Brussels, 13 April 2018

COST 049/18

DECISION

Subject: **Memorandum of Understanding for the implementation of the COST Action "Integrated European Network on Chronic Graft Versus Host Disease (cGvHD)" (EUROGRAFT) CA17138**

The COST Member Countries and/or the COST Cooperating State will find attached the Memorandum of Understanding for the COST Action Integrated European Network on Chronic Graft Versus Host Disease (cGvHD) approved by the Committee of Senior Officials through written procedure on 13 April 2018.

MEMORANDUM OF UNDERSTANDING

For the implementation of a COST Action designated as

COST Action CA17138
INTEGRATED EUROPEAN NETWORK ON CHRONIC GRAFT VERSUS HOST DISEASE (CGVHD) (EUROGRAFT)

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 To establish a European Network to further understand chronic GvHD, through networking and interdisciplinary training. We will improve knowledge of novel cell-based therapies and biomarkers through integration of clinical and laboratory databases and develop practice guidelines for treatment with the aim of reducing the burden of cGvHD. 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 56 million in 2017.

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

Chronic GvHD (cGvHD) is a multi-organ allo and auto immune disorder and a major cause of non-relapse morbidity and mortality following allogeneic haematopoietic stem cell transplantation. It occurs in an estimated 50% of patients per year worldwide and causes a plethora of co-morbidities. There is a lack of coordination at the European research level into cGVHD diagnosis and therapy and this impacts on patient care, due to a non-uniform treatment approach across transplant centres. This COST Action will serve as a platform for industry, clinical teams and researchers from numerous disciplines, including bioinformatics, immunology, epidemiology, genetics and cell biology, to enable the dissemination of integrated clinical and laboratory information via established and improved databases. The COST Action will promote novel research as well as more uniform treatment of the disease. Innovation will be accelerated by coordination, networking and introduction of new technologies and therapies for the benefit of patients by being able to more accurately predict and treat the disease and its co-morbidities. Early career investigators (ECI's) will learn how genomics, proteomics and immunology interact to provide a more personalised medicine approach to treat disease and improve patient outcomes. By studying large-scale populations and coming together as a network, we will further understand the pathogenesis of cGvHD, its subsets and associated co-morbidities and develop a coordinated approach to therapy. Workshops on innovative multidisciplinary research will include, genetics, epigenetics, (DNA methylation, microRNAs free and in exosomes) proteomics, lipidomics, the role of the microbiome, and novel stem cell therapies.

Areas of Expertise Relevant for the Action	**Keywords**
● Clinical medicine: Transplantation ● Clinical medicine: Hematology	● comorbidity prediction of disease ● chronic graft versus host disease ● haematopoietic stem cell transplantation ● geonomics proteomics immunology ● stem cell therapies

Specific Objectives

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

Research Coordination

● To use current databases with sample collections and linked clinical data(available to all participants) to collect and coordinate the incidence and severity of cGvHD and use epidemiology and data on genetic profiles to more fully understand the potential of the disease

● Instigate co-operation of multidisciplinary research groups in order to collate knowledge on novel potential biomarkers (cellular, proteomic, epigenetic or genomic) for cGvHD and their relevance, if any, to the development of co-morbidities.

● From collation of knowledge analyse current biomarkers and compare with those derived after checkpoint inhibitor blockade therapies

● Disseminate and coordinate stratification tools, based on patterns of disease, for cGvHD based on the current NIH consensus criteria which would aid in the development of clinical trials

● Coordinate research on the impact of cGVHD on quality of life and economics in different European countries

● Link with small/medium sized enterprises (SME's), pharmaceutical industries and cell therapy industries to develop innovative proposals for novel clinical trials.

● Assess clinical information for the development of novel personalised approaches to therapy and thus enable the concepts for the development of innovative clinical trials.

● Actively involve less research intensive European countries e.g. ITC and NNC (see Network

Capacity Building

● Build a substantial, collaborative international network of researchers and Early Career Investigators bringing together multi-disciplinary teams, including haematologists, transplanters, geneticists, molecular biologists, cell biologists, epidemiologists, social and economic experts.

● Create a platform for networking activities (consortium meetings; workshops and a global conference) to integrate Early Career Investigators (ECI) and introduce them to the interdisciplinary and multi-disciplinary skills needed to enhance their careers in medicine and science.

● Expand the network to encourage ECI's from COST member countries, COST Inclusiveness Target Countries and COST Near Neighbour Countries to participate and enable standardised practices and knowledge and increased know-how across Europe by the development of Working Groups, Short-Term Scientific Missions (STSMs), seminars and links with Training Schools.

● Training Schools and workshops will specifically relate to the transfer of knowledge to enable ECI's and clinical teams to apply the new NIH Consensus diagnostic criteria for cGvHD and its relation to biomarker utility. German/ Austrian/ Swiss databases and those outside the EU will be included.

TECHNICAL ANNEX

1. S&T EXCELLENCE

1.1. CHALLENGE

1.1.1. DESCRIPTION OF THE CHALLENGE (MAIN AIM)

Allogeneic haematopoietic stem cell transplantation (allo-HSCT) is the main curative therapy for haematological malignancy and some haematological disorders. The success of the procedure (survival rates have remained at 40-50% for over 2 decades) is hampered by post-transplant complications such as infection and relapse of disease. In addition, patient reaction to the incoming transplant can manifest itself as life threatening graft versus host disease (GvHD), which arises in both acute and chronic forms. It occurs in 40-60% of transplant patients and predicting and preventing GvHD would allow clinicians to tailor therapy to an individual patient, encourage a curative graft versus leukaemia response and improve outcomes, including transplant survival rates and long term complications. Most research into GvHD has concentrated on the acute form while the more complex and multifaceted chronic form has been largely poorly investigated and is therefore the focus of this current Action. This Action will for the first time bring together Chronic GvHD (cGvHD) researchers and through a coordinated effort across Europe to develop a new understanding of the chronic form of GvHD. Chronic GvHD is a multi-organ allo- and autoimmune disorder and is the major cause of non-relapse morbidity and mortality following alloHSCT. It occurs in about 50% of patients, or 13-15,000 patients per year worldwide (6-7000 per year in Europe) and is on the increase (1). This causes long term economic and social costs, including people unable to work. The disease causes a plethora of co-morbidities including cardiovascular, gastrointestinal, liver, pulmonary, endocrine (diabetes, hyperlipidaemia, thyroid and adrenal insufficiency, hypogonadism), neuropsychiatric (e.g. depression, chronic neurologic diseases), bone and joint (osteoarthritis, osteoporosis) disorders, infections (bacterial, viral and fungal), and other more specific co-morbidities (solid malignancy, obesity and infertility (2, 3). Chronic GvHD equally affects both men and women, although it is more frequent in male patients transplanted with hematopoietic stem cells from female donors. The most affected organs in cGvHD are skin (77%), lung (50%), mouth (63%), liver (58%), eye (54%), joints (32%), gastrointestinal (20%) and genital tract (16%).To date, cGvHD is well characterised by established and clinically validated cGvHD grading scales and measurements of the National Institute of Health (NIH) Consensus classification (4,5,6). However, there is a lack of understanding of the immunobiology and metabolic triggers that cause the development and further perpetuation of cGvHD and subsequent co-morbidity.
This innovative multiomics and multidisciplinary COST Action brings together a collation of European expertise in research in epidemiology, genetics, immunogenetics, epigenetics, proteomics, lipidomics, the role of the microbiome and novel cell based therapies (7,8,9) (Advanced Therapy Medical Products (ATMP's) which are all associated with inflammation and the immune response.
Treating cGvHD with novel ATMP's and immunotherapies, requires multidisciplinary expertise and the outcomes of this therapy has not yet been documented. This Action will document the effectiveness of these new therapies on the disease and prepare standards and follow up guidelines for use in current practice.

