TITLE: Testosterone Replacement for Testosterone Deficiency due to Testicular Failure/Insufficiency in Infancy

Introductory notes:

1. Within this document the terms *'male'* and '*female*' refer to biological sex; the terms *'boy'* and '*girl*' refer to a *'male child'* and '*female child'* respectively, as defined by the Oxford English Dictionary, used in references cited herein, and as generally understood.
2. A description of the physiology of gonadal and reproductive tract development in the male fetus and infant is provided in Addendum 1 (page 27).
3. A glossary of some key terms is provided as Addendum 2 (page 29).

Part 1. Details of the class of prescribed people

Please describe the class of prescribed people to which the proposed General Treatment Plan relates.		
See below		
Documents are attached and labelled as attachment A	☐ Yes	☒ N/A

The individuals for whom this general treatment plan is proposed are **prescribed individuals** under the Variation in Sex Characteristics (Restricted Medical Treatment) Act 2023, meaning individuals who have a congenital condition that involves sex characteristics and who do not have decision-making capacity regarding their personal health care. This treatment plan is proposed for individuals:

1. who have 46,XY karyotype;
2. who have male genitalia and were assigned male at birth;
3. who have testosterone deficiency due to **a diagnosis of primary testicular failure/insufficiency**;
4. who **do not have** a chromosomal variation (i.e., a karyotype other than 46,XY).

Primary Testicular Failure/Insufficiency

Children who suffer primary testicular failure/insufficiency have 46,XY karyotype and develop testes during early fetal life. The testes are apparently healthy and function normally during the prenatal period of male sex determination and differentiation (first trimester of gestation), but subsequently undergo a traumatic or degenerative change, destroying the cells that produce hormones and sperm (Hegarty 2007; Smith 1991; Spires

DRAFT

2000; Tack 2023; Zenaty 2006). The term "primary" refers to the fact that the pathological process directly affects testicular tissue itself, rather than another component of the hypothalamic-pituitary-testicular axis.

Pathophysiology

As noted above, the testes of affected infants are healthy and function normally during the critical period of male sex differentiation (first 12-14 weeks of gestation), so the internal and external reproductive structures generally develop in a typical fashion for a male fetus: the vas deferens develops, and there are no female internal reproductive structures such as uterus or fallopian tube (Hegarty 2007; Tack 2023: Zenaty 2006); external genital development, including that of the penile corpora and fusion of the urogenital sinus occur normally, the penis is fully formed, and scrotal and urethral fusion are completed without hypospadias (Tack 2023; Zenaty 2006). However, at some point late in pregnancy, during delivery, or after birth, an acute event causes irreparable damage to the testes, leading to degenerative changes and dysfunction affecting all components of testicular tissue – germ cells (the precursors of sperm), Sertoli cells (the supporting cells for germ cells/sperm), and testosterone-producing Leydig cells (Brauner 2011; Mangaraj 2017; Shimura 2025; Tack 2023; Zenaty 2006).

Primary testicular failure/insufficiency occurring early in life can result from a variety of causes, including:

- genetic variation (de Oliveira 2024; McElreavey 2020; Philibert 2007; Shimura 2025; Tack 2023);
- vascular accident/thrombosis (He 2022; Pirgon 2012);
- prenatal torsion or twisting of the testes during their descent from the intraabdominal position in which they originate during fetal life, to the scrotum (Papparella 1999; Pirgon 2012);
- torsion or trauma during the perinatal period (Huang 2025; Thakur 2020; Zenaty 2006);
- unknown or hypothetical prenatal or perinatal factors, such as environmental insult or pregnancy complications (Elamo 2022; Tack 2023).

Damage to the testicular vasculature and parenchyma following any of the above events leads to atrophy (death) of testicular tissue, in a process often referred to as "testicular regression" or "vanishing testis", the result of which is absence of functional testicular tissue or "anorchia" (Brauner 2011; He 2022; Hegarty 2007; Mangaraj 2017; Tack 2023; Zenaty 2006); the final outcome of these events is testicular failure/insufficiency. In such cases, surgical exploration typically reveals only a non-functional fibrotic mass, a vascular nodule or testicular remnants (Hegarty 2007; Pirgon 2012; Smith 1991; Tack 2023; Wright 1986). The variability of clinical features and age at presentation detailed below indicate that degeneration and failure of the testes may occur during the latter prenatal period (after the first trimester), during infancy, or in childhood (Brauner 2011; Hegarty 2007; Smith 1991; Tack 2023; Zenaty 2006). For example, the fact that testes are palpable at birth in some cases provides evidence for a postnatal insult in a subset of patients (Brauner 2011; Zenaty 2006).

DRAFT

Despite variability in the underlying pathological process and age of presentation, affected individuals share a common diagnosis of primary testicular failure/insufficiency resulting in testosterone deficiency, the clinical features of which are detailed below.

1. ***Clinical features***

Bilateral testicular failure/insufficiency is rare, with estimated prevalence of 1:20,000 to 1:40,000 male births (Borrow 1970; Tack 2023; Zenaty 2006). As with all endocrine conditions, children who suffer testicular failure/insufficiency have clinical features of varying severity, largely dependent on the timing of the testicular damage and resultant testosterone deficiency (Brauner 2011). As a point of clarification, the published literature refers to male genital development as "normal" if the penis has a typical structure, the urethral meatus is located at the end of the glans penis, and the scrotum is fully fused. Specifically, there is no hypospadias or other displacement of the urethral meatus, and the scrotum does not appear bifid. The size of the penis and the visible or palpable presence of testes within the scrotum do not contribute to the determination of what is referred to in the literature as "normal" genital structure/appearance. Reduced size of an otherwise typical penis is commonly referred to in medical literature as "micropenis", representing penile length more than 2.0 standard deviations (Ishii 2004; Zenaty 2006) or 2.5 standard deviations (Ishii 2004; Khadilkar 2023; Stancampiano 2022) below the mean length for age, gestation and ethnicity (typically below 2.0-2.5 cm for a full-term newborn male infant) (Cheng 2001). However, this term may be perceived as pejorative by affected individuals and may be distressing to families, so throughout this application descriptive terms such as "small penis" will be used.

Although testicular failure/insufficiency is believed to occur most often during the latter prenatal or early perinatal period, clinical presentation can be substantially delayed, in some cases as late as the teen years (Brauner 2011; Hegarty 2007; Smith 1991; Zenaty 2006). The reasons for presentation include absence of testes from the scrotum (empty or flat scrotum), small penis, or failure to enter puberty. The pattern of genital growth primarily reflects the timing of onset of testosterone deficiency, as detailed below.

a. *Prenatal onset:* When testicular failure/insufficiency occurs during the 2nd or 3rd trimester of gestation, the resulting testosterone deficiency leads to reduced growth in length and girth of the penis (Heksch 2019; Rai 1994; Zenaty 2006). However, the penis is fully formed as a result of response to testosterone during the first trimester of gestation, and there is no hypospadias. In addition to reduced growth of the penis, the other typical feature of prenatal onset testicular failure is shrinkage or atrophy of the testes, leaving a testicular remnant or an empty scrotum (Shimura 2025; Zenaty 2006).
b. *Postnatal onset:* When testicular failure/insufficiency occurs after birth, the penis is again fully formed, without hypospadias, the size of the penis at birth is likely to be within the normal range for typical male infants of similar gestational age, and testes or testicular remnants may be palpable at birth (Brauner 2011; Heksch 2019; Main 2000; Shimura 2025; Zenaty 2006). However, due to testosterone deficiency during the first 6

DRAFT

or so months of life, the penis may fail to undergo the usual postnatal growth that occurs in male infants with normally functioning testes during the period of mini-puberty, when testosterone production by the infant's testes increases markedly (Becker 2020; Rohayem 2024). When testicular failure occurs postnatally, the testes "regress" and become impalpable over time, testosterone production ceases, and penile growth is impaired, such that size may be reduced compared with that of male infants of similar age and ethnicity (Cheng 2001; Main 2000; Zenaty 2006).

Diagnosis of testicular failure/insufficiency is made on the basis of physical findings, hormonal data and imaging. The physiologic treatment for testosterone deficiency is age-appropriate testosterone replacement, as detailed in Part 2 of this plan.

2. ***Non-genital consequences***

Absence of normal testosterone secretion during the late prenatal period and/or infancy has a number of consequences for the somatic growth and development of affected children, as detailed in Part 3 of this plan. Failure of the usual testosterone surge of mini-puberty at around 1-6 months of age results in slower growth in body length/height (i.e., crown-to-heel) than that of male infants who experience the normal testosterone surge (Varimo 2016); in addition, affected infants do not experience the optimizing effect of the testosterone surge on male body composition (Becker 2015; Davis 2019b; Wong 2015).

3. ***Endocrine features***

Although the timing of testicular damage/degeneration differs among affected individuals, the outcome of testicular failure/insufficiency is loss of germ cells (the precursors of sperm) as well as the hormone-secreting cell types (Leydig cells, Sertoli cells). Consequently, affected individuals are infertile and have permanent deficiencies of testosterone, insulin-like 3 (INSL3), anti-Müllerian hormone (AMH) and inhibin B. Because this irreversible condition of testicular failure affects all aspects of testicular function it is sometimes referred to as whole testicular dysfunction (Rey 2024).

Early testicular failure results in loss of a key period of hormone secretion that occurs in all infants, irrespective of gestational age – the mini-puberty of infancy, detailed further in Addendum 1. During this critical window of male development in the first 6 months of life testicular hormones rise to concentrations similar to those of pubertal boys and adult men, returning to low prepubertal values within a few months of the peak (Becker 2020; Johannsen 2018; Rohayem 2024). In those with testicular failure, deficiency of testicular hormones during the period of mini-puberty results in a compensatory increase in gonadotropins (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]) (hormonal changes detailed in Brauner 2011; Misra 2002; Rey 2024; Zenaty 2006).

