedures (45, 46). The WHO contraceptive efficacy trial on hormonal male contraception (47, 48) marked a significant milestone in MC development, indicating good contraceptive effectiveness for the injectable combination hormonal contraceptive for men and paving the way for advances in combined hormonal male contraceptive development. Additionally, the *WHO laboratory manual for the examination and processing of human semen*, first

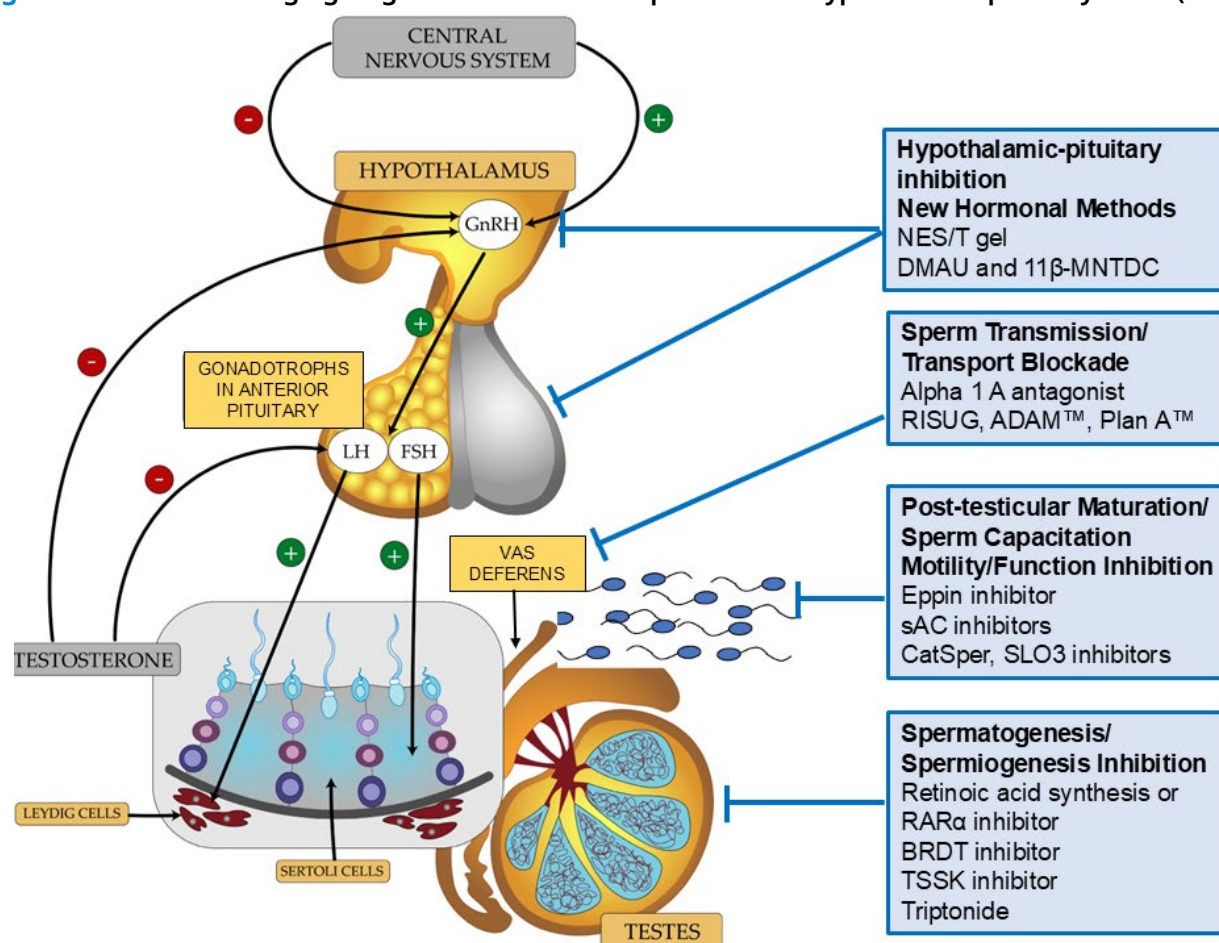
published in 1980 and now in its sixth edition (3), is the global reference document for procedures and methods for the laboratory examination and processing of human semen and is widely used by NMC developers and other practitioners involved in male fertility care. WHO recognizes the critical importance of NMCs in expanding the contraceptive method mix, facilitating choice, alleviating the contraception burden disproportionately shouldered by females, and enhancing men's direct participation in family planning and preventive health care (49).

1.3 Spermatogenesis, sperm function, blockage of sperm transmission/transport and male contraception development

The goal of MC development is to identify new methods that are effective, reversible, safe, acceptable, affordable and available. An understanding of the process of spermatogenesis is necessary, as it is the basis of MC development and, hence, of the standards in the TPP NMC. In contrast to the female reproductive system, where ovulation occurs cyclically from puberty, with production of typically one egg per 21–35 day cycle, spermatogenesis is continuous, and the sperm cycle takes a longer period (from 60 to 80 days), with numerous sperm produced every second (50–52). NMCs are, therefore, designed to target the following three areas: spermatogenesis, sperm function (including sperm motility, morphology and fertilizing capacity) or sperm transmission/transport. The production of sperm is controlled by testosterone produced under the stimulation of luteinizing hormone (LH) and supported by follicle-stimulating hormone (FSH). This relationship is the main target of hormonal male contraceptives, which act to suppress the circulating levels of these hormones and, thus, impair their function in facilitating spermatogenesis (53).

Fig. 1 depicts elements of the spermatogenesis cycle and the targets of the three groups of MC for which these TPPs have been developed, namely: suppression of spermatogenesis, inhibition of sperm function and blockade of sperm transmission/transport (54).

Fig. 1. Overview of emerging targets of male contraception on the hypothalamic-pituitary-testis (HPT) axis



The HPT axis consists of the hypothalamus, pituitary gland, and testes. The hypothalamus releases gonadotropin-releasing hormone (GnRH) in a pulsatile fashion which signals for release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary. LH and FSH drive testosterone (T) production and spermatogenesis in the testes. T and the hormonal contraceptives (T ± a progestin) exert negative feedback on the hypothalamus to inhibit GnRH, LH, and FSH release, therefore suppressing spermatogenesis. Currently clinical trials include nestorone/testosterone gel and androgens with progestogenic action dimethandrolone undecanoate (DMAU) and 11β-methyl-19-nortestosterone dodecylcarbonate (11β-MNTDC). Other methods focus on distinct targets to inhibit spermatogenesis such as retinoic acid synthesis or retinoic acid receptor alpha (RARα), bromodomain testis-specific protein (BRDT) or spermiogenesis including testis-specific serine/threonine kinase (TSSK) and triptonide. Other novel agents that target sperm maturation or capacitation include epididymal protease inhibitor (Eppin), soluble adenylyl cyclase (sAC); cation channel of sperm (CatSper); slowpoke homolog 3 (SLO3). Transport through the vas deferens can be blocked by medications such as α1A inhibitors such as silodosin, cured-in-place hydrogel such as reversible inhibition of sperm under guidance (RISUG), ADAM™, and Plan A™. Arrows with $+$ indicate activation; arrows with $-$ indicate inhibition. Blue arrows ending with a bar indicate emerging male contraception methods and targets.

Source: Wang et al., 2026 (54). Reproduced with permission.

1.4 The assessment of contraceptive efficacy and safety

Contraceptive efficacy is defined as the ability of a contraceptive method to prevent pregnancy, typically expressed as the rate of pregnancy occurrence among users over a defined period. For the purpose of this TPP, contraceptive efficacy should be based on months of exposure of men

to the new agent. Because the man receives the product, while the female partner has a variable duration of cycles, applying Kaplan–Meier analysis to assess 12-month probability of pregnancy risk as the primary endpoint (55, 56) is considered reasonable.

The International Council for Harmonization (ICH), together with the United States Food and Drug Administration (FDA), the European Medicines

Agency (EMA) and other regulatory agencies, have established guidelines for the safety requirements of drugs used for long-term treatment of non-life-threatening conditions (41, 42). These guidelines are applicable to the development of new molecular entities for male contraception. The safety profiles of these products should be very high during drug development, taking cognizance that male contraceptives may be used by young healthy men over extended periods of time.

1.5 Target audience

The target audience for the TPPs is broad. It includes researchers working on male contraceptive methods, drug and device developers, representatives of manufacturers (including biotech engineers), public health experts, epidemiologists, clinicians, policy- and decision-makers, and representatives of regulatory bodies and agencies, donor agencies and international organizations.

1.6 Rationale

The area of NMC development is rapidly progressing, with several candidates in advanced clinical trials. At the same time, research scientists continue to look for novel male-directed contraceptives that are efficacious, safe and acceptable in order to expand

contraceptive options for men and promote shared responsibility for pregnancy prevention.

