Proposal Application Form

I. General information

Acronym:

SOPHIA

Project Title:

Sampling and biomarker **OP**timization and **H**armonization **I**n **A**LS and other motor neuron diseases

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II. Abstracts

Scientific abstract of the project

Amyotrophic Lateral Sclerosis (ALS) is one of the most devastating diseases in neurology affecting some 50,000 individuals at any time in Europe, and causing around 10.000 deaths each year. The motor system (upper motor neurons in the motor cortex and lower motor neurons in the spinal cord) is preferentially affected, but there is an overlap with frontotemporal dementia (FTD). ALS represents a good model for study of all neurodegenerative conditions, as it has a characteristic phenotype, rapid progression and the correlation between diagnosis during life and autopsy diagnosis is close to 100%. However, validated neurochemical biomarkers for monitoring disease activity, earlier diagnosis and defining prognosis are lacking. Active European collaborations are in place for harmonizing clinical datasets, neuroimaging and neuropathology protocols. A preliminary strategy for harmonization of biological and tissue samples has been established. Standardized protocols for clinical data and sample collection are now urgently required for optimization and harmonization of biomarker development.

The overall aim of this proposal is to provide a common European strategy for the prioritization and selection of candidate biomarker domains for optimization and harmonization. This will in turn provide a long term platform by which existing collaborative structures that are relevant to neurodegenerative disease biomarkers (including academic initiatives, co-funding strategies, biobanks, industrial efforts, private-public alliances) are integrated within an inclusive web-based virtual biobank. Samples and clinical, imaging, neurophysiologic and neuropathological datasets provided by participating members can then be optimally utilized to enable state of the art collaborative analyses.

The established platform will act as an important communication channel between this consortium and the broader international ALS/Neurodegeneration field, to ensure that the optimization efforts are consistently applied. This will avoid duplication of work, and will ensure that the outcome of the project will be accessible to, and utilized by all relevant stakeholders. Ultimately, the platform will establish a permanent Interactive European ALS biomarker tool for all researchers, and will enable ongoing optimization/harmonization of novel biomarkers using an integrated and robust pan-European ALS methodology. The platform will allow interaction with those of other cognate groups (e.g the NEALS group within the US), with patient groups and other relevant stakeholders.

Lay Abstract

Amyotrophic Lateral Sclerosis (ALS) is one of the most devastating diseases in neurology affecting some 50,000 individuals at any time in Europe, and causing around 10,000 deaths each year. The main clinical features are weakness and wasting of muscles, but dementia may also occur. ALS represents a good model for study of all neurodegenerative conditions, as it has a characteristic phenotype, rapid progression and the correlation between diagnosis during life and autopsy diagnosis is close to 100%. However, validated neurochemical biomarkers for monitoring disease activity, for generating earlier diagnoses and for defining prognosis are lacking. Active European collaborations are in place for harmonizing clinical datasets, neuroimaging and neuropathology protocols. A preliminary strategy for harmonization of biological and tissue samples has been established. Standardized protocols for clinical data and sample collection are now urgently required for optimization and harmonization of biomarker development.

The overall aim of this proposal is to provide a common European strategy for the prioritization and selection of candidate biomarker domains for optimization and harmonization. This will in turn provide a long-term platform by which existing collaborative structures that are relevant to neurodegenerative disease biomarkers (including academic initiatives, co-funding strategies, biobanks, industrial efforts, private-public alliances) are integrated within an inclusive web-based virtual biobank. Samples and clinical/imaging/neurophysiologic and neuropathological datasets provided by participating members can then be optimally utilized to enable state of the art collaborative analyses.

The established platform will also act as an important communication channel between this consortium and the rest of the ALS/Neurodegeneration field to ensure that the optimization efforts are in line with the whole ALS/ND field, to avoid duplication of work, and to ensure better acceptance and utilization of the project results by all stakeholders. Ultimately, the platform will be used to disseminate the results to the whole ALS/Neurodegeneration field, and will act as a permanent Interactive European ALS biomarker platform for researchers to optimize/harmonize novel biomarkers using an established pan-European ALS methodology. The platform will also allow interaction with those of other cognate groups (e.g the NEALS group within the US) and with patient groups and other relevant stakeholders.

III. Detailed information

1. Background and present state of the art

ALS is one of the most devastating neurodegenerative diseases….

Amyotrophic Lateral Sclerosis (ALS) is one of the most devastating diseases in neurology affecting some 50,000 individuals at any time in Europe, and causing around 10,000 deaths each year. ALS is characterized by degeneration of motor neurons in brain (upper motor neuron) and spinal cord (lower motor neuron) leading to progressive failure of the neuromuscular system. ALS can occur in any individual at anytime in adulthood. Initial manifestations are weakness of limbs, or weakness in the bulbar region leading to abnormalities of speech and swallowing. The patient becomes paralyzed and dies as the result of respiratory failure. The median survival is 3 years after onset of symptoms and 66% of patients with ALS die within the first 1000 days from symptom onset. ALS represents a good model for study of neurodegenerative conditions in general, as it has a characteristic phenotype, rapid progression and the correlation between diagnosis during life and autopsy diagnosis is close to 100%.

…with insufficient tools for early diagnosis and disease progression monitoring and absence of curative therapeutics, due to lack of sensitive and specific diagnostic/monitoring ND biomarkers to be used in large multicentre trials, including risk-stratified cohorts and upcoming multicentre diagnostic and therapeutic trials.

ALS/MND represents a spectrum of neurodegenerative diseases, which include primary lateral sclerosis (PLS), progressive bulbar palsy (PBP), progressive muscular atrophy (PMA), ALS-frontotemporal dementia (FTD) and FTD. The disease spectrum is genetically and clinically heterogeneous which has major implications for diagnosis, prognosis and assessment of the likely specificity and efficacy of neuroprotective therapies. Currently, there is no specific diagnostic test for ALS. The diagnostic process is based on specialist clinical assessment, and the average delay from first symptom to definite diagnosis is 12 months. In such a rapidly progressive disease, this delay is an important obstacle to effective therapeutic intervention. Reliable biomarkers would be valuable in expediting earlier diagnoses, in unlocking key pathophysiological pathways, in subclassification of the heterogeneous disease states, for tracking disease progression and for monitoring response to therapeutic agents. Neurophysiologic and imaging markers of motor neuron loss have been recently developed. A validated novel quantitative motor unit estimation technique (MUNIX) provides an objective measure of the rate of lower motor neuron loss in individual patients. Upper motor neuron and brain involvement can be increasingly quantified by computational neuroimaging analyses. Advanced neuroimaging has an added capability in the identification of disease endophenotypes, and can be used to reflect neuropathology *in vivo* [2]. Notwithstanding, the majority of ALS biomarker discovery research has focused primarily on cerebrospinal fluid. To date, appropriately validated neurochemical biomarkers for earlier diagnosis, measurement of disease activity and defining prognosis are lacking. Although several candidate biomarkers exist, translation into clinical application has been limited by small sample numbers and by reduced availability of well-characterized longitudinal cohorts for independent verification. Moreover, protocols for sample collection and neuroimaging procedures with links to clinical datasets are not uniform, and the ability to share samples and information is accordingly limited.

Hypotheses driven approaches by a number of groups have established that CSF neurofilaments are of prognostic and diagnostic value in ALS and indicate that quantification of the very stable neurofilament heavy chain protein in CSF should be included in longitudinal studies.[3-5] Other potential biomarkers of ALS in CSF identified by more than one research group include TDP-43 and monocyte chemotactic protein -1 (MCP-1).[6-8] For proteomic studies in CSF the situation is more complex. Study cohorts have been small and control samples heterogeneous. Validation of candidates has been limited by the presence artifacts due to variations in sample collection storage and handling protocols (e.g. Control population sampled in a different hospital from ALS patients; e.g. Discussion on Cystatin C fragments in ref 12-13).[9-13]

No reliable blood biomarkers of ALS have been identified to date. Gene expression profiling (GEP) of blood has been used extensively in oncology. This technology has been used to determine biomarker profiles of genes differentially expressed between diseased and control tissue, to identify disease subtypes, to monitor disease progression, and to measure therapeutic response. The ubiquitous expression of proteins encoded by ALS genes (eg SOD1, TDP43, FUS) supports the role of blood as a potential source of biomarkers that reflect the neurodegenerative processes within the CNS.[14] Blood GEP has been performed in Huntington's, Parkinson's and Alzheimer's diseases.[15-17] However, these data have not always been reproducible between laboratories.[18,19] This highlights the need across all

neurodegenerative diseases to optimise, standardise and harmonise methods for sample collection, analysis of gene expression as well as the computation biology approaches for biomarker identification.

Genetic research has identified a wide range of “at risk” variants pointing to multiple pathways, most of which are incompletely characterized by pathology. A significant breakthrough occurred when TDP43 was identified as the major protein component of inclusions in sporadic ALS. TDP43 not only provides a molecular signature for ALS pathology, it also led to the unifying concept of the TDP43-proteinopathy spectrum, spanning from pure lower motor neuron disease cases to frontotemporal dementia phenotypes without motor symptoms. Almost uniquely in neurodegeneration, several of the genetic variants (demonstrated either in human pathology studies or in experimental models) drive TDP43 pathology. This observation offers a realistic opportunity to characterize a molecular pathway/cascade in TDP43 proteinopathy that in turn can interrogate multiple upstream and downstream targets for novel disease modifying strategies.

What is needed? There is an urgent need to develop diagnostic biomarkers to expedite diagnosis, characterize disease burden and to develop biomarkers that are predictive of disease course. This can be achieved by the development of:

- a common strategy for the prioritization and selection of biomarker candidates to be optimized and/or harmonized
- a pan European methodology to perform optimization and harmonization of these biomarkers
- an infrastructure strategy that identifies existing collaborative structures that are relevant to the optimization and harmonization of ND biomarkers, including academic (trans)national initiatives, co-funding strategies, biobanks, industrial efforts, private-public alliances, etc.

Pilot studies - To provide evidence for the need for harmonization and optimization of biomarkers in ALS we performed the following three pilot studies among the participating centers in SOPHIA:

1. Survey on sampling and storage of biosamples and clinical information - A survey was undertaken to determine the current status of collecting samples and level of input of clinical data into the centre database. It was shown that SOPs currently used differ substantially with respect to documentation of clinical symptoms (from 3 to 16 items), temperature of freezing (-20 to -80 ‘C), standardized time of the day for sampling, availability of control samples, etc. This emphasizes the need for harmonization.

2. Effect of sampling and storage on measurement of molecular biomarkers - In a pilot study with 6 participating centers we undertook a centralized measurement of CSF from these centers using standard CSF assays for tau protein, Abeta-Peptide, S-100B, neurofilaments, Cystatin-C and MCP-1. Inter-laboratory differences, even the most stable proteins e.g. tau-protein are immediately apparent. Baseline levels of these proteins showed considerable variation, although a difference in neurofilament levels between ALS and non-ALS patients was still observed (Figure 1a and 1b).

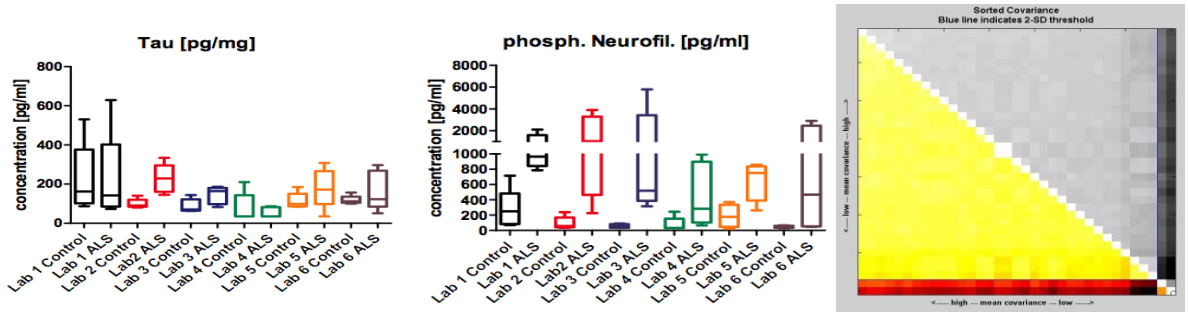

Figure 1 a, b *- Boxplots of tau protein and neurofilament levels ALS and control samples of different centers.*
Figure 1 c *- Sorted covariance of 35 processed high resolution T1 MR images from 7 centers .Datasets beyond and near the 2 S.D. threshold (dark red and darker yellow, respectively) indicate systematic deviations which require in depth analysis of error sources.*

3. Effect of acquisition protocol and scanner on results of MRI studies

A similar pilot approach was used to estimate MRI data quality in 7 centers (Figure 1 c). Covariance analyses were applied to high resolution T1 datasets of controls to screen for scanner and protocol specific outliers. These were quantified in a matrix plot which indicates a threshold of two standard deviations as cutoff (blue line). Based on this screening tool, secondary component analyses will be applied to identify the underlying factors and inform centers on likely causes of deviation within the MRI dataset.

2. Work plan highlighting the originality and novelty

2.1 Aim

Development of optimally informative biomarkers for ALS, and establishment of stakeholder agreement regarding their use. This will be achieved by defining, validating and harmonizing optimal methodologies that can be reliably implemented within a pan-European framework program.

2.2 Methodology

SOPHIA combines a consortium of leading ALS experts in Europe with an innovative and well-defined methodology to optimize biomarkers and harmonize their use across the whole ND field in Europe. SOPHIA is based on the following principles:

- Input from the whole ALS/ND field is crucial to combine strengths in the optimization phase, to avoid duplication of work, and to increase acceptability and uptake of results in the harmonization phase
- A common strategy for all optimization/harmonization efforts in the *grant application phase*, the *project execution phase* and *beyond* provides a solid and sustainable framework for transnational biomarker optimization and harmonization

Pan-European methodology in selection, optimization and harmonization of biomarkers, biomarker assays, and sample/data management

The optimization and harmonization efforts in SOPHIA follow a similar track for patient sampling procedures, data management, biomarker analytical methods and biomarkers. This common approach is outlined in the decision tree below (Figure 2).