Although the full scope of the impact of mini-puberty are still being elucidated, it believed to be an essential period of life for reproductive development and other body functions (Becker 2020; Rohayem 2024), and the physiological importance of mini-puberty is underscored by the fact that this biological event is widely preserved across many species –

DRAFT

from mouse to horse (Quigley 2002; Busch 2023). As detailed in Part 3 of this application, testicular failure/insufficiency in infancy deprives an affected child of a key phase of normal male testosterone secretion and testosterone-dependent developmental processes.

4. ***Gender***

Children with 46,XY karyotype and male genitalia who undergo testicular failure/insufficiency are typically brought to medical attention as boys of varying ages, from the perinatal period to the teen years, indicating that they were assigned male at birth and living in the male gender role at presentation (Brauner 2011; Hegarty 2007; Zenaty 2006). The very young age of most affected children has precluded assessment of gender at the time of presentation for most. However, long-term follow-up studies have assessed psychosocial and gender-related outcomes in young adults treated at various ages for clinical manifestations of early-onset testosterone deficiency. For example, in a study of 15 young men (average age late-20s) with congenital absence of testes who received testosterone replacement in the teenage years, all reported male gender identity (Poomthavorn 2009). Other studies have addressed various psychosocial outcomes in men who were born with small but completely formed penis – a typical feature of late-prenatal and early postnatal-onset testosterone deficiency in about half of cases (Zenaty 2006). This readily identifiable clinical sign has historically been the focus of treatment efforts and outcome studies, irrespective of the underlying cause of reduced penile growth (Bin-Abbas 2019; Callens 2013; Mazur 2005; Reilly and Woodhouse 1989; Wisniewski 2001). These studies reported male gender identity in 46,XY individuals who had reduced penile size but otherwise typical male genital development, were assigned male at birth and were reared male (Bin-Abbas 2019; Mazur 2005; Reilly and Woodhouse 1989; Wisniewski 2001). In a study that included detailed psychosocial assessment Wisniewski and colleagues (2001) reported some degree of gender dysphoria in 2 of 13 men born with small penis; however, neither of these men wished to change gender from male. This study also reported that for the five individuals with small penis who were assigned as female in infancy or early childhood, there was also no subsequent self-initiated gender change. A careful review by Mazur (2005) found no reports of self-initiated gender change in men with history of small penis, and (Callens 2013), in a detailed review of 29 studies of 46,XY individuals with small penis reared male, found no report of self-initiated gender change, dissatisfaction with male gender or gender dysphoria in those whose small penis was not associated with a what the authors referred to as a "disorder of sex development". Most published case series and reviews have not addressed the subject of gender identity or gender variance in children who have testicular regression, the most readily identified cause of early-onset testicular failure (Brauner 2011; Hegarty 2007; Pirgon 2012; Zenaty 2006). However, a large Belgian case series reported that 2 individuals who had variations in the *DHX37* gene manifest as testicular regression and "marked underviririlzation", did not have "typical male gender identity" (one female, one non-binary) (Tack 2023).

It is acknowledged that most of the cited data relating to gender are more than 10 years old, and may be limited by participation bias or other confounding factors. Furthermore, changing focus on choices available to individuals with intersex or VSC and greater public

DRAFT

awareness of individuals with gender variance may result in different gender expression than that reported historically. However, at the time of application, gender variance in individuals with testosterone deficiency due to primary testicular failure who were assigned male at birth and raised male has not been reported.

Part 2. Proposed treatment

Please outline the proposed treatment plan. Ensure you detail the following: • The nature of the proposed treatment or procedure. • How does the proposed treatment vary the class of prescribed people's sex characteristics, and what will be the permanent effect of the treatment? Note: only treatments which permanently alter a person's sex characteristics (or alter in such a way as reversal requires further procedures or treatment), and vaginal dilation require a treatment plan.		
See below		
Documents are attached and labelled as attachment B	☒ Yes	☐ N/A

1. Testosterone Replacement

The goal of **testosterone replacement** for young male children with **testosterone deficiency** due to primary testicular failure/insufficiency is to restore testosterone concentrations to values appropriate for age. This approach to restoring the physiological state follows the same basic principles as treatment of other endocrine deficiencies (e.g., hypothyroidism, hypoadrenalism, etc.), in which hormonal balance is achieved by replacing the deficient hormone.

Because of the rarity of perinatal testicular failure and the age of affected children, ethical and logistic concerns have precluded randomized, controlled studies of testosterone replacement in infancy or early childhood. Therefore, published data on testosterone treatment for very young male children derives primarily from its use in those with small penis, either associated with testosterone deficiency due to testicular failure (Tack 2023; Zenaty 2006), in the context of congenital hypogonadotropic hypogonadism or hypopituitarism (Bin-Abbas 1999), or of mixed/unknown etiology (Burstein 1979; Hatipoglu 2013; Ishii 2004; Khadilkar 2023).

Testosterone replacement approaches are detailed in a review by Mason and colleagues (Mason 2020). Although various testosterone formulations and modes of delivery are available, the bulk of clinical experience of treatment of male infants and young children with testosterone deficiency has been with intramuscular testosterone injections using long-acting testosterone esters such as testosterone enanthate and testosterone cypionate (Bin Abbas 1999; Burstein 1979; Guthrie 1973; Ishii 2004; Laurer 2025; Zenaty 2006). The typical regimen used over the past 50 years can be summarized as comprising 3-4 intramuscular injections of 25-50 mg testosterone enanthate once every 2-4 weeks for 1 or 2 courses. Based on these data, testosterone replacement for children who fulfil the criteria detailed in Part 1 is proposed as follows:

DRAFT

- *Compound and route of administration:* testosterone enanthate by intramuscular injection;
- *Dosage:* 25-50 mg per injection, depending on size of child;
- *Frequency:* one injection every three (3) to four (4) weeks;
- *Duration:* three (3) to four (4) months.

Treatment response and outcomes will be monitored by physical examination, measurement of hormone concentrations using sensitive assays, and assessment for any expected or unexpected effects. Minor variation in injection frequency and duration of treatment is included to allow adjustment based on serum testosterone following injection, as measured by liquid chromatography-mass spectrometry. Depending on response to treatment, a second course of treatment following the above parameters may be prescribed.

2. Psychosocial support

Families/caregivers facing the diagnosis of testicular failure/insufficiency in their baby or young child may experience a wide range of emotions and significant psychosocial stress, with potential impact on parent/parent and parent/child interactions. Therefore, psychosocial support forms a key aspect of the comprehensive care of affected families. Children and parents/carers are offered psychosocial support from the Canberra Health Services Variations in Sex Characteristics Psychosocial Service (VSCPSS), both at the time of initial diagnosis, and also on an ongoing basis until the young person turns 18 years of age. Working in partnership with clinicians, the role of the VSCPSS is to support children and parents/carers to understand the child's variation, coordinate healthcare needs around the variation, provide psychosocial support regarding adjustment to diagnosis and other psychological and emotional issues that may arise, provide support to communicate about the variation with others, connect with peer support services and provide support in decision making when needed. In addition to the VSCPSS, other healthcare providers including psychologists, social workers and general practitioners, as well as independent peer support and community-based services, may also provide information, counseling and support to children and families at various times. Psychosocial support is particularly important during childhood and adolescence to help individuals cope with self-esteem, body image, and relationship concerns. Clinicians are sensitive to the feelings and wishes expressed regarding gender by the children/young people under their care and would refer a child or family who expressed gender concerns at any time for evaluation by the VSCPSS.

3. Benefit-risk assessment for testosterone replacement in male infants/children with testosterone deficiency due to testicular failure/insufficiency.

As with all medical interventions, the decision to undertake testosterone replacement as detailed above should weigh the benefits and risks, and because of the young age of affected children, the benefit-risk evaluation must be made by the child's parents/caregivers in consultation with health care providers and with psychosocial support as needed. While the right of children to contribute to decisions about their bodies is important, so too is their right to obtain safe and effective treatment for their health needs, even when they are too young to understand those needs or the future that lies ahead of them. The goal of testosterone replacement for young male children who have testosterone deficiency due to primary testicular failure/insufficiency (irrespective of penile size) is to replicate the

DRAFT

physiologically elevated testosterone concentrations experienced by male infants with healthy testes during the first six months of postnatal life. This would provide an affected child with the greatest chance to attain his potential, while maintaining all options for the future. In contrast, by failing to treat a diagnosed endocrine deficiency, denial of testosterone replacement for an affected infant/young child may impede the child's genital and somatic growth and development during the first few years of life, thereby limiting options for the future.

The therapeutic approach of intramuscular injections of testosterone enanthate derives from that initiated empirically by Guthrie, Smith and colleagues in the early 1970s for treatment of small penis (Guthrie 1973), and subsequently adopted broadly (reviewed by Mason 2020; Laurer 2025). The absence of randomized, controlled, clinical trial data is typical for rare paediatric conditions, in which both logistic and ethical concerns often preclude such studies. Nevertheless, long-term clinical experience with protocols using testosterone enanthate as described above has provided a substantial body of information from which clinical efficacy and safety data can be gleaned.

In parallel with other hormone deficiencies, the primary purpose of testosterone replacement in infants/children with testosterone deficiency is the restoration of physiological hormonal milieu for age. As detailed in Part 3A of this application, one of the fundamental biological effects of the increase in endogenous testosterone secretion of male infants during the period of mini-puberty is the stimulation of penile growth (Becker 2020; Boas 2006; Fischer 2024; Hagag 2017; Ishii 2015; Rohayem 2024; Semiz 2011), and failure of postnatal penile growth has been reported in infants with testosterone deficiency (Main 2000). By mimicking the testosterone concentrations of mini-puberty, low-dose testosterone enanthate treatment increases penile growth in children with small penis, a clinical feature of testicular failure in about half of cases (Bin-Abbas 1999; Burstein 1979; Guthrie 1973; Lovinger 1975; Mason 2020; Tack 2023; Zenaty 2006). Although formal pharmacokinetic studies in infants and young children have not been undertaken for ethical and practical reasons (for example, significant discomfort and blood volumes required for multiple testosterone measurements), the penile growth response and increase in height velocity (linear growth rate) during testosterone replacement represent sensitive bioassays for treatment effect (Burstein 1979; Guthrie 1973; Lovinger 1975).

