Brussels, 13 November 2018

COST 097/18

DECISION

Subject: **Memorandum of Understanding for the implementation of the COST Action "Aniridia: networking to address an unmet medical, scientific, and societal challenge" (ANIRIDIA-NET) CA18116**

The COST Member Countries and/or the COST Cooperating State will find attached the Memorandum of Understanding for the COST Action Aniridia: networking to address an unmet medical, scientific, and societal challenge approved by the Committee of Senior Officials through written procedure on 13 November 2018.

MEMORANDUM OF UNDERSTANDING

For the implementation of a COST Action designated as

COST Action CA18116
ANIRIDIA: NETWORKING TO ADDRESS AN UNMET MEDICAL, SCIENTIFIC, AND SOCIETAL CHALLENGE (ANIRIDIA-NET)

The COST Member Countries and/or the COST Cooperating State, accepting the present Memorandum of Understanding (MoU) wish to undertake joint activities of mutual interest and declare their common intention to participate in the COST Action (the Action), referred to above and described in the Technical Annex of this MoU.

The Action will be carried out in accordance with the set of COST Implementation Rules approved by the Committee of Senior Officials (CSO), or any new document amending or replacing them:

a. "Rules for Participation in and Implementation of COST Activities" (COST 132/14 REV2);
b. "COST Action Proposal Submission, Evaluation, Selection and Approval" (COST 133/14 REV);
c. "COST Action Management, Monitoring and Final Assessment" (COST 134/14 REV2);
d. "COST International Cooperation and Specific Organisations Participation" (COST 135/14 REV).

The main aim and objective of the Action is to mobilize and characterize aniridia groups across Europe, share new scientific knowledge, technologies and platforms existing in different centres, and evaluate the applicability and translatability of new approaches for treating individuals with aniridia. This will be achieved through the specific objectives detailed in the Technical Annex.

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 96 million in 2018.

The MoU will enter into force once at least seven (7) COST Member Countries and/or COST Cooperating State have accepted it, and the corresponding Management Committee Members have been appointed, as described in the CSO Decision COST 134/14 REV2.

The COST Action will start from the date of the first Management Committee meeting and shall be implemented for a period of four (4) years, unless an extension is approved by the CSO following the procedure described in the CSO Decision COST 134/14 REV2.

OVERVIEW

Summary

Aniridia is a devastating ocular disease requiring intensive eye care, social and community support from birth and throughout an individual's lifetime. A congenital genetic mutation causes an underdeveloped retina, cataract, glaucoma, and a progressive ocular surface disease of stem cell deficiency and loss of corneal transparency. Classified as a rare disease (ORPHA:77), aniridia is extremely challenging for the ophthalmologist, with very few effective treatments available. This stems from a lack of adequate-sized patient populations to conduct coordinated clinical and research activities, and a lack of information exchange in assessing and treating aniridia, with expertise typically limited to geographically-dispersed centers. The goals of ANIRIDIA-NET are therefore to:

1. Build a large, inclusive EU network of ophthalmologists, scientists, trainees, aniridia patient organizations, industry, and special interest groups to create linkages and a rich training ground for a new generation of trainees;
2. Improve aniridia management through evidence-based research, harmonized clinical protocols, pooling/sharing of samples and models, and consensus activities; and
3. Stimulate development of novel diagnostics and treatments for aniridia based on innovative research in regenerative medicine/stem cells, investigational drugs, gene therapy, tissue engineering, transplantation, etc.

Although a rare disease, aniridia is associated with ocular surface pathology such as dry eye, inflammation, stem cell insufficiency, nerve degeneration, and vascularization - problems common to many ocular surface pathologies collectively affecting large populations. Greater collaboration and sharing of information and resources in the area of aniridia is therefore additionally expected to have significant benefits for the treatment of larger patient populations with ocular surface disease.

Areas of Expertise Relevant for the Action	Keywords
● Clinical medicine: Ophthalmology ● Medical biotechnology: Gene therapy, stem cell therapy, regenerative medicine for medical biotechnology ● Basic medicine: Stem cell biology ● Basic medicine: Sensory systems (e.g. visual system, auditory system)	● aniridia ● ocular surface ● PAX6 ● stem cell ● rare disease

Specific Objectives

To achieve the main objective described in this MoU, the following specific objectives shall be accomplished:

Research Coordination

● To identify needs and develop strategies for medical treatment of Aniridia and particularly AAK, through an inclusive group of stakeholders organized into COST Action Working Groups (WGs), where each WG identifies key needs, research and coordination tasks and objectives, and opportunities for collaboration and exchange to achieve stated tasks.

● To optimize / combine the models (eg., Pax6 knockout/knock-in/ CRISPR in vitro models, Pax6 heterozygous mice and zebrafish, treatment/surgical models) through active collaboration across the network.

● To coordinate and conduct individual and multicentre clinical studies (prospective, retrospective chart reviews, randomized trials) and survey-based research by combining aniridia cohorts, patient samples and biobanking for centralized sample/tissue/genetic analysis via a created network to comprise a Europe-wide platform.

● To develop and publish harmonized statements, guidelines, protocols, and recommendations in

areas relating to aniridia (eg., patient examination and assessment, treatment and follow-up, metaanalysis of outcomes, genetic testing, etc.) through regular meetings and active collaboration across the network. These will be reported primarily through international peer-reviewed publications.
● To translate and apply cutting-edge research in stem cells, regenerative medicine, tissue engineering, new drugs and gene therapy, to common models of aniridia. Proof-of-concept studies can lead to preclinical research and first-in-man trials.

Capacity Building
● To identify scientific centres with core technologies, to combine core technologies and expertise of clinicians, academics, and patient associations to bring together aniridia populations to achieve a critical mass of individuals, accessible to investigators across COST countries, for conducting multicentre clinical research related to aniridia.
● To promote the participation of young investigators, women, and ITCs in Action leadership roles for coordinating research specific to aniridia and the anterior segment by mobilizing patient associations and medical expertise in a manner that would maximize training and exchange opportunities.
● To make available a repository and database for aniridia, that includes pooled patient samples for research (obtained by standardized protocols to be decided), clinical examination data, genetic information, genotype-phenotype data, and patient/family information.
● To access large libraries of synthetic and natural compounds and use high-throughput screening for novel potential molecules/drug candidates capable of stabilizing corneal stem cells and/or preventing their degradation.
● To develop, communicate, and apply new imaging protocols and techniques for detailed characterization of the anterior segment in aniridia, using for example advanced techniques such as optical coherence tomography, meibomography and in vivo confocal microscopy.
● To create a platform for direct dialogue between cross-sectoral groups such as patients, scientists, doctors, trainees, pharmaceutical industry and other stakeholders to exchange knowledge and experiences and promote patient-centred medical care and bench-to-bedside patient-oriented research.

1. S&T EXCELLENCE

1.1. CHALLENGE

1.1.1. DESCRIPTION OF THE CHALLENGE (MAIN AIM)

Congenital aniridia is a pan-ocular disorder of abnormal eye development. The name 'aniridia' stems from the Greek 'an' (without) 'iris', and although a characteristic complete or partial absence of the iris is a hallmark sign of the disease, the entire eye is often affected by a misdirected ocular development. Individuals with aniridia most often have an underdeveloped retina (foveal hypoplasia), glaucoma, cataract, nystagmus, dry eye, and a progressive ocular surface disease (keratopathy) characterized by the loss of corneal epithelial stem cell function that leads to conjunctival overgrowth, vascularization and complete loss of corneal transparency.[1] It is this aniridia-associated keratopathy (AAK), that often leads to severe visual impairment or blindness in persons with aniridia, that can start as early as at birth.