There is a lack of coordination at the European research level into cGVHD. This manifests itself and impacts on patient care by lack of coordination and understanding of the cGvHD NIH consensus grading scales and ultimately the burden of disease on European health. This results in non-uniform treatment across transplant centres meaning that not all patients in Europe will obtain the best standards of care.

In addition, there is a lack of knowledge in cell-based therapies, especially Advanced Therapy Medicinal products (ATMPs) in the treatment of GvHD. ATMPs are medicinal products based on gene therapy, somatic cell therapy or tissue engineering and are central to the European Commission vision presented in Horizon 2020. They represent a rapidly growing area in translational research and form the 'next generation' of complex medicines for regenerative medicine and non-curable diseases but pose particular challenges to medicinal product regulation. Worldwide there is a great optimism for the use of these individualized medicinal products in order to cure high risk patients. As an example, to date, treatment of leukaemia patients with gene-modified T cells (so called chimeric antigen receptor - T cells (CAR-T cells) led to impressive cure rates, (mainly in USA and China) sponsored by the billion dollar Pharma industry. Notably, Kymriah, which is based on CAR-T cells, received Federal Drug Agency (FDA) approval for the treatment of acute lymphocytic leukaemia (ALL) in young patients on 30th August 2017 and the application for the respective Marketing Authorization from the European Medicines Agency is expected shortly. In the field of GvHD treatment, the interest in the use of various ATMPs, such as regulatory T cells, Mesenchymal Stem Cells (MSC's), tolerance-inducing Natural Killer Cells, is rapidly increasing. Unfortunately, so far Europe lacks similar sponsoring from the Pharma industry and lacks ATMP exchange programs and data bank collection. Success in ATMP therapy has the potential to significantly impact on society. The future availability of ATMPs to European citizens requires partnerships between academic institutes, hospitals, Manufacturing Organisations, Good Manufacturing Practise (GMP) facilities and industrial stakeholders. Some ATMPs will be developed and attain Marketing Authorisation, whilst others will be manufactured centrally but will still require near-patient end-stage processing.

Although Regulation (EC) 1394/2007 on ATMPs was intended to ensure free movement within the Europe while guaranteeing the highest level of health protection for patients, a significant level of heterogeneity in the regulatory practice across member states has been identified, leading to misunderstandings and creating obstacles to the development and delivery of these medicinal products. Based on previous research on this topic, it has become clear that technology transfer as well as the dissemination of knowledge of EU regulations is critical to the innovative development of ATMPs in Europe. The establishment of a European ATMP network in GvHD treatment sharing knowledge and providing training and consultancy regulations, technologies and resources across Europe therefore is of utmost importance.

This Action will enable the further development ATMPs including the integration of clinical and laboratory databases to monitor the use of ATMPs in cGVHD as well as documenting the use of standard diagnostics and response to therapy. This will enable solutions to bottlenecks to progress, via future novel research, as well as more uniform diagnosis and treatment of the disease. By coordination and networking, the Action will also seek funding for future research, which will lead to the introduction of new technologies and therapies for the benefit of patients, accelerating innovation leading to improved survival figures.

One important aim of the Action will be to introduce Early Career Investigators (ECIs) to the complex disease cGvHD and the role of ATMPs in therapy. It will provide the necessary skills, including leadership and networking opportunities, for the ECIs, by introducing them to a wide range of topics and researchers from industry and academia. This interdisciplinary training is novel and the topics covered will include, epidemiology, immunogenetics, genomics, proteomics, lipidomics and immunology and how they can interact to provide innovative ways to improve therapy and diagnostics with a view to a more personalised medicine approach to treat a complex disease. The ECIs will include clinical and non-clinical academics.

The aim of this Action via networking, coordination of technologies and information, is to aid major research objectives enabling a breakthrough in scientific developments leading to new concepts for improving the survival and quality of life of transplant patients. These objectives include novel concepts for improving diagnostics, predicting outcome and response to therapy. Access to large data sets for this relatively rare disorder cGvHD is a core benefit of the Action. By having access to large-scale populations the Action will further understand the pathogenesis of cGvHD and its associated co-morbidities and develop a coordinated approach to therapy, strengthening European research and innovation via collaboration.

Biomarkers and information on genetics, including micro RNA's and epigenetics, will be collected to identify specific candidate genes controlling cGVHD described in the literature and used to aid in distinguishing different subsets of cGvHD and associated immune dysfunctions and comorbidities. Large cohorts are needed to investigate, which immunogenetic makers, such as human leucocyte

antigen (HLA)-DPB1 or HLA class I-related gene A (MICA) should be considered for additional matching in patients who have more than one potential non-related donor matched for HLA-A, -B, -C, -DRB1 and -DQB1 (10/10 loci) to reduce the risk of cGVHD and other adverse outcomes(10,11).The results of the Action analyses will allow for a more individualised approach to therapy to improve patient outcome, including quality of life and economics in the longer term. The Action will compare biomarkers used to monitor cGvHD with those associated with monitoring response to therapy and disseminate the outcome of these results to the clinical community via workshops and a conference organised by the Action. The information gained will also assess whether a novel personalised approach to therapy may improve outcomes for cGVHD patients by improving quality of life and survival. The Action will also analyse and compare the social and economic impact of cGVHD for European society.