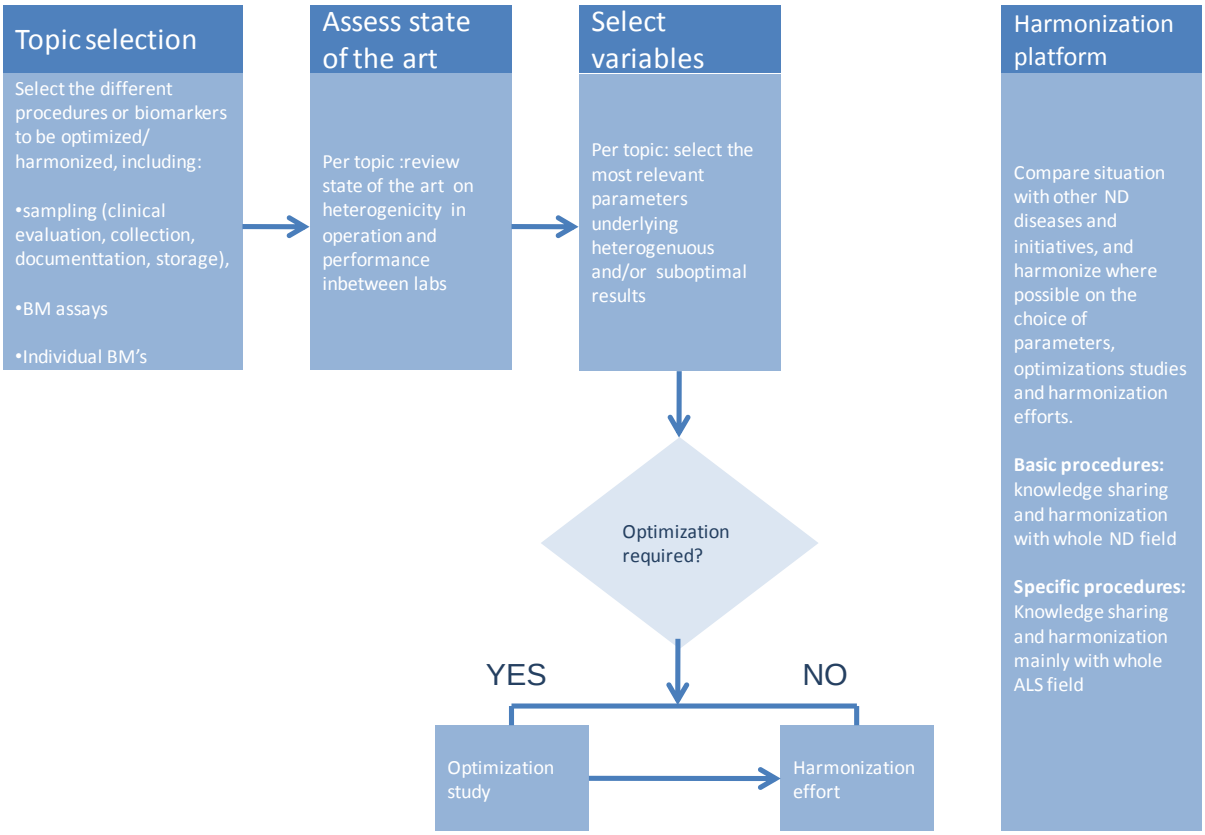

Figure 2 *- Pan-European decision tree for selection, optimization and harmonization of biomarkers, biomarker assays, and sample/data management. Selection and prioritization in each step will be based on annual consensus workshops (See WP4 and 2.7 for details).*

The optimization and harmonization approach as outlined in the decision tree above is an iterative process that will continue beyond the 3-year timeframe of this project. This will be undertaken via the innovation platform (WP4) by deciding on novel optimization/harmonization rounds in annual consensus workshops. The frequency of these optimization/harmonization rounds as well as items to be selected will depend on both performance aspects (e.g. optimization status of biomarkers) and the availability of additional sources of (co-)funding.

2.2.1 Work packages

The work is subdivided in work packages as depicted in figure 3 below. WP 1-3 relate to the optimization and harmonization of: (WP1) data management, (WP2) sampling and molecular biomarkers and (WP3) imaging and neurophysiologic biomarkers. WP4 is dedicated to the two-way communication with the entire ALS/ND field, to ensure that all input is acquired for efficient and effective optimization, and that all results are effectively disseminated for use within the wider neurodegeneration field.

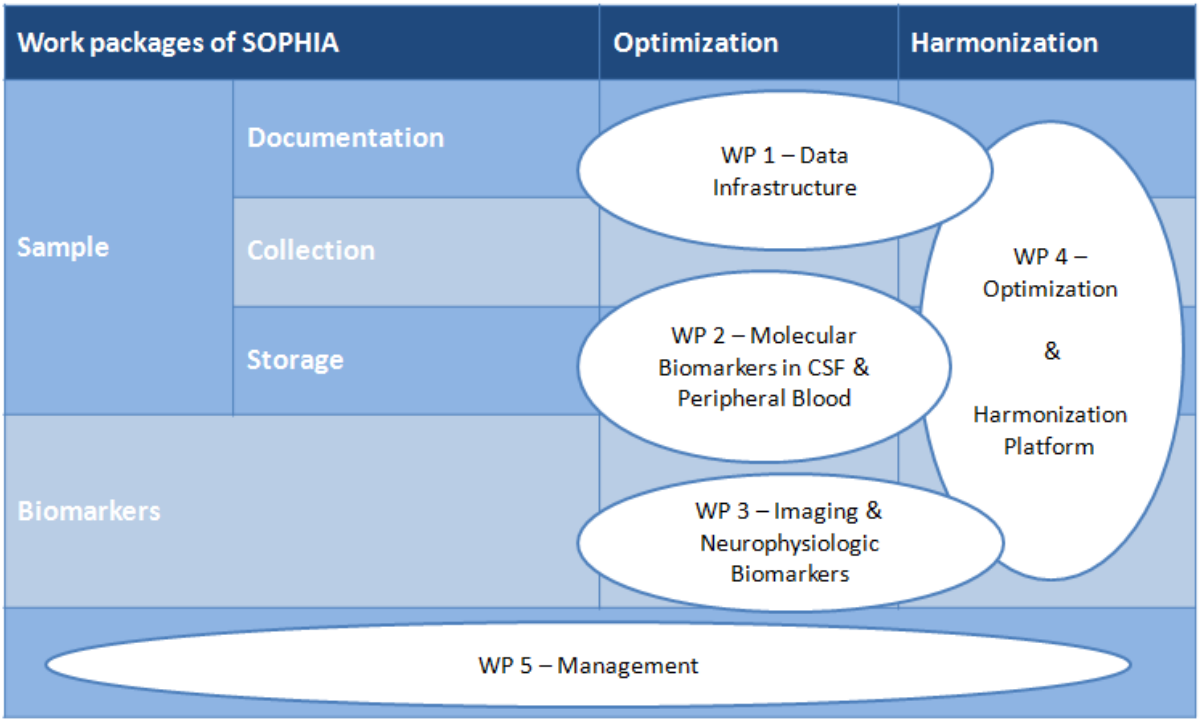

Figure 3 *Graphical overview of the work packages of SOPHIA*

2.2.1.1 Work package 1 Data infrastructure

Contributing partners: NET, BEL, FRA, GER1, GER2, IRE, ITA1, ITA2, POL, POR1, POR2, SPA, TUR, UK1, UK2

WP1 will utilize existing protocols developed by the EUROMOTOR consortium to optimize patient ALS biomarker sample documentation, collection and storage. This will be achieved by generating a minimal clinical dataset from ALS patients, based on current knowledge relating to existing diagnostic criteria and known prognostic indicators. In addition to the provision of clinical datasets, detailed protocols will be developed for uniform biological sample collection, including serum, plasma, urine, cerebrospinal fluid, DNA, RNA, fibroblasts and autopsy material. An integrated logistical framework will be established that will include sample tracking, storage and shipping parameters. The established platform will facilitate pan-European access to rare clinical and genetic variants of ALS/MND, and will include the added value of the establishment of state-of-the-art harmonised neuropathology protocols for optimal tissue collection, dissection, storage and pathological evaluation. The platform will provide

integration of well-established clinical, neuropathology and brain bank based networks and will thus generate data to facilitate a new clinical, genetic and pathological subclassification of sporadic disease as well as genetic variants. The neuropathology component will be coordinated by Professor Paul Ince (Curriculum Vitae on page 42)
Ultimately this work package will provide optimized and harmonized SOPs of patient biomarker assays, analytic methods and neuropathological techniques mapped to defined pathological and genetic subtypes of disease. Utilizing existing technologies including a web-based data repository provided by the EUROMOTOR consortium, this work will provide a fully integrated virtual biobank from which biological samples and clinical/imaging/neurophysiologic and neuropathological datasets provided by participating members can be utilized to enable state of the art collaborative analyses.

Tasks

T1. A core clinical dataset will be defined with validation of data administration across the centres.
T2. A web-based platform incorporating a virtual biobank will be established for the integration of core clinical variables with biomarker datasets from all patients from the participating centres. Auditing and quality control mechanisms will be introduced on the data included in the virtual biobank.
T3. Generation of SOPs for the collection and storing of biological material including serum, urine CSF, DNA, RNA,and fibroblasts.
T4. Collate existing repositories for biological material.
T5. Collate existing neuropathology donor cohorts (Partners 0,3,4,5,6,8,12,13,15,16).
T6. Undertake genetic screening of donor cohort cases as needed.
T7. Development, optimisation and validation of pathology protocols across the different centers.
T8. Dissemination of SOPs for the collection, and storage of biological samples and tissue from ALS patients.
T9. Bio-informatic analysis of neuropathology data with clinical/genetic data to develop disease subclassification.
T10. Clinical coordination including six monthly reporting of activity and progress in the work package.

Deliverables

Nr	Description	Delivery date
1	Establishment of a standardized minimal clinical data set	Month 6
1.1	Definition of relevant clinical variables, inclusion of chronological-progression markers based on validated functional scores.	Month 6
2	Establishment of common IT-platform – a virtual biobank	Month 12
2.1	Development of a Web based interface for accessing clinical parameters and data from biomarkers studies	Month 15
2.2	Development of a Web based logistical interface for tracking biological samples	Month 18
2.3	Established real time tracking of clinical data and biological samples across the consortium	Month 24
3	Consolidated database of existing brain donor cohorts	Month 6
4	Optimize protocols for the collection and storage of CNS and other tissues	Month 6
5	Bio-informatic analysis of neuropathology data with clinical/genetic data to develop disease subclassification.	Month 24
6	Peer reviewed publication of proposed protocols	Month 36
7	Presentation of findings at international symposium on ALS/MND	Month 36
8	Dissemination of findings via Brain Net, European Confederation of Neuropathological Societies, UK Brain Bank Network	Month 36

2.2.1.2. Work package 2 Molecular biomarkers in CSF & Peripheral Blood

Contributing partners: NET, FRA, GER1, GER2, ITA1, ITA2, POL, POR1, POR2, SPA, TUR, UK1, UK2

The proposed WP2 will directly interact with WP1, ensuring collection of a common clinical data set from patients for whom we also have optimally processed CSF and blood samples, with the ultimate goal of generating well defined patient cohorts for scientific interrogation of the biological data. The subsequent use of these cohorts will improve the evaluation of potential diagnostic and prognostic biomarkers, will distinguish different sub-groups of disease, will allow identification of indices of fast and slow disease progression and will improve our understanding of the pathophysiology of disease, thereby leading to the development of more effective treatment approaches. Ultimately, the established SOPs can be incorporated into clinical trials, to monitor the response of patients to the therapeutic compound. Here we will not restrict to classical protein assays but also harmonize and standardize our microarray technology to diagnose patients according to their underlying chromosomal and genetic aberrations, ultimately leading to an ALS profiler.

Tasks

T1: Within the first six months the group will come to a consensus regarding which protocols shall be used for biosampling and which biomarkers shall be measured. This time frame is realistic because of the extensive work done beforehand (see ref 1). At the outset, we propose to perform the following neurochemical profiling in all samples: albumin ratio (sample quality, blood-CSF barrier), ferritin/hemoglobin (sample quality, haemolysis), neurofilaments, MCP-1, progranulin, TDP43, sAPP (ALS-CSF profile). However this will be an open and ongoing process and will incorporate new findings as they are identified (e.g. measurement of progranulin and sAPP).

T2: Implementation of a first integration into a “round-robin” system – this is an interlaboratory qualitity contol program, which involves sending predefined standardized samples (CSF, blood) out as an external quality control of local test performance. We envisage that this will be possible within twelve months, as most of the groups already participate in existing monitoring and teaching initiatives (e.g. academic “round robin” for tau and abeta-peptides of K. Blennow, Sweden). Depending on the progress of this objective, several optimizations will be included. This is likely to be necessary once more advanced assays become available. Regular meetings (skype, telephone) will be held with colleagues representing WP4. For the “round robin” system we will not restrict ourselves to classical antibody assays but will also focus on targeted proteomic approaches such as multiple reaction monitoring (e.g. for TDP43). For the teaching initiative we will make use of the existing protocols of the German Society of Neurochemistry and CSF diagnostics (www.dgln.de; letter of support can be obtained from the coordination) and the “round robin” test organization (INSTAND e.V, www.instand.de (WHO Collaborating Centre for Quality Assurance and Standardization in Laboratory Medicine) letter of support can be obtained from the coordination). Teaching sessions will be undertaken either locally or at international ALS meetings (at least once/year). Additionally we will establish a monitoring system by employing a dedicated scientist with responsibility for quality control who will visit participating laboratories.

T3: For a “round robin” system as proposed in T2, a sufficient amount of test material should be available. Exact specifications have not yet been established for biosamples. Accordingly It will be necessary to obtain biological material (e.g. CSF) for initial analysis, and material with specific characteristics (e.g. CSF from ALS patients with high and low neurofilament levels). A centralized biobank will be built for reference material (CSF, blood specimen, round-robin biobank) and the partners will have the opportunity to share biological material. The biobank will also be used to validate new assays. In Germany ethical approval has already been obtained for this initiative. Samples for this approach will be stored in an anonymous manner. For some “round robin” systems (e.g. S-100B) it may be possible to pool material. A first “round robin” system should be established within the first year.

T4: To analyse the reliability of RNA isolation from peripheral blood for biomarker detection using gene expressionprofiling four different protocols will be evaluated: 1) whole blood, 2) LeukoLOCK isolated WBC, 3) Standard peripheral blood mononuclear cell (PBMC) isolation and 4) generation of lymphoblastoid cell lines. A simultaneous analysis of the relative proportions of specific blood cell subsets will be undertaken for each subject, to ensure that this can be taken into account in the gene expression profiling data generated.

T5: Gene expression profiles of 200 samples (4 blood biosample sources from 25 ALS patients and 25 controls) will be conducted using Affymetrix Exon Arrays and bioinformatic analysis performed to determine the level of concordance between the four different sources and to optimize the method for RNA isolation from blood. The RNA isolation method selected will be determined by the specificity of the emerging gene expression signatures for the ALS disease state, the verification of key gene expression changes by Q-PCR and the feasibility for widespread application in neurodegenerative disease clinics.

Deliverables

Nr	Description	Delivery date
1.1	Common SOPs for CSF, blood, blood products (lympocytes), DNA, RNA	6 month
1.2	First common basic neurochemical data set (e.g. albumin ratio, neurofilaments, MCP-1, progranulin, sAPP)	6 month (WP2) to end
1.3	Common basic neurochemical data set with internal and external quality control system	36 month (WP2)
2.1	Establish monitoring and teaching system for biosampling	6 month – end (WP2)
2.2	Integrate round-robin system in biosampling protocols (in coordination with AD initiative, public round-robin organisations, and national organisations for qualitiy control of neurological biomarkers (internal and external quality management)	12 month – end (WP2)
2.3	Common “round-robin biobank” for internal and external survey	36 month (WP2)
2.4	Common IT-structure for decentralized biomaterialbank (virtual biobank) according to NEALS, Euro-HD, FTLDc, German ALS registry	12 month – end (WP1)
3.1	Collect and process whole blood, LeukoLOCK WBC and PBMC from each individual	Month 12 (WP2)
3.2	Establish lymphoblastoid cell lines from each individual	Month 12 (WP2)
3.3	Blood RNA gene expression profiling	Month 18 (WP2)
3.4	Generate gene expression profiles for each individual from the four sources of RNA	Month 24 (WP2)
3.5	Bioinformatic analysis to establish optimized SOP for blood collection and RNA isolation	Month 30 (WP2)
3.6	Collection of blood using the optimized SOP from 1) ALS patients, 2) ALS disease variants, 3) ALS mimics, 4) other neurological diseases and 5) age and sex matched controls across centres for harmonization and quality control.	Month 36 (WP2)

2.2.1.3. Work package 3 Imaging & Neurophysiological biomarkers

Contributing partners: NET, BEL, FRA, GER1, GER2, IRE, ITA1, ITA2, POL, POR1, POR2, SPA, TUR, UK1, UK2

WP3 extends the clinical data in WP1 with standardized quantification of brain (MRI; upper motor neuron) and spinal cord (MUNIX; lower motor neuron) motor neuron involvement, the hallmarks of ALS. It aims to develop both techniques as widely applicable surrogate markers of disease stage and progression and as markers of therapeutic response in future drug trials. Acquisition of longitudinal MRI and MUNIX data along with other biomarkers will help to understand critical stages of upper and lower motor neuron demise. Thus, WP3 will complement WP1 and WP2 by developing quantitative markers of ALS-related tissue damage. These markers will be included in standardized ALS patient datasets, and will be available for scientific interrogation within the wider neurodegeneration field.
Computational MRI analyses are inherently investigator-independent but contain numerous potential error sources (i.e. protocol, scanner type and analysis tool). MUNIX measurements require standard electrophysiological equipment and validated SOPs exist, but investigator training is essential to establish cross- centre reliability. Thus, to implement optimization and harmonization, MRI requires continuous multicenter comparative analyses feeding identified sources of quality loss back to ALS centres. MUNIX demands analysis of factors influencing test-retest reliability across centres.[23-27]

The existing NISALS initiative (see ref 2) and its recent delivery of broad consensus guidelines has laid the groundwork for WP3 to analyse existing MRI acquisition and analysis parameters for brain VBM and DTI datasets in ALS patients; to harmonise these parameters across EU centres and to link MRI datasets to biofluid (blood and CSF) samples in the same individual. This will in turn allow the later development of a multimodal biomarker profile. In the shorter term, WP3 will help to estimate of the range within which MRI biomarkers report disease severity and progression of ALS in a quantitatively reproducible manner in a multicenter setting; and will implement a quality control "round robin" feedback system for centres wishing to use MRI as biomarker in ALS and other motor neuron diseases.

