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in Science and Technology
- COST -**

Secretariat

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COST 4159/11

MEMORANDUM OF UNDERSTANDING

Subject: Memorandum of Understanding for the implementation of a European Concerted Research Action designated as COST Action BM1105: GnRH deficiency: Elucidation of the neuroendocrine control of human reproduction

Delegations will find attached the Memorandum of Understanding for COST Action as approved by the COST Committee of Senior Officials (CSO) at its 183rd meeting on 30 November 2011.

MEMORANDUM OF UNDERSTANDING
For the implementation of a European Concerted Research Action designated as
COST Action BM1105
GNRH DEFICIENCY: ELUCIDATION OF THE NEUROENDOCRINE CONTROL OF
HUMAN REPRODUCTION

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 identify genes and mechanisms controlling puberty and reproduction; to inform and validate the human research studies by corresponding research in animal and cellular model systems; and to translate the scientific findings into improved patient care, including genetic counseling for GnRH deficient patients and families.
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 68 million in 2011 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 V of the document referred to in Point 1 above.

A. ABSTRACT AND KEYWORDS

The Action will investigate the neuroendocrine mechanisms that are integrated at the hypothalamic level and regulate the complex organ network controlling reproduction. Implicated genes/pathways have been identified through genetic investigations of rare patients with isolated GnRH deficiency, who displays reproductive failure. Despite knowledge of 16 disease genes, multiple additional genes/mechanisms remain undiscovered, requiring higher-order collaborations for full elucidation. Through a collaborative network of physician-scientists and biologists, the Action will deliver: (i) a database with de-identified genetic and phenotypic data on at least 1,000 GnRH-deficient patients, their families, and unaffected controls, (ii) 1 or more disease gene(s) in each patient, and/or 10 or more novel disease genes, (iii) elucidation of newly identified genes' roles in animal/cell-based systems, and (iv) guidelines for genetic counseling of GnRH-deficient patients based on the emerging disease architecture. Reasons for undertaking the Action in the COST framework are: (i) a critical yet fragmented mass of experts exists across Europe, (ii) participants are currently nationally funded, (iii) several participants' countries do not participate in the e-RARE2 European funding scheme for rare diseases. European leadership in reproductive research/medicine will be augmented by the Action's anticipated benefits, (i) collaboration among previously competing groups, (ii) shared use of cutting-edge genetic methodologies, and (iii) recruitment/training of young investigators.

Keywords: GnRH deficiency, Kallmann syndrome, genetics, reproduction, translational research

B. BACKGROUND

B.1 General background

Reproductive capacity, the key element for species survival, depends on a complex organ network involving the hypothalamus, pituitary, gonads, and internal and external genitalia. This system is centrally controlled by incompletely understood neuroendocrine mechanisms integrated at the hypothalamic level, whose elucidation is the research topic of the Action. Vertebrate reproduction depends completely upon the neurosecretion of the decapeptide gonadotropin-releasing hormone (GnRH) from less than 4,000 GnRH neurons in the preoptic area of the hypothalamus. The coordinated pulsatile release of GnRH from this neural network directs the synthesis and secretion of the gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH), which in turn stimulates steroidogenesis and gametogenesis in the gonads. Though all mammalian species depend upon this common pathway to initiate reproduction, little is known about the molecular mechanisms underlying the ontogeny and regulation of GnRH neurons. A powerful source of novel information has been the human disease model of congenital isolated GnRH deficiency, characterized by abnormal development and/or function of GnRH neurons resulting in failure of sexual maturation and infertility. This syndrome has a rich genetic and phenotypic heterogeneity and represents a unique investigative opportunity to understand the biology of genes controlling human reproduction and to develop novel diagnostic tools and targeted therapies for infertility and reproductive medicine.

Most of the implicated genes and pathways have been identified through genetic investigations of rare patients (incidence: 1/10,000-100,000) with selective failure of neuroendocrine reproductive control. This is diagnosed clinically as congenital isolated GnRH deficiency, and includes normosmic isolated hypogonadotropic hypogonadism (nIHH) and IHH with anosmia, termed Kallmann syndrome (KS). Scientific progress in this area has been spearheaded by a handful of competing research groups in the United States, South America, and Europe, which have accumulated sufficient numbers of patients to facilitate genetic studies. Even though 16 disease genes have been identified, in as many as 70% of patients no genetic cause is known, indicating that multiple additional regulatory genes and mechanisms remain undiscovered. To fully elucidate the neuroendocrine control of reproduction in health and disease, and to define novel targeted treatments, collaboration on a higher order of magnitude is necessary.

Over the last few years, several physician-scientists and biologists who are experts in this field have established relevant nationally-funded research programs across Europe. The critical mass now exists to form a European scientific network assembling the largest possible cohort of GnRH-deficient patients and controls and to become the world's leading force in this area. Because the Action aims to comprehensively elucidate the neuroendocrine control of reproduction, basic researchers investigating relevant mechanisms/pathways in model organisms and cellular systems are an integral part of the network, fostering both candidate disease gene discovery and validation.

The advantage of conducting such a COST Action is that it provides a venue for bringing together clinicians, translational investigators and basic scientists. The Action will allow systematic data collection on GnRH-deficient patients in a database that will harmonize existing data sets. This large cohort of patients could then be sorted according to specific phenotypes (through “deep phenotyping”) which will allow novel investigative opportunities among COST investigators, who will enjoy access to advanced genetic analysis methodologies and will share appropriate *in vitro* and *in vivo* research platforms. The Action will accelerate the connectivity for collaborations and funding opportunities for specific targeted areas of interest.