1.1.2. RELEVANCE AND TIMELINESS

Until recently, research involving patients with cGvHD has been hampered by the lack of validated clinical scores based on objective measurements that can be uniformly applied by multiple investigators in different institutions to assess disease activity, and its response after treatment. At present, there are contradictory research results regarding the biological basis of cGvHD mainly due to low patient numbers evaluated in single transplant centres or insufficient characterisation of cGvHD and lack of understanding and knowledge of cGvHD's impact on the immune system. A multidisciplinary and increased collaboration across Europe with collaboration worldwide will enable a better understanding of the disease and aid in the development of new therapies and approach to stratification. CGvHD is a multifaceted complex disease, with different disciplines tending not to collaborate and therefore a novel feature of the Action is the multicentre interdisciplinary approach to combat associated co-morbidities, as well as further studies on sub sets of the condition. Knowledge gained will enable diagnostic tests under development to be tailored to a particular patient's disease characteristics and subtype. The collaborators will gather and analyse data on best practice, collate data and assess the use of novel advanced therapy medicinal products (ATMP's) for therapy of cGvHD. Moreover, the increasing number of transplants across Europe means that that there is a timely requirement to study the long term complication of cGvHD in order to avoid ongoing morbidity and costs.

1.2. OBJECTIVES

1.2.1. RESEARCH COORDINATION OBJECTIVES

The aim of EUROGRAFT Action is to aid current national and individual transplant centre initiatives by developing a strategy for their implementation at a European level. The Action will develop a dissemination platform of know-how and knowledge, via workshops, a conference and Short Term Scientific Missions (STSM's) thereby connecting excellent research groups within Europe, who will act on the global initiatives and foster large-scale innovative research, which at the moment is lacking worldwide. In this regard, the Action will include an analysis of the social and economic impact of cGVHD across European society and differences in the medical treatment of cGVHD and consequences for outcomes by assessment of current information and databases and bringing together experts in medicine, epidemiology and economics.

- To use current databases with sample collections and linked clinical data (available to all participants) to collect and coordinate the incidence and severity of cGvHD and use epidemiology and data on genetic profiles to more fully understand the potential of the disease in a haematopoietic stem cell transplant population. This will include the ability to enable future innovative immunogenetic and genome wide association studies (GWAS) and mRNA profiling across cohorts and allow samples for multiomic (e.g. proteomics, lipidomics and genomic) studies
- Instigate co-operation of multidisciplinary research groups in order to collate knowledge on novel potential biomarkers (cellular, proteomic, epigenetic or genomic) for cGvHD and their relevance, if any, to the development of co-morbidities.
- From collation of knowledge analyse current biomarkers and compare with those derived after checkpoint inhibitor blockade therapies.
- Disseminate and coordinate stratification tools, based on patterns of disease, for cGvHD based on the current NIH consensus criteria which would aid in the development of clinical trials.
- Coordinate research on the impact of cGVHD on quality of life and economics in different European countries.
- Link with small/medium sized enterprises (SME's), pharmaceutical industries and cell therapy industries to develop innovative proposals for novel clinical trials.

- Assess clinical information for the development of novel personalised approaches to therapy and thus enable the concepts for the development of innovative clinical trials.
- Actively involve less research intensive European countries e.g. Inclusiveness Target Countries (ITC) and Near Neighbour Countries (NNC) (see Network as a whole).

1.2.2. CAPACITY-BUILDING OBJECTIVES

- Build a substantial, collaborative international network of researchers and Early Career Investigators bringing together multi-disciplinary teams from complementary areas of science and clinical disciplines, including haematologists, transplanters, geneticists, molecular biologists, cell biologists, epidemiologists, social and economic experts.
- Create a platform for networking activities (consortium meetings; workshops and a conference) to integrate Early Career Investigators (ECIs) and introduce them to the interdisciplinary and multi-disciplinary skills needed to enhance their careers in medicine and science. In particular, this Action will organise specific Training Schools on how to apply the NIH consensus, diagnostic criteria and clinical scoring grades
- Expand the network to encourage ECIs from COST Member Countries, COST Inclusiveness Target Countries and COST Near Neighbour Countries to participate and enable standardised practices and knowledge and increased know-how across Europe by the development of Working Groups, Short-Term Scientific Missions (STSMs), seminars and links with Training Schools.
- Training Schools and workshops will specifically relate to the transfer of knowledge to enable ECIs and clinical teams to apply the new NIH Consensus diagnostic criteria for cGvHD and its relation to biomarker utility. Expansion of the Action to include German/ Austrian/ Swiss databases as well as those from outside the Europe e.g. Canada and International Partner Countries (IPC) countries to include both adult and paediatric transplant cohorts.

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

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

Although early transplantation-related mortality after allogeneic haematopoietic stem cell transplantation has decreased through the introduction of reduced-intensity conditioning (RIC) regimens and more effective anti-infectious agents, little progress has been made in reducing late transplantation-related morbidity and thus the quality of life of patients has suffered resulting in death due to cGvHD, infectious complications or organ toxicities. This has been exacerbated mainly due to failure to reduce the incidence and severity of cGvHD. However, recent progress has been made especially with regard to the clinical criteria defining the disease. This was provided by the NIH consensus conferences on cGvHD that were held in 2005 and 2014, which led to a better understanding of the wide spectrum of disease manifestations and a new clinical severity index, as well as development of clinical tools to monitor disease activity and response to therapy (12,13,14,15). High-dose glucoco-steroids with or without administration of calcineurin inhibitors (CNI) have long served as the mainstay of first-line treatment for cGvHD. In most patients, systemic treatment must be continued for at least 2 years. Long-term glucocorticoid therapy causes numerous complications including infections, osteoporosis, glucose intolerance, dyslipidaemia, hypertension and cataracts. Development of less toxic and more effective steroid-sparing treatments would be of enormous benefit for patients with cGvHD resulting in fewer complications related to treatment, and a lower probability of death (16).
Contradictory research results on the biological basis of cGvHD, low patient cohorts in single transplant centre studies, insufficient characterisation of cGvHD and lack of understanding and knowledge of cGvHD's impact on the immune system, all give rise to a lack of clarity on the diagnosis and treatment of cGVHD. This is in part due to a lack of preclinical tools, including information on robust biomarkers and the heterogeneous nature of cGvHD, affecting multiple organs. In addition, the pathophysiological pathways leading to cGvHD and the associated co-morbidities in humans are largely unknown. This lack of progress in research into cGvHD has hampered the development of innovative and efficient therapies to improve patients' survival and quality of life. Of potential relevance to cGvHD is the fact that in recent years, immune check-point inhibitors which restore the immune system in cancer patients and chimeric antigen receptor T (CAR-T) cell therapy which are used to combat certain cancers, are currently being used to treat haematological malignancies. The identification of biomarkers that predict response or severe adverse events are underway and their relevance /importance to cGvHD will be assessed in this Action.

