

# Project Final Report

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## Section 1 – Final publishable summary report

### dsd-LIFE



**Project title:** Clinical European study on the outcome of surgical and hormonal therapy and psychological intervention in disorders of sex development (DSD)

**Website:** [www.dsd-life.eu](http://www.dsd-life.eu)

**Contractors involved (dsd-LIFE consortium):**

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## 1.1 Executive summary.

dsd-LIFE is a clinical multidisciplinary European study investigating the long-term outcomes such as quality of life (QoL), psychological well-being and psychosocial adaptation, physical and mental health and psychosexual issues and influences of hormone therapies, surgery, psychological and social support and specialized health care in patients included in the medical umbrella term disorders/differences of sex development (DSD).

**Objective 1: To improve clinical practice in the management of disorders of sex development (DSD)**

**Objective 2: To develop recommendations for a better care of patients with DSD for which no dedicated treatment is currently approved**

The medical term classification dsd includes a conglomerate of genetically based diagnoses, which are divided in three major groups: 1. dsd with numeric sex chromosome aberrations, 2. XY dsd and 3. XX dsd. 1. Sex chromosome dsd consists mainly of disorders with gonadal dysgenesis due to sex chromosome imbalances such as Turner syndrome (45,X0 and mosaicism), Klinefelter syndrome (47,XXY), individuals with mixed gonadal dysgenesis (45,X0/46,XY) and individuals with chimeric dsd (46,XX/46,XY). 2. XY dsd comprises individuals with complete and partial forms of testicular dysgenesis, enzymatic defects resulting in disorders of androgen synthesis e.g. 5 $\alpha$ -reductase II and 17 $\beta$ -hydroxysteroid dehydrogenase (HSD) 3 deficiency, defects of androgen action such as complete and partial androgen insensitivity syndrome (CAIS, PAIS) and unclassified hypospadias. 3. The subgroup of XX dsd includes ovarian dysgenesis, congenital adrenal hyperplasia (CAH), vaginal and uterine dysgenesis.

Individuals with dsd often face problems such as impairment of quality of life (QoL), psychological well-being and psychosocial adaptation, which are influenced by sex assignment, hormone therapies, surgery in childhood or adulthood, psychological and social support, metabolism, psychosexual issues, fertility, stigma, patients' views, ethical issues and cultural influences.

In the first period, the consortium developed a study protocol covering all the above-mentioned aspects playing a role in clinical care. Patient related outcome (PRO) was evaluated by an online questionnaire. Moreover, objective medical data was gathered through medical exams and through retrospective data from patient files. Subsequently, ethical approval was obtained in all study centres.

In the second period, the consortium could recruit 1040 individuals with different DSD conditions (Table 1) and an add-on group of males with CAH facing similar problems of life-long hormone therapies and fertility problems (WP2). All PRO and medical data are available in an electronic database.

In the third period, data analysis of the major outcomes QoL, psychological well-being and psychosocial adaptation could be finalized. Moreover, the status of hormone therapies, surgery, psychological support, fertility, physical and mental health status, psychosexual issues, terminology and health care were analysed. However, detailed analyses of outcomes of the distinct diagnosis groups are still in progress (WP3 and WP4). The results from all these important analyses are needed to develop and publish recommendations for better care. Development of recommendations has started through different working groups identifying psychosocial, medical and ethical issues which are needed for recommendations of the four major diagnosis groups of dsd-LIFE such as Turner and Klinefelter syndrome, XY DSD conditions and CAH. As data analysis is still in progress, publication of recommendations is planned after funding of the project in 2018 (WP5).

A further part of dsd-LIFE was communication with the public and dissemination of general knowledge about DSD. A parents' website is available in the six languages of the consortium. An English brochure for parents of newborns with DSD was translated into Dutch, French, German, Polish, Swedish, Arabic, Urdu and Turkish. A brochure for health care professionals in the according languages was also developed and is available in English, Dutch, French, German, Polish, Swedish. Both brochures are available through the website. After funding of the project the website will be still active and summaries of the results of the publications and consequential recommendations will be disseminated in a result section on the website (WP6).

## 1.2 Summary description of project context and objectives:

### Background and Aims

Disorders of sex development (DSD) are a conglomerate of **rare diseases** with an estimated incidence of 1: 4500. The causes of DSD are mainly disorders with gonadal dysgenesis, decreased androgen synthesis or function in XY males or disorders with elevated androgen production in XX females. Decision on sex of rearing is difficult in some cases as the prenatal androgen imbalances result in ambiguous genitalia at birth and furthermore they are likely to influence psychosexual development. Genital constructive surgery is needed in most cases. Lifelong cortisone replacement is needed in DSD due to defects of cortisone synthesis. Sex hormone substitution is indicated in many cases of DSD in puberty and adult life. Decision of sex of rearing, genital surgery and hormone therapies have a life-long impact on the affected individuals, which become evident mainly after puberty. In many cases, psychological counselling is advised. Interpretation of previous outcome studies of DSD is hampered by small patient numbers and conglomerates of diagnoses and therapies. The study **dsd-LIFE** investigates and compares the long-term outcome of **different off-label treatments such as** 1. sex assignment, 2. surgery, 3. hormone therapies and 4. psychological interventions in adequate numbers of adolescents and adults with different known genetic entities of DSD to develop **evidence base recommendations for treatment of DSD for which no dedicated treatment is currently approved**. To reach this aim, the influences and interrelations of sex assignment, genital surgery, hormone therapy, metabolism, fertility, psychological intervention but also cultural influences and patients' views on psychosocial adaptation, health related quality of life (HQoL) and psychological well-being and will be investigated. The long-term impact of the study is **improvement of care** and subsequently higher quality of life with better integration and participation of individuals with DSD in the society.

In 2005, a consensus statement for treatment of DSD was developed by an international multidisciplinary team of paediatric endocrinologists, endocrinologists, surgeons, gynaecologists, psychologists and affected persons. However, no evidence based clinical recommendations do exist apart from this consensus statement on care of DSD.

European recommendations for care of DSD comprising sex assignment, surgery, hormone therapies and psychosocial issues will be developed by dsd-LIFE (see Figure 1). For these recommendations, also non-medical factors such as, for example, ethical considerations, patients' views, stigma and cultural differences will be considered (WP5). Finally, implementation of the recommendations will be promoted in Europe (WP6)

The dsd-LIFE consortium consists of 14 multidisciplinary European centres of excellence with longstanding experience in clinical care of DSD. In addition, one consortium partner has profound expertise regarding the ethical issues of DSD. Knowledge and skills of the collaborators in the consortium are complementary to fulfil the objective of the study.

In the first period, the consortium has developed a study protocol covering all the mentioned aspects above playing a role in clinical care. Patient related outcome (PRO) was evaluated by an online questionnaire. Moreover, objective medical data was gathered through medical exams and through retrospective data from patient files.

In the second period, the consortium could recruit 1040 individuals with different DSD conditions (Table 1) and an add-on group of 121 males with CAH facing similar problems of life-long hormone therapies and fertility problems (WP2). All PRO and medical data are available in an electronic database.

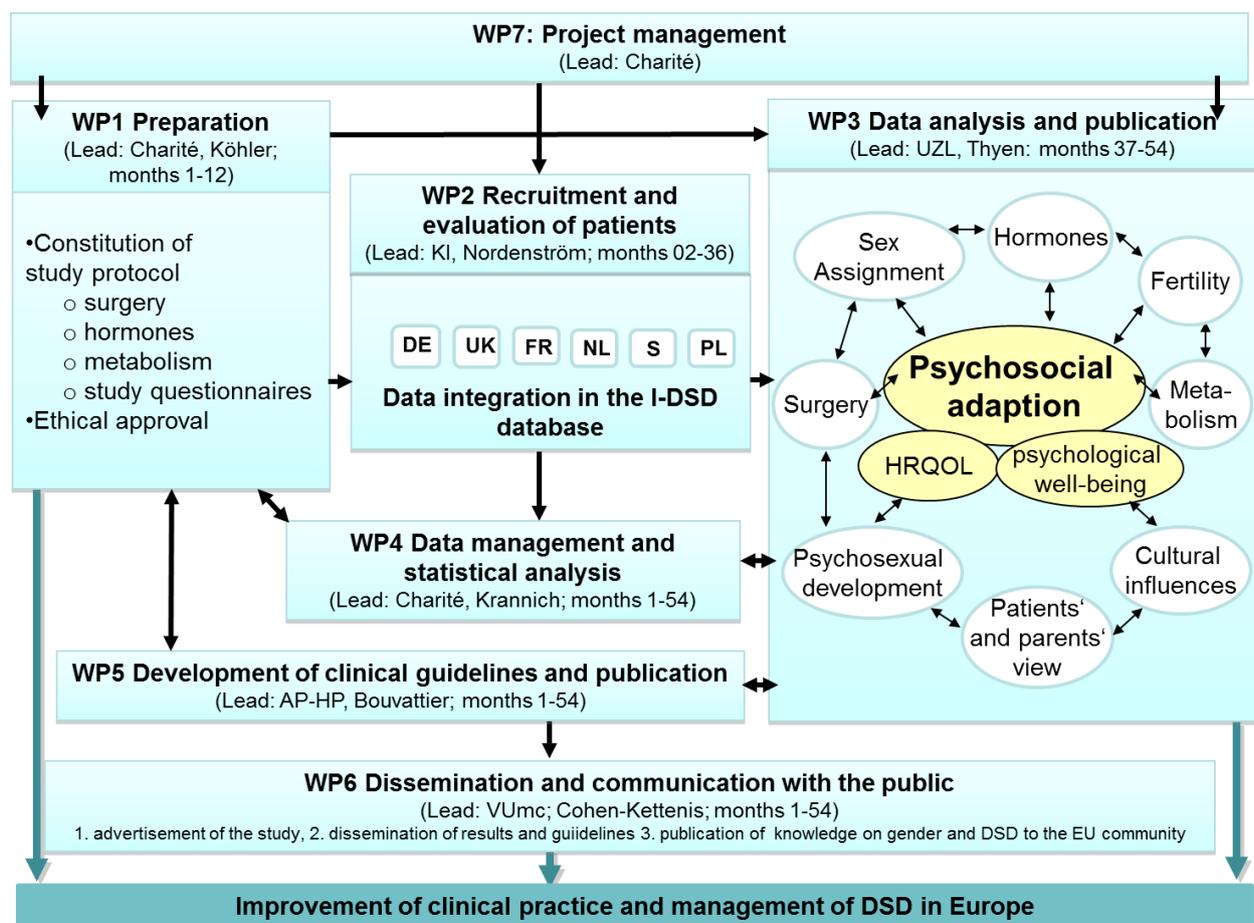
In the third period, data analysis of the major outcomes QoL, psychological well-being and psychosocial adaptation could be finalized. Moreover, the status of hormone therapies, surgery, psychological support, fertility, physical and mental health status, psychosexual issues, terminology and health care were analysed. However, detailed analyses of the distinct diagnosis groups are still in progress (WP3 and WP4). The results from all these important analyses are needed to develop and publish recommendations for better care. Development of recommendations has started through different working groups identifying psychosocial, medical and ethical issues which are needed for recommendations of the four major diagnosis groups of dsd-LIFE such as Turner and Klinefelter syndrome, XY DSD conditions and CAH. As data analysis is still in progress, publication of recommendations is planned after funding of the project at the end of 2018 (WP5).

