Standardised data collection for clinical follow-up and assessment of outcomes in Differences of Sex Development (DSD): Recommendations from the COST Action DSDnet

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Abstract

The treatment and care of individuals who have a Difference of Sex Development (DSD) have been revised over the past two decades and new guidelines have been published. In order to study the impact of treatments and new forms of management in these rare and heterogeneous conditions, standardized assessment procedures across centres are needed. Diagnostic work-up and detailed genital phenotyping are crucial at first assessment. DSDs may affect general health, have associated features or lead to comorbidities which may only be observed through lifelong follow-up. The impact of medical treatments and surgical (non-) interventions warrants special attention in the context of critical review of current and future care. It is equally important to explore gender development early and refer to specialized services if needed. DSDs and the medical, psychological, cultural and familial ways of dealing with it may affect self-perception, self-esteem, and psychosexual function. Therefore, psychosocial support has become one of the cornerstones in the multidisciplinary management of DSD, but its impact remains to be assessed.

Careful clinical evaluation and pooled data reporting in a global DSD registry will allow linking genetic, metabolomic, phenotypic and psychological data. For this purpose, our group of clinical experts and patient and parent representatives designed a template for structured longitudinal follow-up. In this paper, we explain the rationale behind the selection of the dataset. This tool provides guidance to professionals caring for individuals with a DSD and their families. At the same time, it collects the data needed for answering unsolved questions of patients, clinicians, and researchers. Ultimately, outcomes for defined subgroups of rare DSD conditions should be studied through large collaborative endeavours using a common protocol.

1. Introduction

The term Differences (Disorders) of Sex Development (DSD) refers to a heterogeneous group of conditions that affect the urogenital tract and result in atypical sex development. The prevalence of the individual conditions is mostly very low and only a small fraction of all conditions characterised by variations in sex characteristics pose major clinical challenges and/or require multidisciplinary care [1]. Recent outcome studies suggest that having a DSD may impact an individuals' health status and psychological well-being in every stage of life [2-4], though physical or psychological co-morbidities have been rarely studied in detail, especially in adults. Influencing factors include the rarity of the respective conditions, individual drawbacks to participate in medical studies and the dispersion of affected individuals over decentralised health care structures, with frequent loss of patients for follow-up. In addition, the quality of care for individuals with a DSD varies considerably across Europe, between centres and within diagnostic groups. Patient satisfaction with care is lowest among individuals with the rarest conditions [5].

The development of a concrete and evidence-based protocol for structured review and clinical data collection in children and adults who have a DSD, at various age intervals, may be pivotal in addressing these difficulties [6] (Figure 1). It minimizes bias in clinical assessments and can provide guidance to clinicians who do not regularly see these patients. In fact, there is a need to support health care professionals in assessing a small amount of data regularly as part of a holistic routine clinical care. Equally important, it enables exchange of data among clinical centres and in research networks such as the international DSD Registry I-DSD (www. https://i-dsd.org), allowing large-scale multicentre studies. For patients, it can increase understanding of their condition, provide clarity about one's future medical needs, enhance compliance and facilitate discussions with caregivers [7]. From a healthcare point of view, adherence to an evidence-based assessment protocol can serve as a quality indicator and benchmarking tool [8].

Several aspects of DSD management are surrounded by controversy or uncertainty and have led to a thorough revision of clinical practice in recent years [1]. For example, genital surgery in young children is more often avoided nowadays in order to protect childrens' rights of an open future and integrity of the body; and increasing numbers of children grow up with atypical-looking genitalia, of which the psychological impact is not known [9]. Many DSD teams provide psychological support to affected families as a standard component of care nowadays, children are informed early about their condition, and gender issues are openly discussed [6]. Some teams include peer support in the medical management plan [10].

Structured longitudinal assessment of individuals with a DSD across centres may provide future evidence in favour or against these new practices, with specific relevance to (rare)

individual diagnoses, provided that all relevant parameters are considered in parallel and by standardized measurement tools.

In accordance with patient aspirations, the promotion of a standardized protocol that uses a non-binary vocabulary and medical approach can be paramount in inducing societal change as well as amongst the medical community, in attitudes towards gender perception and normative paradigms of sex, including genital characteristics [11]. This will by itself be instrumental in defining the place, timing and the specific medical need of genital surgery.

2. Development of consensus on standardised data collection

The development of a meaningful, holistic schedule for clinical assessment that allows for standardized longitudinal data collection over time in individuals who have a DSD has been the primary goal of an expert multidisciplinary working group, including representatives from patient support groups. This group operated in the period 2013 – 2017 in the framework of the European Cooperation in Science and Technology (COST) Action BM1303 “DSDnet” (www.DSDnet.eu), funded by the European Union Horizon 2020 program. Collaboratively, the group: 1) reviewed the literature on existing instruments for clinical phenotyping at all ages; 2) defined their major strengths and shortcomings as well as hitherto insufficiently covered areas of (para)medical attention; and 3) discussed essential characteristics of a qualitative longitudinal follow-up program until agreement was reached on a protocol for standardised assessment at various ages that was versatile enough to be used in clinical settings as well as within electronic global platforms such as the I-DSD registry.

3. General dataset and ages at which follow-up assessments are recommended

Criteria for referral of a child for expert evaluation are specified in the UK guidelines [12]. At first referral, linking the case to original health records and obtaining consent for sharing data (local, national, international) are crucial. Basic DSD-related information, such as diagnosis, karyotype, birth-assigned sex, and social gender should also be included (Table 1).

Thereafter, appropriate time intervals for clinical revision of patients depend on the respective conditions, patient age, and individual circumstances. However, for registration and research purposes, it was considered crucial to standardise a minimal set of time points, corresponding to important developmental milestones, at which relevant clinical data should be collected (Figure 1).

A summary of neonatal data, where available, should be collected in all cases with later presentation (Table 2). Clinical revision at age 4 years (Table 3) allows for comprehensive assessment of psychological developmental milestones, associated symptoms, and growth patterns, including catch-up growth. The process of informing the child about the condition should start as soon as possible after diagnosis, along with the provision of support in

acquiring a vocabulary to talk about the DSD [13]. Practical advice on this matter can be found at support group resources (e.g. www.dsdfamilies.org or https://www.iglyo.com/wp-content/uploads/2018/10/Supporting-Your-Intersex-Child.pdf). At age 8 years (Table 3), relevant information on growth and development shortly before start of puberty can be obtained. At this age the child understands more complex information about how the body functions and about the specific DSD. Gender identity or eventual dysphoria may be ascertained and children experiencing uncertainty can be referred for expert psychological or psychiatric evaluation and support. Pubertal development and progression (Table 4) may be compromised in many children who have a DSD. Some children may need hormonal induction of puberty. Standardized assessment at start of puberty and the outcome of pubertal development are therefore paramount to document, though most children will need clinical revision more frequently. Transition to adult healthcare should be discussed early on during this period [8, 14].

Much less evidence is available to guide timing of clinical revision in adulthood (Table 5). In favour of standardized assessment of young individuals aged 18-25 is that they are in the process of gaining independence and have recently transitioned to adult care. Many young people are newly forming intimate relationships, which potentiates new concerns and/or required healthcare intervention. Topics such as sexual function, sexual orientation, and gender identity may become central in their lives. In addition, baseline information on typical health issues in adulthood such as bone mineral density, blood pressure, and obesity should be collected. Issues around fertility and forming a family may dominate between ages 25 and 40.

During the age intervals of 40-60 and 60-80, long-term effects of treatment or (lack of) hormonal treatment and co-morbidities may become apparent [8]. Physical and mental health issues of adults living with a DSD are major determinants of overall quality of life (QoL) [4]. It is therefore crucial to capture such information in order to allow for future research and appropriate management.

4. **Genetic and biochemical data**

Most causes of DSD are genetic; however, drugs, environmental toxins, and maternal and placental causes are also relevant and/or may influence outcomes. A clear diagnosis can determine the spectrum of potentially affected organs, current/future health consequences, and treatment options [8].