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

The approach within this Action has not been initiated within Europe and enables the research groups to be competitive with but also collaborative with larger transplant centres in the USA. Enhancing our understanding of inflammatory and immunomodulatory mechanisms involved in cGvHD and associated co-morbidities is of utmost importance for the development of innovative targeted treatment strategies allowing improved patients' outcome and reduction of toxicities related to cGvHD and its therapy. In addition to the NIH-defined clinical data and beyond the current state of the art, the Action will collate information currently available in national and international databases, on therapeutic responses and cGvHD associated with individual organs in individual patients. This information will allow a deeper understanding of the disease on an individual patient basis and enable the development of concepts for a more individual and tailored approach to therapy. EUROGRAFT Action will also assimilate new insights into the burden of cGVHD via quality of life and economic assessments. Furthermore, knowledge will be gathered on new and potential biomarkers which will aid in the generation of new research and clinical strategies. The Action will also build up the network so that there is a consensus on best practice for sample collection and data collection for the implementation of future research. One further aim of the Action will be to compare biomarkers associated with novel cellular therapies with those used to monitor cGvHD and disseminate the outcome for use within the clinical community. Moreover, the Action aims to initiate novel European immunogenetic studies on the best strategy to increase the matching of unrelated donors beyond a 10/10 HLA-loci match when more than one potential donor is available. This will be achieved by disseminating the use of an existing database for recording novel cellular therapy information. Working Groups to deliver this progress beyond the state-of-the-art have been developed under Implementation (Section 3).

1.3.3. INNOVATION IN TACKLING THE CHALLENGE

Novel techniques involving multiomics integrated into a well annotated clinical database is unique, novel and goes beyond the state-of-the-art. It requires close interaction between basic researchers, clinicians, epidemiologists, and statisticians. The Action will have a clinical and international dimension and bring together experts to evaluate data sets and compare results such as GWAS and gene expression profiles. EUROGRAFT Action will therefore integrate research knowledge covering various aspects of disturbed immunoregulation and molecular changes (genomics, epigenetics, lipidomics, and microbiome research) associated with inflammation, and generate breakthroughs into new approaches to clinical trial development. The Action is also innovative in that it capitalizes on recent advances in this field by bringing together large-scale well-established study groups prospectively, contributing large numbers of well-characterized patients with information on novel biomarkers and responses to new therapies. Socioeconomic and epidemiological studies will bring an additional innovative aspect to this Action and will allow to compare the quality of outcomes that are obtained in different European countries by variable financial inputs in the health systems.

1.4. ADDED VALUE OF NETWORKING

1.4.1. IN RELATION TO THE CHALLENGE

A multicentre networking approach is vital for this Action on cGvHD which can be classified as a rare disease. No individual transplant centre nor even any particular European country has access to sufficient patient numbers on their own to allow for this type of research. The added value of networking will primarily allow access to and sharing of patient data which can only be achieved via collaboration with many national and international transplant teams. The networking will allow an assessment of the NIH consensus criteria across Europe enabling a way forward for improved treatment options and patient care. The Action will collaborate with stakeholder groups and gather a critical mass of researchers, pooling resources and disseminating knowledge, then jointly coordinating efforts to enhance integration and knowledge transfer. Collaborative networking on cGvHD will be coordinated and each Working Groups led by experts in the field, via the development of interactive training platforms for researchers, clinicians and patient organisations. Scientific disciplines such as epidemiology, biology and economics, will be included in Training Schools and stake holder days such that the full scope of EUROGRAFT is disseminated to all researchers and interested parties. The Action will facilitate communications and the collation of information from databases containing clinical and laboratory information on patients with cGvHD.

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

Several initiatives have been undertaken at the national/European and international level. In 2005, the NIH consensus group on cGvHD published guidelines for diagnosis, staging and response evaluation of cGvHD for use in clinical trials based on expert opinion and retrospective analyses. These were updated in 2014 to provide clarifications and confirmations.
The NIH consensus conferences on cGvHD that were held in 2005 and 2014 led to:-

- a better understanding of the wide spectrum of disease manifestations
- a new clinical severity index to monitor disease progression and response to therapy
- the assessment of new therapies using innovative clinical trial designs

EUROGRAFT Action will address current challenges at European and international level by initiating the following:-

- **Data Gathering**. The NIH consensus criteria on cGvHD requires that an increasing amount of clinical data will need to be analysed, which includes a longitudinal documentation of cGvHD course, permitting the evaluation of different organ involvements, their evolution over time, clinical responses to treatment as well as the evaluation of established and new biomarkers for objective diagnosis and prognosis of cGvHD and associated co-morbidities.
- **Implementation**. During the last few years the German-Austrian-Swiss cGvHD consortium established guidelines for diagnosis and therapy of cGvHD in clinical practice, achieving a consensus among clinicians representing HSCT centres performing 88% of all allo-HSCT in the respective countries. The aim of this Action will be to go beyond these current initiatives by aiding implementation at the European level of a dissemination platform of know-how and knowledge and connect excellent research groups within Europe who will act on these global and European initiatives and foster large-scale research initiatives which at the moment are lacking world–wide. In particular, these clinical initiatives lack connection with basic research, therefore a European harmonised initiative enabling larger population based research will be complementary to the clinical networks and will be highly effective in producing novel ideas for future efficacious clinical trials.
- **Dissemination and Innovation**. Many of the participants within the Action network have previously worked together on developing novel diagnostics and cellular therapies. The network will collate information on cGvHD needed to develop an extension of the current database set up 15 years ago with the fifth Framework funding, for coordinating and collecting information on acute GvHD. In addition, the Action will collaborate with European and worldwide networks of haematopoietic stem cell transplantation, including European Bone Marrow Transplant Group (EBMT) and International Bone Marrow Transplant Registry (IBMTR), as well as the Working Party on Complications and Quality of Life which will assist in the development and dissemination of new research and clinical trial initiation. EUROGRAFT will also collaborate with the Working Party on Cellular Therapy and Immunobiology which is currently actively working towards updating other clinical databases to include outcome of novel cellular therapies, both for the treatment of the malignancy itself (immune check point inhibitors; CAR-T cells) as well as cellular therapies to treat cGvHD (extracorporeal photophoresis, regulatory T cells, MSCs).
- **International Collaboration**. EUROGRAFT will promote and disseminate both the use and the findings of these databases for use to the clinical and scientific community. The Action will also access the American Society of Bone Marrow Transplantation and Bone Marrow Donors Worldwide which have substantial resources with regard to data sets and access to patient and donor registries. The Action will extend collaboration to ITC and NCC countries.