Dominant inheritance of genetic mutations leading to aniridia often results in multiple persons with aniridia across familial generations. In about 70% of cases, aniridia results from mutations in the PAX6 gene. In the remaining 30% of patients, the disease results from chromosomal rearrangements at the 11p13 region where PAX6 lies, involving contiguous genes such as WT1, linked to WAGR syndrome (Wilms tumor, Aniridia, Genitourinary anomalies, and mental Retardation). Molecular genetic diagnosis is critical to distinguish between the isolated and the syndromic form of Aniridia, and may distinguish different phenotypes and severity of aniridia. For persons and families living with aniridia, the condition can be overwhelming, often necessitating eye care, social and community support from birth and throughout the individual's lifetime. The ocular consequences are likewise extremely challenging for the ophthalmologist, with very few effective treatments available today.

Aniridia is a classified as a rare disease (ORPHA:77, OMIM #106210), with a reported prevalence of 1:64,000 to 1:96,000;[2] however, despite its rarity, most ophthalmologists have experience with one or more cases of aniridia in their practice. Early cataract, adolescent-onset glaucoma, and a progressive keratopathy present particularly difficult medical challenges. The best visual acuity, typically 20/100 to 20/200,[3] is often limited by AAK present in up to 90% of cases,[4] having a variable rate of progression.[5] Various treatments for AAK have been applied, ranging from conservative treatment[6] to penetrating corneal transplantation, keratolimbal allografts,[7] limbal and oral mucosal stem cell transplantation,[8] and keratoprostheses.[9] The bilateral and genetic nature of the disease requires allogeneic or non-ocular sources of tissue, resulting in high rates of rejection and transplant failure and requirement of a long course of immunosuppression. Many of today's treatments only provide a temporary restoration of corneal transparency and limited gain in visual acuity before the disease process recurs and blindness returns.[7-9]

At the same time, the recent rapid increase in knowledge of ocular stem cell biology, increasing genetic and phenotypic characterization of aniridia populations, and new regenerative (pharmaco)therapies are all changing our fundamental understanding of the cornea and may hasten the development of improved, innovative, and regenerative treatments for AAK. A concerted effort driven by clinicians, researchers, patient organizations and other key stakeholders is therefore required, in order to take advantage of new scientific developments and apply these to aniridia, an often forgotten disease which due to its rarity, is overshadowed by conditions affecting larger patient populations. Today within the EU, diverse expertise in the basic mechanisms, clinical aspects and societal implications of aniridia exists in many isolated pockets, with a clear gap in communication and information exchange among these centers. Coordination is therefore required to achieve knowledge dissemination, research

synergies, larger cohort sizes, validation of new treatments, and consensus for evidence-based best practices.

This situation necessitates a specific COST Action to create and mobilize a new pan-European network, ANIRIDIA-NET. The main aim of ANIRIDIA-NET is to create linkages to ensure sustainability of cooperation on aniridia-related research, mobilize and characterize aniridia groups across Europe, share new scientific knowledge, technologies and platforms existing in different centres, and to evaluate the applicability and translatability of new approaches for treating individuals with aniridia.

1.1.2. RELEVANCE AND TIMELINESS

Although classified as a rare disease, aniridia and its associated ocular surface consequences such as dry eye, inflammation, stem cell insufficiency, nerve degeneration, and vascularization are conditions relevant to many other pathologies, which collectively affect very large patient populations. Dry eye disease alone affects over 10% of the general population, depending on geographic region.[10] Studies of the ocular surface in aniridia, where the clinical presentation often has a severe form, may reveal underlying pathologic mechanisms applicable to large patient groups, such as in dry eye disease,[11] breakdown of the stem cell niche[5] or loss of Meibomian gland function.[12] Conversely, emerging or newly approved treatments for conditions such as dry eye disease, bilateral stem cell deficiency, neurotrophic keratopathy, and corneal neovascularization could benefit individuals with aniridia, who may not otherwise have access to these new and cutting-edge therapies.

In the past few years alone, the field has rapidly expanded. For example, induced pluripotent stem cells (iPSCs) from an endogenous adult source can be used to produce cornea-like organoids[13,14] from which stem cell sheets[15] for transplantation can be harvested. A number of protocols now exist for differentiation of iPSCs to corneal epithelial (stem) cell lineages,[16-19] making transformation of adult-sourced cells into limbal epithelial stem cells an intriguing possibility in cases of bilateral stem cell deficiency. In addition, isolation of mesenchymal stromal stem cells for optimal wound healing in the cornea[20] is at an early clinical stage, and a cystic fibrosis drug that reverses the aniridia phenotype in postnatal mice in the case of nonsense mutations[21] is in a clinical trial phase. Indeed, fibrosis is a key feature of aniridia-related pathology in the eye, with significant implications for AAK and glaucoma development. Newly approved drugs for ocular use, such as cenegermin for reversing a corneal neurotrophic deficit[22] and aflibercept and aganirsen that target corneal neovascularization[23] may also be of benefit in AAK.[24] Finally, rapid technological improvements and dramatic cost reduction in areas such as genomics, proteomics, and next-generation sequencing can provide better characterization of individuals, families, and cohorts with aniridia, to gain a deeper understanding of the underlying mutations and their clinical consequences. To date, 472 unique gene mutations have been identified in the PAX6 gene,[25] while our knowledge of the implications of the haploinsufficiency is severely limited.

At the same time, a few organizations in Europe are beginning to coordinate activities such as clinical examination of patient groups and organizing scientific symposia and aniridia conferences. In parallel, there has been a recent recognition that attention to individuals with aniridia early in life may present a window of opportunity for therapy or preventive measures at a time when the eye's function is still relatively normal. Combining efforts can lead to screening and development of new therapies that slow or halt the progression of aniridia-related pathology in the anterior part of the eye.

The challenge is therefore to better mobilize and characterize aniridia groups, to explore new scientific knowledge, technologies and platforms existing in different centers, and to evaluate their applicability and translatability for treating individuals with AAK. This challenge entails educating young researchers, clinicians, patients, and interest groups regarding the rapidly changing scientific and clinical developments of relevance to AAK, coordinating patient cohorts across Europe for future multi-center studies, and achieving consensus on the best treatment practices, research directions, models, and protocols to use.

This challenge is particularly relevant today, as detailed knowledge of AAK and experience with advanced therapies and technologies already exists across Europe; however, a common platform for bringing together complementary expertise is lacking. Moreover, medical knowledge and clinical practice regarding aniridia requires updating, dissemination and harmonization across the member states. Due to the complex, sensitive and reactive nature of an aniridia eye, traditional therapies must be applied with caution and can often worsen the prognosis. Practitioner education and exchange of knowledge is therefore paramount. All persons with aniridia should have access to expert knowledge and cutting-edge therapies to improve their quality of life, despite the rarity of their disease and

regardless of country of residence. Moreover, this challenge is timely as the first advanced therapies, stem cell products, regenerative medicine and gene therapy approaches are gaining approval by regulatory bodies for clinical use. These developments could have a major impact in the lives of those living with aniridia, but need to be understood, communicated, properly evaluated and supported by evidence-based research.

