European Cooperation in the field of Scientific and Technical Research

- COST -

Brussels, 24 May 2013

COST 003/13

MEMORANDUM OF UNDERSTANDING

Subject :	Memorandum of Understanding for the implementation of a European Concerted Research Action designated as COST Action BM1303: A systematic elucidation of differences of sex development (DSDnet)

Delegations will find attached the Memorandum of Understanding for COST Action BM1303 as approved by the COST Committee of Senior Officials (CSO) at its 187th meeting on 15-16 May 2013.

MEMORANDUM OF UNDERSTANDING
For the implementation of a European Concerted Research Action designated as

COST Action BM1303
A SYSTEMATIC ELUCIDATION OF DIFFERENCES OF SEX DEVELOPMENT (DSDNET)

The Parties to this Memorandum of Understanding, declaring their common intention to participate in the concerted Action referred to above and described in the technical Annex to the Memorandum, have reached the following understanding:

1. The Action will be carried out in accordance with the provisions of document COST 4154/11 "Rules and Procedures for Implementing COST Actions", or in any new document amending or replacing it, the contents of which the Parties are fully aware of.

2. The main objective of the Action is to create a global, European-led network to promote DSD research from molecular studies to treatment in order to improve the structured care and health of people with DSD.

3. The economic dimension of the activities carried out under the Action has been estimated, on the basis of information available during the planning of the Action, at EUR 60 million in 2013 prices.

4. The Memorandum of Understanding will take effect on being accepted by at least five Parties.

5. The Memorandum of Understanding will remain in force for a period of 4 years, calculated from the date of the first meeting of the Management Committee, unless the duration of the Action is modified according to the provisions of Chapter IV of the document referred to in Point 1 above.

A. ABSTRACT AND KEYWORDS

Differences or Disorders of Sex Development (DSD) constitute a complex group of rare diseases that are caused by chromosomal, genetic and endocrine metabolic disturbances that affect the endocrine-reproductive system, thereby modulating the sexual phenotype of a given person. DSD poses great challenges for our understanding of sex and gender development in biology, medicine and societal issues. Enormous scientific advances are possible through modern genetic techniques in conjunction with thorough clinical and laboratory assessment. This COST Action will link leading international scientists, clinicians, and stakeholders in the field to characterise DSD with the aim of a diagnosis to all people with DSD with structured, potentially personalised, management and therapies. The Action will aid to the understanding of the clinical heterogeneity as well as reveal the pathophysiological commonalities between different forms of DSD at the molecular level. It will additionally benefit the science in rare diseases of the international community and also the formation of a European Reference Network. Since DSD is an umbrella term for a number of conditions most of which imply more than purely medical or scientific expertise, the Action will pay due attention to the larger societal implications of DSD research.

Keywords: sex and gender development, differences of sex development, genetics, rare diseases, reference networks

B. BACKGROUND

B.1 General background

Differences or Disorders of Sex Development (DSD) constitute a group of rare to very rare congenital conditions affecting the development of the genito-urinary tract and in most instances also the endocrine-reproductive system. DSDs are caused by chromosomal, molecular genetic and endocrine aberrations, which in turn modulate the sexual phenotype of an individual. Several distinct entities, like congenital adrenal hyperplasia (CAH), affect also other organ functions, mostly adrenal or kidney, but also complex syndromes are described.

The incidence is variable in different ethnic groups, for example it has been calculated with 2 births with ambiguous genitalia in 10.000 per year in Germany, and at 1 in 3,000 in Egypt, most probably because of a higher rate of consanguinity. For some distinct entities, the order of magnitude has been established, with the most common form of CAH called 21-hydroxylase (CYP21A2) deficiency 1:11.000, and other forms of DSD such as complete androgen insensitivity (CAIS)

1:40.000, 17β-hydroxysteroid dehydrogenase (HSD17B3) deficiency 1:143.000, whereas in other forms only isolated cases have been described, as for instance in P450 side chain cleavage enzyme (CYP11A1) deficiency. Some unclassified genital malformations such as hypospadias have a higher magnitude, so that overall more than 50.000 individuals may be affected by some form of DSD in Europe.

The exact aetiopathogenesis remains unknown in the majority of the cases. For some conditions, the molecular diagnosis can be achieved in almost 90% of the cases, like CAIS, while in many others like complete gonadal dysgenesis it may be below 20%. For some clinical entities like Mayer-Rokitansky-Küster-Hauser Syndrome (MRKHS) – a syndrome with aplasia of the uterus and renal abnormalities - the molecular pathways and genetic causes are completely elusive at this point. It should also be highlighted that the molecular study of DSD can also provide novel insights into the aetiology of other much more common reproductive disorders such as male and/or female infertility as shown by the recent example of mutations in the gene *NR5A1*, that are known to be a major genetic cause of DSD.

Children with DSD may be born with genitalia that range from being atypical to truly ambiguous and the sex assignment process may be extremely challenging for families and health care professionals. Often, multiple surgical interventions are performed for genital reconstruction to a male or female appearance. The gonads are often removed to avoid malignant development. Hormone replacement therapy is not studied well and usually follows generic patterns of replacement used in other patient populations. In CAH, which is the most frequent form of DSD in 46,XX children, adrenal function is altered mostly with androgen excess and glucocorticoid deficiency, making life-long hormone therapy necessary. Further clinical trials are necessary to study novel therapeutics and to improve outcome.

Many affected adults question a simplified view of sex and gender identity being fully malleable through surgical and hormonal intervention; others demand better evidence on specialized hormone therapy. Furthermore, the impact on gender development through either genetic and endocrine influence or cultural and social modulation of gender identity remains elusive and at present is the subject of controversy frequently publicly debated by legal stakeholders, advocacy groups and professionals. Health care professionals as well as policy makers are even urged to rethink the binary division of the sexes. Therefore, these conditions paradigmatically illustrate the diagnostic, therapeutic, prognostic, social and ethical dilemmas encountered by humans affected by rare congenital conditions and the need of societies to attend to this thoroughly. To support the prospects of a healthy life and unhindered integration into today's society, research on DSD needs to reconsider existing paradigms and aim at replacing the current, generic approach by individualized

diagnostic, therapeutic and ethical management.