A comprehensive diagnostic approach consists of an extensive family history over at least 3 generations, as well as a physical exam of the whole body which includes the genital organs. This will then guide the clinician towards further diagnostic imaging, biochemical and genetic

studies. Guidelines for the clinical, biochemical, and genetic work-up of DSD have been published elsewhere [12, 15, 16].

Collecting genetic information, together with clinical and biochemical data, in a centralized registry allows identification and characterization of DSD subgroups, including those for which a genetic diagnosis has not been achieved so far. It is possible then to test the diagnostic reliability of specific biochemical and genetic parameters and their usefulness for implementation in clinical diagnostic guidelines. It will also enable studies on the impact of a molecular genetic diagnosis on outcome. Indeed, almost 50% of individuals who have a 46,XY DSD have no genetic diagnosis, and it remains debatable whether and how this impacts management and overall quality of life [17].

Although DSDs are congenital conditions, the function of affected organs may decline over time, e.g. testicular function in 45,X/46,XY boys [18]. Therefore, any initially performed diagnostic laboratory investigation may need to be repeated, if in doubt and of therapeutic consequence. Hormonal and other drug treatments need to be controlled with regular intervals for correct dosing, effectiveness and side effects. Biochemical parameters that qualify best for treatment monitoring need to be identified based on prospectively collected data.

In some individuals who have an unknown cause of their condition, genetic work-up has been performed years ago with methods that are currently outdated. In others, whole exome or whole genome sequencing may reveal variants of unknown significance or monogenetic variants in established DSD genes that do not clearly explain the observed phenotype (e.g. heterozygous MAMLD1 mutations) [19]. Finally, DSD genetics may be more complex than initially thought, as demonstrated recently [20]. Therefore, genetic results may also require re-evaluation as new knowledge is gained over time.

5. **Medical fields**

5.1 Family data

A detailed family history, including fertility is essential to explore possible inheritance mechanisms and to lend support for molecular genetic investigations in individuals with milder phenotypes. Phenotypic variability within families may be broad and may comprise subfertility/infertility as the only sign, depending on the severity of the mutation [21, 22].

5.2 Associated conditions

Several co-morbidities and non-gonadal organ dysfunctions are associated with specific DSDs [23]. Further exploration of these associations is important for targeted follow-up of affected individuals and for understanding mechanisms of disease. As many DSD conditions are caused by mutations in transcription factors that regulate the development of several

organ systems, this may result in combined functional defects, as for example in WT1 (kidney involvement), NR5A1 (adrenal involvement, spleen hypoplasia) or GATA4 (cardiac defects) mutations [24-27]. Associated conditions are mostly found in chromosomal DSD such as 45,X/46,XY and may only develop over time, requiring medical attention at each follow-up visit, for example cardiac surveillance in all individuals who have 45,X/46,XY mosaicism [18, 28].

5.3 External and internal genital phenotype

As genital photography and storage faces ethical and legal challenges, standardized tools are needed to objectively describe the genital aspect in detail. Qualitative visual scales such as the Prader [29] or Quigley [30] scales are highly observer-dependent and do not consider internal and external genital status separately. The anogenital distance correlates with prenatal androgen exposure but lacks standardization and is difficult to perform in children above one year [31]. The External Masculinization Score (EMS) is a practical and objective tool, has good inter-observer reliability and correlates with relevant clinical outcomes [12, 32, 33]. Limitations include its restricted applicability – only male neonates - and dichotomous nature (e.g. micropenis yes/no). To overcome these problems, a modified EMS, termed “external genitalia score” (EGS), has been developed. The EGS assesses the same anatomical landmarks as EMS while using a gender-neutral vocabulary applicable in all infants up to two years of age, and a more gradual scale, reflecting the naturally occurring phenotypic variability of external genitalia. Reference ranges for a mixed European population have been determined [34]. Additional parameters such as penile curvature and tissue quality are likely related to (surgical) outcome, but these are currently ill-defined and require further study. Reliable assessment of internal genitalia requires imaging and sometimes surgical procedures such as laparoscopy. Knowledge on the internal anatomy can be helpful in cases where the initial sex/gender of rearing is unclear and to foresee possible complications. Imaging techniques have significant differences in sensitivity, sensibility, and invasiveness. In the longer term, meta-analysis of data will provide further insights on the procedure of choice in specific situations.

The genital phenotype and other sex characteristics change as the individual grows or as a result of hormonal treatment or surgery. Frequent genital inspection is not recommended, but may be helpful in specific situations, especially as it can help parents and children / adolescents to understand that there is a natural variation in clitoral sizes and genital aspect or to discuss eventual parental or patient worries. For example, in 46,XX individuals who have CAH, clitoral size may decrease in response to glucocorticoid treatment after the newborn period. This finding is often very reassuring for parents and may actually convince them that the genital aspect has indeed become unremarkable for a lay person taking care of their baby. On the other hand, clitoral size may increase in periods of undertreatment or non-

compliance [35, 36] and/or adolescent girls may feel insecure about its aspect. Thoughtful genital inspection in an adolescent girl, after having obtained her consent, may sometimes help her discussing eventual worries about the genital aspect and/or reassure her that clitoral sensitivity is most important and that the clitoral aspect falls within the natural variation. Gonadal failure may result in lack or arrest of pubertal development. In such cases, it is important to document genital pubertal progression at the suggested time intervals. Suspicion of complications, e.g. fistulae after hypospadias surgery will also require a genital exam.

In adult life, psychosexual function is an even more important outcome parameter and should be discussed as suggested in Table 5; sometimes, depending on the specific question (eg worries about penile length), this will need to be done in parallel with a genital exam [1, 36].

5.4 Anthropometric data, body composition and bone health

Documentation of birth weight and length, growth, body composition and bone health parameters is crucial as it may reveal long-term outcomes of childhood processes such as the postnatal hypothalamic-pituitary-gonadal activation (the “mini-puberty”) and growth patterns in DSD other than Turner syndrome (TS) and Klinefelter syndrome (KS), where evidence is currently scarce. For example, no data are available on the prevalence and extent of catch-up growth in children with atypical genitalia who were born small for gestational age. In individuals with 45X/46XY karyotypes, growth hormone treatment has variable effects and may need to be optimised [37, 38]. Age at start of puberty induction and dosing of sex steroids may affect the growth pattern and body proportions [39]. Glucocorticoid overtreatment compromises growth and leads to increased weight and BMI in the longer term [40]. Both androgens and estrogens are important for bone mass accrual and maintenance. Overtreatment with glucocorticoids, vitamin D deficiency, physical activity, and hereditary factors may influence bone health [41].

5.5 Medical treatments

Some treatments are offered early in life, but evidence of their long-term efficacy may be lacking, e.g. testosterone (T) or dihydrotestosterone (DHT) for micropenis [42]. The use of some medications is experimental (e.g. aromatase inhibitors to block the effect of sex hormones [43, 44] or metformin to avoid metabolic consequences [45]), but others, such as growth hormone, gluco- and mineralocorticoids, L-thyroxin, insulin and sex hormone replacement therapy are frequently used in DSD and need constant surveillance and adjustments [46-48]. Standardized guidelines are lacking for most DSD conditions, with the exception of TS and KS [46, 49].

Lifelong steroid and sex hormone replacement therapy may induce side effects that negatively (or positively) impact QoL [4] and optimal dosing may vary with age [50, 51]. Very few studies address medical needs to optimise sexual function and to avoid secondary health consequences, especially at older ages. In addition, treatment regimens differ widely across centres and comparison of these protocols may further improve patient management and health-related QoL in the future [2, 52]. Large-scale registration and in-depth analysis of co-morbidities and of chronic use of certain medications aim to improve care and to positively alter outcomes.