Testosterone is a systemic hormone that acts via the androgen receptor, a transcription factor broadly distributed throughout diverse body tissues, from the reproductive tract to the heart, liver, gastrointestinal tract, central nervous system, hair follicles and more (Quigley 1995; Sarkey 2008). Therefore, effects of testosterone deficiency and replacement are recognized in systems beyond the reproductive system. Testosterone treatment in infants induces a brief period of increased height velocity, mimicking the short-lived growth spurt of mini-puberty (Guthrie 1973; Lovinger 1975), thereby restoring the physiological pattern of infant growth that is lost in infants with testosterone deficiency (Varimo 2016). Similarly, the testosterone surge of mini-puberty in male infants with normally functioning testes contributes to the development of healthy male lean body mass and weight in

DRAFT

childhood (Becker 2015; Davis 2019b), and untreated testosterone deficiency in infancy has negative impact on body composition in young male adulthood (Wong 2015). Although data demonstrating testosterone-mediated improvements in male body composition in infancy derive from a population with a less severe form of testosterone deficiency than the subjects of this treatment plan (Davis 2019a), it is reasonable to hypothesise that low-dose testosterone replacement in children with testicular failure would have similar beneficial effects.

A short course of testosterone enanthate treatment has minimal risk of adverse physical effects (see Part 3C), and no significant long-term safety issues have been identified over 50 years of clinical use (Al-Beltagi 2024; Boehm 2015; Mason 2020). The key concern to be weighed by families/caregivers of an affected infant/child, is the fact that the child is unable to contribute to the decision regarding treatment. However, the opportunity to replicate the testosterone surge of mini-puberty is transient, a child affected by testicular failure has the right to receive an available treatment that is safe and effective, and the potential for physiological hormone replacement during infancy/early childhood should not be overlooked. A short course of testosterone replacement would provide the greatest chance of preserving the affected child's options for the future, including the choice of an alternate pathway later in life.

In summary, a well-established, safe and effective testosterone replacement therapy is the most appropriate course of treatment to mimic the testosterone surge of mini-puberty for a 46,XY infant with male genitalia who has testicular failure with demonstrated testosterone deficiency, irrespective of penile size. Treatment will be closely monitored and affected children/families will receive appropriate psychosocial support.

DRAFT

Part 3. Details of the harm related to the proposed treatment

A. What, if any, significant primary harm would the class of prescribed people be at risk of if the proposed treatment was **not** undertaken? Please limit this to significant physical or psychological harms, or risks of harm, that are not related to reducing discrimination or stigmatisation or a perceived risk of discrimination or stigmatisation by performing the proposed treatment.
See Section A below
B. How does the proposed treatment address the primary harm described in section A of Part 3 and how likely is the treatment to address this harm?
See Section B below
C. Describe any associated harms – physical and psychological – that the class of prescribed people would be at risk of if the proposed treatment were undertaken.
See Section C below

Documents are attached and labelled as attachment C	☐ Yes	☒ N/A

A. What, if any, significant primary harm would the class of prescribed people be at risk of if the proposed treatment was not undertaken?

The goal of testosterone replacement in children with testicular failure/insufficiency is to provide restoration of the physiological hormonal milieu that will offer the greatest likelihood of a healthy childhood and maintain the individual's long-term future options. Failure to treat the primary harm – testosterone deficiency resulting from testicular failure/insufficiency – would deprive an affected child of the physiological testosterone-mediated developmental processes of infancy, affecting not only genital development, but also linear growth and body composition, with potential impact on long-term health and wellbeing. Although the biological implications of mini-puberty are not fully understood, this event represents a unique confluence of adult-level hormone secretion with the marked plasticity and growth potential of infant tissue. Thus the timing of testosterone replacement in children with testicular failure is likely to be important, as infancy is a unique, time-limited developmental window. This, restoring the testosterone usually produced during mini-puberty represents a once-in-a-lifetime opportunity.

1. *Penile development.* The normal surge of testosterone secretion during infancy stimulates penile growth (Becker 2020; Boas 2006; Fischer 2024; Hagag 2017; Ishii 2015; Rohayem 2024; Semiz 2011), and testosterone concentration during mini-puberty directly correlates with penile size and growth rate (Boas 2006). Thus, a key harm that would arise as a consequence of untreated testosterone deficiency accompanying testicular failure/insufficiency in infancy would be the loss of an important period of normal penile growth and maturation (Main 2000). Timely testosterone replacement provides an affected child the opportunity to develop and grow in a manner similar to his age-mates during childhood thereby preserving options for the future. Failure to treat testosterone deficiency in infancy denies an affected child the opportunity to experience normal penile growth during a critical period of development.

2. *Linear (skeletal) growth*. Healthy male infants grow more rapidly in length than female infants during the first 6 months of life (Copeland 2016; Kiviranta 2016; Roche 1989), and the speed of growth correlates with magnitude of testosterone secretion (Kiviranta 2016). Conversely, male infants who have inadequate testosterone secretion due to absent mini-puberty show a deceleration in linear growth compared with those whose testosterone secretion is normal (Varimo 2016). Testosterone replacement during infancy induces a brief period of increased height velocity, replicating the short-lived growth spurt of mini-puberty, thereby restoring some of the height potential lost due to testosterone deficiency (Guthrie 1973; Lovinger 1975). These findings indicate that the early postnatal surge in testosterone secretion plays an important role in somatic growth in addition to growth of reproductive structures, and postnatal testosterone deficiency impairs linear growth during infancy. Therefore, failure to provide testosterone replacement for testosterone deficiency could impair physiological linear/skeletal growth in the first year of life.

DRAFT

3. *Body composition.* Testosterone is an anabolic hormone that increases protein synthesis. As a result, the testosterone surge of mini-puberty in male infants with normally functioning testes contributes to the greater lean body mass of boys compared with girls (Davis 2019b), and is associated with optimisation of male body composition over the following 6 years of life (Becker 2015). These findings indicate that the impact of testosterone on development of a healthy body composition occurs not only in infancy, but persists into childhood after testosterone concentrations have waned to low prepubertal values. A randomized, controlled trial demonstrated significant improvements in body composition in children with a less severe form of testosterone deficiency (Klinefelter syndrome) during infancy (Davis 2019a); similar effects could be expected for children with severe testicular failure/insufficiency, such as the subjects of this proposed treatment plan. Furthermore, a study of young adult men with anorchia whose testosterone deficiency was not treated in infancy demonstrated increased visceral adiposity despite testosterone replacement starting in adolescence (Wong 2015). Failure to replace deficient testosterone during infancy would deprive an affected child of the physiological optimization of body composition experienced by male infants with normal testosterone secretion during infancy. As body composition (i.e., the relative amounts and distribution of fat and lean mass) has significant health consequences such as impact on cardiometabolic risk (Amato 2013; Chung 2018), the potential importance of early-life optimization is relevant to the assessment of benefit of testosterone replacement in the target patient population.

4. *Psychological wellbeing.* Long-term follow-up studies have documented the negative psychological impact of conditions affecting development and function of the genitalia and reproductive tract, including anorchia, testosterone deficiency, small penis, and infertility (Callens 2013; Mazur 2005; Wisniewski 2001). Although the nature of these studies does not allow differentiation between the effects on psychological wellbeing of testosterone deficiency itself vs. the resultant genital and reproductive differences, these studies provide clear evidence of significant long-term psychological consequences for many affected individuals. Therefore, in addition to testosterone treatment, as detailed in Part 2 of this plan, psychological support will be an integral component of care for affected children and their families/caregivers (Callens 2013; Wisniewski 2001; Wolfe-Christensen 2012).

In summary, testosterone deficiency in infancy is detrimental to the growth and development of the genitalia and the body as a whole. Withholding testosterone replacement for testosterone deficiency due to testicular failure/insufficiency during infancy would deprive an affected child of a safe and effective treatment to restore physiological hormone balance during a unique and critical period of childhood development. Although penile catch-up growth may be the most readily measureable outcome of testosterone replacement, the endocrine disorder of testosterone deficiency is a systemic condition affecting the body as a whole, and androgen receptors are broadly distributed throughout the body's tissues (Quigley 1995). Testosterone replacement represents a safe and simple

DRAFT

treatment to mitigate the harms of testosterone deficiency and may improve long-term outcomes for affected children. Failure to treat a known hormone deficiency would be contrary to standard of care for endocrine disorders and would deprive an affected child of the right to safe and effective treatment to provide the best opportunity for health and wellbeing.

B. How does the proposed treatment address the primary harm described in Section A of Part 3 and how likely is the treatment to address this harm?

In common with other hormonal deficiencies, the endocrine disturbance of **testosterone deficiency** due to testicular failure/insufficiency – the primary harm – is most appropriately treated by replacing the deficient hormone, **testosterone**, as detailed in Part 2 of this plan. Low-dose intramuscular testosterone injections have demonstrated efficacy since the 1970s to treat one of the most readily detected consequences of perinatal testosterone deficiency – small penis – by stimulating penile growth into the normal range for age (Bin-Abbas 1999; Burstein 1979; Guthrie 1973; Hatipoglu 2013; Lovinger 1975; Mason 2020; Tack 2023; Zenaty 2006) providing a biological marker of systemic testosterone effect (Burstein 1979). Testosterone replacement for affected infants previously treated in our institution using testosterone enanthate has resulted serum testosterone concentrations within the published reference ranges for the period of mini-puberty (Johannsen 2018; Rohayem 2024; Visser U 2025, personal communication). Thus, the available depot testosterone preparation can restore physiological serum testosterone concentrations appropriate for age and development.