Tasks in MRI

T1. Registration of participating EU ALS centres to the Jena MRI database.
T2. Establish bidirectional interface to the core clinical data management in WP1.
T3. Assessment of acquisition parameters driving variability in T1W and DTI datasets
T4. Comparison of group-level results from different analysis platforms (SPM versus FSL versus TIFT).
T5. Identification of a standardised protocol for T1W and DTI acquisition.
T6. Linkage of core dataset (WP1) and non-MRI biomarkers (WP2) to individual MRI datasets to explore the addtional value of a multimodal profile.
T7. Implementation of standardised protocol prospectively in ALS and healthy control subjects.
T8. Publication and international challenge of neurodegenerative disease research groups to test protocol against non-ALS neurodegenerative disease cases.
T9. Re-assessment of variability of both pre-processed MRIs and results post-analysis in prospective data, through multi-site data sharing (inter and intra-site variability).
T10. Correlation with post-mortem neuropathology reports in a subset of centers adhering to the standards of established European brain banks (WP1, WP4).
T11. Application of quality control systems to other MRI modalities i.e. resting state fMRI, MR spectroscopy and advanced fibre track analysis tools of DTI (WP4).
T12. Implementation of a continuous quality control framework which feeds back to participating centres (WP4).

Tasks in MUNIX

T1. In-training session for new evaluators of participating centres.
T2. Each investigator will be required to study 4 patients at their home institution twice. Variability will be analyzed centrally and results fed back to investigators.
T3. Evaluators can proceed with longitudinal measurements if variability is less than 20%.
T4. Test-retest variability (inter- and intra-rater) will be assessed every 6 months.
T5. Test- retest variability across centres will be assessed every 6 months.
T6. Analysis of factors influencing reliability of measurements.
T7. Utilizing the established IT platform (WP1) for collection and analysis of longitudinal data
T8. Analysis of correlation of Munix data with data from other WPs (clinical and neuroanatomical data (WP1), non-MRI data (WP2) and imaging data (WP3).

T4 to T6 have already been successfully analyzed in healthy controls in a multi-centre study

Deliverables MRI

Nr	Description	Delivery date
1	Setup of the Jena-based JPND MRI database. Registration and upload of initial datasets from all participating EU centres	Month 3
2	Harmonisation of the MRI acquisition with clinical data set (WP1) and other sample procedures (WP2)	Month 6
3	Publication of detailed study of variability in acquisition and analysis parameters across multiple centres	Month 18
4	Publication of an optimised protocol for MRI (VBM and DTI analysis) in ALS	Month 24
5	Publication of results of multimodal biomarker analyses (WP1, WP2, WP3)	Month 36
6	Publication of results of monitoring of implemented MRI harmonisation	Month 36
7	EU accessible self-supporting ALS MRI biomarker quality control system	Month 36

Deliverables MUNIX		
Nr	Description	Delivery date
1	Implementation of SOPs MUNIX measurements	Month 1-6
2	Analysis of test-retest variability of MUNIX measurements	Month 16
2.1	Analysis of inter-rater reliability, center-specific	Month 16
2.2	Analysis of intra-rater reliability, center-specific	Month 16
2.3	Analysis of inter-rater and intra-rater reliability across centers	Month 16
2.4	Identification of factors influencing reliability of measurements	Month 16
2.5	Publication of detailed analysis of reliability studies	Month 20
3	Analysis of multicenter longitudinal data on the rate of motor unit loss in individual patients	Month 24
3.1	Evaluation of muscle-specific rate of motor unit loss	Month 24
3.2	Evaluation of variability of measurements as a function surviving motor units	Month 24
4	Publication of multicenter longitudinal data	
5	Publication of results of multimodal biomarker analyses (WP1, WP2, WP3)	Month 36

2.2.1.4. Work package 4 Optimization and Harmonization Platform

Contributing partners: NET, BEL, FRA, GER1, GER2, IRE, ITA1, ITA2, POL, POR1, POR2, SPA, TUR, UK1, UK2

SOPHIA will for the first time establish a pan-European ALS biomarker platform that will act as an important communication channel between this consortium and other stakeholders across the ALS/ND field throughout the course of the project. *First*, prior to the optimization studies, specific input will be requested from major (trans)national ALS/ND initiatives, to ensure a comprehensive view on steps 1, 2, and 3 in the decision tree (Figure 2), and as a safeguard to ensure that the optimizations are in line with the wider ALS/ND field. This will avoid duplication of work, and will ensure maximum utilization of the outcomes by the wider neurodegeneration field. *Second*, the platform will be used to disseminate the results to the whole ALS/ND field. The platform will act as a permanent Interactive European ALS biomarker forum/website that will allow interaction with patient groups and industry, and that will act as a platform for researchers who wish to optimize/harmonize novel biomarkers according to the pan-European ALS methodology. The platform will provide SOPs and other relevant documentation for the European neurodegeneration research community.

Tasks

T1: Creation of an interactive website. Website text will explain the ALS biomarker pan-European methodology, including decision steps to be made, in the process of biomarker optimization and harmonization. The website will be linked to relevant websites including ENCALS (www.encals.eu), and EUROMOTOR (www.euromotor.eu). It will have two main sections: (1) an open access section for the general public, patient organizations, industry, policy makers, etc. These stakeholders will have access to the open innovation platform, newsletters, the section explaining the pan European methodology as outlined in this grant proposal, and the FAQ section. (2) There will be a restricted section that will be only accessible to the scientific ALS and ND community upon (free) membership. This section will contain the virtual biobank, and data retrieval and deposition features, to allow patient and sample data exchange during the process of establishing and maintaining the virtual biobank (see WP1).

T2: This task includes retrieving input from the general ND field via the open innovation platform for ALS biomarker optimization and harmonization. This input will be retrieved in two ways: (1) via annual stakeholder consensus workshops, and (2) via specific questions raised by the SOPHIA consortium or the stakeholder platform (see 2.7 for details) within specific timeframes during step 1, 2 and 3 of the decision tree (Figure 2) in a participation-oriented approach. The open innovation platform will be set-up according to a common methodology described for open innovation platforms in the life sciences (http://gupea.ub.gu.se/bitstream/2077/22640/1/gupea_2077_22640_1.pdf).

T3: Dissemination of SOPHIA results to the general ND field, including end-users. This will be done by presentation of project results in annual ALS/ND progress meetings. Where possible,

these meetings will be integrated with other funded initiatives within this JPND call. Second, dissemination will be achieved via bi-annual newsletters that will be published on the website, sent to coordinators of other major (trans)national initiatives and to all participating JPND national funding agencies.

T4: Teaching programs will include on-line consultancy on SOP implementation, including a FAQ section on the website. The website will include detailed descriptions of optimized and harmonized SOPs, including trouble shooting sections. Monitoring and teaching will be implemented by installation of quality control systems.

Deliverables

Nr	Description	Delivery date
1	Interactive European ALS biomarker website, that serves as a vehicle to support implementation of the pan-European methodology on ALS biomarker optimization and harmonization	Month 3
2	Annual consensus workshops	Month 12, 24, 36
3	Open innovation platform to assess current performance (in terms of biomarker sensitivity, specificity, assay robustness, costs, patient acceptability etc.) and consensus derived solutions to improve performance	Month 6
4	Dissemination and implementation of optimized and harmonized SOPs	Month 12-36
5	Bi-annual newsletters	Month 6, 12, 18, 24, 30, 36
6	SOP implementation teaching programs	Month 12, 24, 36

2.2.1.5. Work package 5 Management

Contributing partners: NET, BEL, FRA, GER1, GER2, IRE, ITA1, ITA2, POL, POR1, POR2, SPA, TUR, UK1, UK2

Tasks

T1: ***Overall project management (M1-36)***
WP5 will lead the task devoted to the overall management of the project and the consortium. The Project Coordinator (PC) will be the unique interface with the JPND. The PC will take responsibility for the distribution of information received from relevant partners within the consortium. Task 1.1. also includes the communication and arrangement of consortium meetings and the preparation and distribution of agendas and minutes for each management meeting.

T2: ***Planning and scheduling (M1-36)***
This task will provide for management and planning of different actions during the project's lifetime. Activities that have to be performed in this task are:

- defining and checking consequences according to budget, scheduling and objectives;
- communicating and arranging meetings.

T3: ***Progress and cost reporting (M1-36)***
This task will establish a clear reporting structure to JPND and for internal communication within the project. Activities that have to be performed in this task are:

- providing administrative/financial data and relative explanations requested for each annual reporting period;
- maintaining a document repository for reporting;
- submitting on time reports and cost claims.

T4: ***Monitoring, control and quality management (M1-36)***
This task aims at ensuring that all project objectives are achieved within the work plan time and resource constraints. It will guarantee the effective and efficient progress of work.
Activities to be performed include:

- progress control;
- cost control.

In this context the coordinator will periodically prepare the status on expenditure for each single partner and a summary of the overall consortium, which will be communicated by the coordinator to each partner and/or all consortium.

- checking schedules, deliverables and milestones;
- risk analysis, preparation and management of contingency plans (PC, the EB and all partners);
- assessment of deliverables (PC, Executive Board and Advisory Board).

T5: Ethical and legal issues (M1-36)

Ethical issues (e.g. informed consent, data protection), and legal issues (e.g. handling of intellectual property rights (IPR), patenting, etc), will be dealt with according to national regulations, as described in section 6. The Executive Board establishes the rules for the access and exploitation of the pre-existing knowledge of the individual partners and of the results obtained so far. This task is strictly related to the implementation and maintenance of the Consortium Agreement signed between the Project partners defining and implementing technical, managerial, financial and IPR related provisions to enable partners to carry out their work.

Deliverables

Nr	Description	Delivery date
1	Annual progress report	Month 12, 24
2	Final report	Month 36

2.3. Structure of consortium

The SOPHIA consortium is specifically designed to address the objectives as stated in the JPND call text on the development, optimisation and harmonization of ND biomarkers. The project structure has been set up to maximize participation across Europe and includes a core group of WP leaders which will coordinate all the efforts required to deliver the success of the project.

The consortium brings together major patient biosample and data collections, leading research networks and prominent European ALS/MND experts. Each partner has specific competencies in one or more key aspects of the research plan so that considerable interdisciplinary added value can be achieved. The composition of the SOPHIA consortium was based on the following main inclusion criteria for the partners:

1. Leading level of expertise in one or more of the proposed WPs, as measured by the scientific track record of the partner;
2. Access to well characterized patient cohorts and sample collections;
3. Access to other stakeholder groups, including other (trans)national initiatives relevant to ND biomarker optimization and harmonization; patients and patient advocacy groups; industry; other end-users including professionals, governments (Ministries of Health) and research funding bodies, to ensure both efficient consultation of stakeholders, as well as dissemination of the results and achievements of the SOPHIA consortium.
4. Complementary research expertise and geographical distribution as well as the other factors mentioned above, to guarantee a balanced consortium across all relevant criteria.

The applicants have significant experience in working together successfully in large international collaborations including: epidemiology studies (EURALS); multicentre neuroimaging initiatives (NISALS); molecular mechanisms of neurodegeneration (MITOTARGET); clinical drug trials (eg riluzole, copaxone, ONO-2506, pentoxyfylline, olesoxime, dexpramipexole) and integration of large scale biological data sets (Euro-MOTOR). The applicants also incorporate members of the UK

DeNDRoN collaboration, which has developed a validation process using neuropathological endpoints and which includes members of the BrainNet Europe Consortium.

2.4. Involvement of participants in consortium

SOPHIA shows transnational added value in performing optimization and harmonization efforts in a true collaborative effort, as is outlined in Table 1 below. This table shows extensive involvement of the different partners over the different categories of work in the project. The table also reflects the complementary expertises of SOPHIA consortium partners, as the tasks are distributed to leading experts on that specific subarea only.

	0. NET	1. BEL	2. FRA	3. GER 1	4. GER 2	5. IRE	6. ITA 1	7. ITA 2	8. POL	9. POR 1	10. POR 2	11. SPA	12. SWI	13. TUR	14. UK 1	15. UK 2
Molecular Biomarkers CSF	X		X	X	X		X	X		X	X	X	X	X	X	X
Molecular Biomarkers peripheral blood	X		X	X	X		X	X	X	X	X	X	X	X	X	X
Pathology	X		X	X	X	X	X		X				X		X	X
MRI	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Neurophysiology	X	X	X	X	X	X		X	X	X	X		X	X	X	
Phenotyping	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sample collection	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 1 *– Collaborative efforts of SOPHIA*

2.5 Availability of well-characterized patient groups/samples

Table 2 below summarizes the shared availability and expected new samples/year from well-characterized ALS patients. Similar numbers are available from ALS mimics (patients referred to ALS clinics but diagnosed with other disease) and healthy controls.