In the last decade, progress has been made through international collaborative efforts to define a nosology for anomalies affecting sex development. The poor understanding of the underlying pathophysiology as well as the historical use of mainly mythological terms for descriptive diagnostic purposes (such as hermaphroditism, male or female pseudohermaphroditism etc.) led to a consensus conference in 2005 driven by the European Society for Paediatric Endocrinology (ESPE) in collaboration with the US-American Pediatric Endocrine Society (PES) and the Asian-Pacific Pediatric Endocrine Society (APPES). A new nomenclature and classification was developed based on the concept of precision of inclusion of genetic pathways to allow for a new ontology of disease descriptions. Starting from the chromosomal set, normally either 46,XY or 46,XX, further delineation is made for abnormalities of gonadal development versus conditions affecting hormone synthesis or action. Significant flexibility exists to incorporate so far unclassified or syndromic disorders. Cases of numerical chromosomal aberrations or conditions of development of both testicular and ovarian tissue are incorporated into this classification. This classification has since been widely accepted and is increasingly used around the world both by clinicians and researchers, and has also found a rapid way into clinical text books.

Research on rare conditions requires a structured approach towards linking expert research insights of various specialities with relevant patient data and promotion of clinical centres of reference. The relative scarcity of people with rare conditions and their overall distribution implies that international collaboration between clinical and research networks is crucial in order to develop new knowledge and tools for diagnosis and treatment. The participants who developed this Action believe it is mandatory that the international research community works together on these issues in a manner that is inclusive of all interested stakeholders and includes academics, clinicians, small to medium enterprises (SMEs), and patient organisations from both COST and non-COST countries. The main motivation of this COST Action is to link up researchers from various specialities at all levels of experience to expedite scientific exchange in order to harmonise research and diagnostic approaches as well as clinical management. This will encourage and nurture European support networks for DSD. An interdisciplinary COST Action is the most appropriate framework to ensure the European leadership in this field and to complement nationally funded programmes as well as focussed small international projects.

B.2 Current state of knowledge

The initial events of human sex development are genetically determined. In early foetal

development the urogenital ridge has the capacity to develop as either a testis or ovary. Murine studies have shown that the genital ridge is established by a complex interaction between several genes (NR5A1, PBX1 etc.) and signalling pathways. This may be associated with development of other organ systems, such as adrenal or kidney. In the XY gonad the activation of SRY expression leads to the upregulation of SOX9 via a synergy with NR5A1 that initiates the formation of Sertoli cells. Sertoli cells secrete AMH and also produce the signals necessary for the formation of the main steroidogenic lineage of male gonads, the Leydig cells. In the foetal XX gonad, the supporting cell precursors accumulate β-catenin in response to RSPO1/WNT4 signalling which represses SOX9 activity leading to the formation of the supporting cell lineages of the ovary. At later developmental stages, FOXL2 represses SOX9 expression. In the XY gonad, once SOX9 levels reach a critical threshold, several positive regulatory loops are initiated, including autoregulation of its own expression and formation of feed-forward loops via FGF9 or PGD2 signalling. SOX9 promotes the testis developmental pathway, including Amh expression, and it actively represses genes involved in ovarian development (e.g. WNT4 and FOXL2). In a similar fashion, DMRT1 has been proposed to be a positive regulator of SOX8/SOX9 expression and a negative regulator of FOXL2 expression. Thus human sex development can be viewed as a "battle of the sexes' with the maintenance of somatic sex identity achieved by suppression of the alternate state by mechanism(s) that remain to be elucidated. Several lines of evidence suggest that other genetic factors are involved in this cascade. These include the fact that in many cases of DSD including familial cases, the genetic aetiology is unknown (Bashamboo and McElreavey, 2013). This is also supported by the recent identification of mutations associated with DSD in a poorly characterised MAP kinase signalling pathway. Furthermore, the downstream targets of many known factors, such as SOX9, DMRT1, and NR5A1 etc. are not fully resolved. Mutations in these downstream genes could contribute to DSD. In addition, many cases of DSD exhibit discrete somatic anomalies that require further phenotypic characterisation. These cases may carry mutations in pleiotropic developmental genes.

Once the testis has been determined, the sex dimorphic development of the urogenital tract is dependent on androgens secreted by the Leydig cells. Steroid synthetic pathways in the adrenal and the gonad regulate androgen biosynthesis. Since the concentration of testosterone in the foetal circulation is relatively low, target cells in the prostate and the external genitalia express 5α-reductase type 2, an enzyme that converts testosterone into the ten-fold more potent androgen 5α-dihydrotestosterone, which can also be generated via an alternative route as exemplified in DSD due to P450 oxidoreductase deficiency, with a likely role of this pathway for 46,XX DSD in 21-hydroxylase deficiency. Androgens in turn exert their action through modulation of target genes via

the androgen receptor (AR) that acts as a transcription factor. The effects of androgens on urogenital development are highlighted by the lack of a prostate in humans with complete androgen insensitivity syndrome (CAIS). In addition, some XX DSD patients suffering from 21-hydroxylase deficiency that are exposed intrauterine to high androgen levels develop prostatic tissue. Although the biological consequences of androgens have been known for many years the precise molecular mechanism involved are poorly understood. The previous EuroDSD project was successful in identifying several important androgen-receptor cofactors, however the active AR protein-complex remains to be characterised. In addition, many of the downstream genetic pathways modulated by androgens have not been identified. Mutations involving these pathways may contribute to otherwise unexplained DSD cases with 46,XY androgen insensitivity or conversely androgen excess in XX individuals. However, the genetic aetiology in most of the DSD subgroups is currently unknown.

Applying classical genetic approaches to understand DSD has proven difficult. The reasons for this are twofold. Sex determination as a process is not conserved in evolution, hence data on sexual development from model organisms such as the Drosophila or C elegans cannot be extrapolated to the human. This contrasts with other developmental processes, which are highly conserved. Second, familial cases of DSD published in the literature are rare. This is due in part to the reduction in fitness due to the nature of these anomalies that primarily affect the reproductive system and it may also be due in part to a lack of recognition and awareness by the medical community that such familial cases may exist. The latter has been addressed by projects such as EuroDSD but further progress is necessary. Although the analyses of the human and mouse have revealed several genes and genetic pathways that are involved in sex development, a substantial proportion of human cases are still unexplained, varying within each defined DSD subclass. Most likely, –omic approaches can circumnavigate many of the traditional obstacles that have hindered our understanding of the aetiology of DSD. Next generation sequencing approaches are expected to identify highly relevant novel genetic causes of DSD. These data can help to address many questions not only relating to the condition itself but also more fundamental questions in developmental biology of the mechanisms involved in cell-fate determination and maintenance, cellular reprogramming, modulation of gene expression and hormonal signalling.