2. IMPACT

2.1. EXPECTED IMPACT

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

Through interdisciplinary collaboration EUROGRAFT will achieve in the short term further clarification of the aetiology, pathogenesis, classification and diagnosis of cGVHD to allow for the development of more effective treatments and preventative strategies based on a personalised and informed approach. In particular, further insight into the co-morbidities associated with the disease will be assessed. The roles of the immune system, the cardiovascular system and pathophysiology will be further defined and analysed via assessment of inflammatory and immunoregulatory biomarker pathways, epigenetics

including DNA methylation, histone modifications, miRNA profiling and novel lipidomics and proteomics information.
Preventing or predicting cGvHD in the longer term will allow more personalised and stratified subgroups based on improved donor selection, disease pattern and approach to therapy, avoiding prolonged and intense immunosuppression, which may in turn exacerbate the co-morbidities associated with the disease including increased infectious complications and relapse of original disease. This would ultimately reduce the health cost to Europe and also bring economic benefits in the form of the development of new approaches to therapy based on predicted personal response to treatment.
Identifying, assessing and coordinating clinical data sets as well as known data on potential biomarkers using immunogenetics, epigenetics, proteomics, genomics, immunology and pathology will aid in the future diagnosis of subgroups of the disease and future research studies. Epidemiology studies will be combined with knowledge of genomics to inform on the impact of the environment on disease occurrence and severity. This information will ultimately inform patients and patient groups on the personalised approach to treating cGvHD.
The Action will develop novel interactive Training Schools, workshops and seminars which will raise the awareness and knowledge of ECIs for clinical, academic and industrial careers in the longer term.

2.2. MEASURES TO MAXIMISE IMPACT

2.2.1. PLAN FOR INVOLVING THE MOST RELEVANT STAKEHOLDERS

This Action will use a number of tools to ensure that the relevant stakeholders, including ECIs, are involved in and can benefit from the Action activities. The Action will establish an international network of stakeholders including clinical practitioners and associations of health care professionals, patient associations, health authorities and the biotech industry. Such stakeholders include:

- Bloodwise (a leukaemia charity which conducts yearly Patient and Clinician days); the Stefan-Morsch Foundation and the Anthony Nolan organisation (who collect and assess patient and donor genetic information) and aim to provide novel immunogenetic information required for selection of more suitable donors.
- Industry e.g. well known biotech companies to assess the analyses for impact on the development of potential new therapies, especially ATMP's and aid in commercialisation of existing intellectual property.
- Interaction with SMEs by inviting them to give workshops and seminars on their latest technological advances within the field.
- Joint research initiatives, in novel biomarker development or therapeutics for example, will be brought to the attention of national and international funding bodies e.g. the Medical Research Council (MRC), the Wellcome Trust and the European Medicines Agency (EMA) as well as officials from Horizon 2020, to encourage support in this area, by inviting representatives. They will be invited to workshops and the conference and will benefit from the international collaboration and dissemination of network knowledge. Stakeholder involvement will be through annual stakeholder days which will include Combined Patient and Clinical Research days developed at several centres across the Action. Such events will foster the interaction between stakeholders and the Action network and allow for dissemination and question and answer sessions, all with the aim of dissemination of Action results and that the information gathered is in line with patient, as well as clinical expectations of improved transplant outcome.
- ECIs will be contacted via current or previous Marie Curie Innovative Training Networks within the partnership, as well as individual institutions, via the website, EBMT meetings and the European School of Haematology.

2.2.2. DISSEMINATION AND/OR EXPLOITATION PLAN

In order to plan for the dissemination and exploitation of the Action, members of the Management Committee (MC) will be assigned tasks which will be reviewed at MC meetings (n=3) and these will include:-

- the establishment of the dissemination and exploitation plan
- the establishment of a web platform with stakeholders, including patient involvement and interaction with ECIs and industry
- research project preparation for Horizon 2020,and global funding instruments

These tasks will be monitored throughout the Action with expected deliverable of joint publications; a website and interactive web platform; a publication and survey of uptake of NIH consensus and a collaborative approach for research on cGvHD. The target audiences for the COST Action include the haematopoietic stem cell transplant research community within Europe and worldwide, including those communities associated with the development of advanced therapy medicinal products (ATMP's) and

extending exploitation and dissemination to research groups that have specialist knowledge on co-morbidity issues such as cardio vascular and auto immune disease. The Action will also aim to target patient groups and regulators e.g. European Medicines Agency (EMA); Medicines and Healthcare products Regulatory Agency (MHRA) and industry including SME's, policy and decision makers at the European level and the public at large via social media.

These stakeholders will be targeted in the following manner:-

- The Scientific Community will also be targeted via the public website, Action flyers, poster and "standard" power point presentations presenting the Action, as well as via scientific publications in peer-reviewed journals such as Blood, Haematologica, Nature Medicine; talks and posters in scientific conferences e.g. Annual Society of Haematology (ASH), Annual European Bone Marrow Transplant group (EBMT), American Society of Bone Marrow Transplant (ASBMT) meetings, as well as national and International Society of Cellular Therapies (ISCT) conferences. Workshops will include:-
- NIH Consensus on grading and diagnostic cGvHD
- Novel biomarkers in predicting outcome to therapy for cGvHD
- Emerging cellular therapies and novel technologies including ATMP's
- EUROGRAFT will network with scientists and research initiatives working in related domains via training sessions, and seminars (or webinars) and organisation of conference(s). The dissemination will be included to stakeholder organisations such as the European Group for Bone and Marrow Transplantation; International Bone Marrow Transplant Registry; Bone Marrow Donors Worldwide and American Society of Bone Marrow Transplantation.
- Stakeholders such as patient groups and general practitioners as well as SME's will be invited to workshops, meetings and the conference organised as well as patient research/family days (Stakeholder days).
- Politicians at European level, as well as patient groups and the media (local and international press) will be invited to conferences so that discussions can take place on the socio-economic impact of cGvHD and on how to reduce costs if novel diagnostics and biomarkers are introduced as well as how the mitigation of costs in hospitals could be achieved with the impact of improved knowledge and clinical practise e.g. could improved diagnosis and therapy allow cGvHD treatment in an outpatient and more cost effective setting?
- EUROGRAFT Action aims to interact and communicate, via a joint workshop and conference, with other relevant COST Actions in order to further disseminate and foster interaction.
- The general public will be given access to the Action via a public website, an exhibition traveling through transplant centres, and social media e.g. Twitter and Facebook and via liaison with popular science media, e.g. through annual press releases and/or interview. To aid dissemination, information will be translated into more than one language where possible.

2.3. POTENTIAL FOR INNOVATION VERSUS RISK LEVEL

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

EUROGRAFT will deliver potential breakthroughs and innovation via the following tasks:-

- Centralising the information (clinical and laboratory) collected from cohorts across Europe under NIH guidelines. Using NIH Consensus criteria for diagnosis and monitoring will enable a step forward in planning innovative clinical trials and their potential implementation across Europe. This will be undertaken by updating and extending an existing clinical and laboratory database set up under European funding for acute GvHD. In addition, the Action will include European database on cGvHD which holds transplant outcome data across European countries.
- Data sharing will promote increased research into cGVHD and allow bioinformatics approaches to be explored for future implementation. Data on co-morbidities will allow the interaction of experts within the field of cardiology, autoimmune disease and pathology to come together with a common aim to further understand the subsets of disease and allow a more patient stratified approach to therapy.
- Involvement of experts in cellular therapies and novel treatments used in cancer therapy, dermatology and autoimmune disease such as dendritic cell (DC) vaccines; microbiome analysis and faecal transplantation, induced pluripotent stem (iPS) cells, extracorporeal photopheresis will widen the opportunities for further therapeutic intervention.
- Epidemiological data for the incidence and severity of cGvHD and its co-morbidities will enable a further understanding of the disease and disease course which can be applied to individual patient care.
- Prognostic algorithms predicting the disease based on biomarker knowledge will be developed and will be used to further monitor response to therapy, giving rise to improved outcomes and reduced health care costs.