		0. NET	1. BEL	2. FRA	3. GER 1	4. GER 2	5. IRE	6. ITA 1	7. ITA 2	8. POL	9. POR 1	10. POR 2	11. SPA	12. SWI	13. TUR	14. UK 1	15. UK 2
Phenotype data	**Available**[1]	2000	800	8000	3000	150	1400	2100	700	400	250	250	433	420	75	1200	500
	New[2]	300	50	1000	250	30	100	120	120	80	25	25	75	50	25	120	100
CSF	**Available**	40	0	1000	1000	20	0	20	250	30	20	20	12	0	100	70	35
	New	30	10	250	150	30	20	75	80	30	10	10	25	0	25	75	25
Serum	**Available**	750	0	1000	1000	20	0	50	400	400	130	130	133	0	100	69	60
	New	250	40	250	150	30	75	75	100	80	25	25	75	25	25	75	100
Autopsy	**Available**	150	10	200	20	3	0	45	0	15	0	0	0	30	0	170	75
	New	20	5	100	10	5	10	10	0	2	0	0	0	10	0	10	25
MRI	**Available**	200	100	2000	1000	200	50	120	400	100	0	0	200	0	100	100	60
	New	150	25	200	250	30	20	100	100	50	0	0	25	20	25	50	20

Table 2: *well-characterized samples of well characterized ALS patients.*

1. *Available: Numbers refer to the # samples currently available for ALS. Similar numbers of samples are available for ALS mimics and healthy controls in each centre.*
2. *New: Numbers refer to the # expected ALS samples to be collected in 2012. Similar numbers of samples will be collected for ALS mimics and healthy controls in each center.*

2.6. Time plan

WP	Deliverable	Year 1				Year 2				Year 3			
		1	2	3	4	1	2	3	4	1	2	3	4
1	Establishment of a standardized minimal clinical data set												
	Definition of relevant clinical variables, inclusion of chronological-progression markers based on validated functional scores.												
	Establishment of common IT-platform – a virtual biobank												
	Development of a Web based interface for accessing clinical parameters and data from biomarkers studies												
	Development of a Web based logistical interface for tracking biological samples												
	Established real time tracking of clinical data and biological samples across the consortium												
	Consolidated database of existing brain donor cohorts												
	Optimize protocols for the collection and storage of CNS and other tissues												
	Bio-informatic analysis of neuropathology data with clinical/genetic data to develop disease subclassification												
	Peer reviewed publication of proposed protocols												
	Presentation of findings at international symposium on ALS/MND												
	Dissemination of findings via Brain Net, European Confederation of Neuropathological Societies, UK Brain Bank Network												
2	Common SOPs for CSF, blood, blood products (lympocytes), DNA, RNA												
	First common basic neurochemical data set (e.g. albumin ratio, neurofilaments, MCP-1, progranulin, sAPP)												
	Common basic neurochemical data set with internal and external quality control system												
	Establish monitoring and teaching system for biosampling												
	Integrate round-robin system in biosampling protocols (in coordination with AD initiative, public round-robin organisations, and national organisations for qualitiy control of neurological biomarkers (internal and external quality management)												
	Common “round-robin biobank” for internal and external survey												
	Common IT-structure for decentralized biomaterialbank (virtual biobank) according to NEALS, Euro-HD, FTLDc, German ALS registry												
	Collect and process whole blood, LeukoLOCK WBC and PBMC from each individual												
	Establish lymphoblastoid cell lines from each individual												
	Blood RNA gene expression profiling												
	Generate gene expression profiles for each individual from the four sources of RNA												
	Bioinformatic analysis to establish optimized SOP for blood collection and RNA isolation												
	Collection of blood using the optimized SOP from 1) ALS patients, 2) ALS disease variants, 3) ALS mimics, 4) other neurological diseases and 5) age and sex matched controls across centres for harmonization and quality control.												
3	Setup of the Jena-based JPND MRI database. Registration and upload of initial datasets from all participating EU centres.												
	Harmonisation of the MRI acquisition with clinical data set (WP1) and other sample procedures (WP2)												
	Publication of detailed study of variability in acquisition and analysis parameters across multiple centres.												
	Publication of an optimised protocol for MRI (VBM and DTI analysis) in ALS.												
	Publication of results of multimodal biomarker analyses (WP1, WP2, WP3)												
	Publication of results of monitoring of implemented MRI harmonisation												
	EU accessible self-supporting ALS MRI biomarker quality control system.												
	Implementation of SOPs MUNIX measurements												
	Analysis of test-retest variability of MUNIX measurements												
	Analysis of inter-rater reliability, center-specific												
	Analysis of intra-rater reliability, center-specific												
	Analysis of inter-rater and intra-rater reliability across centers												
	Identification of factors influencing reliability of measurements												
	Publication of detailed analysis of reliability studies												
	Analysis of multicenter longitudinal data on the rate of motor unit loss in individual patients												
	Evaluation of muscle-specific rate of motor unit loss												
	Evaluation of variability of measurements as a function surviving motor units												
	Publication of multicenter longitudinal data												
4	Interactive European ALS biomarker website, that serves as a vehicle to support implementation of the pan-European methodology on ALS biomarker optimization and harmonization												
	Annual consensus workshops												
	Open innovation platform to assess current performance (in terms of biomarker sensitivity, specificity, assay robustness, costs, patient acceptability etc.) and consensus derived solutions to improve performance												
	Dissemination and implementation of optimized and harmonized SOPs via bi-annual newsletters and teaching programs												
	Bi-annual newsletters												
	SOP implementation teaching programs												
5	Annual progress report												
	Final report												

Table 3: *Gantt chart indicating the deliverble dates of SOPHIA*

2.7. Project coordination and management

Due to the size of the consortium and the complexity of the project content we aim to facilitate an accountable and efficient way to manage SOPHIA through efficient decision-making and a financially as well as scientifically transparent management structure (see figure 3 below).

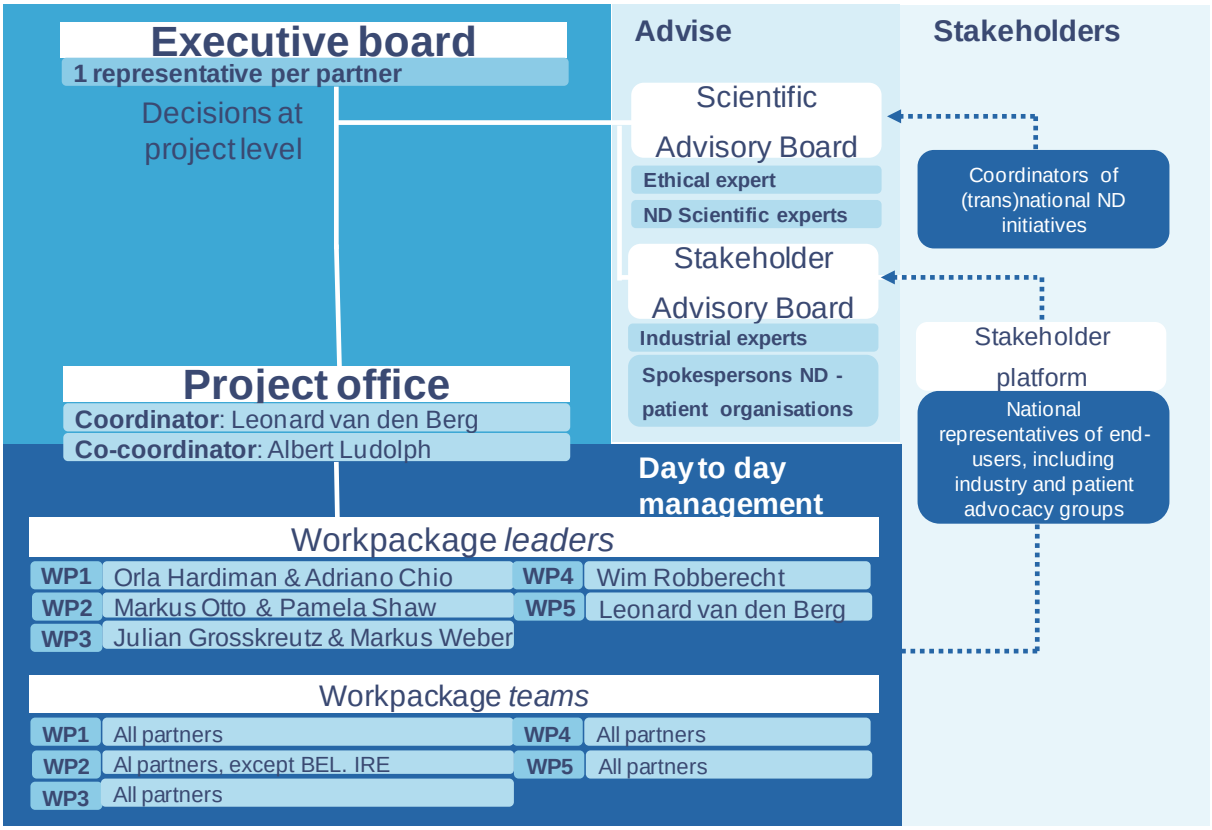

Figure 4 *– Management structure of SOPHIA*

The **Project Coordinator** (PC) is responsible for representing the Consortium in the communication with JPND; ensuring smooth operation of the project, guaranteeing that all efforts are focused towards the objectives, enabling proper decision making; granting proper implementation of the partners' rights and obligations. The PC is the chairman of the EB and as such responsible for chairing the EB meetings and acting as the primary spokesman on behalf of the participants of SOPHIA for all formal written and verbal communication with the JPND board. Prof. Ludolph will act as vice-coordinator (VC) in the project. The VC is the vice-chair of SOPHIA and shall preside over the EB in the PC's absence.

The **Executive Board (EB)** is the highest decision-making body in SOPHIA. Its main responsibility is to ensure a correct implementation of the project in accordance with the JPND contract and the Consortium Agreement. At the same time the EB acts as the central management team of SOPHIA, being responsible for overall monitoring the scientific and financial progress of the project activities towards the main objectives of the project. The activities of the EB are based on agreed deliverables and associated milestones, within the budgetary limits.
The EB consists of one representative per project partner. The EB is chaired by Prof. Leonard van den Berg. Decisions will be made by consensus whenever possible. When a major dispute arises, a decision will be made by simple majority. Each partner will have a vote.

The EB will meet at least once a year, preceding the contractual reporting obligations to the JPND council. These meetings will be used to review the progress of SOPHIA, discuss problems and set future directions. As such, the EB is the appropriate decision making body in:

- Consortium composition: identification of and corrective measures to (including termination) defaulting, adding or replacement of partners and the change of the Coordinator;
- Agenda setting: definition of the scientific agenda and monitoring of the overall course of the project, including major deviations in the course, objectives and/or financial budgets of the activities that require consulting the JPND and amendments to the JPND contract;
- Changes in the Consortium Agreement: changes in the rights and obligations of the partners and/or decision-making procedures that necessitate amendments in the agreement;
- Reporting to the JPND council: agree on the completeness and quality of all formal reports to the JPND.

In terms of the central management of SOPHIA the EB furthermore has the following specific responsibilities:

- Monitoring the inter-work package alignment and progress of the work package deliverables towards the overall objectives of SOPHIA;
- Drafting of the annual progress reports to the JPND;
- Liaising with the national funding agencies, the Scientific Advisory Board, the Stakeholder Advisory Board as well as the different stakeholder groups.

Extraordinary meetings can be convened at any time, following a written request by any member of the EB to the Coordinator. At other times, communication between the consortium members and other partners involved will take place by means of postal mail, e-mail and telephone.

Work Package Teams (WP Teams) are responsible for an effective and efficient implementation of the work associated with a specific work package. The WP Teams consist of a Work Package Leader, leading investigators of the consortium partners who are active in that work package and expert scientists in the area (called: participants). The WP Leader also takes seat in the EB on behalf of the WP team members. The WP Teams are responsible for:

- Monitoring the progress of the activities towards the specific deliverables and objectives of the WP, based on the defined milestones and means of verification;
- Taking decisions on minor alterations in work package related activities and associated budgets. These alterations may not have any impact beyond the boundaries of the WP itself;
- Periodic progress reporting to the EB, including suggestions for corrective measures in case of contingencies, delays and/or disputes that necessitate changes in the consortium, and/or changes in the Consortium Agreement;
- Recommending the EB on new initiatives from other research groups or industry, or other developments in ND field;
- The WP Leaders are the main contacts in all communication between the WP Teams and the EB.

SOPHIA will seek regular advice through the EB from eminent scientists assembled in the **Scientific Advisory Board** (ScAB) and stakeholders in the **Stakeholder Advisory Board** (StAB). The Advisory Boards will provide expert advice on the content, quality of the deliverables, ethical issues, general philosophy and direction of the project, corrective measures in the content of the work if necessary and the dissemination and exploitation of project results. The StAB will contain leading industrial experts and European representatives for ND patient organizations (European Parkinson's Disease Association, Alzheimer Europe). The StAB will be chaired by Brian Dickie, director of the Motor Neuron Disease Assocation. The Consortium has obtained full commitment from ALS patient organizations from all participating countries for this biomarker initiative.
The **Stakeholder platform** consists of national representatives for patient organizations, national policy makers and industrial end-users and has an important role in the development of SOPHIA. It will fulfil two major tasks: (1) providing the scAB and stAB and WP4 with expert knowledge and necessary input from their field of expertise reflecting the specifics of different kinds of stakeholders (professional stakeholders, policy-making stakeholders, end-using stakeholders), and (2) acting as information broker on ND biomarker research in Europe and thus being part of the SOPHIA promotion and dissemination activities.

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3. Justification of requested budget

JPND Call 2011
Budget of the project plan (in €)
Acronym: SOPHIA
Coordinat(Leonard van den Berg (NET)

	Last Name (group leader)	Country	Funding org.[1]	Personnel	Consumables	Equipment	Travel	Other direct costs[2]	Overheads[3]	Total cost	Total requested budget
NET	Van den Berg	NL	ZonMW	€ 183.500	€ 90.000	€ -	€ 18.000	€ -	€ 58.300	€ 349.800	€ 349.800
BEL	Robberecht	BE	IWT	€ -	€ -	€ -	€ -	€ -	€ -	€ -	€ -
FRA	Salachas	FR	FNRA	€ 270.000	€ -	€ 4.300	€ 18.300	€ -	€ 14.630	€ 307.230	€ 307.230
GER1	Otto	DE	BMBF	€ 150.000	€ 60.000	€ -	€ 30.000	€ -	€ 48.000	€ 288.000	€ 288.000
GER2	Grosskreutz	DE	BMBF	€ 69.350	€ 7.800	€ 3.000	€ 2.997	€ -	€ 16.629	€ 99.776	€ 99.776
IRE	Hardiman	IR	HRB	€ 150.000	€ 20.500	€ 10.100	€ 5.700	€ -	€ 46.575	€ 232.875	€ 232.875
ITA1	Chio	IT	MdS	0	0	0	0	0	0	€ -	0
ITA2	Silani	IT	MdS	€ 80.000	€ 36.000	€ -	€ 8.280	€ 75.000	€ 12.428	€ 211.708	€ 211.708
POL	Kuzma	PL	NCRD	€ 41.600	€ 45.000	€ 21.200	€ 10.800	€ 28.500	€ 19.480	€ 166.580	€ 166.580
POR1	De Carvalho	PT	FCT	€ 40.500	€ 44.000	€ -	€ 5.100	€ -	€ 9.955	€ 99.555	€ 99.555
POR2	Costa	PT	FCT	€ 32.550	€ 40.700	€ -	€ 9.500	€ -	€ 16.550	€ 99.300	€ 99.300
SPA	Mora Pardina	ES	ISCIII	€ 52.209	€ 43.000	€ -	€ 3.600	€ 12.500	€ 20.750	€ 132.059	€ 132.059
SWI	Weber	CH	SNSF	€ 200.000	€ 61.400	€ -	€ 2.800	€ -	€ 26.420	€ 290.620	€ 290.620
TUR	Parman	TR	TÜBİTAK	€ 100.000	€ 25.000	€ -	€ 13.500	€ -	€ -	€ 138.500	€ 138.500
UK1	Shaw	UK	MRC	€ 60.071	€ 141.570	€ -	€ 7.260	€ -	€ 30.042	€ 238.943	€ 191.155
UK2	Turner	UK	MRC	€ 112.494	€ 8.100	€ 1.998	€ 2.997	€ -	€ 110.310	€ 235.899	€ 188.719
Total				**€ 1.542.275**	**€ 623.070**	**€ 40.598**	**€ 138.834**	**€ 116.000**	**€ 430.070**	**€ 2.890.846**	**€ 2.795.878**

[1] abbreviation of funding organisation
[2] e.g. subcontracting, provisions, licensing fees; may not be eligible costs in all countries (will be handled according national regulations).
[3] overhead costs: funding according to national regulations

Please note: Partner BEL will not receive any funding within this call, as the IWT will only fund privately held organisations. Also due to national funding regulations, Partner ITA1 will not receive direct funding, and is therefore featured as subcontractor to Partner ITA2. Finally, as in some countries only a percentage of the eligible cost will be funded, we have included a 'Total cost' column next to the 'Total requested budget' column.