1.2. OBJECTIVES

1.2.1. RESEARCH COORDINATION OBJECTIVES

To tackle the challenge of improving our scientific understanding and medical treatments for aniridia and particularly AAK, the following research coordination objectives will be implemented:

1. To identify needs and develop strategies for medical treatment of Aniridia and particularly AAK, through an inclusive network of academics, clinicians, ophthalmic industry, patient organizations, clinical trial support organizations, and other stakeholders organized into distinct COST Action Working Groups (WGs), where each WG identifies key needs, research and coordination tasks and objectives, and opportunities for collaboration and exchange to achieve the stated tasks.

2. To optimize / combine the models (eg., Pax6 knockout/knock-in/ CRISPR in vitro models, Pax6 heterozygous mice and zebrafish, treatment/surgical models) through active collaboration across the network.

3. To coordinate and conduct individual and multicentre clinical studies (prospective, retrospective chart reviews, randomized trials) and survey-based research by combining aniridia cohorts, patient samples and biobanking for centralized sample/tissue/genetic analysis via a created network to comprise a Europe-wide platform.

4. To develop and publish harmonized statements, guidelines, protocols, and recommendations in areas relating to aniridia (eg., patient examination and assessment, treatment and follow-up, meta-analysis of outcomes, genetic testing, etc.) through regular meetings and active collaboration across the network. These will be reported primarily through international peer-reviewed publications.

5. To translate and apply cutting-edge research in stem cells, regenerative medicine, tissue engineering, new drugs and gene therapy, to common models of aniridia. Proof-of-concept studies can lead to preclinical research and first-in-man trials.

1.2.2. CAPACITY-BUILDING OBJECTIVES

Following the research coordination objectives outlined above, ANIRIDIA-NET aims to build the following capacities:

1. To identify scientific centres with core technologies (eg., stem cell manufacture, biomaterials, therapeutics and drug discovery, genomic resources), to combine core technologies and expertise of clinicians, academics, and patient associations to bring together aniridia populations to achieve a critical mass of individuals, accessible to investigators across COST countries, for conducting multicentre clinical research related to aniridia.

2. To promote the participation of young investigators, women, and ITCs in Action leadership roles for coordinating research specific to aniridia and the anterior segment by mobilizing patient associations and medical expertise in a manner that would maximize training and exchange opportunities.

3. To make available a repository and database for aniridia, that includes pooled patient samples for research (obtained by standardized protocols to be decided), clinical examination data, genetic information, genotype-phenotype data, and patient/family information.

4. To access large libraries of synthetic and natural compounds and use high-throughput screening for novel potential molecules/drug candidates capable of stabilizing corneal stem cells and/or preventing their degradation.

5. To develop, communicate, and apply new imaging protocols and techniques for detailed characterization of the anterior segment in aniridia, using for example advanced techniques such as optical coherence tomography, meibomography and in vivo confocal microscopy

6. To create a platform for direct dialogue between cross-sectoral groups such as patients, scientists, doctors, trainees, pharmaceutical industry and other stakeholders to exchange knowledge and experiences and promote patient-centred medical care and bench-to-bedside patient-oriented research

1.3. PROGRESS BEYOND THE STATE-OF-THE-ART AND INNOVATION POTENTIAL

1.3.1. DESCRIPTION OF THE STATE-OF-THE-ART

As aniridia is bilateral and limbal stem cells become progressively dysfunctional with age, autologous limbal stem cell transplantation is not possible. An allogeneic source of limbal stem cells must be used, which often has poor outcome due to immune rejection and failure of the host to support the transplanted stem cell niche postoperatively. Following stem cell transplantation patients experience an initial gain in vision, only to later lose this gain in typically 1 to 2 years.[26] Currently the best long-term survival of cultured allogeneic limbal stem cell transplants was reported to be 3 years in 50% of aniridic eyes, through long-term systemic immunosuppression up to 15 months using for example cyclosporine.[27] Living related stem cell donors have the possibility to yield better long-term outcomes in aniridia, however very little clinical data has been assembled to evaluate this.

Alternative sources of autologous stem cells could be beneficial for avoiding potential risks of systemic immunosuppression. Cultured oral mucosal epithelial transplantation (COMET) has been used to treat patients with aniridia; however, oral mucosal cells do not normally express PAX6, and in a series of aniridia patients receiving COMET[8], vision temporarily improved but gradually deteriorated with loss of corneal transparency after 1 – 2 years. Similar outcomes are observed with keratectomy and amniotic membrane transplantation in aniridia. Keratoprostheses may be useful in the most refractory cases, however, systematic studies and reviews are required to assess the outcomes for aniridia.

A major problem is poor survival and differentiation of stem cells after transplantation. Identification and discovery of novel molecules capable of enriching the stem cell population ex vivo and differentiation of transplanted stem cells in vivo is desired. There is likewise an urgent yet unmet need in searching for factors to preserve and support existing limbal stem cells and their function early in life, during a window before AAK progresses and the stem cell niche breaks down. Thus far no specific drug or effective treatment for AAK is available. Outcomes of existing procedures are extremely poor as treatment does not address the underlying molecular defect or ensure a suitable niche for transplanted stem cells to survive. The non-sense mutation targeting drug Ataluren may be a promising treatment for restoring normal ocular function in aniridia[21], but only targets specific *PAX6* mutations, has not yet been tested clinically, and has not been formulated topically for treatment of AAK.

In basic research, development of new therapeutic tools is hampered by limited primary culture of patient cells and lack of in vitro models of aniridia for drug discovery and screening. Limbal epithelial cells from persons with aniridia have altered differentiation properties, and further studies are required to evaluate the mechanisms of cell differentiation in aniridia.[28] Regarding the lack of autologous therapies, no aniridia-specific iPSC lines have as yet been generated from patient-sourced material, although this technology exists. siRNA knockdown in cells does not adequately model the Pax6 haploinsufficiency, and no CRISPR model has yet been reported. There is a real need for relevant cell models for aniridia, additionally ones using human limbal cells. The state-of-the-art in this area includes Pax6 mutant models (Pax6+/-, conditional knockouts, overexpressing mice, and chimeric models), and other mouse models to test hypotheses about PAX6 function in human anterior segment biology. Corneal wounding assays and transplants are performed in normal and Pax6 mutant mice, in conjunction with direct assays for stem cell activity using thymidine analogue double labelling.

For individuals and families living with aniridia, early signs of multiple organ effects are observed in individuals with aniridia, primarily outside the medical arena. Sporadic reports of non-ocular anomalies in some cases include olfactory and auditory deficits, while many non-published findings of dermatologic, mucous membrane, endocrine and other anomalies exist. The prevalence and extent of these findings is unknown; no literature exists concerning these aspects, while for those living with aniridia the symptoms are real and are often treated as isolated and unrelated conditions. From a clinical

point of view, patients with aniridia require frequent monitoring from early childhood but do not often receive frequent follow-ups. Besides AAK progression, there is a high risk of developing amblyopia, glaucoma and cataract, and while these can lead to blindness, surgical procedures entail a risk of triggering AAK progression or aniridia fibrosis syndrome. Development and dissemination of knowledge and practice is critical, but today is not widespread or harmonious within the medical community. As aniridia has no known cure, it is imperative that multiple areas of need are addressed, to improve quality of life and care for those affected today while researching and developing more effective treatments for the future.