Although direct comparative studies of early vs. delayed testosterone replacement have not been conducted for both practical and ethical reasons, a long-term follow-up study showed a trend toward greater penile length in men who had small penis (a feature of testicular failure in about half of affected infants, Zenaty 2006) and were treated during infancy, compared with those whose treatment was delayed (Wisniewski 2001).

In summary, testosterone replacement for the primary harm of testosterone deficiency can restore physiological hormone concentrations for age (Visser 2025), thereby providing the appropriate hormonal stimulus for recovery of penile growth in those affected by small penis, catch-up of infantile linear (height) growth (Guthrie 1973; Lovinger 1975), and optimization of male body composition (Davis 2019a; Mason 2020).

C. Describe any associated harms – physical and psychological – that the class of prescribed people would be at risk of if the proposed treatment were undertaken.

There is no testosterone replacement preparation specifically formulated or approved for use in paediatric patients in Australia. Testosterone enanthate (Primoteston®) is approved by the Australian Therapeutic Goods Administration (TGA) for *"Androgen replacement therapy for confirmed testosterone deficiency in males"*. The prescribing information (PI; attached) states *"Primoteston Depot is not indicated for use in children and adolescents"*. The regulatory term "not indicated" in this statement means that the product does not have

DRAFT

an approved "indication" for paediatric treatment and does not represent a judgement regarding clinical appropriateness, efficacy or safety of treatment.

The absence of a specific product or formulation for paediatric testosterone replacement exemplifies a well-known issue throughout paediatric medicine: rarely are pharmaceutical treatments developed, tested or approved specifically for children, resulting in the standard practice of tailoring the dosages of medications approved for adults to adjust for the smaller body mass of children. Based on an empirically derived regimen, a short course of intramuscular testosterone injections during infancy has been standard of care for over half a century for treatment of reduced penile size, which is associated with testosterone deficiency due to testicular failure/insufficiency in about 50% of cases (Bin-Abbas 1999; Burstein 1979; Guthrie 1973; Lovinger 1975; Mason 2020; Tack 2023; Zenaty 2006); no serious adverse reactions or other harms have been reported as a consequence of this low-dose testosterone treatment. Although one early study showed mild bone age advancement during treatment, the maturational effect plateaued by 9 months after treatment discontinuation (Guthrie 1973) and was not observed in other studies (Bin-Abbas 2019; Mason 2020). A European Consensus Statement comments regarding treatment of testosterone deficiency during infancy and childhood: "as the duration of treatment is brief, no major concerns regarding virilization or the development of secondary sexual characteristics exist; however, erections might be observed." (Boehm 2015).

Potential adverse reactions in adults listed in the PI include "injection site pain, injection site erythema, and cough and/or dyspnoea during or immediately after the injection". Other potential adverse outcomes related to long-term testosterone use in adult men are unlikely to apply to infants treated with very low dosages for a short period and have not been reported. However, one testosterone preparation used in adults (Sustanon®) is specifically contraindicated for use in children under 3 years of age, due to potential allergic reaction to one of the excipients.

No data are available regarding the psychological impact of short-term testosterone replacement in infants and young children. However, it is possible that parents and caregivers could experience difficulties due to expectations around treatment effect. Potential psychosocial issues can be addressed by the VSCPSS and other healthcare providers, offering parents and carers the opportunity to discuss expectations and further their understanding of the benefits and risks of treatment. Long-term psychosocial follow-up will be provided for the affected child and family, and additional support may be obtained from peer and community-based organisations. Professional and peer support will likely be particularly important as an affected child progresses through the social challenges inherent in childhood and adolescence.

DRAFT

Part 4. Alternative treatments

A. What alternative treatment options have been considered? Please describe these. These may include treatment deferral, medical and non-medical interventions and temporary measures. You may attach further documentation, if required.		
See Section A below		
B. How does each alternative option identified above address the primary harm described in Part 3? How likely is it the treatment will effectively address that harm?		
See Section B below		
C. With respect to each alternative option identified above, describe any associated harms – physical and psychological – the class of prescribed people would be reasonably likely to suffer, if the alternative options were undertaken.		
See Section C below		
Documents are attached and labelled as attachment D	☐ Yes	☒ N/A

DRAFT

A. What alternative treatment options have been considered? Please describe these. These may include treatment deferral, medical and non-medical interventions and temporary measures.

In common with other hormonal deficiencies, the endocrine disturbance of **testosterone deficiency** in infancy is most appropriately treated by replacing the deficient hormone, **testosterone**, as detailed in Part 2 of this plan. The alternative options discussed below include other forms of testosterone replacement, no treatment, delayed treatment, and complementary non-pharmacologic approaches. Surgical treatments for some of the physical conditions associated with infantile testosterone deficiency, such as insertion of testicular prostheses for anorchia, or phalloplasty for small penis, are not discussed, as these do not address the underlying endocrine disturbance, nor the broader goals and potential benefits of testosterone treatment beyond the reproductive system.

1. Alternative Methods of Testosterone Replacement

Various approaches to testosterone treatment are available, including different testosterone esters for intramuscular injection (enanthate, cypionate), subcutaneous testosterone injections (Figueiredo 2022; Spratt 2017; Wilson 2018) and topical testosterone (Arisaka 2001; Chioma 2018; Rogol 2019). While all of these options are feasible, there is limited published information regarding outcomes of treatment with these modalities in infancy compared with intramuscular long-acting testosterone (Chioma 2023; Mason 2020).

2. No Treatment or Delayed Treatment

Failure to treat testosterone deficiency due to testicular failure/insufficiency during infancy would deny an affected child the right to a safe and effective treatment to restore the physiological hormonal milieu and the opportunity to experience the benefits associated

with the increase in circulating testosterone during infancy, as detailed in Part 3 of this application. By definition, testosterone replacement for infantile testosterone deficiency that is delayed until later in childhood or the adolescent years fails to address the specific endocrine disorder described herein, of testosterone deficiency during infancy. No study has directly compared early vs. delayed testosterone replacement for testicular failure; however, replacement of hormone deficiencies at the time of diagnosis is standard of care for other endocrine disorders and similarly makes physiologic sense in the case of testosterone deficiency during infancy. Although postponing testosterone replacement for children with testicular failure/insufficiency until adolescence would allow them to participate in decision-making, this approach has no physiological basis and would represent an untested experimental approach of leaving an endocrine deficiency untreated for an extended period of time, and therefore cannot be medically justified.

3. Other Interventions

Additional interventions integral to the care of children and families/carers affected by primary testicular failure/testosterone deficiency include psychosocial support for families who may need help understanding and navigating the challenges of diagnosis and decisions regarding treatment, adapting to their child's variation(s), and addressing their own psychological and emotional responses to their child's condition. Psychosocial support will be offered by the VSCPSS, in collaboration with paediatric endocrinologists, to all families whose children may need testosterone replacement, both at the time of initial presentation and at any time thereafter, during infancy, childhood and/or adolescence.

Psychosocial support is particularly important during childhood and adolescence to help children cope with self-esteem, body image issues and future concerns regarding sexual function and infertility (Al-Beltagi 2024; Tsang 2010). Long-term follow-up studies have documented the psychological impact of conditions associated with testosterone deficiency, including small penis, testicular absence (anorchia) and infertility (Al-Beltagi 2024; Callens 2013; Dwyer 2019; Tsang 2010; Wisniewski 2001). Psychosocial support is therefore crucial to the comprehensive care of all children and families dealing with testosterone deficiency in infancy and early childhood. It is also important that children and parents/carers are provided with the opportunity to connect with peer and community organisations and services who may provide additional support and connection with others who may have similar conditions and/or experiences.

B. How does each alternative option identified above address the primary harm described in Part 3? How likely is it the treatment will effectively address that harm?

1. Alternative Methods of Testosterone Replacement

Although no data are available in infants, subcutaneous testosterone injection would likely address the primary harm of testosterone deficiency in infancy in a manner similar to intramuscular testosterone, as has been demonstrated in adults. In a study conducted in adult female-to-male transgender individuals subcutaneous testosterone administration resulted in normal male serum testosterone concentrations; all participants preferred the subcutaneous route compared with intramuscular injections (Spratt 2017). Similarly, a group of hypogonadal adult men rated the subcutaneous route more tolerable, with lower pre-injection anxiety and reduced pain during and after injection (Wilson 2018). Unfortunately,

DRAFT

lack of available information on use of this product in very young children would preclude its current use within our institution.

Topical testosterone would also likely be effective, based on a Japanese study of 5% testosterone ointment application in 50 prepubertal male children aged 5 months to 8 years that demonstrated significant, clinically relevant increases in serum testosterone and penile length, with no significant untoward effects reported (Arisaka 2001). Similar results were demonstrated in studies of children older than 1 year of age with small penis associated with hypospadias (Chalapathi 2003; Nerli 2009) and in pubertal induction in teenage boys with absent testes (Rogol 2019). Although data on the use of topical testosterone in infants are limited, these studies in older children suggest that this approach theoretically represents a feasible alternative to intramuscular testosterone replacement. However, this approach has not been adopted broadly (Laurer 2025), likely in part due to the challenges associated with dose titration, and the risks of inadvertent transfer of testosterone to caregivers of children receiving treatment, with potential unwanted androgenic effects.

2. No Treatment or Delayed Treatment

No treatment or delayed treatment would not address the primary harm of the endocrine disturbance of testosterone deficiency in infancy. The choice to withhold testosterone replacement during infancy represents a decision not to restore an affected child's endocrine system to its physiologic balance – deliberately prolonging a state of testosterone deficiency in such infants would represent an illogical and experimental approach to management, out of alignment with the principles of treatment of other endocrine disorders. Furthermore, failing to take advantage of the unique developmental window of mini-puberty to provide testosterone replacement may significantly restrict an affected child's future choices, as discussed in Part 6 of this plan.

