European Cooperation in the field of Scientific and Technical Research

- COST -

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COST 004/13

MEMORANDUM OF UNDERSTANDING

Subject :	Memorandum of Understanding for the implementation of a European Concerted Research Action designated as COST Action BM1304: Applications of MR imaging and spectroscopy techniques in neuromuscular disease: collaboration on outcome measures and pattern recognition for diagnostics and therapy development

Delegations will find attached the Memorandum of Understanding for COST Action BM1304 as approved by the COST Committee of Senior Officials (CSO) at its 187th meeting on 15-16 May 2013.

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

COST Action BM1304
APPLICATIONS OF MR IMAGING AND SPECTROSCOPY TECHNIQUES IN NEUROMUSCULAR DISEASE: COLLABORATION ON OUTCOME MEASURES AND PATTERN RECOGNITION FOR DIAGNOSTICS AND THERAPY DEVELOPMENT

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

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

2. The main objective of the Action is to advance novel MRI and MRS techniques for both diagnosis and quantitative monitoring of neuromuscular diseases through sharing of expertise and data, joint development of protocols, opportunities for young researchers and creation of an online atlas of muscle MRI and MRS.

3. The economic dimension of the activities carried out under the Action has been estimated, on the basis of information available during the planning of the Action, at EUR 44 million in 2013 prices.

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

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

A. ABSTRACT AND KEYWORDS

Neuromuscular diseases (NMD) form a large group of individually rare diseases that are present in all populations and affect people of all ages. Many of them result in chronic disability, posing a significant healthcare burden for society. Diagnosis and therapy development for NMD has rapidly expanded in recent years and there is an urgent need to develop objective, non-invasive outcome measures to monitor disease progression and treatment effect. The use of novel magnetic resonance imaging and spectroscopy techniques (MRI and MRS) applied to NMD is showing increasing promise in this regard, but progress has been hindered by the rarity of the conditions and lack of options for pooling data from different groups. This COST Action will overcome the main hurdles to rollout of MR techniques by sharing expertise and data, validating protocols across platforms and exploring the potential of MRI and MRS as a helpful diagnostic tool and a quantitative outcome measure in NMD clinical trials. The objectives of standardizing applications of MRI and MRS in NMD, training of early stage researchers and the development of an online atlas of neuromuscular imaging will enhance knowledge of scientists and healthcare professionals and ultimately benefit patients with NMD.

Keywords: Magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), neuromuscular disease, outcome measures, trial readiness

B. BACKGROUND

B.1 General background

Neuromuscular diseases (NMD) are individually rare but collectively affect ~3 million people worldwide, are incurable and a significant cause of chronic disability and reduced life expectancy. Rare diseases (RD) are a major focus of current European Union health policy, with the new International Rare Diseases Research Consortium (IRDiRC) initiative aiming to develop diagnosis for all RD and 200 new treatments by 2020.

The development of diagnostic algorithms for NMD has benefited immensely from the fairly easy accessibility of muscle and peripheral nerve tissue through biopsies. Analysis of biopsy samples has helped to classify NMD and to gain a better understanding of their underlying pathomechanisms. Despite these advantages, diagnostic biopsies are nevertheless invasive procedures that are limited by the number of times they can be applied, their sample size and their restriction to certain anatomical areas. Advances in genetic diagnosis have also shown that many of the more than 300

genetically distinct NMD (http://www.musclegenetable.fr/) share similar unspecific histological features. In recent years expert centres have applied non-invasive Computerized Tomography (CT) and Magnetic Resonance Imaging (MRI) to obtain a more comprehensive picture of the distribution and extent of pathology in NMD. Imaging techniques are used to describe the effects of disease on muscle morphology, signs of inflammation and the replacement of muscle tissue by fat and connective tissue. It is now recognised that the selective pattern of involvement can be very typical for a specific NMD and muscle imaging is therefore being increasingly used by experts for the diagnostic workup of patients.

The improved diagnostic characterisation of patients with NMD has also contributed to the development of new therapeutic approaches for these rare diseases. One of the biggest challenges for the field is the urgent need to develop reliable outcome measures (OMs) to monitor disease progression and treatment effect. Due to the lack of more objective OMs, current clinical trials use endpoints that depend on the physical ability and cooperation of patients. The limited number of sensitive OMs and the need to avoid invasive techniques in a population with compromised muscle function makes MRI and MR spectroscopy (MRS) techniques particularly attractive as a tool for patient assessment. MRI and MRS techniques applied to muscle could potentially quantify aspects of disease progression and pathology and thereby contribute to the time- and cost-effective evaluation of therapeutic interventions. Specialised protocols that have enabled the use of these techniques to quantitatively assess treatment effect earlier and with greater sensitivity than other measures have so far only been developed and tested independently in a few expert centres. However, because of the relatively low prevalence of any specific NMD, clinical trials almost always have to be multicentric and multinational. To maximise the potential of MRI and MRS techniques and their application in clinical trials, a coordinated approach to validate and implement agreed protocols across trial sites in Europe is therefore necessary. The benefit of this concept is reflected in increased interest in quantitative MR from the pharmaceutical industry and recommendations from regulatory bodies to include these techniques in trial protocols.

There are currently several challenges that prevent the most effective use of imaging techniques for the diagnosis and assessment of NMD: 1) The limited pool of scan data available to fully understand the disease-specific spectrum of pathology and diagnostic value of muscle MRI. Muscle MRI has replaced CT in diagnostic imaging, but the number of scans available for a specific NMD is still fairly limited as scans have generally only been carried out in specialized centres on small cohorts of patients. Selective patterns of muscle involvement have mainly been described in phenotypically homogenous cohorts, without a good understanding of the spectrum of muscle pathology in more mildly or more severely affected patients, or patients of different age, ethnic

background or gender. In addition, results from imaging studies have not been comprehensively correlated with clinical findings and specific genotypes and in most cases longitudinal data are missing. It is important to collect these data in larger cohorts of patients for a better understanding of the natural history of NMD and also to enable not only these new data but also the data already available in individual centres to be more effectively shared between centres. 2) Lack of agreed standard operating procedures (SOPs) for quantitative MRI and MRS and their implementation as an outcome measure in multicentric trials. Protocols for quantitative MR techniques, e.g. Dixon and T2 acquisition, have been developed in a few expert centres without cross-centre and cross-vendor validation and agreement. Despite attempts to address this and willingness on the part of the expert centres to provide training, many clinical sites that are currently participating in NMD trials still cannot apply quantitative muscle imaging because of the lack of expertise and standard protocols, even though both pharmaceutical companies and regulatory authorities would like to explore imaging techniques as potential OMs to monitor therapeutic efficacy. 3) Lack of knowledge about the added value of new imaging techniques, targets and contrast agents. New imaging techniques and contrast agents have revolutionized our understanding of the anatomy, function and pathology of organs like the brain and the heart and diseases like cancer. In contrast, very little is known about how these tools (e.g. diffusion tensor imaging, DTI) can be applied to and optimized for muscle imaging and the assessment of NMD. 4) Missing algorithms for muscle image texture analysis. Texture analysis is the quantification of patterns of signal intensity within images of any kind. At the most fundamental level the aim of texture analysis is to provide an objective quantification of the spatial patterns which can be seen in an image. Texture analysis could attempt to quantify different fat infiltration patterns in different muscle groups across different NMD. So far no algorithms for texture analysis of muscle pathology detected by MRI exist. To develop valuable protocols for muscle image texture analysis a training set of muscle imaging data is needed to statistically establish which parameters distinguish or measure a defined abnormality and then a different set of data to test the predictive power of the findings.