A further part of dsd-LIFE was communication with the public and dissemination of general knowledge about DSD. A parents' website including all relevant information about DSD and useful links was developed in the six languages of the consortium. An English brochure for parents of newborns with DSD was translated into Dutch, French, German, Polish, Swedish, Arabic, Urdu and Turkish. Additionally, a brochure for health care professionals was developed and is available in English, Dutch, French, German, Polish, Swedish. Both brochures are available on the website. After funding of the project the website will be still active and summaries of the results of the publications including recommendations will be disseminated in a result section on the website (WP6).

### Work strategy and general description

In the first period of the study we developed the study protocol to analyse the main outcome measures health related quality of life (HRQoL), psychological well-being and psychosocial adaptation and the co-founding factors sex assignment, hormone therapies, surgery in childhood or adulthood, psychological and social support, metabolism, psychosexual development, fertility, stigma, patients' views, ethical issues and cultural influences. The study protocol was developed in different working groups (WGs) to bundle the expertise of the different European specialists: WG1: medical issues; WG2: psychology, HRQoL and psychosexuality; WG3: surgery including gynaecology/urology; WG4: ethical issues. The study protocol was developed in close interaction with the different patient support groups for XY DSD, congenital adrenal hyperplasia (CAH), Turner and Klinefelter syndrome and with the scientific adviser AISSG (androgen insensitivity support group UK). The self-constructed part of the English patient reported outcome (PRO) questionnaire was translated according to the required international guidelines for translation of study questionnaires in German, French, Dutch, Swedish and Polish and was pilot tested at month 11 (WP1).

Figure 1 Aims, structure and WPs of dsd-LIFE



Programming of the dsd-LIFE database was finalized at month 16 (WP4). Ethical approvals for dsd-LIFE were obtained in 6 countries from month 6- 20 (WP1).

The focus of the second period of the project was recruitment of patients with the different diagnoses XY DSD, Turner syndrome, Klinefelter syndrome and CAH. The recruitment mainly took place in the centres from 1<sup>st</sup> February 2014- 30<sup>th</sup> September 2015. In Germany, the UK, the NL and Sweden patients were also recruited by patient support groups. At month 31 prolongation of the project was approved to reach a representative number of the rarest diagnoses included in the XY DSD group, which were most difficult to recruit. Finally, the consortium could recruit 1161 patients. 1040 patients with DSD and an add-on group of 121 CAH males facing similar problems and subsequently can be considered in a broader sense as DSD. The diagnoses are quite equally distributed: 301 Turner syndrome 218, Klinefelter syndrome, 222 XY DSD, 226 CAH, a group of other rare DSD conditions such as 45,X/46,XY, 21 XX gonadal dysgenesis, 6 XX males and 1 47,XYY male with gonadal dysgenesis and the 121 CAH males. With the prolongation of the project sufficient numbers of the rarest XY DSD diagnoses could be recruited. It was planned to recruit up to 1500 patients, but the reached numbers of patients are sufficient to perform statistical analysis, especially for the specific subgroups of rare diagnoses (WP2).

Data cleaning and verification of diagnosis was a next crucial step before starting data analysis (WP4).

Publication proposals were permanently collected within the consortium. The publications were divided in type 1 and type 2 publications. The type 1 publications cover the major outcomes of the project such as hormone therapies, health status and metabolism, fertility, surgery, sexual functioning, tumor risk, psychosexual outcomes, mental health, QoL, health services and ethics. The type 2 publications cover the specific medical, psychosocial, surgical and ethical issues of the distinct subgroups. So far, overall 71 publication proposals could be planned within the consortium. Data analysis and submission of 10 type 1 publications was finalized. Data analysis of 31 type 2 proposals is in progress. Moreover, about 30 more publication proposals are planned to be revised before data analysis (WP3 and WP4).

The dsd-LIFE website with general information about the study (month 3), a section with information about DSD for parents and the general public (month 34) in the six languages of the dsd-LIFE countries were created. A flyer for participants was developed in the different languages. An English brochure for parents was translated into Dutch, French, German, Polish and Swedish, Urdu, Arabic and Turkish (month 36). Furthermore, a project flyer for dissemination to the scientific audiences was finalized with support of GABO-mi (month 13).

At the beginning of the study, information about the study was disseminated at several European and national meetings of dsd, gynaecology, endocrinology, psychology and urology. Moreover, the study was presented to the different national patient support groups for Turner and Klinefelter syndrome, XY dsd, and CAH in D, UK, NL and F. A press release of the study was initiated at month 12 at Charité Berlin, Germany. A website of dsd-LIFE was created for Horizonhealth.eu: <http://www.horizonhealth.eu/project/clinical-european-study-outcome-surgical-and-hormonal-therapy-and-psychological-intervention>. A brochure for health care providers was developed in English and translated into Dutch, French, German, Swedish, Polish. The brochures for parents and health care providers are available on the website. In 2016 and 2017, first results of dsd-LIFE could be disseminated at several national and European scientific meetings and a European meeting with support groups in Berlin. In the future, it is planned to disseminate the results of dsd-LIFE ongoing through the website and further scientific meetings (WP6)

During preparation of publications and data analysis it became obvious that only preparatory work for the recommendations was possible (such as describing the current state of the art and developing a skeleton with the main issues relevant for improvement of psychosocial and medical care). Publication of recommendations before the findings from the data analysis are available and published was not possible. Subsequently, an amendment was made that recommendation papers should be published after publication of the major outcomes of the whole cohort and the specific outcomes of the distinct diagnoses. (WP5).

Moreover, the dsd-LIFE consortium is in close contact with the COST action dsd-net. The clinical recommendations will be developed in close crosstalk with the WG1 "Harmonization and standardization of phenotyping and clinical management" of dsd-net.

### **Management structure and procedures**

The Project Coordinator ensured the smooth operation of the project and guaranteed that all efforts were focused towards the objectives. She submitted all required progress reports, deliverables, financial statements to the European Commission, and, with the assistance of project management partner ARTTIC she was responsible for the proper use

of funds and their transfers to participants. The dsd-LIFE office was established by and based at the coordinator in Berlin and at ARTTIC in Munich. The Project Office at the Coordinator was concerned with the scientific management and the co-ordination of all research activities. The Project Office at ARTTIC was responsible for administrative, financial and contractual management and the organisational co-ordination of the project activities.

The Project Governing Board was in charge of the political and strategic orientation of the project and acted as the arbitration body. It met once a year unless the interest of the project required intermediate meetings. The Project Steering Committee consisted of all work package leaders and the Coordinator and was in charge of monitoring all activities towards the objective of the project in order to deliver as promised, in due time and in the budget. The Project Steering Committee met every six months during the funding period and had monthly phone conferences. Furthermore, a scientific advisory board was implemented to ensure a high standard of research and monitor the progress of the project by taking part in the annual Governing Board Meetings.

### 1.3 Description of the main S&T results/foregrounds of dsd-LIFE

The dsd-LIFE study was conducted through 7 work packages.

#### Work Package 1 Preparation (month 1-12)

WP1 ensured proper preparation of the study including discussion, decisions and translation of adequate tools to answer the research questions of DSD-Life and announcement of the study.

- To bundle complementarity and to share and amplify expertise of the partners in working groups in the study protocol
- To develop the study protocol to answer the main questions of DSD-Life
- To advertise the study to all the potential audiences, in particular, patient organisations and physicians to optimize recruitment of patients
- To translate the study protocol
- To obtain ethical approval in the different national study centres

The work of WP 1 work is displayed in focused paragraphs, which describe the necessary steps during the project.

#### *Development of the study protocol*

Development of the study protocol was a complex task as a heterogeneous group of confounding factors as sex assignment, hormone therapies, surgery, psychological and social support, metabolism, psychosexual development, patients' views and cultural influences influencing the three main outcome measures HRQoL, psychological well-being and psychosocial adaptation had to be considered. In addition, the study protocol should cover not only the major common problems of all the conditions included in the umbrella term dsd, but also specific issues of the heterogeneous dsd conditions had to be identified. Subsequently, development of the study protocol was performed in different working groups (WGs) covering the major fields of the study (see Figure 2).

In month 1, according to milestone 1, the different working groups were constituted to bundle expertise for development of the study protocol at the kick-off meeting of the study: WG1: Medical issues (lead: B. Köhler), WG2: Psychosocial issues: psychology, psychosexuality and HRQoL (lead: U.Thyen; P. Cohen-Kettenis), WG3: Surgery including urology and gynaecology (lead: A. Nordenskjöld; L. Duranteau), WG4: Ethical issues (lead: C. Wiesemann). From month 2-9, an English master version of the dsd-LIFE study protocol by the 4 WGs with input and feedback from patient support groups for XY dsd, CAH, Klinefelter and Turner syndrome in the UK, D, NL, F and S was developed. This process needed several feedback rounds by email and phone conferences.

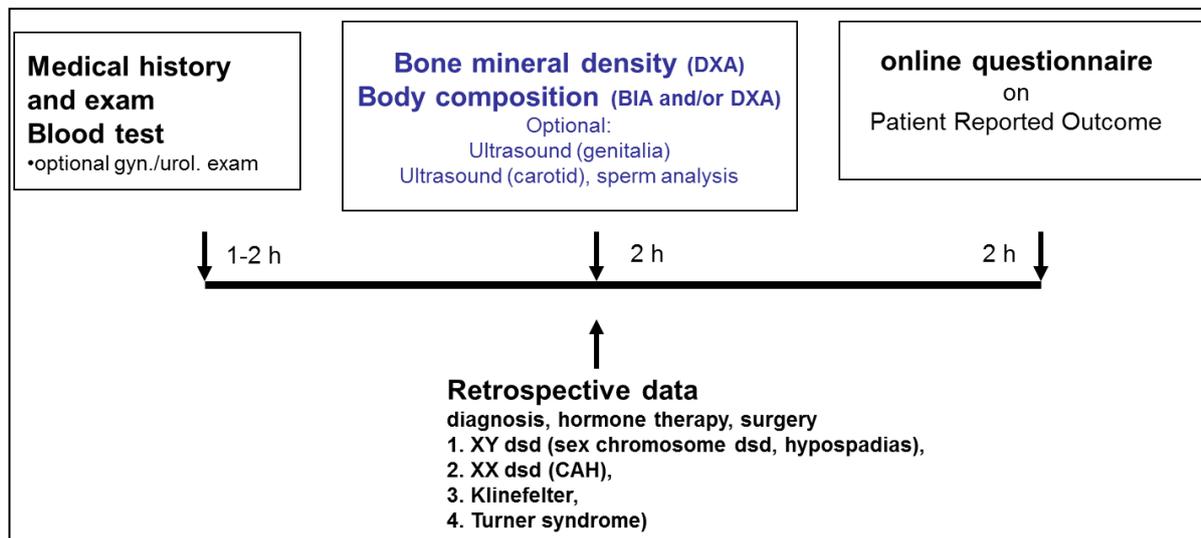
Each working group has developed their relevant part of the study protocol. WG1 (Medical issues) has developed the medical case report forms (CRFs) for medical history and medical exams applying to all patients. Retrospective medical CRFs were developed for the different diagnoses included in dsd: XY dsd, XX dsd (subgroups: XX gonadal dysgenesis and CAH) and sex chromosome dsd (subgroups: Klinefelter and Turner syndrome).

