European Cooperation in the field of Scientific and Technical Research
- COST -

Brussels, 22 November 2013

COST 046/13

MEMORANDUM OF UNDERSTANDING

Subject :	Memorandum of Understanding for the implementation of a European Concerted Research Action designated as COST Action BM1306: Better Understanding the Heterogeneity of Tinnitus to Improve and Develop New Treatments (TINNET)

Delegations will find attached the Memorandum of Understanding for COST Action BM1306 as approved by the COST Committee of Senior Officials (CSO) at its 188th meeting on 14 November 2013

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

COST Action BM1306
BETTER UNDERSTANDING THE HETEROGENEITY OF TINNITUS TO IMPROVE AND DEVELOP NEW TREATMENTS (TINNET)

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

1. The Action will be carried out in accordance with the provisions of document COST 4114/13 "COST Action Management" and document COST 4112/13 "Rules for Participation in and Implementation of COST Activities" , or in any new document amending or replacing them, the contents of which the Parties are fully aware of.

2. The main objective of the Action is the creation of a pan-European network for identifying pathophysiologically and clinically meaningful subtypes of tinnitus and their neurobiological underpinnings in order to develop and improve new effective treatments for tinnitus. .

3. The economic dimension of the activities carried out under the Action has been estimated, on the basis of information available during the planning of the Action, at EUR 48 Million in 2013 prices.

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

5. The Memorandum of Understanding will remain in force for a period of 4 years, calculated from the date of the first meeting of the Management Committee, unless the duration of the Action is modified according to the provisions of section *2. Changes to a COST Action* in the document COST 4114/13.

A. ABSTRACT AND KEYWORDS

Tinnitus is the perception of sound in the absence of an environmental acoustic stimulus. In Europe over 70 million people experience tinnitus and for 7 million it creates a debilitating condition. There are no established treatment approaches available for curing tinnitus. Better treatment is urgently needed.

Brain research has created a paradigm shift by demonstrating that tinnitus is the consequence of altered neural activity in specific brain networks rather than an ear problem. Based on the understanding of tinnitus as brain disorder, first promising therapeutic approaches have already been developed by individual groups participating in this Action.

However further development is hampered by the heterogeneity of tinnitus and limited knowledge about the neuronal underpinnings of the different tinnitus subtypes.

This Action will foster the establishment of a pan-european multidisciplinary network with the major goal to facilitate (1) the identification of meaningful criteria for tinnitus subtyping, (2) the neurobiological underpinnings of the different tinnitus subtypes and (3) their relevance for response to treatment. This knowledge is essential for developing of new treatment approaches, their clinical investigation and the speed of translation into marketable products.

This COST Action intends a stepwise approach which involves identification of (1) meaningful clinical and demographic characteristics for tinnitus subtyping, (2) tinnitus related changes of brain activity in the different forms of tinnitus, (3) intermediate genetic phenotypes for the identification of genetic factors in the pathogenesis of tinnitus and (4) predictors for response to various treatments. This approach requires a coordinated effort from basic scientists, technicians and clinicians of different disciplines working together in ongoing close collaboration.

Keywords: otolaryngology, neuromodulation, tinnitus database, pathophysiology of tinnitus, psychiatry

B. BACKGROUND

B.1 General background

Subjective tinnitus is a common and distressing symptom that is characterized by the perceived sensation of sound in the absence of an internal or external stimulus. Tinnitus can take the form of continuous buzzing, hissing or ringing, or a combination of these or other characteristics. It can be heard in one or both ears, but it can also be referred to the head. Tinnitus can occur intermittently or

have a pulsatile character. The intensity of the phantom sound can vary from a subtle noise just above hearing threshold, to high intensity sounds which cannot be masked by any external noise. Based on recent data from a large Norwegian survey of more than 50,000 adults, 21.3% of men and 16.2% of women are bothered by their tinnitus, with 4.4% and 2.1%, respectively, reporting high tinnitus intensity. In fact, for 1-2 in 100 adults, tinnitus markedly affects their ability to lead a normal day-to-day life and the extent of this disability leads many people to seek help. Based on these epidemiological studies it is estimated that in Europe over 70 million people experience tinnitus and that for about 10 million it creates a debilitating condition. Severe tinnitus is often associated with depression, anxiety and insomnia, resulting in an enormous socio-economic impact. It has been estimated that 13 million people in Western Europe and in the US approach their doctor regularly because of their tinnitus symptoms. The market value of the segment 'symptomatic relief from tinnitus' is estimated to be € 800 million. These figures are expected to increase due to increasing occupational and leisure noise and due to the demographic development.
Recent advances in neuroscientific methods have led to enormous progress in the understanding of tinnitus and prompted the development of innovative treatment approaches in the last years. However further progress is hampered by the fact that tinnitus represents a highly heterogeneous condition. Thus many findings coming from small samples cannot be replicated and remain inconclusive. This problem is related to the current research structure with many separate groups working largely in isolation and being funded locally or nationally. In order to effectively address the heterogeneity of tinnitus a coordinated effort is required to enable the analysis of large samples. Thus COST, which funds networking and capacity building activities, is optimally suited to transform these currently still separated research groups into an efficient research network. By standardizing research methodology, facilitating knowledge exchange, enabling better coordination of research projects and ensuring regular transfer of latest results the COST Action will represent a quantum leap for tinnitus research. the COST Action will fill the currently still existing knowledge gap, which hampers the development of new therapies.