As such, the network created through the COST mechanism will be separate yet complementary to any number of European funding mechanisms which we anticipate will be obtained through the collaborations facilitated by COST. Because the participants are currently funded at the national level, COST is an appropriate framework for the project. At present, the Action's research is outside the scope of current (2011) and planned (2012) Framework Programme Seven calls. Though it would be thematically well-suited for the e-RARE2 mechanism which specifically funds research on rare diseases, several of the network researchers' countries do not participate in e-RARE2. The consortium created through COST will pave the way for future funding to support research by facilitating scientific discoveries and collaborations that will target various European funding mechanisms. Moreover, launching the project via COST will facilitate the recruitment of additional established as well as young researchers at a Europe-wide level to this line of research. Through a Training School, young investigators will be attracted to and trained in reproductive research, helping to set up a scientific network that will not only sustain itself over the next decades but will embrace and produce consecutive generations of researchers and physician-scientists. For these reasons, COST is the most suitable instrument to help initiate the network.

B.2 Current state of knowledge

Historically, the main approaches to elucidate the neuroendocrine control of human reproduction have been: (i) genetic analysis of affected patients/families harboring large chromosomal aberrations that included the responsible genes, (ii) identification of disease genes in patients presenting with complex syndromes that include GnRH deficiency as a reproductive phenotype, and (iii) sequencing of plausible disease genes with potential roles in reproduction identified through the study of animal or cellular systems. The pace of discovery has been piecemeal, and despite current knowledge of 16 disease genes, the majority of GnRH deficiency's genetic components remain uncharted. New gene discovery has predominantly come from elite research centers in the U.S., South America, and Europe, each operating independently and competing with others at a high level. Each new gene discovery has had such major impact as to create a new line of biological research into the mechanistic basis of the respective gene's and pathway's role(s) in the neuroendocrine control of reproduction using animal and cellular model systems.

In total, hundreds of labs (in academia as well as in industry) around the world are pursuing research that would have been impossible without the gene discoveries of the comparatively few competing human genetic research groups. For example, the discovery of *GPR54* as a novel gene for human GnRH deficiency by a French group in 2003, soon after confirmed by a U.S. team, is a classical example of how human investigation can inform basic science to focus on an important biologic target. Over the last few years it became clear that GPR54 and its ligand Kisspeptin comprise one of the most powerful stimulatory systems of GnRH secretion across mammalian species. Importantly, European groups have been pioneers in administering Kisspeptin to humans. Clinical studies demonstrate the power of Kisspeptin to overcome genetic defects in specific pathways (tachykinin). In another line of translational medicine, molecular chaperones are being tested to rescue defective G-protein coupled receptors (GPCRs) critical for reproduction, such as GNRHR and LHR. The fact that European researchers are actively engaged in this area which holds great promise for developing targeted treatment approaches (personalized medicine), is another reason why the collaborative European network formed by the Action will be extremely well-positioned to become the global research leader.

Over the last 2 decades, cytogenetics, homozygosity mapping, and candidate gene approaches have been successful in elucidating more than 16 genes underlying human GnRH deficiency. Mutated genes are involved in fate specification, proliferation, developmental migration, secretory function, and/or survival of GnRH neurons, forming the basis for our understanding of GnRH biology. Several of these genes effecting GnRH secretion and action have been discovered by European research groups (*KALI*, *GNRHR*, *FGFR1*, *GPR54*, *PROK2*, *PROKR2*, *FGF8*, *GNRH*, etc). Whereas isolated GnRH deficiency was originally thought to be strictly monogenic (i.e., caused in each patient by a single mutation in one of a small number of genes), translational studies have challenged this view by demonstrating complex genetics (oligogenicity) in several families. Translational studies have also demonstrated that isolated GnRH deficiency is not always congenital and lifelong as traditionally thought, but can actually recover with a fully functional reproductive axis in adult life. This can occur even in patients who carry pathogenic mutations, suggesting a role for both genetic and environmental factors in this disease.

The current state of the art is in flux, because similar to other areas of genetic research, recent technological progress has fostered the development of methods for genetic analysis that can accelerate the discovery rate for new loci in GnRH deficiency (as in other areas of biology) leading to a deeper understanding of the neuroendocrine control of human reproduction. These advances include the analysis of copy number variation; the mapping of disease genes to genomic regions that are identical-by-descent among affected family members (autozygosity mapping); and, most promisingly, the recent advent of whole-exome DNA sequencing. With the emergence of “next-generation” sequencing technologies, links between genomic variants and simple/complex traits are already being rapidly uncovered, yet this next phase of discoveries requires novel collaborations and multidisciplinary teams incorporating complementary approaches. Gene discovery will mostly start in patients, with basic science-derived insights being used to filter and prioritize candidate genes resulting from human investigations for validation and characterization of the evolving systems biology of the underlying signaling pathways. This approach is essential to fully harness the potential for genetic knowledge to advance medical practice via genetic diagnoses and personalized medical care (i.e., patient-tailored health-risk assessments and treatment plans).