Particular attention has been given to the prenatal treatment of a foetus possibly affected by 21-hydroxylase deficiency with dexamethasone administered to the mother. Benefit-risk ratio is still unclear and it is currently regarded as experimental [36]. From another perspective, drugs such as pain killers given to pregnant women and (environmental) toxins may affect foetal sexual development and fertility [53]. This important domain is largely unexplored, and collecting detailed information related to this topic is essential for future exploration.

5.6 Fertility and documentation of gonadal cancers

Fertility is strongly reduced in all forms of DSD, for biological and/or psychosocial reasons. Contemporary assisted reproductive techniques (ART) can increase chances to have biological children for some azoospermic individuals with 46,XY DSD and for some who have viable eggs [54, 55]. Uterus transplantations have resulted in live births [56]. It is anticipated that improvement of hormonal therapies and new technologies (e.g. in vitro generation of induced primordial germ cell-like cells) [57] may further increase fertility rates in the future. Assessment and documentation of reproductive capacity of the gonads independent of the patients' social gender has the aim of understanding condition-specific fertility chances [58]. It can also facilitate access to international research protocols in this field through recruitment of registered patients.

The mechanisms underlying germ cell cancer development in DSD are increasingly understood. Routine prophylactic gonadectomy to prevent germ cell cancer development is no longer recommended in all individuals at risk; guidelines for selective gonadectomy and surveillance of retained gonads have been published [59, 60]. Given the recent practice changes, no long-term outcome data on tumour risk in adulthood are available today, and with the possible exception of complete androgen insensitivity [60, 61], individualized management is hampered by a paucity of condition-specific data [59, 62]. Therefore, current recommendations may need to be adjusted based on future insights. With a molecular genetic diagnosis more often reached today, and with systematic registration of pathology results and centralized review of challenging cases, further progress in this matter can be achieved [63].

6. **Surgical fields**

6.1 Childhood surgery

There are few evidence-based indications for gonadal or genital surgery in early childhood. Gonadal biopsy may, in exceptional cases, support important decisions, e.g. in relation to sex of rearing in the context of suspected (ovo)testicular DSD [64]. Following international criticism of early genital surgery, many centers have restricted such procedures [9]. Although debated, early surgery is still offered by some centres for 46,XX CAH patients with severe genital virilization and for 46,XY patients with hypospadias. Other centers have restricted such procedures and consider alternative options such as raising severely virilised 46,XX CAH children as males and offer extensive parental support to enhance the information and decision–making process. The developmental, familial, and societal impact of growing up with atypical-looking genitalia is currently not well understood. Psychosocial support appears crucial, and detailed documentation of such decisions in a multicentre registry is essential to allow urgent studies on their appropriateness and long-term consequences [65]. Systematic registration can also demonstrate the time and pace needed to definitively implement the proposed practice changes.

There is no scientific evidence nor expert consensus on how surgery or refraining from surgery impacts the individual, family, society, or risk of stigmatization [1]. Standardized and detailed documentation of performed procedures, complications and reasons for and outcome of (non-) intervention are therefore crucial [9]. As the focus of many performed genital surgeries nowadays is more on function than in relation to gender assignment, a specific description should be used for the intervention or the reasons to intervene rather than referring to “feminising / masculinizing” genital surgery.

6.2 Genital examinations

Genital examinations should be limited and should have a clear and transparent purpose. Living with atypical-looking genitals and/or having had genital surgery may pose psychological and psychosexual challenges that require timely referral to a psychologist or sexologist. This person can then further perform a psychological evaluation, using standardized diagnostic measures and propose appropriate support if needed. The applied methodology depends on the specific goal of such an assessment. No DSD-specific questionnaires to assess psychological and/or psychosexual functioning currently exist, and interpretation of results is seriously hampered by methodological limitations, highlighting the need for psychologists with good knowledge of and experience with the various conditions and for further professional training in this field [66].

6.3 Follow-up of adults

Follow-up of adults who had genital surgery in infancy is rarely organized in the routine clinical setting. High-quality outcome and longitudinal studies are scarce. Difficulties include differences in technical terms, modifications of surgical techniques over the years, heterogeneity of DSD conditions and reporting bias of surgeons towards the techniques they are most experienced with [67]. Comprehensive assessment ideally includes recording complications and redo surgery (also in adulthood), cosmetic appearance, functional outcome (micturition, sexuality), and quality of psychosexual life as a minimum, all in relation to preoperative findings and assessed both by a professional and by self-assessment [68-71]. The hypospadias objective penile evaluation score (HOPE) has been designed for standardized cosmetic evaluation by a professional of hypospadias surgery [72]. Although practical and objective, HOPE has important shortcomings, such as the use of genital pictures, lack of evaluation of the scrotum and of possibilities for self-assessment, most notably of penile size, which is considered crucial by many patients [73]. A subjective cosmetic evaluation of hypospadias surgery can be obtained with the penile perception score (PPS) and its paediatric variant (PPPS) [74, 75]. All the above lack functional parameters such as micturition pattern, and erection and ejaculation capacity. A suggestion for a non-photography based modified HOPE score, with addition of relevant functional and self-perceived assessments is provided in Supplementary Table 1.

Different measures have been used for gynaecological and sexual function assessments of the female genitalia (e.g. [67, 71, 76]). Standardized tools for assessing long-term functional and cosmetic outcome of female genital surgery are in development. Items that are important to assess are listed in Supplementary Table 2.

7. **Psychosocial fields**

Trends in sex assignment have changed over the years [33]. Sex and gender are fundamental in the development of a person's identity, as well as the individual's integrity, self-esteem, and social relations. Inappropriate focus or a normative perspective on genital, sexual, and psychological issues may cause annoyance or stigmatization. Therefore, questions about a person's gender experience and gender well-being should be posed with respect for the individual's integrity and in an open-ended way that does not presume a particular gender, or increase shame and stigma [66]. Both children and adolescents should be given the possibility to talk about these issues without a parent being present [13].

Assessment of an individual's mental well-being and need for psychosocial support should be part of standard care throughout life. Physical or mental health problems are highly prevalent in individuals who have a DSD [2, 8]. Importantly, not the specific diagnosis but the personal health status predicts quality of life (QoL) [4]. Overall, individuals with a DSD report

good QoL but studies are often contradictory, possibly due to differences in local treatment and care, age and cultural context and differences in methodology. Appropriate QoL questionnaires should focus on social and psychological domains that are relevant for individuals who have a DSD [77]. In addition, patient reported outcome measures related to QoL at all life stages are considered most crucial by patients and it is clear that they have a central place in holistic care [78]. Formal QoL assessment in the context of routine clinical practice is unusual, but as a minimum, it is suggested to record the impact of the condition on the patients' daily life by including a relevant proxy for this. While awaiting more specific key questions, preferably developed by support groups and other stakeholders, a generic set of simple questions is proposed here, that can be adjusted to all ages.

Considering all conditions together, the prevalence of gender dysphoria is only slightly increased in DSD. However, assessing gender identity and gender-related behaviour according to a strict binary or pathologising model will insufficiently capture the broad spectrum of gender-related outcomes [79]. Currently, hardly any instrument is available that allows gender assessment according to a spectral rather than a bimodal paradigm. Therefore, new measures and instruments, using a non-binary vocabulary and taking all possible gender outcomes into account need to be developed. In addition, gender role behaviour rather than gender well-being has been given (too) much attention in the past. Indeed, it is crucial not to misinterpret behaviour or sexual orientation as signs of gender dysphoria [11].

From the beginning, psychosocial support for parents, aiming at an enhanced understanding of the medical context and the diagnostic investigations are crucial factors for coping with psychological distress [80]. Parent-child bonding, coping abilities and symptoms of stress are important indicators of parental needs on this matter [12]. In the presence of a genital difference, parents need guidance on how to raise resilient children and how to communicate early with their child about the condition, including consequences for gender development and past and future treatment options [81]. To what extent psychosocial support and early information may contribute to optimization of outcomes has never been documented in the context of DSD. Providing further evidence in favour of such support may convince policy makers to invest in psychological counselling, as an important part of preventive care and as a valuable alternative to genital surgery, amongst others [82, 83].