A first European consortium has successfully completed a project in FP7 termed EuroDSD (Grant No. 201444), which received global attention for its support of integrated biochemical, molecular, and genome-wide research to characterize patients with monogenic and poorly defined DSD. The participants created a database, which holds a unique data series on clinical, genetic, and endocrine features of people affected with DSD of known and unknown cause. The EuroDSD collaborative

platform was implemented as a security-oriented registry incorporating pseudanonymized patient data with an associated communication platform supporting interactions and data and biomaterial sharing between clinical centres and researchers according to the consortium needs. Data security has been paramount to the success of EuroDSD and the system has been rigorously defined to utilise advanced authentication, authorisation and auditing capabilities to minimise potential risks according to best international information governance practice. The global database is unique in the field of DSD and is currently secured and sustained through an MRC grant and is called I-DSD (International DSD Database, www.i-dsd.org). It allows further research on a large panel of patients with different forms of DSD. However, the I-DSD registry is still not generally used and requires more elaborate modules to improve clinical classification and research development.

Although solid groundwork has been initiated by the EuroDSD project, this has not yet led to the identification of the underlying pathophysiology for all forms of DSD, nor has the clinical utility of novel techniques for individualized diagnosis and therapy decision been evolved. Furthermore, the relatively small number of participants could not integrate the comprehensive spectrum of experts and patient representatives needed to ensure a broader approach to the scientific and cultural aspects of normal and unusual sex development. In contrast, a COST Action will extensively link scientists from various fields to encompass basic, translational, and clinical research and also actively pursue research on societal aspects of DSD.

The success of this COST Action will build extensively on: the previous national and international achievements and the international community that is now formed; on the existing and sustained I-DSD database; the increasing availability of bioresources and processes for sample handling through I-DSD, and the achievements of molecular genetic and biochemical studies for DSD.

Through this COST Action the participants will contribute towards the ambitious goal of the International Rare Diseases Research Consortium (IRDiRC) to find a diagnosis for all people affected with DSD and thus lay the foundations for improved long-term care through novel and potentially individualised therapies in the future. To achieve this, the Action will initiate previously unprecedented international clinical trials for hormone replacement and hormone therapy (e.g. in gonadectomised patients or in patients with congenital adrenal hyperplasia) that are urgently needed.

B.3 Reasons for the Action

The concurrence of an evolving European-led global network, the process of unravelling the understanding of molecular mechanisms, and the increasing availability of specific genetic and

laboratory diagnostic tools and growing public recognition of the specific problems of affected people with DSD provides a unique opportunity to make world-wide progress in the implementation of both translational and clinical research dedicated to DSD. Therefore, this Action aims to address scientific, economic, and societal needs in the field of DSD.

The Action is especially timely since in a majority of cases, the underlying genetic diagnosis and pathophysiology is not understood yet. Currently, there is a gap between the phenotypic explanation and the pathophysiology of commonalities and disparities between distinct entities of DSD. This COST Action will provide a solid foundation for the molecular characterisation of DSD, which will be the basis for major advances in the description of the genetic control of sex development. This will be translated to a systematic standardization of diagnostic aspects and quality control both for data and samples collected, and ultimately for clinical management and therapy. The existing I-DSD database contains core data and sample information on known and unknown cases of 46,XY and 46,XX DSD as well as their family members wherever appropriate. These data have been compiled from an international clinical and research community and may also be used for local data storage, however, a network on the wider use of this information pool is still lacking and will be implemented. The I-DSD registry is currently using the database to perform studies examining trends in sex assignment and the prevalence of non-genital anomalies in cases of DSD. The use and further development of this worldwide database on DSD will be an integral part of Action.

Therefore, the Action will enhance international collaboration to catalyze European-led excellence in clinical, basic, and translational research in the field of sex development. The different approaches undertaken will also exemplify research strategies for rare diseases in close collaboration with other international projects and COST Actions. At this time, treatment options for DSD patients have been regarded as unsatisfactory, both in surgery and in hormone replacement. This hold true also for patients with CAH, as the timing of surgery is seen different from other cases of DSD, and hormone therapy with glucocorticoids needs further evaluation and structured clinical trials. These options have to be harmonised and specific guidelines need to be developed. At this time there is a high need for a coordinated European forum for interaction between researchers, clinicians, and patients to provide the basis for prospective clinical studies and trials. A structured European Reference Network linking clinicians and scientists will help to overcome these obstacles.

The Action will bridge the gaps between clinical medicine, biochemistry, molecular genetics and molecular biology with the inclusion of informatics by bringing together leading European groups and companies to deliver innovation and invention and, through partnership with the private sector, translation of inventions to new commercialized products will be ensured. The coordination of a

recommendation on laboratory assessment will lead to the formulation of assay systems which will be commercially exploitable to diagnostic laboratories. The Action will include SMEs working in biotechnology and laboratory development to explore the feasiblity of commercial laboratory diagnostics in an international context.
Recently, the public, legal, and political awareness of differences of sex development has increased enormously in many nations and societies. This Action will address these issues with the patient advocacy groups, professional care takers, and policy makers to increase the information on DSD and to integrate this knowledge into challenges of sex and gender as well as debates on ethical and legal guidance and patient rights in DSD issues.
The Action will aim to enhance synergy in research and clinical science through: (i) holding a regular training school programme and fostering Short-Term Scientific Missions (STSM) to attract and train younger researchers and to enhance scientific collaboration and knowledge, (ii) organising five Working Groups to focus on specific deliverables through the exchange of expertise and knowledge between different fields and specialities, (iii) providing a web-based information exchange between different research programmes and research projects on DSD, as well as creating a common platform of public information on DSD to provide educational materials to caretakers and affected people and their families.

