Brussels, 24 March 2020

COST 030/20

DECISION

Subject: **Memorandum of Understanding for the implementation of the COST Action "Cognitive decline in Nephro-Neurology: European Cooperative Target" (CONNECT) CA19127**

The COST Member Countries and/or the COST Cooperating State will find attached the Memorandum of Understanding for the COST Action Cognitive decline in Nephro-Neurology: European Cooperative Target approved by the Committee of Senior Officials through written procedure on 24 March 2020.

MEMORANDUM OF UNDERSTANDING

For the implementation of a COST Action designated as

COST Action CA19127
COGNITIVE DECLINE IN NEPHRO-NEUROLOGY: EUROPEAN COOPERATIVE TARGET (CONNECT)

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

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

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

The main aim and objective of the Action is to create an interdisciplinary network to study cognitive impairment in kidney disease, thereby accelerating research and improve patient care, bridging the existing gaps between nephrology and neurology/neuroscience, epidemiology, and bioinformatics. This will be achieved through the specific objectives detailed in the Technical Annex.

The economic dimension of the activities carried out under the Action has been estimated, on the basis of information available during the planning of the Action, at EUR 84 million in 2019.

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

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

OVERVIEW

Summary

Fragmentation between neurological and nephrological expertise has frustrated research into the mechanism of cognitive decline secondary to kidney disease. By for the first time bringing these fields together in CONNECT we establish a novel multidisciplinary field to improve patient diagnosis and care.

The developed world is experiencing a growing number of patients with chronic kidney disease (CKD), a complex systemic and potentially fatal disease. With improved long-term life expectancy as the result of kidney replacement therapies, more attention has been given to comorbidities, including cognitive impairment. In CKD patients, both the central and peripheral nervous system are frequently affected. Eventually, this decreases quality of life and eventually dementia with loss of independence in everyday activities.

CONNECT aims to coordinate research on cognitive impairment in CKD. This requires exchanging clinical information between nephrologists and neurologists, and between neuroscientists and kidney physiologists, guided by big data analysts. This collaborative network will define new experimental paradigms, their translational value and, in turn, focus on new interventions in the field of cognitive impairment.

At the core of this COST Action lie activities that bridge the gaps between these fields and prepare early-stage researchers and clinicians to start new research lines. The interdisciplinary consortium from 22 countries will focus on 1) Pre-clinical research, 2) Clinical trials, 3) clinical practice, 4) Data management and analytics, and 5) Inclusiveness and dissemination of the Action. This COST Action will alleviate disparities in CKD patient care and enable breakthrough research enabling patient diagnosis and early treatments.

Areas of Expertise Relevant for the Action	Keywords
● Clinical medicine: Nephrology ● Clinical medicine: Clinical neurology ● Basic medicine: Metabolism, biological basis of metabolism related disorders ● Basic medicine: Neuropsychology ● Health Sciences: Epidemiology	● Renal disease ● Cognitive impairment ● Big Data analysis

Specific Objectives

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

Research Coordination

● Gain understanding of the current state-of-the-art CKD and cognitive animal models available, imaging tools available for animal models
● Coordination of pre-clinical research efforts on MCI-CKD (merge currently separated research lines). Publication of state-of-the-art review on putative mechanisms of MCI in CKD and open questions as evident from preclinical models
● Define the needs for clinical research and clinical trials to be conducted
● Development and publication of MCI-CKD clinical trial guidelines and/or best practices
● Coordinate clinical cohort and trial data collection
● Define methodological challenges in clinical trials
● Develop a common clinical understanding of MCI-CKD
● Develop and publish guidelines for testing for – and/or treatment of – MCI-CKD
● Map the software and analytical needs of preclinical and clinical researchers
● Disseminate CONNECT outcomes and guidelines to relevant stakeholders from health care professionals, researchers, pharmaceutical industry, politics and the public to ensure uptake by the broader scientific and clinical community and general public