B.2 Current state of knowledge

Traditionally, tinnitus was considered to be a disorder that was primarily confined to the ear. However, the observation that tinnitus is not abolished by transection of the auditory nerve clearly indicates its central nervous system origin. Both animal models of tinnitus and neuroimaging research in patients suffering from tinnitus have provided important insight into the neuronal mechanisms involved in the pathophysiology of tinnitus. In short, alterations of neural firing and

oscillatory activity, alterations of neural synchrony and temporal coherence, and changes in the tonotopic maps of the auditory cortices have been observed in connection with tinnitus. These changes of neural activity seem to arise from dysfunctional activation of neural plasticity induced by altered sensory input, namely auditory deprivation in most cases, but also altered somatosensory input in some patients. The mentioned adaptive processes are mainly driven by mechanisms of homeostatic plasticity which alter the balance between excitatory and inhibitory function of the auditory system at several levels (dorsal cochlear nucleus, inferior colliculus, medial geniculate body and auditory cortex) in order to compensate for the reduced input.

In addition to altered activity in central auditory pathways, recent research has increasingly identified further central nervous system components of tinnitus. Brain networks involved in tinnitus pathophysiology differ from patient to patient and include the frontal cortex, the anterior cingulate, the insula and the medial temporal lobe including amygdala, hippocampus and parahippocampus. These brain areas are related to attention-, salience-, distress- and memory-related aspects of tinnitus. Depending on the individual clinical characteristics different networks seem to be involved to a different extent.

For decades it has been assumed that tinnitus cannot be cured. Therefore treatment strategies were restricted to approaches that facilitate habituation to tinnitus such as counselling, cognitive behavioural therapies and different forms of sound therapies. Recent neuroscientific research has demonstrated that tinnitus is related to neuroplastic alterations of brain activity. This implies that there is no reason to believe that tinnitus cannot be cured. Moreover neuroscientific research has identified targets for more causally oriented treatments and prompted the development of innovative approaches. These methods attempt to specifically counteract tinnitus related neuroplastic changes in the brain by specific input to the auditory system, by pharmacological treatment; by neurobiofeedback; by various forms of electrical stimulation of brain structures, either through implanted electrodes, via transcranial direct current stimulation or by inducing electrical current in the brain with transcranial magnetic stimulation. All these specific treatment strategies have in common that they require exact knowledge of tinnitus related neuronal changes in the patients under treatment.

First results from the mentioned innovative hypothesis driven approaches are promising, but also characterized by a high interindividual variability. An increasing number of start-up biotech- and health-tech-companies focus on the field. Further development and refinement of these methods is critical and can only be achieved by addressing the heterogeneity of tinnitus. This in turn requires a coordinated effort of clinical researchers on a large scale together with imaging experts, genetic researchers and specialists for clinical trial organisation and medical data management. In chronic

pain, which resembles in many aspects tinnitus it has been demonstrated that such a multidisciplinary collaboration has substantially improved the understanding of the different forms of chronic pain, the development of specific treatment strategies and finally the routine management of pain patients.

Thus in summary recent advances in neuroscientific methods enabled the establishment and refinement of a testable brain model of the different forms of tinnitus and the development of innovative treatment strategies targeting tinnitus specific neuroplastic alterations in the brain. With these developments, in the last 2 to 3 years, tinnitus research has reached the stage of acceptance as an independent, worthwhile research topic, acknowledged by high impact journals. Funding for these high impact publications was mainly derived from USA-based agencies, even though some of the PIs were Europeans. When analysing the amount of peer reviewed publications within the tinnitus field, European research centres dominate but work in isolation from each other. At present, the European Commission does not fund any projects which focus on the pathophysiology or treatment of Tinnitus. Two projects on auditory perception are funded in the seventh Framework programme (CALYXX MMF and ZEBRAFISH PERCEPTION). These projects are not directly related to tinnitus, but progress will be monitored and researchers will be contacted.

B.3 Reasons for the Action

The aim of the Action is the identification of pathophysiologically and clinically meaningful subtypes of tinnitus. This in turn is required for increasing the efficacy of currently available treatments by assigning the most effective treatment to the individual patient. Moreover the identification of pathophysiologically meaningful tinnitus subtypes is critical for the development of new effective treatments. Based on growing knowledge about the neuronal mechanisms of tinnitus in the last years many innovative treatment approaches have been developed by various separate groups from different countries and different disciplines and using a large variety of methods. All these methods have in common that they aim at targeted modulation of the neuroplastic changes underlying tinnitus, either by specific auditory stimulation, by conditioned learning, by pharmacologic treatment, by brain stimulation or by a combination of different treatments. Promising results in pilot studies illustrate the potential of the various approaches. However, most results are characterized by a high interindividual variability, indicating the relevance of tinnitus subtypes which differ in their response to specific treatments. Thus there is an urgent need for identifying pathophysiologically distinct subgroups for optimizing and further validating these treatment interventions. Moreover the identification of valid subtypes will enable to

better predict treatment response to the various currently already available treatment and thus represents a critical prerequisite for investment from the health industry in the Tinnitus field. The identification of tinnitus subtypes achieved by this COST Action will coordinate research efforts across research groups in many European countries.