In rare diseases such as GnRH deficiency, each patient represents a potential unique opportunity for scientific discovery. Thus, the application of advanced genetic research methods to even small groups of patients or to unique patients may lead to the discovery of novel reproductive control systems. However, characterizing the genetic architecture of GnRH deficiency and achieving comprehensive elucidation of central reproductive control will require the application of these technologies on as large a patient cohort as possible. Thus, a central innovative feature of the Action will be the creation of a combined Europe-wide patient cohort of unprecedented size (at least 1,000 patients) in which systematic application of gene discovery techniques can be applied as indicated by each patient's unique features. An associated web-based repository (database) will hold de-identified genotype and phenotype data on participating patients, their family members, and appropriate ethnic controls. This database will provide the central reference point of the network's activities by serving as a key tool to initiate genetic investigations and collaborations between participating researchers. De-identified genetic and phenotypic information will be accessible by all network researchers via a web interface, with the ability to both contribute and curate information on the patients that participants are treating (clinicians) or investigating (geneticists). Ultimately, the goal is to perform whole-exome sequencing on all recruited patients, which is expected to identify the majority of the mutated genes contributing to GnRH deficiency. Thus, the Action will be innovative by adapting new approaches to address an existing problem, and by applying these approaches on a scale that has not been feasible in the past.

To achieve its ambitious results the network will also: (i) involve the majority of physicians caring for these patients across Europe, (ii) directly reach out to patients, families, and advocacy groups, (iii) involve geneticists with access to and expertise on the latest platforms for gene discovery and bioinformatic analysis, (iv) implicate sufficient and diverse basic researchers to provide mechanistic validation of the identified disease genes in animal, cellular, or in silico model systems and elucidation of the mechanisms by which they contribute to the neuroendocrine control of reproduction, as well as to identify and prioritize new biologically plausible candidate disease genes.

B.3 Reasons for the Action

The main reasons for launching the Action is that GnRH deficiency is a rare disease, and its genetic architecture is more complex than originally thought, including the existence of several disease genes, potentially acting in concert to cause the disease in each patient. Thus, to fully elucidate the genetic basis of the disease and thereby to understand the neuroendocrine control of human reproduction, very large numbers of well-phenotyped patients are required. These exceed the ability of any individual research group or referral center, and can only be achieved through multinational collaboration. Therefore, due to the complexity of the molecular and cellular mechanisms involved, there is need for a network of experts to thoroughly elucidate the centrally operating genes and signaling pathways that control human reproduction. Moreover, cutting-edge genetic research methodologies, such as comparative genome hybridization (cGH) array and whole-exome/whole-genome sequencing, promise to facilitate the elucidation of genetic diseases like GnRH deficiency in the coming decades. However, these technologies are associated with high cost of use and require accessibility to expertise and bioinformatic tools not available to most clinical research groups. The Action will enable researchers to pool resources and thus competitively bid for use of advanced genetic methodologies and/or to partner with developers of genetic research platforms to foster discoveries in the field not otherwise feasible.

In these manners, the network will foster collaboration in the field of the neuroendocrine control of reproduction on an unprecedented scale, which will catalyze European excellence in clinical, basic, and translational reproductive research. The action is thus mainly aimed at European scientific advance. Nevertheless, beyond the inherent scientific value of the undertaking, tangible benefits are envisaged as well as translational applications of the discoveries made (further explained in C.4), which are directly relevant to the declining birth rates that European societies are experiencing. These could include: (i) identification of molecular targets for discovery of fertility-promoting drugs (and/or novel contraceptives, such as a drug for male contraception); and (ii) expert treatment of infertility and genetic counseling of infertile patients and their families.

The Action will aim for maximally productive outcomes by: (i) holding a Training School program to attract and train young researchers in reproductive research, (ii) organising the Action into 4 Working Groups (WGs) to focus on specific deliverables by leveraging the expertise of the participants within each domain (i.e., clinical, genetics, basic science, etc.), (iii) establishing a web-accessible database platform for sharing patient data and investigator profiles and identify individuals with complementary expertise. These features will maximize the creation of new multidisciplinary collaborations to obtain funding and accelerate scientific discovery in the field.

B.4 Complementarity with other research programmes

There is no overlap or duplication between the Action and any current or planned European research projects. The Action is a framework for enhancing connectivity among European researchers working in the field of GnRH biology and reproduction. Because for specific projects to be advanced funding needs to be obtained, the Action will create a platform to systematize and pool resources and data so that new strategic programs, collaborations, and projects will emerge, as well as a sizeable group of investigators and scientists who will be able to respond quickly and efficiently to future calls for proposals to support research. Thus, one of the ultimate goals of the Action is to facilitate enhanced competitiveness for this important area to be funded in the near future at the European level.

C. OBJECTIVES AND BENEFITS

C.1 Aim

The overall aims of the Action are to identify genes and mechanisms responsible for sexual maturation by studying patients with GnRH deficiency, a “prismatic” disease that facilitates insights into the neuroendocrine control of human reproduction; to inform and validate the human research studies by corresponding research in animal and cellular model systems; and to translate the scientific findings into improved patient care, including genetic counseling. These aims will be achieved by pursuing the following specific objectives (and corresponding deliverables).