Moreover, a self-constructed questionnaire investigating the patient reported outcome (PRO, patients view) of medical and psychological care, hormone therapies and surgery was developed in close cross-talk with support groups. WG2 (Psychosocial issues) has chosen internationally validated questionnaires possibly appropriate for the study covering the following fields: socioeconomic, HRQoL, psychological well-being, psychosexuality, body image, gender satisfaction, shame, stigma, autism, self-efficacy and satisfaction with health care. Moreover, a self-constructed questionnaire was developed for experienced psychological and social support.

WG3 (Surgery including urology and gynaecology) developed CRFs for description of the genital phenotype at diagnosis, surgical history and gynaecological and urological outcome.

WG4 (Ethical issues) collected the issues of the different patient support groups for XY dsd, Turner, Klinefelter and CAH by a pre-survey. The issues of the support groups were gathered and integrated in the different parts of the study questionnaire: medical part (surgery and hormone therapy), general health care, psychosocial issues and the ethical part.

Figure 2 Study protocol of dsd-LIFE



### **Design of a flyer for recruitment**

From month 2-11, an English master version of the patient flyer to advertise the study to all possible audiences and participants was developed. The flyer was created by B. Köhler (Charite) and U. Thyen (UZL), the national coordinators P. Cohen-Kettenis (VUMC), H. Claahsen-van-der-Grinten (RUMC), C. Bouvattier (AP-HP), A. Nordenström (KI), M. Szcaras-Czapnik (IPCZD) and Margret Simmonds (AISSG, the English support group for androgen insensitivity syndrome) who is also member of the scientific advisory board. Information about the background, the aim and the planned investigations for participants included in dsd-LIFE are described in the flyer. The final content and wording of the flyer was thoroughly revised by Margret Simmonds (AISSG) from the scientific advisory board. Moreover, the flyer was given to other support groups for Turner syndrome, Klinefelter syndrome, congenital adrenal hyperplasia (CAH) and XY dsd in D, UK, NL to gather their opinions and agreement on wording and understandability of the flyer.

The patient flyer was translated in the other 5 languages (German, French, Swedish, Dutch, Polish) of the consortium. The patient flyer is available on the website and was distributed to the national patient support groups by email.

From month 2-the end of the study, advertisement of the study to all possible audiences was an ongoing activity. dsd-LIFE was advertised to all relevant patient support groups during constitution of the study protocol. Moreover dsd-LIFE was advertised at international and national scientific meetings (please see WP6)

Germany: Intersexuelle Menschen, AGS Initiative, Turner Vereinigung Deutschland,, Deutsche Klinefelter-Syndrom Vereinigung.; the Netherlands: DSD Nederland, Nederland Netwerk Intersekse/DSD, NVACP Adrenal support group, Turnercnontact Nederland, Klinefelter vereeniging; France: Association Surrénales, Association AGAT, Association des Groupes Amitié Turner, Association Francaise du Syndrome de Klinefelter; Sweden: INIS, Riksföreningen Congenital Adrenal Hyperplasia, Svenska XXY & Klinefelterföreningen, Svenska Turnerföreningen; UK: AISSG UK, Turner Syndrome Support Society, Klinefelter Syndroem Association, Climb CAH support group; PL: no support groups

### **Intake of ethical approvals**

From month 8-14, ethical approvals were taken in. Ethical approval for the UK (BHAM) was provided with a delay at month 20 (May 2014) due to the laborious multi-step process of submitting the ethical application to the Integrated Research Application System (IRAS), followed by a loco-regional approval process through the Research & Development Office of the involved NHS Trusts NIH and the university.

### **Translations of the study protocol**

From month 9-11, the English master study protocol was translated in German, French, Dutch, Swedish and Polish according to the international required guidelines for translation of study questionnaires (EORTC Translation Module). Two forward translations were conducted through two independent national native speaking translators of the target language with good English knowledge in F, D, S, PL and NL. The translations were reconciled through the two independent translators and a specialist (psychologist or doctor) fluent in English and familiar with the precise meanings and aims of the questions. Headings and introductions of the different parts of the questionnaire have been translated through the same process. Backward translations were conducted through English native speaking translators with very good command of the target language. Review of forward and backward translations were performed by two local project-members with good knowledge of both English and the target language, one of the forward translators and experts with experience in instrument development and translation.

Focusing on conceptual differences, the backward translation was compared with the English pilot draft. The two local project-members reviewed the translation process item-by-item by comparing the back-translated items to the English source items and suggested a version for the final forward translation either by confirming the result of the reconciliation process or by suggesting an alternative translation if necessary. All changes in wording or meaning of the items were conducted in the process of generating the final forward translation.

### Summary of WP1

WP1 ensured preparation and advertisement of the study. WGs to develop the study protocol answering the main research questions were installed. The study protocol was developed by these WGs covering medical, psychosocial and ethical issues. Subsequently, the study protocol was translated into Dutch, German, French, Polish and Swedish (D.1.2, month 9 and D.1.5, month 11). A study flyer for participants and a project flyer for the scientific community to advertise the study was developed and translated into Dutch, German, French, Polish and Swedish (D.1.1, month 11). Moreover, WP1 was responsible for intake of ethical approvals (D.1.3 and D.1.4, months 8-14).

## Work Package 2 Recruitment and evaluation of patients (Month 1-36)

WP2 ensured recruitment and evaluation of the study cohort, biobanking and integration of patients data in the I-DSD database

- To ensure recruitment of participants by all clinical study centres and associated patient groups
- To ensure nursing and medical staff confident and competent to perform assessment
- To ensure patients recruited into the study have standardised physical and psychological assessment as per study protocol
- To perform systematic biobanking of blood and urine for future research
- To achieve recruitment and evaluation of up to 1500 subjects at completion of recruitment phase
- To enter participants' data in I-DSD database

The work of WP2 is displayed in focused paragraphs, which describe the necessary steps during the project.

### Recruitment of patients

The participating sites are of varying size with different numbers of patients at each clinic or hospital. All sites were asked to estimate the number of patients before the start of recruitment, and the estimated number of recruited patients was set to 50 % of the total number of patients (Month 02-36).

### Development of standard operating procedures (SOPs) and training of medical staff to perform the study according to the SOPs

A written standard operating procedure, SOP, was prepared, and contains all different steps during the study were described in detail (see Deliverable 2.1): Preparations before the start of the study, enrolment, data collection, the use of the data base, activities at the completion of the study. The procedure when a patient wants to end study participation before completing the study was described.

Binders with the SOP material were prepared in November 2013. The binders contain the SOP for the procedures and the instructions for the somatic assessment. Each binder has a list of content and a register for easy overview of the material and access to the different parts of instructions (see Deliverable 2.1)

A small booklet, A5 size, with the SOP was prepared. The instructions for somatic, both medical gynaecological and urological examination, and laboratory tests were prepared, A5 size, for the physicians to have easy access to the instructions in the clinical assessment of the patients. An excel sheet was prepared and mailed to all centres for a general overview of number of patients who denied participation or gave consent to participation.

Training sessions for the different teams have taken place, either in local meetings or via skype conferences.

The recruitment of patients has started in all sites but Birmingham. The reason for the delay in Birmingham was due to the delay in obtaining ethical approval.

### **Recruitment and evaluation of participants**

The initial recruitment and evaluation of patients was slow but the rate of inclusion of patients increased over time. In September 2014 354 patients were recruited, in November 2014 427, and in March 2015 855 patients were included. All sites were able to recruit and include patients in a similar fashion, and followed the standard operating procedures (SOP) for the study. All sites had education concerning the procedures at start of recruitment. The final number of patients recruited after 6 months' extension was approved was 1161. The extension also enabled a larger inclusion of the rarer forms of DSD. In total, 1040 participants with DSD (see Table 1) and 121 participants of males with congenital adrenal hyperplasia (CAH) facing similar problems of infertility and life-long hormone therapy could be recruited. Although the estimated number of 1500 participants could not be reached, the numbers in most the different subgroups are large enough for statistical analysis. The minimum number of patients required for analysis was estimated to 500, which has been exceeded with more than twice that number (Month 2-36)

### **Biobanking of blood and urine for future advanced translational research**

The biobanking of blood/serum and urine had to be handled differently in the different sites due to local restrictions in obtaining ethical approval in the different countries. In Germany (Charite UZL WWU LMU) and in UK (Birmingham), Sweden (KI) Poland (MUL, IPCZD) biobanking was possible with the patients' consent. In the Netherlands (VUMC, RUNMC) ethical approval to save the samples to analyse within the study, with patients' consent was obtained. In France (AP-HP, CHUT, CHRUM, HCL) no ethical approval for biobanking nor saving samples could be obtained from the ethical committee (Month 13-36).

### **Integration of patients in the I-DSD database**

The inclusion of patients in the I-DSD data base was handled differently in the different sites. The French centres did not have ethical approval for asking the patients about inclusion into the I-DSD registry. All centres have had inclusion into the dsd-LIFE data base as first priority but entered the patients that have given informed consent later to the I-DSD registry (Month 2-36).

### **Summary of WP2**

WP2 ensured all procedures which were necessary to perform standardized recruitment. The first step was training of study nurses and medical staff to perform the study according SOPs (D.2.1. month 14-16). The next steps were supervising recruitment through reports on patient numbers after 6 and 12 months of recruitment and to take measures to enhance patient numbers (D.2.2 and D.2.3. reports on patient numbers at after 6 months and 12 months of recruitment respectively). Moreover, it supervised biobanking (D.2.4. month 36) and integration of patients participating in dsd-LIFE into the I-DSD database according the national ethical approvals. The dsd-LIFE consortium could recruit 1040 patients with DSD and an add-on group of males with CAH, which are considered as DSD in a broader sense.

## **Work Package 3 Data analysis and publication**

WP3 ensures data analysis, interrelations and publication covering outcomes of the various off-label treatment/intervention options and key problems of individuals with DSD.

- To combine, amplify and coordinate different expertise of the consortium in data analysis
- To design structured data analysis plans focusing on treatment options, their relationships to main outcome measures and other determining factors
- To optimize dissemination of results and scientific publications by working groups within the consortium

The Work Package (WP) work done is displayed in focused paragraphs, which describe first the necessary steps during the project for task 1 to 5 and second focus on the status of each task and the major part of analysis and publication of main outcome measures.

WP03 prepared general information for the entire consortium about 'guidelines of good scientific practice', 'authorship guidelines' and 'conflict of interest'. To coordinate the different expertise in the consortium and to assure good scientific practice a general agreement related to authorship among the Steering committee was accepted by all consortium partners [Months 18 to 20]. To secure the standards of the steering committee in all (future) publications related to dsd-LIFE, WP03 prepared a standard operation procedure for authorship [Months 39 to 42], informed all scientists involved in dsd-LIFE [Months 42] and supervised and guided the entire publication process [ongoing], e.g.