1.3.2. PROGRESS BEYOND THE STATE-OF-THE-ART

Within ANIRIDIA-NET, we propose to mobilize patient associations and advocacy groups to promote a dialogue with medical practitioners and researchers, enabling patient-driven research. One area of potential groundbreaking research is in the emerging concept of aniridia as a syndrome. Systematic questionnaire-based research and retrospective chart reviews will examine the prevalence of non-ocular abnormalities and social issues across large aniridia cohorts. Where relevant, specialists and experts outside the field of ophthalmology (dermatologists, endocrinologists, ENT physicians, dieticians, geneticists and social workers) will be engaged. Another related area of patient experience is of treatment failure. Selective reporting of success or partial success in treatments of aniridia likely mask the true picture of diagnosis, treatments, and failures that are under-reported in this specific population. Clinicians and patients both stand to benefit significantly from sharing experiences and reporting of all outcomes. Research to identify treatment-outcome relationships could feed into the development of best-practice guidelines for AAK management. Additionally, systematic literature reviews and studies will be commissioned to gather the best available evidence for practice and for further research.

As proposed here, centralized management of patient samples and cohorts would provide a significant benefit to researchers within an infrastructure that does not exist today. Clinicians and researchers could gain access to patient samples (epithelial cells, somatic cells, tear film samples, excised tissue, blood) for research studies and clinicians would be able to collaboratively access various patient cohorts for sufficiently powered clinical studies despite the rarity of this disease. Funding will occur through existing researcher funding, charitable organizations and foundations.

To address the lack of long-term effective treatment for AAK, ANIRIDIA-NET will mobilize competencies within the network to investigate a number of clinical and basic research questions. For example, studies are envisioned for investigating efficient donor site selection and limbal culture protocols, different immunosuppression regimens, induction of tolerance, immunogenicity reduction for allogeneic stem cell transplantation (for example by modulating HLA expression), and testing of new protocols for measuring glaucomatous damage by new IOP and OCT imaging modalities. In addition, advanced imaging techniques will be used to investigate loss of stem cell function at a very young age (in vivo confocal microscopy, OCT), monitor inflammation (tear film analysis and imaging), and invasion of the cornea by blood and lymph vessels (using novel high-resolution OCT). Combined aniridia cohorts will enable testing of novel topical pharmacotherapies (such as ataluren, recombinant human nerve growth factor, new anti-angiogenic agents such as aflibercept and aganirsen, anti-inflammatory therapy, autologous serum, MSC exosomes, etc.) as adjuvants to surgical procedures. Moreover, decision making in cases of aniridia can be challenging: in some cases a lamellar or penetrating corneal graft can provide visual improvement for many years, while in others, epithelial healing problems result in graft failure after a few months. Improved and detailed clinical grading and classification of aniridia patients is a major goal for improving the outcome of corneal surgeries, and ANIRIDIA-NET will contribute by developing consensus statements and protocols to be applied in practice. Because of special considerations in infants and children, protocols and guidance statements will be issued separately for children and adults.

At the level of basic research, a unique model of AAK has been developed by genome editing a non-sense mutation found in persons with aniridia. The mutation inserted with CRISPR/cas9 into immortalized human limbal stem cells displays PAX6 haploinsufficiency, altered cell proliferation, migration and adhesion. A tagged form of recombinant PAX6 protein efficiently enters these cells, restores PAX expression and rescues the phenotype *in vitro* (manuscript in revision). These CRISPR/cas9 limbal cells can be amplified and used to screen for PAX6-activating molecules by high-throughput screening (HTS) to identify potential pharmacological molecules (including FDA-approved drugs) among several libraries. Molecules of interest include recombinant PAX6 protein and PAX6-AAV under a PAX6 MiniPromoter allowing restricted expression to PAX6 expressing cells. Selected drugs will be analyzed in vitro for potential rescue of corneal phenotype and in vivo in aniridia models available within the proposed network.

In addition, ANIRIDIA-NET proposes to establish the first aniridia-iPSC lines from aniridia patients to validate selected compounds in a patient genetic/epigenetic context, through a multicenter collaboration. Such cell lines will bring new insights into development of aniridia by examining early commitment. Different iPSC lines from aniridia patients carrying different mutations will serve as "disease on dish" tools to match the genotype of patient cells for studying molecular bases for different mutations, resulting phenotype and susceptibility to therapy. Correlation of PAX6 mRNA and protein level and how this is differentially regulated in patients will also be investigated.

Expertise within ANIRIDIA-NET will be used to develop new mouse models carrying targeted mutations that mimic the spectrum of human point mutations and that may further contribute to genotype-phenotype analysis. New inducible Pax6 mutations can also be developed, that might better model the age-related changes in pax6 mutant corneas. A new *in silico* model will also be made available, for the purposes of recapitulating the pax6-mutant ocular surface to identify cellular parameters of migration and stem cell activity that are abnormal in aniridia. The model is currently built to reflect the mouse cornea, but can be upgraded to create an *in silico* human cornea.

Further expertise and collaborative possibilities within ANIRIDIA-NET go beyond the current state-of-the-art and include: collaboration among centres studying eye embryology to understand pathways and processes leading to misdevelopment, 'biomechanical modulation therapy' where a pathological mechanical environment is pharmacologically restored to re-establish a functioning limbal stem cell niche, an organogenesis approach growing a functional cornea from adult-sourced cells, combination of genotype/phenotype data existing across various centres, use of SD-OCT to predict visual development in patients, making molecular genetic testing widely available to clinics and patients, use of hematic derivatives for ocular surface disease, and focusing experience with existing tissue-engineered products for use in aniridia.

1.3.3. INNOVATION IN TACKLING THE CHALLENGE

ANIRIDIA-NET proposes a number of innovative approaches, applying state-of-the-art and novel concepts to aniridia for the first time. A major pillar is patient-driven research, where individuals, families and aniridia patient associations have for the first time a specific forum to impact clinical practice and research, based on communication of real and pressing needs. Examples of this are the lack of engaging pediatric specialists, referrals for genetic testing and counselling, and an expressed need of aniridia individuals and families to investigate methods that could potentially prevent or delay the development of AAK at an early age/stage. Current treatments are variable and sometimes conflicting, and controlled studies will investigate the most promising treatments, including development of imaging and biomarker-based clinical endpoints. Likewise, streamlined guidelines will be developed for limbal stem cell transplantation (methods, protocols) and postoperative care (immunosuppression, adjuvant therapies) using the best available evidence.

Within ANIRIDIA-NET, novel cellular models are proposed based on CRISPR/cas9 and cellular reprogramming technologies that will expand our knowledge of the disease and enable screening and validation of candidate molecules potentially capable of rescuing the proliferative and differential potential of dysfunctional limbal stem cells, to prolong or prevent loss of their function. High-throughput screening platforms and large libraries of synthetic and natural molecules, as well as cellular and animal models are available within the network to develop this innovative approach. Additional candidate proteins/cytokines will be identified by comparative analysis of tear film fluid in aniridia and healthy patient cohorts to identify key deficiencies. Demonstration that small compounds can counteract PAX6 haplo-insufficiency in patient-specific cellular models and in animals can lead to eventual therapeutic application in an aniridia population. In addition, another approach of reprogramming adult aniridia cells to iPSCs has never before been attempted, but can for the first time be realized with the combined competencies and resources of multiple groups within ANIRIDIA-NET. To determine whether reprogramming and subsequent *in vitro* differentiation to limbal stem cells yields stable and viable cells with normal Pax6 expression, clonogenic potential and normal phenotype is a starting point for understanding the opportunities and limitations of this potential breakthrough approach for treatment of AAK using autologous cells.