C.2 Objectives

The secondary objectives (and corresponding deliverables) of the Action are:

- To reach out to and include clinicians, physician-scientists, genetic counselors, and basic researchers from all European countries (deliverable: Europe-wide network of experts);
- To recruit collectively a cohort of at least 1,000 well-phenotyped patients with GnRH deficiency, and to create a common web-accessible database for storing de-identified genetic and phenotypic data on patients, their families, and unaffected controls of the same ethnic origins (deliverable: database);
- To facilitate the joint investigation of specific patients/families with unique phenotypes identified through the database (deliverable: joint clinical and scientific research projects: publications);
- To facilitate access to and shared use of cutting-edge platforms for genetic research (deliverable: genetic studies, publications);
- To identify 1 or more gene(s) contributing to the disease in each patient, and/or at least 10 novel disease genes (deliverable: genes, publications);
- To characterise the role of each newly identified gene in animal models and cell-based systems (deliverable: genes, publications);
- To fully describe the phenotypic spectrum of GnRH deficiency (including its response to hormonal treatment) and to delineate the underlying genotype-phenotype correlations (deliverable: publications);
- To create guidelines for genetic counseling of GnRH-deficient patients and their family members based on the emerging disease architecture (deliverable: genetic counseling guidelines – endorsement by medical society, publication);
- To connect adult and pediatric endocrinologists to optimize therapeutic approach for patients in transition between childhood and adulthood, and to share clinical experience/protocols to identify the influence of hormonal regimens on clinical endpoints such as quality of life and fertility (deliverables: clinical treatment guidelines – endorsement by medical society, publication);
- To recruit and train 100 or more young investigators in reproductive research (deliverables: summer school participation and full-time research/fellowship positions);

- To facilitate joint applications for national and European funding (deliverable: research-supporting grants);
- To reach out to patients, their families, and patient advocacy groups to provide support, education and expert clinical care (deliverable: online, telephone, and in-person interaction capabilities at the national level as well as across the network).

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

Because GnRH deficiency is not only a rare disease (incidence: 1/10,000-100,000) but is also characterized by substantial genetic heterogeneity, it is very difficult to recruit a large enough cohort to fully describe its clinical spectrum, delineate its genetic architecture, and document the genotype-phenotype correlations. Thus, networking within the Action will be crucial for assembling the largest possible European cohort to facilitate the required large-scale genetic studies (objectives 2, 3, 5, and 7). Characterizing the role of the new genes/pathways in the neuroendocrine control of reproduction (objective 6) will require interdisciplinary research across groups with expertise in multiple complementary scientific areas. Networking among experts with the Action will facilitate the required collaboration to achieve this goal. Corresponding to the rarity of patients with GnRH deficiency, investigators studying the disease and the molecular mechanisms of neuroendocrine reproductive control are also relatively few across Europe. Traditionally, these groups have engaged in high-level competition among themselves and with American and South America-based teams, which has yielded discoveries of outstanding importance in the field and of broad impact in reproductive biology and medicine. However, the scientific opportunities and challenges of the post-genomic era impose new demands on research in the field. To take full advantage of cutting-edge genetic research platforms such as whole-exome and, in the future, whole-genome sequencing (objective 4), it is urgently required to pool resources (including funding) and expertise, to sustain and accelerate scientific discovery and productivity. Thus, the Action is a unique opportunity for the independently-operating European groups to join into a critical mass collaborating at will and with the capacity to assume the leading role in the field (objective 1).

This critical mass will also have the ability to expand the research community in the field by recruiting and supporting early/mid career investigators (objective 9) and facilitating their mobility across Europe. The network will also have the authority, with its participating genetic counselors, to establish formal guidelines for counseling patients with GnRH deficiency and their families (objective 8), which are currently lacking. Support, education, and expert clinical care of GnRH-deficient patients on a Europe-wide scale (objective 10) will be catalyzed by both the critical mass of the expert network (objective 1) and the large patient cohort (objective 2). Ultimately, to sustain itself and to expand productively, the network will require continued funding to support the research, ideally not only on the national level but on a European scale (objective 10). This will be fostered by the scientific discoveries facilitated by the Action, by the interactions and collaborations established through the network, as well as by the access to advanced genetic research methodologies (objective 4). The ultimate goal is to produce scientific discoveries of sufficient impact to justify inclusion of this line of research into FP funding priorities.

C.4 Potential impact of the Action

It is becoming increasingly clear that tapping the full potential of genetic investigation and elucidating the complex genetic architecture of human disease is best done by incorporating complementary approaches from multiple disciplines. As such, the Action will create a platform for multidisciplinary connectivity by bringing together clinicians, translational investigators and basic scientists in the field of neuroendocrine reproductive biology and medicine. From this network novel collaborations and research approaches will emerge. By connecting previously isolated and competing pockets of expertise and by facilitating the sharing of data in the form of clinical phenotypes and genotype-phenotype correlations, new opportunities for investigation and collaboration will be identified and we anticipate this will push the boundaries of the field. Sharing information on so-called “negative experiments” will reduce redundancy and support the efficient use of resources, because it will help prevent various groups by independently pursuing lines of investigation that, unbeknownst to them, have been previously proven unsuccessful in another team’s experience. The Action will facilitate enhanced capacity for responding to funding calls at the national and European level to support the research, thus sustaining and expanding itself over the long term. Next generations of expertly trained manpower to foster the research will be nourished through channels for short term exchange, mentoring, and a Training School.

Importantly, the Action aims to create opportunities for translating the scientific breakthroughs into utilities for both healthcare providers and patients. The jointly created website will offer information and clinical resources for physicians, genetic counselors and other healthcare providers, as well as patient-oriented educational and advocacy materials to link with and support patients, their families, and patient advocacy groups. Network-associated stakeholders in the pharmaceutical industry are well-positioned and eager to translate scientific discoveries into novel diagnostics and therapeutics to address unmet medical needs in reproductive medicine.