Associated risks and mitigation are given in the Risk and Mitigation/Contingency Table.

3. IMPLEMENTATION

3.1. DESCRIPTION OF THE WORK PLAN

3.1.1. DESCRIPTION OF WORKING GROUPS

In this section, the individual Working Groups, their tasks and expected outcomes (deliverables) are outlined. The overall work plan consists of 5 Working Groups, led by experts in the field, all collating data on aspects of cGvHD, including epidemiology, social economics, interpretation and implementation of the NIH consensus diagnosis and clinical criteria, biomarkers and assessment of novel therapeutic options. All the Working Groups will interlink via common themes such as clinical criteria, economics and response to therapy. The Working Groups will bring together using novel techniques, results which will be integrated into a well annotated clinical database forming a unique and novel platform for use in investigating cGvHD, including epidemiology and clinical response to standard and novel therapies.

WG 1 Development of an epidemiological platform

The development of an epidemiological platform on cGvHD within EUROGRAFT is a novel approach to understanding the disease incidence and associated comorbidities. Results of the analysis will enable a deeper understanding of the incidence of the disease and enable additional data to be included in current European wide databases for use in future clinical trials.

Objective: To assess epidemiological data on cGvHD in a joint effort of clinicians and epidemiologists in order to assess its impact on patient outcomes and response to therapy in transplant centres within Europe.
Task 1: To survey existing epidemiological data on cGvHD in participating transplant centres
Task 2: To organise two meetings per year in addition to teleconferences to discuss and analyse the existing data and approaches to enhance current common databases.
Task 3: To survey existing biobanks of cGvHD tissue and samples among collaborating biobanks for cGvHD research purposes.

Milestones:

- Survey and report on assessment of data available in existing biobanks completed and results summarized. M24

Deliverables:

- Report on incidence of cGvHD across transplant centres in Europe M12
- Training School, “Epidemiology and epigenetics of cGvHD”. M36
- Six STSM’s across the Working Group. M6-M42

WG 2 WorkingGroup on molecular and cellular biomarkers of cGvHD

This Working Group will assess the type and amount of biomarker information which is currently available in the literature and assess those which are worthy of further validation and study**.**

Objective: Identification of molecular and cellular cGvHD biomarker panels based on surveys of research findings and development of future research strategies to advance this panel.

Task 1: To survey European research centres on existing data on potential biomarkers of cGvHD (immunogenetics, genomics, proteomics, and cellular subpopulations of the immune system) and assess whether the data can be included in existing databases. Via bioinformatics approaches develop meta-analysis of collected data.
Task 2: To organise two biomarker group meetings per year in addition to monthly teleconferences to discuss and analyse the existing data on biomarkers for laboratory and clinical diagnosis of cGvHD.
Task 3: Organize two Training School, the first on future strategies to identify new biomarkers by unbiased high throughput technologies, including, genome wide association studies (GWAS), expression profiling, proteomics, and multidimensional immuno-phenotyping in large

European cohorts. Organize a second Training School on “Novel biomarkers for cGvHD”. Both open to ECIs including medical doctors in specialist training and including follow on STSMs to leading European institutions.
Task 4: Development of a set of Documents to supply a tool for validation of both, biomarkers and cellular subpopulations, for monitoring of immune reconstitution post haematopoietic stem cell transplantation.

Milestones:
- Survey data on existing cGvHD biomarkers and cellular subpopulations M12
- Report -Develop a personalised approach to cGvHD therapy and the basis of a European Strategy paper M42

Deliverables:
- Guidelines/Report for usage of biomarkers in cGvHD diagnosis and early treatment regimens M42
- Documentation and delivery of two Training School including future strategies M24; M42 and 6 Short Term Scientific Missions (STSMs) M6-M42
- Two Training Schools on “omics research” including genomics, lipidomics and proteomics and bioinformatics in cGvHD research”, and “Training School for translational research in cGvHD including cellular therapies” M18, M30. The training will be available across the WG’s and network but also accessible to ECIs outside of the network.

WG 3 Working Group on Socio-economics and quality of life

CGvHD is a long term complex disease which has several co-morbidities and as such impacts on the quality of life of patients. By studying the societal impact of the disease via documented quality of life assessments, including reduced working days due to hospital stays, EUROGRAFT will allow an improved assessment of the burden on society of cGvHD at both the individual and European level.

Objective: Estimate the burden of cGvHD to transplant communities and to societal impact. Assessment of the quality of treatment compared to financial input in different European countries by close interaction of clinicians and experts in economics.

Task 1: To survey transplant data (EBMT; International Bone Marrow Transplant Registry IBMTR) on economic loss due to days in hospital, quality of life etc. due to cGvHD.
Task 2: To develop approaches to calculate direct economic loss due to cGvHD and to correlate this with quality of life assessment scores.
Task 3: To develop approaches to calculate indirect economic burden due to cGvHD; and to compare the quality of treatment in different countries.
Task 4: To organise two meetings per year and monthly teleconferences to discuss and analyse quality of life and economic loss due to cGvHD in order to optimise models of predicting and preventing the disease.

Milestones:
- Report -Survey data on quality of life and direct and indirect economic loss due to cGvHD in Europe M12;Outcome assessment M42

Deliverables:
- Report-Summary of evaluated quality of life and socio-economic direct and indirect costs caused by cGvHD in Europe M24
- Report -Common consensus protocol for quality of life and economic loss calculation due to cGvHD.M36
- Report-Guidelines for prevention and predicting cGvHD in health including quality of life and economy aspects.M42
- Training School on socio-economics of cGVHD. M36
- Six STSMs across the Working Group. M6-M42

WG 4 Working Group on diagnostic criteria and response assessment in cGvHD

The NIH consensus criteria needs to be implemented uniformly if diagnosis and treatment of cGVHD is to be optimized. The aim of this Working Group will be to aid in both the understanding and implementation of the NIH Consensus via Training Schools and workshops.

Objective: Investigation of the implementation and use of the NIH-defined diagnostic criteria of cGvHD and NIH recommendations for response assessment in daily clinical routine care across Europe.