Many registries such as I-DSD are developing sections that include possibilities for self-reporting of relevant outcome measures, such as reasons for genital surgery or not having such surgery, and self-reported QoL. Altogether, considering the voices of people with DSD and their parents, research and care of DSD can move from a researcher driven to a participant driven approach.

Conclusions and Perspectives

Consensus was reached on standardized assessments of individuals who have a DSD and on the ages at which clinical revision should be performed in order to capture crucial developmental milestones and/or long-term consequences of the various conditions. In the clinical setting, the tool will ensure and support a high quality of clinical care. Long-term and wide use of this instrument, e.g. through the I-DSD Registry, will allow answering critical research questions in the future specifically in relation to outcome, treatment options, comorbidities in adult age and fertility. In addition, patient reported outcome measures, obtained through patient portals, are expected to become increasingly important and may be also implemented in the i-dsd registry in the near future.

Figure Legend and Tables' List:

Figure 1 – Scheme of the longitudinal I-DSD registration tool showing time points, ages for data entry, starting at the age of diagnosis. Neonatal data, including genetic information if available, should always be entered regardless of the age at diagnosis.

Table 1 - Neonatal assessment (within first month of birth)

Table 2 - Clinical assessment (at any age if first assessment after 1 month of age)

Table 3 - Table 3. Childhood assessment (at age 4 years and 8 years)

Table 4 - Table 4. Adolescent assessment (at start of puberty and end of puberty)

Table 5 - Table 5: Adult assessment (once per interval: 18-25; 25-40; 40-60; 60-75 years)

Supplementary Table1 - Tool for assessment of hypospadias (repair)

Supplementary Table 2 – Gynaecological assessment tool for longitudinal DSD care

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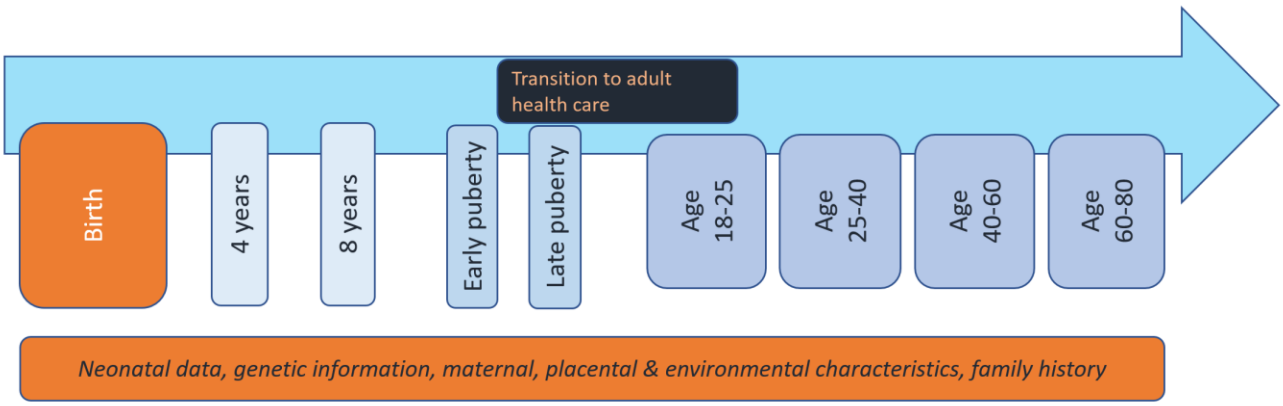
Transition to adult health care
Birth
4 years
8 years
Early puberty
Late puberty
Age 18-25
Age 25-40
Age 40-60
Age 60-80
Neonatal data, genetic information, maternal, placental & environmental characteristics, family history

Figure 1

Table 1. Neonatal assessment (within first month of birth)

General					
Date of Assessment dd/mm/yyyy	**Age at Assessment, years**	**Gestational Age, weeks**	**Birth Weight, grams**	**Birth Length, cm**	**Birth Head Circumference, cm**
Weight, kg	**Height, cm**	**BMI, kg/m^2**	**Mothers Height, cm**	**Fathers Height, cm**	**Mid Parental Height, cm**
Original Sex Assigned Male/ Female/ Both/ Not assigned/ Other	**Current Gender** Male/ Female/ Both/ Not assigned/ Other	**Child raised as** Male/ Female/ Both / Other	**Associated Conditions***	**Known Syndrome** Yes/ No	
External Phenotype					
Meatus Typical female/ Perineal/ Scrotal/ Penoscrotal/ Penile/ Coronal/ Typical male	**Left Gonad Location** Impalpable/ Inguinal/ Inguinoscrotal/ Labioscrotal	**Right Gonad Location** Impalpable/ Inguinal/ Inguinoscrotal/ Labioscrotal	**Genital Tubercle Length, mm** <10/ 10-20/ 21-25/ 26-30/ >30	**Phallus Size** Within/ Below/ Above the reference range for male; Within/ Below/ Above the reference range for female	**Labioscrotal Fusion** Yes/ No
Anogenital Distance 1$^{\#}$ (AGD1), mm	**Anogenital Distance 2$^{\#\#}$ (AGD2), mm**	**External Masculinisation Score (EMS)**	**External Genitalia Score (EGS)**		
Internal Phenotype					
Imaging Modality- Left Gonad US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	**Imaging Modality- Right Gonad** US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	**Left Gonad Morphology** Absent/ Streak/ Testis/ Ovary/ Ovotestis/ Other	**Right Gonad Morphology** Absent/ Streak/ Testis/ Ovary/ Ovotestis/ Other	**Imaging Modality- Uterus** US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	**Uterus Morphology** Absent/ Müllerian remnants/ rudimentary/ Normal/ Not known
Imaging Modality- Left Fallopian Tube US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	**Imaging Modality- Right Fallopian Tube** US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	**Left Fallopian Tube Morphology** Absent/ Rudimentary/ Normal/ Not known	**Right Fallopian Tube Morphology** Absent/ Rudimentary/ Normal/ Not known	**Distance- Vaginal Confluence to Bladder Neck, cm**	**Distance- Vaginal Confluence to Introitus, cm**
Imaging Modality- Left Vas Deferens US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	**Imaging Modality- Right Vas Deferens** US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	**Left Vas Deferens Morphology** Absent/ Rudimentary/ Normal/ Not known	**Right Vas Deferens Morphology** Absent/ Rudimentary/ Normal/ Not known		

Surgery					
Left Gonad Biopsy Yes/ No/ Not known	**Right Gonad Biopsy** Yes/ No/ Not known	**Left Gonadectomy** Yes/ No/ Not known	**Right Gonadectomy** Yes/ No/ Not known	**Genital reconstructive surgery**** None/ clitoral surgery / vaginal surgery / labioscrotal surgery / hypospadias surgery / urethral surgery other than hypospadias; age	**Reasons for genital reconstructive surgery** Functional / cosmesis / both **Post Surgical Complications** Yes/ No/ Not known; if yes, describe.
Psychosocial					
Change in Legal Sex Yes/ No/ Not known	**Psychosocial Support Offered to Parents** Yes/ No/ Not known	**Ongoing Psychosocial Support** Yes/ No/ Not known			
Medication					
Testosterone Yes (IM, Oral, Transdermal)/ No/ Not known **Oestrogen** Yes (IM, Oral, Transdermal)/ No/ Not known	**DHT** Yes (IM, Oral, Transdermal)/ No/ Not known **Other Drugs** Yes/ No/ Not known	**Aromatase Inhibitor** Yes/ No/ Not known	**GnRH analogues** Yes/ No/ Not known	**Glucocorticoids** Yes/ No/ Not known	**Fludrocortisone** Yes/ No/ Not known
Lab Tests					
LH Low/ Normal/ High/ Not known **Free Testosterone** Low/ Normal/ High/ Not known **hCG Stimulation Test** Specify protocol	**FSH** Low/ Normal/ High/ Not known **Dihydrotestosterone** Low/ Normal/ High/ Not known **Androstenedione** Low/ Normal/ High/ Not known	**AMH** Low/ Normal/ High/ Not known **Oestradiol** Low/ Normal/ High/ Not known **Total Testosterone** Low/ Normal/ High/ Not known	**Inhibin B** Low/ Normal/ High/ Not known **17-OHP** Low/ Normal/ High/ Not known **Dihydrotestosterone** Low/ Normal/ High/ Not known	**Androstenedione** Low/ Normal/ High/ Not known **Urine Steroids** Normal/ Abnormal	**Total Testosterone** Low/ Normal/ High/ Not known