The agreement of the consortium to add 'on behalf of the dsd\_LIFE group' to the list of authors in publications addressing the central aims of the project has been a major step in the consolidation of the work process and appreciation of multidisciplinary contributions. This is an international accepted method to honour/acknowledge everyone who took part in the project (PI, Scientific lead of every country, Research associates and Collaborates). WP01, WP03 and WP07 leader created the list of persons to be mentioned in the acknowledgements in every paper [Months 36 to 38]. Decisions were based on the 'Proposals for Safeguarding Good Scientific Practice –

Recommendations of the Commission on Professional Self-Regulation in Science (DFG – German Research Foundation, 2013), including information about the USA, Denmark and the United Kingdom’ and the ‘Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, updated Dec 2015 ([www.icmje.org](http://www.icmje.org))’.

We also reviewed the issue of participation of international acknowledged experts, and as such member of the Scientific Advisory Board of DSD-Life, in writing teams and issued a guideline how to determine authorship [Months 39 to 42]. This was based on ‘The European Charter for Researcher [<http://ec.europa.eu/euraxess/index.cfm/rights/europeanCharter>], (German version L 75; 67-77) and the ‘Proposals for Safeguarding Good Scientific Practice – Recommendations of the Commission on Professional Self-Regulation in Science (DFG – German Research Foundation, 2013)’.

WP03 encouraged the process of collaboration among scientists and clinicians within the consortium but also attracting collaborators from the national teams of the scientific leads of the steering committee [ongoing]. WP03 provided leadership for the working/writing groups established at the time of the general assembly in Stockholm and assigned to certain sub-themes (Endocrinology, General health, Fertility, Sexual functioning, Surgical outcomes, Tumor risk/ Gonadectomy, Psychosexual outcomes, Mental health, Quality of life and Health services/ Ethics). WP03 identified topics related to more than one working/writing group and ensured scientific cross-talk and cooperation [Months 20 to 54]. WP03 made sure that multidisciplinary work was established in the working/writing groups to improve the network of information sharing during data analyses and publication process [Months 44 to 54]. During the writing process WP03 encouraged the exchange among writing teams through regularly international telephone or skype conferences as well as meetings of the working/writing groups.

To coordinate the work related to statistical analysis and to support every working/writing group in the most efficient way and to improve the later publications, a codebook for data analysis and a summary brochure about all standardised instruments was developed by WP03 and WP04 [Months 33 to 36]. Printed versions of the codebooks were sent to all participating centres [Months 37 to 38]. After feedback of the local statisticians, an Addendum was realised and circulated as well [Months 45]. The codebook was based on the English database and comprised the variable name and value of about more than 1000 items on past and present medical care and health status (Clinical Report Form). It included also the variable name, variable value and all corresponding domain information of the items of the standardized instruments (Patient reported outcomes). In the summary brochure the development, the practical use and the content of all standardized instrument was described for the WHOQOL-BREF, Hospital anxiety and depression scale (HADS), Adult ADHD Self-Report Scale (ASRS-v1.1), Autism Spectrum Quotient (AQ10), Body Image Scale (BIS or BI-1) and five further questionnaires. The brochure focussed also in more detail on references, normative data and the translated languages available. WP03 collected updates of the references and sent them to the specific writing/working groups or in case of general interest to the whole consortium [Months 38 to 54].

Working/writing groups drafted publication proposals for later analyses of data and submitted them to WP03. Until Month 35 over 70 proposals were reviewed and revised by WP03. Every proposal received up to four feed-back rounds with individualized comments from WP3 leader and the scientist in charge to improve and clarify the methods of data analyses and thus later publications [Months 21 to 38]. All abstracts and their individual comments were circulated including general recommendations for data analysis, avoiding overlap and the utilization of a shared patient classification system. Priority for publication was on type 1 papers, addressing the primary study aims. The final publication plan for type 1 papers (D3.4) was accepted by the Steering committee at the last Steering committee meeting [Months 39] (Table 1).

WP03 provided a common framework to identify priorities in data analysis and publication strategy: Type 1 publications deal with the description of the study population and analysis strategies, of the main results of the primary study aims and of important associations among primary outcomes. All type 1 publications were analysed by WP04 centrally to ensure very high standards of data handling, statistical expertise and thus avoiding loss of time due to misinterpretation and misunderstandings. Type 2 publications were defined as analyses of sub-themes and/ or subgroups to be analysed with statistical support in the scientific centres. WP03 developed a standardized procedure to apply for subsets of the data in the centres. These so-called type 2 publications deal with secondary analyses on of important associations and of any paper on a specific DSD subgroup. Submission process of proposals and review by WP03 were similar to the process for type I publications. Type 2 proposals were voted by the STC on a regularly basis in the monthly telephone conferences. Until the end of the reporting period 36 proposals got a positive

vote by the STC [Months 40 to 54] (Table 2). After acceptance of the proposal by the STC, WP03 organised the preparation of the data set which was delivered by WP04 to the local statisticians in the centres. WP03 followed the data analyses and the writing process of all type 2 publications. The progress of each proposal was updated once or twice per month [Months 44 to ongoing.]. Information was made visible for all scientists involved in dsd-LIFE on an information platform (called Millarium WP07). Updates of information related to analyses of data, writing process, and publications occurred monthly. In case of important (new) information, WP03 informed all partners separately about the current update of the information platform. Reports on presentations (oral presentation or poster) of dsd-LIFE data occurred bimonthly, and published abstracts were made visible for the Consortium partners on Millarium as well.

#### Cooperation of WP03 with other WPs

The **baseline paper** presents the goals of the project, a description of the methods and the sample. The principle investigator (WP01) and the KKS Berlin (WP04) were responsible for good preparation and speedy workflow. WP03 has been instrumental moderating and guiding the planning of this baseline publication as a cornerstone and reference for all further publications. The description of the project and the study population was finalized by end of January 2016 [Months 40]. In addition, an early sample description allows decisions regarding statistical power for type 2 papers. A first draft of the structure of the basic methodological paper was sent to WP03 for revision [Month 36]. After many review rounds the publication was submitted to an open access journal to ensure homogeneity among all subsequent publications from DSD Life [Month 51].

WP03 supported WP04 in discussions about dealing with missing data and scoring algorithms for standardized instruments. Special effort lay on the WHOQOL-BREF [D3.1], the Hospital anxiety and depression scale (HADS), and the Youth Health Care measure-satisfaction, utilization, and needs (YHC-SUN) [D.3.1]. For the latest, cooperation with the University of Greifswald was established for analyses of item functioning and dimension structure of the items used in dsd-LIFE.

**Creation of a Publication Plan (Month 36-40)**

Accomplished in Month 40 [D3.3], the updated version is attached in table 2 and table 3 [Month 54].

**Dissemination and publication of study results (Month 42-54)**

In a multidisciplinary consortium including different professionals from endocrinology, gynecology, urology, pathology, surgery, biostatistics, psychosocial medicine, psychology and social science we encountered varied professional cultures and different experiences in research. Some partners were more experienced in clinical studies, others in laboratory studies; some had worked with quantitative statistical data, others with qualitative empirical data or theoretical work. WP 03 was successful to maintain the scientific exchange process and to implement shared procedures.

WP 3 had planned from the beginning to produce numerous separate publications regarding separate research questions but using the same original patient sample. In this case authors may use the original data base, if all the outcome parameters were defined in the original dataset. Due to errors in the clinical classification of participants the locking and final approving of the data base was delayed by approximately six months.

In the reporting period, we invested major resources in the creation of a commonly shared basic paper describing the design and methodology, the instruments and the entire study sample. As we expected numerous publications using subsets of the sample we advised writing teams referring to the basic sample description and describe all deviations from the classification or use of variables in their proposals. The main issue is transparency, so no matter what the individual research purpose might be, is used it should be obvious for the reader why and how changes were made and how they were justified.

In close collaboration with WP 6 (recommendations) it became obvious that only preparatory work for the recommendations were possible (such as describing the current state of the art) before the findings from the data analysis had not become available. We therefore reorganized the process of analysis and preparation of publications. WP 3 greatly appreciated the amendment that recommendation papers should be published only after the major findings of dsd-LIFE have been communication between the writing teams and the respective recommendation groups.

However, first presentation of results has been made available to both the scientific community and the advocacy groups, especially at the

- 2<sup>nd</sup> International Workshop on Klinefelter Syndrome, March 10<sup>th</sup> to 12<sup>th</sup>, 2016 in Munster/ Germany
- 55th ESPE Annual Meeting – European Society for Paediatric endocrinology, September 10<sup>th</sup> to 12<sup>th</sup>, 2016 in Paris /France
- European Congress of Andrology, September 21<sup>st</sup> to 23<sup>rd</sup> 2016 in Rotterdam/ The Netherlands
- EuroPSI –European Network for Psychosocial Studies in Intersex/DSD, September 23<sup>rd</sup> to 24<sup>th</sup>, 2016 in Surrey/ UK (England)
- 25. Scientific meeting of the DGfS (German society for language research), October 8<sup>th</sup> to 10<sup>th</sup>, 2016 Frankfurt M/ Germany
- Symposium organized by Transparent „Promotion of Health Care Standards for transgender, gender variant and intersexual children and youth“, November 3<sup>rd</sup>, 2016 in Zagreb/ Croatia
- Annual meeting of the German children's and adolescents' urologists, January 20<sup>th</sup> to 21<sup>st</sup>, 2017 in Mannheim / Germany
- 5th National Polish Meeting of Gynaecologists, February 24<sup>th</sup> to 25<sup>th</sup>, 2017 in Torun/ Poland
- 46. Annual Meeting of the German Society for Psychosomatic Medicine in Gynaecology and Obstetrics, March 1<sup>st</sup> to 4<sup>th</sup>, 2017 in Dresden/ Germany
- National Swedish hypospadias meeting, March 17<sup>th</sup>, 2017 in Lund/ Sweden
- Symposium for (DSD) support groups organised by dsd-LIFE, March 21<sup>st</sup>, 2017 in Berlin/ Germany

Further presentations (poster and/ or oral presentation) will be held at

- the 28<sup>th</sup> ESPU congress – European Society for Paediatric Urology, April 19<sup>th</sup> to 22<sup>nd</sup>, 2017 in Barcelona/

- Spain,
  - the 6<sup>th</sup> International I-DSD Symposium, June 29<sup>th</sup> to July 1<sup>st</sup>, 2017 in Copenhagen, Denmark and

the 10<sup>th</sup> International Meeting of Pediatric Endocrinology, September 14<sup>th</sup> to 17<sup>th</sup>, 2017 in Washington, DC/ USA.