Establishing muscle imaging as an important tool for the diagnosis and assessment of patients with NMD will help to provide more patients with a specific diagnosis and to accelerate the elaboration of clinical trials and new treatment strategies. It will be a task of the COST Action to coordinate the collation of MRI data and to define typical patterns of muscle involvement and the spectrum of pathology. It will also be important to better define when muscle MRI can be helpful in the diagnosis of a disease. In addition, the lack of a forum and strategy for the dissemination and spreading of expertise in neuromuscular imaging has hindered progress. The proposed COST Action will facilitate collaboration between clinical neuromuscular experts, radiologists, MR

physicists and computer vision specialists, which is currently very fragmented within and between centres that look after patients with NMD. Because the value of muscle imaging for the diagnosis and assessment of neuromuscular patients has only recently been appreciated there is a shortage of trained researchers to apply and further develop muscle imaging techniques, which needs to be addressed through coordinated training schemes.

The COST Scheme is the most appropriate mechanism to facilitate the collaboration of healthcare professionals, researchers, patients and industry to develop, agree and implement imaging techniques for NMD, as it stimulates interdisciplinary interaction and methodological sharing across European centres. COST is uniquely placed to catalyse the necessary non-competitive collaboration between groups that complements the research being carried out in the individual centres and enables the field to innovate. Many of the tasks that will contribute to the success of this Action are around consensus building, protocol and data sharing, the dissemination of knowledge and the training of early stage researchers. The fact that many trials in NMD will involve centres from both Europe and the US and possibly Japan, Australia and South America is a further reason why this Action is making use of the COST Framework, which also allows researchers from Non-COST Countries to join the consortium provided funding can be sourced through reciprocal agreements or participants' own funding sources. The fact that many researchers from Non-COST Countries have expressed their interest in the Action emphasises its relevance at an international level even beyond Europe. Whereas EUREKA! initiatives are often driven by industry and the EU Framework Programme focuses on the funding of research projects, this Action is driven by academic researchers and focuses on COST objectives including networking and the harmonisation of imaging protocols across trial sites in Europe. Research in this area, including acquisition of scans relevant for the success of the Action, is already ongoing and will be funded through either public health funding or research grants. Facilitating the implementation of imaging guidelines for the diagnosis and assessment of NMD through the COST Action will help to overcome the fragmentation that is currently hindering translational research in NMD in Europe.

B.2 Current state of knowledge

It is only very recently that muscle MRI has become part of the diagnostic algorithm for a few NMD, where it is already apparent that it adds diagnostic value, discriminating between patients with different diseases who are phenotypically very similar. Some specialized diagnostic centres are now requesting a muscle MRI for a subset of congenital myopathies to guide genetic testing. Previously, muscle CT and MR imaging for NMD had only been used for research purposes by a

few groups to gain a better understanding of the extent and distribution of muscle pathology and to see whether this could provide clues to pathomechanisms. When it became evident that patterns of selective muscle involvement detected by MRI are often disease-specific, clinical experts in individual centres started to apply muscle MRI in their cohorts of patients. Most publications that describe muscle pathology by MRI used T1 weighted images in small cohorts of neuromuscular patients with similar phenotypes. The regions of interest that are imaged are normally the pelvic girdle and lower limb muscles. There is still fairly little experience in describing muscle pathology by whole-body MRI or MRI of the truncal and upper limb muscles, although several centres are now starting to explore these applications more systematically. Furthermore, there is almost no NMD for which imaging data covering the entire phenotypic spectrum exist.

As well as the increasing appreciation of the diagnostic relevance of muscle imaging, the increase in clinical trial activity and the need to establish reliable OMs and biomarkers for monitoring disease progression and therapeutic efficacy has led to MRI and MRS studies with a focus on quantitative outcomes. The degree of muscle pathology is generally described semi-quantitatively using different scales that have been suggested in the literature. Developing MRI and MRS as objective OMs in clinical trials requires the development of protocols that quantify either muscle morphology or specific aspects of muscle pathology like fatty infiltration, inflammation and fibrosis. Protocols have again been developed in specialized centres using different technologies and machines and have in some cases only been applied in pre-clinical models. When clinical trials with antisense oligonucleotides started in Duchenne muscular dystrophy (DMD), no agreed protocol for quantitative muscle imaging was in place. A first multicentric European study applied quantitative muscle imaging using the 3-point Dixon technique to a cohort of adult patients with limb girdle muscular dystrophy 2I and monitored disease progression over a 12 months period. Their experience highlighted the importance of agreed protocols that can be implemented in different centres with different MR machines. Discussions between a small number of clinical trial sites with imaging expertise and pharmaceutical companies have now introduced quantitative MRI and MRS into clinical trial protocols for antisense oligonucleotide treatment in DMD patients and for trials in Pompe disease. The recently funded FP7 project SKIP-NMD is planning to carry out a Phase I/IIa clinical trial in DMD with systemically delivered morpholino antisense oligonucleotides to skip exon 53 and to monitor muscle pathology by quantitative MRI and MRS. Similar initiatives in DMD using muscle imaging have now also started in the US, but protocols between these initiatives have not been harmonized and results may not be comparable.

Within the FP6 Network of Excellence TREAT-NMD (2007-11), an MR Working Group held 3 expert workshops on OM development and pattern recognition resulting in publications on

harmonised protocols for cross-platform use of quantitative techniques and laying the groundwork for consensus development and data and protocol sharing. These pilot collaborations are a strong indicator of the likely success of this COST Action. The scientific impact of bringing together the leading groups in the field will be extensive: data sharing is essential in order to overcome the challenges of the rarity of the conditions, but has historically been difficult to achieve owing to research competition and IP issues. This Action will be innovative in the way it brings together representatives from various stakeholder groups to share knowledge and expertise in muscle imaging in a pre-competitive space. In the field of rare diseases, networking between patients, healthcare professionals, scientists and industry is critical to reach consensus and develop standardized operating procedures. The innovative character of the Action is reflected in the creation of 4 Working Groups addressing specific aspects of diagnosis, protocol development and new imaging techniques for NMD.

B.3 Reasons for the Action

Despite their promise, several factors have prevented MR techniques from reaching their full potential in NMD. There remains a lack of understanding of the added value of muscle imaging in these conditions because most centres lack both the required expertise and sufficient numbers of diagnosed patients. Together with the large variations in platforms and protocols used in different centres that make cross-compatibility of results difficult to achieve, these shortcomings require a coordinated approach and an expert network that agrees to collect data to improve the diagnosis and objective assessment of muscle pathology in this group of rare diseases.

There is an immediate need to collect baseline muscle MRI and MRS data for the development of OMs for upcoming trials in myotonic dystrophy, facioscapulohumeral muscular dystrophy (FSHD) and congenital and limb girdle muscular dystrophies. In the longer term the dissemination of protocols and SOPs and the training of Early Stage Researchers (ESRs) will help to establish a network of clinical trial sites that can participate in academic and commercial studies that require muscle MRI and MRS. This is relevant to the entire neuromuscular field, as some of the current expert centres are now short of trial-naive patients for planned studies and empowering centres in Eastern and Southern Europe to deliver all necessary assessments for a clinical trial, including muscle imaging, will improve their involvement and patient recruitment time.

The COST Action will deliver scientific and technological advances, as the development of standardized imaging protocols for NMD is a key deliverable for academia and pharmaceutical companies. The Action will also have a clear impact on societal needs, as it will provide

recommendations for the application of a non-invasive tool that can guide biopsies, can in some cases replace biopsies and suggest a specific diagnosis, all of which is directly beneficial for patients. The Action's contribution to the development of improved trial protocols by providing reliable outcome measures, which are particularly important for small patient cohorts in the rare disease field, will directly benefit patients, their doctors and the pharmaceutical industry. The societal impact can be translated into economic benefits, as a more accurate assessment of response to treatment will reduce clinical trial costs and therapy development. In addition, disseminating information about the diagnostic relevance of muscle MRI can shorten time to final diagnosis and therefore pays for itself. By facilitating diagnosis and therapy development, the Action will also contribute to the objectives of IRDiRC.