Adrenal Stimulation Test	**17-OHP**	**11-deoxycortisol**	**Pregnenolone**	**17-OH Pregnenolone**	**DHEA**
Specify protocol	Low/ Normal/ High/ Not known	Low/ Normal/ High/ Not known	Low/ Normal/ High/ Not known	Low/ Normal/ High/ Not known	Low/ Normal/ High/ Not known

*Associated conditions: CNS, Heart, Renal, Skeletal, Skin, ENT, Eyes, Blood and Lymp, Craniofacial, Adrenal, GI Tract, Haematological, Respiratory, SGA (Small for Gestational Age), Short stature, Non-defined syndrome, Other. ** **Genital reconstructive surgery** field may be repeated.

AGD 1: Distance from the centre of the anus to the posterior base of the labioscrotal folds; ##AGD 2: Distance from the centre of the anus to the anterior base of the phallus

Table 2. Clinical assessment (at any age if first assessment after 1 month of age)

General					
Date of Assessment dd/mm/yyyy	**Age at Assessment, years**	**Gestational Age, weeks**	**Birth Weight, grams**	**Birth Length, cm**	**Birth Head Circumference, cm**
Weight, kg	**Height, cm**	**BMI, kg/m^2**	**Mothers Height, cm**	**Fathers Height, cm**	**Mid Parental Height, cm**
Original Sex Assigned Male/ Female/ Both/ Not assigned/ Other	**Current Gender** Male/ Female/ Both/ Not assigned/ Other	**Child raised as** Male/ Female/ Both / Other	**Associated Conditions***	**Known Syndrome** Yes/ No	
External Phenotype					
Meatus Typical female/ Perineal/ Scrotal/ Penoscrotal/ Penile/ Coronal/ Typical male	**Left Gonad Location** Impalpable/ Inguinal/ Inguinoscrotal/ Labioscrotal	**Right Gonad Location** Impalpable/ Inguinal/ Inguinoscrotal/ Labioscrotal	**Genital Tubercle Length, mm** <10/ 10-20/ 21-25/ 26-30/ >30	**Phallus Size** Within/ Below/ Above the reference range for male; Within/ Below/ Above the reference range for female	**Labioscrotal Fusion** Yes/ No
Anogenital Distance 1$^{\#}$ (AGD1), mm	**Anogenital Distance 2$^{\#\#}$ (AGD2), mm**	**External Masculinisation Score (EMS)**	**External Genitalia Score (EGS)**		
Internal Phenotype					
Imaging Modality- Left Gonad US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	**Imaging Modality- Right Gonad** US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	**Left Gonad Morphology** Absent/ Streak/ Testis/ Ovary/ Ovotestis/ Other	**Right Gonad Morphology** Absent/ Streak/ Testis/ Ovary/ Ovotestis/ Other	**Imaging Modality- Uterus** US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	**Uterus Morphology** Absent/ Müllerian remnants/ rudimentary/ Normal/ Not known
Imaging Modality- Left Fallopian Tube US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	**Imaging Modality- Right Fallopian Tube** US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	**Left Fallopian Tube Morphology** Absent/ Rudimentary/ Normal/ Not known	**Right Fallopian Tube Morphology** Absent/ Rudimentary/ Normal/ Not known	**Distance- Vaginal Confluence to Bladder Neck, cm**	**Distance- Vaginal Confluence to Introitus, cm**
Imaging Modality- Left Vas Deferens US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	**Imaging Modality- Right Vas Deferens** US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	**Left Vas Deferens Morphology** Absent/ Rudimentary/ Normal/ Not known	**Right Vas Deferens Morphology** Absent/ Rudimentary/ Normal/ Not known		

Surgery					
Left Gonad Biopsy Yes/ No/ Not known	**Right Gonad Biopsy** Yes/ No/ Not known	**Left Gonadectomy** Yes/ No/ Not known	**Right Gonadectomy** Yes/ No/ Not known	**Genital reconstructive surgery**** None/ clitoral surgery / vaginal surgery / labioscrotal surgery / hypospadias surgery / urethral surgery other than hypospadias; age	**Reasons for genital reconstructive surgery** Functional / cosmesis / both **Post Surgical Complications** Yes/ No/ Not known; if yes, describe
Psychosocial					
Change in Legal Sex Yes/ No/ Not known	**Psychosocial Support Offered to Parents** Yes/ No/ Not known	**Ongoing Psychosocial Support** Yes/ No/ Not known			
Medication					
Testosterone Yes (IM, Oral, Transdermal)/ No/ Not known **Oestrogen** Yes (IM, Oral, Transdermal)/ No/ Not known	**DHT** Yes (IM, Oral, Transdermal)/ No/ Not known **Other Drugs** Yes/ No/ Not known	**Aromatase Inhibitor** Yes/ No/ Not known	**GnRH analogues** Yes/ No/ Not known	**Glucocorticoids** Yes/ No/ Not known	**Fludrocortisone** Yes/ No/ Not known
Lab Tests					
LH Low/ Normal/ High/ Not known **Free Testosterone** Low/ Normal/ High/ Not known **hCG Stimulation Test** Specify protocol **Adrenal Stimulation Test** Specify protocol	**FSH** Low/ Normal/ High/ Not known **Dihydrotestosterone** Low/ Normal/ High/ Not known **Androstenedione** Low/ Normal/ High/ Not known **17-OHP** Low/ Normal/ High/ Not known	**AMH** Low/ Normal/ High/ Not known **Oestradiol** Low/ Normal/ High/ Not known **Total Testosterone** Low/ Normal/ High/ Not known **11-deoxycortisol** Low/ Normal/ High/ Not known	**Inhibin B** Low/ Normal/ High/ Not known **17-OHP** Low/ Normal/ High/ Not known **Dihydrotestosterone** Low/ Normal/ High/ Not known **Pregnenolone** Low/ Normal/ High/ Not known	**Androstenedione** Low/ Normal/ High/ Not known **Urine Steroids** Normal/ Abnormal **17-OH Pregnenolone**	**Total Testosterone** Low/ Normal/ High/ Not known **DHEA**

	Low/ Normal/ High/ Not known	Low/ Normal/ High/ Not known

*Associated conditions: CNS, Heart, Renal, Skeletal, Skin, ENT, Eyes, Blood and Lymp, Craniofacial, Adrenal, GI Tract, Haematological, Respiratory, SGA (Small for Gestational Age), Short stature, Non-defined syndrome, Other. ** **Genital reconstructive surgery** field may be repeated.