To coordinate the work related to statistical analysis and to support every working/writing group in the most efficient way and to improve the later publications, a codebook for data analysis and a summary brochure about all standardised instruments was developed **by WP03 and WP04.**

### Summary of WP3

The tasks of WP3 were to coordinate the different expertise of the consortium in data analysis, structure it and optimize dissemination of results. As a first step a publication plan was developed and finalized. This publication plan includes type 1 publications covering the main outcomes of dsd-LIFE in the whole cohort and type 2 proposals covering in-depth analyses of subgroups (D3.3. month 40). Until the end of the reporting period 36 proposals got a positive vote by the STC (see table 2 and 3). After the end of recruitment and data cleaning analysis of psychosocial adaption, HRQOL and psychological well-being in different genetic DSD entities (D3.1. month 54) and outcomes of various off-label treatment/ intervention regimens in different genetic DSD entities (D3.2. month 54) could be finalized. As a first step for structurized publication the baseline publication describing the design, methods, goals and the cohort of dsd-LIFE was initiated. The publication was submitted to an open access journal to ensure homogeneity among all subsequent publications from DSD Life. Ten type 1 publications describing the major outcomes of dsd-LIFE were submitted to scientific peer reviewed journals (D3.4, month 54). About further twenty type 2 publications are in preparation, most of them close to submission to a scientific peer reviewed journal. Dissemination of results could be started at European and national scientific meetings 2016 and 2017 and a support group meeting 2017.

## Work Package 4 Data management and statistical analysis

WP4 will ensure proper data management of all data acquired in the outcome study and perform statistical analysis to answer the research questions of the study.

- To assure the appropriate methodology for answering the research questions
- To manage data, which contains designing and creating the database, data entry, processing data
- To manage statistical analysis of therapeutic interventions and outcome measures
- To identify and control influencing factors of outcome measures

The work of WP4 is displayed in focused paragraphs, which describe the necessary steps during the project.

Finalization of methodological and statistical aspects of the study protocol

We finalized the statistical aspects of the study protocol and a General Statistical Analysis Plan (SAP) to describe the main analysis of our exploratory study. The focus of the analysis was on the investigation and comparison of the long-term outcome of treatments such as sex assignment, surgery, hormone therapies, and psychological interventions in adolescents and adults that are used in patients with various causes of DSD. According to this determinants and predictors, the classical epidemiological procedures were performed. Related to the usual epidemiological parameters, 95%-confidence intervals were calculated. For history and correlating data, multiple linear, non-linear or logistic regressions models were used. Beside the most common graphs, like histograms or boxplots etc., further graphs like correlograms and mosaic plots were generated, to outline the main relations, regarding to the main outcomes. Depending on data quality and research questions, generalized linear models for covariate adjusting, factorial considerations or mixed designs were performed. Related to large effect findings, the possible power was estimated exploratory. Furthermore, the generated models were verified critically by cross validation and/or bootstrapping. Several subgroup analyses were planned. Controlling for potential confounders were performed by using multiple statistical models, to adjust for these variables (Month 02-12).

Construction of the database

The data base for the study was constructed by the Centre for Coordination of Clinical studies. Looking at task 2 (data management) we constructed a valid and save database for clinical studies according to FDA 21 CFR Part 11. The required data for the analysis were acquired and transferred electronically from site to a central database at the Coordinating Centre of Clinical Trials at Charité using an Electronic Data Capture system (EDC). We created electronic case report form (eCRF) who allows the easy documentation of study data. To guarantee safety, access to the eCRF the authentication by the study participants was required. Therefore, we created access rights (read or enter data) who were defined depending on the function in the study (Principle, clinical investigator, CRA, patient etc.). The forms created are the following:

### 1. Group assignment

Group and sex assignment with selected option: CAH, Klinefelter, Turner syndrome and XX gonadal dysgenesis and XY DSD

### 2. Medical history

Medical interview by a physician

### 3. Medical examination

Assessment of: General examination, Metabolic parameters, Hormones (less than 6 months), Ultrasound uterus, ovaries and testis, Spermogram, DEXA-Scan, BIA etc., Genital assessment, Assessment of: Gynecological outcome, Urological outcome and Histology of the gonads

#### 4. *PRO (Patient Reported Outcome)*

Assessment of: Basic information, Your well-being, Past care and support, Current care and support, Psychosexual issues, Dealing with your condition, Your feelings in relationships, Ethical issues

#### 5. Retrospective

Assessment of: CAH (at diagnosis), CAH (9 months), CAH (6 years), CAH (tanner 2), CAH (16 years - transition 1 of 2), CAH (16 years - transition 2 of 2) – or – Klinefelter (at diagnosis), Klinefelter (tanner II), Klinefelter (16 years - transition) – or – Turner (at diagnosis), Turner (tanner II), Turner (16 years - transition) – or – XY DSD (at diagnosis), XY DSD (tanner II), XY DSD (16 years to transition 1 of 2), XY DSD (16 years to transition 2 of 2) + Ambiguous Genitalia and Surgical History.

The main result was the ICH-GCP (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) compliant data base and RDE system. It can be accessed from all participating study centers worldwide via webbrowser. Because of the sensitive data, the system used a secure data connection (using Secure Sockets Layer protocol, SSL) to transfer the data from the study centers on the central database. Furthermore, the database was designed according the planned statistical analysis and the future delivery management process with focus on plausibility, consistency, identification of missing data and range checks of the data [month 15]

#### Data management

During the second period, entering data into the database was the main task for the participating sites. Thus, administration of the database and the required logins (see Table 1) for the sites was the main responsibility of the data management team. This especially included support for the users regarding challenges during data entry, handling of the database and password settings. The data management team was available via phone during the main working hours and via email whilst the remaining time, so that problem solving was guaranteed timely. Data entry of the sites continued until 30th of September. Periodical messages containing information on the actual filling status of the most important medical data were sent to the sites in order to increase the amount of complete data and thus data quality in the database. The current status of the database including detailed information on the most important parameters that need to be entered in the database was shown and discussed at the annual general assembly meeting in June 2015. Figure 3 shows the recruitment status per site after data cleaning. The detailed report on missing information showed that the diagnosis, the genotype and the karyotype has been entered in different CRF forms and had to be homogenized. The data regarding medical history, physical examination, metabolic parameters, hormones, DEXA-scans, surgical history and retrospective data were also missing for several individuals. The filling status could be improved through 3 monthly data quality checks during recruitment. The PROs (patient reported outcome) were partially or completely filled out by about 90% of the individuals. Overall, the fill in status matched the expected amount and the data quality was good (Month 16-36) .

#### Statistical analysis of outcome measures according to treatment

After closing the database in January 2016 and data cleaning of the more than 3000 items collected per individual, the database was in principle available for analysis in the beginning of January 2016 (see D4.2). A delay occurred within the elaboration of diagnostic data: The diagnosis of all participants had to be re-reviewed, to base the data analysis on the most accurate diagnostic basis possible. All karyotypes were checked to classify all participants according the Chicago classification in 3 major groups: 1. Sex chromosome DSD, 2. XY DSD and XX DSD. The entered diagnoses of the XY DSD participants were checked and confirmed by two experienced independent paediatric Endocrinologists (B. Köhler, Berlin; M. Szarras-Czapnik; Warsaw). The CAH patients were checked and classified clinically and genetically according severity by two experienced independent paediatric Endocrinologists (H. Claahsen- van der Grinten, Nijmegen, A. Nordenström, Stockholm). The participants with Turner syndrome were classified according the Mortensen classification. There was considerable number of participants with implausible information about the diagnosis and they had to be clarified by going back to the physician in charge and asking for detailed clinical information for classification. Due to clarification of these implausibilities cleaning of the database was delayed by 3 months and could be finalized in month 42 (March 2016). This need for elaboration delayed the initiation of data analysis and a complete analysis for the prioritized “type 1 paper publications” became possible from April 2016 on, 3 months after the initial estimation. On second level, the diagnosis specific type 2 papers would be publishable in a

parallel, with second level prioritization. Parallel to the finalization of the database, the scripts for preparing (e.g. calculating scores from standardized questionnaires, derived parameters, grouping variables for specific research questions) and performing the statistical analysis (descriptive statistics, hypothesis tests, regression models etc.) were written with the help of preliminary data as well as proposals for the type 1 publications. Incorporated in these proposals were analysis plans for each planned paper that were developed in collaboration with the authors, the steering committee and WP03.

After the data became available for statistical analysis, first the manuscript for the basic publication - describing the project dsd-LIFE itself, the participant demographics for the whole cohort as well as in comparison to a European reference group, and data quality - was finalized as a basis and reference for all other planned publications. Thereafter, the analysis of the remaining 10 type 1 publications evaluating the dsd-LIFE cohort and in parts per diagnosis group covering the topics quality of life, psychosexual outcomes, surgical interventions, fertility, hormone treatments, mental health, general health, sexuality, health services and terminology were performed centrally at the KKS Charité in close contact with the responsible authors/project partners. By now, all the analyses for all type 1 publications are finished.

Beside analysing the type 1 publications, proposals for diagnosis specific, subordinated type 2 papers covering the topics in more depth were agreed upon by the steering committee based on the same kind of proposals as for the type 1 publications. The respective author(s) received a dataset for their specific research questions and the analyses were performed locally with the support of statisticians on-site. Over 30 data packages were sent to the respective sites by now. It is planned to further deploy the data until at least the end of 2017 based on future publication propositions.

A total of 1161 participants were recruited for dsd-LIFE, where the most were recruited in Nijmegen and Stockholm (see figure 1). The 1161 recruited participants consisted of the main group of 1040 individuals with DSD and 121 XY CAH males as an add-on group. The distribution of included diagnoses is shown in figure 3. The sample sizes of the four main groups (Turner, Klinefelter, XY DSD, and CAH) were sufficiently high to detect meaningful differences between the groups with an appropriate power. In addition, even some of the smaller subgroups were still large enough to evaluate the proposed research questions yielding relevant results. The mentioned sample sizes allowed us to implement multivariate analyses in order to adjust for confounders when evaluating effects of interesting parameters (Month 31-54).

The analyses for all type 1 publications (including the basic publication describing the study) are finished and the manuscripts are either already submitted or are shortly before submission.

Data packages for accepted type 2 proposals were sent to the sites and are analysed on-site. Further data deliveries are planned.

#### Summary of WP4

The tasks of WP4 were construction of the data base, data management, statistical analysis including identification of influencing factors of main outcome measures. After finalization and translation of the study protocol, the database was constructed in 6 languages (D4.1, month 15). During recruitment data management included 3-6 monthly data checks and answering all questions related to recruitment (month 16 to 36). After the end of recruitment data cleaning and verification of diagnoses was performed to prepare the database for data analysis (D4.2, months 42). After that final step data analysis for the type 1 publications analyzing the main outcomes and influencing factors was finalized in close cooperation with WP4 until the end of funding of the project (D4.3, month 54). Moreover, about 20 data packages for type 2 analyses were sent to the respective centres.

## Work Package 5 Development of clinical recommendations

The objectives of WP 5 are development, provision and dissemination of evidence-based recommendations for better clinical care of patients with different genetic entities of DSD.

- To develop recommendations
- To provide recommendations
- To disseminate recommendations

The work of WP5 is displayed in focused paragraphs, which describe the necessary steps during the project.