C.5 Target groups/end users

As discussed, stakeholders and end users of the Action's expected results are: (i) researchers (including but not limited to the participants), (ii) clinicians, genetic counselors, and other healthcare providers such as nurse practitioners (representatives of all these disciplines have participated in preparing the proposal), (iii) patients, their families and advocacy groups, and (iv) European pharmaceutical and biotechnology firms.

During preparation of the proposal, numerous patients expressed enthusiasm for the Action, mentioning as an additional benefit the ability to access the network of experts regardless of location in or mobility within Europe.

D. SCIENTIFIC PROGRAMME

D.1 Scientific focus

The scientific focus of the Action is to utilize the unique biologic opportunity provided by the human disease model of GnRH deficiency to identify the genes involved in the neuroendocrine control of reproduction, elucidate the biology of these genes, and translate the discoveries back to patients. Stated simply, the larger the size of the well-phenotyped cohort of patients, the greater the chance of finding new disease genes. As such, the Action will both increase the chances of identifying unique consanguineous families with great potential for successful genetic linkage studies, as well as enable the screening of a large cohort of unrelated patients to find genes that are mutated in small percentages (~1-2%) but which nevertheless have critical scientific impact (such as *GPR54*). Thus, the major innovative aspects of the proposal are the creation of a patient cohort of unprecedented size, to exceed 1,000 patients whose phenotypes will be thoroughly characterized according to uniform practices across the network. Such a cohort will allow for systematic application of gene discovery techniques and will create opportunities to cluster studies of patients with unique rare features. Ultimately, the goal will be to perform whole-exome sequencing on all patients, which is expected to identify the majority of the mutated genes contributing to GnRH deficiency. Initially, however, these studies will produce long lists of rare sequence variants and corresponding candidate disease genes. These genes will then be filtered by cross-referencing basic science information including expression studies, mouse KO models, cell culture studies, and signaling pathway analyses, both wet bench and in silico. These critical tasks will be the focus of collaborative work performed by the large European consortium of clinical, translational and basic scientists brought together through the Action. This filtering will allow investigation and elucidation of the roles of specific genes in GnRH biology. Given the volume and complexity of the data, bioinformatic tools will be critical to analyze raw data and identify rare variants of interest. Thus, the Action will be tremendously valuable in enabling clinical investigators and their peers in basic science and bioinformatics are mutually empowered through translational partnerships, which is critical for success in the new era of human genetics heralded by “next-generation” methodologies.

The assembly of a Europe-wide cohort of GnRH-deficient patients will be achieved through participation of their respective physicians in the network; through referral of patients to network members by other physicians; or through patient self-referral facilitated by the patient-oriented section of the Action's website (see Dissemination);

The most important research tasks to be coordinated by the Action are:

- The detailed characterisation and recording of each patient's phenotype, termed "phenotyping", which will be performed in a comprehensive and systematic manner across participating physicians and patients;
- The expert treatment of GnRH deficiency in new patients, to assess response to treatment as part of the disease phenotype;
- The elucidation of each patient's genotype for all known GnRH deficiency genes ("genotyping"). This will be done either through conventional Sanger-based sequencing or through novel technologies such as development of a gene-chip or other parallel mutation detection technology;
- The discovery of novel genes for GnRH deficiency using advanced genetic research methodologies such as comparative Genome Hybridization (cGH) array, autozygosity mapping, and whole-exome sequencing;
- The study of the functional roles of the new disease genes in animal models (such as mouse knockouts) and cellular systems, to characterize the respective signaling pathways and to document the deleterious nature of the identified disease-associated mutations;
- The further investigation of the emerging genetic and signaling networks in GnRH deficiency, using both hypothesis-based as well as assumption-free high-throughput methodologies such as gene expression profiling, protein interaction networks, and in silico analyses, to identify potential new candidate disease genes for validation by sequencing in patients, and to fully elucidate the neuroendocrine networks controlling reproduction;
- The systematic linkage of each patient's phenotype with the underlying genotype, termed "genotype-phenotype correlation", so that patterns will emerge within individual families as well as across the patient cohort;

- The delineation of the inheritance pattern of the disease phenotype associated with mutations in the various underlying genes;
- The assessment of the frequency and extent of additive/synergistic contributions of multiple mutations in different genes to the disease phenotype in each patient (termed “oligogenicity”);
- The development of guidelines for genetic counseling of patients and their families based on the patterns and strengths of genotype-phenotype correlations, and their clinical validation on a pilot basis.

The Action will not only be open to scientists/physicians wishing to join it after the Action’s initiation, but it will actively try to attract new participants by raising awareness of its existence, goals, and activities via relevant announcements and open invitations through national and European medical and scientific societies to their members. These will include the European Society of Endocrinology, European Society for Paediatric Endocrinology, European Society of Human Genetics, European Society of Human Reproduction and Embryology, Federation of European Neuroscience Societies, and other related fora, with participation and dedicated sessions at the societies’ annual scientific meetings.

Technologies for genetic research, pathway analysis, and systems biology are rapidly developing, and unforeseen scientific ideas and research opportunities can emerge, especially as new participants with diverse areas of expertise and research capabilities join the network. For these reasons, the framework of the Action will be deliberately open and flexible to incorporate additional disciplinary perspectives and research tasks during the implementation phase. Such an example might include the discovery of a novel disease gene that may have translational implications for development of a “biologic” (e.g., a corresponding recombinant protein for the treatment of infertility or as a contraceptive).