AGD 1: Distance from the centre of the anus to the posterior base of the labioscrotal folds; ##AGD 2: Distance from the centre of the anus to the anterior base of the phallus

Table 3. Childhood assessment (at age 4 years and 8 years)

General					
Date of Assessment dd/mm/yyyy	**Age at Assessment, years**	**Weight, kg**	**Height, cm**	**BMI, kg/m²**	**Mothers Height, cm**
Fathers Height, cm	**Mid Parental Height, cm**	**Original Sex Assigned** Male/ Female/ Both/ Not assigned/ Other	**Current Gender** Male/ Female/ Both/ Not assigned/ Other	**Child raised as** Male/ Female/ Both / Other	**Associated Conditions*** **Known Syndrome** Yes/ No
Bone Age					
Bone Age Date dd/mm/yyyy	**Bone Age Result, years**	**Bone Age Method** TW20/ Radius-ulna-short bone/ Greulich & Pyle			
External Phenotype					
Meatus Typical female/ Perineal/ Scrotal/ Penoscrotal/ Penile/ Coronal/ Typical male	**Left Gonad Location** Impalpable/ Inguinal/ Inguinoscrotal/ Labioscrotal	**Right Gonad Location** Impalpable/ Inguinal/ Inguinoscrotal/ Labioscrotal	**Genital Tubercle Length, mm** <10/ 10-20/ 21-25/ 26-30/ >30	**Phallus Size** Within/ Below/ Above the reference range for male; Within/ Below/ Above the reference range for female	**Labioscrotal Fusion** Yes/ No
External Masculinisation Score (EMS)	**External Genitalia Score (EGS)**				
Internal Phenotype					
Imaging Modality- Left Gonad US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	**Imaging Modality- Right Gonad** US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	**Left Gonad Morphology** Absent/ Streak/ Testis/ Ovary/ Ovotestis/ Other	**Right Gonad Morphology** Absent/ Streak/ Testis/ Ovary/ Ovotestis/ Other	**Imaging Modality- Uterus** US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	**Uterus Morphology** Absent/ Müllerian remnants/ rudimentary/ Normal/ Not known
Imaging Modality- Left Fallopian Tube US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	**Imaging Modality- Right Fallopian Tube** US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	**Left Fallopian Tube Morphology** Absent/ Rudimentary/ Normal/ Not known	**Right Fallopian Tube Morphology** Absent/ Rudimentary/ Normal/ Not known	**Distance-Vaginal Confluence to Bladder Neck by Imaging, cm**	**Distance- Vaginal Confluence to Introitus by Imaging, cm**

Imaging Modality- Left Vas Deferens US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	**Imaging Modality- Right Vas Deferens** US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	**Left Vas Deferens Morphology** Absent/ Rudimentary/ Normal/ Not known	**Right Vas Deferens Morphology** Absent/ Rudimentary/ Normal/ Not known		
Surgery					
Left Gonad Biopsy Yes/ No/ Not known	**Right Gonad Biopsy** Yes/ No/ Not known	**Left Gonadectomy** Yes/ No/ Not known	**Right Gonadectomy** Yes/ No/ Not known	**Genital reconstructive surgery**** None/ clitoral surgery / vaginal surgery / labioscrotal surgery / hypospadias surgery / urethral surgery other than hypospadias; age	**Reasons for genital reconstructive surgery** Functional / cosmesis / both **Post Surgical Complications** Yes/ No/ Not known; if yes, describe
Psychosocial, Gender Identity					
Any Change in Legal Sex Yes/ No/ Not known	**Psychosocial Support Offered to Parents** Yes/ No/ Not known	**Ongoing Psychosocial Support for Parents** Yes/ No/ Not known	**Psychosocial Support Offered to Child** Yes/ No/ Not known	**Ongoing Psychosocial Support for Child** Yes/ No/ Not known	**Age-appropriate Information to Child** Yes/ No/ Not known
Has Child Questioned Their Gender Yes/ No/ Not known	**Is Child Distressed About Gender Identity or Assignment** Yes/ No/ Not known				
Medication					
Testosterone Yes (IM, Oral, Transdermal)/ No/ Not known **Oestrogen** Yes (IM, Oral, Transdermal)/ No/ Not known	**DHT** Yes (IM, Oral, Transdermal)/ No/ Not known **Other Drugs** Yes/ No/ Not known	**Aromatase Inhibitor** Yes/ No/ Not known	**GnRH analogues** Yes/ No/ Not known	**Glucocorticoids** Yes/ No/ Not known	**Fludrocortisone** Yes/ No/ Not known
Lab Tests					
LH Low/ Normal/ High/ Not known	**FSH** Low/ Normal/ High/ Not known	**AMH** Low/ Normal/ High/ Not known	**Inhibin B** Low/ Normal/ High/ Not known	**Androstenedione**	**Total Testosterone**

				Low/ Normal/ High/ Not known	Low/ Normal/ High/ Not known
Free Testosterone Low/ Normal/ High/ Not known	**Dihydrotestosterone** Low/ Normal/ High/ Not known	**Oestradiol** Low/ Normal/ High/ Not known	**17-OHP** Low/ Normal/ High/ Not known	**Urine Steroids** Normal/ Abnormal	
hCG Stimulation Test Specify protocol	**Androstenedione** Low/ Normal/ High/ Not known	**Total Testosterone** Low/ Normal/ High/ Not known	**Dihydrotestosterone** Low/ Normal/ High/ Not known		
Adrenal Stimulation Test Specify protocol	**17-OHP** Low/ Normal/ High/ Not known	**11-deoxycortisol** Low/ Normal/ High/ Not known	**Pregnenolone** Low/ Normal/ High/ Not known	**17-OH Pregnenolone** Low/ Normal/ High/ Not known	**DHEA** Low/ Normal/ High/ Not known

*Associated conditions: CNS, Heart, Renal, Skeletal, Skin, ENT, Eyes, Blood and Lymp, Craniofacial, Adrenal, GI Tract, Haematological, Respiratory, SGA (Small for Gestational Age), Short stature, Non-defined syndrome, Other. ** **Genital reconstructive surgery** field may be repeated.

Table 4. Adolescent assessment (at start of puberty and end of puberty)

General					
Date of Assessment dd/mm/yyyy	**Age at Assessment, years**	**Weight, kg**	**Height, cm**	**BMI, kg/m²**	**Mothers Height, cm**
Fathers Height, cm	**Mid Parental Height, cm**	**Original Sex Assigned** Male/ Female/ Both/ Not assigned/ Other	**Current Gender** Male/ Female/ Both/ Not assigned/ Other	**Adolescent raised as** Male/ Female/ Both / Other	**Associated Conditions*** **Known Syndrome** Yes/ No
Bone Age, Bone Mineral Density					
Bone Age Date dd/mm/yyyy	**Bone Age Result, years**	**Bone Age Method** TW20/ Radius-ulna-short bone/ Greulich & Pyle	**Bone Mineral Density** Yes/ No/ Not known	**Bone Mineral Density Date** dd/mm/yyyy	**Bone Mineral Density Result** Osteopenia/ Osteoporosis/ Normal
Puberty					
Breast Stage 1/ 2/ 3/ 4/ 5/ Not Known	**Genital Stage** 1/ 2/ 3/ 4/ 5/ Not Known	**Axillary Hair Stage** 1/ 2/ 3/ 4/ 5/ Not Known	**Pubic Hair Stage** 1/ 2/ 3/ 4/ 5/ Not Known	**Left Testicular Volume, ml**	**Right Testicular Volume, ml**
Stretched Penile Length; cm	**Spontaneous Puberty** Yes/ No/ Not known	**Pubertal Induction** Yes/ No/ Not known	**Induction with Oestrogen** Yes (Oral, Transdermal)/ No/ Not known	**Induction with Testosterone** Yes (IM, Oral, Transdermal)/ No/ Not known	**Menarche** Spontaneous/ Induced/ Not known
Hirsutism Yes/ No/ Not known	**Gynaecomastia** Yes/ No/ Not known				
Internal Phenotype					
Imaging Modality- Left Testis US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	**Imaging Modality- Right Testis** US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	**Left Testis Morphology** Absent/ Normal/ Small/ Abnormal	**Right Testis Morphology** Absent/ Normal/ Small/ Abnormal	**Imaging Modality- Uterus** US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	**Uterus Morphology** Absent/ Normal/ Hypoplastic/ Abnormal
Imaging Modality- Left Ovary US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	**Imaging Modality- Right Ovary** US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	**Left Ovary Morphology** Absent/ Streak/ Normal/ Polycystic	**Right Ovary Morphology** Absent/ Streak/ Normal/ Polycystic		
Surgery					