B.4 Complementarity with other research programmes

The leading experts in the field of sex development of COST and non-COST countries support this Action aiming to establish a world-leading research programme. Previously, the EuroDSD project has been funded by the 7th EU framework programme (Grant no. 201444) and has been successfully finished. Currently, a small-or medium-scale focused research project DSDLife is funded by HEALTH.2012.2.4.4-2 as an observational trial in rare diseases, which is a “Clinical European study on the outcome of surgical and hormonal therapy and psychological intervention in DSD”. The coordinator and several members of the DSDLife consortium are already participants in this Action. This COST Action will therefore hold a close interaction with the consortium and incorporate their findings.
In several countries, national networks are organized and formed. This Action will link these programmes and foster exchange between them. Through its participants, it has a close interaction with several national and international research programmes:
- The International DSD database (i-dsd registry), funded by the Medical Research Council of the UK, which is an international database incorporating core data on patients with DSD. Several

participants of the Action are attached to this project either in the coordination or in the advisory board. I-DSD has offered support to DSDLife.
- CAIS-Study, a multi-centred clinical trial in Germany on: “Comparison of the clinical and metabolic effects of estradiol and testosterone in gonadectomized patients with 46,XY DSD due to complete androgen insensitivity”, supported by the German Ministry for Science and Education
- Existing and emerging national networks on DSD:

- Centre National Maladies Rares sur les Anomalies Génito-Sexuelles, France
- Scottish DSD Network, Scotland, United Kingdom
- Netzwerk DSD e.V., Germany
- DSD Working Group of the Spanish Society for paediatric Endocrinology and GIDSEEN (Working Group on Identity and Sexual Differentiation) of the Spanish Society for Endocrinology and Nutrition.
- Belgian-Luxemburg DSD network and registry, BSGPE (Belgian Study Group for Pediatric Endocrinology) BelLux DSD group
- Sveriges Nationella Nätverk för DSD, Sweden
- Spanish CIBERER (Centre for Biomedical Research Network on Rare Diseases) and DSD Registry at ISCIII (Spanish Research Institute on Rare Diseases, Ministery of Health).
- Finnish network on molecular genetics in DSD (funded by Foundation of Pediatric Research)
- Program of Human Sexual Development funded by NHMRC, Australia
- Japanese Network on DSD

- DSD translational network USA funded by NIH

Furthermore, this Action will hold close contacts with EPIRARE on databases on rare diseases and development of a common database platform. Their findings and strategies will be implemented into the work of the Action in due course. The Action will also develop common strategies on the diagnosis and management of rare diseases through the interaction with the COST Actions BM1208 "European Network on Imprinting Disorders" and BM1105 "GnRH deficiency: Elucidation of the neuroendocrine control of human reproduction".
In addition to these research programmes, this Action will interact with relevant world-wide and European stakeholders working on rare diseases: EUROGENTEST, EUROBIOBANK, EURORDIS; Orphanet, RDConnect, and also EUCERD and IRDiRC. The different partners interact with national support groups. The Action will be in close relation to the "DSD Working Group" of the European Society for Paediatric Endocrinology.

C. OBJECTIVES AND BENEFITS

C.1 Aim

The aim of the Action is the creation of a global, European-led network to promote DSD research from molecular studies to treatment in order to improve the structured care and health of people with DSD.

C.2 Objectives

Research on complex rare disorders requires a structured approach towards linking expert research insights of various specialities with relevant patient data and promotion of clinical centres of reference. The often small number of patients with rare disorders and their overall distribution implies that international collaboration between clinical and research networks is crucial in order to develop new knowledge and tools for diagnosis and treatment.
To reach its aim, the Action will strive (i) to provide the possibility of a diagnosis for all people with DSD**,** which will be achieved through the coordination of the evolving data of novel genetic techniques leading to (ii) the identification of novel genes involved in sex development and their correlation to clinical and biochemical data. This will lead to (iii) the development of diagnostics tools and management strategies that are clinically appropriate and are acceptable to affected people and their families and that are ultimately also commercially exploitable**.** The Action will aim to

develop a series of applications, products and protocols both in biochemical and genetic analysis that will be highly specific for the pathology of DSD and valuable in a clinical setting. Ultimately, the Action will promote (iv) translation of these findings into improvement of accessibility for expert patient care**.** This will be achieved through the creation of a pan-European network joining forces and complement studies in order to alleviate health care problems from people with DSD to (v) finally increase their quality of life and to reduce health care costs through the (vi) formation of a structured European Reference Network (ERN). ERNs on rare diseases are currently under debate to be implemented from 2013 onwards within the European Union to structure and develop international expertise through a linkage of national centres of expertise.
The objectives of the Action are:

- To create a world-wide network of clinicians, clinician-scientists, basic researchers, SMEs and advocacy groups on DSD. Deliverables will be: Action website and forum; Scientific report on annual meetings; Report on implementation of internal communication strategy; Report on Centres of Expertise; Provision of educational materials on DSD in multiple languages

- To coordinate and access cutting-edge platforms for genetic research. Deliverables will be: Recommendation papers for large-scale rare diseases research with special focus on DSD

- To advance laboratory assessment of DSD in an age-related manner through the development, comparability, and accessibility of specific techniques also involving mass spectrometry. Deliverables will be: Recommendation papers for laboratory assessment of DSD for diagnostic purposes as well as follow-up under specific hormonal therapies (e.g. for congenital adrenal hyperplasia)

- To facilitate the joint investigation of specific patients/families identified through the I-DSD database. Deliverables will be: Joint clinical and scientific research papers

- To further develop the classification system of DSD and to develop clinical diagnostic and management guidelines. Deliverables will be: Work-flow for standardised clinical recording of DSD; Standard operating procedures for laboratory analysis; Translation

and validation of standardised tools to different languages; Training workshops on clinical management

- To promote scientific and public awareness of DSD. Deliverables will be: Organisation of international workshops; Research-industry round tables, and Short-Term Scientific Missions for early stage researchers; Workshops for advocacy groups; Report on review of concepts of sex, gender, normality and disease of relevance for DSD; Public information through website and press release

- Fostering preparation of large-scale European projects in "Health and Growth" and "Horizon 2020" in DSD research. Both basic research and international clinical trials will be targeted. Deliverables will be: Evaluation of achievements through (i) number of active partners, (ii) number of activities through COST Action, (iii) number of collaborative peer-reviewed publications, (iv) number of collaborative research projects both on national and international level.

C.3 How networking within the Action will yield the objectives?

The objectives of this Action will be achieved through structured concerted efforts of experts across different disciplines including paediatrics, endocrinology, genetics, surgery, ethics, biology, bioinformatics with the inclusion of patient advocacy groups sharing a common interest in the study of DSD.
This COST Action will supply a common unified platform for DSD-related research and will stimulate partners across Europe and the world, enabling successful collaboration through coordinated activities into an integrated project. This will be achieved through regular meetings in a hierarchical manner. Already experts and their groups from 15 COST countries have expressed their interest and support for this Action. The Action will cooperate intimately with expert groups from around the world. In addition to the COST-countries, experts from Russia, Australia, Japan, Brazil, Egypt, Indonesia, and the USA are supporting this Action. Collaboration with non-COST countries will give the Action a relevant and up-to-date role at the international level, both in scientific and dissemination activities. The Action will connect its participants through:

- *Short-Term Scientific Missions (STSM) and training workshops.* These will be organised to train early stage researchers in basic and clinical science to obtain specific

skills in the field of sexual development and DSD. This encompasses laboratory, genetic, and bioinformatic training. A focus will also be lead on STSMs involving early stage researchers in clinical studies.