3. Other Interventions

Other interventions such as psychosocial services or interaction with peer support groups provide valuable support for families dealing with the immediate and long-term physical differences associated with their child's condition, including testicular failure/insufficiency, small penis and infertility. Therefore these services should be offered routinely as adjunctive therapies during treatment of children with testosterone deficiency due to testicular failure/insufficiency.

C. With respect to each alternative option identified above, describe any associated harms – physical and psychological – the class of prescribed people would be reasonably likely to suffer, if the alternative options were undertaken.

1. Alternative Methods of Testosterone Replacement

Based on published information regarding subcutaneous testosterone injections in hypogonadal adult men and in female-to-male transgender individuals, there does not appear to be any greater risk of harm from use of subcutaneous vs. intramuscular testosterone injection (Figueiredo 2022; Spratt 2017, Wilson 2018). In addition, the US FDA

DRAFT

has approved an autoinjector device for self-administration of subcutaneous testosterone enanthate (Kaminetsky 2019). The key risk of this alternative route of administration is the lack of information regarding its use in this very young children.

Use of topical testosterone gel in in children, most of whom were beyond infancy, has been associated with mild localized reactions at the application site, including itchy rash and transient hyperpigmentation (Arisaka 2001). Nevertheless, as this treatment effectively increased serum testosterone, it would represent a feasible alternative, unlikely to pose any greater risk than intramuscular testosterone (Arisaka 2001). However, as noted in Part 4B, this approach has not been adopted broadly, likely in part due to the challenges associated with dose titration, and the risks of inadvertent transfer of testosterone to caregivers of children receiving treatment, with potential unwanted androgenic effects. Furthermore, there is no experience within our institution of the use of this treatment modality. Assuming clinical efficacy and safety can be demonstrated in infancy, neither the subcutaneous nor the transdermal mode of administration is likely to present a greater risk of psychological distress to either the affected child or caregivers than the standard treatment approach of intramuscular testosterone.

2. No Treatment or Delayed Treatment

Failure to treat testosterone deficiency during infancy would deprive an affected child of the opportunity to experience the important systemic effects of the postnatal testosterone surge of male mini-puberty, including physiological penile growth, improved linear/skeletal growth and optimization of body composition. Therefore, there is a greater risk of potential harm from lack of treatment or delayed treatment than there would be from timely testosterone replacement. Given the long history over many decades of safe and effective use of short-term intramuscular testosterone as physiological replacement, the alternative of delaying or denying treatment for a child with a clearly demonstrated endocrine deficiency could be considered experimental and cannot be supported.

3. Other Interventions

Psychosocial services and peer supports provide valuable opportunities for children and parents/carers to understand the child's variation and the associated emotional responses, and to build relationships and communication within families. Such support can help to strengthen the child's body image, identity and self-esteem, and provide the opportunity to connect with others who may have similar conditions and/or experiences. Families can be referred to services such as VSCPSS by their general practitioners and/or medical specialists and can also self-refer. However, accessing psychosocial support is voluntary, and families retain the choice to enter, leave or return to the service at their discretion. Although such support is generally received positively, it is possible that a child or family may experience distress at some time during their interactions with either professional or community support services. However, psychosocial support services such as VSCPSS and appropriate peer/community-based groups are uniquely placed to manage emotional responses to the stress associated with adaptation to a challenging situation.

DRAFT

Part 5. Relative effectiveness of treatment

Provide a comparison of the effectiveness of the proposed treatment and the alternative treatment options at minimising the overall harm (including the primary harm and any associated harms).		
As detailed in items 1-4 below, the proposed treatment with intramuscular injections of low-dose testosterone enanthate, complemented by psychosocial support from the VSCPSS and appropriate peer/community support services, provides the most effective and appropriate treatment approach for 46,XY infants with male genitalia who have testosterone deficiency due to testicular failure/insufficiency.		
Documents are attached and labelled as attachment E	☐ Yes	☒ N/A

1. Proposed Treatment with Low-dose Intramuscular Testosterone

By mimicking the testosterone surge of male mini-puberty a short-term course of testosterone replacement represents the simplest, most physiological, direct and timely approach to treating the endocrine disorder of testosterone deficiency due to testicular failure/insufficiency in a 46,XY infant with male external genitalia. As detailed in Part 3 of this application, intramuscular testosterone replacement is a safe and effective treatment with a proven record over 5 decades (e.g., Burstein 1979; Guthrie 1973; Mason 2020), and remains the standard of care internationally (Laurer 2025). Testosterone replacement in infants with testicular failure/insufficiency treats the primary harm of testosterone deficiency, as well as the associated harms, including inadequate postnatal growth and maturation of the penis – a feature that accompanies testicular failure in about 50% of cases (Zenaty 2006), loss of the normal testosterone-dependent linear growth spurt (Kiviranta 2016; Varimo 2016) and deficits of male body composition (Becker 2015; Wong 2015).

As detailed in a recent review, patients with testicular failure/insufficiency require lifelong testosterone replacement to prevent long-term systemic complications of hypogonadism (Tack 2023). Therefore, to minimize the harm of testosterone deficiency treatment should mimic physiology as closely as possible, by starting promptly upon diagnosis of the deficiency. The approach of providing testosterone replacement for testosterone deficiency during infancy parallels the treatment of other endocrine disorders to minimise the potential significant harms of untreated hormone deficiencies: for example, congenital hypothyroidism is promptly treated with thyroid hormone from birth, and hypoadrenalism is treated with adrenal hormone replacement. Therefore, testosterone replacement during infancy represents the most physiological and effective treatment option for affected children.

2. Alternative Methods of Testosterone Replacement

Based on studies detailed above in children over 1 year of age and in men, subcutaneous and transdermal testosterone treatment would likely have similar efficacy to intramuscular testosterone. However, there are no comparative studies in infants on which relative effectiveness can be assessed. Furthermore, topical testosterone poses potential issues with

DRAFT

dose titration and inadvertent transfer to caregivers, and there is no experience within our institution of the use of this treatment modality.

3. No Treatment or Delayed Treatment

Withholding treatment would provide no benefit for the ***primary harm*** of testosterone deficiency in infancy, the consequences of which are detailed above, and would enforce an ongoing non-physiologic state of testosterone deficiency throughout infancy. An affected child has the right to receive a safe and effective treatment to optimise health and wellbeing, and there is no biological rationale for withholding testosterone replacement. Therefore the assessment of relative effectiveness of no treatment would be negative and medically unsupportable.

There are no randomized controlled trials of delayed vs. timely testosterone replacement in children with testicular failure/insufficiency. However, in a long-term follow-up study of adult men with small penis of various etiologies, testosterone replacement delayed until the age for puberty was generally less effective in increasing penile size than treatment started in infancy, and the majority of subjects received counseling for sexual difficulties or severe teasing (Wisniewski 2001). Many individuals had other features associated with their testosterone deficiency, including poor quality of the penile corpora, gynecomastia, and/or limited sexual hair growth. Two-thirds of participants were dissatisfied with penile appearance and half were dissatisfied with regard to sexual function. Nevertheless, none of the affected men wished to change gender. Thus, at least in this study, delayed testosterone replacement was less effective than treatment during infancy for increasing the growth of a small penis – a feature of testicular failure in about half of affected infants (Zenaty 2006).

Withholding or delaying testosterone replacement deprives a child suffering from testosterone deficiency of the opportunity for penile 'catch-up' growth, an issue that carries substantial risk of stress and psychological harm to affected individuals during childhood, adolescence and adulthood (Al-Beltagi 2024; Callens 2013; Wisniewski 2001). In addition, withholding testosterone replacement fails to address the other physiological deficits due to absence of the testosterone surge of mini-puberty, such as the linear growth (height) spurt and optimization of male body composition, as detailed in Part 3. Although delaying testosterone replacement for an infant with testicular failure until adolescence would allow the affected individual to provide his own decision regarding treatment, it would deprive him of the right to receive the physiological benefits of appropriate treatment of his endocrine deficiency in an appropriate time. Therefore, delayed treatment does not represent an acceptable alternative to timely treatment and cannot be medically justified.

4. Other Interventions

Although other therapeutic modalities such as VSCPSS and interaction with community and peer support services do not address the primary harm of testosterone deficiency, nor the associated secondary physical harms detailed above, such support may be effective in helping families to understand the condition and their own responses to it. Support from these sources may help to build resilience for families coping with diagnosis and decisions

DRAFT

regarding the benefits and risks of testosterone replacement, thereby fostering overall positive therapeutic outcomes. Nevertheless, these therapeutic approaches cannot provide effective treatment equivalent to that of testosterone replacement for the physiological effects of testosterone deficiency associated with testicular failure/insufficiency.

Part 6. Restrictiveness of the treatment options

What are the implications of the proposed treatment on what decisions can be made in future by the class of prescribed people or their decision makers in relation to their sex characteristics? How does this compare to the alternative treatments?		
See below		
Documents are attached and labelled as attachment F	☐ Yes	☒ N/A

Testosterone treatment for testosterone deficiency resulting from testicular failure/insufficiency during infancy offers the least restrictive treatment option, because this approach provides affected children with the greatest opportunity for physiological growth and development, both genital and somatic, during a critical period of life. No future options are precluded or restricted by early treatment. To the contrary, all of the child's potential for healthy growth and development is retained by early treatment, whereas non-treatment or delayed treatment deprives the child of some of that potential. Thus, because non-treatment or delayed treatment would impose greater restrictiveness on future decisions, as the opportunity for physiological growth and development during infancy would be denied, this approach cannot be medically justified and is not supported.