D.2 Scientific work plan methods and means

The human means required to achieve the Action's objectives include:

- Clinicians catering to patients with GnRH deficiency from the majority of European countries to assemble the largest possible and most diverse patient cohort;
- GnRH-deficient patients willing to participate actively and to enroll their family members to power the genetic studies;
- Geneticists with expertise on and access to both standard and cutting-edge genotyping methodologies such as autozygosity mapping and next-generation sequencing to fully sequence known disease genes and to identify novel ones;
- Basic scientists using cellular systems, animal models, and in silico methods to characterize the functional roles of novel disease genes and to unravel the biology of gene networks underlying the neuroendocrine control of reproduction. Use existing and newly developed knockout mouse models and other systems to establish the functional relevance of newly discovered genes as the cause and pathogenic mechanism of GnRH deficiency;
- Genetic counselors to take the lead in establishing guidelines for the counseling of GnRH-deficient patients and their families and to oversee their clinical application;
- Information technology experts to establish, curate, and administer the cohort-associated database;
- Technology transfer specialists to assess the potential of the Action's scientific discoveries for commercial exploitation and to manage procedures for patent protection, licensing, and partnering with industry where indicated;
- Industry (pharma/biotech) leaders to collaborate in translating the Action's deliverables into novel diagnostics and therapeutics for reproductive medicine.

The technical means required to achieve the Action's objectives fall into three broad categories:

- Information technology infrastructure to create a web-accessible disease-focused database and associated website; to facilitate communication and sharing of information among all Action participants; and to allocate space and provide online collaboration tools for the management of each of the various research projects that will be particular to select participants;

- Shared instruments to facilitate consistent and comprehensive phenotyping of patients, including questionnaires for patients translated in the respective European languages, structured history and clinical examination forms, standard imaging and laboratory examination panels, and universally accepted diagnosis criteria;
- Genetic research platforms made accessible to Action participants for patient genotyping and novel gene discovery, including Sanger-based and next-generation sequencing, comparative Genome Hybridization (cGH) arrays for detection of copy number variation, and high-density SNP arrays for autozygosity mapping.

Major parts of the overall work plan will be to establish the Action's website and investigator training program. In general terms the website will include: (i) investigator information, (ii) shared data sets, (iii) patient outreach, (iv) guidance documents, and (v) online collaboration and research management tools. The investigator training program will facilitate short term exchanges and a summer school to train the next generation of investigators in this area. These plans and the other research tasks listed in D.1 will be undertaken by four interdependent and collaborative Working Groups (WGs). The objectives for each are listed below.

Clinical Group - WG 1

- Identify phenotype ontologies and establish consensus on phenotypic characteristics for database entry.
- Create and publish clinical guidelines for clinicians to access on the website on the evaluation and treatment of GnRH deficiency.
- Compile list of specialized referral centers and contacts for website and enhance outreach to other clinicians.
- Enroll patients and appropriate control subjects, and document their phenotypes in a comprehensive and consistent manner.
- Establish and curate a web-accessible database of the de-identified clinical and genetic information on the cohort.
- Develop patient-oriented education/advocacy materials for the website.

- Establish guidelines for genetic counseling once the genetic architecture of the disease has been sufficiently elucidated.
- Correlate the patients' phenotypes with the results of the genetic analyses (together with WG2 members).

Genetics & Bioinformatics Group – WG 2

- Provide expertise for new genetic technologies including whole-exome sequencing and detection of copy number variation.
- Facilitate access of network investigators to advanced genetic research platforms.
- Enable researchers to partner at will to jointly investigate select families with unique phenotypic features and/or larger patient cohorts.
- Identify the gene(s) mutated in each patient and contribute this information to the database.
- Characterise the spectrum of mutations in each gene across the entire patient cohort.
- Elucidate the genotype-phenotype correlations (together with WG1 members).
- Establish guidelines for sharing negative results on the website, to prevent duplication of efforts and facilitate optimal use of investigators' resources.

Basic Research Group – WG 3

- Help prioritize candidate genes among the list of likely candidates identified through whole-exome sequencing based on expression studies, cellular studies, in silico analyses (WG2) etc.
- Identify biologically plausible candidate genes for GnRH deficiency through studies in model systems which will then be tested for mutations in the patients' DNA samples (by WG2).
- Characterise in appropriate assays the roles of novel disease genes in the neuroendocrine control of reproduction identified through human genetic investigations, thus providing both validation and mechanistic insight.

Education and Training – WG 4

- Plan training program for Training School.
- Identify appropriate faculty.

- Organise and coordinate the training program.
- Perform evaluation and elicit feedback on the training program.
- Facilitate Short Term Scientific Missions.
- Coordinate annual meeting.

E. ORGANISATION

E.1 Coordination and organisation

The Action aims to facilitate collaboration across member states by creating infrastructure that will enhance multidisciplinary research approaches and accelerate the pace of scientific discovery in the field of GnRH-related disorders and reproductive medicine. In terms of organization, the Action includes: (i) Steering Committee, (ii) Management Committee, (iii) 4 Working Groups.

Steering Committee (SC). The SC will consist of the Working Group leaders, Chair and the Vice-Chair. The SC will meet biannually to assess progress in relation to the overall scientific milieu of the field and will refine specific objectives and approaches as needed.