The area of "Personalised medicine" based on genotyping of patients is another untapped area of innovation within aniridia care. As treatment outcomes of AAK are quite variable, personalized treatment based on genotyping and mutation analysis that would be set up centrally within the network, could be used to guide treatment for individual patients. For example, when new medications are being developed and approved for clinical use, ANIRIDIA-NET proposes to collaborate to enable the first trials

of these in aniridia cohorts, such as topical anti-scarring and anti-inflammatory agents, new regenerative hematic derivatives, neurotrophic agents, anti-angiogenic compounds, and stem cell maintaining molecules. New surgical techniques to keep the cornea free of blood and lymph vessels will be also translated to clinical use in aniridia. Imaging techniques of advanced OCT imaging modes and angiography will additionally be applied for the first time to better diagnose the cornea and optic nerve head in aniridia, for improving transplantation outcomes and glaucoma management. Genotyping will enhance the customizability of medication, as specific genotypes react differently to different drugs. Much experience exists within the network regarding proof-of-concept, Phase I – III trials, and obtaining marketing authorizations and approvals for innovative medical products incorporating tissue-engineered materials, stem cells, and new pharmacotherapies; these approaches will now be refined/modified for use in aniridia. An established clinical trial support network and translational research platform already existing within ANIRIDIA-NET members will facilitate the translation of new concepts to multicentre translational and clinical studies within the time frame of the action. This infrastructure includes a multidisciplinary eye care team that includes experienced ophthalmologists, optometrists, nurses and medical assistants working within a group of referral hospitals. Additionally, a system is in place among the proposers for handling clinical trial administrative authorizations and regulatory affairs, providing study supplies, advising investigators on protocol design, independent data and safety monitoring, centralised manufacturing supervision, as well as general coordination and daily operational management of the clinical studies for all participating hospitals.

1.4. ADDED VALUE OF NETWORKING

1.4.1. IN RELATION TO THE CHALLENGE

Because aniridia is a rare disease, networking is a requirement to make progress in our understanding and treatment of the disease and of its associated social and practical consequences. Moreover, many disciplines and specialties are required to address the various aspects of aniridia and none of these exist in a single institution or country. Networking is therefore the key for ANIRIDIA-NET.

Interaction amongst researchers with complementary experience in gene manipulation (CRISPR, knockdown, miRNA, transfection, etc.), in vitro cell models, animal models, stem cells (growth, culture, differentiation and transplantation, iPSC, mSC, amniotic membrane, etc.) and groups providing patient-derived samples are all required for the basic science goals of ANIRIDIA-NET. Translational expertise from various ophthalmology clinics will additionally be required as new potential gene-based and cell-based therapies are developed for validation in ocular surface disease, inflammation and corneal transplantation models. The sum of this experience does not exist within a single center or clinic, but is spread over many European institutions and subspecialties. ANIRIDIA-NET will specifically aim to widely distribute knowledge, samples, and models, or foster their uptake through collaborations.

Besides providing a centralized repository of samples for research, the aniridia community will also play an integral role in promoting a dialogue between patients and ophthalmologists, and promoting discussions among medical specialists (dermatology, endocrinology, etc.) as well as social workers, optometrists and other allied health professionals existing within the network. Importantly, networking of patient associations in collaboration with multiple academic hospitals and a clinical trial support system will be instrumental for mobilizing larger numbers of patients to participate in clinical studies and clinical trials, for example for evaluating new protocols, therapies, or the course of the ocular disease. Such networking is not possible on the national level within Europe, as no single country has the available patient populations and centres of expertise.

Collaboration and connections amongst clinicians having aniridia patients in different countries also provides added value, as procedures, protocols, knowledge and standards of care need to be developed that are harmonized across Europe and have appropriate buy-in from many countries. This multinational approach will be the best way to achieve consensus and adopt a high standard of care for the aniridia community. This networking relies on the deep experience of both successes and failures that is present among many of the ANIRIDIA-NET members in their respective countries.

Scientifically, many academic centres have specific expertise in a focused area, for example corneal surgery, animal models, histology, genetics, immunology, developmental biology, etc. Other centres are experts in, for example, a particular clinical imaging method or laboratory protocol. Many ideas for collaborative projects are proposed to bring together key competencies of different centres. ANIRIDIA-NET will capitalize on these complementary areas of expertise through a network of trainees to participate in research exchanges across different centres through workshops, meetings, and STSMs.

This will expose trainees and research groups to a multidisciplinary approach to investigating novel research questions.

1.4.2. IN RELATION TO EXISTING EFFORTS AT EUROPEAN AND/OR INTERNATIONAL LEVEL

ANIRIDIA-NET members are actively involved in EU-funded research projects and networking activities connected to areas of diverse expertise needed for addressing the challenges of aniridia, but none with specific aniridia focus. These linkages will enable merging of knowledge, resources and existing networks from large EU-funded projects and actions to address the specific challenges of ANIRIDIA-NET. In this way, knowledge gained from new, ongoing, and prior EU-funded projects can be further disseminated, re-used, and built upon, but specifically focussing on aniridia. Other activities such as conference symposia and aniridia-themed conferences exist at an international and European level, and ANIRIDIA-NET will leverage these events to further the goals of the various working groups, promote dissemination of action activities, and encourage the participation of young investigators and trainees as well as patient representation.

The proposing network has close cooperation and connections with associations, organizations, and companies within and outside Europe, and close access to experts in other areas of the world. These connections will be used to further the goals of ANIRIDIA-NET and its working groups, and broaden the existing activities, for example to provide more frequent conferences, meetings, and symposia, and to communicate and exchange knowledge and experiences across continental borders.

Many existing networks, projects, and associations are not primarily focused on aniridia, but are generally focused on ophthalmology, rare diseases, retinal (and not corneal) disease, stem cells, etc. ANIRIDIA-NET represents the first network focusing on aniridia, and is a unique network that addresses the disease from scientific, clinical, and social, patient-based points of view. Patient associations exist, but are often disconnected from the medical and scientific communities. ANIRIDIA-NET would strive for re-directing existing experience, expertise and knowledge to addressing common goals.

Rather than developing procedures and infrastructure from scratch, ANIRIDIA-NET proposes to leverage existing models for project internal assessment and dissemination tools, EU regulations, reporting, open data, common database tools, patient registries, etc. already available from different EU framework projects for example within the fields of rare diseases, stem cells, and ophthalmology. This will enable the network to focus resources on addressing the stated challenges with an efficient, streamlined management and information exchange process.

2. IMPACT

2.1. EXPECTED IMPACT

2.1.1. SHORT-TERM AND LONG-TERM SCIENTIFIC, TECHNOLOGICAL, AND/OR SOCIOECONOMIC IMPACTS

Although a rare disease, aniridia affects individuals in every European country. When individuals with aniridia inevitably seek eye care, the condition presents a major challenge for the ophthalmologist, while outside the hospital, families, the social network and wider community at large can benefit from a better understanding of the disease, its consequences and requirements. Because there is no integrated, pan-European network for aniridia today comprising scientists, clinicians and patients, ANIRIDIA-NET will aim to achieve the following impacts:

Expected short-term impacts.

1. A pan-European Aniridia patient registry and clinical research network with a repository of clinical data and patient samples would propel research in aniridia by giving access to samples for research and access to patient cohorts for clinical studies. A key enabler of the network is providing an active training ground for the next generation of scientists and clinicians to address the considerable challenges of treating, and living with aniridia.

2. A centralized, high-throughput molecular genetic diagnostic platform providing quick mutational analysis to obtain fast and unambiguous information to guide treatment decisions, providing a basis for research into genotype-phenotype relationships.