- *Outreach activities, dissemination and transfer of knowledge.* The Action benefits from intensive interaction with EU projects and Joint Programming Initiatives on similar fields, existing networks and associations dealing with rare diseases as described above. It will integrate expertise and interdisciplinary teams both at scientific and institutional levels. This will be achieved through scientific meetings and workshops.

- Creation of a *common public website*, which acts as a forum for discussion of the partners involved as well as a platform of knowledge with relevant links connecting national and international research projects. It will report on previous measures of this COST Action as well as announce upcoming events. Also it will call for welcoming additional participants in this Action. Integration of patient organisations and further relevant stakeholders for the distribution of important information and educational material is anticipated. The Action will assure openness and flexibility in order to permit the inclusion, at the implementation stage, of perspectives and activities not foreseen during the preparation of the proposal.

C.4 Potential impact of the Action

This Action gives the opportunity to identify the underlying pathophysiological and genetic mechanisms of DSD, to identify new causes of DSD, and translate these into evidence-based diagnostic tools. This will lead to structured diagnostic and management procedures and ultimately benefit all patients with DSD to alleviate health care problems, advice appropriate therapies, and foster their integration into society. It will also broaden concepts of sex and gender in our changing societies, acknowledging legal, political, cultural, and religious perspectives.

Impact for the Patients

The Action will allow improvement of communication between basic research through the utilization of –omics technology both employing next generation sequencing and modern biochemical laboratory techniques and clinical science and subsequently permit a possible diagnosis of all forms of DSD. The Action will promote international clinical trials to study the possibility of

therapeutic regimens based on diagnosis and structured clinical description. Specific measures will aim at patients and their families to improve their knowledge of their condition, encourage involvement in research and participation in clinical trials. Additionally, emphasis will be put on the scientific evaluation of the impact of transmission of complex and highly sensitive medical information to patients and families. Creation of educational material will be promoted to deliver information for and among patients. This will signify major advances for clinical and psychological care of DSD patients with structured diagnosis and personalized treatment options, both in timing of surgical interventions as well as hormone therapy and counselling.

Impact on Society and Public Health Systems

DSD constitutes a defined, but heterogeneous group of rare conditions. Rare diseases as a whole produce an enormous economic impact to society, because affected persons often do not find adequate diagnosis and managed care, thereby inducing enormous negative impact on them. Only the understanding of the aetiopathogenesis of disease, development of standards for management and care, and bringing knowledge to health care providers as well as to affected individuals meets the goal of preventing chronic disabling disease and meeting the optimal prerequisites for uninhibited quality of life. DSD constitutes a very special group of rare conditions, because on the one hand, they are mostly not life threatening, nor should they constitute an obvious physical inhibition in most daily activities. However, the sensitive nature of affected organs, the decision-making of sex assignment, as well as the discussion on multiple surgical interventions and the lack of individualized hormonal therapy are great challenges to health care providers and have a major impact on the quality of life of those affected and their families. In addition, the social context of raising a child and living with DSD has all too often been misunderstood and ignored. A novel disease ontology with detailed clinical phenotyping and assessment of the underlying genetic and metabolic disturbances, as well as a structured information system on DSD, will overcome this gap and will allow for new diagnostic applications and better therapeutic decision-making. The Action will strive for the implementation of a visible European Reference Network on conditions around DSD in concordance with the recommendations made by the European Union Committee of Experts on Rare Diseases (EUCERD). As DSD challenges the current concept of the two sexes and consequent gender classification in bio-medicine and society, also concepts for other diseases might benefit enormously. The Action will in this respect pay due attention to the larger societal implications of DSD research.

Impact on the Scientific Community

The International Rare Diseases Consortium (IRDiRC) has been established to team up researchers and funding agencies to achieve two main objectives with immediate impact, namely to diagnose

most if not all rare diseases and to deliver 200 new therapies by 2020. The accomplishment of these objectives will have major ultimate impact on the healthcare systems because access to diagnosis will be better and quality of life of patients with rare diseases will be improved due to access to personalized medicine. However, the IRDiRC goals will also have major societal implications, because with enhanced availability of proband data and sample, a harmonisation and transparency of databases and bioresources will be achieved, which will improve future research possibilities at better distribution of funding resources.

This Action will attend to the IRDiRC principles appropriately and in depth to reach the potential impacts described. The immediate impact of the Action will be the provision of better and faster means for a correct diagnosis with options to personalized treatment. The stratification of genomic analysis and the identification of biochemical profiles as biomarkers are hallmarks in conjunction with a very detailed clinical description. This builds on a new disease classification already developed, which now needs structured approaches for better diagnosis. Furthermore, the Action can use and increase an already existing pool of proband data and bioresources with further expert centres from around the globe entering new data and providing new biomaterials according to strict and already elaborated ethical and legal criteria. This work will set the stage for better and new therapeutic strategies in DSD and thus meet the objectives of IRDiRC for an ultimate global impact.

C.5 Target groups/end users

The target groups of this Action as well as the end users of the results to be obtained are:

- Clinicians of various sub-specialities involved in the diagnosis, management, and treatment of DSD
- Geneticists and biologists involved in the molecular diagnosis of DSD
- Basic scientists working on the understanding of the principles of sexual development
- SMEs and industry developing cutting-edge platforms and tools for diagnostics in rare diseases
- Young researchers interested in normal and different sexual development from various aspects, reaching from biological principles to ethical issues on gender

- Individuals with DSD and patient organisation seeking information, advice and structured management for their condition

- Policy makers involved in the legal, ethical, and societal aspects of differences of sex development and rare diseases in general.