TPPs NMC are crucial in guiding consensus among MC product developers, regulatory authorities, procurement agencies and other key stakeholders on the optimal characteristics of NMCs, including the minimal essential characteristics for their usability, while taking cognizance of end user preferences and public health priorities in sexual and reproductive health (SRH).

This is the first TPP for NMC from WHO, published in line with the organization's core function to provide global technical leadership for public health.

1.7 Scope

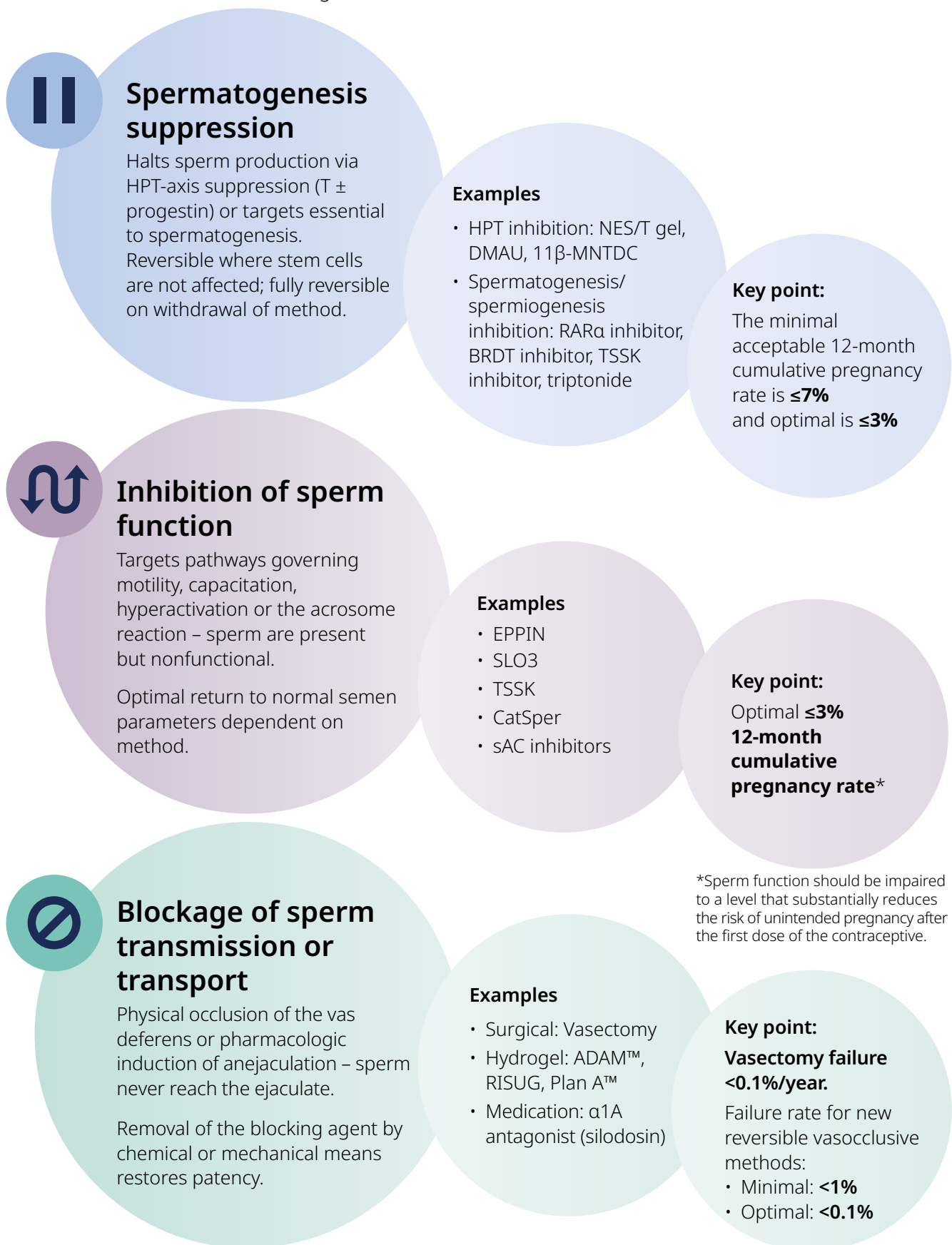
This document includes TPPs NMCs with the following modes of action:

- spermatogenesis suppression
- inhibition of sperm function
- blockage of sperm transmission or transport.

Fig. 2 provides an overview of the modes of action, examples of NMC candidates, and effectiveness profiles associated with each of the three TPPs described in this document.

Fig. 2. NMC modes of action

This document includes the following:



Abbreviations: 11β-MNTDC – 11β-methyl-19-nortestosterone dodecylcarbonate, BRDT inhibitor – bromodomain testis-specific protein, CatSper – cation channel of sperm, DMAU – dimethandrolone undecanoate, EPPIN – epididymal protease inhibitor, HPT – hypothalamic-pituitary-testis, NES/T gel – Nestorone®/Testosterone, RARα inhibitor – retinoic acid receptor alpha inhibitor, RISUG – reversible inhibition of sperm under guidance, sAC – soluble adenylyl cyclase, SLO3 – slowpoke homolog 3, T – testosterone, TSSK – testis-specific serine/threonine kinase.

2 Methodology for development of target product profiles for novel male contraceptives

The WHO Department of Sexual, Reproductive, Maternal, Child and Adolescent Health and Ageing, also referred to as Advancing Life Course Health and Reproduction (LHR), which includes the UNDP-UNFPA-UNICEF-WHO-World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), plays a unique role in convening high-quality multisite/country research as well as developing normative documents in the field of SRH by assembling researchers, scientists, donors, policy-makers and implementers. Its position, and its internationally recognized mandate and strong technical expertise in this field, makes WHO LHR/HRP a unique international entity able to accelerate progress in the development and further dissemination of the TPP NMC.

The TPP NMC was developed in accordance with the second edition of *WHO target product profiles, preferred product characteristics, and target regimen profiles: standard procedure* (57). Recognizing the advances in male contraceptive development, with several candidates in clinical trials, WHO LHR/HRP undertook a global study on men and women's knowledge, attitudes and behaviours concerning male contraception. The findings of this study added to the body of evidence concerning men's willingness to use NMCs and on their female partners' willingness to rely on NMC as their sole contraceptive method (39).

Consultations with stakeholders involved in male contraceptive development – for example, the Male Contraceptive Initiative (MCI), stakeholders working on male engagement in SRH (for example, UNFPA) and discussions in conferences such as the International Consortium for Male Contraception (ICMC) – surfaced the need to start preparations for market introduction as well as the need to develop global regulatory standards for the development and implementation of NMCs. This prompted WHO to start work on the first TPPs for NMCs, earmarking it as a priority technical product and granting the requisite approvals for their development.

2.1 TPP Development Group

Consistent with WHO's organizational requirements, a TPP Development Group (DG) was established to oversee the TPP development process. International experts with significant experience in men's reproductive health and research, including male contraceptives, andrology, and biomedical sciences, were identified to be part of this group. Once the list of potential members was finalized, WHO explored their interest in becoming members of the TPP DG, with specified terms of reference. Their CVs, individual agreements and declarations of interest (DOIs) were submitted to the WHO Secretariat. All DOI forms were carefully reviewed and assessed in collaboration with the WHO Office of Compliance, Risk Management and Ethics (CRE). A summary of the assessment and recommendations for mitigating potential risk follows:

- None of the candidates was receiving remuneration for being employed/contracted by a private-sector entity working on male contraception.
- The research grants declared predominantly 1) targeted the sperm function in the female tract or 2) were linked to basic research.
- The patents declared were not considered male contraception, have not been licensed yet or are without personal benefit.

In light of the above discussions, the WHO Secretariat in consultation with the CRE invited the proposed experts to be members of the TPP DG. However, whenever any topic related to the declared interests was discussed, the affected TPP DG members were recused from active discussion and decision-making on the matter/approach/product in question. Additionally, the ethics unit noted the possible bias of some candidates who declared interests related to female contraception; these were monitored, and no instances of concern occurred during the meeting or at any time throughout the TPP development.

2.2 Decision-making

A landscape review of existing and novel male contraceptives was conducted to inform the development of TPPs. WHO-approved recommendations and guidance for implementing

quality assurance were foundational for the TPP development. Under the supervision of the WHO Steering Group, the TPP DG was tasked to advise WHO on the critical characteristics and performance specifications needed for the development of this first WHO TPP NMC and to provide recommendations on optimal and minimal criteria for all defined NMC product features. The DG decided to focus on developing TPPs for male contraceptives that act on suppression of spermatogenesis, inhibition of sperm function or blockade of sperm transmission or transport since these were the NMCs already in clinical trials. Between 30 January 2025 and 11 December 2025, the TPP DG met monthly on a virtual platform where the DG experts discussed and proposed the parameters for each TPP and agreed on the content and value for each parameter. Appropriate literature, including published systematic reviews on the topics, informed these discussions.