3. Stronger cooperation between experts, researchers, patients and practitioners will result in better and broader dissemination of expert knowledge and improve the standard of care of aniridia through consensus-based and evidence-based activities (eg., standardized patient monitoring/examination and treatment/surgery protocols, guidelines for children, preclinical studies of new treatments, etc.).

4. Bringing patient associations in direct contact with scientists and clinicians, providing up-to-date medical information and research, and promoting patient-centred research activities, eg. investigating the overlooked social aspects of living with aniridia.

5. To support the International Rare Diseases Research Consortium (IRDiRC) objective to increase the number of diagnostic tests for patients suffering from rare diseases and to develop 200 new therapies for rare diseases by 2020.

Expected long-term impacts.

1. A centralized repository of aniridia patient samples to enable better definition of the clinical course of the disease, better understanding of mechanisms leading to aniridia, and personalized medicine approaches based on individual variability according to genotype/phenotype.

2. Through improved medical care and scientific breakthroughs, a better quality of life, stronger social inclusion and a higher socioeconomic capacity of persons affected by aniridia would enable them to better contribute to their communities.

3. Basic research into stem cell biology will form the basis for new treatments (iPSC, MSC, gene therapy) to restore limbal function through the support of existing or transplanted cells, or the use of novel sources of autologous cells suitable for transplantation, with benefits for corneal blindness not restricted to aniridia.

4. Providing a sustainable platform for patient-doctor-scientist dialogue and formation of research constellations that will persist even after the formal conclusion of the COST Action. Such constellations are expected to bring new ideas for large research projects.

Improve the aniridia patient´s quality of life by keeping the native cornea as transparent as long as possible, through novel stem cell, anti-inflammatory, anti-angiogenic and neurotrophic treatments applied at a young age. Prevention or even delay of corneal blindness will give a socioeconomic impact on healthcare costs and improved productivity of persons in society.

2.2. MEASURES TO MAXIMISE IMPACT

2.2.1. PLAN FOR INVOLVING THE MOST RELEVANT STAKEHOLDERS

Of note, the proposing consortium of ANIRIDIA-NET has a number of connections within different stakeholder groups across different sectors that can be leveraged to maximize the impact of the action. Where connections do not already exist with target stakeholders, these will be actively sought by invitation to participate in action activities. Many connections exist within the broad base of proposers, in order to bring these stakeholders into the Action activities. Where appropriate, these stakeholders will be engaged to provide expertise, services, or other inputs to achieve the objectives of the action and maximize its impact:

1. Engaging ophthalmological societies/organisations to facilitate in dissemination of results and adoption of standards, guidelines, and protocols.

2. Connecting the action with the European Reference Network for rare eye diseases to tap into existing knowledge and relevant resources.

3. Invitation of innovative European SMEs and larger companies to join the network, where relevant products include new drugs, new tissue-engineered regenerative products, genetic/diagnostic testing, etc.

4. Clinical trial support centers for planning, obtaining ethical/regulatory approval and implementation of national or multicentre European clinical studies with aniridia cohorts

5. Through aniridia patient associations, reach out to patients, families and caregivers to increase awareness and participation in ANIRIDIA-net

6. Through an academic and clinical network, identify young investigators and trainees at various career stages and promote their participation in activities such as STSMs, workshops and meetings

7. Competent authorities and notified bodies within the different member countries will be engaged when applying for clinical investigations of new products and proof-of-principle/safety studies in human subjects

Allied professionals relevant to aniridia such as opticians, contact lens fitters and social workers, as well as other medical specialties such as clinical genetics, haematology, paediatrics, etc. will be invited to participate in discussions and in action activities, such as formulation of guidelines and statements, WGs, meetings, symposia, etc.

2.2.2. DISSEMINATION AND/OR EXPLOITATION PLAN

The target audiences for the dissemination of the results of this Action include: i) academic, clinical and industry partners in this COST action; ii) Early Stage Researchers; iii) researchers in academia and industry involved in ophthalmology and tissue engineering as well as basic clinicians, clinical researchers involved in the diagnosis and treatment of visual impairment with a special emphasis on keratopathy in aniridia; iv) Scientific societies and bodies in which the Action members are represented such as the Association for Research in Vision and Ophthalmology (ARVO), European Association for Vision and Eye Research (EVER), European Society of Ophthalmology (SOE), Academia Ophthalmologica Internationalis, International Council of Ophthalmology (ICO); v) The clinical community and key opinion leaders (KOL's) for the clinical adoption of the new findings on aniridia; vi) International and national patient organisations with their respective local annual meetings and bulletins; vii) European and national government policy makers, since new developments in corneal and ocular surface research and treatments will benefit the European population and should ideally be covered by the Health Insurances, and viii) European general public to inform about new developments and create awareness of the impact corneal and ocular surface disease especially in aniridia.

Dissemination methods include the following. The Action website (including logo) is a key tool in disseminating the goals, activities, and outcomes of the Action, and will have specific areas for Action participants, researchers in academia and industry, the general public, and specific information for the large and diverse group of aniridia patients. The area for Action participants will contain information related to Working Group (WG) activities. The area for interested researchers in academia and industry will contain links to peer-reviewed publications related to consensus statements, clinical guidelines, the latest corneal and ocular surface research in aniridia, and electronic newsletters related to the progress of the Action activities. Interested parties can subscribe to the newsletter through the website. The area for the general public will include explanation of the latest research developments, a newsroom, and upcoming events, symposia, and conferences. Links to the website will be found the Action member institutional pages and on websites of different influential scientific societies.

Symposia, workshops and meetings: Action partners will organize a one day clinical/scientific symposium in the first year as well as the last year of the Action, where interesting research goals and results will be presented and discussed. Early stage researchers will be given the opportunity to present verbally and as posters. Action partners will also organize special sessions/workshops at well-attended scientific conferences such as Tissue Engineering and Regenerative Medicine (TERMIS), Clinical Ophthalmology, ARVO, EVER, and the American Academy of Ophthalmology. Additionally, special meetings will be organized with KOLs and national government organizations to inform about the developments of the Action.

Organizationally, a Dissemination Manager will be nominated during the first Management Committee (MC) meeting. The Dissemination Manager will be responsible for the dissemination activities including the Action website, with contributions from MC and Action members. During MC meetings the Dissemination plan and activities will be evaluated and modified as needed. The final report of the MC will contain policy recommendations both on public health issues as on research directions. These recommendations will be disseminated to the relevant policy makers at the national and European levels.

Other dissemination tools to be used include COST Action flyers to be printed and distributed at conferences and meetings, advertisements to be placed at no-cost in ophthalmology journals, trade

magazines and websites/bulletin boards, all linking to the Action website. Social media such as LinkedIn, ResearchGate, Mendeley, etc., will also be used to disseminate information and results to professional and scientific communities. All publications will be open access to facilitate wide dissemination.

Involving patient associations, patients, and families with aniridia will facilitate dissemination and exploitation as these represent a relatively large number of strongly motivated individuals. For example, actions taken by associations have led to development of national protocols and clinical guidelines. Many persons with aniridia and their families are highly connected via mobile devices and social networking, and these platforms will be used to disseminate knowledge and to seek active participation in events and research studies. Exploitation activities will extend to companies and SMEs producing innovative products and therapeutics, which can be trialled first in aniridia cohorts, where the potential benefit may be greater than in other diseases. Entering the ophthalmic market and demonstrating efficacy in the cornea may represent further means for expanding the use of existing products and therapies. Of note, several SMEs are represented in the network while many contacts to large companies (eg. pharmaceutical companies) exist.