Early physiologic testosterone replacement poses no impediment to an affected individual subsequently choosing an alternative path, such as variant gender. The subsequent hormonal treatment and/or surgical procedures, if desired, to reshape body features would be similar to those required for a typical transgender teenager or adult.

In conclusion, timely **testosterone replacement** represents the most physiological approach to treatment of the endocrine disorder of **testosterone deficiency** associated with testicular failure/insufficiency. Children who experience testicular failure/insufficiency lose all functional testicular tissue and have no chance of fertility or recovery of testicular function. Therefore, affected children should be offered the opportunity to reach their full potential by providing testosterone treatment to optimize growth and development during the critical period of infancy and preserve their options for the future.

DRAFT

References

Al-Beltagi M, Saeed NK, Bediwy AS, Shaikh MA, Elbeltagi R. 2024. Microphallus early management in infancy saves adulthood sensual life: A comprehensive review. World J Clin Pediatr 13(2): 89224.

Amato MC, Guarnotta V, Giordano C. 2013. Body composition assessment for the definition of cardiometabolic risk. J Endocrinol Invest 36(7):537-43.

Arisaka O, Hoshi M, Kanazawa S, Nakajima D, Numata M, Nishikura K, Oyama M, Nitta A, Kuribayashi T, Kano K, Nakayama Y. 2001. Systemic effects of transdermal testosterone for the treatment of microphallus in children. Pediatr Int 43(2):134-6.

Becker M, Oehler K, Partsch CJ, Ulmen U, Schminzler R, Camman H, Hesse V. 2015. Hormonal 'minipuberty' influences the somatic development of boys but not of girls up to the age of 6 years. Clin Endocrinol (Oxf) 83(5):694-701

Becker M, Hesse V. 2020. Minipuberty: why does it happen? Horm Res Pediatr DOI: 10.1159/000508329

Bin-Abbas B, Conte F, Grumbach M, Kaplan S. 1999. Congenital hypogonadotropic hypogonadism and micropenis: Effect of testosterone treatment on adult penile size—Why sex reversal is not indicated J Pediatr; 134: 579-83

Boas M, Boisen KA, Virtanen HE, Kaleva M, Suomi AM, Schmidt IM, Damgaard IN, Kai CM, Chellakooty M, Skakkebæk NE, Toppari J, Main KM. 2006. Postnatal penile length and growth rate correlate to serum testosterone levels: a longitudinal study of 1962 normal boys. Eur J Endocrinol 154(1): 125-9

Boehm U, Bouloux P-M, Dattani MT, de Roux N, Dode C, Dunkel L, Dwyer AA, Giacobini P, Hardelin J-P, Juul A, Maghnie M, Pitteloud N, Prevot V, Raivio T, Tena-Sempere M, Quinton R, Young J. 2015. European Consensus Statement on congenital hypogonadotropic hypogonadism – pathogenesis, diagnosis and treatment. Nat Rev Endocrinol 11: 547-564

Borrow M, Gough MH. 1970. Bilateral absence of testes. Lancet; 1: 366.

Bourayou R, Giabicani E, Pouillot M, Brailly-Tabard S, Brauner R. 2015. Premature pubarche before one year of age: distinguishing between mini-puberty variants and precocious puberty. Med Sci Mon 2; 21:955.

Brauner R, Neve M, Allali S, Trivin C, Lottmann H, Bashamboo A, McElreavey K. 2011. Clinical, biological and genetic analysis of anorchia in 26 boys. PLoS One; 6:e23292.

Burstein S, Grumbach MM, Kaplan SL. 1979. Early determination of androgen-responsiveness in important in the management of microphallus. Lancet 10 November 1979: 983-986

Busch AS, Paturlanne JM, Neuhaus N, Wistuba J, Schlatt S, Juul A, Omran H. 2023. Male minipuberty in human and non-human primates: planting the seeds of future fertility. Reproduction. 166(4):R63-72.

DRAFT

Callens N, De Cuypere G, Van Hoecke E, T'sjoen G, Monstrey S, Cools M, Hoebeke P. 2013 Sexual quality of life after hormonal and surgical treatment, including phalloplasty, in men with micropenis: a review. J Sex Med 10(12): 2890-903.

Chalapathi G, Rao KL, Chowdhary SK, Narasimhan KL, Samujh R, Mahajan JK. 2003. Testosterone therapy in microphallic hypospadias: topical or parenteral? J Pediatic Surg 38 (2): 221-3

Cheng PS, Chanoine J-P. 2001. Should the definition of micropenis vary according to ethnicity? Horm Res Pediatr 5(6): 278-281

Chioma L, Papucci G, Fintini D, Cappa M. 2018. Use of testosterone gel compared to intramuscular formulation for puberty induction in males with constitutional delay of growth and puberty: a preliminary study. J Endocrinol Invest 41(2): 259–63.

Chioma L, Cappa M. 2023. Hypogonadism in male infants and adolescents: new androgen formulations. Horm Res Paediatr 96: 581–589

Chung ST, Onuzuruike AU, Magge SN. 2018. Cardiometabolic risk in obese children. Ann NY Acad Sci 1411(1): 166-83.

Copeland KC and Chernausek S. 2016. Minipuberty and growth. Pediatrics. 138(1): e2016130

Davis SM, Reynolds RM, Dabelea DM, Zeitler PS, Tartaglia NR. 2019a. Testosterone treatment in infants with 47, XXY: effects on body composition. J Endocr Soc 3(12): 2276-85

Davis SM, Kaar JL, Ringham BM, Hockett CW, Glueck DH, Dabelea D. 2019b. Sex differences in infant body composition emerge in the first 5 months of life. Journal of Pediatric Endocrinology and Metabolism. Nov 1;32(11):1235-9.

de Oliveira FR, Guaragna MS, Maciel-Guerra AT, Barros BA, de Mello MP, Guerra-Junior G, Fabbri-Scallet H. 2024. DHX37 and the implications in disorders of sex development: an update review. Horm Res Paediatr 97(5): 433-44

Dwyer AA, Smith N, Quinton R. 2019. Psychological aspects of congenital hypogonadotropic hypogonadism. Front Endocrinol 10: 353.

Elamo HP, Virtanen HE, Toppari J. 2022. Genetics of cryptorchidism and testicular regression. Best Pract Res Clin Endocrinol Metab. 36(1): 101619.

Figueiredo MG, Gagliano-Jucá T, Basaria S. 2022. Testosterone therapy with subcutaneous injections: a safe, practical, and reasonable option. J Clin Endocrinol Metab. 107(3):614-26.

Fischer MB, Mola G, Priskorn L, Scheel L, Hegaard HK, Sundberg K, Frederiksen H, Andersson AM, Juul A, Hagen CP. 2024. Longitudinal Evaluation of Fetal and Infant AGD in Healthy Children: Association with Penile Size, Testosterone, and DHT. J Clin Endocrinol Metab 109(12):3087-95.

DRAFT

Guthrie RD, Smith DW, Graham CB. 1973. Testosterone treatment for micropenis during early childhood. J Pediatr 83(2): 247-252

Hagag AA, Erfan AA, Elrifaey SM, Gamal RM, Harakan AI. 2017. Penile and testicular measurements in male neonates and infants: Single center Egyptian study. Endocr Metab Immune Dis Drug Target 17(4):309-16.

Hatipoğlu N, Kurtoğlu S. 2013. Micropenis: etiology, diagnosis and treatment approaches. J Clin Res Pediatr Endocrinol 5(4):217.

He TQ, Wen R, Zhao YW, Liu L, Hu JJ, Liu Y, Peng QL. 2022. Testicular regression syndrome: a retrospective analysis of clinical and histopathological features in 570 cases. Front Pediatr 31; 10: 1006880.

Hegarty PK, Mushtaq I, Sebire NJ. 2007. Natural history of testicular regression syndrome and consequences for clinical management. J Pediatr Urol; 3: 206-208

Heksch RA, Matheson MA, Tishelman AC, Swartz JM, Jayanthi VR, Diamond DA, Harrison CJ, Chan YM, Nahata L. 2019. Testicular regression syndrome: practice variation in diagnosis and management. Endocr Pract 25(8): 779-86.

Huang C, Ma Y, Bai D, Hao C. 2025. Perinatal testicular torsion diagnosed as an intraperitoneal mass: case report and literature review. Front Pediatr 13:1501645.

Ishii T, Sasaki G, Hasegawa T, Sato S, Matsuo N, Ogata T. 2004. Testosterone enanthate therapy is effective and independent of SRD5A2 and AR gene polymorphisms in boys with micropenis. J Urol 172(1): 319-24.

Ishii T, Matsuo N, Inokuchi M, Hasegawa T. 2015. A cross-sectional growth reference and chart of stretched penile length for Japanese boys aged 0-7 years. Horm Res Pediatr 82(6):388-93.

Johannsen TH, Main KM, Ljubicic ML, Jensen TK, Andersen HR, Andersen MS, Petersen JH, Andersson AM, Juul A. 2018. Sex differences in reproductive hormones during mini-puberty in infants with normal and disordered sex development. J Clin Endocrinol Metab. 103(8):3028-37.

Kaminetsky JC, McCullough A, Hwang K, Jaffe JS, Wang C, Swerdloff RS. 2019. A 52-week study of dose adjusted subcutaneous testosterone enanthate in oil self-administered via disposable auto-injector. J Urol; 201(3):587-594

Khadilkar V, Mondkar SA. 2023. Micropenis. Ind J Pediatr 90(6): 598-604.