After initial discussions and setting of the parameters, the DG divided into three smaller working groups to critically review each parameter and the related profile values. Each team tackled one of the three TPPs based on their knowledge of the field and published literature. As this is the first TPP NMC developed by WHO, the DG focused on providing guidance on the minimal and the optimal criteria for all defined product features. All members of the TPP DG reviewed the draft content and participated in regular update and feedback rounds organized via email and tele/videoconferences. Revisions were agreed by consensus. Disagreements on the technical content were resolved through discussion and, if necessary, through open voting. The profiles were then revised or updated based on the discussions and any additional evidence obtained.

2.3 Delphi survey

Following the drafting of the TPPs, a Delphi survey was undertaken to obtain concurrence on specific parameters requiring full agreement. MC TPP 2 "Inhibition of Sperm Function" was excluded from the Delphi survey because it already had full consensus among all members of the TPP DG. All 15 members of the TPP DG completed the Delphi surveys for MC TPP 1 "Suppression

of Spermatogenesis” and MC TPP 3 “Blockade of Sperm Transmission/Transport”. A 75% threshold was applied to assess the level of agreement. This threshold was reached for TPP 1. Disagreements on the proposed value for “Effectiveness” in TPP 3, “Blockade of Sperm Transmission/Transport”, were discussed further at the TPP DG meeting on 8 December 2025, and, through open voting, the majority of TPP DG members approved the adjustment of the value. Analysis of the two Delphi surveys found no other disagreements between members of the TPP DG. (Results are available upon request via email to WHO [srhcf@who.int])

2.4 Public review

The draft TPP document was posted on the WHO LHR/HRP website for public review for 28 days, from 3 March 2026 to 3 April 2026. Potential TPP end users were invited to assess the profiles, their feasibility and their acceptability, using a structured questionnaire. The targeted users included reproductive health experts, health care providers working in andrology, researchers in the field of SRH, including male contraceptive product developers and manufacturers. The TPP DG discussed comments in a meeting on 30 April 2026. Their comments were used to revise the TPPs. The revised TPPs were circulated to all TPP DG members, and further revisions were made before finalization and submission for requisite approvals by WHO.

3

Target product profiles for novel male contraceptives



3.1 Target product profiles for novel male contraceptives that suppress spermatogenesis



3.2 Target product profiles for novel male contraceptives that inhibit sperm function



3.3 Target product profiles for novel male contraceptives that cause blockade of sperm transmission/transport

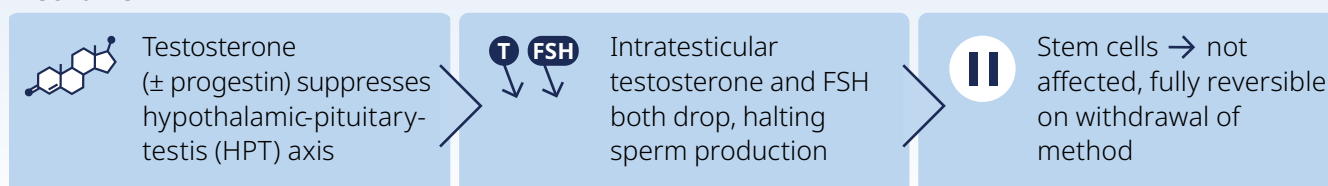


3.1 Target product profiles for novel male contraceptives that suppress spermatogenesis

Goal: development of a safe, reversible method of male contraception that functions by suppressing sperm production.

Fig. 3. TPPs for NMCs that suppress spermatogenesis

Mechanism



	Minimal	Optimal
Effectiveness	90% of men suppressed to $\leq 1\text{M}$ sperm/mL ejaculate within 12 weeks	95% of men suppressed to $\leq 1\text{M}$ sperm/mL ejaculate within 8 weeks
Return to fertility ($\geq 16\text{M}$ sperm/mL ejaculate)	12 months	6 months
Target price	<\$30/month	<\$5/month

Route



Oral



Injectable



Gel



Implant

3.1.1 Preamble

Mechanisms of action of spermatogenesis suppression agents. Hormonal MC methods using testosterone alone or testosterone combined with a progestin (or another gonadotropin-suppressing agent) suppress the hypothalamic-pituitary-testis (HPT) axis (similar to female hormonal contraception). In men this decreases the intratesticular testosterone concentrations and suppresses follicle-stimulating hormone, leading to profound spermatogenesis suppression (54) (see Fig. 1). Circulating testosterone is maintained by administration of testosterone at a physiological level. Spermatogonia (stem cells in the testis germinal epithelium) are not affected and so, when hormones are withdrawn, full spermatogenesis resumes, resulting in reversible MC (53, 54). Development of this group of NMC methods is the most advanced, with analysis ongoing for phase 2b trials providing efficacy and safety data. The next step would be a phase 3 clinical trial or trials for regulatory approval.

Targets for other approaches to NMC include genes, proteins or signalling molecules that are important for sperm production, maturation or function. These MC targets can be verified using gene knockout models (experimental deletion of the gene) in animals and screens for inhibitors of the target protein using high-throughput screening of existing and new compounds. Drugs identified as affecting these targets would then undergo efficacy in vivo, toxicology and preclinical studies before human studies are undertaken (54, 58). New agents directly target the testis; agents such as inhibitors of retinoic acid biosynthesis (59) and retinoic acid receptor α antagonist (60) induce reversible infertility by arresting spermatogenesis either at spermatogonial differentiation or at the spermatocyte and spermatid stage and induce apoptosis of the elongated spermatocytes (61). Preclinical studies have demonstrated that withdrawal of these agents results in reversal of the inhibition of spermatogenesis and return to fertility (60). Retinoic acid receptor α inhibitors are in phase 1 safety and tolerability clinical trials (62). Other compounds that directly affect spermatogenesis include bromodomain testis-specific protein (BRDT) inhibitors (63) and testis-specific serine/threonine kinase (TSSK) inhibitors, which act on post-meiotic sperm and spermiogenesis thus affecting sperm morphology (64). In rodents triptonide induces abnormal sperm morphology and decreases fertilizing capacity; in primates triptonide decreases sperm concentration (65).

Biomarkers of efficacy of spermatogenesis suppression: sperm concentration and output. Clinical trials of hormonal MC initially used suppression of spermatogenesis to a sperm concentration of ≤ 3 million sperm/mL of ejaculate as the threshold for entry into the efficacy phase of testing, where couples used the NMC as the sole method of contraception (47, 48). This was reduced by NMC development experts to ≤ 1 million sperm/mL ejaculate (66). Large multicentre clinical trials with testosterone alone (67, 68) or testosterone with a progestin (69) verified that, when the male's sperm concentration is suppressed to ≤ 1 million sperm/mL ejaculate, the hormonal MC is as effective as hormonal female reversible contraceptive methods. Despite these data from relatively large clinical trials, it should be noted that residual sperm may be able to initiate a pregnancy. There are data to suggest that men of different ethnicities may have different rates of spermatogenesis suppression (70, 71). Based on the results of the clinical studies, a reduction of sperm concentration to azoospermia in most men and/or severe oligozoospermia (≤ 1 million sperm/mL ejaculate) has been used as a biomarker and a goal for spermatogenesis suppression agents (72). This should be verified for non-hormonal agents, which may have different thresholds for contraceptive efficacy.

Efficacy goal for agents that suppress spermatogenesis. The failure rate used in contraceptive development is expressed as the number of unintended pregnancies per year in

females while their male partners are using NMC. Calculated with the Kaplan–Meier analyses (43, 55), the rate of unintended pregnancy with a NMC should be similar or better than that of effective

female methods such as female combined hormonal contraceptives – that is, lower than roughly a 7% risk of unintended pregnancy in 12 months (73, 74).