4. Added value of the proposed collaboration

The European ALS community has established an active consortium (www.ENCALS.eu) with an annual young investigator's meeting. Several 2-3 day workshops were held in 2010 on European Collaboration on databases/biobanks (Naarden (European Neuro Muscular Center (www.ENMC.org)), molecular biomarkers (Reisensburg (Ulm) see also ref 1), and neuroimaging (Oxford, see also ref 2), and members have generated a series of consensus statements and standard operating procedures for biomarkers.[1,2] These recent initiatives are an excellent foundation for European collaboration but more focused projects and funding is required for larger international collaborations to obtain the numbers of samples necessary to perform large biomarker validation studies in ALS and other motor neuron diseases.[20]
A number of international initiatives (outlined in Table 3) have aims that are cognate with SOPHIA. Within Europe these include the ENCALS, EUROMOTOR and EURALS projects, which are existing projects developed by SOPHIA partners with aims that are complementary to the current project. Previously funded EU projects, including BBMRI have developed useful methodologies and have addressed many of the legal and ethical issues that arise in the context of data sharing.
As ALS overlaps with FTLD, shared initiatives in biomarker development will be pursued. In a international context, the US based North Eastern ALS Consortium (NEALS) has already developed a virtual biobank (www.alsconsortium.org) upon which the SOPHIA platform will be modeled.[21] Close collaboration between SOPHIA and NEALS will ensure international harmonization of methodologies.
The US based NINDS has recently generated common data elements for clinical datasets. As many of the partners of SOPHIA are also members of the NINDS ALS CDE expert group, harmonization of clinical datasets will be established. Successful collaborative initiatives in neuropathology include: Brain Net Europe; UK DeNDRoN Neuropathology Special Interest Group and the UK Brain Bank Network. Brain Net Europe has successfully developed new diagnostic protocols for the evaluation of βamyloid, tauopathy and synucleinopathy for pathology research and diagnosis, and is well positioned to undertake a similar systematic approach towards diagnostic consensus in ALS.

Initiative		**SOPHIA**	
Name	**Aim**	**Input to be obtained**	**Output delivered**
BBMRI	Pan European bi banking	Methodology, management of ethical, legal & IP constraints	Disease specific virtual biobank
Brain Net Europe	Harmonization of Pan European brainbanking in ND	methodology, SOPS	Disease specific network
DeNDRoN	UK based support structure for ND research	UK based networks	European based disease specific network
ENCALS	European consortium for collaborative research in ALS	Existing collaborations	Targeted biomarker-based collaborations within existing consortium
EURALS	European consortium of population based ALS Registers	population based incident cohorts	Existing collaborations and data collection
EUROMOTOR	Identify causes of ALS using a system biology approach	Existing databases and prospective collection of clinical data & biological samples	Development of detailed dataset & virtual biobank
FTLDc	Consortium to study FTD	Overlaps between ALS and FTD	Exploitation of overlap between ALS and FTD: Expansion of markers to ALS
NEALS	US based clinical trial consortium	Expertise in virtual biobanking	Development of European based virtual biobank: harmonization of data joint initiatives
NINDS	US based initiative: CDE for ND	Established evidence based CDEs	Harmonization of clinical dataset
NISALS	Harmonization of neuroimaging data in ALS	Neuroimaging SOPs	Existing collaborative networks, utilization of SOPs
ROAMER	European roadmap for mental health research	Alignment of policy and agenda setting	Integration of biomarker optimization and harmonization program in roadmap
UK MRC Brain Bank Network	Coordination and harmonization of Brain Bank activity	UK based network	Brain banking harmonization

***Table 4**. How SOPHIA capitalizes on and adds value to current (tran)national initiatives*

5. Possible exploitation of expected project results *(including data management and data sharing)* and potential health and clinical impact

ALS is one of the most devastating neurodegenerative diseases for which no therapy exist. As such, the existence of a set of optimized and standardized methods for collection, preservation and analysis of different biomarkers necessary to evaluate diagnosis and disease progression of ALS and other motor neuron diseases will be an enormous advance in the investigation of this condition at several levels, possibly transferable to other forms of neurodegeneration.

The impact would involve many different areas:

1- Systematic multicentre investigation to permit an earlier and more reliable diagnosis has two major implications:
   a. Less time consuming expensive investigations before reaching the final diagnosis of ALS, avoiding unnecessary interventions such as surgical procedures
   b. Earlier clinical trial entry with high chances of defining an effective drug
2- All methods, database, biomarker essays, and biomarker in SOPHIA will be shared with other members of the scientific community devoted to ALS and to other ND.
3- The concept of this project (pan-European SOPs) can be expanded to other ND resulting in a driving force for shared biomarker research.
4- Better understanding of ALS etiopathogenesis and natural history.
5- The project will increase the interest of the international scientific community in relation to ALS.
6- Identification of consistent biomarker in ALS will permit less expensive, smaller, and shorter trials with better stratified early ALS patients, with increased probability to find an effective drug.
7- Availability of more precise measures of disease activity and disease progression will improve trial design and thereby attract pharmaceutical industry to investigate new compounds in ALS.
8- Improved patient care as a systematic questionnaire is applied to permit a proper evaluation. A potential biomarker will allow a more scientific evaluation of all interventions.
9- Patients association satisfied with higher care quality: all interventions will be more appropriately measured due to this project.
10- The finding of potential biomarker(s) will allow the development of new European commercial opportunities to develop biomarker detection kits for use in neurodegeneration clinical practice.
11- The project will demonstrate the impact of a large European multicentric project in relation to a relatively rare disorder acting as a template for other conditions in the future.
12- SOPHIA will for the first time establish an Interactive European ALS biomarker website, that serves as a vehicle to support implementation of the pan-European methodology on ALS biomarker optimization and harmonization. This platform engages with end-users in an early stage, thereby improving acceptation and implementation of project results by these stakeholders. Possibilities for co-funding and member fees will be examined to ensure that this platform will be sustainable. When successful, this platform can be extended to / implemented in other ND areas.

6. Ethical issues *(e.g. informed consent, data protection, use of animals),* and legal issues *(e.g. handling of intellectual property rights (IPR), patenting, etc), according to national regulations*

Regarding this topic there will be an ethical advisory board installed. Candidates are Bert Gordijn, Dublin, Ireland; Pascal Borry, Leuven, Belgium; Joseph Glaza Bratislava, Slovaky; Su Mason Sheffield, United Kingdom; ETHOX, Oxford, United Kingdom.

Ethical issues:

All centers shall conduct this project in strict compliance with any local laws, regulations and guidelines, good clinical practices and any other relevant professional standards.

1. **Ethical approval:** Prior to start of the project each center will seek ethical approval with the pertinent Institutional Review Board(s) (IRB) and or Ethics Committee(s) (EC)
2. **Informed consent:** A signed consent form which has been approved by the IRB/EC will be obtained from each subject participating in any of the WPs
3. **Data protection:** It is understood by all investigators, that data collected during this project will be defined as personal data under European Union Directive 95/46EC. The Institution will ensure that all study subjects are aware that the data collected from them will be defined as personal data and will provide written consent for the processing, disclosure and transference of those data.
4. **Biobanking:** Investigators will ensure that the collection and use of participants' human biological materials and data are scientifically, legally and ethically appropriate. This implies compliance with institutional, national and OECD guidelines for biobanking (http://www.oecd.org/dataoecd/41/47/44054609.pdf)

Legal issues:

1. **Publications:** The participating centers understand and agree that participation in the project involves a commitment to publish the data from this project in a cooperative publication.
2. **Patent rights and Inventions:** In the event a centre makes any discoveries and inventions these shall become the exclusive property of the pertinent institution. Plans for management of knowledge and intellectual property within the project will be governed by the Project Coordinator and the Executive Board that will establish the IPR strategies of the project. In principle, knowledge of all results will be shared by all partners, and intellectual property of the results will be of all the investigators who have participated in achieving such results. The rules for exploitation of the results, including any patent generated by the project will be regulated by a Consortium Agreement to be signed among the partners. This will establish project specific individual rules for the dissemination and exploitation of project results in accordance with national rules set by the national funding agencies, with particular reference to access rights related to pre-existing knowledge ("Background") of the partners and to exploitation of results generated by the project itself ("Foreground"). Publication of project results will be regulated, so that it might not negatively affect the protection of such results. Policies regarding the transfer of knowledge will be also regulated, as will be the access to data and knowledge generated by other projects in which the partners are involved and that is necessary or useful for the project implementation.

7. Brief CVs

Curriculum Vitae - Coordinator –The Netherlands– Prof. Leonard H. van den Berg

Organization information		Personal information group leader	
Full legal organization name	Universitair Medisch Centrum Utrecht	Gender	Male
Institute	Department of Neurology	Title	Prof. MD. PhD.
Street or P.O. Box	P.O. Box 85500	First name	Leonard H.
ZIP code	3508 GA	Family name	Van den Berg
City	Utrecht	Position in institute	Professor
Country	The Netherlands	Phone number	0031 88 7557939
Internet home page	www.umcutrecht.nl	Email address	lberg@umcutrecht.nl
National funding organization full name		www.umcutrecht.nl	
National funding organization abbreviation		ZonMw	

Relevant publications which demonstrates the competence to carry out the project	
	Authors, Title, Name journal, Year/issue/pages
1	Van Es MA, Schelhaas HJ, Ticozzi N, Andersen PM, Weber M, et al, Silani V, Gasser T, Ludolph AC, Robberecht W, *et al*, van den Berg LH. Angiogenin variants in Parkinson's disease and amyotrophic lateral sclerosis. Annals of Neurology 2011, in press
2	Blauw HM, Al-Chalabi A, Andersen PM, *et al*, van den Berg LH. A large genome scan for rare CNVs in amyotrophic lateral sclerosis. Hum Mol Genet 2010;19:4091-9.
3	Van Es MA, Veldink JH, van den Berg LH et al. Genome-wide association study identifies 19p 13.3 (UNC13A) and 9p 21.2 as susceptibility loci for sporadic amyotrophic lateral sclerosis. Nat Genet 2009;41:1083-1087.
4	Van Es MA, van Vught PW, Blauw H, Franke LW, et al, Sleegers K, van Broeckhoven C, Robberecht W, Andersen PM, *et al*, van den Berg LH. Genetic variation in DPP6 is associated with susceptibility to amyotrophic lateral sclerosis. Nature Genet 2008;40:29-31.
5	Blauw HM, Veldink JH, van Es MA, van Vught PW, Saris CGJ, van der Zwaag B, Franke L, Burbach JPH, Wokke JHJ, Ophoff RA, van den Berg LH. Genome-wide copy number variation in amyotrophic lateral sclerosis. Lancet Neurol 2008;7:319-326.

Description of patents related to the present topic
None

Description of ongoing projects related to the present topic, indicating funding sources and possible overlaps with the proposal
1. Founder of the Netherlands ALS Center (www.alscentrum.nl), collaboration between the UMC Utrecht, the Academic Medical Center (AMC) Amsterdam and the UMC St Radboud in Nijmegen. Three national investigator-initiated trials have been successfully executed (creatine, sodium valproate, lithium). 2. Nation-wide prospective population-based study (2006) aiming at a complete ascertainment of incident ALS patients in the Netherlands. Detailed ALS database and biobank of >3,000 individuals is now available. Approx. 400 patients and 800 controls are included each year. 3. Elected chairman of ENCALS (2009) (European Network to find the Cure for ALS), a Europe-wide network of ALS Care and Research Centres. ENCALS fosters high standards of care and research collaborations (biomarkers), and holds an annual meeting for ALS research. 4. Coordinator FP7 EU grant 'European multidisciplinary ALS network identification to cure motor neuron degeneration' in call entitled 'Tackling Human Diseases through Systems Biology Approaches' (European Consortium (14 partners), 2011-2015) None of these projects show financial overlap with SOPHIA.

Curriculum Vitae – Co-coordinator – Germany – Prof. Albert Ludolph

Organization information		Personal information group leader	
Full legal organisation name	University of Ulm	Gender	Male
Institute	Department of Neurology	Title	Professor
Street or P.O. Box	Oberer Eselsberg 45	First name	Albert
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City	Ulm	Position in institute	Director
Country	Germany	Phone number	0049 7311771200
Internet home page	www.uni-ulm.de	Email address	Albert.Ludolph@rku.de
National funding organisation full name		Bundesministerium für Bildung und Forschung	
National funding organisation abbreviation		BMBF	

Relevant publications which demonstrates the competence to carry out the project	
	Authors, Title, Name journal, Year/issue/pages
1	Kerstin E. Braunstein, Judith Eschbach, Krisztina Ronavoros, Rana Soylu, Elli Mikrouli, Yves Larmet, Frederique Rene, Jose-Luis Gonzalez De Aguilar, Jean-Philippe Loeffler et al. A point mutation in the dynein heavy chain gene leads to striatal atrophy and compromises neurite outgrowth of striatal neurons. Human Molecular Genetics, 2010, Vol. 19, No. 22: 4385–4398
2	Luc Dupuis, Pierre-François Pradat, Albert C Ludolph, Jean-Philippe Loeffler. Energy metabolism in amyotrophic lateral sclerosis. Lancet Neurol 2011; 10: 75–82
3	Albert C. Ludolph. Urgently needed—biomarkers for amyotrophic lateral sclerosis. Ludolph, A. C. Nat. Rev. Neurol. (2011) 7: 13–14
4	Petra Steinacker, Andreas Hawlik, Albert Ludolph, Markus Otto et al. Neuroprotective Function of Cellular Prion Protein in a Mouse Model of Amyotrophic Lateral Sclerosis. The American Journal of Pathology (2010), Vol. 176, No. 3: 1409–1420
5	Nicolai Treiber,Pallab Maity, Karmveer Singh, Matthias Kohn, Alexander F. Keist, Florentina Ferchiu, Lea Sante, Sebastian Frese et al. Accelerated aging phenotype in mice with conditional deficiency for mitochondrial superoxide dismutase in the connective tissue. Aging Cell (2011) 10: 239–254

Description of patents related to the present topic
None

Description of ongoing projects related to the present topic, indicating funding sources and possible overlaps with the proposal
1. EU FRAMEWORK 7 HEALTH 2010 TWO STAGE GRANT 2010 - 2015 Euro-Motor: Systems Biology in ALS. 2. German ALS Network (funded by BMBF) 3. German FTLD Network (funded by BMBF) 4. Pioglitazone Trial 5. Dexpramipexol Trial None of these projects show financial overlap with SOPHIA.