In order to achieve maximally productive outcomes and deliver the expected results, this Action will: 1) Hold Working Group (WG) meetings to coordinate the extended collection of muscle MR scans to establish a phenotypic spectrum of muscle pathology for those NMD where MRI will be of diagnostic relevance (e.g. congenital and myofibrillar myopathies). The collections of images will directly lead to the compilation of an online imaging atlas for NMD. 2) Hold WG meetings that will lay the ground for the publication and dissemination of agreed SOPs for quantitative MRI and MRS for use in multicentric neuromuscular trials and organize training schools for MR staff from different centres at a central location to ensure correct implementation of the developed imaging protocols. This implementation strategy will be supported by site visits from experts (Short-Term Scientific Missions, STSMs) to provide onsite training on local MR equipment. In addition STSMs aimed specifically at ESRs will provide training opportunities on MRI and MRS protocol development and application. 3) Hold expert WG meetings for the protocol development of new imaging techniques including new contrast agents, currently not applied in NMD patients in a routine clinical setting. The focus will be on pre-clinical studies and their translation to the clinic. Outcomes of the WG meetings will feed into WG2, STSMs and training schools. 4) Hold WG meetings between different image texture analysis experts and discuss the different strategies to deal with nuclear magnetic resonance (NMR) images of NMD patients in order to extract additional information on muscle structure that is not directly accessible or visible.

The Action will organise a final international conference on neuromuscular imaging to promote European research and development in translational medicine in rare diseases.

B.4 Complementarity with other research programmes

The COST Action will not fund research per se, but will provide a collaborative forum for

healthcare professionals, researchers and patient and industry representatives working on the improvement of diagnostic and assessment standards for patients with NMD. Currently no networking activities or international projects that specifically address the harmonization of muscle imaging are in place, which is why this Action aims to establish an expert forum and dissemination platform. The Action will work closely with relevant Working Groups from the TREAT-NMD Alliance, which provides a platform for translational research in rare inherited NMD that was initially funded under FP6, such as the Outcome Measure Working Group and the Antisense Oligonucleotide Working Group. The latter is supported by a COST Action (BM1207, Networking towards clinical application of antisense-mediated exon skipping) and exchange of relevant knowledge and knowhow between the Actions is envisaged through joint meeting participation. Previous participants from TREAT-NMD imaging workshops will be encouraged to join the Action's activities. Principal investigators and sponsors for neuromuscular trials involving quantitative muscle imaging will be invited to Working Group meetings of the Action. Current and planned FP7 projects that will use muscle imaging in antisense oligonucleotide trials in DMD are SKIP-NMD (funded) and SCOPE-DMD (under evaluation). Both of these antisense oligonucleotide focussed research projects are planning to use MRI and MRS as exploratory outcome measure for the assessment of treated DMD patients in a few selected centres. In contrast to the COST Action these projects have no specific education and dissemination strategy for imaging techniques beyond the selected trial sites and both projects would benefit from outcomes of the COST Action. The Action will also seek close links with the planned BIOIMAGE-NMD consortium, an FP7 project (submission stage) on pre-clinical and clinical imaging studies in DMD, including diffusion tensor and PET imaging. Research results from this project would directly feed into the Working Group discussions from the proposed COST Action. In contrast to the proposed COST Action the BIOIMAGE-NMD project does not support international networking meetings or training schools. It is also foreseen that Working Groups 3 and 4 of the Action will establish links with COST Action Td1007 (Bimodal PET-MRI molecular imaging technologies and applications for in vivo monitoring of disease and biological processes). The COST Action does not specifically address muscle imaging, but knowledge sharing between the Actions will be of mutual benefit.
Where appropriate the Action participants will work closely with members of the 3 IRDiRC Scientific Committees for Diagnostics, Therapies and Interdisciplinary aspects and relevant members of the FP7 funded Neuromics project that aims to diagnose new NMD by next generating sequencing approaches.

C. OBJECTIVES AND BENEFITS

C.1 Aim

to advance novel MRI and MRS techniques for both diagnosis and quantitative monitoring of neuromuscular diseases through sharing of expertise and data, joint development of protocols, opportunities for young researchers and creation of an online atlas of muscle MRI and MRS.

C.2 Objectives

Secondary objectives will be achieved via four Working Groups (WGs), each of which has a specific focus, defined outcomes and agreed deliverables.

Objective 1: Improve diagnosis and understanding of muscle pathology (WG1)

Knowledge about the onset of muscle pathology detected by imaging, about the degree of progression, the spectrum of selective involvement across the whole body and about modifiers of these parameters is still very sparse for the majority of NMD. This lack of information might delay the diagnosis of patients with NMD and impede our understanding of disease mechanisms. *Specific objectives: 1.1:* Hold 2 WG meetings per year that coordinate the collection of an agreed number of standardized MR images for defined diseases. 1.2: Establish and validate a secure Information Technology (IT) platform to share medical images between experts. 1.3: Establish an online inventory of muscle MR images with associated standardised clinical and genetic data from NMD prioritized by the consortium (including a spectrum from pre-symptomatic to advanced, whole-body images, where appropriate cardiac images). 1.4: Define regions of interest (ROI) for each disease, indicating the optimal muscle to biopsy or to be used for outcome measurements in a clinical trial setting (showing most reliable change over time). 1.5: Develop a user friendly digital NMD atlas of muscle MR images with public access.

Objective 2: Develop multicentric outcome measures (OMs) (WG2)

The most important reason why quantitative muscle MRI and MRS is currently not applied routinely across trial sites in multicentric studies is because of the lack of standardized and validated MR protocols for both data acquisition and data analysis. Trial participants therefore either need to all travel to a single centre or there is a risk that data is not comparable across centres. Protocols may need to be tailored for specific diseases. There is also a global lack of young researchers, (MR physicists and radiographers) with expertise in this area, and given its rapid growth it is essential to encourage new researchers to specialise in this field. Enabling STSMs for young researchers to gain expertise in different departments is crucial to catalyse development of expertise in the “next generation”. *Specific objectives: 2.1:* Hold 2 expert WG meetings per year

that serve to develop SOPs for imaging protocols relevant for quantitative muscle imaging in natural history studies and clinical trials. 2.2: Publish optimised protocols for Dixon acquisition (Iterative Decomposition of water and fat with Echo Asymmetry and Least-squares estimation, IDEAL vs non-IDEAL, and fat spectrum simulation) and T2 acquisition using new approaches (partially Spoiled Steady State Free Precession, pSSFP, acquisitions) validated in a multicentric, cross-platform setting. 2.3: Hold 1 training school per year for MR staff from different centres at a central location, coordinated by the Action's Dissemination and Training Committee (DTC). 2.4: Offer up to 4 STSMs per year for ESRs to train in muscle imaging at centres of excellence. ESRs from Eastern Europe will be encouraged to make use of the offer as will those who are working in neuromuscular centres with an interest in clinical trials. Applicants are selected by the DTC. 2.5: Provide expert site visits for onsite training on outcomes of WG1 and WG2 to ensure implementation of the relevant protocols. 2.6: One international conference on neuromuscular imaging as a show case for European translational research in rare diseases.