The strategy of this COST Action is to standardize and coordinate clinical, neuroimaging and genetic assessment of tinnitus patients and to aggregate data in a large scale database in order to identify tinnitus subtypes and their neurobiological underpinnings. This will facilitate the developments of new therapies and improve the efficacy of currently available treatments.

The expected result is the identification of meaningful subtypes of tinnitus and their neurobiological underpinnings. This in turn will improve tinnitus treatment by enabling to better assign current and to better tailor future treatments to specific patient subgroups. Since the high heterogeneity of tinnitus is considered as the major obstacle for the development of more effective treatment strategies, this COST Action will address the current bottleneck in the development process of innovative treatment approaches. This approach requires a coordinated effort from clinicians and technicians of different centres and disciplines and bio- and health-tech companies working together in ongoing close collaboration, which will be achieved by this COST Action. Specific regularly meeting of Working Groups (WG) will be the backbones of this research network. Communication across WG will be ensured by yearly meetings of all involved researchers and further supplemented by regular web-based communication.

The COST Action will facilitate the establishment and the expansion of a modularly organized database, including demographic, clinical, imaging, genetic and treatment data.

This continuously growing database will significantly speed up the development process of innovative treatment approaches and generate the knowledge for achieving a breakthrough in the treatment of tinnitus. This will meet both socio-economical needs and produce scientific and technological advances. The estimated 10 million people in Europe and many more worldwide in whom tinnitus is causing disability and invalidity will benefit from newly developed therapeutic options. The reduction of the tinnitus related socio-economic burden will relieve social systems.

The Action will create a highly productive environment for the European bio- and health-tech industry in a market, which is huge, still almost untapped and expected to further grow.

Moreover a more detailed understanding of the different forms of tinnitus will represent an important scientific progress since it will elucidate mechanisms underlying phantom perceptions in other modalities and perception in general. Innovative treatments, if successful in tinnitus, could be transferred to other related pathologies such as chronic pain or posttraumatic stress disorder.

This COST Action is a unique effort and the only international network worldwide focussing on

large scale data driven subtyping of tinnitus patients and correlations with neurobiological changes and molecular genetics. This Action has the potential to provide the necessary framework for the set-up of a global initiative for the benefit of society and the many patients suffering from tinnitus.

B.4 Complementarity with other research programmes

As mentioned in B.2 there are no other EU funded programmes on tinnitus.

C. OBJECTIVES AND BENEFITS

C.1 Aim

The aim of the Action is the creation of a pan-European network to identify pathophysiologically and clinically meaningful subtypes of tinnitus and their neurobiological underpinnings. This will be facilitated by standards for clinical assessment and outcome measurement, by large-scale multi-centric data assessment and by data management in a quality controlled database. These data will be complemented by neuroimaging and by the search for genetic markers. Tinnitus is highly prevalent, can cause a high burden in concerned individuals and has enormous socio-economic impact. First promising new treatment approaches have been developed in the past few years, but their further development is hampered by the pathophysiological diversity of tinnitus, resulting in high interindividual variability in treatment outcomes. Thus the traditional research structure of many groups working largely in isolation and investigating small samples is insufficient for addressing the heterogeneity of tinnitus and for identifying valid subtypes.

C.2 Objectives

This COST Action is focussing on the following objectives
The proposed pan-european coordinated effort will include the following objectives:
(1) Clinical and audiological assessment of tinnitus patients according to common standards
(2) Data management in a central database and identification of subtype candidates
(3) Developing standards for neuroimaging studies and probing the neurobiological entity of the defined subtypes by large-scale analyses of neuroimaging data
(4) Identifying the involvement of genetic factors in the pathogenesis of the different subtypes of tinnitus
(5) Development of standards for outcome measurements in clinical trials and central data

collection

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

The objectives will be achieved under the umbrella of this COST Action by joining experts working in complementing disciplines in academics and industry with their main interest on tinnitus: audiologists, otologists, neurologists, psychiatrists, psychologists, neuroscientists, clinical-trial- and neuroimaging-specialists and geneticists. The COST Action will provide an excellent platform for unifying and harmonizing assessment routines and methodological standards, which is a prerequisite to identify meaningful characteristics for tinnitus subtyping and the pathophysiological factors involved in the different forms of tinnitus. With this COST Action, Europe-wide collaboration will be facilitated with a significant impact on tinnitus research world-wide by networking of renowned scientific experts from various disciplines and many COST countries. The Action will accelerate the successful coordination of local research activities into an integrated project by regular meetings and training workshops.