Task 1: To survey use of NIH-defined diagnostic criteria of cGvHD in daily clinical routine care within European countries.
Task 2: To develop an on-line toolbox of documents and Training Schools regarding the implementation of the NIH-defined diagnostic criteria on a European scale including in one Training School per year, and monthly teleconferences for case discussions on staging and severity scoring of cGvHD.
Task 3: To survey patient reported outcome measures used in daily clinical routine for assessment of cGvHD activity, co-morbidities and side-effects of immunosuppressive treatments within European countries; subgroup identification e.g. identified patterns of disease.
Task 4: To investigate patient care models of cGvHD throughout Europe.

Milestones:
- Report-Survey data on routine use of NIH-defined diagnostic criteria in Europe M12
- Annual Training Schools on NIH-defined diagnostic criteria M12,M24,M36,M48
- Report -Survey data on routine use of NIH-recommended response assessment criteria in Europe M18
- Report -Survey data on routine use of patient reported outcome measures M24
- Report -Overview on patient care models of cGvHD in Europe M36

Deliverables:
- On-line tool box for Training Schools of NIH-defined diagnostic criteria of cGvHD M6
- Harmonized guidelines for response assessment in clinical routine M36
- Consensus document on recommended patient care in cGvHD in Europe M48
- Six STSMs across the Working Group M6-M42

WG 5 Working Group on immunotherapy for the treatment of cGvHD

Patients with cGvHD (30-50%) can become refractory to standard therapy, new treatment options and the assessment of current novel therapies are urgently needed to improve the long term outcome and quality of life. In this Working Group the Action will bring together experts in cGVHD and clinical trial development, especially in the realm of cellular therapies with the aim of developing concepts for new approaches including personalized approaches to therapy.

Objective: Investigation of immunotherapeutic challenges for the treatment of cGvHD resistant to conventional therapy.

Task 1: To survey existing and newly developed immunotherapeutic options for the treatment of cGvHD including monoclonal antibodies, ATMPs,and exosomes.
Task 2: One meeting/year will be organized in order to harmonize good manufacturing practice (GMP) protocols for immunotherapy trials for cGvHD in Europe and to assess efficacy/safety criteria in both pre-clinical models and clinical scenarios.
Task 3: To define hurdles in immunotherapy trials and to develop an on-line toolbox of documents and Training Schoolsin order to standardise quality control for the use of novel therapies e.g. antibodies ATMP's and exosomes.
Task 4: To assess and refine pre-clinical animal models for cGvHD to test efficacy of various immunotherapeutic strategies including ATMPs.
Task 5: To survey established and recently defined pathophysiologic mechanisms involved in development of cGvHD that provide a rationale for selection of different immunotherapeutic strategies in individual patients.
Task 6: To survey established and recently developed markers for immune monitoring during and after immunotherapy.

Milestones:
- Report - Survey data on various immunotherapy trials for cGvHD treatment M12
  Workshop on advanced personalized immunotherapeutic medicine for both the scientific and public community; M24
- Report -Survey data on pathophysiological aspects of cGvHD M24
- Report- Survey data on immune monitoring during immunotherapy M36

Deliverables:

- Report -Harmonized guidelines for both GMP manufacturing and quality control of cGvHD therapy e.g. antibodies, ATMPs and exosomes M24
- On-line Training Schools regarding safety issues/side effects of novel immunotherapeutic strategies. M15
- On-line tool box of documentation re quality control for the use of novel therapies M24
- Report-Harmonized guidelines for immune monitoring during immunotherapy M42
- Six STSMs across the Working Group M6-M42

Deliverables across all WG's

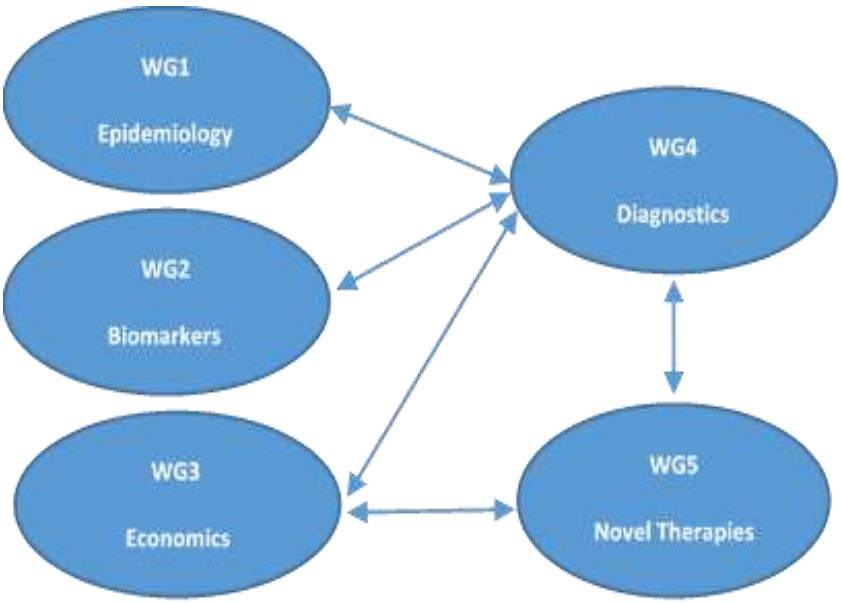
- Document and survey involvement (of PhD students/candidates, ECIs, researchers, clinicians, health policy makers, patients) for Training Schools, events and a conference M6-M42;
- Conference programme M36;
- Programme documentation and feedback of Training Schools and workshops M42
- Programme book/abstract book and overview of a conference M48
- To organise a conference "Innovative methods of predicting, diagnosing and treating cGvHD including epidemiological factors" M42
- Annual Stakeholder days M12, M24, M36, M48.

3.1.2. GANTT Diagram

	Year 1 Q1-4					Year 2 Q1-4				Year 3 Q1-4				Year 4 Q1-4			
	1	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48
WG 1- Epidermiological data surveys:					R				S/R				T				
Biannual Meetings			M		M		M		M		M		M		M		M
WG 2- Biomarker surveys; workshops; reports					S		TS		T		TS				R/T		
Biannual Meetings			M		M		M		M		M		M		M		M
WG 3- Socio economic surveys; workshops;					S				R				R/T		R		
Biannual Meetings			M		M		M		M		M		M		M		M
WG 4-NIH consensus in Europe diagnostic			T*		SR/T		SR		SR/T				R/T				R/T
Biannual Meetings			M		M		M		M		M		M		M		M
WG 5-Immunotherapy treatment for cGvHD					SR/T	T			R/T*				R		R		
Biannual Meetings			M		M		M		M		M		M		M		M
Global Conference / Stakeholder Day					SH				SH				SH		C		SH
Writing Publications					P				P				P				P
Management Meeting	K	MC							MC							MC	

KO=Kick off meeting; S= Survey; R= Report; SR= Survey and Report; T= Training Workshop; TS= Training School; M = Meeting; MC= Management Committee

3.1.3. PERT CHART (OPTIONAL)



3.1.4. RISK AND CONTINGENCY PLANS

The following contingency plan will be put in place to mitigate against general risks to the Action and problems arising from the failure of any WG activity. Where an activity is in danger or likely to fail, the MC will be informed immediately to bring the team together to search for possible solutions.