Objective 3: Explore new contrasts, new targets and new imaging techniques for NMD (WG3)

New imaging techniques and contrast agents evolve with the development of improved MR technology and need to be tested against established protocols for their added value in the quantitative assessment of muscle pathology. *Specific objectives: 4.1:* Hold 2 expert consensus WG meetings per year to confidentially share pre-clinical and clinical data with the intention to develop joint protocols for new imaging techniques. 4.2: Publish joint reports on experimental validation of new contrasts relevant for the diagnosis and/or assessment of NMD and recommendations for their application by non-experts.

Objective 4: Explore strategies for muscle imaging texture analysis (WG4)

Muscle architecture disorganization is a frequent end-stage feature of chronic NMD and particularly of muscular dystrophy. These structural changes translate into abnormal dispersion of the NMR signal distribution within muscles. The NMR signal heterogeneities result in increased standard deviation of muscle signal intensities. This very simple index has been shown to identify dystrophic muscle in animal models and to normalize when dystrophin expression is restored. However it does not take into account possible particular spatial distribution of muscle signal intensities. Texture analysis algorithms may reveal topographical patterns and improve diseased muscle characterization. *Specific Objectives: 4.1:* Hold Working Group meetings of experts to define strategies of muscle texture analysis and to define the best NMR contrast for these techniques to be applied. 4.2: Compare results obtained with different approaches and determine their merits for monitoring disease evolution. 4.3: Publish joint reports and manuscripts on the relative performances of all techniques tested.

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

The Action's objectives will be achieved through networking within and between 4 WGs and through multidisciplinary interactions with relevant complementary ongoing and/or planned European research projects funded through ESF, FP, EUREKA! and COST. A Steering Group (SG) and the Management Committee (MC) of the Action will monitor progress of the WGs against agreed deliverables and make sure that the main objective of the Action is achieved.

WG1: Diagnosis and muscle pathology: Parties from the COST Action participated in a workshop on pattern recognition in genetic muscle diseases organized by TREAT-NMD and a workshop report has been published in a supplement issue on muscle MRI in *Neuromuscular Disorders.* Workshops of the WG will be attended by clinical experts for NMD coming from Neurology, Paediatric Neurology and Genetics. In preparation for the workshop a WG coordinator will ask participants to provide inventories of muscle images obtained in their centres. WG participants will review the disease specific imaging collections, will try to define patterns of involvement for specific diseases, identify how many images for which disease and which part of the phenotypic spectrum still need to be collected and will establish guidelines for an online registry of the images that will finally result in a publically accessible imaging atlas for NMD. This model will be applied to various NMD throughout the funding period of the Action.

WG2: Multicentric outcome measures (OMs): First protocols for quantitative muscle imaging have been published by participants of the COST Action in a supplement issue on muscle MRI in *Neuromuscular Disorders.* Further development of the protocols that are applicable for clinical trials will be discussed at WG meetings. Meetings will be attended by MR physicists, radiologists and clinical imaging experts as well as by experts in outcome measures, as the MRI findings need to be correlated with outcome measures from physical assessments that are normally the primary endpoints in clinical trials. Meetings will also be attended by representatives from pharmaceutical companies involved in neuromuscular clinical trials. Patient representatives will also participate in the discussions about protocol development, as the protocol burden needs to be acceptable and tolerable for patients.

WG3: New contrasts, new targets and new imaging techniques: WG meetings for the protocol development of new imaging techniques will primarily be attended by MR physicists, radiologists and pre-clinical imaging experts. Small expert workshops have already taken place in the past at meetings of the International Society for Magnetic Resonance in Medicine (ISMRM). WG participants will prioritize which imaging techniques should be further developed for the application

in NMD and how duplication of research efforts can be avoided.
WG4: Muscle imaging texture analysis: Texture analysis specialists have already launched an informal initiative for muscle imaging and have started to circulate sets of images between groups. Experts in texture analysis as well as MRI physicists and radiologists will organise meetings to continue the data sharing process, discuss possible strategies for texture analysis as well as data acquisition issues. WG meetings will serve to discuss and interpret the results obtained with the different analysis techniques. The findings of this study as well as the developed tools will be presented and validation strategies established.
Meeting reports from all the WGs will be published in scientific journals and a lay summary will also be available through the Action website and other relevant websites for the neuromuscular community and radiologists. The location of training schools will be chosen so that they are easily accessible for MR staff from centres in Eastern and Southern Europe. Participants from the COST Action as well as invited speakers will provide teaching on both diagnostic aspects of muscle imaging and on quantitative MRI and MRS. The DTC of the Action will be responsible for the invitation of selected speakers, for the advertisement and selection of ESRs for STSMs and for the selection of site visits by experts to supervise the implementation of protocols on local machines. The ESRs will visit imaging facilities at sites from Action participants that can provide training on data acquisition and analysis. The international conference on neuromuscular imaging will be organised by a program committee with representatives from various Action participants.

C.4 Potential impact of the Action

As described in Section B (Background), the Action can maximise the benefits of imaging techniques for the diagnosis and assessment of patients with NMD by bringing imaging experts and representatives from various neuromuscular stakeholder groups together to reach consensus on the relevance of muscle MRI for diagnostic algorithms and the most suitable quantitative MRI and MRS protocols. Training and development opportunities for ESRs will help interest a new generation of MR physicists, radiographers and NMD specialists in the emerging field of neuromuscular imaging. WG1) In the short term neuromuscular patients without a specific diagnosis will benefit from collected and shared expert knowledge about patterns of muscle pathology that are indicative of a specific disease and can guide genetic testing. In the long term the online imaging atlas will help to educate an extended field of clinicians about NMD. WG2) Overcoming the main hurdles to the rollout of MR techniques (validating protocols across platforms and sites, sharing expertise so that staff can run protocols reliably) will maximise the potential of

MRI and MRS as a quantitative OM in clinical trials. Its sensitivity to change compared to standard motor function measures may also enable trial results to be achieved more quickly. International consensus will enable recommendations to be provided to regulatory bodies, industry and academia regarding protocol optimisation for robust multicentric trial results. Implementing imaging protocols in centres in Eastern and Southern Europe will extend the number of qualified trial sites and will thereby help to recruit patients into the growing number of natural history studies and trials that require muscle imaging as an outcome measure. WG3) The development and application of protocols for novel imaging techniques will contribute to the improved characterisation and understanding of NMD. The next step will be to transfer the best proposals to WG2 and to enrich the range of OMs available as routine tools. WG4) The identification of new image texture analysis algorithms will also contribute to the advancement of science and knowledge in NMDs. The optimised texture analysis tools that will result from this study will be incorporated in the list of recommended imaging OMs for clinical studies.

C.5 Target groups/end users

The end users of the Action results will be several neuromuscular stakeholder groups. The immediate target group of the Action are neuromuscular clinicians, radiologists and basic scientists involved in imaging. Representatives from all these stakeholder groups have contributed to the proposal. The wider neuromuscular community will exploit those results from the Action with a direct impact on the diagnosis and care of patients. Patients with rare disease are very well educated about their conditions and neuromuscular patient organisations will be interested in the outcomes of the Action and their translational relevance. As the Action will help build the scientific evidence for muscle MRI and MRS as a reliable outcome measure to monitor disease progression and therapeutic efficacy, pharmaceutical companies will be interested to integrate imaging techniques into trial protocols. Industry participation in the workshops will be encouraged by the MC of the Action. Regulatory authorities have already suggested that MRI and MRS might be appropriate methods to complement results from physical assessments and will review outcomes from the Action.

D. SCIENTIFIC PROGRAMME

D.1 Scientific focus

The scientific programme of the Action has been developed to achieve the objectives and benefits

described in Section C. Contributions to the proposal were mainly provided by clinicians and researchers involved in the Working Groups and the proposal was reviewed by a muscular dystrophy patient organisation. Each of the 4 proposed Working Groups has specific tasks that need to be addressed in a collaborative effort to achieve the objectives.