Kiviranta P, Kuiri-Hänninen T, Saari A, Lamidi M-L, Dunkel L, Sankilampi U. 2016. Transient postnatal gonadal activation and growth velocity in infancy. Pediatrics. 138(1): e20153561

Laurer E, Rohayem J, Hogler W, Heger S, Castro S, Rey RA, Nordenstrom A, Howard SR. 2025. Endocr Abstracts 110 P1036, DOI: 10.1530/endoabs.110.P1036

DRAFT

Lovinger RD, Kaplan SL, Grumbach MM. 1975. Congenital hypopituitarism associated with neonatal hypoglycemia and microphallus: four cases secondary to hypothalamic hormone deficiencies. The J Pediatr 87(6):1171-81.

Main KM, Schmidt IM, Skakkebæk NE. 2000. A possible role for reproductive hormones in newborn boys: progressive hypogonadism without the postnatal testosterone peak. J Clin Endocrinol Metab 85(12):4905-7.
Mangaraj S, Choudhury AK, Mohanty BK, Baliarsinha AK. 2017. Congenital anorchia: A report of two cases and a brief review of the literature. J Integrat Nephrol Androl 4(4): 141-143

Mason KA, Schoelwer MJ, Rogol AD. 2020. Androgens during infancy, childhood and adolescence: physiology and use in clinical practice. Endocr Rev 41: 421-456

Mazur T. 2005. Gender dysphoria and gender change in androgen insensitivity or micropenis. Arch Sex Behav. 34(4):411-21.

McElreavey K, Jorgensen A, Eozenou C, Merel T, Bignon-Topalovic J, Tan DS, Houzelstein D, Buonocore F, Warr N, Kay RG, Peycelon M. 2020. Pathogenic variants in the DEAH-box RNA helicase DHX37 are a frequent cause of 46,XY gonadal dysgenesis and 46,XY testicular regression syndrome. Genet Med 22(1):150-9

Misra M, MacLaughlin DT, Donahoe PK, Lee MM. 2002. Measurement of Mullerian inhibiting substance facilitates management of boys with microphallus and cryptorchidism. J Clin Endocrinol Metab 87(8): 3598-602.

Nerli RB, Koura A, Prabha V, Reddy M. 2009. Comparison of topical versus parenteral testosterone in children with microphallic hypospadias. Pediatr Surg Int 25: 57-9

Papparella A, Zamparelli M, Cobellis G, Amici G, Saggiomo G, Parmeggiani P, Fioretti GP. 1999. Laparoscopy for nonpalpable testis: is inguinal exploration always necessary when the cord structures exit the inguinal ring? Pediatr Endo Innov Tech 3:29-33.

Philibert P, Zenaty D, Lin L, Soskin S, Audran F, Léger J, Achermann JC, Sultan C. 2007. Mutational analysis of steroidogenic factor 1 (NR5a1) in 24 boys with bilateral anorchia: A French collaborative study. Hum Reprod; 22: 3255-61

Pirgon O. 2012. Vanishing Testes: A Literature Review. J Clin Res Pediatr Endocrinol; 4(3): 116-120

Poomthavorn P, Stargatt R, Zacharin M. 2009. Psychosexual and psychosocial functions of anorchid young adults. J Clin Endocrinol Metab 94(7):2502-5.

Quigley CA, de Bellis A, Marschke KB, El-Awady MK, Wilson EM, French FS. 1995. Androgen receptor defects: historical, clinical and molecular perspectives. Endocr Rev 16(3): 271-321

Quigley CA. 2002. The postnatal gonadotropin and sex steroid surge – insights from the androgen insensitivity syndrome. J Clin Endocrinol Metab 87(1): 24-28

DRAFT

Quigley CA, Vilain E. Genetic basis of gonadal and genital development. Chapter 142 in Jameson JL and De Groot L (eds) *Endocrinology*, 6th Edition, 2010, Elsevier.

Reilly JM, Woodhouse CR. 1989. Small penis and the male sexual role. J Urol 142: 569-71

Rey RA, Grinspon RP, Gottlieb S, Pasqualini T, Knoblovits P, Aszpis S, Pacenza N, Usher S, Bergada I, Campo SM. 2013. Male hypogonadism: an extended classification based on a developmental, endocrine physiology-based approach. Andrology 1:3-16
Rey RA, Grinspon RP. 2024. Anti-Müllerian hormone, testicular descent and cryptorchidism. Front Endocrinol 15:1361032.

Roche AF, Guo S, Moore WM. 2019. Weight and recumbent length from 1 to 12 mo of age: reference data for 1-mo increments. Am J Clin Nutrit 49(4):599-607.

Rogol AD, Swerdloff RS, Reiter EO, Ross JL, ZumBrunnen TL, Pratt GA, Brennan JJ, Benesh J, Kan-Dobrosky N, Miller MG. 2014. A multicenter, open-label, observational study of testosterone gel (1%) in the treatment of adolescent boys with Klinefelter syndrome or anorchia. J Adol Health. 54(1):20-5.

Rohayem J, Alexander EC, Heger S, Nordenström A, Howard SR. 2024. Mini-puberty, physiological and disordered: consequences, and potential for therapeutic replacement. Endocr Rev 45: 460–492

Sarkey S, Azcoitia I, Garcia-Segura LM, Garcia-Ovejero D, DonCarlos LL. 2008. Classical androgen receptors in non-classical sites in the brain. Horm Behav 53(5):753-64.

Semiz S, Küçüktaşçi K, Zencir M, Sevinç O. 2011. One-year follow-up of penis and testis sizes of healthy Turkish male newborns. Turk J Pediatr 53(6):661-5.

Shimura K, Ichihashi Y, Nakano S, Sato T, Hamajima T, Numasawa K, Narumi S, Hasegawa T, Ishii T. 2025. DHX37 variant is one of the common genetic causes in Japanese patients with testicular regression syndrome/partial gonadal dysgenesis without Müllerian derivatives. Horm Res Paediatr 98 (2): 206-13

Smith NM, Byard RW, Bourne AJ. 1991. Testicular regression syndrome—a pathological study of 77 cases. Histopathology 19(3): 269-72

Spires SE, Woolums CS, Pulito AR, Spires SM. 2000. Testicular regression syndrome. A clinical and pathologic study of 11 cases. Arch Pathol Lab Med. 124:

Spratt DI, Stewart II, Savage C, Craig W, Spack NP, Chandler DW, Spratt LV, Eimicke T, Olshan JS. 2017. Subcutaneous injection of testosterone is an effective and preferred alternative to intramuscular injection: demonstration in female-to-male transgender patients. J Clin Endocrinol Metab 102(7): 2349–55.

Stancampiano MR, Suzuki K, O'Toole S, Russo G, Yamada G, Ahmed SF. 2022. Congenital micropenis: etiology and management. J Endocr Soc 6(2): bvab172.

DRAFT

Tack LJ, Brachet C, Beauloye V, Heinrichs C, Boros EM, De Waele K, Van Der Straaten S, Van Aken S, Craen M, Lemay A, Rochtus A, Casteels K, Beckers D, Mouraux T, Logghe K, Van Loocke M, Massa G, Van de Vijver K, Syryn H, Van De Velde J, De Baere E, Verdin H, Cools M. 2023. Etiology, histology, and long-term outcome of bilateral testicular regression: a large Belgian series. Hum Reprod Open 2023 (4): hoad047

Thakur R, Bhatia A, Sood S, Chaudhary R, Bhatia R, Kumar GR. 2020. Ruptured Scrotum and Gangrenous Testis in a Newborn Ending up in Orchidectomy after Vaginal Breech Delivery: A Case Report. Ann Internat Med Dent Res 6(4):22.

Tsang S. 2010. When size matters: a clinical review of pathological micropenis. J Pediatr Health Care 1;24(4): 231-40.

Varimo T, Hero M, Laitinen E-M, Miettinen PJ, Tommiska J, Känsäkoski J, Juul A, Raivio T. 2016. Childhood growth in boys with congenital hypogonadotropic hypogonadism. Pediatr Res. 79(5): 705-709

Wilson DM, Kiang TK, Ensom MH. 2018. Pharmacokinetics, safety, and patient acceptability of subcutaneous versus intramuscular testosterone injection for gender-affirming therapy: a pilot study. Bull Amer Soc Hosp Pharmacists. 75(6): 351-8.

Wisniewski AB, Migeon CJ, Gearhart JP, Rock JA, Berkovitz GD, Plotnick LP, Meyer-Bahlburg HFL, Money J. 2001. Congenital micropenis: long-term medical, surgical and psychosexual follow-up of individuals raised male or female. Horm Res; 56:3–11

Wiygul J, Palmer LS. 2011. Micro-penis. Sci World J. 11:1462–1469.

Wolfe-Christensen C, Fedele DA, Kirk K, Phillips TM, Mazur T, Mullins LL, Chernausek SD, Lakshmanan Y, Wisniewski AB. 2012. Degree of external genital malformation at birth in children with a disorder of sex development and subsequent caregiver distress. J Urol 188 (4 Suppl):1596-1600.

Wong SC, Scott D, Lim A, Tandon S, Ebeling PR, Zacharin M. 2015. Mild deficits of cortical bone and increased adiposity in young adults with Klinefelter syndrome or anorchia treated with testosterone from adolescence. J Clin Endocrinol Metab 100(9): 3581-9.

Wright JE. 1986. The atrophic testicular remnant. Pediatr Surg Int; 1:229-231.

Zenaty D, Dijoud F, Morel Y, Cabrol S, Mouriquand P, Nicolino M, Bouvatier C, Pinto G, Lecointre C, Pienkowski C, Soskin S, Bost M, Bertrand AM, El-Ghoneimi A, Nihoul-Fekete C, Leger J. 2006. Bilateral anorchia in infancy: occurrence of micropenis and the effect of testosterone treatment. J Pediatr 149:687-9

DRAFT

Addendum 1. Overview of gonadal and reproductive tract development in the male fetus and infant

Human reproductive development is controlled by genetic, cellular and hormonal networks at three levels – the hypothalamus, the pituitary gland and the gonads; thus, this system is referred to as the hypothalamic-pituitary-gonadal (HPG) axis. In the first few weeks of embryonic development the primitive gonadal ridge forms as an undifferentiated area of tissue in the lower abdomen, differentiating into the testis by 7-8 weeks' gestation in the 46,XY fetus (Quigley 2010; Rey 2013). From around 8 weeks' gestation testosterone secretion by the Leydig cells of the fetal testes is stimulated by maternal human chorionic gonadotropin (hCG) from the placenta, beginning the process of male sex differentiation.