D. SCIENTIFIC PROGRAMME

D.1 Scientific focus

The scientific focus of this Action is structured in the objectives described above and will be achieved through the work plan devised in Working Groups (WG) below. This Action will take out its scientific activities for a highly heterogeneous group of rare diseases and realise this by connecting four different inter-dependent strings: First, clinicians will harmonise and standardise clinical age-related external and internal phenotyping and integrate this into the database I-DSD. They will create new guidelines for clinical assessment of DSD. This will increase the chances of identifying unique individuals and families from around the world with great potential to find new genes that are important in DSD. Second, genetic and biology experts will characterize new genes, variants, proteins and regulatory pathways contributing to normal and abnormal sex development. They will develop the model systems required to prove the pathophysiology of any given variant. Third, a European infrastructure will combine these data to create an unprecedented pool of individuals and biomaterials with clinical information and research data to link within the existing and improved I-DSD database. This will be the foundation for the identification of novel disease entities in DSD and the creation of new diagnostic measures and their translation into diagnostic tools. Fourth, the integration of patient organisation and ethical experts will focus on an increasing awareness for the problems of rare diseases affecting sex and gender and will discuss gender-related legal and cultural issues. Their participation will identify future clinical research needs and investigator-driven clinical trials regarding hormonal and surgical therapies as well as counselling strategies.

D.2 Scientific work plan methods and means

The Action will actively promote different Working Groups to work within a structured work plan in order to achieve the objectives and deliver the deliverables. A stronghold will be the Action

website and forum. This website will integrate existing research projects, national networks, and the I-DSD database and thus effectively communicate developments in DSD research to the clinical and scientific community, the advocacy groups, and the general public. An investigator training programme will foster Short-Term Scientific Missions in order to educate the next generation of investigators in the area. The specific means will be undertaken by the Working Groups with the following work plan:

The *WG-1 "Harmonisation and Standardization of Clinical Phenotyping and Management"* has the duty to elaborate a workflow on clinical assessment for better characterisation and care of DSD. Specifically it will:

- Identify phenotype ontologies and establish consensus on phenotypic (time-dependent morphology) characteristics

- Create stringent clinical work-flow for assessment of individuals in conjunction with the I-DSD database

- Enhance enrolment of patients

- Develop specific criteria for centres of expertise (CoE) for DSD according to specific needs and EUCERD recommendations

- Compile a list of specialized CoE in Europe and contacts for the website and enhance outreach and dissemination to clinicians around the world

- Create the prerequisites for a European Reference Network on DSD

- In cooperation with WG-4 develop patient-orientated information/education materials

- Correlate phenotypes with genotypes according to the results of genetic and laboratory analysis (with WG-2 and WG-3)

WG-2 "Biology and Genetics" will bring together experts in basic and translational science to provide the expertise for the application of novel molecular technologies in DSD. Specifically it

will

- Provide expertise for the application of new genetic technologies on the basis of next generation sequencing.

- Create a network of investigators with access to advanced genetic research platforms

- Characterise the spectrums of genetic variations in the patient cohort made available through the I-DSD database.

- Align with bioinformatics to facilitate the exchange of large-scale data in DSD research

- Prioritize candidate genes and develop adequate model systems for the elucidation of their effects on normal and unusual sex development.

- Elucidate genotype-phenotype correlations (together with WG-1 and WG-3)

- Provide guidelines for the sharing of positive and negative results in the forum to facilitate optimal use of resources.

- Translate findings into new diagnostic genetic products as well as software solutions that will be commercially exploitable under European leadership in biomedicine.

WG-3 "Harmonisation of Laboratory Assessment" will coordinate recommendations on laboratory assessment for DSD with regards to technologies involved and analyses to be investigated. Specifically it will:

- Identify appropriate laboratory determinations useful in DSD diagnostics

- Develop age-related, assay-specific reference intervals for DSD differential diagnosis

- Develop guidelines for the usefulness of specific laboratory analysis in I-DSD database

- Elucidate correlations between laboratory findings, genotype, and phenotype for DSD differential diagnosis (in collaboration with WG-1 and 2).

- Develop assays for rapid screening of the steroid metabolome in DSD, which will be available commercially to diagnostic laboratories

- Develop laboratory approaches for appropriate biomarkers to follow hormonal therapies in DSD patients with need for hormone substitutions and therapies (including CAH).

WG-4 "Experiences and Perceptions of Research" aims at exploring the currently used models of clinical care through the integration of experts in bioethics and gender studies together with DSD advocacy groups. Specifically it will:

- Explore models of clinical care and communication that facilitate good clinical practice and research and integrate them into clinical guidelines.

- Formulate needs for patient-orientated research and future clinical trials

- Explore patient-acceptability of research tools (e.g. examination, questionnaires, databases, genetics, biobanks, imaging) necessary for assessing outcome. This report will be published and made available on the Action website.

- Integrate experts from bioethics and gender theory to incorporate concepts of sex and gender in biomedical research with recommendations and reports for professionals and policy makers.

- Interact with other WGs for the preparation of management guidelines and patient-orientated considerations.

- Support an umbrella advocacy group for people with DSD

WG-5 "Dissemination and Capacity Building" aids the Management Committee in the public distribution and communication policies of the Action. Specifically it will:

- Develop the Action website

- Coordinate the integration of Working Group results

- Translate scientific efforts into public dissemination

- Develop the training modules and educational programmes with priority for early-stage researchers and select appropriate faculty

- Organise the Short-Term Scientific Missions

- Coordinate and promote research proposals and provide contacts with funding agencies. Especially clinical trials will be promoted with the MC through the evolving European Reference Network and contacts with policy makers.

- Communicate advances in DSD research and understanding to political decision bodies through press releases and meetings.

E. ORGANISATION

E.1 Coordination and organisation

This COST-Action will follow the recommendations of the document "Rules and Procedures for Implementing COST Actions". The Action will aim to coordinate mainly already existing and emerging national networks and programmes dealing with DSD research. The overall organisational structure of the Action identifies the bodies responsible for specific aspects of project management, and outlines the procedures for decision-making. A detailed work plan will be created with explicit milestones to deliver the deliverables listed with the objectives in Section C2. This will be achieved by creating an infrastructure that enhances multidisciplinary research through the implementation of (i) a Steering Committee, (ii) a Management Committee, (iii) five Working Groups.
The *Steering Committee (SC)* will consist of the Working Group leaders, a Chair and a Vice Chair. The SC is 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 SC shall thus control the execution of the project with regards to the project schedule and the description of work and monitor corrective actions; propose all significant modifications of the work plan to the MC for approval; propose changes in work sharing and membership to the WGs to the MC; propose the global and detailed

provisional budget of the WGs to the MC for approval; report and be accountable to the MC. Specifically, all WGs will report the execution of milestones to reach their deliverables (see Section C) to the SC and provide alternative pathways if deliverables are delayed or not achieved. The SC will meet biannually and will additionally communicate through the web-site, via e-mail and through conference calls.