WG1: Diagnosis and muscle pathology

Focus and research tasks: In a number of NMD the pattern of selective muscle involvement detected by MRI can almost be pathognomonic and can help guide genetic testing, target the optimal muscle for biopsy, and explore pathomechanisms. Yet MRI for diagnostic purposes is still not applied in a standardized fashion across neuromuscular centres and often depends on the interest of individual investigators. Patients might both miss out on the opportunity to have an MRI that could contribute to a proper diagnosis and the selection of an appropriate biopsy site or might have an MRI with no added value. Although diagnostic scanning is resulting in an increasing body of MR data, these data may never be published or publicly shared and thus are lost to science. Pooling these data through effective networking will help to define the spectrum of selective patterns of pathology (including muscles not normally biopsied, e.g. diaphragm, trunk, neck and head), to answer questions about why certain muscles are spared from pathology despite ubiquitous protein expression and to better understand disease onset, progression and pathophysiology. Tasks for WG1 will be to coordinate the pooling of diagnostic scans scattered across neuromuscular centres in Europe, to develop a secure online inventory and to agree a policy that will regulate data sharing and ownership, patient confidentiality, dissemination strategies and publications. Recommendations about the diagnostic relevance of MRI in certain clinical phenotypes will need to be elaborated. It is already known that MRI can be very helpful to guide genetic testing in patients with myofibrillar myopathies, collagen VI related myopathies and RYR1-associated myopathies, but that it adds little or nothing to the diagnosis of DMD, several of the limb girdle muscular dystrophies, myotonic dystrophy and several of the hereditary neuropathies. For a large number of NMD the added value of MRI is not yet known, which is mainly due to the rarity of the diseases. Over the period of the Action WG1 will address this issue by allowing both centres involved in the Action and centres currently not involved to pool images from a broad spectrum of NMD in a secure online database that will form the basis of a publically accessible imaging atlas for NMD.

WG2: Multicentric outcome measures (OMs)

Focus and research tasks: While the concept that quantitative MR protocols have much to offer as OMs in NMD clinical trials is now well accepted, developing robust protocols validated on the numerous different MR platforms remains a challenge and is a prime example of an area where non-competitive international collaboration between groups is the only way to advance the field as a

whole. This WG will build on and refine already published harmonised cross-platform protocols for Dixon acquisition for quantitative evaluation of fat infiltration and for T2 acquisition for quantitative evaluation of muscle oedema / inflammation and will develop the latest innovative techniques to the point where they can be reliably used in a cross-platform setting. The WG will also review published and non-published data on muscle MRS that have been suggested as outcome measures and will develop and refine protocols that can be used across centres and vendors. An important task for the WG is to keep track of the performance of new NMR scanners, operating systems and sequences updates and to establish and maintain procedure equivalence and consistency across sites. This task requires that imaging centres that operate NMR scanners from different vendors acquire data in such a way that parametric maps generated from image analysis are directly comparable. Scanners with increased performance are regularly introduced and are sold as new systems or major upgrades are proposed for retrofit into existing systems. This makes it necessary to keep track of protocols and sequence changes on all existing platforms and to make sure that instructions for quantitative imaging of NMD exist or are properly updated for each type of platform. WG2 will also evaluate the clinical application of new MR protocols developed by WG3. While this may seem similar to the previous task, the focus of this task is to evaluate the technical improvements proposed by researchers from WG3, to determine their added value as compared to standard solutions proposed by manufacturers, and, if the evaluation is positive, to establish corresponding protocols for different platforms and to integrate these new protocols into established imaging examinations.

OMs defined by MRI and MRS parameters will need to be correlated with clinical outcome measures and other biomarkers that have been suggested for NMD or are currently under investigation. Aside from the availability of validated protocols, perhaps the single biggest barrier to wider use of MR techniques as OMs in clinical trials is lack of expertise in standard imaging departments in the use of these novel quantitative techniques. The task of this Working Group will therefore be closely linked to a coordinated communication and dissemination strategy supported by the SG.

WG3: New contrasts, new targets and new imaging techniques

Focus and research tasks: The development of multicentric protocols for quantitative T2, Dixon and 31P MRS at rest has been the turning point in the use of MRI & MRS as an OM in NMD. For the field to continue to advance, new techniques must be applied to muscle and new targets affected in NMD (e.g. spinal cord and diaphragm) addressed. Such research focus is already beginning in individual labs, but muscle MR still lags behind the brain imaging field and it is essential to accelerate progress by sharing concepts / protocols at an early stage. Tasks of this WG are to bring

together researchers in a “firewalled”/confidential setting to share unpublished data, work on novel ideas, and develop joint protocols e.g. ultra short echo time (UTE) for fibrosis visualisation, Carr Purcell Meiboom Gill (CPMG) pulse sequences for T2 deconvolution, diffusion tensor imaging (DTI) for microstructure muscle organisation, and magnetisation transfer (MT) for interaction between water and macromolecules. These techniques will then feed into WG2 once they have reached a sufficiently advanced stage for cross-platform validation and publication.

WG4) Muscle imaging texture analysis

Focus and research tasks: Texture analysis of NMR images has been investigated by several groups and some applications to NMD were proposed. Previous work focused mainly on fat infiltration detection and provided results that did not provide any added value when compared to standard MRI contrasts. The aim of this WG is to identify texture features that can reflect structural changes in the muscle and that can be complementary to other outcome measure, including relaxation times and fat ratio. In order to improve the efficiency of the technique, attention has to be paid to the image acquisition process and the best contrast or combination of contrasts has to be established. This task involves scientists from different fields (NMR physicists and image processing specialists). Another task for WG4 is the construction of an image database that contains all the NMR contrasts used in the context of multi-centric outcome measures. In a second step, texture analysis techniques have to be systematically tested on the data and the most promising techniques will be optimized.

D.2 Scientific work plan methods and means

This COST Action will consist of four Working Groups (WG1-4) that will share expertise and collaborate on the corresponding objectives and research tasks described in section C and D1. All WGs will have 2 meetings per year throughout the duration of the COST Action (see Section F). WGs will be coordinated by a WG coordinator with support from WG members as described in section E2. The meetings will be the main networking forum and consensus building mechanism. The meetings will be open to participants that want to join the Action.

WG1: Diagnosis and muscle pathology

Work plan and methods: This WG will mainly consist of clinicians that have expertise in muscle pathology and muscle imaging and have scanned neuromuscular patients for diagnostic purposes and for the collection of natural history data. In order to achieve the tasks in WG1, the WG coordinator will identify leads for specific diseases or disease groups based on their clinical and

imaging expertise. The leads will coordinate the pooling of existing images for the diseases/disease groups they are responsible for. The WG will first focus on NMD for which imaging data are already available. For these diseases (e.g. congenital myopathies, myofibrillar myopathies, limb girdle muscular dystrophies, FSHD, channelopathies) the WG will review current suggestions for typical MRI patterns, which are often based on recommendations from a single centre with a possible bias towards e.g. paediatric or adult cohorts. Algorithms for pattern recognition that have already been published by individual centres will also be reviewed. An inventory of existing images and published algorithms will help to come to an agreement among the WG participants whether there are enough data to speak of a selective pattern of muscle involvement, or whether additional scans need to be collected. The Working Group will agree on criteria (e.g. number of scans, age range, range of disease severity, genetic mutations) that will define a typical pattern of muscle involvement in a given NMD and criteria that would be compatible with (but not typical) for a specific NMD. The criteria will be refined throughout the duration of the Action.