3.1.2 TPPs for NMCs that suppress spermatogenesis

Parameter	Product profile				
Goal of product	The goal of this TPP is the development of a safe, reversible method of male contraception that functions by suppressing sperm production.				
Target population	Men over the age of 18 years at risk of fathering an unintended pregnancy. Clinical trials have not included men under the age of 18 years because the safety of MC agents for pubertal testes is not known and, as of 2026, is not available. The minimum age of use may vary based on local legislation or regulations governing contraceptive use and clinical trials, and it may be lowered over time as additional safety data become available.				
Intended use	The intended use of a male contraceptive that suppresses spermatogenesis is to prevent unintended pregnancy in the female sexual partner when the man/couple do not wish to have a child at a given time in their reproductive lives.				
Target use setting	Health care settings, particularly at the primary care level (level 1) or above (health care facility levels 2 and 3), in ambulatory clinics or doctors' offices outside of health care facilities, and in pharmacies. They may also be prescribed in clinics or family planning centres or available via telehealth. A broad range of health care personnel can provide these methods, including primary care and family planning providers such as nurses and midwives, general doctors and specialist providers, including urologists, endocrinologists and gynaecologists.				
Effectiveness	The product should prevent pregnancy to the same extent as current reversible female user-controlled contraceptive methods. (Typical-use 12-month cumulative pregnancy rates are about 7% for female combined hormonal patches and pills and, for perfect use, about 3% [73, 74]). For agents that suppress spermatogenesis, clinical efficacy studies suggest that, if sperm output is suppressed to ≤ 1 million sperm/mL ejaculate, the efficacy of preventing pregnancy is similar to that of female hormonal contraceptive methods (67, 69). <table> <tr> <th>Minimal</th><th>Optimal</th></tr> <tr> <td> 90% of men with sperm suppression to ≤ 1 million sperm/mL ejaculate. - Time to suppression to ≤ 1 million sperm/mL ejaculate: within 12 weeks. - Failure to prevent pregnancy: Kaplan–Meier 12-month cumulative pregnancy rate $\leq 7\%$. </td><td> 95% of men with sperm suppression to ≤ 1 million sperm/mL ejaculate. - Time to suppression to ≤ 1 million sperm/mL ejaculate: within 8 weeks. - Failure to prevent pregnancy: Kaplan–Meier 12-month cumulative pregnancy rate $\leq 3\%$. </td></tr> </table>	Minimal	Optimal	90% of men with sperm suppression to ≤ 1 million sperm/mL ejaculate. - Time to suppression to ≤ 1 million sperm/mL ejaculate: within 12 weeks. - Failure to prevent pregnancy: Kaplan–Meier 12-month cumulative pregnancy rate $\leq 7\%$.	95% of men with sperm suppression to ≤ 1 million sperm/mL ejaculate. - Time to suppression to ≤ 1 million sperm/mL ejaculate: within 8 weeks. - Failure to prevent pregnancy: Kaplan–Meier 12-month cumulative pregnancy rate $\leq 3\%$.
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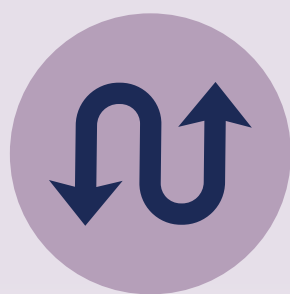
Parameter	Product profile				
Equipment	- Tablets will need a container tested for pharmaceutical use, providing sterility, protection from heat and humidity, a child-proof opening top. - Injectables will need disposable needles and, preferably, prefilled syringes with fixed or adjustable volume delivery; painless delivery preferred. Gels will need metered pumps or containers with controlled delivery volume, or packets with fixed volumes of the gel.				
Target use	Minimal and optimal: Suppression of sperm production (≤ 1 million sperm/mL ejaculate) in two consecutive samples about a week apart. Alternative thresholds may be appropriate with other agents that have mixed mechanisms of action, but no data are available for these agents at present.				
Mode of action	Suppression of sperm production to azoospermia or severe oligozoospermia (≤ 1 million sperm/mL ejaculate). <table> <tr> <th>Minimal</th><th>Optimal</th></tr> <tr> <td>90% of men who use the product consistently achieve suppression to ≤ 1 million sperm/mL ejaculate in 12 weeks.</td><td>95% of men compliant with the method achieve suppression to ≤ 1 million sperm/mL ejaculate in 8 weeks.</td></tr> </table>	Minimal	Optimal	90% of men who use the product consistently achieve suppression to ≤ 1 million sperm/mL ejaculate in 12 weeks.	95% of men compliant with the method achieve suppression to ≤ 1 million sperm/mL ejaculate in 8 weeks.
Minimal	Optimal				
90% of men who use the product consistently achieve suppression to ≤ 1 million sperm/mL ejaculate in 12 weeks.	95% of men compliant with the method achieve suppression to ≤ 1 million sperm/mL ejaculate in 8 weeks.				
Contraindications	For all products these include: - known hypersensitivity to any component of the investigational product; - abnormal serum chemistry values that may indicate clinically significant liver or kidney dysfunction; - uncontrolled hypertension or severe heart failure; - known history of primary testicular disease or disorders of the hypothalamic-pituitary axis; and - known history of significant cardiac, renal, hepatic or other chronic diseases. For products containing androgens (testosterone) and other hormones, additional contraindications or specific warnings may apply, including: - history of severe depression or other major psychiatric disorders; - history of, or high risk factors for, thromboembolic disease; - prostate-specific antigen (PSA) levels ≥ 4 ng/mL (should be within the reference range by age and population); - history of prostate, testicular or breast carcinoma (only for products containing androgens); and - symptoms of significant lower urinary tract obstruction (International Prostate Symptom Score >15).				

Parameter	Product profile	
Efficacy	Minimal	Optimal
1. Biomarkers as surrogates for efficacy before prevention of pregnancy studies 2. Prevention of pregnancy studies using Kaplan–Meier assessment for cumulative pregnancy rates	1. Typical use: suppression of sperm to ≤ 1 million/mL ejaculate achieved in 90% of men. 2. Kaplan–Meier 12-month cumulative pregnancy rate of $\leq 7\%$.	1. Perfect use: suppression of sperm to ≤ 1 million/mL ejaculate achieved in 95% of compliant men. 2. Kaplan–Meier 12-month cumulative pregnancy rate of $\leq 3\%$ per year.
Time to result	Minimal	Optimal
	Suppression of sperm production to ≤ 1 million/mL ejaculate within 12 weeks.	Suppression of sperm production to ≤ 1 million/mL ejaculate within 8 weeks.
Route of Administration	Minimal	Optimal
	• Oral tablets or gel dose: self-administered daily. • Injections: monthly or longer. • Implants: once every 6 months or longer.	• Oral or other daily formulation: self-administered daily. • Injections: once in 3 months, 6 months or 12 months. • Implants: once every 12 months; preferably biodegradable.
Dosage schedule	Minimal	Optimal
	Used for several years, depending on the users' preference.	Used indefinitely, depending on the couples' preference.
Return to normal range of semen parameters/ characteristics	Minimal	Optimal
	Return to reference range of sperm concentration (at least 16 million/mL ejaculate) within 12 months.	Return to reference range of sperm concentration (at least 16 million/mL ejaculate) within 6 months.

Parameter	Product profile	
Side-effect profile	Minimal	Optimal
	• Serious side-effects similar to or less frequent or less severe than those of products approved for similar conditions (for example, female hormonal contraceptives, testosterone). • Less than 10% incidence of moderate adverse events such as depression or changes in libido or erection. • Any increased incidence of birth defects in children born after use of a male contraceptive above the expected incidence in the general population would be unacceptable. • Rare serious adverse events would be tracked in future post-marketing surveillance when products become available.	• No serious side-effects. Any side-effects would be mild or moderate (<10% incidence of the most common side-effects). • Less than 5% of users with moderate/severe adverse events, including decreased libido or erection, or depression.
Shelf life	Minimal	Optimal
	1 year without refrigeration.	More than 2 years without refrigeration.
Infrastructure	Minimal	Optimal
	• Trained health care providers for counselling and screening for contraindications, at least via telemedicine. • Efficacy and biomarker testing available via mailed samples.	• Trained health care providers for counselling and screening for contraindications, including via telehealth. • Methods to be self-administered and efficacy/ biomarker testing available at the health service delivery point or at home (for example, at-home sperm test kit), with immediate results, or samples can be mailed. • Injection provided as prefilled syringes to be administered by user after training by provider.
	• Trained and qualified staff to administer any medications requiring implantation or injection, providers trained for both implant insertion and removal. • User-controlled methods (daily use of gel or oral pills) require trained health workers only to provide supplies and to check for contraindications in labelling.	

Parameter	Product profile	
Product kit	According to the specific product. All materials required for one individual to use the product, including devices and other consumables (for example, alcohol swabs) included in packaged, self-contained kit (either packaged individually as one product per kit or sufficient for the number of applications in the product kit box – for example, 30, 50 or 100). Product kit should include detailed information, for example: Oral – dosage, when and how to take, missed doses, what to avoid, etc. Gel application – areas of application (shoulder or upper arms). Instructions on how to apply the gel. (Must wash hands after each application. Wait as long as possible before showering or washing. Wash application site or wear clothing to cover application site before close skin contact with another person, to avoid skin-to-skin transfer of active product.) Injections – instructions on how to use the prefilled syringes and body sites that can be used for injections, use of alcohol swabs. Implants – require training in insertion (and removal) – detailed instructions on how to insert implants. Appropriate disposable trocar for insertion should be supplied. Biodegradable products may be an option.	
Additional consumables required but not provided in the product kit	Potentially, prefilled syringes, canisters of gel or bottles of tablets for dispensing medication. For injectables, if prefilled syringes are not available, vials, needles and syringes for administration.	
Product kit stability and storage conditions	Minimal	Optimal
	12 months stability stored at room temperature (20–25 °C or 68–77 °F) at 70% humidity.	24 months stored at room temperature (20–25 °C or 68–77 °F) at 90% humidity.
Operating conditions	The minimal or optimal characteristics may differ according to different products and excipients (for example, a canister of gels with alcohol content is flammable). To be discarded or recycled according to manufacturer's recommended procedures. Acceptable temperature variation would depend on stability testing for each product.	
Environmental tolerance of packaged product kit	Minimal	Optimal
	For orals, gels and other user-controlled methods, ambient temperature between 15 °C and 40 °C at altitudes up to 2000 metres, extremely low relative humidity.	For orals, gels and other user-controlled methods, ambient temperature between 10 °C and 45 °C at altitudes up to 4500 metres; both low and high relative humidity.
Training required	Minimal	Optimal
	Counselling should be available online and in person and should take no more than 30 minutes.	Counselling should be either in person or available online, with the ability to ask questions of experts, and should take no more than 15 minutes.
Clean water	Clean water should be available for the administration of oral dosage forms and cleaning of any instruments used during administration (for example, with implants). Sterilization of needles or trocars is required or, preferably, single-use/disposable materials.	