Management Committee (MC). The MC under a leadership of a Chair will have the overall responsibility for coordinating and achieving the Action's objectives including the creation and maintenance of a web-accessible platform for translational research on reproduction, training programs, and an annual meeting bringing together the Action participants. The web-accessible platform will be used to capture and share both systematic phenotyping studies and basic science results to facilitate collaboration and rapid response to calls for applications with the broad goals of obtaining additional funding, fostering multidisciplinary collaborations, and accelerating the pace of elucidation of the neuroendocrine control of reproduction. As such, the MC will oversee the overall process and monitor progress in achieving milestones, as well as prepare and submit the Action progress reports. The Chair will manage overall implementation of the Action interdisciplinary research projects and international collaborations as well as coordinate the WG efforts and track metrics in reaching milestones and achieving objectives. The Chair will provide a link between the WG and MC to ensure regular communication and updates on progress.

Working Groups (WG). The Action participants fall into 3 broad areas of expertise: clinical, translational, and basic research. The 4 planned WGs will be formed by drawing from the pools of individuals within the core areas of expertise: Clinical Group (WG 1), Genetics/Bioinformatic Group (WG 2), Basic Research Group (WG 3), and Education & Training (WG 4). Defining the objectives of each of the working groups and allowing individual investigators to self-select groups will ensure that the WG have focused and motivated compositions. The WGs will not be isolated silos of expertise. Rather, a major strength of the Action will be the connectivity between these WG both in the scientific collaborations stemming from the Action and in the collaborative work between WGs to achieve Action objectives.

Milestones will be incremental, specific to each of the WGs, and will contribute to the envisioned web-based platform for disseminating information and facilitating collaborations and new investigative opportunities. As such, important initial milestones include:

Clinical Group (WG 1):

- Harmonise phenotypic definition and structured data collection for sharing on web-based platform;
- Create clinical evaluation guidelines for diagnosis, prognosis, and treatment of GnRH deficient patients;
- Publish these guidelines on the website along with a listing of specialized clinical & research referral centers;
- Prepare patient-focused educational/advocacy materials and publish them on the website;

Genetics & Bioinformatics Group (WG 2):

- Provide annual update on technological advances in the field and in human genetics in general;
- Identify the first novel gene for GnRH deficiency through whole-exome sequencing;
- Identify the first novel gene for GnRH deficiency through analysis of copy number variation;
- Identify a novel gene for GnRH deficiency through autozygosity mapping in a consanguineous family;

- Establish an in silico protein interaction network relevant to the neuroendocrine control of reproduction;
- Reach consensus and develop rules for sharing negative genetic results via the Action website, and populate the database with negative genetic results where available;
- Oversee the ethical conduct of genetic research, including appropriate handling of genetic information uncovered as part of whole-exome sequencing in genes unrelated to GnRH deficiency that might be clinically important for patients (such as sudden death genes) according to internationally accepted practices as they develop;
- Develop guidelines for genetic counseling to be disseminated via the Action’s website.

Basic Research Group (WG 3):

- Generate a list of available tools/model organism to validate human findings;
- Validate a novel disease gene identified through a next-generation methodology;
- Identify a candidate gene for GnRH deficiency that is subsequently validated in human genetic studies;
- Validate a prediction of the in silico protein interaction network (WG2) to elucidate a novel mechanism/pathway in the neuroendocrine control of reproduction.

Education & Training (WG 4):

- Assemble and post investigator profiles ;
- Assemble faculty and students, and conduct the first summer school for young investigators;
- Organise Short-Term Scientific Missions (STSMs) as part of a defined research project focused on novel gene discovery through application of whole-exome sequencing to a select family with GnRH deficiency identified through the database (with WG2);
- Establish contact and interact with organizations that specialize in organizing thematically focused scientific conferences, such as “Keystone Symposia” and “Gordon Research Conferences”, to promote hosting an international biannual conference on “the neuroendocrine control of reproduction” to further facilitate showcasing of the Action’s achievements, exchanging scientific information, attracting young investigators through travel grants, and networking with the international research community on the field.

A major milestone for the Action will be the website going live including shared phenotyping and genotyping results. An additional major milestone will be achieved when the first grant is awarded to a collaborative project stemming from this Action. Inclusion of research into the neuroendocrine mechanisms of human reproduction into Framework Programme funding priorities will signify achievement of the ultimate milestone of the Action.

E.2 Working Groups

To achieve the Action's objectives, 4 interrelated and complementary WGs will be formed. Each WG will capitalize on the expertise of its members and leverage the expertise of collaborating WGs to achieve its respective goals (as listed in D.2).

WG1 – Clinical Group: physicians, epidemiologists, and clinical investigators

WG2 – Genetics & Bioinformatics Group: geneticists and bioinformatics specialists

WG3 – Basic Research Group: biologists and physician-scientists

WG4 – Education and Training: clinicians, epidemiologists, geneticists, biologists, and physician-scientists

A joint annual meeting of the network's Working Groups will be a major instrument for assessing and coordinating the network's activities and strengthening its collaborative nature. This will be preceded by a summer school for junior scientists (in years 2, 3, 4) working on or interested in reproductive biology, with the goal of fostering a lasting tradition of European excellence in this area.

E.3 Liaison and interaction with other research programmes

In the final year, the Action will hold the annual meeting as part of a conference on the neuroendocrine control of reproduction to demonstrate the Action's achievements and the potential for translational applications in this area. Invitations will be extended to European scientific leaders and top Framework Program scientific administrators to emphasize and underscore the importance of this area and lobby for inclusion in Framework Programme funding priorities.