Capacity Building

● Bridge the preclinical MCI and CKD fields to form an interdisciplinary field
● Exchange knowledge of existing and new clinical cohorts and clinical trial conduction in MCI-CKD
● Involve clinical researchers currently not conducting clinical trials within MCI-CKD
● Foster knowledge exchange: a) Educate nephrologists on tests used for cognitive impairment and its treatment, and b) Educate neurologists on the diagnosis and role of CKD in MCI and its treatment
● Develop a joint research agenda to investigate MCI-CKD
● Train researchers in the use of bioinformatic tools for big data
● Create an international platform for MCI-CKD research to ensure active participation of clinicians and scientists to ensure growth of the field during, and after completion of, the COST Action

TECHNICAL ANNEX

1 S&T EXCELLENCE

1.1 SOUNDNESS OF THE CHALLENGE

1.1.1 DESCRIPTION OF THE STATE-OF-THE-ART

Proposition: CONNECT aims to advance research on mild cognitive impairment in kidney patients, its likely causes and what this may tell us in relation to more widespread forms of dementia, including Alzheimer disease. To date, fragmentation between neurological and nephrological expertise has frustrated research into the causative effect of kidney disease on cognitive function. By bringing these fields together the CONNECT Action establishes a novel multidisciplinary field to enable research and improve patient care.

Neurodegenerative diseases and brain disorders resulting in cognitive impairment affect an increasing proportion of the aging population in Europe and worldwide, with a high disease burden for affected individuals, their family, and high costs for the health care system. It is unlikely that interventions may be useful in advanced stages, when patients have developed dementia; therefore cognitive impairment should be identified and managed at earlier stages. However, these diseases represent a major clinical and preclinical challenge in research and the underlying causes remain to be identified. Bench-to bedside translation is inadequate and no definitive cure for such disorders is yet available. Thus, it is surprising that very little attention has been devoted to a prevalent and potentially preventable form of cognitive impairment: cognitive impairment in patients with chronic kidney disease (CKD). Addressing cognitive impairment in patients with CKD becomes more urgent when considering that 10-15% of the general population in industrialised countries have CKD[1] and 30-60% of those with advanced CKD have cognitive impairments[2,3] (Figure 1). The developed world is experiencing a growing number of patients with CKD in an aging population. The current European number of patients receiving kidney replacement therapy is 924 patients/million population (ppm)/year, with 10-fold differences among countries[4]. While the number of age-adjusted end-stage kidney disease (ESKD) patients has begun to stabilize or fall in many countries, the absolute prevalence is increasing because of an aging population. CKD is a complex and potentially fatal disease, because it: 1) has systemic effects on all organs; 2) the balance of plasma volume, electrolytes, acid–base and minerals, metabolites, hormones, uremic toxins, and proteins is disturbed; and 3) treatments require multidisciplinary teams to treat comorbidities, plan drug regimens, and arrange special diets. The current treatments that have significantly extended life expectancy in CKD and ESKD patients are dialysis and kidney transplantation. However, with increased patient life expectancy, the QoL of patients has decreased for several reasons. These include the extended and invasive treatments, and comorbidities that arise from the systemic nature of CKD. In the 30-60% of advanced CKD diagnosed with cognitive impairment[2,3], both the central and peripheral nervous systems are frequently affected in various ways. These include peripheral neuropathies, cognitive decline, asterixis, and epileptic seizures.

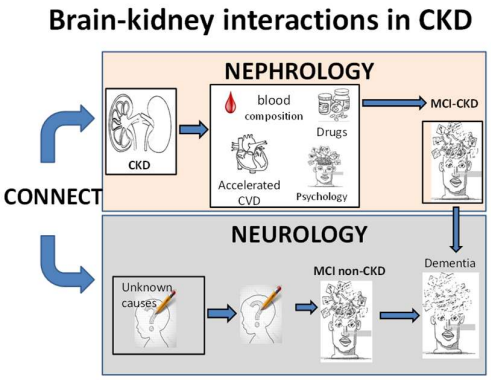


Figure 1. MCI is a frequent secondary event in patients with chronic kidney disease (CKD) .

Among cognitive dysfunctions, the most frequent is Mild Cognitive Impairment (MCI), a condition in which individuals demonstrate focal or multifocal cognitive impairment with minimal impairment of instrumental activities of daily living and does not cross the threshold for dementia diagnosis[5]. In CKD patients MCI is already prevalent in early stages of the disease and doubles in frequency compared to the age-matched general population[6]. Although MCI can be the first cognitive manifestation of Alzheimer disease (AD), it might return to neurologically intact functions if secondary to other reversible disease processes such as CKD.