2.3. POTENTIAL FOR INNOVATION VERSUS RISK LEVEL

2.3.1. POTENTIAL FOR SCIENTIFIC, TECHNOLOGICAL AND/OR SOCIOECONOMIC INNOVATION BREAKTHROUGHS

The current absence of a concerted effort focused on the rare disease of aniridia gives ANIRIDIA-NET a high probability of achieving breakthroughs on scientific, medical, and social levels, even if only some of the action objectives are met. Many of the state-of-the-art technologies and much knowledge concerning aniridia has been developed by ANIRIDIA-NET members, who are now poised to extend results to investigate the next generation of technologies, models, and practices with specific focus on aniridia. This cannot be done, however, in isolation and the action will be critical for bringing together multiple teams and centres of excellence to achieve the action's objectives. Breakthroughs also extend past scientific and medical goals. ANIRIDIA-NET will for the first time establish a forum for much-needed dialogue between patients, families, medical professionals and scientific researchers. The result is expected to create new synergies opening up new areas for research, and providing researchers with a high level of motivation to uncover new knowledge and develop better standards of care.

Scientific and technological breakthroughs are likely to be achieved by applying advanced stem cell techniques and models, drug screening platforms and genetic engineering approaches, for the first time combining these with unique repositories of patient samples and models of aniridia. Much remains unknown about factors regulating stem cells and the limits of programmability of such cells, particularly in aniridia, and therefore the potential for innovation is high. Risk is relatively low, as new knowledge and new directions will be gained regardless of the findings. Related to this technology is the establishment of a centralized repository of patient samples, which in itself represents a breakthrough for this rare disease.

Medical breakthroughs such as improved stem cell transplant survival based on adjuvant therapy, immune suppression/modulation, investigation of stem cell function at an early stage, and new types of transplantation as well as non-transplantation stimulation/maintenance treatment options have a high potential to improve vision outcomes in aniridia patients today. Breakthroughs also extend to consensus statements, harmonized examination/treatment protocols, and systematic studies of effectiveness of various measures. The first studies examining non-ocular syndromic effects in aniridia, as well as the social situation and consequences of living with aniridia based on questionnaire studies, will represent landmarks in the field. Performing such studies gives a large potential benefit for very little risk.

Bringing practitioners and the aniridia community into direct dialog through ANIRIDIA-NET will enable creation of databases, referral resources, potential innovations in disease management, will empower patients and other caregivers, to break through the traditional barriers of doctors, scientists, and society, representing a potential social breakthrough, entailing mutual benefit for a low level of risk.

3. IMPLEMENTATION

3.1. DESCRIPTION OF THE WORK PLAN

3.1.1. DESCRIPTION OF WORKING GROUPS

Working Groups and Deliverables to be finalized at the COST Action MC Meeting in Spring 2019.

WG1: Clinical Guidelines: harmonization/consensus on clinical examinations, treatment guidelines, patient information, clinical endpoints.
Deliverables 1.1 Manuscript of best practice European guidelines for clinical examination and data acquisition in aniridia cohorts (M18), **1.2** Manuscript of state-of-the art treatment guidelines for AAK including a set of agreed upon clinical endpoints for future studies (M36), **1.3** Draft harmonized patient brochure/information (M32).

WG2: Clinical and Cohort Studies: combining patient cohorts for multi-centre clinical studies, combining tissue/blood/tear samples for biomarker, genetic and high-throughput molecular analysis.
Deliverables 2.1 Plan/protocol for clinical study with multiple aniridia cohorts/centres (eg., new AAK therapies) (M24), **2.2** Common harmonized protocol for centralized biobanking of patient samples (M36).

WG3: Stem cells and Regenerative Medicine: stem cell biology, tissue engineering, gene delivery (eg. viral vectors), gene modification (CRISPR/Cas9 technology) or gene modulation (through miRNA) for treatment of aniridia.
Deliverables 3.1 Report on methods to improve limbal stem cell survival after transplantation (M24), **3.2** Report on progress of gene/stem cell/tissue engineering approaches for PAX6 haploinsufficiency (M42).

WG4: Transplantation, Inflammation and Immunity: evaluation of new/emerging transplantation techniques for AAK, dry eye disease, surgical outcomes, fibrosis, immune response, inflammation, and corneal neovascularization in AAK.
Deliverables 4.1 Manuscript describing success/failures of surgical treatments for AAK across centres (M18), Manuscript describing keratoprosthesis use and outcomes in aniridia (M24), **4.2** Consensus statement of evidence-based approaches to improve/modulate the ocular surface prior to transplantation (M42).

WG5: Aniridia models for collaborative research: (stem) cell-based, small animal, dry eye, transplantation, therapy, imaging in animals, opportunities for collaboration and centralized analysis
Deliverables 5.1 Report on use of models of aniridia-related pathology for testing new therapies or diagnostics (M24).

WG6: Patient-driven research: associations providing input into new research questions and studies, aniridia syndrome, non-ocular complications, survey studies, obtaining patient samples for research
Deliverables 6.1 Prioritized list of research questions with the greatest unmet patient need arising from patient association-Action forum (M24), **6.2** Manuscript of survey-based patient study across Europe (M36)

3.1.2. GANTT DIAGRAM

The given dates for the various tasks, deliverables and milestones (details in section above) are the latest date for completion of the particular activity. Many activities may of course, be completed earlier than the indicated dates and/or in parallel.

Working Group	Year 1				Year 2				Year 3				Year 4			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
1						1.1					1.3	1.2				
2								2.1				2.2				
3								3.1						3.2		
4						4.1		4.2						4.3		
5								5.1								
6								6.1				6.2				

3.1.4. RISK AND CONTINGENCY PLANS

Progress in tasks and objectives will be monitored by the MC and WG Leaders and Co-leaders, to identify risks of not performing the stated tasks and/or not achieving or delay in achieving certain deliverables or milestones. Monitoring will be continuous while reporting of potential risks and implementation of mitigation measures will occur in conjunction with the annual MC/WG meetings and/or

through electronic communication where required. A table of foreseen risks and possible mitigation measures is given below. This list will be updated as required, but at a minimum at each annual MG/WG meeting for the Action.

Actualization of a given risk will trigger the MC, Chair, or Co-chair to evaluate the event and contact appropriate MC and WG Leaders/co-leaders. Potential mitigation measures will be discussed and a course of action will be planned. One advantage of a large consortium is that other individuals with specific competencies can be contacted to aid in mitigation, replacement, or problem-solving, depending upon the nature of the risk.