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

This COST Action will respect an appropriate gender balance in all its activities and the Management Committee will place this as a standard item on all its MC agendas. The Action will also be committed to considerably involve early-stage researchers. This item will also be placed as a standard item on all MC agendas. The Action proposer is female and as such, working to achieve gender balance is an important issue. This action aims to conduct short term scientific exchanges and a summer school to engage early stage investigators and develop the next generation of researchers to help create a lasting tradition of European excellence in the field. As such, both the summer school and the short term exchanges (mentored by female members of the Action) represent important means to attract and retain female investigators and develop gender balance.

F. TIMETABLE

	YR1	YR2	YR3	YR4
<hr/> <i>WEBSITE: public</i> <hr/>				
list of referral centers & patient information (WG1)	X	X	X	X
clinical & genetic counseling guidelines (WG1,2)		X	X	X
<hr/> <i>WEBSITE: members</i> <hr/>				
investigator profiles (WG4)	X	X	X	X
phenotype & genotype database (WG1-3)		X	X	X
<hr/> <i>TRAINING & EDUCATION</i> <hr/>				
annual meeting (WG4)	X	X	X	X
summer school (WG4)		X	X	X
<hr/> <i>RESEARCH MILESTONES</i> <hr/>				
novel gene discovery & validation (WG2-4)	X	X	X	X
in silico protein interaction network (WG2-4)		X	X	X
collaborative grant applications (WG1-4)			X	X
Action collaboration grant funded				X

G. ECONOMIC DIMENSION

The following COST countries have actively participated in the preparation of the Action or otherwise indicated their interest: BE, CH, CY, DE, DK, EL, ES, FI, FR, IE, IT, PL, PT, RS, SI, TR, UK. On the basis of national estimates, the economic dimension of the activities to be carried out under the Action has been estimated at 68 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 be relevant for a broad range of audiences including patients, clinicians, genetic counselors, scientists, and industry (pharma/biotech). Because these diverse groups span a broad range of interests, the plan for disseminating information is audience-specific and will be channeled through 3 avenues: (i) scientific publications, (ii) the Action's website, and (iii) the annual meeting.

H.2 What?

Patients - The website (its public areas) is the medium which will afford the Action the potential to reach the most individuals and the broadest patient audience. Outreach to patients will be a focus of WG1, taking the form of four main efforts:

- Posting expert, peer-reviewed, patient-centered education and advocacy materials on the Action website. This “guidebook” and web-based materials will be provided in plain language and in a user-friendly manner to educate patients and their families;
- Listings of specialised centers and expert clinicians in each European country to help guide patients seeking consultation;
- Opportunities to enroll in current and planned clinical trials on GnRH deficiency, to benefit from novel treatments as well as to contribute to further investigation of the disease;
- Provision of relevant links to other rare disease websites and support groups.

Clinicians - In addition to informal person-to-person contact across the medical community, publications and the website will be used to reach clinicians:

- Review and original peer-reviewed articles authored by COST participants will be central to disseminating findings to clinicians, and recent publications will be highlighted in monthly website updates;
- Using the website to reaching clinicians to expand the network of providers will be an objective of WG1;
- The Action will post “Clinical Evaluation and Management Guidelines” representing the gold standard for evaluation to assist clinicians in correctly diagnosing patients with GnRH deficiency, conducting comprehensive and thorough evaluations, and providing evidence-based treatment, including pubertal maturation and fertility.

Genetic Counselors - The website will be the primary venue for reaching this audience:

- WG1 and WG2 will work to identify genotype-phenotype correlations, and as the genetic architecture of GnRH deficiency is elucidated, genetic counseling recommendations/guidelines will be posted on the website;
- Recognising the value of interdisciplinary care for GnRH-deficient patients, genetic counseling professionals will also be included in the annual meeting (WG4).

Scientists - Disseminating information to the scientific community will include the shared information available to COST participants on the password-protected area of the Action website as well as to the broader scientific public. This will be achieved in a following way:

- For COST participants the shared phenotype database, genotype information, expression and cellular studies, and shared negative results (WG1, WG2, WG3) will be available via password on the Action website;
- The scientific publications (both review and original peer-reviewed articles) will inform the broader scientific community. Further, recent publications will be highlighted on the Action website;

- The Short-Term Scientific Missions and Training Schools (WG4) will be an important venue for disseminating information to develop young investigators and share investigative approaches among COST members;
- The Action website will provide investigator profiles to enable new collaborations to be developed across Europe;
- Select forerunners in GnRH deficiency research from outside Europe (elite team leaders from the U.S.A and South America), as well as group leaders from India, China, Singapore and other emerging research hubs will be invited to participate in the annual meeting, to facilitate global exchange of ideas and world-wide dissemination through formation of a global scientific network for this rare disease.

Industry (pharma and biotech) - The Action anticipates bi-directional exchange of information with industry partners, in part facilitated by the website and the annual meeting. Specific plans for productive dissemination to industry include:

- Recruitment of additional industry participants through direct reach to major pharmaceutical companies during the Action's launch;
- Invitation of key industry leaders in the field of reproductive medicine to participate in the annual meeting;
- Collaboration with participants from industry to assess patentable discoveries and to foster commercial exploitation.

H.3 How?

The plans for dissemination are targeted to reach specified audiences, are linked to an achievement timeline (Table, part F), and represent important Action milestones. As such, the Steering Committee and Management Committee will track these metrics and will update and revise the dissemination plans as needed.