As for most NMD there is still a lack of MRI data, the WG will prioritize for which diseases it would be most helpful to collect imaging data for diagnostic purpose and have consensus WG meetings. There will also be dedicated WG meetings to share muscle images with an interesting pattern of muscle involvement in undiagnosed patients. Such a workshop will help to collect cohorts of patients that might share the same underlying diagnosis, which can be useful to identify new disease genes. The Action's Steering Group will support the WG coordinator in setting up an online inventory for images and to develop an online muscle imaging atlas that will be publically available.

WG2: Multicentric outcome measures (OMs)

Work plan: In order to achieve the tasks in WG2, consensus has to be reached on what are the most appropriate protocols to assess muscle pathology by various MRI and MRS techniques. Already published protocols and SOPs will be reviewed and refined by the WG. The main SOPs to be reviewed will be on

a) quantitative mapping of muscle replacement by fat

b) muscle T2 mapping,

c) P31 NMR spectroscopy.

NMR physicists and specialists of the WG2 will at their respective sites monitor the introduction of technical upgrades and novelties, will communicate their findings to their colleagues, will propose changes and adaptations to the existing instructions, and will have Working Group meetings to reach consensus and propose SOPs that are updated and adapted to most NMR imaging platforms. Another task of the WG2 will be to determine which OMs are the most sensitive indicators of

disease progression and of a positive response to treatment. Depending on the pathophysiology of a specific NMD, e.g. whether the disease shows a strong inflammatory component or muscle atrophy, the WG will establish which imaging protocol is most appropriate to monitor the disease and how imaging results correlate with clinical changes over a certain time period. Input from patient representatives and clinical trialists (both from academia and industry) will help to make sure that the protocols are not too burdensome for patients, economically justifiable and accepted by regulatory authorities. By focusing on training opportunities for MR staff in academic centres, this WG will also ensure the preparedness of the field for upcoming trials.

Throughout the duration of the Action the WG will integrate technical improvements proposed by WG4 into already established imaging SOPs. The refinement of protocols will be discussed with patient representatives and clinical trialists for their clinical feasibility and whether applications in a paediatric population are appropriate.

Putative new SOPs will be on:

a) quantitative imaging of muscle fibrosis using ultra-short TE sequences

b) quantitative diffusion imaging and evaluation of muscle disorganisation

c) 23Na imaging

d) magnetic transfer contrast imaging.

The WG will propose which SOPs should be applied in natural history studies and clinical trials and how imaging readouts can be correlated with outcomes from physical assessments like the 6-min walk distance (6MWD) and blood, serum and urine biomarkers that are currently under investigation. The WG with support of the SG aims to communicate and collaborate closely with the TREAT-NMD Alliance, pharmaceutical industry and academic trialists. Representatives from these groups have either already expressed their interest to participate in the Action or may join the Action when appropriate.

WG3: New contrasts, new targets and new imaging techniques

Work plan: For each of the tasks that will be addressed by the work plan of WG3, the most experienced researcher in the sub-field in question will be in charge of coordinating the preparation of a consensus document for a research strategy. Research strategies will be developed for:

a) optimizing muscle fat content determination by better modelling of the fat spectrum in the fat-water separation algorithm

b) extraction of the muscle fat content from the T2 acquisition schemes, and more generally speaking, the investigation of all possible methods that might speed up acquisitions by the simultaneous acquisition of fat content and T2 information;

c) improvement of T2 mapping specificity by T2 spectrum calculation and identification of the

cell/tissue compartment involved

d) identification of skeletal muscle interstitial fibrosis by:

- visualization of connective tissue component by optimization of ultra-short T2 sequences

- quantification of “signal loss” in fully quantitative Dixon imaging

- zero quantum NMR imaging and magnetization transfer contrast

e) evaluation of the added value of skeletal muscle diffusion tensor imaging to standard T2 mapping

f) 23Na imaging for the investigation of sarcolemmal leakiness

The absence of satisfactory solutions and the crucial functional implication of fibrosis justify the diversity of the suggested approaches. Mapping of T1 shortening post Gadolinium chelate injection is a validated method to quantify myocardium fibrosis in adult cardiology. Due to the high proportion of paediatric cases in the neuromuscular population, the technique is unlikely to be transposable to muscle fibrosis evaluation in NMD, but might serve as a reference for the validation of new contrast agents.

Muscle fibre orientation display based on diffusion tensor orientation is a fancy application, with little practical use. Other sophisticated methods will be implemented and tested in order to obtain specific information on muscle fibre dimension, fibre bundles disorganization and sarcolemmal permeability.

WG4) Muscle imaging texture analysis

Work Plan: To achieve the tasks of WG4, which is composed of image processing experts as well as NMR physicists and radiologists, it will be coordinated by a specialist with a multidisciplinary background. The tasks will be addressed by the following work plan:

a) The construction of a data base of images including healthy controls and patients with selected diseases of interest.

b) The identification of NMR contrasts with minimum impact from fat infiltration on the texture analysis results. The selection will start from the sequences introduced in WG2 and possible candidates are proton density images and fat corrected T2 weighted images. In collaboration with WG3, sequence parameter optimisation will be implemented to improve texture analysis performances.

c) The use of statistical analysis techniques as well as classification approaches and the selection of texture parameters that best reflect changes in muscle structure. This step will be carried out with

the help of radiologists. The results will be correlated with novel outcome measures generated in WG3.
d) The evaluation of the impact of imaging artefacts and image inhomogeneity, as well as some correction techniques, on the performance of the different texture parameters.
e) The application of algorithms to other types of NMDs, with the objective of determining whether the texture indices will correlate with the same structural changes as in the initial data set.
f) The introduction of a texture-analysis approach in a multi-centre study in order to evaluate the impact of the MRI scanner type and configuration on the performance of each feature, and to study the robustness of the selected texture features. In case of positive results texture parameters will be integrated in WG2.

E. ORGANISATION

E.1 Coordination and organisation

The COST Action will follow standard COST management procedures through the formation of a Management Committee (MC) and four Working Groups (WGs). The COST Action will be formally led by the MC. In addition, to ensure there is a smaller group of participants who are highly active in the Action, committed to meeting its objectives and able to be more immediately responsive than the full MC, a Steering Group (SG) will immediately be implemented. This SG will consist of the Action Chair and Vice Chair, coordinators of the 4 WGs, the Dissemination and Training Manager (see below) and a patient representative.

Management Committee
In-person MC meetings will take place every 6 months and will normally coincide with a WG scientific workshop. Ad-hoc meetings outside this timeframe may be convened by the Action Chair by teleconference if required for any urgent purpose.
In addition to the responsibilities set out in the Rules and Procedures, the tasks of the Management Committee will include:

- Appointment of WG coordinators (as well as Action Chair, Vice-Chair).

- Appointment of a Dissemination and Training Committee (DTC) to coordinate the clear need for the outputs of this Action to be exploited and put into general practice and to

review applications for STSMs from ESRs and other researchers/experts, and a Dissemination and Training Manager to lead this Committee.

- Assessment of the progress made by the WGs and STSMs in meeting their respective objectives and milestones, based on update reports to be requested from the SG on a quarterly basis.

- Implementation of mitigating actions in the event that WGs fail to meet their milestones or objectives in a timely fashion.

- Ratification of a collaboration agreement to be drafted by the SG and put into place prior to any STSM or data sharing activity to cover issues of IPR and confidentiality

- Promotion of cooperation and exchange between the Working Groups.

- Promotion and approval of STSMs, according to the recommendations of the STSM evaluation committee.

- Establishment of a conference secretariat for the Action conference, including a local organising committee and a scientific committee.

- Preparation of Annual Reports.