Parameter	Product profile	
Waste/disposal requirements	Minimal	Optimal
	Used containers should be discarded in household trash in a manner that prevents accidental application or ingestion by children or pets. Injection syringes and needles must be disposed of according to national guidelines.	Used containers are recyclable. Biological products are disposed of in special biohazard containers. Syringes are placed in sharps containers and disposed of according to national guidelines.
Device control	Minimal	Optimal
	For all formulations, expiration dates based on stability testing should be included in the package labelling. Contraceptive gels: 2 years Pills: 2 years Injectables: 2 years Implants: 1 year	Expiration dates in addition to physical methods (for example, chemical strips, visual inspection to exclude precipitation of injected solutions) to check the full potency of the contraceptive. Contraceptive gels: 3 years Pills: 4 years Injectables: 3 years Implants: 3 years
Regulatory requirements, compliance with appropriate standard/regulations	- Any male contraceptive will require registration as a medicinal product or medical device and approval prior to clinical use in accordance with national legislation. - FDA/EMA approval, aligned with the required standards and regulatory processes of each country according to International Council for Harmonization (ICH) guidelines. - WHO provides a list of WHO-listed authorities, that is, regulatory authorities or regional regulatory systems that comply with all the relevant indicators and requirements specified by WHO for regulatory capability as defined by an established benchmarking and performance evaluation process. See https://www.who.int/initiatives/who-listed-authority-reg-authorities.	
Health service user identification capability	Ideal: providers should be qualified medical professionals with current, unexpired licences. For implantation and removal of implants, an additional training certification may be required.	
Target price per product kit	Minimal	Optimal
	Less than US\$ 30 per month or US\$ 360 per year for effective contraception in low- and middle-income countries.	Less than US\$ 5 per month or US\$ 60 per year. Very low cost to low- and middle-income countries. Scalable global production.

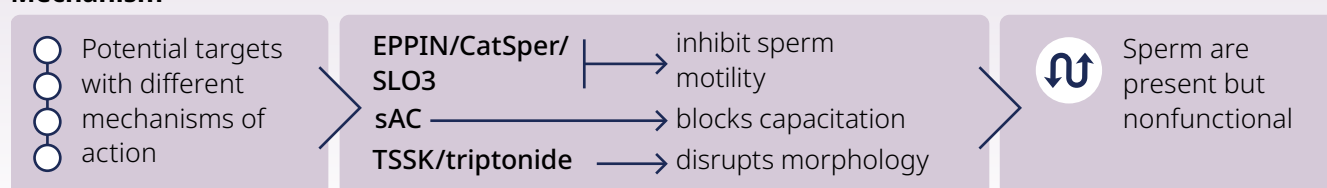


3.2 Target product profiles for novel male contraceptives that inhibit sperm function

Goal: development of a safe, reversible method of male contraception that functions by inhibiting sperm function and reducing the capability of sperm to reach the ovum, penetrate the egg or fuse with it to achieve fertilization.

Fig. 4. TPPs for NMCs that inhibit sperm function

Mechanism



	Minimal	Optimal
Effectiveness	Acceptable 12-month cumulative pregnancy rate is $\leq 7\%$	Acceptable 12-month cumulative pregnancy rate is $\leq 3\%$
Return to fertility (sperm function at normal range) <i>Dependent on method</i>	1 month	1 day
Target price	<\$30/month	<\$5/month

Route



Oral



Injectable
(IM or SC)



Transdermal



Sublingual

Abbreviations: CatSper – cation channel of sperm, COCs – combined oral contraceptives, DMPA – depot medroxyprogesterone acetate, EPPIN – epididymal protease inhibitor, IM – intramuscular, NET-EN – norethisterone enanthate, sAC – soluble adenylyl cyclase, SC – subcutaneous, SLO3 – slowpoke homolog 3, TSSK – testis-specific serine/threonine kinase

3.2.1 Preamble

This TPP describes several potential targets that inhibit sperm function including sperm motility, development of normal morphology, capacitation and sperm fertilizing capacity. The mechanisms of action differ widely. NMCs for this category that are in development may differ in time to effectiveness and duration of use based on their mechanism of action and route of administration. High-throughput screening can be used to identify potential candidate drugs, usually inhibitors of a target protein important in sperm function. Many of these targets have been verified in in vitro systems and then in preclinical studies. As of 2026 clinical studies are imminent but have not yet started. These agents are, therefore, less developed than those that suppress spermatogenesis or block sperm transmission/transport (54, 58, 75).

Mechanisms of action, The target inhibitors have different mechanisms of action (Table 1). It should be noted that the efficacy of these methods has been demonstrated, to date, only in preclinical studies. Because the mechanisms of action are so different, the time to efficacy depends greatly

on the method. For example, soluble adenylate cyclase is being developed as a rapid onset and offset method. Other approaches that inhibit sperm hyperactivation, which usually occurs in the Fallopian duct, could be developed as a male- and female-controlled NMC.

Table 1. Mechanism of action for NMC that inhibit sperm function

Mechanism of action	Example (reference numbers)	Status (2026)
Blockade of semen liquefaction and impaired sperm motility	EPPIN (76–80)	Preclinical
Inhibition of sperm hyperactivated motility via inhibition of calcium influx	CatSper inhibitors (81–85)	Preclinical
Inhibition of sperm motility, acrosome reactivity and hyperactivation via inhibition of potassium efflux	SLO3 inhibitors (86–88)	Preclinical
Reduction in sperm motility, reduced ability of sperm to undergo capacitation via inhibition of cAMP formation in sperm, and consequently impaired acrosome reaction	Soluble adenylate cyclase (sAC) inhibitors (89, 90)	Preclinical
Reduction in sperm numbers, motility and morphology, consequently reducing fertilizing capacity via inhibition of testis-specific kinases	TSSK inhibitors (64, 91)	Preclinical
Reduction in normal sperm morphology and motility by disruption of mechanisms in spermiogenesis	Triptonide (65)	Preclinical

Biomarkers for effectiveness of agents that inhibit sperm function. For novel compounds such as EPPIN (epididymal protease inhibitor) that impair

sperm motility, the surrogate biomarker could be sperm motility. With the current data available for fertile and infertile men, it is not certain what the

lower threshold for sperm motility and morphology is that will prevent pregnancy in women (92). Further work will be required to learn how much sperm motility must be lowered to provide contraception. It may be that, for agents that alter sperm motility and morphology, a near-complete absence of motile or normal sperm will be required (72). For other compounds that affect sperm function, specific biomarkers need to be developed for each of the compounds in addition to sperm function tests such as acrosome reaction, hyperactivated motility or a combination of functional tests. Work will be required to determine the threshold levels of sperm functions, such as hyperactivated motility and acrosomal exocytosis, that are necessary for fertilization. The proposed biomarkers should be validated in fertile and infertile patient cohorts to establish clinically relevant ranges. In addition, their

predictive validity could be assessed by the degree to which the inhibitors or compounds impair these sperm functions and reduce fertilization success and then validated by efficacy in preventing pregnancy.

Efficacy goals for male contraceptive methods that inhibit sperm function.

Efficacy goals should be the same as for agents that suppress spermatogenesis. The failure rate used in contraceptive development is expressed as the number of unintended pregnancies per year in females while their male partners are using NMC. Calculated with the Kaplan–Meier analyses (55, 72), the rate of unintended pregnancy with a NMC should be similar or better than that of effective female methods such as female combined hormonal contraceptives – that is, lower than roughly a 12-month cumulative pregnancy rate of 7% (73, 74).