Curriculum Vitae – Partner 1 – Belgium – Prof. Wim Robberecht

Organization information		Personal information group leader	
Full legal organisation name	Vlaams Instituut voor Biotechnologie vzw	Gender	Male
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National funding organisation full name		Agentschap voor Innovatie door Wetenschap en Technologie	
National funding organisation abbreviation		IWT	

Relevant publications which demonstrates the competence to carry out the project	
	Authors, Title, Name journal, Year/issue/pages
1	R Lemmens*, et al., W Robberecht. Mutant SOD1-induced motor axonopathy in the zebrafish as a novel model to identify therapeutic targets and genetic modifiers in ALS. Hum Mol Genetics 2007; 16:2359-65
2	P Van Damme*, et al. Astrocytes regulate GluR2 expression in motor neurons and their vulnerability to excitotoxicity. Proc Natl Acad Sci USA 2007; 104: 14825-30
3	P Van Damme, et al. Progranulin functions as a neurotrophic factor to regulate neurite outgrowth and enhance neuronal survival. J Cell Biology, 2008; 181: 37-
4	Geneviève Gowing*, et al. Ablation of proliferating microglia does not affect motor neuron degeneration in ALS caused by mutant SOD1. J Neurosci 2008; 28:10234-44
5	T Philips, W Robberecht. Neuroinflammation in ALS. Lancet Neurology, 2011;10:253-63

Description of patents related to the present topic
None

Description of ongoing projects related to the present topic, indicating funding sources and possible overlaps with the proposal
1. Validation of the use of a zebrafish model as a screening tool to identify modifying genes in ALS – Role of EphA4 in the mechanism of motor neuron degeneration in fish, mice and humans (John Hopkins University). 2. Axonal determinants as modifiers of motor neuron degeneration – A translational approach (GOA). 3. Tubulin acetylation in motor neuron degeneration a translational approach (AFM14471) 4. ELP3 and the Biology of Amyotrophic Lateral Sclerosis (King's College London) 5. Translantional research into the role of the ephrinreceptor EphA4 in motor neuron degeneration in ALS. (FWO G.0695.10). None of these projects show financial overlap with SOPHIA.

Curriculum Vitae – Partner 2 – France – François Salachas, MD.

Organization information		Personal information group leader	
Full legal organisation name	Assistance Publique-Hopitaux de Paris	Gender	Male
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City	Paris	Position in institute	Assistant Professor
Country	France	Phone number	+33 14 2162472
Internet home page	www.aphp.fr	Email address	francois.salachas@psl.aphp.fr
National funding organisation full name		Agence Nationale de la Recherche	
National funding organisation abbreviation		ANR	

Relevant publications which demonstrates the competence to carry out the project	
	Authors, Title, Name journal, Year/issue/pages
1	Belzil VV, Daoud H, St-Onge J, Desjarlais A, Bouchard JP, Dupre N, Lacomblez L, Salachas F, Pradat PF, Meininger V, Camu W, Dion PA, Rouleau GA. Identification of novel FUS mutations in sporadic cases of amyotrophic lateral sclerosis. Amyotroph Lateral Scler. 2011 Mar;12(2):113-7. Epub 2011 Jan 24.
2	Millecamps S, Salachas F, Cazeneuve C, Gordon P, Bricka B, Camuzat A *et al.* SOD1, ANG, VAPB, TARDBP, and FUS mutations in familial amyotrophic lateral sclerosis: genotype-phenotype correlations. J Med Genet. 2010 Aug;47(8):554-60. Epub 2010 Jun 24.
3	Sanjak M, Salachas F, Frija-Orvoen E, Theys P, Hutchinson D, Verheijde J, Pianta T, Stewart H, Brooks BR, Meininger V, Douillet P; Xaliproden [SR57746A] ALS International Study Group. Quality control of vital capacity as a primary outcome measure during phase III therapeutic clinical trial in amyotrophic lateral sclerosis. Amyotroph Lateral Scler. 2010 Aug;11(4):383-8.
4	Belzil VV, Valdmanis PN, Dion PA, Daoud H, Kabashi E, Noreau A, Gauthier J; S2D team, Hince P, Desjarlais A, Bouchard JP, Lacomblez L, Salachas F, Pradat PF, Camu W, Meininger V, Dupré N, Rouleau GA. Mutations in FUS cause FALS and SALS in French and French Canadian populations. Neurology. 2009 Oct 13;73(15):1176-9.
5	Arnaud L, Salachas F, Lucien N, Maisonobe T, Le Pennec PY, Babinet J, Cartron JP. Identification and characterization of a novel XK splice site mutation in a patient with McLeod syndrome. Transfusion. 2009 Mar;49(3):479-84.

Description of patents related to the present topic
None

Description of ongoing projects related to the present topic, indicating funding sources and possible overlaps with the proposal
1. COSLA project: Multicentric French Study of Endophenotype, natural History, biological Prognosis Factors in 1000 ALS patients (Pr V. Meininger). Funded by ARSla 2. Metabolomic Multicentric study for early diagnosis in ALS (Pr Andres. Tours) funded by PHR. None of these projects show financial overlap with SOPHIA.

Curriculum Vitae – Partner 3 – Germany – Prof. Dr. Markus Otto

Organization information		Personal information group leader	
Full legal organisation name	University of Ulm	Gender	Male
Institute	Department of Neurology	Title	Prof. Dr.
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National funding organisation full name		Bundesministerium für Bildung und Forschung	
National funding organisation abbreviation		BMBF	

Relevant publications which demonstrates the competence to carry out the project	
	Authors, Title, Name journal, Year/issue/pages
1	Otto M, Bowser B, Turner M et al. Roadmap and standard operating procedures for biobanking and discovery of neurochemical markers in ALS, Amyotroph Lat Sclerosis 2011 accepted
2	Steinacker P, Rist W, Swiatek-de-Lange M, Lehnert S, Jesse S, Pabst A, Tumani H, von Arnim CA, Mitrova E, Kretzschmar HA, Lenter M, Wiltfang J, Otto M. Ubiquitin as potential cerebrospinal fluid marker of Creutzfeldt-Jakob disease. Proteomics 2010b; 10: 81-9
3	Steinacher P, Hendrich C, Sperfeld AD, Jesse S, v. Arnim C, Lehnert S, Pabst A, Uttner I, Tumani H, Lee V.M.Y, Trojanowski JQ, Kretzschmar HA, Ludolph AC, Neumann M, Otto M. TDP-43 in cerebrospinal fluid of patients with frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Archives of Neurology 2008; 65: 1481-7
4	Brechlin P, Jahn O, Steinacher P, Cepek L, Kratzin H, Lehnert S, Jesse S, Mollenhauer B, Kretzschmar H, Wiltfang J, Otto M. Cerebrospinal fluid-optimized two-dimensional difference gel electrophoresis (2D-DIGE) facilitates the differential diagnosis of Creutzfeldt-Jakob Disease. Proteomics 2008; 8: 4357-4366
5	Wiltfang J, Esselmann, H, Smirnov, A, Bibl, M, Cepek, L, Steinacker, P, Mollenhauer, B, Buerger, K, Hampel, H, Paul, S, Neumann, M, Maler, M, Zerr, I, Kornhuber, J, Kretzschmar, HA, Poser, S, Otto, M (2003) beta-amyloid peptides in cerebrospinal fluid of patients with Creutzfeldt-Jakob disease. Ann Neurol 54: 263-267

Description of patents related to the present topic
None

Description of ongoing projects related to the present topic, indicating funding sources and possible overlaps with the proposal
1. since 2011 board of speakers of the German competence net dementia (KNDD, funding by BMBF) 2. since 2011 speaker of German Frontotemporal lobar degeneration consortium (funded by BMBF) – www.ftld.de 3. since 2010 leading physican – European project on development of nanotools for diagnosis of ND (NaDiNe, coordinator: J. Kuttner, Danemark) 4. since 2009 - Elected chair - German Society of Neurochemistry and Laboratory diagnosis 5. since 2007 coordinator of interdisplinary research program – Neuroproteomics of Parkinsons dementia funded foundation of State of Baden-Württemberg None of these projects show financial overlap with SOPHIA.

Curriculum Vitae – Partner 4 – Germany – Julian Grosskreutz, PD, MD

Organization information		Personal information group leader	
Full legal organisation name	University Hospital Jena	Gender	Male
Institute	Department of Neurology	Title	PD. MD.
Street or P.O. Box	Erlanger Allee 101	First name	Julian
ZIP code	07747	Family name	Grosskreutz
City	Jena	Position in institute	Director Neuromuscular Unit
Country	Germany	Phone number	+49 36 419323426
Internet home page	http://www.neuro.uk-j.de	Email address	julian.grosskreutz@med.uni-jena.de
National funding organisation full name		Bundesministerium für Bildung und Forschung	
National funding organisation abbreviation		BMBF	

Relevant publications which demonstrates the competence to carry out the project	
	Authors, Title, Name journal, Year/issue/pages
1	Turner MR, Grosskreutz J, Kassubek J, Abrahams S, Agosta F, Benatar M, Filippi M, Goldstein LH, van den Heuvel M, Kalra S, Lulé D, Mohammadi B; first Neuroimaging Symosium in ALS (NISALS). Towards a neuroimaging biomarker for amyotrophic lateral sclerosis. Lancet Neurol. 2011 May;10(5):400-3.
2	Grosskreutz J, Peschel T, Unrath A, Dengler R, Ludolph AC, Kassubek J. Whole brain-based computerized neuroimaging in ALS and other motor neuron disorders. Amyotroph Lateral Scler. 2008 Aug;9(4):238-48.
3	Dengler R, von Neuhoff N, Bufler J, Krampfl K, Peschel T, Grosskreutz J. Amyotrophic lateral sclerosis: new developments in diagnostic markers. Neurodegener Dis. 2005;2(3-4):177-84.
4	Grosskreutz J, Kaufmann J, Frädrich J, Dengler R, Heinze HJ, Peschel T. Widespread sensorimotor and frontal cortical atrophy in Amyotrophic Lateral Sclerosis. BMC Neurol. 2006 Apr 25;6:17.
5	Müller-Vahl KR, Kaufmann J, Grosskreutz J, Dengler R, Emrich HM, Peschel T. Prefrontal and anterior cingulate cortex abnormalities in Tourette Syndrome: evidence from voxel-based morphometry and magnetization transfer imaging. BMC Neurosci. 2009 May 12;10:47.

Description of patents related to the present topic
None

Description of ongoing projects related to the present topic, indicating funding sources and possible overlaps with the proposal
1) Evaluation of high resolution T1 MRI as a carrier of MND biomarker signals (MNDA UK; IZKF Jena) 2) Multimodal MRI in motor neuron diseases: staining neuropathology in vivo (in house) 3) Development of diffusion tensor imaging alterations during the course of ALS (IZKF Jena) 4) Impaired sensorimotor integration in ALS: an MEG study (BIOMAG Center Jena) 5) NISALS II (Jena): Implementing MRI as biomarker in ALS (DGM Germany, in house) Significant parts of the work of NISALS involves standardization of MRI data to make data between centers quantitatively comparable. The JPND call provides an excellent opportunity to streamline this process and pair up with standardization of molecular biomarkers. MRI provides an excellent endophenotype and quantifies both disease course and severity, which is the core task of the NISALS initiative and the JPND call. None of these projects show financial overlap with SOPHIA.

Curriculum Vitae – Partner 5 – Ireland – Prof. Orla Hardiman

Organization information		Personal information group leader	
Full legal organisation name	The Provost, Fellows, Foundation Scholars, and other members of Board, of the College of the Holy and Undivided Trinity of Queen Elizabeth near Dublin	Gender	Female
Institute	Trinity College Dublin	Title	Prof.
Street or P.O. Box	College Green	First name	Orla
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Internet home page	www.tcd.ie www.mnd.ie	Email address	orla@hardiman.net
National funding organisation full name		Higher Education Authority	
National funding organisation abbreviation		HEA	

Relevant publications which demonstrates the competence to carry out the project	
	Authors, Title, Name journal, Year/issue/pages
1	Elamin M, Phukan J, Bede P, Jordan N, Byrne S, Pender N, Hardiman O. Executive dysfunction is a negative prognostic indicator in patients with ALS without dementia. Neurology. 2011 Apr 5;76(14):1263-9. PubMed PMID: 21464431.
2	Kiernan MC, Vucic S, Cheah BC, Turner MR, Eisen A, Hardiman O, Burrell JR, Zoing MC. Amyotrophic lateral sclerosis. Lancet. 2011 Mar 12;377(9769):942-55. Epub 2011 Feb 4.. PubMed PMID: 21296405.
3	Byrne S, Bede P, Elamin M, Kenna K, Lynch C, McLaughlin R, Hardiman O. Proposed criteria for familial amyotrophic lateral sclerosis. Amyotroph Lateral Scler. 2011 May;12(3):157-9. Epub 2011 Jan 5. PubMed PMID: 21208036.
4	cLaughlin RL, Phukan J, McCormack W, Lynch DS, Greenway M, Cronin S, Saunders J, Slowik A, Tomik B, Andersen PM, Bradley DG, Jakeman P, Hardiman O. Angiogenin levels and ANG genotypes: dysregulation in amyotrophic lateral sclerosis. PLoS One. 2010 Nov 10;5(11):e15402. PubMed PMID: 21085671; PubMed Central PMCID: PMC2978104
5	Donaghy C, Pinnock R, Abrahams S, Cardwell C, Hardiman O, Patterson V, McGivern RC, Gibson JM. Ocular fixation instabilities in motor neurone disease. A marker of frontal lobe dysfunction? J Neurol. 2009 Mar;256(3):420-6. Epub 2009 Mar 18. PubMed PMID: 19306041.

Description of patents related to the present topic
None

Description of ongoing projects related to the present topic, indicating funding sources and possible overlaps with the proposal
We are currently funded by the Euro-MOTOR grant (European multidisciplinary ALS network identification to cure motor neuron degeneration; Grant Agreement No 259867) to population-based incident cases and controls, and to provide biological material (plasma, urine, DNA & RNA) to our European partners.. Our current work is funded by the Irish Health Research Board (CSA 03/2007; HPF/2009/17; HPF/2010/62)and focuses on deep phenotyping, neuroimaging, neuropsychology and population genetics of ALS. The overall objective is to identify subgroups of ALS for genetic stratification and to provide insights into disease pathogenesis and clinical outcome. We are a recruiting centre for the Biogen-Idec sponsored Phase 3 Empower (Dexpramipexole) study. I am also the PI of a population based study of young onset neurodegeneration in the Dublin area. None of these projects show financial overlap with SOPHIA.

Curriculum Vitae – Partner 6 –Italy – Prof. Adriano Chio

Organization information		Personal information group leader	
Full legal organisation name	University of Turin	Gender	Male
Institute	Department of Neuroscience, ALS Center	Title	Prof.
Street or P.O. Box	Via Cherasco 15	First name	Adriano
ZIP code	10126	Family name	Chio
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Country	Italy	Phone number	+39 01 16335439
Internet home page	www.unito.it	Email address	achio@usa.net
National funding organisation full name		Italian Ministry of Health	
National funding organisation abbreviation		No abbreviation	

Relevant publications which demonstrates the competence to carry out the project	
	Authors, Title, Name journal, Year/issue/pages
1	De Marco G, Lupino E, Calvo A, Moglia C, Buccinnà B, Grifoni S, Ramondetti C, Lomartire A, Rinaudo MT, Piccinini M, Giordana MT, Chiò A. Cytoplasmic accumulation of TDP-43 in circulating lymphomonocytes of ALS patients with and without TARDBP mutations. Acta Neuropathol. 2011; 121:611-622
2	Johnson JO, Mandrioli J, Benatar M, Abramzon Y, Van Deerlin VM, Trojanowski JQ, Gibbs JR, Brunetti M, Gronka S, Wuu J, Ding J, McCluskey L, Martinez-Lage M, Falcone D, Hernandez DG, Arepalli S, Chong S, Schymick JC, Rothstein J, Landi F. *et al*. Exome sequencing reveals VCP mutations as a cause of familial ALS. Neuron. 2010; 68:857-64
3	Chiò A, Schymick JC, Restagno G, Scholz SW, Lombardo F, Lai SL, Mora G, Fung HC, Britton A, Arepalli S, Gibbs JR, Nalls M, Berger S, Kwee LC, Oddone EZ, Ding J, Crews C, Rafferty I, Washecka N, Hernandez D, Ferrucci L, Bandinelli S. *et al*. A two-stage genome-wide association study of sporadic amyotrophic lateral sclerosis. Hum Mol Genet. 2009; 18:1524-1532
4	Chiò A, Mora G, Calvo A, Mazzini L, Bottacchi E, Mutani R, and the PARALS. Epidemiology of ALS in Italy: a 10-year prospective population-based study. Neurology, 2009; 72:725-731.
5	Chiò A, Calvo A, Moglia C, Mazzini L, Mora G; PARALS study group. Phenotypic heterogeneity of amyotrophic lateral sclerosis: a population based study. J Neurol Neurosurg Psychiatry 2011; 82:740-746 .