- Organisation of contacts and common workshops with the appropriate ongoing COST Actions and other relevant scientific platforms to address problems of common interest.

- Ensuring that the Action outputs are delivered with the most efficient use of COST resources.

Steering Group

The SG consists of the Action Chair and Vice Chair, the coordinators of the 4 WGs and the Dissemination and Training Manager. It will meet by teleconference every two months.

To ensure the Action is able to make rapid progress, the SG will be constituted immediately after the launch of the Action and will take on primary responsibility for driving progress on the following activities, which are then ratified by the MC as appropriate:

- Establishment of the Action website to host all information about Action events, conferences and outcomes, publish calls for applications for STSMs from ESRs and encourage new groups to participate, to host all SOPs and other documentation that may be publicly disseminated, and to host the MR Atlas that is the primary outcome of WG1. The website will be maintained by the Action Chair with assistance from the local admin team using a content management system that enables access rights to be given to select other participants as appropriate and will be regularly maintained as it is one of the primary dissemination tools of the Action.

- Drafting of a collaboration agreement on IP and confidentiality to be ratified by the MC and put into place across all participants of the Action, with the aim of promoting sharing of unpublished and confidential research data within the group.

- Monitoring of progress against the milestones established for each WG, for Dissemination and Training, and for STSMs, with each member of the SG responsible for their own WG or area and responsible for reporting to the MC on a quarterly basis or an ad-hoc basis if urgent intervention is required.

- Disseminating the policy for coordination of national research based on the objectives of the Action and as described in full in the Scientific Programme, including the creation of research teams, conference and training events and STSMs.

- Monitoring activity in the field, including activity funded by European and global mechanisms, and actively seeking new links and collaborations and inviting appropriate experts to join the Action as appropriate, to ensure maximization of collaboration and avoid duplication of effort.

The perspective of patient representatives will be actively taken into account to ensure this Action's objectives and outcomes meet their needs.

E.2 Working Groups

Four WGs will be established according to the scientific programme outlined in Part D. Each WG will be managed by a WG Coordinator assigned by the MC, assisted by up to 3 other WG members as vice-coordinators if appropriate for particular activities (e.g. acting as a planning committee for workshops). Where possible, WG coordinators and vice-coordinators will be from different institutions to reflect the breadth of expertise and groups involved in the Action, and inclusion or promotion of ESRs to these positions will be encouraged. The tasks of WG coordinators will include:

- Sitting on the SG for the Action and fulfilling all its objectives as defined in E1.
- Coordination of the activities within the WG to meet the objectives and milestones.
- Planning the appropriate WG meetings and all other scientific meetings within their own WG.
- Leading the writing or delegating lead authorship if appropriate, of reports and academic publications associated with WG deliverables.
- Promoting joint research activities between institutions engaged in the WG activities, including STSMs on specific research areas, and the writing of common publications.
- Participation in the plenary and SG meetings.

WG meetings will take place every 6 months and will be a mixture of strategic planning meetings and broader workshop-type meetings that aim to achieve specific consensus between experts or similar WG objectives. Both types of meeting will have the aims of exchanging information and ideas, stimulating synergy between researchers, clinicians, institutes and countries, to address the topics specific to each WG and to plan joint research.

E.3 Liaison and interaction with other research programmes

There are a number of Framework Programme (FP) initiatives with activities in related areas, none

of which address the objectives of this COST Action (no overlap of activities) but all of which would benefit from links with the Action and which in turn could provide useful input to the Action. The most significant projects are described here, but it is the task of the Steering Group to monitor the field to ensure that new links are developed through the course of the Action. A significant NIH grant to US groups has recently enabled US colleagues to develop their MR collaborative research and Europe risks lagging behind without an active consortium to go beyond individual research activities and drive pre-competitive collaboration. In addition to 15 leading groups from 8 COST countries who have so far signed up to this Action, US experts have signalled their willingness to contribute and there is thus a real opportunity to develop a strong global consortium.

TREAT-NMD (www.treat-nmd.eu) was an FP6 Network of Excellence for rare inherited neuromuscular disorders that has now transitioned to a post-FP-funding "Alliance" of leading NMD specialist groups worldwide. It has an extensive and widely used website, a monthly newsletter reaching 3500 stakeholders, and arranges meetings of NMD experts, and is thus an ideal partner for this Action to disseminate its outcomes and increase its reach to the appropriate expert community and to patient stakeholders.

Neuromics (www.rd-neuromics.eu) is a new FP7 initiative for omics research in neuromuscular and neurodegenerative disorders. Its objectives relating to personalised therapy development will certainly benefit from the additional knowledge that this Action brings in the area of quantitative outcome measures suitable for use in clinical trials.

RD-Connect (www.rd-connect.eu) is a new FP7 infrastructure platform for sharing rare disease research data, in particular omics data and registry and biomaterial data, and links will be developed with this platform to ensure outcomes such as SOPs may be disseminated to rare disease researchers as appropriate.

IRDiRC (www.irdirc.org), the International Rare Diseases Research Consortium, is a collaboration between major medical research funders worldwide which has the objectives of developing 200 new rare disease therapies and diagnostics for all rare diseases by 2020. All IRDiRC members will be informed of the potential relevance of this Action to the projects they fund and links will be sought with any relevant projects.

National initiatives in participating countries will also be monitored to ensure synergies, for example the UK Medical Research Council's Centre for Neuromuscular Diseases, a joint initiative between leading expert NMD centres in the UK, and equivalent national funding initiatives in other countries. These will provide excellent opportunities for seeking additional participants who may wish to join the Action and also for disseminating its results. Similarly, existing bilateral initiatives between countries such as the CAPES COFECUB collaboration between France and Brazil which

is currently funding exchange of early stage researchers between MR labs offer opportunities for enhancing COST outcomes outside COST countries.
Links will also be initiated with related COST Actions, including the "MRI PET" COST Action, and the new Action "Networking towards clinical application of antisense-mediated exon skipping", which in looking at biochemical outcome measures in a related neuromuscular disorder may also reveal complementary data.
Trial-related projects such as the FP7-funded SKIP-NMD (exon skipping in Duchenne muscular dystrophy) and industry-sponsored trials will also actively be brought in, as they may be among the first projects to benefit from the new SOPs to be developed.

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

Gender balance

The She Figures 2012 publication reveals a number of positive trends for women in science; for example, the share of women among scientists and engineers has grown significantly (+5.4% on average per year between 2002 and 2010, compared to +3.1% for men). In 2010, tertiary-educated women employed as professionals or technicians now outnumber their male counterparts by 3 percentage points. However, it also indicates that women remain a minority in scientific research, accounting for 33% of researchers in the EU in 2009. This COST Action recognises the importance of gender balance and will monitor it during the course of the Action. A significant number of the experts involved in the COST Action at the application stage are women, including some internationally recognised researchers as well as a number of early stage researchers in the participating MR labs. The COST Action will aim to encourage retention of these researchers and in particular to promote their career development, as the gender gap at a leadership level has been identified as one of the causes of the perpetuated gender imbalance in sciences. The specific objectives described below and aimed at the retention and career development of ESRs will include gender balance as one of their criteria.