The *Management Committee (MC)* will oversee and coordinate the key issues of the action. It consists of two representatives from each participating COST country, including the Lead and the co-lead of each WG. The MC will meet once a year during the four year duration of the Action and will be in contact through the website forum and the Chair. The Chair will manage the implementation of the Action. The MC will be responsible for the overall strategy of the Action and its constant evaluation. It will receive reports through the SC on the achievements of milestones and deliverables by the WGs and has to approve any diversion from the work plan. The MC will manage the allocation of the funds and coordinate the work programme. Therefore, the MC will manage the operations and scopes of the WGs, including the programme of dissemination, consisting of workshops, training programmes (with STSM), and open scientific symposia. The MC will also liaise with other significant projects and programmes in Europe and around the world (EUCERD, IRDiRC, Orphanet, EURORDIS, COST Actions on Rare Diseases etc.), fostering multidisciplinary collaborations and future funding possibilities.

The *Working Groups (WG):* To facilitate the organization and management, the Action is structured in WGs, which together comprise the objectives. Each WG will be headed and coordinated by a principal investigator as WG Lead who will be complemented by a Co-Lead. They are responsible for the management of their WGs and the achievement of milestones and deliverables through the work plan. The WG Lead supervises and adjusts the process flow. The designated WG Lead has an integrating function and is responsible for engaging and communicating with all partners in the WG. The WG Lead will report on the progress of the WG in relation to the deliverables achieved and any issues causing delays to the SC. To ensure and document that this is being achieved the WG Lead will periodically send an internal Interim Report to the SC in a structured form.

The activities of the Action will lead to three main strings of the work:

(i) The MC will supervise the establishment of the WGs to form the network with the participants introducing their special expertise. A primary meeting will be held at the beginning of the Action to integrate participants and relevant stakeholders and define the milestones to reach the deliverables. STMS will be introduced as a module to enhance scientific exchange with emphasis to young scientists and to ensure communication between participants of different WGs. Regular meetings and workshops will lead to clear definition of participant roles and contributions. A main structural

element will be the Action Website, which serves as a communication platform to establish contact and communication, define and use the standard operating procedures and clinical work-flows, and link to additional information on centres of expertise and the evolving reference network.
(ii) During the course of the Action, a detailed working programme will be established on the ground of the consolidation of the WGs, the coordination by the SC and the overall strategy assessment of the MC. Due to the overlapping objectives of the WGs, interactions between the WGs will be established to foster regular exchange and synergy. The achievement of first deliverables will be presented to a wider community, further participants, and possible end-users for feedback and reassessment of strategy. This will be done through public symposia and public dissemination in addition to reporting, workshops, and training programmes with the Action, as well as regular releases on the website.
(iii) During the final period of the Action, objectives will have been reached and deliverables obtained. This will lead to final statements and publications, which will be integrated into guidelines and recommendations, both for basic research and clinical applications. This will be made publically available to lead to improvement of patient management and care, and also to improvement of scientific approaches to complex rare diseases affecting the genito-urinary tract. Effective communication to funding organisations will lead to further coordinated research projects and clinical trials of the newly formed scientific network as well as to the formation of a structured European Reference Network on DSD.

E.2 Working Groups

As outlined above, five Working Groups will be established. Each WG will be chaired by a WG-Lead and a Co-Lead, which will be elected at the first meeting. Each WG consists of different expert groups, but some experts may be present in more than one WG. All members of each WG will meet once a year to establish and consolidate their work programme and to enhance submission of deliverables. The investigators within each WG will communicate through the website, as well as through conference calls and e-mails. As outlined above, several objectives require communication between WGs to established broader guidelines and recommendations. WG-4 is peculiar in that it also hosts the representatives of advocacy groups. This WG will correspond regularly with the other WGs in order to make patients' opinions known and visible. This is particularly important in DSD research, as trust and reliance in the medical and scientific society have been a major point of debate in the recent past. Hopefully the integration of advocacy groups into a scientific network will lead to future collective approaches for clinical out-come studies and structured clinical trials and

create a consensus for management guidelines. WG-5 will integrate the communication within and between WGs into dissemination possibilities and report also regularly to the SC.

E.3 Liaison and interaction with other research programmes

The Action aims to integrate researchers and stakeholders of other research programmes to a large extent. Development of common strategies on the diagnosis and management of rare diseases can be achieved through the interaction with the COST Actions BM1208 “European Network on Imprinting Disorders” and BM1105 “GnRH deficiency: Elucidation of the neuroendocrine control of human reproduction”. These Actions also have common interests in international databases of rare diseases patients as well as the integration of results of genetic analyses. Interaction with these Actions is foreseen through concerted conferences and interdisciplinary meetings. Specific researchers may interact at satellite symposia of large-scale international conferences. Members of other research programmes may be invited to specific workshops, to give seminars, to exchange information via forum website and to interact with other members of the Action via conference calls etc.

The Action aims to inform European scientific administrators of its work and progress in order to facilitate the proposal of future research programmes in rare diseases. This will ensure further scientific progress and leadership in the field.

E.4 Gender balance and involvement of early-stage researchers

This COST Action deals with aspects of sex and gender specifically. It is the aim of the consortium to attain new aspects to the understanding of biologic development of the two sexes. The results will also contribute to a better understanding of how processes of gender are involved in this development. This can be considered a major contribution to important theoretical debates on sex and gender. Within the organisational structure, a person taking charge of gender balance and early-stage researcher balance will be appointed to advise the MC accordingly. The annual report from the WGs and the SC will contain a passage detailing these issues.

The Action will address gender balance specifically as outlined: The gender balance will be respected in all activities and females will be specifically encouraged to participate, especially also as WG Leads or Co-Leads, or to serve on the MC. The selection of WG participants with specific attention for cultural and religious diversity and gender equality will be targeted to assure female participation to equality. Each participant is committed to encourage young female scientists for

participation to STSMs in order to sustain their career development and to improve their scientific networks. To integrate scientists with families and young children, the Action will support appropriate child care and coordinate its meetings to respect main holiday times. The Action will monitor the gender balance through yearly surveys and reports to the MC.
Early-stage researchers will be strongly and continuatively involved in the Action through the organization of STSMs for an extensive exchange of knowledge between the different communities and to create their own personal career profile at an international level. Capacity building for young researchers is foreseen by means of STSMs, one-week Training Schools and plenary workshops in which they will present their works. Beside the individual opportunities for young scientists supplied with STSMs, two Training Schools will be organized during the last years of the Action. These will be disseminating knowledge, methodologies and results in order to supply young researchers with instruments for their specialization and growth in a collaborative context and to enhance their networking capacity. A network of early-stage researchers shall be created to function as a “think tank” and to promote an extensive exchange of knowledge at this level. If selection of a participant will be necessary it will take into account both candidates profiles/curricula and gender balance. Furthermore, early-stage researchers are encouraged to become WG leads or co-leads.
Global Dimension: The Action will connect with further European countries, Arabian countries, and experts from the USA, Australia, Russia, Japan, Indonesia, and South America. In several non-COST countries, networks and programmes on DSD are evolving. In Australia, a similar approach to DSD with the implementation of a database corresponding to I-DSD is taken and genetic studies are pursued. In the USA, a translational research programme on DSD is funded by the NIH. The coordinators of these projects have voiced their interest in this COST Action to link the Action with their programmes. It is foreseen that more countries will express their interest, both from developing and developed nations.