Description of patents related to the present topic
None

Description of ongoing projects related to the present topic, indicating funding sources and possible overlaps with the proposal
The Turin ALS centre is involved in the EUROMOTOR project (European Community's Health Seventh Framework Programme (FP7/2007-2013), grant agreement n° 259867), and is the coordinating centre for the Clinical work package. The EUROMOTOR project has the aim of collecting a large number of ALS patients from population-based epidemiological registers and creating a bio-repository bank for exposomic, metabonomic, genomic and proteomic studies. The centre is also involved in a project on Neuroimaging in ALS with advanced techniques, including MRI and PET-TC. The project is funded by Compagnia di San Paolo, Turin, Italy (Bando Neuroscienze 2008, grant n. 23/A). The Turin ALS center funded and lead the Italian ITALSGEN Consortium, which includes 16 Italian ALS centers and has collected 2,500 sALS, 120 fALS and 2,500 controls DNA. ITALSGEN has been founded by the Italian Ministry of Health (Ricerca Sanitaria Finalizzata 2007, grant 27), ALSA (Grant 621), Fondazione Vialli e Mauro (grant 6) and Federazione Italiana Giuoco Calcio (grant 3) for GWAS and exome sequencing. None of these projects show financial overlap with SOPHIA.

Curriculum Vitae – Partner 7 –Italy – Prof. Vincenzo Silani, MD

Organization information		Personal information group leader	
Full legal organisation name	Istituto Auxologico Italiano	Gender	Male
Institute	Department of Neurology, Laboratory of Neuroscience	Title	Prof. MD.
Street or P.O. Box	Piazzale Brescia 20	First name	Vincenzo
ZIP code	20149	Family name	Silani
City	Milano	Position in institute	Director
Country	Italy	Phone number	+39 02 619112937
Internet home page	www.auxologico.it	Email address	vincenzo@silani.com
National funding organisation full name		Italian Ministry of Health	
National funding organisation abbreviation		No abbreviation	

Relevant publications which demonstrates the competence to carry out the project	
	Authors, Title, Name journal, Year/issue/pages
1	Corrado L., Ratti A., Gellera C., Buratti E., Castellotti B., Carlomagno Y., Ticozzi N., Mazzini L., Testa L., Taroni F., Baralle F.E., Silani V., D' Alfonso S. High frequency of TARDBP gene mutations in Italian patiens with Amyotrophic Lateral Sclerosis. Human Mutation 2009, 30, 688-694.
2	Ticozzi N., LeClerc A.L., Keagle P., Glass J.D., Wills A.-M., van Blitterswijk M., Bosco D.A., Rodriguez- Leyva I., Gellera C., Ratti A., Taroni F., McKenna-Yasek D.M., Sapp P.C., Silani V., Furlong C.E., Brown Jr., R.H.,Landers J.E. Paraoxonase Gene Mutations in Amyotrophic Lateral Sclerosis Ann Neurol, 2010, 68, 102-107.
3	Bossolasco P., Cova L., Calzarossa C., Servida F., Mencacci N. E., Onida F., Polli E., Lambertenghi Deliliers G., Silani V. Widespread metalloproteinase alterations in amyotrophic lateral sclerosis. J Mol Med, 2010, 88, 553-564.
4	Agosta F., Chiò A., Cosottini M.,De Stefano M., Falini A., Mascalchi M., Rocca M.A., Silani V., Tedeschi G., Filippi M. The present and the future of neuroimaging in amyotrophic lateral sclerosis. AJNR Am J Neuroradiol, 2010, 31, 1769-1777.
5	Shatunov A., Mok K., Newhouse S., Weale M. E., Smith B., Vance C., Johnson L., Veldink J.H., Van Es M., Van Den Berg L., Robberecht W., van Damme P., Hardiman O. *et al*. Chromosome 9p21.2 in sporadic amyotrophic lateral sclerosis in the UK and seven other countries: a genome-wide association study. Lancet Neurol, 2010, 9, 986-994.

Description of patents related to the present topic
None

Description of ongoing projects related to the present topic, indicating funding sources and possible overlaps with the proposal
Prof. Vincenzo Silani at the IRCCS Istituto Auxologico founded and leads the Italian SLAGEN Consortium (2009) composed of six founding Italian ALS Centers and nine other contributing Centers. The Consortium has collected 2500 SALS and 2000 control DNA in a single collaborative database. The SLAGEN Consortium has been supported by the Italian Ministry of Health (Ricerca Finalizzata 2007 no. 31) for the Italian GWA Study to be completed. He also founded the EXOMEFALS Consortium with the Fondazione-IRCCS Istituto Carlo Besta of Milan and the Department of Neurology of the University of Massachusetts, USA (2009). The main purpose of the EXOMEFALS Consortium is the identification of novel FALS-associated genes through exome capture and short-read sequencing. The Consortium has collected 200 FALS samples from eight Italian ALS Centers and has been supported by AriSLA (EXOMEFALS, 2009). IRCCS Istituto Auxologico Italiano is part of NISALS, European Consortium devoted to MRI in ALS, coming together right now. None of these projects show significant overlaps with SOPHIA. None of these projects show financial overlap with SOPHIA.

Curriculum Vitae – Partner 8 – Poland – Magdalena Kuzma -Kozakiewicz, MD, PhD

Organization information		Personal information group leader (partner)	
Full legal organisation name	Medical University of Warsaw	Gender	Female
Institute	Department of Neurology First Medical Faculty	Title	MD. PhD.
Street or P.O. Box	Żwirki i Wigury 67	First name	Magdalena
ZIP code	02-091	Family name	Kuzma-Kozakiewicz
City	Warsaw	Position in institute	Assistant Professor
Country	Poland	Phone number	+48 22 5992857
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National funding organisation full name		National Centre for Research and Development	
National funding organisation abbreviation		NCRD	

Relevant publications which demonstrates the competence to carry out the project	
	Authors, Title, Name journal, Year/issue/pages
1	Kuźma M, Jamrozik Z, Barańczyk-Kuźma A. Activity and expression of glutathione S-transferase pi in patients with amyotrophic lateral sclerosis. Clin Chim Acta 2006 Feb; 364 (1-2): 217-21
2	Habisch H.J, Janowski M., Binder D., Kuzma-Kozakiewicz M., Widmann A., Habich A., Schwalenstoecker B., Hermann A., Brenner R., Lukomska B., Domanska-Janik K, Ludolph A.C., Storach A.. Intrathecal application of neuroectodermally converted stem cells into a mouse model of ALS: limited intraparenchymal migration and survival narrows therapeutic effects. J Neural Transm 2007;.114: 1395-406
3	Kuzma-Kozakiewicz M., Kwieciński H. New therapeutic targets for amyotrophic lateral sclerosis (ALS) Experts Opinion on Therapeutic Targets, 2011;15(2):127-43
4	Kuzma-Kozakiewicz M., Usarek E., Ludolph A., Barańczyk-Kuźma A. Tau expression differs in mice hybrids with dynein heavy chain 1 and superoxide dismutase-1 mutations Neurochem Res 2011;36(6):978-85
5	Berdyński M., Kuzma-Kozakiewicz M., Ricci C., Kubiszewska J., Łusakowska A., Kwieciński H., Battistini S., Żekanowski C. Recurrent G41S mutation in Cu/Zn superoxide dismutase gene (SOD1) causing familial amyotrophic lateral sclerosis in a large Polish family. ALS, accepted for publication, June 2011

Description of patents related to the present topi
None

Description of ongoing projects related to the present topic, indicating funding sources and possible overlaps with the proposal
1. Transgenic animals-based study funded by the Ministry of Science and Higher Education of Poland - N N401 417436: The role of MAP-proteins in pathogenesis of MND (2009-2011) 2. Scientific project funded by the Ministry of Science and Higher Education of Poland: N N402 373539: The role of kinesins in pathogenesis of ALS (2010-2012) 3. RNA and protein-based approach to neuropathology and molecular base of ALS funded by the Polish-Norwegian Research Fund PNRF-204-AI-1/07: Medical treatment and clinical evaluation of the treatment efficacy of patients with myasthenia gravis and amyotrophic lateral sclerosis – comparison between Poland and Norway (2008-2011). The project aimed to build electronic databases of clinical phenotype and treatment strategies of patients with ALS and MG and to compare the patient populations between the two countries. None of these projects show financial overlap with SOPHIA.

Curriculum Vitea – Partner 9 – Portugal – Prof. Mamede de Carvalho

Organization information		Personal information group leader	
Full legal organisation name	Instituto de Medicina Molecular	Gender	Male
Institute	Neuromuscular Unit	Title	Prof.
Street or P.O. Box	Av Prof Egas Moniz	First name	Mamede
ZIP code	1649-028	Family name	de Carvalho
City	Lisbon	Position in institute	Director of the Neuromuscular Unit
Country	Portugal	Phone number	+35 12 17999411
Internet home page	www.imm.fm.ul.pt/web/imm/home	Email address	mamedemg@netcabo.pt
National funding organisation full name		Fundação para a Ciência e Tecnologia	
National funding organisation abbreviation		FCT	

Relevant publications which demonstrates the competence to carry out the project	
	Authors, Title, Name journal, Year/issue/pages
1	Pinto A, Almeida JP, Pinto S, Pereira J, Oliveira AG, de Carvalho, M (2010). Home telemonitoring of non invasive ventilation decreases healthcare utilization in a prospective controlled trial of ALS patients. J Neurol Neurosurg Psychiatry 81: 1238-1242
2	de Carvalho M, Pinto S, Costa J, Evangelista T, Ohana B, Pinto A (2010). A randomised, placebo-controlled trial of Memantine for Functional Disability in Amyotrophic Lateral Sclerosis. Amyotr Lat Scler 11: 456-460
3	de Carvalho M, Pinto S, Swash M (2011). Does the motor cortex influence denervation in ALS? EMG studies of muscles with both contralateral and bilateral corticospinal innervations. Clin Neurophysiol 122; 629-635
4	Carrilho R, de Carvalho M, Kuehl U, Pinto S, Pinto A, Kromminga A, Costa J. Erythropoietin and amyotrophic lateral sclerosis. Amyotr Lat Scler: in press
5	Lee T, Li YR, Ingre C, Weber M, Grehl T, Gredal O, de Carvalho M, Meyer T, Tysnes OB, Auburger G, Gispert S, Bonini NM, Andersen PM, Gitler AD. Ataxin-2 intermediate-length polyglutamine expansions in European ALS patients. Hum Mol Genet: in press

Description of patents related to the present topic
None

Description of ongoing projects related to the present topic, indicating funding sources and possible overlaps with the proposal
Respiratory rehabilitation in amyotrophic lateral sclerosis: Clinical and biochemical impact (funding source: national granted project by the Fundação para a Ciência e Tecnologia, PIC/IC/8265/2007, total budget is €193.000 for 3 national institutions (IMM, ITQB and Universidade de Aveiro. The project was planned to be finished by the end of 2011). This is a clinical project involving respiratory impairment in ALS, respiratory care, respiratory exercise, neurophysiology of the respiratory muscles and the potential changes of two molecular biomarkers, Epo and VEGF (without concerns about optimization and harmonization of measurement between centres). This project shows no financial overlap with SOPHIA.

Curriculum Vitae – Partner 10 – Portugal – Dr Julia Costa

Organization information		Personal information group leader	
Full legal organisation name	Instituto de Tecnologia Química e Biológica	Gender	Female
Institute	Laboratory of Glycobiology	Title	Dr.
Street or P.O. Box	Avenida da República	First name	Júlia
ZIP code	2780-157	Family name	Costa
City	Oeiras	Position in institute	Principal Investigator
Country	Portugal	Phone number	+35 12 14469437
Internet home page	www.itqb.unl.pt	Email address	jcosta@itqb.unl.pt
National funding organisation full name		Fundação para a Ciência e a Tecnologia	
National funding organisation abbreviation		FCT	

Relevant publications which demonstrates the competence to carry out the project	
	Authors, Title, Name journal, Year/issue/pages
1	Gomes, C., Keller, S., Altevogt, P., Costa, J. (2007) Evidence for secretion of Cu, Zn superoxide dismutase via exosomes from a cell model of amyotrophic lateral sclerosis. Neurosci. Let. 428, 43-46.
2	Palma, A.S., de Carvalho, M., Grammel, N., Pinto, S., Barata, N., Conradt, H.S., Costa, J. (2008) Proteomic analysis of plasma from Portuguese patients with Familial Amyotrophic Lateral Sclerosis. Amyotrophic Lateral Sclerosis 9, 339-349.
3	Gomes, C., Escrevente, C., Costa, J. (2010) Mutant superoxide dismutase 1 overexpression in NSC-34 cells: Effect of trehalose on aggregation, TDP-43 localization and levels of co-expressed glycoproteins. Neurosci. Lett. 475, 145–149.
4	Costa, J., Gomes, C., de Carvalho, M. (2010) Diagnosis, Pathogenesis and Therapeutic Targets in Amyotrophic Lateral Sclerosis (Review article). CNS Neurol Disord Drug Targets 9, 764-78.
5	Carilho, R., de Carvalho, M., Kuehl, U., Pinto, S., Pinto, A., Kromminga, A., Costa, J. (2011) Erythropoietin and Amyotrophic Lateral Sclerosis: plasma level determination. Amyotrophic Lateral Sclerosis 00, 000.

Description of patents related to the present topic
None

Description of ongoing projects related to the present topic, indicating funding sources and possible overlaps with the proposal
2009-2012 Respiratory Rehabilitation in Amyotrophic Lateral Sclerosis: clinical and biochemical impact, FCT, PIC/IC/82765/2007. Collaboration with Prof. Mamede de Carvalho (Principal Investigator), Instituto de Medicina Molecular, Faculty of Medicine, University of Lisbon. This project shows no financial overlap with SOPHIA.