Risk	Means of Mitigation/Contingency
Unable to attract ECI's to join the network	Advertise at all major haematological stem cell transplant events including Conferences and at the European School of Haematology – which attracts students to their workshops on a yearly basis. Advertise via past and current Marie Curie Innovative Training Networks and encourage participation.
Lack of ability to escalate ideas to clinical trial due to regulatory or funding issues	Decide amongst network early in the Action which type of novel therapy to focus on and engage with the regulatory bodies (e.g. European Medical Agency - EMA)
Incomplete or lack of patient data	Low risk due to already initial development of databases and international registries of data which can be utilised with a complete set of clinical and laboratory data across the proposers of over 3000 transplants, with over 40,000 transplants registered at the EBMT registry (17).
Unable to develop robust biomarker algorithms for predicting and monitoring cGvHD	Medium risk – some biomarkers are already known but need collating to assess robustness on large cohorts
Data too diverse to enable subgroup analysis to be adequately carried out	Low risk- due to international collaboration and known registries this should be able to be overcome at the consortium level.

3.2. MANAGEMENT STRUCTURES AND PROCEDURES

The Action will be organised according to COST rules and procedures in particular "Rules for Participation in and Implementation of COST Activities".
Management Committee (MC) is responsible for the coordination, implementation and management of the Action's scientific and networking activities in line with the Memorandum of Understanding (MoU), with a view to achieving the Action objectives. The Action Chair Vice-Chair and WG Leaders will be elected at the first MC Meeting. The MC will be composed of up to two representatives of each COST Member Country and the MC members will be nominated by the COST National Coordinators. The MC will include representation of the ECI. The internal decision making process of MC will follow the Rules of Procedure for Management Committee. The MC will also oversee and ensure a fair gender balance as well as dissemination and open access. The MC will meet regularly to evaluate the progress of the Action towards its objectives but will be in close contact via email and phone conferences throughout the lifetime of the Action and at least monthly.

- Working Groups (WGs): Five WGs will perform the scientific Action activities, which will be coordinated according to the published rules and procedures. Each WG will report annually on their activities and progress towards objectives, including Deliverables and Milestones, and will provide a final report evaluating the results achieved. The WGs will meet a minimum of twice per year in order to monitor progress. This will take place in addition to monthly teleconferences with WG participants and ensure the WGs keep focused on the Milestones and Deliverables, with any deviations being efficiently reported to the MC for any contingency plan.
- Website and dissemination: The Action website will enable continuous communication and exchange of information between WGs. There will also be a focus group for the development of the Action website who will liaise and report to the MC. The WGs will form a 'LinkedIn' group for the Action to facilitate sharing knowledge and disseminating results to a wider audience. Dissemination and exploitation will be itemised on the agenda at each MC meeting and a focus group will be formed at the first Management Committee Meeting which will be responsible for discussing, monitoring and documenting dissemination and developing the exploitation plan.
- Where possible, MC meetings will align with WG meetings, workshops and conferences. MC and WG meetings will take place at different locations reflecting the geographical distribution of the participating COST Participating Countries in the Action. There will be regular monthly contact via email and video conference / Skype.

3.3. NETWORK AS A WHOLE

The aim of the Action will be to provide long term sharing of research and clinical experience on cGvHD which will include epidemiology, bio banking, molecular biology, immunogenetics, immunology, genomics (mRNA and miRNA profiling) including the role of extra cellular vesicles in serum, clinical diagnosis and insights into novel therapies including extra corporeal photophoresis, the microbiome, as well as the role of somatic and gene therapeutic ATMP's. The Action also includes quality of life and socio-economic assessments. The Action will involve a collection of experts with expertise in the field of haematopoietic stem cell transplantation, including the largest transplant centres in Europe and collaboration and sharing of data with ITC. Experts will also include those in the fields related to haematopoietic stem cell transplantation, associated complications and cGVHD co-morbidities, thus opening up and widening the basic knowledge of clinical medicine to participants, as well as ECIs.

The collaborations developed will strengthen existing collaborative links via Seventh Framework Programme Marie Curie Innovative Training Networks but also further new interdisciplinary networks on topics such as the role of the microbiome, extra cellular vesicles and cellular therapies, which have been little studied for their potential in cGVHD. Interdisciplinary Working Groups will therefore come together to develop novel strategies to solve some of the underlying problems of cGvHD and develop new and exciting ways forward for therapy, clinical trials and new research projects. Importantly, this will involve discussion with SME's at the cutting edge of diagnostics (e.g. epigenetics), techniques for good manufacturing practice (GMP), a pre-requisite for clinical use via ATMPs and drug development.

The Action will consist of participants with expertise in transplant medicine, immunogenetics, immunology, lipidomics, epidemiology, animal pre-clinical studies, statistics and cellular therapies together with 4-6 SME's involved in novel biomarker discovery, cellular therapies and diagnostics. The Action will strive towards equal gender balance. In addition the Action will invite an International Partner Country, with a large data base on childrens transplantation. The participants within the ITC countries also give added value in the way of paediatric expertise, immunogenetics, clinical data bases and cohorts.

EUROGRAFT Action aims to expand the network in the first 1-3 years to outreach to countries with little expertise in haematopoietic stem cell transplantation such as Near Neighbour Countries (NCC) countries, (Algeria, Jordan Lebanon and Tunisia), aided by collaboration with the EBMT Outreach programme, which supports emerging transplant programmes and transplant centres in countries with limited resources and/or experience. EUROGRAFT Action will work together with the EBMT Outreach programme and facilitate and encourage collaboration, through building long-lasting relationships between transplant centres and members, providing training and support for transplant programmes, with a view to harmonisation of standards and practice across Europe and beyond. Outreach countries are defined as countries classified as lower & upper-middle income according to the World Bank Classification, these will include NNC and ITC countries. Although the majority of EBMT members (81%) are located in Western Europe, the proportion of its centres from outside this area is rising, with a particularly strong increase in membership from Eastern Europe and Balkan countries over the past few years. A contact list of centres in Outreach countries will be made available to the network in order to invite participation of researchers and clinicians in these countries to participate in conferences and Training Schools and to share research findings and training materials. Due to their initial involvement in the NIH consensus criteria, colleagues from the USA will be invited to participate in Action's conferences to give advice and expertise.