F. TIMETABLE

The duration of the Action is four years.

Activity/Deliverable	Year 1	Year 2	Year 3	Year 4
Primary Meeting	X			
Website online and updated (3-monthly) through communication with WGs	X	X	X	X

MC meetings and reporting	X	X	X	X
SC meetings (bi-annually) and reporting	X	X	X	X
WG-meetings and reporting to SC	X	X	X	X
STMS	X	X	X	X
Training Schools		X	X	X
Closing meeting and final report				X
Monitoring and Evaluation of Milestones and Deliverables as outlined in C.1 and 2	X	X	X	X
Specific Research Deliverables				
Report on internal communication strategy	X			
Work-flow on standardized assessment of DSD and updates	X	X	X	X
Recommendation on large-scale genetic research with up-dates		X	X	X
Standard operating procedures on laboratory assessement and follow-up on DSD and up-dates		X	X	X
Review of concepts of sex, gender, normality and disease of relevance for DSD				X
Fostering preparation of large-scale European projects		X	X	X

G. ECONOMIC DIMENSION

The following COST countries have actively participated in the preparation of the Action or otherwise indicated their interest: AT, BE, BG, CH, DE, DK, ES, FI, FR, IT, NL, PL, SE, SI, UK. On the basis of national estimates, the economic dimension of the activities to be carried out under the Action has been estimated at 60 Million € for the total duration of the Action. This estimate is valid under the assumption that all the countries mentioned above but no other countries will participate in the Action. Any departure from this will change the total cost accordingly.

H. DISSEMINATION PLAN

H.1 Who?

The Action will include a broad array of clinicians, clinical scientists, basic scientists, patient

advocacy groups, and relevant stakeholders, who are interested in the field of sexual development and DSD. Other relevant stakeholders include industry for health care products, policy makers for child health, gender-related issues, and rare diseases related issues, as well as funding bodies for rare diseases research. The Action will require a multi-cultural approach that acknowledges the variations of communication style and need in different geographical/social/ethnic locations. This will require considerable discussion and consultation with local teams through the WGs and the MC. The dissemination plan will take their specific aspects and interests in its major dissemination strings into account: Through the website, regular meetings and workshops, scientific publications, public information and lay publications.

H.2 What?

The results of the Action will be made available to the larger scientific community via peer-reviewed publications in scientific journals, presentations at scientific meetings and presentation on the website. Publication policy within the consortium is such that collaborative results will be jointly analysed and published. All partners are committed to the principles of good scientific practice. This Action aims to achieve a unique communication platform for the different interest groups in sexual development and DSD. The website, regular meetings and workshops, scientific publications, public information and lay publications can be utilized for all of these means in differentiated manners.

The clinicians and clinician-scientists will employ the communication platform of the website to establish contact and communication, define and use the standard operating procedures and clinical work-flows and link to additional information on centres of expertise and the evolving reference network. Participating clinicians and clinician-scientists may participate in workshops and public scientific meetings, and gather information through publications of the Action.

Clinical and Basic scientists will be participating in the workshops and meetings as COST participants, and further interested scientists may join the network through the information posted on the website. Younger and early-stage researchers may participate in the training schools and will profit from STSMs. The scientific publications including the recommendations will be available to the broader scientific community and will be linked or made available through the website.

Patients and advocacy groups will communicate through the website, public information and press releases, and specific information materials that will be useful for patient and family education on DSD. They will also profit from public listings of centres of expertise and the evolving European Reference Network to find adequate health care. Interested patients may also actively participate in

clinical trials posted through the website.
Policy makers and other relevant stakeholders will obtain information through the website and also through press releases of the Action.

H.3 How?

The development and maintenance of the Action Website is of major importance for the dissemination and information about this COST Action. The MC will consider the website to be the main method to inform about and promote the activities and results of the Action. The website will be constructed in line with the COST requirements and it will include information about the participants and members and the activities of the Action (including member contact details and their specifications, future meetings, workshops, past and current STSMs and training programmes).
A focus will be placed on the dissemination of standard operating procedures, work-flows, and recommendations as well as educational materials. These will also be available through the public domain of the website and will be promoted to national and international societies to enhance public availability. An internal, password-protected part of the website will be available to participants to allow regular updates on progress of the Working Groups, allow for internal discussions, and make internal minutes and reports of the MC and SC available to participants. A special section will be available to early-stage researchers with both information on STSMs and training programmes, including links to educational materials on disease entities, and also materials for career-development.
Events include the internal workshops, training programmes, and the possibility of STSMs. Efforts will be made to invite international speakers and teachers to participate in these events to promote the highest scientific expertise and also broaden the network to span a world-wide interest group on DSD. The STSMs will facilitate specific knowledge transfer between clinical and scientific centres, allow for career development, and foster professional exchange. The Action will promote and organise public scientific conferences and satellite meetings at major conferences to enhance dissemination of the activities and results.
Publications will include scientific papers established by the participants of the Action. The Action will promote networking to facilitate synergy and to avoid duplications in scientific work. This will acknowledge the scientific output and justify COST support. Joint publications will also include recommendation papers that will streamline further research and translate scientific knowledge into structured clinical practice. A special focus will be on educational material for patients and the lay

public to enhance knowledge and public awareness on DSD with emphasis on cultural and societal aspects.

From the start of the Action the following indicators of the effectiveness will be monitored:

- Number of scientists entering the website and subscribing to the Action mailing list and to the scientists' database. Special attention will be paid to scientists from countries so far not participating in the Action.

- Number of announcements relative to job offers, student fellowships, conferences, and seminars made on the Action's website.

- Number of collaborative publications among members of the Action.

- Number of public-outreach initiatives, such as talks in schools, foundations and cultural societies.

- Number of proposals generated by this Action.