Left Gonad Biopsy Yes/ No/ Not known	**Right Gonad Biopsy** Yes/ No/ Not known	**Left Gonadectomy** Yes/ No/ Not known	**Right Gonadectomy** Yes/ No/ Not known	**Genital reconstructive surgery**** None/ clitoral surgery / vaginal surgery / labioscrotal surgery / hypospadias surgery / urethral surgery other than hypospadias / phalloplasty; age	**Vaginal Hypoplasia** Yes / No/ Not known **Medical management of vaginal hypoplasia** Dilation / Surgery / None **Type of Vaginoplasty** Intestinal / Peritoneal / Davydov / Vecchietti / Baloon / Other
Post Surgical Complications Yes/ No/ Not known; if yes, describe	**Gonadal Germ Cell Cancer** Yes/ No/ Not known	**Left Gonad** None/ GCNIS/ Gonadoblastoma/ Seminoma/ Non-seminoma/ Dysgerminoma/ Other	**Right Gonad** None/ GCNIS/ Gonadoblastoma/ Seminoma/ Non-seminoma/ Dysgerminoma/ Other		
Psychosocial, Gender Identity					
Change in Legal Sex Yes/ No/ Not known	**Psychosocial Support for Parents** Yes/ No/ Not known	**Ongoing Psychosocial Support for Parents** Yes/ No/ Not known	**Psychosocial Support Offered to Child** Yes/ No/ Not known	**Ongoing Psychosocial Support for Child** Yes/ No/ Not known	**Age-appropriate Information to Child** Yes/ No/ Not known
Has Child Questioned Their Gender Yes/ No/ Not known	**Is Child Distressed About Gender Identity or Assignment** Yes/ No/ Not known	**Physical or Mental Health Status Interferes with Daily Life Activities (education, work)** Yes / Partially / No	**Physical or Mental Health Status Interferes with Social Activities (hobbies, friends, relations)** Yes / Partially / No		
Sexual Health					
Menses Yes/ Primary amenorrhoea/ Secondary amenorrhoea **Number of Offspring**	**Age at Menopause, years** **Assisted Conception** Yes/ No/ Not known	**Fertility Desired** Yes/ No/ Not known	**Tissue Storage** Yes/ No/ Not known	**Sperm Assessment** Yes/ No/ Not known	**Sperm count, per million/ml** x million per ml/ Normal/ Abnormal/ Not Reported

Medication					
Testosterone Yes (IM, Oral, Transdermal)/ No/ Not known	**DHT** Yes (IM, Oral, Transdermal)/ No/ Not known	**Aromatase Inhibitor** Yes/ No/ Not known	**GnRH analogues** Yes/ No/ Not known	**Glucocorticoids** Yes/ No/ Not known	**Fludrocortisone** Yes/ No/ Not known
Oestrogen Yes (IM, Oral, Transdermal)/ No/ Not known	**Other Drugs** Yes/ No/ Not known				
Lab Tests					
LH Low/ Normal/ High/ Not known	**FSH** Low/ Normal/ High/ Not known	**AMH** Low/ Normal/ High/ Not known	**Inhibin B** Low/ Normal/ High/ Not known	**Androstenedione** Low/ Normal/ High/ Not known	**Total Testosterone** Low/ Normal/ High/ Not known
Free Testosterone Low/ Normal/ High/ Not known	**Dihydrotestosterone** Low/ Normal/ High/ Not known	**Oestradiol** Low/ Normal/ High/ Not known	**17-OHP** Low/ Normal/ High/ Not known	**Urine Steroids** Normal/ Abnormal	
hCG Stimulation Test Specify protocol	**Androstenedione** Low/ Normal/ High/ Not known	**Total Testosterone** Low/ Normal/ High/ Not known	**Dihydrotestosterone** Low/ Normal/ High/ Not known		
Adrenal Stimulation Test Specify protocol	**17-OHP** Low/ Normal/ High/ Not known	**11-deoxycortisol** Low/ Normal/ High/ Not known	**Pregnenolone** Low/ Normal/ High/ Not known	**17-OH Pregnenolone** Low/ Normal/ High/ Not known	**DHEA** Low/ Normal/ High/ Not known

*Associated conditions: CNS, Heart, Renal, Skeletal, Skin, ENT, Eyes, Blood and Lymp, Craniofacial, Adrenal, GI Tract, Haematological, Respiratory, SGA (Small for Gestational Age), Short stature, Non-defined syndrome, Other. ** Genital reconstructive surgery field may be repeated.

Table 5: Adult assessment (once per interval: 18-25; 25-40; 40-60; 60-75 years)

General					
Date of Assessment dd/mm/yyyy	**Age at Assessment, years**	**Weight, kg**	**Height, cm**	**BMI, kg/m²**	**Mothers Height, cm**
Fathers Height, cm	**Mid Parental Height, cm**	**Original Sex Assigned** Male/ Female/ Both/ Not assigned/ Other	**Current Gender** Male/ Female/ Both/ Not assigned/ Other	**Adult raised as** Male/ Female/ Both / Other	**Associated Conditions*** **Known Syndrome** Yes/ No
Bone Age, Bone Mineral Density					
Bone Age Date dd/mm/yyyy	**Bone Age Result, years**	**Bone Age Method** TW20/ Radius-ulna-short bone/ Greulich & Pyle	**Bone Mineral Density** Yes/ No/ Not known	**Bone Mineral Density Date** dd/mm/yyyy	**Bone Mineral Density Result** Osteopenia/ Osteoporosis/ Normal
Puberty					
Breast Stage 1/ 2/ 3/ 4/ 5/ Not Known	**Genital Stage** 1/ 2/ 3/ 4/ 5/ Not Known	**Axillary Hair Stage** Yes/ No/ Not Known	**Pubic Hair Stage** 1/ 2/ 3/ 4/ 5/ 6/ Not Known	**Left Testicular Volume, ml**	**Right Testicular Volume, ml**
Spontaneous Puberty Yes/ No/ Not known	**Pubertal Induction** Yes/ No/ Not known	**Induction with Oestrogen** Yes (Oral, Transdermal)/ No/ Not known	**Induction with Testosterone** Yes (IM, Oral, Transdermal)/ No/ Not known	**Menarche** Spontaneous/ Induced/ Not known	**Hirsutism** Yes/ No/ Not known
Gynaecomastia Yes/ No/ Not known					
Comorbidities					
Osteoporosis Yes/ No/ Not known	**Type II Diabetes** Yes/ No/ Not known	**Chronic Kidney Disease** Yes/ No/ Not known	**Chronic Liver Disease** Yes/ No/ Not known	**Central Nervous System** Yes/ No/ Not known	**Hypertension** Yes/ No/ Not known
Other Yes/ No/ Not known; if yes, describe					
Internal Phenotype					
Imaging Modality- Left Testis	**Imaging Modality- Right Testis**	**Left Testis Morphology**	**Right Testis Morphology**	**Imaging Modality- Uterus**	**Uterus Morphology**