Many of the applicants have already successfully collaborated in the past within the Tinnitus Research Initiative database workgroup (http://database.tinnitusresearch.org/) initiated by the Tinnitus Research Initiative (www.tinnitusresearch.org). Within this project a first step towards standardisation of patient assessment and outcome measurement has been made (*30*). Moreover a tinnitus database has been established (*31*) and standards for clinical trials have been proposed (*32*). To date the database contains data from more than 2900 tinnitus patients. The expertise gained by this group is indeed very valuable in terms of clinical characterisation, phenotype definition, establishment of neuroimaging techniques and outcome standardisation, which are major objectives of this COST Action. Furthermore the activities of this COST Action can be based on an established and working infrastructure. Even if this infrastructure is planned to be further developed within this Action, patient recruitment can be immediately started in parallel, which will tremendously accelerate the progress within the Action.

Short Term Scientific Missions (STSMs) and training workshops will be organised to train early stage scientists and clinical researchers in neuroimaging as well as in specific skills in tinnitus assessment. Outreach activities, establishment and realisation of standards, dissemination of knowledge, and transfer of know-how are an essential part of this COST Action and are going to be achieved by training workshops, scientific meetings, and conferences. The internet will be used for information transfer and dissemination by the creation of an interactive website which will serve as platform for information and discussion for clinicians, researchers and patients.

C.4 Potential impact of the Action

This COST Action is a unique effort and the only international network world-wide focusing on subtyping of tinnitus, the identification of the neuronal correlates of these subtypes and their molecular genetics. The heterogeneity of tinnitus is the major reason for inconsistent results in tinnitus studies, both in neuroimaging studies and clinical trials, and represents the major barrier in the development of innovative and more efficient treatments for tinnitus. This barrier will be addressed by this COST Action which will identify clinical criteria for pathophysiologically distinct subtypes of tinnitus. The Action will further improve the understanding of the pathophysiological mechanisms of the different forms of tinnitus and provide crucial information for the development of innovative hypothesis driven treatment approaches. Thus the Action has high potential impact on many different levels.

- With prevalence rates between 10 and 15% for tinnitus perception and 1-2% for severe disabling tinnitus Tinnitus is a frequent disorder. There are currently no established treatments available for curing tinnitus or effectively reducing its loudness. Thus the development of new effective treatments has high impact for the many million people who currently suffer from tinnitus.
- The high prevalence rates together with the high impairment of many people suffering from tinnitus result in an enormous socio-economic burden. Costs caused by tinnitus related sick-leave or disability pension will be reduced by more effective treatments.
- Treatment of Tinnitus represents a huge market, that is currently still untapped and that is expected to grow further. A network of researchers, clinicians and health industry representatives provides a research infrastructure that represents a substantial competitive advantage for bio-tech- and health-tech-companies in the field. This infrastructure will make Europe to the leading location in the competition for the world-wide tinnitus market.
- Knowledge generated in this COST Action has important implications for the understanding and treatment of other diseases that overlap in their pathophysiology with tinnitus. Newly developed treatments that are effective for tinnitus may represent promising candidates for the treatment of related disorders such as chronic pain syndromes or posttraumatic stress disorder.
- A better understanding of tinnitus and improved treatments will also bring further insight into the physiology of the auditory system and related brain pathways and have a tremendous influence on hearing research.

C.5 Target groups/end users

Tinnitus patients will benefit, since the COST Action will increase the chances that efficient new treatments will soon be available. As a consequence medical research and the health- and pharma-industry will focus more on this hitherto neglected area. This in turn will result in further progress, better treatment facilities and an overall increase of the quality of tinnitus research and clinical management. Tinnitus patients as represented by the European Federation of Tinnitus Associations (www.eutinnitus.com) were involved in the preparation of the proposal.

The European bio- and health-tech-industry will benefit from the Action, since the research infrastructure of this COST Action will be worldwide unique and represent an important competitive advantage. The identification of pathophysiologically distinct subtypes and the development of valid and standardized outcome measurements will be essential steps in the development of new and innovative treatment strategies. Representatives from companies working in the field were involved in the preparation of the proposal.

Clinical and basic researchers involved in the project will benefit from the chance to increase the quality of their research through the facilitated collaboration with multiple experts. Moreover research will become more efficient through the coordination of research efforts within the COST Action.

Clinicians will benefit from the possibility to offer more effective treatments for tinnitus. More efficient treatments will also increase the quality of treatment through standardisation, e.g. by development of guidelines.

National and international health authorities and social systems will be end users by a reduction of direct and indirect costs (see C.4).

The scientific community will benefit from better understanding of phantom perception as a model for other neuropsychiatric disorders and as a model for perception in general.

D. SCIENTIFIC PROGRAMME

D.1 Scientific focus

This COST Action will encourage experts from different fields interested in tinnitus to exchange scientific knowledge and to collaborate by means of regular meetings, staff exchanges, workshops for early stage clinicians and scientists and conferences. Four main scientific goals will be achieved by this Action:

- Establishment of standards for clinical and audiological assessment of tinnitus patients and controls for detailed phenotypic characterization by the participating experts from the clinics

- Establishment of standards for neuroimaging of tinnitus patients and controls

- Establishment of a standardized web-based European tinnitus database and biobank for storage of clinical and neuroimaging data from patients and controls and for subsequent investigation of genetic factors of the different forms of tinnitus

- Establishment of standards for outcome measurements in clinical trials and integration of these longitudinal data from specific interventions in the database