### Development of recommendations for clinical care

The aim of WP 5 was to develop evidence-based recommendations for clinical care of individuals with DSD. DSD recommendations should consider clinical questions: medical and psychosocial care, benefits and harms of different treatment options and patient experiences with healthcare intervention (month 1-54).

A structure for the recommendations was developed by the lead of WP5 (Claire Bouvattier, month 15). As DSD patients are affected by very distinct genetic entities, the currently available published data were searched and studies were checked: relevant systematic reviews, consensus, guidelines (Cochrane, medline, etc). The quality of the different studies was classified and relevance to the questions of interest, bias, categorization of the evidence levels (1-4) and strength of the recommendations were assessed. For example, recent guidelines were published for Turner syndrome, Klinefelter syndrome and CAH. For these diseases, dsd-LIFE focussed on non-developed specific areas. Conversely, very few data were available for psychosocial care in XY DSD. We discussed during the steering committee meeting in Amsterdam 2013 to identify and include recommendations and specific points in the already recently published guidelines for CAH, Klinefelter and Turner syndrome. For the rare diseases (no data) included in XY DSD, we will be able to provide basic recommendations to harmonize the therapeutic strategies.

The dsd-LIFE consortium decided to work on specific recommendation for DSD subgroups (XY DSD, 45,X, 47,XXY, CAH) including a psychosocial part, which applies to all conditions (month 15). The consortium decided on working groups ("recommendation groups") for the setup of the different recommendations and to develop a skeleton including the major research questions during the third General assembly meeting in Stockholm 2015 (month 33).

The skeleton was equally structured for all 4 diagnosis specific recommendation groups XY-DSD with Hypospadias (Lead: B. Köhler, A. Nordenskjöld), CAH (Lead: H. Claahsen, N. Reisch), Klinefelter (Lead: C. Bouvattier) and Turner (Lead: C. Pienkowski, B. Borgström). The psychosocial group (Lead: A. de Vries, E. Bennecke) had an individual structure.

The skeleton was filled in with central scientific, diagnosis specific and guideline based results from existing scientific literature until spring 2016 (month 45), to later be filled with findings from dsd-LIFE, added as recommendations.

When analysis of results of dsd-LIFE will be completed, we will have details on the outcome of the various treatment regimens (sex assignment, surgery, hormone therapy, and psychological interventions) on quality of life and psychological wellbeing in the distinct genetic entities. Evidences will be translated to clinical practice guidelines. Economic health care considerations will also be discussed in the guidelines.

### Dissemination of recommendations

During the third period of the project it became obvious that recommendations cannot developed only from the data of the type one publications analyzing the main outcomes in the whole cohort, but also analyses from the more specific type 2 analyses are needed. As all planned analyses could not be performed until the end of the project. The scientific officer agreed to publish and submit the results of the type 1 analyses also as recommendations (month 52-54).

So far the consortium could disseminate results of dsd-LIFE at several national and international meetings:

- 2<sup>nd</sup> International Workshop on Klinefelter Syndrome, March 10<sup>th</sup> to 12<sup>th</sup>, 2016 in Munster/ Germany
- [55th ESPE](#) Annual Meeting – European Society for Paediatric endocrinology, September 10<sup>th</sup> to 12<sup>th</sup>, 2016 in Paris /France
- European Congress of Andrology, September 21<sup>st</sup> to 23<sup>rd</sup> 2016 in Rotterdam/ The Netherlands
- EuroPSI –European Network for Psychosocial Studies in Intersex/DSD, September 23<sup>rd</sup> to 24<sup>th</sup>, 2016 in Surrey/ UK (England)
- 25. Scientific meeting of the DGfS (German society for language research), October 8<sup>th</sup> to 10<sup>th</sup>, 2016 Frankfurt M/ Germany
- Symposium organized by Transparent „Promotion of Health Care Standards for transgender, gender variant and intersexual children and youth“, November 3<sup>rd</sup>, 2016 in Zagreb/ Croatia
- Annual meeting of the German children’s and adolescents’ urologists, January 20<sup>th</sup> to 21<sup>st</sup>, 2017 in Mannheim / Germany
- 5<sup>th</sup> National Polish Meeting of Gynaecologists, February 24<sup>th</sup> to 25<sup>th</sup>, 2017 in Torun/ Poland
- 46. Annual Meeting of the German Society for Psychosomatic Medicine in Gynaecology and Obstetrics, March 1<sup>st</sup> to 4<sup>th</sup>, 2017 in Dresden/ Germany
- National Swedish hypospadias meeting, March 17<sup>th</sup>, 2017 in Lund/ Sweden
- Symposium for (DSD) support groups organised by dsd-LIFE, March 21<sup>st</sup>, 2017 in Berlin/ Germany

Further presentations (poster and/ or oral presentation) will be held at

- the 28<sup>th</sup> ESPU congress – European Society for Paediatric Urology, April 19<sup>th</sup> to 22<sup>nd</sup>, 2017 in Barcelona/ Spain,
- the 6<sup>th</sup> International I-DSD Symposium, June 29<sup>th</sup> to July 1<sup>st</sup>, 2017 in Copenhagen, Denmark and
- the 10<sup>th</sup> International Meeting of Pediatric Endocrinology, September 14<sup>th</sup> to 17<sup>th</sup>, 2017 in Washington, DC/ USA.

Publication of recommendations

Until the end of funding of dsd-LIFE 10 type 1 publications were submitted for publication (See Table 2 and receipts of submission).

WP5 is in close crosstalk with WP3 data analysis, which is the basis for WP5. In order to save time, drafted an updated “skeleton synopsis” for the different recommendation for XY dsd, CAH, Turner and Klinefelter syndrome, which will be completed during data analysis of dsd-LIFE. The skeleton consists of the following topics.

Summary of WP5

The tasks of WP5 were development, provision and dissemination of evidence-based recommendations for better clinical care of patients with different genetic entities of DSD. As a first step a set up and the needs for recommendations was presented by the lead of WP5 (C. Bouvattier) at month 15. As a second step recommendation groups for the big groups of diagnoses included in dsd-LIFE such as XY DSD conditions, Klinefelter and Turner syndrome, CAH and a comprehensive psychosocial group were installed in 2014. As some recent European recommendations are already existing (e. g. for Turner syndrome, Klinefelter syndrome and CAH), dsd-LIFE will – for these diagnosis – focus on non-developed diagnosis specific mostly psychosocial areas as well as on inclusion of recommendations, resulting from the future dsd-LIFE data. For the rare diseases included in XY DSD, no actual clinical recommendations are available yet and here, the project dsd-LIFE will be able to provide actual clinical recommendations for clinical care. Based on the above named reason, dsd-LIFE will specially focus on recommendations for XY DSD conditions. A skeleton of relevant issues for the recommendations was developed and filled with data available from the

literature (month 45). However, recommendations could not be finalized until the end of funding of the project as not all results of data analysis were available, but are planned at the end of 2018.

## Work Package 6 Dissemination and communication with the public

WP6 ensures dissemination of the study results to the public including health care providers, patients, educational institutions and the general public. Moreover, WP6 intends to enhance knowledge on novel gender concepts and DSD in the EU community.

- To reach all the potential audiences in particular patient organisations and health care professionals
- To increase knowledge of patients about their condition in order to enhance empowerment of patients with DSD
- To increase knowledge on gender and DSD of the general public to improve acceptance and decrease stigmatization of DSD
- To increase awareness of patient health care providers of the results of the project and consequent adjustments of the novel clinical guidelines

The work of WP6 is displayed in focused paragraphs, which describe the necessary steps during the project.

### Instruments for dissemination

Shortly after the start of the project, the project logo and website were created to inform professionals, patients and the public about dsd-LIFE (<http://www.dsd-life.eu/>) (see D6.1)

Furthermore, a dissemination plan was developed and finalized. This document was discussed at the Steering Committee meeting and the General Assembly and finally approved by all participants (see D6.6).

In order to inform patients about the study, a special section for patients was created in all 6 languages, on the general dsd-LIFE website (see D6.1). Purpose of the study, procedure for participants and contact information, as well as an explanation of current nomenclature are to be found in this section.

There were general press releases set up in all 6 dsd-LIFE countries. These press releases also had the function to make patients aware of the study.

As no data could be presented or discussed at the start of the study no attempt has been made so far to contact general media, such as TV stations, magazines or newspapers.

During the last period of dsd-LIFE the logo and website continued to be in use. Providing information for parents and professionals and keeping patients and the public informed was the main task of dsd-LIFE during this study period. The logo was used at presentations and other public documents (e.g. press releases) (month 1-54)

In July 2014, a dsd-LIFE facebook page was constructed to inform potential participants about dsd-LIFE <https://www.facebook.com/dsd-LIFE-913811035302920/timeline/>

### Contact and information of patient support groups

Right from the start, as a part of D6.2, contact was made with all existing support groups that clinicians and members of present support groups were aware of, in all participating countries. This was done in order to ask these groups whether they were willing to give input in the early stages of the study.

Representatives of support groups were invited at the kick-off meeting to guarantee their input right from the beginning of the project. Bringing them together in a partially parallel meeting also allowed for an exchange of ideas, views and concerns. Representatives of an organisation from the UK (AISSG), one from Germany (Elterngruppe der XY-Frauen), and one from the Netherlands (DSD Nederland) attended the meeting. One representative (Ms Simmonds of AISSG) is also member of the advisory board. Again, input from support groups, is considered of great importance and having one member in the advisory board may guarantee that there is continuous communication between patients and researchers during the whole project. Although the broad study goals were already set in the study proposal, the representatives gave their comments on many, more specific, research questions and the feasibility of certain aspects of the study. They also gave suggestions on how to raise the patients' interest in participating in the study.

In the next phase, some support groups gave indeed considerable feedback about patient questionnaires while they were being constructed. This was particularly relevant for those instruments that capture experiences with care, ideas about care and ideas about discrimination and/or stigmatisation. Also, the first drafts of the Patient Reported Outcomes (PRO) instrument were tested by some patients. Each country has appointed a contact person on patient support group matters. These are W. Arlt (UK), P. Cohen-Kettenis (Netherlands), B. Koehler (Germany), A. Nordenström (Sweden), C. Bouvattier (France). No support group exists in Poland. Here information was given to patients through the participating clinicians.

At the end of the project in March 2017, a support group meeting has been organized in Berlin to report on results of dsd-LIFE. All attendant reported that the meeting was highly informative and successfully provided opportunity to participate in discussions on the results.

The Dutch participants, professionals and support group representatives, started new Dutch group “DSD together.” This was meant to obtain a closer collaboration and better communication between all DSD related support groups in the future. The Polish professionals reported that the meeting had been informative and inspiring. As a result they intend to stimulate patients in their country to form support groups, similar to those in the other 5 countries. So far support groups did not exist in Poland. Policy makers (representing the Health Ministry) from Germany were invited and attended the meeting as well (month 1-54).

Information of the general public about DSD and gender issues

After some discussions about the design of the website, it was decided to first collect all available materials on DSD conditions that already existed. This implied that every working group member searched websites on the various DSDs in their language and order booklets or pamphlets. This information on websites and booklets / pamphlets was sent to the coordinators of the website (A. de Vries and P. Cohen-Kettenis). They put this information into a matrix to get an overview of the existing materials and missing information in the 6 languages. Materials that were already known to be of low quality or not appropriate for parents were excluded.