Risk	**Probability**	**Impact**	**Mitigation Measures**
Lack of resources/funding for the scientific/clinical tasks/studies proposed	Low	Medium	Funding exists at partner sites through existing EU projects, national and other sources. Some new ideas for project proposals will be the basis of new grant applications.
Difficulty in coordination/consensus among large groups with diverse interests/agendas	Medium	Medium	Concrete, achievable tasks with broad consensus will be addressed first. Smaller groups may be necessary where divergence exists. Management tasks and oversight distributed across MC and WGs.
Unavailability of cohorts and/or patient samples	Low	High	Highly motivated patient organizations and associations, strong clinic involvement will ensure participation.
Underperformance of certain members, groups or leaders	Low	Medium	Many different WGs exist, and Leader/Co-leader structure used for redundancy. MC actions will be taken and size of network will ensure willing and able groups.
Delay in performing tasks, achievement of deliverables or milestones	Medium	Medium	Success defined as diverse expertise brought together for a common cause (aniridia), concrete progress towards certain goals regardless of final result/time frame.
Low involvement of early-stage researchers, ITCs and women	Medium	Medium	Oversight by MC, WG Leaders, and STSM Manager to continuously monitor participation and representative division among various groups. Adjustments made to prioritize certain groups where necessary (STSMs, meeting locations, etc.).
Limited involvement of patients and non-medical stakeholders	Low	High	Oversight by Patient Liaison Officer, WGs and Leaders with specific mandates to mobilize these groups. Level of motivation is high, so risk of non-participation is low.
Inadequate dissemination or exploitation of technologies, activities and results for uptake by SMEs	Medium	Medium	Dissemination Manager will oversee communication with SMEs and companies within and outside the network. The MC will assist in recruiting companies and SMEs to join the Action, and to actively participate in WG activities (eg., planning of trials). Strong industry connections exist, and these will be exploited where appropriate. The Dissemination Manager will ideally be from the non-academic sector.

3.2. MANAGEMENT STRUCTURES AND PROCEDURES

The Action will be coordinated and organized by the Management Committee (MC). The MC will operate as specified in "Rules and Procedures for implementing COST Actions". An Action Chair, Vice Chair and 6 WG Leaders and Co-Leaders will be elected at the first MC meeting/Action kickoff meeting. The Action Chair, the Vice Chair and Working Group (WG) Leaders will form a Scientific Steering Board. During the first MC meeting, a Short-Term Scientific Mission (STSM) Manager and a Dissemination Manager will be elected. Responsibilities and tasks of each of the organizing elements are as follows:

The Management Committee (MC) is responsible for the general planning and coordination of the Action. The MC will plan annual MC and WG meetings, often held in conjunction with large conferences. STSMs, the annual Training Schools and other events are planned with the Dissemination Manager.

The Core Group (CG) is composed of Action Chair, Vice Chair, 6 WG Leaders and 6 WG co-leaders, STSM Manager, Dissemination Manager and Patient Liaison Officer. The CG is responsible for the scientific focus of the Action. This includes harmonization of research topics in WGs and communication between WGs. Together with the STSM Manager the technical programmes of the STSMs, symposia, and Training Schools will be developed.

Working Group Leaders will be responsible for organizing and chairing annual WG meetings and semi-annual teleconferences, preparing the agenda of the meetings, recording minutes and action items and with the WG co-Leaders communicate outputs to other WGs and the MC. From prior experience, members join one or several WGs of interest, and communication amongst WG members is best facilitated by e-mail such that one member may stay involved across several themes of interest. WG Leaders and co-Leaders are responsible for obtaining the critical mass of investigators, ensuring activities, deliverables and milestones are achieved on time, or are amended and reported accordingly.

The STSM Manager is responsible for organizing the STSMs but also training meetings/schools, thematic workshops for partners, symposia or conferences. The STSM manager will discuss with and be supported by the MC and the different partners hosting the events. The STSM Manager will also ensure a good balance of trainee activities and exchanges, to ensure maximal reach, ITC participation, and geographic distribution of events. The STSM Manager in consultation with the MC, will ensure ITC target participation including representation across the MC, WG leadership and during WG activities and training schools.

The Dissemination Manager is responsible for dissemination and outreach activities carried out also including the Action website. The website will be organized in such a way that all the members of the Action will be able to post content on the website in order to facilitate the discussion and information exchange and the dissemination of aims, objectives, activities and findings of the Action. The Dissemination Manager is also responsible for producing information materials about the Action and distributing this to the different target audiences. This will include the collection and dissemination of scientific publications, flyers, announcements and promotions of workshops and conferences, etc. Together with the MC, the Dissemination manager will also ensure adequate participation with companies and SMEs within the action, and identification of further industry representatives to contact. Uptake and possible exploitation of the knowledge and technologies developed within ANIRIDIA-NET will be discussed among SME partners, the MC and Dissemination manager at regular MC meetings.

Patient Liaison Officer: a member of the MC will be elected to be the main contact with patient associations and advocacy groups and national patient societies. This will be key for a two-way communication between these groups and the MC, and will also be critical for coordinating patient participation in WG activities.

Gender balance and involvement of early-stage researchers. This COST Action will respect an appropriate gender balance in all its activities and this will be reflected as an item on all MC agendas. The Action will also be committed to considerably involve early-stage researchers, and will also be an agenda item to monitor and follow-up. The MC, WG leaders and co-leaders will be as equally gender and geographically balanced as feasible, with representation proportional to the network, i.e., at least 40% ITC and 40% female involvement across the MC and WGs. Constitution of management bodies, STSMs, training schools, etc., will strive to reflect at minimum the proportion of women and early-stage researchers that exists within the Action. Established female scientists and clinicians have already played a major role in formulating and developing this proposal. Specific opportunities for training for early-stage researchers include annual training schools, workshops of the WGs, STSMs, and

representation as WG Co-Leaders and national representatives in the MC. Support will be given to young investigators to present their own work at international conferences with a high scientific level. Finally, specific information for early-stage researchers on job openings, grants, postdoc and PhD positions will be posted on the Action's website.

3.3. NETWORK AS A WHOLE

The Action will represent a critical mass of expertise and interest, from a wide network of academic and clinical institutions, private sector SMEs, health care organizations, standards organizations, non-profit associations and other relevant bodies with an interest in furthering the knowledge, dissemination, and training in the area of aniridia research and patient care. It is expected that outreach and dissemination activities will continue during the Action and it is foreseen that other countries, institutions, and investigators (in particular early career investigators) will join the Action. The reach of this Action is therefore expected to considerably increase over time.

The network will consist of members from COST countries with high number of ITCs. Active participation from Early Career Investigators and female researchers is expected. The Network will be geographically dispersed and will have broad and deep expertise in the areas of ophthalmology, biology, medicine, biotechnology, tissue engineering, stem cells and regenerative medicine, genetics, materials science, clinical trials, product development, standards and regulations, and patient advocacy. Many of the investigators are world-leading in their fields, including the first to achieve siRNA silencing, gene therapy and CRISPR knockdown in relevant models, first to develop and market new regenerative medicine products for the eye, and many more such pioneers with a long list of achievements. With these areas of complementary expertise being represented, and based on the strong motivation of the network as a whole for tackling this rare and overlooked but devastating disease, the potential for achieving significant progress and breakthroughs for the aniridia community from this Action is high. Knowledge gained and scientific and technological breakthroughs expected to be obtained in this Action will benefit not only the network, but dissemination measures and channels already in place will ensure wider impact across Europe and globally. For example, the ophthalmology community is strongly interconnected globally, through personal networks, associations, conferences and scientific publications. Progress made in aniridia will be rapidly communicated and new knowledge has a high probability of quick adoption; although a rare disease, aniridia is one of the most challenging conditions to manage.

The Action will be comprised of a critical mass of geographically disperse members with experience in running and managing large EU projects and Actions. Moreover, the network will possess vast experience in supervision of trainees as the next generation of scientists and clinicians. Trainees will under ANIRIDIA-NET gain a rich geographically and culturally diverse experience and will be exposed to multi-faceted aspects of aniridia while receiving a solid foundation in scientific, medical, social and cultural aspects. These experiences, combined with a broad set of contacts, deep knowledge of procedures and regulations, management experience and infrastructure will ensure a smooth and efficient implementation of ANIRIDIA-NET.

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