To date, interdisciplinary research collaborations have been minimal in the field to study MCI secondary to CKD, limiting our current understanding and potential therapies. The CONNECT Action defines MCI-CKD as a novel term and research field. Thus, 1) the underlying mechanisms linking CKD to MCI have not been identified yet, and 2) it is not yet known how MCI-CKD patients relate to patients with MCI in the general population. It remains to be elucidated to what extent MCI-CKD is an independent clinical entity and how diagnosis and treatments can be tailored to the needs of CKD patients. At the same time, new technological innovations have significantly improved the current state of the art in kidney, brain and cognitive research in both health and disease. By setting up the CONNECT Action, advantage can be taken of the progress in individual research fields to accelerate interdisciplinary research on MCI-CKD.

Current state-of-the-art in preclinical research: For research on CKD and cognitive impairment, possibilities to advance the field are boosted by newly available preclinical models and technologies. Technical advancements have made the brain less of a black box and have given more insights into brain function in health and disease. These include many new technologies, including 1) Human functional brain imaging (e.g. fMRI, brain tractography, brain resting state); 2) Animal models for functional (brain) imaging: 2-photon microscopy, optogenetics, functional neuroanatomy, and neurochemistry; 3) Animal models for kidney physiology and pathophysiology, including mouse models and 2-photon microscopy; 4) Human & animal cognitive tests; and 5) Omics tools such as metabolomics, proteomics, and single cell transcriptomics. The above tools have greatly improved our understanding of kidney failure and cognitive function but have to date not been used to study the causative links between CKD and cognitive impairment.

Current state-of-the-art in clinical research and trials: Recent clinical trials investigating MCI-CKD have identified that cognitive impairment is an early consequence of CKD. These studies: 1) investigated the risk factors for MCI-CKD and 2) used EEG and MRI to compare MCI-CKD with cognitive impairment in the general population. Current clinical studies identified: 1) the above-mentioned risk factors for development of MCI-CKD, 2) that neural synchronization is different between MCI-CKD patients from MCI patients in the general population, as assessed by EEG, and 3) that MCI-CKD is mostly characterized by deep white matter loss and reduced grey matter volume[7]. Moreover, recent studies using Diffuse Tensor Imaging, fMRI or PET imaging have been used to study brain architecture in more detail and to characterize brain activity in MCI-CKD and MCI in the general population. Comparison of these studies suggests different mechanisms that could differentiate these types of cognitive impairment as separate clinical entities. However, data describing direct comparisons between MCI-CKD and MCI in the general population are scarce and this topic needs to be addressed more systematically. Therefore, findings from comparison of these studies remain speculative to date. In addition, combined forms of other neurodegenerative disorders (e.g. AD) and CKD have not been characterized in depth, both in terms of the resulting cognitive impairment and treatment. A small number of clinical trials has analysed the effect of CKD in patients classified as AD, a neurodegenerative disorder not caused by CKD. Strikingly, CKD accelerates AD[8] progression and changes its EEG pattern[9]. Notably, cognitive impairment in CKD is somehow quantitatively similar to cognitive impairment in other autoimmune inflammatory disorders, such as ANCA-vasculitis and rheumatoid arthritis[10]. However, the same clinical trials also indicate that MCI-CKD is qualitatively different (in terms of cognitive domains involved) from cognitive impairment due to vascular disease. Finally, the transition from MCI to dementia in CKD patients is currently poorly addressed and understood. It remains to be determined whether novel dialysis modalities such as hemodiafiltration may be effective for MCI-CKD. Recently it has been suggested that hemofiltration might be used for AD[8], though its efficacy is poorly explored. It is also yet unclear whether the current treatments for Alzheimer dementia including memantine and donepezil are also effective for MCI-CKD. Some reports suggest that their dosage should be adjusted to kidney function, at least for donepezil[11]. Another study describes some benefit from the use of donepezil in a case of AD with CKD[12]. Finally, the role of drugs counteracting vascular damage and systemic inflammation[13] (e.g., renin-angiotensin blockers and statins) has never been addressed in MCI-CKD. Treatments like candesartan have been successfully used in pre-clinical MCI-CKD animal models[14].