3.2.2 TPPs for NMCs that inhibit sperm function

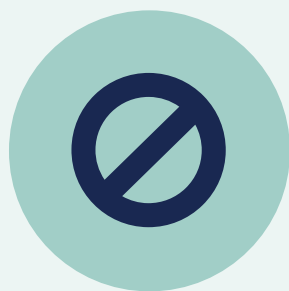
Parameter	Product profile
Goal of product	The goal of this TPP is the development of a safe, reversible method of male contraception that functions by inhibiting sperm function and reducing the capability of sperm to reach the ovum, penetrate the egg vestments, or fuse with the egg to achieve fertilization. This could include agents that target sperm motility, capacitation, hyperactivation or the acrosome reaction. (Agents that inhibit binding and fusion with an egg would be categorized as new female contraceptive methods.)
Target population	The target population is men over the age of 18 years (post-puberty, to ensure full development of spermatogenesis and functional sperm) at risk of fathering an unintended pregnancy. Clinical trials have not included men under the age of 18 years because the safety of MC agents for pubertal testes is not known and, as of 2026, is not available. The minimum age of use may vary based on local legislation or regulations governing contraceptive use and clinical trials, and it may be lowered over time as additional safety data become available.
Intended use	The intended use of a male contraceptive that impairs sperm function is to prevent unintended pregnancy when the man/couple do not wish to have a child at a given time in their reproductive lives.
Target use setting	Health care settings, particularly at the primary care level (level 1) or above (health care facility levels 2 and 3), in ambulatory clinics or doctors' offices, on demand outside of health care facilities, and in pharmacies. These could also be prescribed in clinics or family planning centres or available via telehealth. A broad range of health care providers can offer these methods, including primary care and family planning providers such as nurses and midwives, general doctors and other specialist providers including urologists, endocrinologists and gynaecologists.

Parameter	Product profile	
Effectiveness	Product should result in the prevention of pregnancy in the female partner to the same extent as current reversible female user-controlled hormonal contraceptive methods (combined oral contraceptives [COCs] and injectables such as depot medroxyprogesterone acetate [DMPA] and norethisterone enanthate [NET-EN]). The minimal acceptable 12-month cumulative pregnancy rate is less than 7%, and optimal is less than 3%. For pericoital time-dependent, as-needed methods, efficacy should be higher than that of other user-controlled, as-needed methods, such as the male condom (12-month contraceptive failure rate in typical use of 13%, and perfect use, 3%). Medications must be taken within a specified time period before intercourse; non-adherence to this time period may allow more failures than with condoms. It is prudent to set a threshold failure rate comparable to that of reversible female hormonal user-controlled methods, that is, about 7% per year for typical use.	
Equipment	Tablets need a container tested for pharmaceutical use that protects from heat and humidity, as well as a child-proof opening top. Injectables need disposable needles and, preferably, prefilled syringes with fixed or adjustable volume delivery. Painless delivery preferred. Gels need metered pumps or containers with controlled delivery volume. Alternatively, they can be supplied in packets with fixed volumes of the gel.	
Mode of action/ target use	Potential targets for male contraceptives that impair sperm function are shown in Table 1.	
Contraindications	Contraindications depend on the mechanism of action of the compound. They include: • hypersensitivity to any component of the investigational product; • history of severe male factor infertility; • with potassium or calcium channel blockers, potential for contraindications in settings of known ion channelopathies (for example, Brugada syndrome, long QT syndrome), although this is speculative at this point; and • for sAC inhibitors, history of nephrolithiasis (symptomatic or incidental) may be a contraindication.	
Efficacy	Minimal	Optimal
	Should be superior to the typical pregnancy rate observed with the sole use of a male-controlled barrier method (condoms) (that is, a 12-month cumulative pregnancy rate of <13%) and similar to the efficacy of female hormonal contraceptive methods (12-month cumulative pregnancy rate of $\leq 7\%$).	Better than the efficacy of female hormonal contraceptives (that is, a 12-month cumulative pregnancy rate of $\leq 3\%$). For time-dependent, as-needed methods, efficacy should be same as that of the perfect-use condom failure rate (12-month cumulative pregnancy rate of 2%) and similar to that of reversible, user-controlled female methods (12-month cumulative pregnancy rate of $\leq 3\%$).

Parameter	Product profile	
Time to result	The time to efficacy will depend on the individual method. This will need clinical studies. All these agents are currently at preclinical stages of development.	
	Minimal	Optimal
	Depending on the method, sperm function should be impaired to a level that substantially reduces the risk of unintended pregnancy after one month of administration.	Depending on the method, sperm function should be impaired to a level that substantially reduces the risk of unintended pregnancy after the first dose of the contraceptive.
Route of administration	Minimal and optimal: • Daily oral, transdermal or sublingual dosing is acceptable. • Weekly to monthly subcutaneous injection or intramuscular injection is acceptable. • Intravenous or other parenteral routes are unacceptable. • Drug should be safe to use for an extended period or indefinitely without concern related to long-term exposure.	
Dosage schedule	Minimal and optimal: Depends on the method. Minimum dose to achieve desired efficacy and safety standards.	
Return to normal range of semen parameters/ characteristics	Minimal	Optimal
	Depending on the method, sperm function (for example, motility) should return to the normal range as applicable within one month after contraceptive cessation.	Depending on the method, sperm function (for example, motility) should return to the normal range as applicable within one day after contraceptive cessation. Any instance of failure of fertility to return is unacceptable.
Side-effect profile	Minimal	Optimal
	• Side-effects would be mild (<20% incidence at most). • Any serious adverse event, such as death, heart attack or stroke, would be unacceptable. • Any increased incidence of birth defects in children born after use of a male contraceptive above the expected incidence in the general population would be unacceptable.	• Side-effects would be minimal and mild (<5% incidence at most). • Rare serious adverse events would be tracked in future post-marketing surveillance when products become available.
Shelf life	Minimal	Optimal
	Product is usable when stored at room temperature for 1 year without refrigeration. In cases where the product requires refrigeration, temperature requirements should not exceed those of common childhood vaccines provided at the primary level (2–8 °C or 36–46 °F).	Longer than 2 years without refrigeration.

Parameter	Product profile	
Infrastructure	Minimal	Optimal
	• Trained providers for counselling and screening for contraindications, at least via telemedicine. • Efficacy and biomarker testing available via mailed-in samples. • Staff qualified to administer any medications requiring injection or insertion of implants.	• Trained providers, including community health workers, for counselling and screening for contraindications. • Methods ideally self-administered and user-controlled without the need for trained providers. • Efficacy/biomarker testing would be available on site or at home (for example, sperm-check kit), with immediate results. • Staff qualified to administer any medications requiring injections or insertion of implants.
Product kit	Product kit should include detailed information on proper use and administration of the male contraceptive. • Oral – frequency of dosing (for example, daily), time of day, whether to take with food or on an empty stomach, and other instructions regarding what to do in case of a missed dose, etc. • For injections – safe administration, dose frequency, how to safely dispose of used syringes. • For implants – the ideal state is a single-use/disposable sterile inserter and trocar.	
Additional consumables required but not provided in the product kit	Potentially, prefilled syringes or bottles of tablets for dispensing medication. If prefilled syringes are not available, vials, needles and syringes for administration.	
Product kit stability and storage conditions	Minimal	Optimal
	12 months stability stored in ordinary refrigerator (2–8 °C or 36–46 °F) for 12 months prior to use.	12 months stability stored at room temperature (20–25 °C) for periods of up to one year.
Environmental tolerance of packaged product kit	This will depend on the different products and excipients in each formulation. For example, an alcohol-containing transdermal formulation has the potential for flammability and should be stored away from heat sources and open flames. Heat excursions greater than 25 °C can be harmful for many solid dosage forms and should be avoided.	
Training required	Minimal	Optimal
	Counselling to providers-in-training should be available online and should take no more than 30 minutes.	Counselling to providers-in-training should be either in person or available online, with the ability to ask questions of experts, and should take no more than 15 minutes.
Clean water	Minimal: clean water should be available for administration of oral dosage forms and cleaning of any instruments used during administration (for example, with implants).	

Parameter	Product profile	
Waste/disposal requirements	Minimal	Optimal
	Used containers should be discarded in household trash in a manner that prevents accidental application or ingestion by children or pets. Injection syringes and needles must be disposed of according to national guidelines.	Used containers are recyclable. Biological products are disposed of in special biohazard containers, and syringes are placed, in sharps containers and disposed of according to national guidelines.
Device control	Minimal	Optimal
	For all formulations, expiration dates based on stability testing should be included on the package.	Expiration dates on packaging. Also, physical methods (for example, chemical strips, visual inspection to exclude precipitation of injected solutions) to check the potency of the contraceptive.
Regulatory requirements	- Any male contraceptive will require registration as a medicinal product or medical device and approval prior to clinical use in accordance with national legislation. - Additional approvals may be required depending on jurisdiction of use. For example, FDA approval would be required for use in the USA and EMA approval in the European Union. - WHO provides a list of WHO-listed authorities, that is, regulatory authorities or regional regulatory systems that comply with all the relevant indicators and requirements specified by WHO for regulatory capability as defined by an established benchmarking and performance evaluation process. See https://www.who.int/initiatives/who-listed-authority-reg-authorities.	
Health service user identification capability	Ideal: providers should be qualified medical professionals with current, up-to-date practice licences. For implantation, additional training certification may be required.	
Target price per product kit	Minimal	Optimal
	Less than US\$ 30 per month or US\$ 360 per year for effective contraception in LMICs.	Less than US\$ 5 per month or US\$ 60 per year in LMICs; scalable global production.