Curriculum Vitae – Partner 11 – Spain – Jesus S. Mora Pardina, MD

Organization information		Personal information group leader (partner)	
Full legal organisation name	Servicio Madrileño de Salud	Gender	Male
Institute	Hospital Carlos III	Title	MD.
Street or P.O. Box	Sinesio Delgado, 9	First name	Jesus S.
ZIP code	28029	Family name	Mora Pardina
City	Madrid	Position in institute	Director ALS Unit
Country	Spain	Phone number	+34 91 4532675
Internet home page	www.madrid.org/hospitalcarlosIII	Email address	jmora.hciii@salud.madrid.org
National funding organisation full name		Instituto de Salud Carlos III	
National funding organisation abbreviation		ISCIII	

Relevant publications which demonstrates the competence to carry out the project	
	Authors, Title, Name journal, Year/issue/pages
1	Salas Campos T, Rodriguez-Santos F, Esteban J, Cordero Vázquez P, Mora Pardina JS. Spanish adaptation of the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R). Amyotrophic Lateral Sclerosis, 2010; 11: 475-477.
2	Salas T, Mora J, Esteban J et al. Spanish Adaptation of the Amyotrophic Lateral Sclerosis Questionnaire ALSAQ-40 for ALS patients. Amyotrophic Lateral Sclerosis 2008; 9 (3): 168-172.
3	Mora JS, Valera F, Macías AI, et al. Initial Design and Evaluation of a New Clinical Assessment Tool to Quantify Motor Deficits in ALS Patients: The Madrid Quantitative Neuromuscular Assessment, MAQUINA. Amyotrophic Lateral Sclerosis 2010, 11 (supp 1) 151-152.
4	Mora JS, Salas T, Marín S, et al. Social Care and Out of Pocket Disease Cost in Patients and Families with Amyotrophic Lateral Sclerosis in Spain. Amyotrophic Lateral Sclerosis 2010, 11 (supp 1) 130.
5	Campos Y, Martin R, Esteban J, Mora J, et al. Hyperactivity of the Mitochondrial Respiratory Chain in Fibroblasts of patients with ALS. Amyotrophic Lateral Sclerosis 2010, 11 (supp 1) 100.

Description of patents related to the present topic
None

Description of ongoing projects related to the present topic, indicating funding sources and possible overlaps with the proposal
GSK-3β levels in peripheral blood mononuclear cells in patients with amyotrophic lateral sclerosis. Inserso/Ministry of Health 2010-11. Coinvestigator. Grant number: Inserso 15/10 Mitochondrial alterations in fibroblasts in patients with ALS: role of the mitochondrial DNA haplogroups in disease development. Instituto de Salud Carlos III 2009-2012. Coinvestigator. Grant number: PS09/2341. Phase II/III multicenter, randomized, parallel group, double-blind, placebo controlled study to assess safety and efficacy of TRO19622 in Amyotrophic Lateral Sclerosis patients treated with riluzol. Funding promotor: Trophos SA. EudraCT number 2008-007320-25. Trial largest recruit center with 67 patients. Multicenter study, randomized, double-blind, placebo controlled, on the safety and efficacy of Dexpramipexole in subjects with Amyotrophic Lateral Sclerosis. Funding promotor: Biogen Idec. Protocol number: 223AS302. EudraCT number: 2010-022818-19. On recruitment. None of these projects show financial overlap with SOPHIA.

Curriculum Vitae – Partner 12 – Switzerland – PD Dr. Markus Weber

Organization information		Personal information group leader (partner)	
Full legal organisation name	Kantonsspital St.Gallen	Gender	Male
Institute	Neuromuscular Diseases Unit/ALS Clinic	Title	PD. Dr.
Street or P.O. Box	Kantonsspital St.Gallen	First name	Markus
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City	St. Gallen	Position in institute	Director
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Internet home page	www.kssg.ch	Email address	markus.weber@kssg.ch
National funding organisation full name		Swiss National Foundation	
National funding organisation abbreviation		SNF	

Relevant publications which demonstrates the competence to carry out the project	
	Authors, Title, Name journal, Year/issue/pages
1	de Carvalho M, Chio A, Dengler R, Hecht M, Weber M, Swash M. Neurophysiological measures in amyotrophic lateral sclerosis: markers of progression in clinical trials. Amyotroph Lateral Scler Other Motor Neuron Disord. 2005; 6:17-28
2	Neuwirth C, Nandedkar S, Stålberg E, Weber M. Motor unit number index (MUNIX): A novel neurophysiological technique to follow disease progression in amyotrophic lateral sclerosis. Muscle Nerve. 2010;42(3):379-84.
3	Neuwirth C, Nandedkar S, Stålberg E, Barkhaus PE, de Carvalho M, Furtula J, van Dijk JP, Baldinger R, Castro J, Costa J, Otto M, Sandberg A, Weber M. Motor Unit Number Index (MUNIX): A novel neurophysiological marker for neuromuscular disorders; test-retest reliability in healthy volunteers. Clin Neurophysiol. 2011 Mar 9. [in press]
4	Neuwirth C, Nandedkar S, Stålberg E, Barkhaus PE, de Carvalho M, Furtula J, van Dijk JP, Baldinger R, Castro J, Costa J, Otto M, Sandberg A, Weber M. Motor Unit Number Index (MUNIX): Normal values of five different muscles in healthy subjects from a multi-centre study. Clin Neurophysiol. 2011 Jun 18. [in press]
5	Weber M, Neuwirth C, Thierbach J, Schweikert K, Czaplinski A, Petersen J, Jung HH, Birve A, Marklund SL, Andersen PM.Familial ALS patients with SOD mutations in Switzerland show very diverse phenotypes and extremely long survival. J Neurol Neurosurg Psychiatry. 2011 Jun 23. [in press]

Description of patents related to the present topic
None

Description of ongoing projects related to the present topic, indicating funding sources and possible overlaps with the proposal
Multicenter longitudinal study in ALS patients applying the MUNIX method to assess test-retest reliability (intra-rater and inter-rater)(funding source: Swiss ALS foundation, no grant number). During this project and the JPND call longitudinal data will be generated which can be merged and analyzed together. Tissue donation program: we have collected 30 full autopsies with a post mortem delay of less than 6 hours which will be available for WP1 (funding source: internal resources). There is no overlap with SOPHIA.

Curriculum Vitae – Partner 13 – Turkey – Prof. Yesim Parman, MD.

Organization information		Personal information group leader (partner)	
Full legal organisation name	Istanbul University	Gender	Female
Institute	Istanbul Medical Faculty – Neurology department	Title	Prof. MD.
Street or P.O. Box	Millet Cad-Capa	First name	Yesim
ZIP code	34390	Family name	Parman
City	Istanbul	Position in institute	Professor
Country	Turkey	Phone number	+90 21 24142000
Internet home page	www. Istanbul.edu.tr	Email address	parmany@istanbul.edu.tr
National funding organisation full name		The Scientific and Technological Research Council of Turkey	
National funding organisation abbreviation		TÜBİTAK	

Relevant publications which demonstrates the competence to carry out the project	
	Authors, Title, Name journal, Year/issue/pages
1	Deymeer F, Serdaroğlu P, Poda M, Gulsen-Parman Y, Özçelik T, Özdemir C Segmental distribution of muscle weakness in SMA III: implications for deterioration in muscle strength with time. Neuromuscul Disord. 1997 Dec;7(8):521
2	Yayla V, Oge AE, Deymeer F, Gurvit H, Akca-Kalem S, Parman Y, Oflazer P. Cortical excitability in Duchenne muscular dystrophy. Clin Neurophysiol. 2007 Nov 27.
3	Emel E, Ergün SS, Kotan D, Gürsoy EB, Parman Y, Zengin A, Nurten A. Effects of insulin-like growth factor-I and platelet-rich plasma on sciatic nerve crush injury in a rat model. J Neurosurg. 2011 Feb;114(2):522-8.
4	Deymeer F, Serdaroglu P, Parman Y, Poda M. Natural history of SMA IIIb: muscle strength decreases in a predictable sequence and magnitude. Neurology. 2008 Aug 26;71(9):644-9.
5	Parman Y. Hereditary neuropathies. Curr Opin Neurol. 2007 Oct;20(5):542-7. Review.

Description of patents related to the present topic
None

Description of ongoing projects related to the present topic, indicating funding sources and possible overlaps with the proposal
Collaboration with the Molecular Biology and Genetics Dep of the Bogazici University- Istanbul and Prof Murat Gunel – Harvard University-Neurogenetics and Neurosurgery Dep. for familial ALS cases. This collaboration shows no financial overlap with SOPHIA.

Curriculum Vitae – Partner 14 – United Kingdom – Prof. Pamela Shaw

Organization information		Personal information group leader (partner)	
Full legal organisation name	University of Sheffield	Gender	Female
Institute	Sheffield Institute for Translational Neuroscience (SITraN)	Title	Prof.
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ZIP code	S10 2HQ	Family name	Shaw
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National funding organisation full name		Medical Research Council	
National funding organisation abbreviation		MRC	

Relevant publications which demonstrates the competence to carry out the project	
	Authors, Title, Name journal, Year/issue/pages
1	Kirby J, Ning K, Ferraiuolo L, Heath PR, Ismail A, Kuo S-W, Valori CF, Cox L, Sharrack B, Wharton SB, Ince PG, Shaw PJ *and Azzouz M* (2011) PTEN/AKT pathway linked to motor neuron survival in human SOD-1 related amyotrophic lateral sclerosis (ALS). Brain 134:506-17 *Equal contribution.
2	L Ferraiuolo, J Kirby, AJ Grierson, M Sendtner, PJ Shaw. Molecular and cellular pathways of motor neuron injury in amyotrophic lateral sclerosis.Nature Reviews Neurology 2011 (In Press).
3	Cox LE, Ferraiuolo L, Goodall EF, Heath PR, Higginbottom A, Mortiboys H, Hollinger HC, Hartley JA, Brockington A, Burness CE, Morrison KE, Wharton SB, Grierson AJ, Ince PG, Kirby J*, and Shaw PJ* (2010) Mutations in CHMP2B in lower motor neuron predominant amyotrophic lateral sclerosis (ALS). PLoS One 5:e9872.
4	Ferraiuolo L, Higginbottom A, Heath PR, Barber S, Greenald D, Kirby J & Shaw PJ. Dysregulation of astrocyte-motor neuron cross-talk in mutant SOD1 related amyotrophic lateral sclerosis (2011) Brain (In Press).
5	Ferraiuolo L, Heath PR, Holden H, Kasher P, Kirby J, and Shaw PJ (2007) Microarray analysis of the cellular pathways involved in the adaptation to and progression of motor neuron injury in the SOD1 G93A mouse model of familial ALS. J Neurosci 27:9201-9219.

Description of patents related to the present topic
None

Description of ongoing projects related to the present topic, indicating funding sources and possible overlaps with the proposal
(1) MEDICAL RESEARCH COUNCIL 2008 – 2011 TDP-43 and alternative splicing in motor neurone disease. (2) MOTOR NEURONE DISEASE ASSOCIATION AND WELLCOME TRUST 2005 – 2011 Creation of a national DNA and cell line repository for genetic research into motor neurone disease. (3) MOTOR NEURONE DISEASE ASSOCIATION 2009 – 2011 Comparison of gene expression profiles in two SOD1G93A mouse models showing strain specific difference in motor neuron disease phenotype. (4) EU FRAMEWORK 7 HEALTH 2010 TWO STAGE GRANT 2010 -2015 Euro-Motor: Systems Biology in ALS. (5) MOTOR NEURONE DISEASE ASSOCIATION 2010-2012 £162,761 Screening microRNAs as blood based biomarkers for motor neurone disease (MND). (6) Biogen Idec Randomised controlled trail of dexpramipexole in ALS 2011-2013. None of these projects show financial overlap with SOPHIA.

Curriculum Vitae – Partner 15 – United Kingdom – Dr Martin Turner

Organization information		Personal information group leader	
Full legal organisation name	Oxford University Nuffield Department of Clinical Neurosciences	Gender	Male
Institute	Nuffield Department of Clinical Neurosciences	Title	Dr.
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Relevant publications which demonstrates the competence to carry out the project	
	Authors, Title, Name journal, Year/issue/pages
1	Turner MR, Grosskreutz J, Kassubek J, Abrahams S, Agosta F, Benatar M, Filippi M, Goldstein LH, van den Heuvel M, Kalra S, Lulé D, Mohammadi B & Other members of The 1st NISALS. Towards a neuroimaging biomarker in amyotrophic lateral sclerosis. Lancet Neurology 2011; 10: 400-3.
2	Turner MR, Kiernan MC,Leigh PN, Talbot K. Biomarkers in amyotrophic lateral sclerosis. Lancet Neurology 2009; 8: 94-109.
3	Bowser R, Turner MR, Shefner J. Biomarkers in ALS: Opportunities and limitations, Nature Reviews Neurology. 2011 in press.
4	Kiernan MC, Vucic S, Cheah B, Turner MR, Eisen A, Hardiman O, Burrell J, Zoing MC. Amyotrophic Lateral Sclerosis. Lancet 2011; 377: 942-55.
5	Filippini N, Douaud G, Mackay CE, Knight S, Talbot K, Turner MR. Corpus callosum involvement is a consistent feature of amyotrophic lateral sclerosis. Neurology 2010; 75: 1645-72.

Description of patents related to the present topic
None

Description of ongoing projects related to the present topic, indicating funding sources and possible overlaps with the proposal
The Oxford Study for Biomarkers in Motor Neuron Disease (‘BioMOx’) is a 5-year Medical Research Council study (2008-2013) recruiting a cohort of 70 ALS/MND patients having serial 6-monthly MRI, CSF and blood extraction with the aim of identifying diagnostic, prognostic, monitoring and mechanistic biomarkers. This project shows no financial overlap with SOPHIA.

Curriculum Vitae – United Kingdom – Prof. Paul Ince

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National funding organisation abbreviation		MRC	

Relevant publications which demonstrates the competence to carry out the project	
	Authors, Title, Name journal, Year/issue/pages
1	Alafuzoff I, Ince PG, et al. Staging/typing of Lewy body related α-synuclein immunoreactive pathology a study of the BrainNet Europe consortium Acta Neuropathol 117:635-52 (2009)
2	Savva GM, Wharton SB, Ince PG, Matthews F, Brayne C on behalf of MRC-CFAS. Age, neuropathology and dementia. New Eng J Med 360:2302-9 (2009)
3	Strong MJ, Grace GM, Freedman M, Lomen-Hoerth C, Woolley-Levine S, Goldstein LH, Murphy J, Shoesmith C, Rosenfeld J, Leigh PN, Bruijn L, Ince P, Figlewicz D. Consensus criteria for the diagnosis of frontotemporal cognitive and behavioural syndromes in amyotrophic lateral sclerosis. Amyotroph Lat Scler 10:131-46 (2009).
4	Mackenzie IRA, Neumann M, Bigio EH, Cairns NJ, Alafuzoff I, Kril J, Kovacs GG, Ghetti B, Halliday G, Holm IE, Ince PG, et al. Nomenclature for neuropathologic subtypes of frontotemporal lobar degeneration Acta Neuropathol 117:15–18 (2009)
5	Mackenzie IRA, Bigio EH, Ince PG, et al. Pathological TDP-43 distinguishes sporadic ALS from ALS with SOD-1 mutations. Ann Neurol 61; 427-34 (2007)

Description of patents related to the present topic
None

Description of ongoing projects related to the present topic, indicating funding sources and possible overlaps with the proposal
1) Medical Research Council – Project Grant 2010-2014 (£1.5m) Epidemiological neuropathology of dementia - The Cognitive Function and Ageing Neuropathology Study. PG. Ince (Principal Investigator), C. Brayne, S. Love, F.E. Matthews, J.A.R. Nicoll, D Walsh, S.B. Wharton. 2) Medical Research Council – Strategic Award 2010-2012 Brain Bank Network James Ironside (PI) as Network Member and MRC Board representative to the Network Steering committee 3) UK NIHR (DeNDRoN) – Neuropathology Special Interest Group. PG Ince (Chairman) None of these projects involve funded activity related to the SOPHIA proposals. However Chairmanship and Steering Committee membership for the two UK Brain Bank networking initiatives will facilitate delivery of the collaborative expertise required for the success of SOPHIA.