Current state-of-the-art in diagnosis and treatment:

- **Chronic kidney disease** can be diagnosed by various health care professionals and treatments depending on disease stage. Most commonly, CKD is first suspected by general physicians or internists based on blood- and urine tests (increased plasma creatinine and the presence of proteinuria). Hypertension and edema may also prompt a possible diagnosis. More rarely, radiologists incidentally discover kidney abnormalities in imaging studies requested for another reason. After diagnosis, nephrologists will usually proceed with additional tests, including blood-,

urine- and imaging tests, and a needle biopsy of the kidney may be required for diagnosis. In some cases, genetic tests may also help in securing a diagnosis. The leading therapeutic approaches to slow CKD progression are renin-angiotensin inhibitors and blood pressure control. In case of diabetic kidney disease, the nephrologist will also prescribe treatments to control the glycemic index and may prescribe SGLT2 inhibitors, given their recently demonstrated cardio-kidney protection (though not standard treatment yet). Some glomerulopathies may also respond to immunosuppressive treatments and rare causes of CKD have can their own therapeutic approaches, such as Vaptans for Autosomal Dominant Polycystic Kidney Disease. Complications of CKD can be controlled - at least in part - by medications for hypercholesterolemia, anemia, blood pressure and edema. When kidney function is insufficient to maintain homeostasis, even after medical support, the only remaining treatment options are peritoneal dialysis, hemodialysis, and kidney transplantation. The most up to date guidelines are kept by European Renal Best Practice (ERBP) and the Kidney Disease Improving Global Outcomes (KDIGO).

- **Acquired cognitive impairment** does not have a singular cause. According to current scientific knowledge, several neurodegenerative processes may lead to cognitive impairment, such as Parkinson disease or AD, small strokes, reduced blood flow, or build-up of toxins. Identifying pending cognitive impairment at an early stage has become an increasingly important challenge to physicians. Central to this diagnostic scheme is MCI, not only because it is generally regarded as the borderland between the cognitive changes of aging and very early dementia but especially because it can be a **reversible** disorder once the cause has been identified. MCI is approximately twice as frequent in patients with CKD than in the age-matched population[6]. Established risk factors for MCI include traditional cardiovascular risk factors, which are more common in CKD and in dialysis patients, but also poor nutrition, anemia, acidosis, disturbed sleep, depression, uremia toxins, polypharmacy, and type and adequacy of kidney placement therapies. Moreover, cognitive impairment correlates with markers of kidney function, including estimated glomerular filtration rate (eGFR), and albuminuria, which is also a marker of endothelial damage and microvascular disease[15]. The latter is also suggested by recent evidence of a similar incidence of MCI in CKD and vasculitis[10]. Cognitive impairment in patients with CKD might present with various conditions characterized by deficits in several key cognitive domains, including memory, processing and emotion-depression. To better understand whether this cognitive decline is reversible or progressing to full-blown dementia, CKD patients should be carefully analysed from a neurological point of view. Function of cognitive domains can be variably assessed by neurologists and neuropsychiatrists using a variety of screening tests such as the Montreal Cognitive Assessment (MoCA), or the Mini-Mental State Examination. No drug treatment is currently recommended or proven for MCI. Supportive treatments for reversible MCI associated with CKD may include increased physical activity, reduction of homocysteine levels, and correction of anemia.
- **So far, diagnosis and treatments for MCI-CKD have not been routinely implemented**. Because early stages of kidney disease may not lead to symptoms, and patients often present with only 30% of kidney function, irreversible kidney and cognitive damage may have occurred. The most up-to-date guidelines are represented by the KDIGO CKD guidelines, although these do not address the relation between CKD and MCI. However, most recent reviews and studies on the topic advocate that CKD patients should be screened and monitored routinely for MCI as part of their standard of care[16].