The heterogeneity of tinnitus represents the major barrier for advances in the understanding of the pathophysiology of tinnitus, its molecular genetics and the development of more effective treatments. This COST Action will address this heterogeneity by standardized clinical and audiological phenotypisation of a large international sample of tinnitus patients. Standardized neuroimaging and genotypisation will enable subsequent investigation of the pathophysiology and molecular biology of the clinically phenotyped subforms of tinnitus. Finally standardized data from various treatment interventions will enable to test the relevance of the previously defined subtypes for response to specific therapeutic interventions.
This COST Action will impact the current *state of the art* in the investigation of the pathophysiology of tinnitus, since it will:

- gain insight into the role of various clinical and audiological factors involved in tinnitus heterogeneity through interaction of expert groups across complementing fields

- gain insight in the etiopathogenesis and the pathophysiology of the different forms of tinnitus by large-scale standardized neuroimaging of the clinically phenotyped tinnitus patients

- gain insight into the role of genetic factors as well as genetic/environmental factor interaction in the etiopathogenesis of the different forms of tinnitus

- gain insight in the relevance of specific clinical, audiological or demographic characteristics for response to specific treatments

- encourage clinicians and basic scientists to join forces and contribute to this field of research in order to stimulate fruitful exchanges of ideas and interdisciplinary discussion

- improve the training and broaden the spectrum of clinicians and basic scientists in the field of tinnitus

D.2 Scientific work plan methods and means

In this COST network, for the first time guidelines for the recruitment and the clinical and audiological assessment of tinnitus patients and controls as well as standards for neuroimaging and outcome measurement will be established.
Clinical data in tinnitus patients and controls as well as environmental factors (hearing impairment, stress, trauma), results from neuroimaging and genetic investigations will be collected according standardized procedures in a database.
Previous genetics endeavours in complex disease have shown that uniform sample recruitment standards and detailed phenotyping as well as appropriate endophenotyping using intermediate traits are an inevitable prerequisite to succeed. These tools will be developed by specialized working groups in this Action.
Participants of this COST Action will join forces for systematic analyses of clinical characteristics, information from the case history, audiological characteristics as well as neuroimaging data in order to identify genetic factors in tinnitus and to correlate genetic, environmental (hearing loss, stress, trauma) and endophenotypic (personality traits, molecular, physiological and neurobiological readouts) data.
The outcome will ultimately shed light on the heterogeneity of tinnitus, including the pathophysiology and molecular biology of the different forms. This will improve the diagnostics and therapy of the different forms of tinnitus. For information dissemination an Action website will be established with the following aims:

- Platform of information for the Action partners and clinicians and scientists interested in this field

- The database containing all SOPs and relevant information will be implemented in a password protected area which will only be accessible by registered users

- Information platform for patients and their relatives
- Public availability of guidelines for characterization and genetic analyses
- Dissemination of COST Action's results

The scientific objectives of the Action listed in D.1 will be converted by means of five interactive Working Groups (WGs):

WG 1 Clinical: Establishment of a standard for patient assessment and characterization.

Due to the fact that tinnitus is a complex condition with a multifactorial origin, experts in this group will consist of otologists, audiologists, neurologists, psychiatrists, psychologists, neurophysiologists, clinical trial methodologists and representatives from the industry. Based on a previously started consensus process (*30*) experts from different disciplines will join forces and further develop standardization procedures for easy, practicable and meaningful patient characterization. Guidelines for detailed clinical definition and phenotypic characterization of cases and controls will be developed. Importantly, not only tinnitus characteristics (e.g. loudness, frequency, modulatory factors) but also comorbid conditions (e.g. hyperacusis, depression, anxiety) and impact (tinnitus related handicap, quality of life) will be assessed. Furthermore, data on environmental factors (hearing impairment, head- or necktrauma, stress) will be collected.
This working group will perform the following central tasks:

- Development of harmonized guidelines for demographic and clinical assessment of patients and controls as well as definition of criteria for control recruitment
- Development of standards for audiological assessment of patients and controls
- Development of a web-based tool for demographic and clinical assessment, symptom scoring instruments and specific validated self-report questionnaires
- Dissemination of the guidelines and standards
- Organization of Short Term Scientific Missions, allowing medical professionals to benefit from clinical training in the setting of established clinics dedicated to the assessment and management of tinnitus and related disorder
- Implementation of guidelines and recommendations on the COST Action website

WG 2 Database establishment and implementation on the website

This working group will work on standards for data management and standards (e.g. predefined statistical analysis plans) and strategies for data analyses.

Therefore, experts in this group will join forces and consist of complementing disciplines such as clinicians, clinical trial specialists, data documentation specialists, biostatisticians and mathematicians.