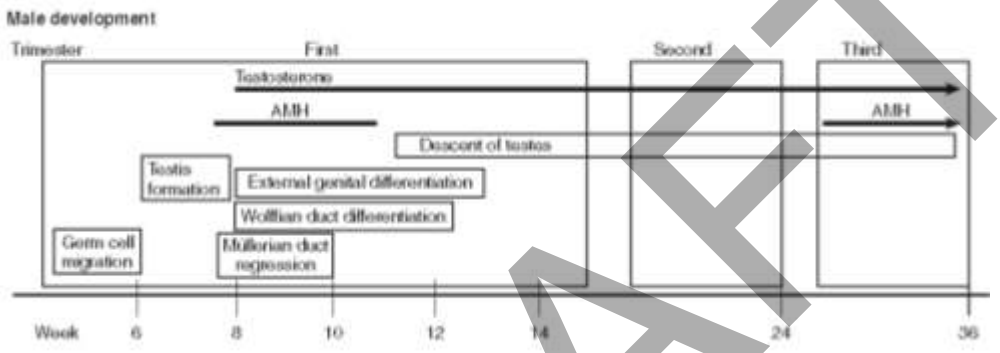


Figure 1: Timeline of male reproductive tract and genital development (from Quigley, 2010).

As shown in Figure 1, the high concentration of testosterone within the vicinity of the fetal testes promotes differentiation of the embryonic Wolffian duct system into male internal reproductive tract structures (epididymis, vas deferens, seminal vesicle). Testosterone in conjunction with its more potent metabolite, dihydrotestosterone, induces masculinization of the urogenital sinus and genital ridge, forming the penis with enclosed tubular urethra, and promoting fusion of the labioscrotal folds to form the scrotum (i.e. masculinization of external genitalia). Anti-Müllerian hormone (AMH) secreted by testicular Sertoli cells induces regression of the Müllerian ducts, thereby suppressing development of uterus and fallopian tubes. Thus, typical male and female fetuses are anatomically distinct by the end of the first trimester, and male sex differentiation (reproductive structures and genitalia) is complete by around 14 weeks' gestation, known as the 'critical period' of male sex differentiation.

Beginning in the second trimester of gestation, the fetal hypothalamus and pituitary gland become involved in control of testicular function. The combined actions of fetal luteinizing hormone (LH) and follicle-stimulating hormone (FSH), under the control of gonadotropin-releasing hormone (GnRH) secreted by the fetal hypothalamus stimulate increased testosterone production and substantial growth of the male reproductive and genital structures. However, during the third trimester of gestation, the fetal testes become quiescent due to suppression of the HPG axis by high concentrations of maternal estrogens to which the fetus is exposed via the placenta.

DRAFT

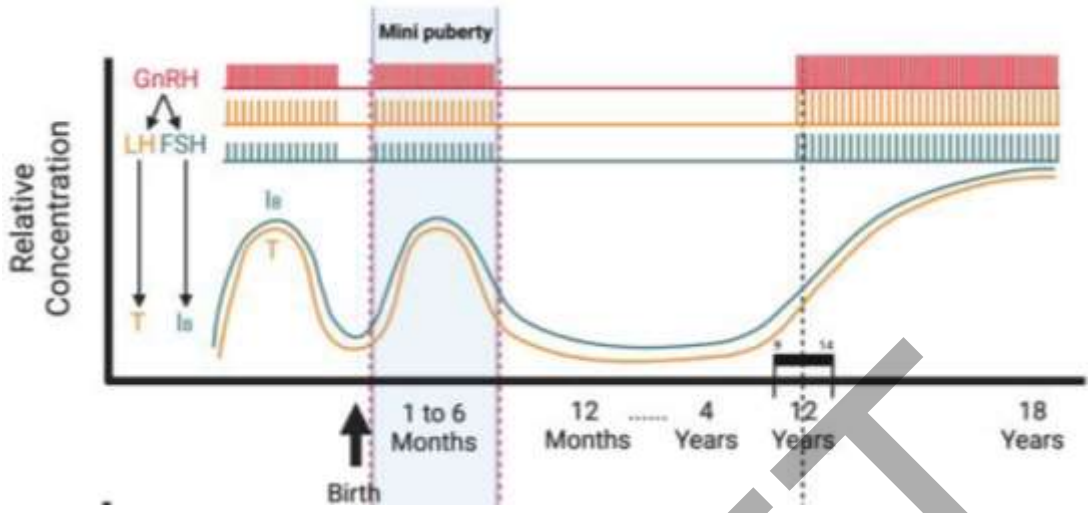


Figure 2: Physiologic activity of male hypothalamic-pituitary-gonadal axis from 2nd trimester of gestation to 18 years of age. Secretion of gonadotropin-releasing hormone (GNRH) from the hypothalamus, luteinizing hormone (LH) and follicle stimulating hormone (FSH) from the pituitary gland are shown at the top as short pulses. Curves at the lower part of the figure represent testosterone (pink line) and inhibin B (blue line) secreted by the testes. The mini-puberty of infancy is shown as the peaks of testosterone and inhibin B secretion from 1 to 6 months of age (from Rohayem 2024).

After the baby separates from the placenta at birth his circulating estrogens from his mother decline rapidly, and the infant takes control of his own hormone secretion. As shown in Figure 2, GnRH secretion by the hypothalamus is reawakened and concentrations of pituitary gonadotropins and testicular hormones, most importantly testosterone, surge, peaking at around 2-3 months of postnatal life, before declining again around 6 months of age (Becker 2020; Quigley 2002; Rey 2013; Rohayem 2024). Peak testosterone concentrations during the postnatal surge are similar to those of an adult man, but the phenomenon is short-lived, resulting in its name – the 'mini-puberty' of infancy. This dramatic developmental event represents a period of hormonal priming of the reproductive tract, with a key consequence being the increased capacity for sperm production in adult life (Rohayem 2024). Penile length and growth during mini-puberty directly correlate with serum testosterone concentrations (Boas 2006), and the rate of penile growth is greater during mini-puberty than at any other time prior to the onset of puberty itself. Thus mini-puberty represents a transient but important period of normal postnatal male development that cannot be replicated.

DRAFT

Addendum 2: glossary of terms used in this document

Anorchia: absence of one or both testes in a 46,XY individual with male phenotype
Anti-Müllerian hormone (AMH): a peptide hormone produced by the Sertoli cells of the testes that causes regression of the fetal Müllerian dust system
Boy: male child; young male human
Congenital: a condition present at birth
Follicle-stimulating hormone (FSH): a pituitary hormone that plays a significant role in maturation of testicular germ cells into sperm
Germ cells: precursor cells in the testes that differentiate into sperm at maturity
Girl: female child; young female human
Gonadal dysgenesis: failure of differentiation of the primordial gonad into testis
Hypogonadism: inadequate function of the testes with respect to both germ cell development and hormone secretion
Hypothalamic-pituitary-gonadal axis: the tightly-regulated hormonal system including the hypothalamus, pituitary gland and testes that controls development and function of sexual and reproductive function
INSL3: insulin-like 3 (abbreviated INSL3) is a peptide hormone produced by testicular Leydig cells that plays a significant role in the process of prenatal testicular descent from abdomen to scrotum
Klinefelter syndrome: a condition in which individuals with male phenotype have an additional X chromosome, resulting in 47,XXY karyotype (other variants may have more than 1 additional X chromosome)
Leydig cells: cells within the testes that produce and secrete testosterone and insulin-like hormone 3
Linear growth: growth of the individual in length (during infancy and early childhood when measured recumbent) or height, when measured standing
Luteinising hormone (LH): a pituitary hormone that stimulates production and secretion of testosterone by Leydig cells
Mini-puberty: a limited period during infancy when the hypothalamic-pituitary-testicular axis becomes highly active, resulting in a marked surge in secretion of testosterone by Leydig cells which peaks around 3 months of age
Müllerian duct (s): the precursor(s) of female internal reproductive structures; development is suppressed during male fetal development by anti-Müllerian hormone (AMH)
Sertoli cell: a population of specialized cells of the testes responsible for support of germ cells/ sperm
Somatic growth: physical growth and development of the body
Testicular regression: the process whereby a previously healthy testis with normal function during early fetal life undergoes a degenerative process resulting in atrophy (death) of testicular tissue
Testosterone: the primary steroid hormone produced by the testes, which has both androgenic (masculinizing) and anabolic (protein-building) effects
Vanishing testes: the disappearance of previously healthy testes after initially normal function during fetal life
Visceral adiposity: deposition of excess adipose tissue (fat) around the abdominal organs
VSCPSS: Canberra Health Services Variations in Sex Characteristics PsychoSocial Service
Wolffian duct(s): the fetal precursors of male internal reproductive duct structures (epididymis, vas deferens, seminal vesicles)

Prepared by: Charmian A. Quigley, MBBS, FRACP; Sarah Hosking, MBBS, FRACP; Tony Lafferty, MBBS, FRACP; Uma Visser, MBBS, MMed, FRACP
Paediatric Endocrinologists, Canberra Health Services
Date: 16 September 2025

DRAFT

Checklist of optional attachments	
☐	Attachment A – Prescribed people
☒	Attachment B – Proposed treatments
☐	Attachment C – Harms
☐	Attachment D – Alternative treatments
☐	Attachment E – Relative efficacy of treatment
☐	Attachment F – Restrictiveness of treatment

DRAFT