On the basis of the overview, a proposal was made for the structure of the website by the coordinators. The working group members were then asked to write texts.

The proposal was that there should be a central page with general information (“what is DSD?”). This page has links to websites explaining the process of sexual differentiation in more detail and factors that *may influence that process* with DSDs as a result. Another link be to a very recently produced document “Early days.” This is a beautiful document, written by a mother of a child with DSD. However, it specifically deals with situations parents come across *if their children are born with ambiguous genitals*, which is a minority of the children with DSD (see also above, task 2).

A few issues are of general importance but do not explain what DSD is. These issues have a separate place on the website. They refer to

- clinical care of DSD (what can you, as a parent, expect)
- information management (what do I tell to my child, how and when; what may other people know about my child’s DSD)
- boys or girls? (explaining the concepts of sex and gender)
- the importance of multidisciplinary work (not always available, but parents are encouraged to ask for assistance from other than medical disciplines)
- general things to remember

Once all colleagues agreed upon the texts that were written by all members of the working group the text was sent to the participating members of the support groups. They had quite a few comments and specific ideas about terminology. For them it was important that the text would not be medical/technical, that undue stigmatization would be prevented by avoidance of referrals to illness / disorder / treatment and that the information would be correct but not unnecessary scaring.

It appeared to be quite a challenge to find a balance between giving accurate information to parents on one side and reassurance on the other. Estimates of where the focus should be differ between individuals, groups (lay, professional) and disciplines (medical, mental health).

What was helpful in the process was the notion that this website is a living document. Important and relevant text parts may be added or adjustments may be made if there is reason to do so, because of new research data (coming from dsd-LIFE), treatment protocols, insights or initiatives.

It was decided to first translate the texts into the 6 languages of dsd-LIFE: Dutch, English German, French, Polish and Swedish. On December 1<sup>st</sup> 2014 the English and Dutch versions were online and the other languages followed in early 2015. By now, all languages are available. The working group members were asked to check their websites and make corrections. During the General Assembly Meeting in June 2015 the last call for corrections of the various

language versions was made and last corrections were added. The information for parents is now complete on the website of dsd-LIFE (Month 01-54).



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**The Project**

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Information management

Boys or girls?

Importance of multidisciplinary work

Remember

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[DSD-LIFE - The work leading to these results has received funding from the European Union.](#)

## What is dsd?

Most people assume that girls have girls' genitals, female reproductive organs, female hormone levels and a female chromosome pair (XX), whereas in boys all the characteristics are typically male (testes, testosterone, XY chromosomes). Yet this is not always the case. In a number of situations some parts of the development has been typical for boys and other parts have been typical for girls. These situations are more common than most imagine, and in many cases do not involve medical interventions. The conditions are known as a Disorder / Difference or Variation of Sex Development (DSD).

DSD is an umbrella term for different conditions. They have been categorized in larger groups with similar features. The most prevalent conditions are categorized as follows:

1. Conditions with an uncommon sex chromosome configuration, such as Turner syndrome, Klinefelter syndrome, mixed gonadal dysgenesis (45,X0/46,XY), and 46,XY/46,XX.
2. 46,XY chromosome conditions, including testicular dysgenesis (underdevelopment of the testes) and disturbances of testosterone synthesis or action.
3. 46,XX chromosome conditions, including ovarian dysgenesis (underdevelopment of the ovaries), congenital adrenal hyperplasia (CAH), and non- development of the uterus or vagina.

Children who have a DSD are not all alike. There is much variation between DSDs and not all that is known about a specific DSD will be applicable to every child with that type of DSD. *The clinical care of each child may therefore need a different approach, depending on the type of DSD.* These are types of care that may be needed;

- Children with DSD may need hormone therapies. In some cases it may be necessary to start medication (e.g. cortisone) at birth. In other cases, hormone therapies will start at puberty.
- In later life, some children may want to have plastic genital surgery, whereas most will be satisfied with their bodies.
- Sometimes external and/or internal genitalia of your child may look different from those of other children (🔗 [click here](#) for a very clear and extensive brochure). These children can only after careful examination be assigned to the male or female sex. If they are raised as girls they usually experience themselves as girls; if they are raised as boys they usually experience themselves as boys.
- A very small number of children might need help in untangling their feelings about being a boy or a girl. Some of them may eventually develop an identity that is neither typically male or female (★ [click here](#) for more information).

DSDs often require complex decisions relating to clinical care and other important aspects of life. Families need guidance and support in making these decisions. For instance, parents may wonder what they should tell to other people about their child before the sex assignment

**Consortium**



**Quicklinks**

📄 [The project Flyer](#)

Information of families having a child with DSD

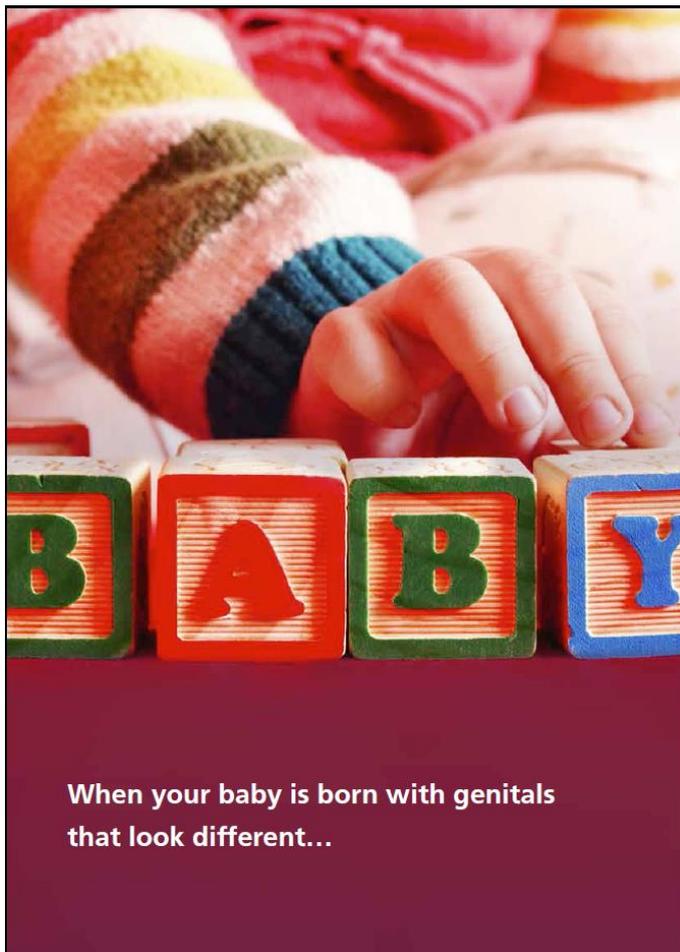
Early Days brochure

Ellie Margritte is a representative from the UK based support group organisation dsd-families. She and her organisation had just recently published an English brochure 'Early Days', written for parents with a newborn with ambiguous genitalia. Within dsd-LIFE this brochure was considered a very nicely written and valuable document.

It was agreed that, with the help of dsd-LIFE, the brochure was translated and became available in the respective six languages of the participating countries in dsd-LIFE. These translations were decided to be part of the deliverable 6.3, the parent brochure. The English Early Days brochure was translated in Dutch, Polish, Swedish, French, German, Urdu, Arabic, Turkish.

All Early Days translations are available on the dsd-LIFE website. As the original English version was done by the dsd-families organization, the intellectual property of these translations remain with dsd-families. The Early Days brochure in the respective languages are therefore not only be available through the dsd-LIFE website, but also through the dsd-families website; [www.dsd-families.org](http://www.dsd-families.org)

A professional graphic designer who worked for some time with DSD experts finalized the brochures. This way, the pdf's in the various languages looked alike and are easy to download and print. It seemed important to have a printed version available for parents who recently heard that their newborn has a DSD that included having ambiguous genitalia. They often need to stay in the hospital until the child has been given a sex assignment. In such circumstances, a paper version of the brochure, describing the consequences of their child's condition would be more practical than having the information on a website only (Month 10-24).



### Information of health care providers

In the past months, WP 6 developed a brochure for health care professionals. This was done in English and translated in the 6 languages of dsd-LIFE. The text was adjusted according to the national situation. Margaret Simmonds, representative of support groups in general in our advisory board, has commented on the text. Margaret Simmonds also helped with providing links to existing information. This brochure is available on the website (Month 24-54).

### Summary of WP6

The tasks of WP6 were dissemination of knowledge about the study and information about DSD in general to reduce stigmatization of the patients. WP6 was in close cross-talk with support groups in performing these tasks. As a first step an attractive dsd-LIFE logo and website with information about the study, the different DSD conditions and gender issues for parents and the general public and discussion about nomenclature was developed in the 6 dsd-LIFE languages (Dutch English, French, German, Polish, Swedish) (D6.1, month 3). A dissemination plan was developed and finalized (D6.6, month 6 and D6.7, month 54). A brochure for parents having a child with a XY DSD condition and for health care professionals was developed in the dsd-LIFE languages during the second and third periods of the project. The parents' brochure is also available in Arabic, Turkish and Urdu (D6.3, month 24 and D6.4, month 54). Both brochures are available on the website. Interaction with the different support groups and dissemination of knowledge was very successful. Support groups were already present at the kick-off meeting and contributed greatly to the development of the ethical part of the patient report outcome (PRO) questionnaires, commented on various texts that were made for patients, such as in the flyer and the website (D6.2, month 10). The support group representative from AISSG fulfilled an active role in the scientific advisory board. The support group meeting in March 2017 in Berlin was very much appreciated and was described as highly informative, provided opportunities to participate in discussions on the results and network with other support groups (D6.5, month 54).

## Work Package 7: Project management

Ensures the proper overall management of the project in order to strengthen and support the Participants to achieve the objectives, complete the milestones in time and deliver the deliverables

Makes sure that the consortium's contractual duties are carried out. Advise and guide the Participants to comply with the EU regulations and their contractual and legal requirements. Abide by the "good practice" of resources management as presented in the Financial Guidelines

Set-up an effective communication infrastructure and foster the integrative process within the consortium

Ensures that knowledge produced within the project is disseminated to the relevant target groups through publications and training.

## 1.4 The potential impact

### Its purpose

The major aims of dsd-LIFE are:

1. improvement of clinical care of persons with disorders/differences of sex development (DSD)
2. information of the general public in the EU about DSD.

To reach the first aim the dsd-LIFE consortium was analyzing all major issues, which were important for care of persons with DSD through the data available from an online questionnaire, medical interview and medical examinations of 1040 adolescents and adults with DSD. These issues are e.g. hormone therapies, surgery, psychosexual issues, psychological support, fertility, physical and mental health, body image and self-esteem, health care, QoL, and ethical issues. The work has been performed by the consortium through type 1 analyses including the whole cohort and type 2 analyses of specific issues in the different diagnoses included in the study such as Turner, Klinefelter syndrome, XY DSD and congenital adrenal hyperplasia (CAH).