3.3 Target product profiles for novel male contraceptives that **cause blockade of sperm transmission/transport**

Goal: development of a long-acting and reversible or permanent method of contraception for males through occlusion of the vas deferens resulting in sperm transport blockade or a short-acting reversible MC that completely blocks ejaculation (anejaculation).

Fig. 5. TPPs for NMCs that cause blockade of sperm transmission/transport

Two possible mechanisms

1. Vas occlusion Blocks sperm transport



Injected compound (hydrogel or polymer) blocks the vas deferens (RISUG, ADAM™)



Physically stops sperm from reaching the ejaculate

Reversal is possible by flushing/dissolving

2. Medication Blocks sperm transmission



Sildenafil relaxes smooth muscle in the vas deferens and seminal vesicles

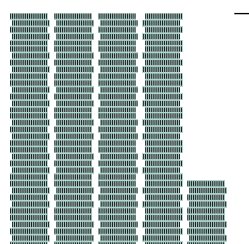


Causes anejaculation, without affecting erection or orgasm
→ reversible as the drug clears

Anejaculation preferably within a few hours after administration

		Minimal	Optimal
Efficacy	1. Vas occlusion <i>Azoospermia: 8 to 12 weeks after the occlusion</i>	<1% chance of pregnancy during one year of use	<1 pregnancy in 1000 couples during one year of use
	2. Medication	12-month cumulative pregnancy rate is ≤7%	12-month cumulative pregnancy rate is ≤3%
Return to fertility (sperm in ejaculate)	1. Vas occlusion	1 year	3 years
	2. Medication	Anejaculatory effect reverses in ~24 hours	

Target price



\$150+
Surgical vasectomy



\$30-75
Vas occlusion kit
Ideally a separate kit for each side of the scrotal sac

<\$2/dose
Medication

Route

1. Vas occlusion



Minimally invasive procedure (no-scalpel technique), performed by a trained provider

2. Medication



Oral, on-demand

3.3.1 Preamble

Blockade of sperm transport for male contraception has been successfully achieved with vasectomy and condoms. Indeed, these are the only methods of male contraception currently approved by regulatory authorities.

The contraceptive efficacy of vasectomy is very high (over 99%), and 12-month cumulative contraceptive failure rates are less than 0.1 pregnancy/year (93). Acceptance of vasectomy for contraception varies widely among regions and countries, but across LMICs just <0.1% of men rely on vasectomy (94). Further, the rate of vasectomies has decreased over the past 20 years. The current approach to vasectomy is universally the no-scalpel method (95), preferred for its demonstrated safety compared with scalpel-based entry methods (96–98).

Vasectomy is not reliably reversible. Reversal of vasectomy requires skilled surgeons, and even so the success rate and return to fertility is not guaranteed (99, 100). Pregnancy rates after reversal depend on the interval since vasectomy (101) and the age of the patient and his partner. While antisperm antibodies may develop after vasectomy, studies do not support the view that antisperm antibodies affect pregnancy rates after vasectomy reversal (102–104). In general, vasectomy techniques, success rate and assessment of post-vasectomy semen analyses follow the American Urological Association Guidelines (93), to which other professional urology associations also adhere (105).

Novel approaches to blocking sperm transmission/transport: mechanisms of action.

Research continues to progress on the injection of hydrogels into each vas deferens to occlude them. In theory, when fertility is desired, the hydrogel could be flushed out with fluids or solvents without surgery, thus reinstating the patency of the vas and subsequent fertility. Early clinical studies in India utilized styrene maleic anhydride (SMA) in a solvent vehicle of dimethyl sulfoxide (DMSO). Phase 1 and 2 clinical trials of this method, known as RISUG (reversible inhibition of sperm under guidance), showed azoospermia in all men (106, 107). The product is now being developed as Plan A™ – preclinical studies are complete, with early clinical studies demonstrating a high success rate (108).

Other studies of vas occlusion offered successful occlusion but not reversibility (109–111). A two-component hydrogel called ADAM™ has completed preclinical studies and is currently in Phase 1 clinical trials (112) to demonstrate efficacy and reversibility. These vas occlusion methods utilize disposable injection systems and require visual identification of the vas deferens through a no-scalpel vasectomy technique.

An alternative approach to blocking sperm transmission is the use of alpha 1 adrenoreceptor ($\alpha 1A$) receptor antagonists such as silodosin. Silodosin is a highly selective $\alpha 1A$ antagonist, and has been FDA approved since 2008 for the treatment of benign prostatic hypertrophy (BPH). Pharmacological blockade of $\alpha 1A$ with silodosin leads to relaxation of smooth muscle in the bladder and prostate, an improvement of urine outflow from the bladder, and a decrease in urinary symptoms in men with BPH or other causes of lower urinary tract symptoms (113). Silodosin's pharmacologic action also relaxes smooth muscle in the seminal vesicles and the vas deferens, frequently leading to a lack of emission and ejaculation, a condition called "anejaculation" during sexual activity. The absence of an ejaculate makes conception impossible. Investigators in India demonstrated complete anejaculation in 63 men 3 hours after dosing and no unintended pregnancy was reported over one year in these 63 couples who followed a regimen of engaging in intercourse only 3 hours after silodosin dosing (114). These studies need to be verified.

Biomarkers of blockade of sperm transmission/transport.

A single post-vasectomy semen analysis without centrifugation demonstrating azoospermia or less than 100 000 motile sperm/mL of ejaculate is defined as a success for vasectomy and provides a 12-month cumulative pregnancy of <0.1%. The sample can be submitted as early as 8 weeks after vasectomy. If there is persistent motile sperm, counselling for repeat vasectomy should be offered

6 months after the initial surgery (93). Surrogate biomarkers for vas occlusion with polymers or hydrogels should follow the vasectomy guidelines that are accepted throughout the world. Success of reversibility is demonstration of motile sperm in the ejaculate after the block is dissolved and/or flushed out (100).

For $\alpha 1A$ inhibition the data is very limited but suggest that complete blockade of sperm transmission (i.e. complete anejaculation) may be required for contraceptive effect which may depend on the timing of drug dosing and nature of intercourse. Additional study of this approach to male contraception in formal efficacy trials will be required.

Goals of efficacy and reversibility of vas occlusion as an NMC method. As vasectomy has been proven to be safe and effective, with a very low 12-month contraceptive failure rate of <0.1% (18), the goal of successful sperm transport blockade by vas occlusion should be the same as that for vasectomy (that is, <100 000 non-motile sperm in the ejaculate). The injection of occlusive agents into the vas deferens offers the possibility of flushing or dissolving the occlusive agent when reversal is desired. Alternatively, occlusive agents that are biodegradable after a certain period of years would avoid the need for skilled surgeons for removal or reversal (105). The use of an $\alpha 1A$ antagonist suggests that no ejaculate or very low sperm concentration and correct timing of administration will be required for effective contraception.

3.3.2 TPPs for NMCs that cause blockade of sperm transmission/transport

Parameter	Product profile	
Goal of product	The goal of this TPP is the development of a long-acting and reversible or permanent method of contraception for males through occlusion of the vas deferens resulting in sperm transport blockade or a short-acting reversible MC that completely blocks ejaculation (anejaculation).	
Target population	Minimal Men seeking contraception who can give consent for the procedure and understand the mechanism of action of the medication. For procedures, this will depend on local/country legislation and regulations governing provision of contraceptive methods requiring minimally invasive surgery.	Optimal For permanent occlusion: males or couples who have achieved their desired family size or number of children and who have been informed of the permanence of the contraceptive and the possibility of non-reversibility. For reversible occlusion: males seeking a long-acting but reversible method of contraception. For medication: men over the age of 18 desiring short-term/temporary immediate blockade of sperm transmission for male contraception.
Intended use	These methods prevent unintended pregnancy by blocking, or occluding, the vas deferens bilaterally, thereby preventing sperm transport into the ejaculate, or by preventing ejaculation and, thus, preventing the possibility of pregnancy. The intended use is to prevent conception by preventing the passage of sperm cells along the vas deferens during ejaculation in men who no longer want to have a child (for permanent methods) or long term (for reversible methods) or are interested in a medication that will temporarily block ejaculation.	