ESRs

As explained in the scientific section, the rapid growth in utility of MR in this field has resulted in a deficit of adequately trained ESRs – indeed, some labs struggle to recruit adequately qualified technologists and physicists and this is recognized as one of the bottlenecks to wider rollout of the cutting-edge techniques being developed in individual centres. The COST Action has a comprehensive strategy for encouraging ESRs and is committed to maximizing opportunities for

training and exchange as this will benefit all participating labs and the field as a whole. For career development, ESRs will be strongly encouraged to take on a coordination role in WGs, chair discussions in workshops and sessions at the Action conference, take on lead authorship in preparing scientific publications and be proactive in steering the Action agenda to support their training and development. STSMs within and also between the different WGs will help to coordinate the research strategies in the field through the establishment of improved cooperation between the participating institutes. Exchange and mobility of scientists will not only strengthen the cooperation within and between the institutes but also provide unique opportunities for the training of young scientists. Furthermore, for promising ESRs to go on to apply for their own investigator grants, scientific study visits abroad and international experience are often a prerequisite, and this COST Action thus has the potential to act as a stepping stone for such promising individuals to gain the required experience to go on to become principal investigators in their own right.
Funds for STSMs will be awarded competitively by the DTC based on applications received after promotion of the opportunities online and in participating labs. The committee will award funding according to the relevance to the Action's objectives and the quality of the candidate. STSMs should directly contribute to fulfilment of a specific Action objective and usually contribute towards a joint academic publication.

F. TIMETABLE

The proposed duration of the Action is 4 years. WGs will meet every six months, with an initial 'kick off' workshop involving all WGs. Subsequent WG meetings will normally take place on consecutive days or together to ensure cross-fertilization, with the aim of at least one annual meeting that is a combination of WG meetings. Where appropriate these workshops will be held with other COST Actions or FP Programme projects to allow for the cross-fertilisation of outputs and ideas. Management Committee meetings will take place every six months, linked with the scientific meeting of a WG where possible. SG meetings will take place every three months by conference call.
The preliminary timetable is provided below. Flexibility will be built in to enable WG meetings to take place together or separately depending on progress and need to share results.

	Y1Q1	Y1Q2	Y1Q3	Y1Q4	Y2Q1	Y2Q2	Y2Q3	Y2Q4
WG1	X		X		X		X	
WG2	X		X		X		X	
WG3	X		X		X		X	

WG4	X		X		X		X	
MANAGEMENT	X		X		X		X	
STEERING GROUP	X	X	X	X	X	X	X	X
CONFERENCE								
SCIENTIFIC ACTIVITY								
	Y3Q1	Y3Q2	Y3Q3	Y3Q4	Y4Q1	Y4Q2	Y4Q3	Y4Q4
WG1	X		X		X		X	
WG2	X		X		X		X	
WG3	X		X		X		X	
WG4	X		X		X		X	
MANAGEMENT	X		X		X		X	
STEERING GROUP	X	X	X	X	X	X	X	X
CONFERENCE							X	
SCIENTIFIC ACTIVITY	* * *	* * *	* * *	* * *	* * *	* * *	* * *	* * *

G. ECONOMIC DIMENSION

The following COST countries have actively participated in the preparation of the Action or otherwise indicated their interest: BE, CH, DE, DK, EL, FI, FR, IT, NL, PL, UK. On the basis of national estimates, the economic dimension of the activities to be carried out under the Action has been estimated at 44 Million € for the total duration of the Action. This estimate is valid under the assumption that all the countries mentioned above but no other countries will participate in the Action. Any departure from this will change the total cost accordingly.

H. DISSEMINATION PLAN

H.1 Who?

To maximize the dissemination of the results of this COST action, multiple target audiences have to be considered. The outcomes of WG1 will be of benefit to a wide variety of clinicians, physiotherapists, pathologists, outcome measures specialists and clinical researchers working in the neuromuscular field as well as MR specialists working on muscle imaging and should therefore be disseminated to clinical research networks and professional societies, specialist neuromuscular networks and national clinical networks and radiology networks and societies. It will also be

important to ensure clinically relevant outcomes such as recommendations of which diseases benefit from MR from a diagnostic perspective and which do not are incorporated into national and international guidelines where applicable, and appropriate national guideline-producing bodies will therefore be informed where appropriate.
The outcomes of WGs 2, 3 and 4 will be of interest to a variety of MR professionals (radiographers, physicists, clinical radiologists) and in particular it will be crucial to disseminate the standard operating procedures generated to all centres involved in clinical research protocols in NMDs where MR is used as an outcome measure. This dissemination and training aspect in particular for WG2 is essential for the roll-out of the techniques to such labs and must be considered a high priority for the WG. Since the techniques are expected to be useful in the monitoring of treatment effect, and the majority of treatment trials in these conditions are industry-sponsored, industry participants are a further key stakeholder in this regard and must be partners providing input into the process. Furthermore, patients with neuromuscular disease of course represent a key stakeholder as they need to provide input into acceptability of protocol design in terms of patient burden and need to understand the potential benefits and limitations of these new techniques.

H.2 What?

The COST Action will make use of a wide variety of dissemination methods to reach stakeholders. The primary dissemination outcome of WG1 will be the online atlas of muscle imaging itself. This will be a permanent and publicly available online resource for the community and the dissemination strategy will have a dual focus: maximizing awareness of the availability of the resource as a reference for professionals, and encouraging contributions from professionals who have scan data they would like to incorporate.
For working group 2, the dissemination mechanisms include the publication of peer-reviewed academic journal articles providing comprehensive guidelines and standard operating procedures for optimised techniques, plus the training schools to roll out the technique in new centres. Wherever possible in line with copyright restrictions, full text of articles will be made available via the Action website together with any appropriate supplementary material: the nature of these publications as guidelines means that maximizing accessibility is important.
For all WGs, oral presentations and posters at neuromuscular and neurology conferences such as the World Muscle Society or European Paediatric Neurology Society and at radiology/MR conferences such as the International Society for Magnetic Resonance in Medicine will be a key dissemination mechanism.

The Action Conference planned for Y4 will be a major dissemination event spanning all stakeholders.

H.3 How?

The Action will aim for a high profile in all its dissemination activities for the practical reason that all of its outcomes require uptake and implementation by the community for maximum impact. Participants in the Action, including the proposer, have experience in dissemination activities in Framework-funded projects and will make full use of their prior knowledge and networks of contacts.
The dissemination methods will be used in the following ways:
Web

- Publication of news items, summary reports, events listings, STSM calls etc. on websites of high profile related projects with whom the Action has a relationship (TREAT-NMD, RD-Connect...) – linked to the Action website

- Publication of reports, full text of guidelines, academic publications etc. on the Action website

- Publication of details of events, STSMs, background information and practical information for Action members on the Action website (which will have an intranet/filesharing facility for sharing of non-public documents)

- Development and maintenance of the Muscle Imaging Atlas as a permanent and publicly accessible online resource

- Active maintenance of and contribution to the Action website and Atlas to give it a profile in its own right.

Academic publications and conference presentations

- Consensus reports, SOPs, guidelines, scientific papers on new outcomes – where possible these will always be peer-reviewed academic publications as this is still the

recognised mechanism for scientific acceptance; however, attention will be paid to ensuring open access to the published article and to publishing additional data and background via the Action website

- Oral presentations and posters at appropriate scientific meetings will have a similar role in terms of traditional scientific recognition. ESRs will be actively encouraged to present COST outcomes at meetings and opportunities sought amongst the related networks to present at meetings where large numbers of the target stakeholders will be in attendance

Training schools

- Training schools in the techniques will be held at a central location to enable the hands-on training of groups of specialists who need to develop the skills to carry them out in the approved way to enable cross-centre comparability

Reports and recommendations

Outcomes of relevance for healthcare will be summarised in key findings documents to be provided to the appropriate healthcare bodies

Outcomes of relevance for industry will be disseminated via similar summary documents to maximise the uptake of approved standards at the protocol design stage.

Efforts will be made by all individual Action participants at local, national and European levels to improve the dissemination of results to the appropriate stakeholders through use of direct contact, distribution of stakeholder reports and presentations at scientific seminars.