This working group will perform the following central tasks:

- Standards for data handling and quality control
- Standards for statistical analysis procedures
- Development of strategies for hypothesis driven data analyses
- Development of strategies for data driven analyses
- Organization of Short Term Scientific Missions, to train scientists in data management and statistical data analyses
- Dissemination of standards and registration of predefined analyses plans on the COST Action website
- Implementation of the database into the COST Action's website

WG 3 Neuroimaging

This working group will work on standards for neuroimaging studies and on large-scale analyses of neuroimaging data. Experts in this group will include clinical researchers and specialists in neuroimaging methods including electroencephalography (EEG) and magnetic resonance tomography (MRI). In order to identify the neurobiological mechanisms of the different forms of tinnitus, this working group will concentrate on the following topics:

- establish standard operation procedures (SOPs) for data acquisition and analysis
- development and standardization of innovative data-analysing methods (e.g. connectivity analysis, individual component analysis)
- Implementing neuroimaging data in the database

- Testing the neurobiological entity of clinically defined subtypes
- Testing neuroimaging as an endophenotypization strategy in tinnitus research
- Preparation and submission of grant proposals to national, European, and international funding agencies, in order to ensure continuous support of studies
- Organization of Short Term Scientific Missions, with the goal to train pre- and post-doctoral scientists in imaging acquisition and analysis
- Implementation of SOPs and imaging data on the COST Action website

WG 4 Genetics

This multidisciplinary WG will bring together experts from molecular genetics as well as statistics and bioinformatics, in addition to clinicians with the goal to unify biobanking efforts for tinnitus across Europe, creating a pan-European resource to study the underlying genetic basis of tinnitus. Main goals of this WG will include the following tasks:

- Documentation of biobanking efforts (blood) for people with tinnitus and defined controls all over Europe
- Establishment of SOPs for sample collection, storage and sharing and
- Establishment of SOPs for genetic analysis of the human genome
- Search for genetic susceptibility variants predisposing to the different forms of tinnitus by the above mentioned techniques
- SOPs for statistical analysis of genotypic data and correlation with clinical and neuroimaging data
- SOPs for gene-gene and gene-environment interaction studies
- Organization of Short Term Scientific Missions, with a goal to train pre- and post-doctoral scientists in genetic research methodology
- Preparation and submission of grant proposals to national, European, and international funding agencies, in order to ensure continuous support of studies

- Implementation of SOPs and results on the COST Action website

WG 5 Standards for Treatment outcome measurement and central collection of results

The objective of this Working Group is to establish standards for outcome measurements in clinical trials to enable data collection of treatment results in the central database. Participants of this Action have recently proposed a standard for the performance of clinical trials in tinnitus (*32*).

The WG will also be responsible for expanding the common central database to longitudinal data in order to collect information about treatment response of individual patients to defined treatments. Such longitudinal data will provide the possibility to test tinnitus subtyping criteria for their clinical relevance and to identify response predictors for specific treatments.

This WG will bring together clinicians, experts for clinical research methodology, statisticians, and representatives of the health industry. Patient organisations will be involved for specification of outcome measurements relevant for patients.

Main goals of this WG will include the following tasks:

- Establishing and further developing standards for clinical trials in tinnitus
- Establishing standards for outcome measurement both in clinical trials and in clinical routine
- Developing standards for describing and defining specific therapeutic interventions
- Extending the database to accommodate longitudinal data
- Developing statistical methods for analysing longitudinal data
- Developing statistical methods to identify clinical, neuroimaging or genetic treatment predictors
- Developing strategies to advance the database in a self-learning expert system to assist clinicians in treatment decisions
- Dissemination of the guidelines and standards
- Organization of Short Term Scientific Missions, allowing medical professionals to benefit from clinical training in the setting of established clinics dedicated to the assessment and management of tinnitus and related disorder

- Implementation of guidelines and recommendations on the COST Action website

E. ORGANISATION

E.1 Coordination and Organisation

The achievement of the envisaged objectives is only possible by connecting experts from complementing fields working in tinnitus on international level. Due to the flexibility of COST Actions, coordination of nationally funded projects will be made possible. The COST Action will provide an excellent platform to achieve this on a pan-European level: to bring together experts in the field and to join forces and complement studies to increase power.
Each research centre is fully equipped to perform their own studies and funding of the research of the different partners has been validated nationally.
The structure of this COST Action follows the recommendations contained in the Rules of Procedure document. A Chair and a Vice-Chair will be elected by the Management Committee (MC) at the Kick-off Meeting. Both will preside the MC. Furthermore, the grant holder will be appointed at the Kick-off Meeting. The MC supervises the five Working Groups (WGs). Each WG is managed by a Coordinator (Working Group Leader) and a Co-Coordinator. Together with the Chair and Vice-Chair of the MC, WG Coordinators and Co-Coordinators form the Steering Committee (SC). Certified Quality Engineers responsible for the SOPs for the different WGs should be recruited to insure proper diffusions of SOPs for the different partners.
The MC will appoint the WG leader who will implement the Action and will continuously monitor their progress. The MC will also be responsible for the establishment of contacts with other European and international programmes and associations, as well as governmental bodies. Finally, the MC will prepare reports related to the Action and organize the preparation and submission of a proposal for a large-scale FP8 project. The MC will also discuss access to database and biobank for partners and publications policies.

Steering Committee (SC)

The Steering Committee (SC) is responsible for monitoring the progress of the Action and will link the different WGs. Under the instruction of the MC, the SC will oversee the management and evaluation of the Action.

Working Groups (WGs)

As outlined in section D.2, five Working Groups (WG) will be established for this Action. Each WG will be chaired by a Coordinator (Working Group Leader) and a Co-coordinator who are going

to be elected by the MC during its first meeting. Coordinator and Co-coordinators are responsible for the coordination, organization and supervision of their WG's meetings. Each WG assigns Local Organizers for each meeting. The composition of all Working Groups will be interdisciplinary.