US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy **Imaging Modality- Left Ovary** US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy **Imaging Modality- Right Ovary** US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	Absent/ Normal/ Small/ Abnormal **Left Ovary Morphology** Absent/ Streak/ Normal/ Polycystic	Absent/ Normal/ Small/ Abnormal **Right Ovary Morphology** Absent/ Streak/ Normal/ Polycystic	US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	Absent/ Normal/ Hypoplastic/ Abnormal
Surgery					
Left Gonad Biopsy Yes/ No/ Not known	**Right Gonad Biopsy** Yes/ No/ Not known	**Left Gonadectomy** Yes/ No/ Not known	**Right Gonadectomy** Yes/ No/ Not known	**Genital reconstructive surgery**** None/ clitoral surgery / vaginal surgery / labioscrotal surgery / hypospadias surgery / urethral surgery other than hypospadias / phalloplasty; age	**Vaginal Hypoplasia** Yes / No/ Not known **Medical management of vaginal hypoplasia** Dilation / Surgery / None **Type of Vaginoplasty** Intestinal / Peritoneal / Davydov / Vecchietti / Baloon / Other / Unknown
Post Surgical Complications of Genital Surgery Yes/ No/ Not known; if yes, describe	**Gonadal Germ Cell Cancer** Yes/ No/ Not known	**Left Gonad** None/ GCNIS/ Gonadoblastoma/ Seminoma/ Non-seminoma/ Dysgerminoma/ Other	**Right Gonad** None/ GCNIS/ Gonadoblastoma/ Seminoma/ Non-seminoma/ Dysgerminoma/ Other	**Breast Surgery** None / breast reconstruction/augmentation / reduction/ mastectomy	**Post Surgical Complications of Breast Surgery** Yes/ No/ Not known; if yes, describe
Psychosocial, Gender Identity					
Change in Legal Sex Yes/ No/ Not known	**Psychosocial Support Offered** Yes/ No/ Not known	**Ongoing Psychosocial Support** Yes/ No/ Not known	**Full Information about Condition** Yes/ No/ Not known	**Gender Role** Female/ Male/ Both/ Neither/ Not known	**Physical or Mental Health Status Interferes with Daily Life Activities (education, work)** Yes / Partially / No **Physical or Mental Health Status Interferes with Social Activities (hobbies, friends, relations)**

					Yes / Partially / No
Sexual Health					
Menses Y/ Primary amenorrhoea/ Secondary amenorrhoea	**Age at Menopause, years**	**Fertility Desired** Yes/ No/ Not known	**Tissue Storage** Yes/ No/ Not known	**Sperm Assessment** Yes/ No/ Not known	**Sperm count, per million/ml** x million per ml/ Normal/ Abnormal/ Not Reported
Number of Offspring	**Assisted Conception** Yes/ No/ Not known				
Medication					
Testosterone Yes (IM, Oral, Transdermal)/ No/ Not known	**DHT** Yes (IM, Oral, Transdermal)/ No/ Not known	**Aromatase Inhibitor** Yes/ No/ Not known	**GnRH analogues** Yes/ No/ Not known	**Glucocorticoids** Yes/ No/ Not known	**Fludrocortisone** Yes/ No/ Not known
Oestrogen (E) Yes (IM, Oral, Transdermal)/ No/ Not known	**Progestin (P)** Yes (Oral, Subcutaneous, IM, IUD) / No/ Unknown	**Combined E/P (HRT/OC***)** Yes (Oral, Transdermal, Vaginal)/ No/ Not known	**Other Drugs** Yes/ No/ Not known		
Lab Tests					
LH Low/ Normal/ High/ Not known	**FSH** Low/ Normal/ High/ Not known	**AMH** Low/ Normal/ High/ Not known	**Inhibin B** Low/ Normal/ High/ Not known	**Androstenedione** Low/ Normal/ High/ Not known	**Total Testosterone** Low/ Normal/ High/ Not known
Free Testosterone Low/ Normal/ High/ Not known	**Dihydrotestosterone** Low/ Normal/ High/ Not known	**Oestradiol** Low/ Normal/ High/ Not known	**17-OHP** Low/ Normal/ High/ Not known	**Urine Steroids** Normal/ Abnormal	
hCG Stimulation Test Specify protocol	**Androstenedione** Low/ Normal/ High/ Not known	**Total Testosterone** Low/ Normal/ High/ Not known	**Dihydrotestosterone** Low/ Normal/ High/ Not known		
Adrenal Stimulation Test Specify protocol	**17-OHP** Low/ Normal/ High/ Not known	**11-deoxycortisol** Low/ Normal/ High/ Not known	**Pregnenolone** Low/ Normal/ High/ Not known	**17-OH Pregnenolone** Low/ Normal/ High/ Not known	**DHEA** Low/ Normal/ High/ Not known

*Associated conditions: CNS, Heart, Renal, Skeletal, Skin, ENT, Eyes, Blood and Lymp, Craniofacial, Adrenal, GI Tract, Haematological, Respiratory, SGA (Small for Gestational Age), Short stature, Non-defined syndrome, Other. ** Genital reconstructive surgery field may be repeated. ***Hormonal replacement treatment/Oral contraceptives

Supplementary Table 1: Tool for assessment of hypospadias (repair)

Assessment prior to surgery	
External genitalia score (EGS), glans diameter, penile length, anogenital distance, penile deviation	Assess androgen action *in utero* and objective description of hypospadias with a special interest on surgical items (severity of hypospadias, possible prognostic parameters)
Intraoperative assessment	
Age at surgery	
Hormonal stimulation prior to surgery	
Type of surgery	Surgical details (technique, staged repair)
Postoperative assessment and follow-up (core set of outcome parameters)	
Date of follow-up	Follow-up at crucial time-points (postoperative period, time of potty training, adolescence)
Complications	Surgical and other complications
Repeat surgery	When, why and what type of surgery
Cosmesis	Validated score (hypospadias objective penile evaluation score, HOPE score [1], modified) assessing surgical correctable items including meatal position, shape of meatus, shape of glans, shape of skin, cosmesis of scrotum, penile curvature and penile torsion
Function	Uroflow + ultrasound for residual volume Questionnaire for erectile dysfunction (International Index of Erectile Function 5, IIEF-5)
Psychology	Validated questionnaires for health related quality of life and sexual quality of life

[1] van der Toorn F, de Jong TP, de Gier RP, Callewaert PR, van der Horst EH, Steffens MG, et al. Introducing the HOPE (Hypospadias Objective Penile Evaluation)-score: a validation study of an objective scoring system for evaluating cosmetic appearance in hypospadias patients. Journal of pediatric urology. 2013;9:1006-16.

Supplementary Table 2. Gynaecological assessment tool for longitudinal DSD care

EXTERNAL GENITALIA					
	Pubic hair	Normal	scanty, hypertrophic		
	Labia Majora	Normal	asymmetric, hypertrophic, hypotrophic, absent		
	Labia Minora	Normal	asymmetric, hypertrophic, hypotrophic, absent		
	Clitoris (size mm)		hypertrophic, hypotrophic,		
	Ano – vulvar distance (from posterior labial commissure to the anus in mm):				
VAGINA					
	Lenght cm		scanty, hypertrophic		
	Width cm		asymmetric, hypertrophic, hypotrophic, absent		
GENITAL FUNCTION					
Clitoris sensitivity (woman perception	self stimulation	Normal	absent sensitivity, low sensitivity, discomfort, pain		
	partner stimulation	Normal	absent sensitivity, low sensitivity, discomfort, pain		
Vaginal sensitivity	self stimulation	Normal	absent sensitivity, low sensitivity, discomfort, pain		
	partner stimulation	Normal	absent sensitivity, low sensitivity, discomfort, pain		
Dispareunia		No/Yes	always, occasional, sporadic (pain intensity from 0 to 10)		
Bleeding		Normal	always, occasional, sporadic		
Discharge		Normal	always, occasional, sporadic		
AGE AT GENITAL SURGERY					
Date of surgery		ddmmyyyy	ddmmyyyy	ddmmyyyy	ddmmyyyy
SURGERY DESCRIPTION					
Time from last surgery		years/months			
JUDGEMENTS ON SURGERY					
Are you happy with the surgery performed on your genitalia?					Yes/ No
If you had surgery during infancy or before you could decide on your surgery, do you agree with your					Yes/ No
Do you think the age of the surgery you had was appropriate? (for every surgery done)					Yes/ No
Did the surgery met your objections?					Yes/ No
VAGINAL DILATION					
Previous use of vaginal dilators?		No/Yes	Age at first vaginal dilation treatment		
			Size of biggest dilator used (1 to 5)		
Currently using dilators?		No/Yes	Size of dilator in use (1 to 5)		