Parameter	Product profile
Target use setting	Health care settings, particularly at the primary care level (community-based facilities preferably to further universal health care) or above (health care facility levels 2 and 3), in ambulatory clinics or doctors' offices, on demand outside of health care facilities, or outreach services setting. Health workers: primary care providers, family planning providers, other specialist providers (urologist-surgeons, health professionals trained to perform the procedure of vas deferens blocking).
Effectiveness	For vas occlusive methods, azoospermia or a sperm concentration <100 000 non-motile sperm/mL of ejaculate. The product should result in prevention of pregnancy in the female partner with efficacy similar to that of highly effective female methods of contraception (female sterilization) in both typical and perfect use scenarios. For medications, complete blockade of sperm transmission or no ejaculate. The efficacy should be higher than that of other user-controlled, as-needed methods such as the condom (typical-use pregnancy rate 13%, perfect-use pregnancy rate 3%). Medications must be taken within a specific timeframe before intercourse and may lead to more failures than condoms. It is prudent to align the failure rate with reversible female hormonal user-controlled methods, that is about 7% for typical use over 12 months.
Equipment and provider proficiency	• WHO advises that a vasectomy procedure be performed by a health or paramedical professional trained in performing no-scalpel vasectomy; this includes competencies in accessing the vas deferens (18, 25, 115). Requirements should be similar for vas occlusion methods, where injection under direct visualization of the vas deferens is required for inserting/injecting (cure-in-place) the occluding agent within the lumen of the vas deferens (105). For vas blockage, minimally invasive procedures, such as the no-scalpel technique, are the preferred approach (18, 93). • Depending on the method of vas deferens blocking, the procedure is expected to include the following: • minimally invasive surgical access with small incisions to allow visual inspection of the vas deferens bilaterally, with minimal need for post-procedure repair/closure; • usual no-scalpel vasectomy instruments – device kits provided by the manufacturer of an injection system designed for the vas occlusion product; • may use a syringe for injection of agents that block the vas deferens; and • percutaneous injection techniques may require ultrasound or other modalities to visualize the lumen of the vas deferens. • Generally, these procedures are to be done using direct visualization or using special instruments for better visualization, although percutaneous procedures may be possible. • In practice, all procedures should be performed under aseptic and antiseptic conditions. • For medications, providers should be familiar with the mechanism of action to counsel men about the correct timing of usage and the potential for side effects (for example, orthostasis and sinus congestion).
Target use	Minimal and optimal: blocking the vas deferens bilaterally by injecting an occluding agent.

Parameter	Product profile	
Mode of action	The vas deferens blocking methods prevent the passage of sperm cells along the vas deferens to the ejaculatory ducts, thereby preventing the release of sperm during an ejaculation. Importantly, there may be residual sperm cells in the portion of the vas deferens distal to the site of occlusion until around 12 weeks after the vas occlusion. α1A antagonists block ejaculation while allowing for erection and orgasm. Appropriate timing and proper use of these medications should allow for complete anejaculation and effective contraception.	
Considerations following the medical eligibility criteria (MEC) for male voluntary surgical contraception (11)	1. Caution for young males because this group is more likely than older groups to have the procedure reversed (116, 117). 2. Caution for those with scrotal tumours, cysts or previous scrotal injury, which should be managed before any procedure. 3. Delay the use of this method for men with local infection, systemic infection or gastroenteritis, filariasis or elephantiasis, undiagnosed intra-scrotal mass. 4. Potential special considerations for coagulation disorders, cryptorchidism, inguinal hernia, severe or advanced HIV clinical disease. 5. Most men should be able to safely use α1A antagonists.	
Efficacy	Minimal • For vas blocking methods: <1% failure rate (<1% chance of pregnancy during one year of use). • For medications: 12-month cumulative pregnancy rate of $\leq 7\%$.	Optimal • For vas blocking methods: <0.1% failure rate (< one pregnancy in 1000 couples during one year of use). • For medications: 12-month cumulative pregnancy rate of $\leq 3\%$.
Time to azoospermia/anejaculation	Azoospermia: 8 to 12 weeks after the occlusion of the vas deferens. Anejaculation: preferably within a few hours after administration of the agent.	
Reversal of vas occlusion to restore fertility	Minimal For vas blocking methods: The vas deferens occlusion material may be a hydrogel or other material that may be biodegradable after a certain time as defined by the manufacturer. Demonstration of sperm in ejaculate after reversal at least 1 year after vas deferens blocking. Reversal may also be achieved through an injection to dissolve any previous blocking agent or by flushing the prior block. Presence of motile, morphologically normal sperm after the reversal procedure shows evidence of reversal but does not equate a return to fertility. For medications: anejaculatory effect should be reversed in ~24 hours	Optimal Demonstration of sperm in ejaculate after reversal at least 3 years after vas deferens blocking. Reversal may be achieved through injection of another substance to dissolve the block or flushing the blocking material, through ultrasound, or by removal of the blocking agent by chemical or mechanical means.

Parameter	Product profile	
Side-effect profile	Minimal	Optimal
	Pain at operative site and other complications uncommon (<5% of men). For medications: sinus congestion, weakness and orthostasis are possibilities, as is pelvic discomfort during orgasm. Rare serious adverse events would be tracked in future post-marketing surveillance when products become available.	Pain, hematoma, infection uncommon (<1% of men). New blocking agents need to be evaluated in preclinical trials and monitored in post-marketing phase 4 studies for possibility of carcinogenesis.
Required instruments	Minimal	Optimal
	Mechanical and electrical devices.	Other equipment and supplies, such as autoclave/sterilizer, soaking solutions and high-level disinfectants.
Duration of instrument use	Minimal	Optimal
	Sharp and pointed vas dissecting forceps are reported to dull after 40 uses.	The instruments last longer, especially if well maintained.
Infrastructure Depends on method or preferred technique of vas occlusion.	Minimal	Optimal
	For office- or clinic-based procedures, areas for privacy and antisepsis.	Surgical suites, especially for surgical procedures.
Health workforce	Minimal	Optimal
	Trained providers for counselling and screening for contraindications, and training to perform the procedure.	Trained service providers and primary care or family planning providers in a clinic set-up, at best with on-call clinicians and partner specialists who may address complications.
Product kit	The product to be delivered by a disposable syringe injection system or kit. This will differ among manufacturers. Equipment in the kit should preferably leave minimal environmental footprint, for example, use of compostable plastics as appropriate. Preferably, all materials required for product use, including devices or other consumables, should be included in a packaged, self-contained kit to be used for one individual. The kit for use on one side of the scrotal sac may require another set (or partial re-use) for the other side.	
	In addition to the vas deferens blocking instruments, the method requires anaesthetics and injections, drapes and operating gowns, running water for washing and sterilization equipment for the instruments. For injectable methods, the product will likely be delivered in a disposable syringe injection system or kit.	
Additional consumables required but not provided in the product kit		

Parameter	Product profile	
Operating conditions	While most surgeons and health workers performing minor surgery prefer cooler air-conditioned rooms, vas deferens occlusion or vas deferens blocking is best done where temperatures are high enough to avoid causing retraction of the scrotum so that the vas deferens to be manipulated more easily. The temperature of the operating room should be at least 20–25 °C or 70–80 °F (95).	
Training required	Minimal Training in counselling and in basic and/or comprehensive family planning – in particular, counselling that vas occlusion may not be reversible. Training on a preferred method of blocking the vas deferens.	Optimal In-house capacity to address complications or have referral arrangements. Capacity for reversal/removal of the vas deferens blockade. In some countries placement of the vas blocking agent may require a board-certified urologist or completion of a certification course.
Clean water	Minimal: clean running water should be available for cleaning, washing and for instrument processing.	
Waste/disposal requirements	Minimal Used containers should be discarded in household trash in a manner that prevents accidental application or ingestion by children or pets. Injection syringes and needles must be disposed of according to national guidelines.	Optimal Used containers are recyclable. Biological products are segregated in special leak-proof biohazard containers and disposed of according to national guidelines. Syringes are placed in puncture-resistant sharps disposal containers and disposed of according to national guidelines.
Regulatory requirements	Prior to clinical use, vas deferens occlusive male contraception will require registration as a medical device in accordance with national legislation and appropriate standard regulations (for example, by health ministries or departments, medical device regulatory agencies, health insurance agencies, environmental agencies and other national/subnational offices). Additional approvals may be required depending on jurisdiction. For example, FDA approval would be required for use in the USA and EMA approval within the EU. WHO provides a list of WHO-listed Authorities, that is, regulatory authorities or regional regulatory systems that comply with all the relevant indicators and requirements specified by WHO for regulatory capability as defined by an established benchmarking and performance evaluation process. See https://www.who.int/initiatives/who-listed-authority-reg-authorities . Medicines used in vas occlusion also should be approved by a WHO-listed authority.	

Parameter	Product profile
Cost per acceptor or couple-year of protection	The range of costs to a user of a surgical procedure for permanent male sterilization is US\$ 150 and higher. Where vasectomy is not provided free of charge, the range of costs to a user of a surgical injectable kit for long-acting contraception is around US\$ 30 to 40, but the possible need to use one kit for each side may bring the costs to US\$ 50 to 75. Since these are highly effective permanent or long-acting methods with high couple-years of protection, the costs per year of use progressively decline, making it much cheaper over a lifetime than other methods that incur recurrent costs. Medications should cost less than US\$ 2 per dose. Annual cost would depend on frequency of sexual intercourse.

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