Short-Term Scientific Mission (STSM)

An STSM Officer will be appointed by the MC. The STSM Officer will be responsible for the set-up of Working Group-independent COST tasks related to scientific communication for maintenance of a COST Action specific website and its regular update, and for the organization of the communication between the SC and the WGs.

Dissemination Manager (DM)

The Dissemination Manager will be responsible for the organization of the international scientific conferences and the development of a programme module for a future EU Framework Call.
The respective timeline of the envisaged events is included in section F.

Milestones

The following milestones will be achieved during this Action:

- Creation of the Action website as a platform for information and communication among Action participants, interested clinicians and scientists (non-members who are interested), patients as well as the general public
- Publication of guidelines for the clinical assessment and outcome measurement of tinnitus patients
- Publication of guidelines for neuroimaging of tinnitus patients
- Publication of biobanking efforts for tinnitus research in Europe
- Creation of the database collecting demographic and clinical data and implementation on the website in a password protected area
- Guidelines and SOPs for the biobanking: sample and data collection and storage and sharing of resources
- Annual workshops of each WG
- Short-Term Scientific Missions

- Staff exchange between clinical and scientific groups
- International conferences in the second and fourth year of the Action

E.2 Working Groups

As a useful way to extend the Action beyond the participation, a working group structure has been established to efficiently share workload and thereby speed up the realization of the aims of the Action. The tasks and the scientific programme of the working groups have been described in detail in section D. Each Working Group is constituted by different teams from various different disciplines, but particular teams can be involved in different WGs. A meeting of all WG members will take place at the annual workshop of each WG to be held e.g. at the annual meeting of the Tinnitus Research Initiative.
The intended structure enables the group to integrate new partners and early researchers rapidly. In order to cover specific topics of interest experts will be invited to WG meetings. WGs will also approach further representatives from bio-, health-tech- and pharma-industries for collaborative efforts in the development and evaluation of new diagnostic and therapeutic approaches.
The participants of each WG will communicate by conference-calls and web-based interfaces on a regular basis. All five WGs will be inter-related and will be linked by the SC. WG 1 will be closely connected to WG 2, establishing guidelines and tools (practicable inventories) for clinical characterization of patients and controls (WG 1) and implementing these data in a database (WG 2). In turn, WG 3 and WG 4 will be both closely connected to WG 2 for integrating neuroimaging (WG 3) and genetic data (WG 4) into the database (WG 2). WG 5 will establish standards for outcome measurement based on standards defined in WG 1. Tinnitus subtyping characteristics as identified in WG 2 (clinical), WG 3 (neuroimaging), WG 4 (genetic) will be tested for their clinical relevance as predictors for treatment outcome in WG 5.
WGs 1, 3, 4, 5 will support WG 2 in the design of the database and all WG will contribute to implementation of WG-specific information (results, SOPs, guidelines) on the website in a password protected area.

E.3 Liaison and interaction with other research programmes

Currently there exist no EU funded research projects on tinnitus. Research projects in the fields of

auditory physiology and sensory perception as well as in pain or other chronic diseases will be monitored by the WGs. Moreover participants of this COST Action will be proactive in informing investigators of projects funded by other research programmes. If there will be overlap in research methods or research content, investigators will be invited to meetings of this COST Action. Joint seminars, meetings or symposia are then scheduled as a second step.

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

This COST Action will respect and promote an appropriate gender balance in all its activities and the Management Committee (MC) will place this as a standard item on all its MC agendas. The lead-PIs of partner institutes will ensure the provision of fair working conditions and, where needed, install measures to help reconcile work and private life by promoting, for instance, family-friendly working conditions. All PIs will raise awareness on gender issues throughout the project so as to address the impacts of gender differences on the research and training activities to ensure the highest level of gender fairness and equality. The Action will also be committed to considerably involve early-stage researchers (ESR) and will strictly follow an equal opportunity "recruitment" policy. This item will also be placed as a standard item on all MC agendas.
In particular, so far 10 out of the 29 involved COST Action participants are female (34,48 %). In addition, 10 out of the 29 Cost Action participants (34,48 %) are early stage researchers or PostDocs that have either recently finished their PhD or established their own research group. All of the participants have in fact early stage researchers (PhD and MD students) in their research groups who will of course be involved in the COST Action as well.

F. TIMETABLE

The COST Action is scheduled as a four year programme.
The Action will begin with the Kick-off Meeting and during this meeting the MC as well as the Coordinators of the working groups will be elected.
A website will be established for information and communication in which all essential information concerning this Action will be implemented and which will be updated on a regular basis (twice a year).
The Action will be closed with a final conference combined with all WG meetings

	Year 1				Year 2				Year 3				Year 4			
Coordination	X				X				X				X			
Kick-off Meeting	X															
Website set up		X														
Website update				X		X		X		X		X		X		X
MC Meeting	X				X				X				X			
SC Meeting		X		X		X		X		X		X		X		X
WG1 Meeting			X				X				X				X	
WG2 Meeting			X				X				X				X	
WG3 Meeting			X				X				X				X	
WG4 Meeting			X				X				X				X	
WG5 Meeting			X				X				X				X	
Scientific Conference			X				X				X				X	
Final Conference																X

G. ECONOMIC DIMENSION

The following COST countries have actively participated in the preparation of the Action or otherwise indicated their interest: BE, CH, CZ, DE, ES, FR, HU, IT, NL, PL, SE, UK. On the basis of national estimates, the economic dimension of the activities to be carried out under the Action has been estimated at 48 Million € for the total duration of the Action. This estimate is valid under the assumption that all the countries mentioned above but no other countries will participate in the Action. Any departure from this will change the total cost accordingly.