### How the foreground might be exploited, when and by whom:

The results of the analyses are published e. g. in scientific journals. Moreover, publication of clinical recommendations developed from the results from the study is planned in 2019. The results of dsd-LIFE will lead to better care of all patients with DSD. Additionally, knowledge about DSD is distributed through the dsd-LIFE website, publication, presentations of results at scientific meetings and support group meetings.

### IPR exploitable measures taken or intended

Not taken or intended

### Further research necessary

Through data analysis of dsd-LIFE further issues for research can be identified, such as e.g. how to implement the results and recommendations from dsd-LIFE into care clinical care and how to empower patients in management of their condition.

### Socio-economic impact and the wider societal implications of the project

Improvement of clinical care

So far dsd-LIFE is the largest clinical outcome study of DSD worldwide. The major aim of DSD-Life is improvement of clinical care and management of DSD, as during recent years, dissatisfaction and complaints of individuals with DSD with medical treatment have considerably increased.

To improve clinical care of DSD psychosocial adaptation, QoL and psychological well-being, medical treatments, fertility, psychosocial care and consideration of individual psychosexual development of persons affected by DSD are indispensable major issues which have to be considered. In addition, non-medical factors such as patients' and parents' view, patients' and parents' participation in decision- making, ethical and cultural aspects are major influencing factors and should be strongly considered for best clinical care of individuals with DSD. Furthermore, the specific needs of different genetic entities of DSD have to be respected. Outcomes, treatment options and influencing factors should be analysed separately for the specific conditions. Altogether, evaluation of these issues through dsd-LIFE will result in improvement of clinical care and management. Finally, life of individuals with DSD will be

considerably ameliorated in Europe.

#### Impact of social participation of individuals with DSD

The major results relevant to health and well-being were already distributed to all support groups involved in dsd-LIFE. The goal of informing support groups is enhance empowerment of individuals with DSD in self-management of their condition. Moreover, bringing together all individuals with DSD should increase empowerment of the whole DSD group on a political level and stimulate social support within the group. Subsequently, dsd-LIFE will have an important impact on future life and social participation of individuals with DSD in Europe

#### Dissemination of knowledge about gender issues

Dissemination of the knowledge about DSD and gender concepts to health care professionals is an additional prerequisite to improve clinical care of individuals with DSD. For that reason, integration of DSD and gender concepts in the curricula of health care providers such as medical students, nurses, midwives is necessary. Dissemination of knowledge about DSD and gender issues to these audiences could be started through the project. The results of dsd-LIFE should be integrated in future educational programmes about gender issues which are relevant for DSD.

#### Consideration of child health aspects

The majority of DSD manifest at birth or puberty and subsequently treatment is started often very early in life. Treatments and interventions have strong influence on child and psychosexual development. However, the impact of DSD and various off-label treatment/interventions on sexual development as gender and sexual identity, psychosocial adaption, HRQOL, psychological well-being can only be seen and evaluated after puberty or in adulthood. Therefore, the evaluation of long-term consequences of the different treatments through dsd-LIFE will also have a strong impact on child health.

#### Development of clinical recommendation

The major final aim of dsd-LIFE is to improve care of DSD through the development of clinical recommendations in Europe. The specific needs of the different genetic entities included in the umbrella term DSD will be respected. In addition to medical issues, especially psychosocial needs, ethical aspects and patients' views will be considered in the recommendations. Especially new insights will be gained through the patients' view on their condition and the medical categorization of DSD.

### **Contribution to Community and social objectives**

#### Inclusion and networking with support groups

An important part of dsd-LIFE was and is to involve patients, particularly patient support groups in all phases of the study. In the first period of the project, patient support groups were involved in constitution of the study protocol and the patient flyer. Moreover, the study was advertised to all relevant patient support groups in the UK, D, NL, F and S. Only in Poland this was not possible, as no patient support groups exist there. During this first and second period of the project we could already see dissemination of knowledge about dsd-LIFE within patient support groups or patient blogs.

At the end of the third period we organized a meeting with the involved support groups to disseminate and discuss first results of the study. All support groups appreciated our approach to be involved in scientific discussion leading to better care. Altogether, the meeting was a great success as the support groups mainly from the Netherlands and Germany started networking and are planning to create a "DSD group" including all diagnoses such as Turner, Klinefelter, XY DSD conditions and CAH. A press release about the meeting was sent out by Charité.

#### Alleviation of negative impact of the disease on the quality of life of patients and their families

Information of parents, patients and health professionals about DSD is important to alleviate negative impact of the condition on QoL patients and their families and subsequently education of the general public and all persons

involved in DSD care is a major aim of dsd-LIFE. To disseminate knowledge about DSD the consortium has developed a website providing information material about DSD for parents and patients. A brochure which was developed by an English support group for families having a newborn child with DSD has been translated into French, German, Dutch, Polish, Swedish, Urdu, Arabic, Turkish. Moreover, an English brochure for health care professionals was developed. This brochure was also translated into French, German, Dutch, Polish, Swedish and is available on the website. Additionally, both brochures are now distributed through the European multidisciplinary DSD treatment teams.

### **Main dissemination activities and exploitation of results**

#### Exploitation of results

During the third period of dsd-LIFE we could reach the crucial goals of the study which are data analysis and publication of the main outcomes of the whole cohort. For data analysis, working groups on the important issues such as QoL; psychological well-being and psychosexuality, mental and physical health, endocrine issues, health services and ethical issues were installed. These working groups are working closely together in data analysis and dissemination of results. From the results of the major outcomes in the whole cohort and specific outcomes and issues of the distinct diagnosis groups recommendations for improvement of care will be finalized. Summaries of the publications will be available on the website to inform the general public about the results and their impact on care. Only development of recommendations will be performed after the funding period of the project when more results will be available.

So far, the consortium has so far analysed the major outcomes such as QoL, psychological well-being and psychosocial adaptation, surgery, hormone therapy, psychological support, health status, fertility and gender issues, partnership and sexuality, self-esteem and body image, satisfaction with health services and participants' views on terminology in the whole cohort of 1040 individuals with DSD. Results will be disseminated through the publications to the scientific community and through the dsd-LIFE website to the general public .

#### Dissemination to the scientific community and support groups

The first results were already distributed in 2016 and 2017 at national and European scientific meetings and to support groups. Dissemination to the scientific community and support groups on an international level are planned for 2017. Moreover, as in-depth analysis of outcomes and therapies of the distinct diagnoses included in dsd-LIFE is still ongoing continuous dissemination is planned for the following years.

#### Information of the General Public

Dissemination of knowledge about dsd is an important aim of the project. During the first and second period of the study we developed a website with all important information and links to other recommended sources providing knowledge about DSD. Moreover, information about specialized centres in the 6 European countries was made available. The dsd-LIFE website for scientific information about the project, a project flyer, a website with general information about DSD and information for participants and a patient flyer are available in Dutch, English, French, German, Polish and Swedish. A special part about the ongoing discussion and criticism of the term DSD within the different national patient support groups has been included on the website. But also, information on specialized care in national DSD centers has been provided through the website so that the affected individuals can find appropriate care according the actual medical state of the art for their rare condition. Moreover, after publication the results of the study will be disseminated to the general public through e.g. health, parents', youth women's, men's and psychology magazines in the European community to lead to more knowledge about DSD in the society and subsequently reduce stigma of DSD.

#### Dissemination of information brochures

Since the second period of the project the brochure for parents is available in French, German, Dutch, Polish, Swedish, Urdu, Arabic, Turkish in addition to the original English version. The brochure is disseminated through the dsd-LIFE website: <https://www.dsd-life.eu> and the dsdfamilies website: <http://www.dsdfamilies.org> and the COST action dsdnet: <http://www.dsdnet.eu>. Since the beginning of 2017, the brochure for health care professionals is also

available in English, French, German, Dutch, Polish and Swedish and will be distributed through the website, the centres. Additionally, both brochures will be distributed through the DSD centres of the COST action dsdnet: <http://www.dsdnet.eu>.

### **Outlook and future research**

Finalization and dissemination of recommendations for a better care of DSD

In the last decade, many adults with DSD have expressed considerable dissatisfaction with medical treatment. Discontent concerned especially surgical and hormonal therapy but also general care and attitudes of physicians and society towards individuals with DSD. Moreover, long-lasting consequences of the disorders on QoL and impaired participation of individuals with DSD in the society became evident. These issues were taken into account for the first time in a multidisciplinary manner by the consensus group meeting of experts in management of DSD consisting of paediatric endocrinologists, surgeons, psychologists, geneticists and also members of advocacy groups in Chicago 2005. Subsequently, a consensus statement for management of DSD has been developed (Hughes, Houk et al. 2006). However, the consensus statement is not evidence-based due to the rarity of the conditions. dsd-LIFE will lead to recommendations for better care of patients with DSD for which no dedicated treatment is currently approved in the EU. The recommendations will cover the fields of psychosocial support, surgery, hormonal therapy, psychosexual development, health care, ethics and cultural context in distinct genetic entities of DSD.

Concepts for empowerment of individuals with DSD to handle the conditions including development of self-confidence through psychological counselling, activation of resources for social support and thinking of other partner relationships than the classic heterosexual model are necessary to improve participation in the society.

Concepts on gender and DSD should be developed for the curricula of nursery teachers and schools and will be disseminated to increase awareness and acceptance of DSD from childhood on.

The recommendations will be disseminated to physicians through scientific meetings, publication in scientific journals but also to other health-professionals such as general physicians, nurses, social workers, and midwives through the national and European societies. Furthermore, the recommendations will be disseminated to patients' organizations. Dissemination of the recommendations to physicians, scientific communities and advocacy groups will lead to better information of health professionals and patients and improved clinical practice in the management of DSD in the EU. Data analysis is still in progress and more in-depth analysis of outcomes of the specific diagnosis groups are planned. Subsequently, finalization and publication of recommendations for better care are planned at the end of 2018.

The recommendations for individuals with DSD will also include management and counselling of children with DSD and their families. The recommendations will include treatment, communication and counselling concepts for the different periods of child development covering: birth, childhood, adolescence. Special emphasis will be development of recommendations for management of the most vulnerable phase of a child with DSD at birth, when decisions on sex of rearing have to be taken. Concepts for information and coping strategies of families having a newborn with DSD will include information and handling strategies of the family's social environment as relatives, friends and wider social surrounding. Contact to adults, other families having children with DSD and patient support groups will be encouraged. In childhood and adolescence, concepts for management of DSD will comprise psychological counselling of the families with regard to gender issues of their child with DSD and handling of DSD in kindergarten, school and towards friends. Moreover, recommendations for counselling of families having a child with DSD in pregnancy have to be disseminated in all European countries. Choosing the adequate specialized centre with adequate diagnostic possibilities and a multidisciplinary DSD team is recommended for these cases. But, equally important contact to other families with DSD and support groups will be encouraged.

Dissemination of results through scientific meetings has already started and is an ongoing future activity, subsequently the results of dsd-LIFE provide the basis for future research in the field of DSD.

## **Section 2 – Use and dissemination of foreground**

Please see PARTICIPANT PORTAL.

## **Section 3 – Report on societal implications**

Please see PARTICIPANT PORTAL.