H. DISSEMINATION PLAN

H.1 Who?

Dissemination is responsible for the communication on the COST Action particularly its findings and its recommendations, both to the internal audience, the scientific community, the patients and their relatives and the potential medical users of the outcomes. In more detail the target audience includes other researchers working in the tinnitus field or in related fields, other research frameworks focussing on the auditory system, tinnitus or adjacent disorders, research institutes, Standard Bodies, patients and patient organisations, health care providers and the pharma-, bio- and health-tech-industries.
Moreover relevant results will be communicated to policy makers on the regional, national and European level and to the general public.

H.2 What?

The dissemination plan will be built upon the following pillars:
A public web portal will make the results of the Action easily available to a wide audience. The portal will be created at the beginning and will be regularly updated to reflect the actual state of collaboration. It will serve as a community building platform and will provide public access to publications and other results of the work. This web portal will also ensure visibility of the COST Action and its content for potentially interested participants and thus contribute to capacity building.
A password protected web portal will be used for internal documentation. Organisational information, working plans, meeting protocols, a specific calendar for this COST Action and all other working documents can be accessed at this protected web portal by participants. There will be specific sections for the MC and the WG with access only for respective members.
A **Newsletter** will provide regular information about COST activities. This Newsletter will be sent to all participants, but also to potentially interested scientists or clinicians, to patient organisations, to related scientific, audiological and medical organisations and to potential industrial partners.
Web-based communication tools for internal communication will further include an internet discussion forum, videoconferences (e.g. skype) and E-mail
Broad Communication: External visibility to the Action will be created towards various media. In particular, at the launch, partners in each country will contact their national press agencies, and create direct visibility for the Action and the European interest in this topic. The communication activities will be supported by all consortium partners (and their internal PR offices). Yearly updates will be sent as well. Moreover many participants are regularly interviewed by print media (journals, magazines), radio or television broadcasting cooperation. They will use these

opportunities to inform the public about latest progress and latest results.

Publications in Scientific Journals: The members of this Action have an excellent track record in publishing in high-profile international journals, and intend to continue so. Publications will include original research reports, reviews, state of the art reports, interim reports, technical notes, case reports, perspectives, proceedings and guidelines.

Major Scientific journals in this area include Nature, Nature Medicine, Nature Neuroscience, Science, Journal of Neuroscience, Proceeding of the National Academy of Science, Human Brain Mapping, Neuroimage, BMC Biology, BMC Neuroscience, PLoS Biology, PLoS Medicine, PLoS One and others.

There will be a major focus on publishing in open access journals to ensure free access to research results.

Books: State of the art reports, reviews and guidelines will also be published in books. Many participants of this Action contributed to the first edition of the Textbook of Tinnitus (*37*). Important results of this COST Action will be directly integrated in further editions of this textbook (2nd edition planned for 2014/2015).

National and International Conferences and Symposia: The results of the work will be disseminated by presentations in international conferences. In addition to Tinnitus conferences (Tinnitus Research Initiative Meeting, International Tinnitus Seminars), ENT and audiology conferences, pain, neurology and psychiatry conferences and neuroscientific meetings will be attended. A specific focus will be the organisation of thematic research symposia.

Events and/or Workshops: Regular workshops will be organised by the WG and four meetings will be organised by the MC. Preliminary and final results as well as methodological developments and standards will be communicated at these meetings. Moreover there will be educational activities and seminars with specific focus for young researchers and for scientists from adjacent disciplines who are interested in entering the field.

Education and Training: Moreover the outcome of this COST Action will be disseminated and taught via various training activities including academic tutorials (organized in association with major conferences), summer schools or clinical courses.

H.3 How?

All partners of this intended COST Action are committed to a proper communication of the results. It is the principle of all dissemination activities to use research and collaboration results and to create value within the targeted communities of the European Union to ensure government funding.

The choice of the dissemination method will be motivated by the purpose and the target audience. Internal communication will rely particularly on regular meetings and web-based communication (E-mail, web-based video conferences, password protected web portal). Dissemination of findings and recommendations to the scientific audience will use scientific publications, conference presentations, symposia, courses or books. Industrial partners and patient organisations will be directly contacted, informed via the website and the Newsletter and invited to workshops Public Health Bodies as well as local-, national and European policy makers will be directly contacted. The general public will be informed via press releases and contributions to mass media (newspaper, radio, television) and can find more detailed information on the website.
The dissemination plan will be updated during the course of the COST Action according to experiences, preliminary evaluations, newly identified needs and opportunities.