Current state-of-the-art in big data analytics. One of the most challenging issues of modern scientific approaches is analysis of big datasets (bioinformatics). Current approaches allow gathering of large amounts of experimental data. Scientists in the field of neurology apply fMRI, MRI and connect-omics and obtain massive amounts of data about brain anatomy and function. In the field of nephrology, techniques including proteomics, metabolomics, genomics, and transcriptomics, allow the collection of impressive amounts of information regarding blood and urine constituents in CKD patients. The main issue with these approaches is that data gathering is relatively easy, whereas data analysis and interpretation are still very challenging. This is especially true when using the classical data analysis paradigm known as "one-protein - one disease". Therefore, most scientists apply these high-throughput assays for hypothesis generation and subsequently switch to classical data analysis, focusing on only one or a few variables, thereby losing most of the power these techniques offer.

1.1.2 DESCRIPTION OF THE CHALLENGE (MAIN AIM)

CONNECT aims to create a European COST Action platform for MCI-CKD to accelerate research and improve patient care. CONNECT will bridge the currently existing knowledge gaps between nephrology and neurology and will do so for both clinical practice and research. Thereby, the Action will: 1)

accelerate research in the newly established field of MCI-CKD, 2) improve diagnosis of MCI-CKD patients, and 3) improve the quality of treatments and QoL for patients.

The challenges include:

A. **Findings from preclinical research are not shared between kidney science and neuroscience**. Advanced preclinical animal models and state of the art tools have been developed and optimized, but research stays within the boundaries of the respective fields of nephrology or neuroscience. As a result, methods such as the 5/6th nephrectomy model and tools such as 2-photon microscopy, optogenetics, functional neuroanatomy, and neurochemistry are underutilised to study the pathology and causative links between CKD and cognitive function.

B. **Clinical research into MCI-CKD is still in its infancy.** Because of the early stage of the field, few and inconsistent clinical cohorts and trials in the patient subgroups provides limited disease insights. The patient groups span CKD patients that are 1) not on dialysis, 2) on dialysis, and 3) have received kidney transplantation. Of particular interest is the increased attention given to patients that only receive conservative/supportive treatment of ESKD. Comparative studies on risk factors and brain anatomy and function in patients with MCI-CKD and MCI in the general population suggest that these are divergent clinical entities. However, interpretation of these results is complicated by several problems, as toxic effects of uremic substances cannot be excluded and only few studies directly compared diverse patient groups. There is thus a strong need for clinical trials that study MCI-CKD patient subgroups and MCI patients in the general population within a single study.

C. **Treatment of MCI-CKD is fragmented between different clinical expertise.** In Europe alone, an average of 924 ppm undergoes kidney replacement therapy for CKD, but cognitive function in these patients is insufficiently addressed. This may be due to low awareness of **nephrologists for the signals of cognitive impairment** in their patients, especially because the early signs of MCIare difficult to recognize. Conversely, **neurologists are not sufficiently experienced with systemic effects of CKD and uremic toxins**, and often underestimate the contribution of CKD to cognitive impairment. Thus, patients experiencing cognitive impairment caused by CKD may not receive an adequate diagnosis and the necessary health care support. Together, this currently leads to underdiagnosis and undertreatment for MCI-CKD patients, resulting in reduced QoL.

D. **Bioinformatics is demanding and data from different sources is not integrated.** Management and analysis of big data is a challenge in clinical cohorts and trials, but also in clinical and preclinical research for both omics and imaging data. Because data are generally collected, structured, and analysed for the purpose of the primary study, comparative- or meta-analysis is very impractical, if not impossible. Researchers need training on how to deal with these enormous amounts of data. Attention to structured data management will enhance the reusability of data and enable, amongst others, the connections of clinical research cohorts to increase study relevance. In addition, more efficient analysis, for instance of omics and imaging data, will aid in identification of MCI-CKD risk factors, biomarkers, and understanding of brain function.

Relevance and timeliness

There is a pressing unmet medical need in the diagnosis and treatment options for CKD patients who suffer from cognitive impairment. Patients are diagnosed and treated too late, or not at all, because combined diagnosis for MCI-CKD as a single clinical entity is not regularly performed. Moreover, clinical treatments are lacking because risk factors and treatments are not yet defined. To resolve this unmet need, the stakeholders in MCI-CKD should be brought together now in a COST Action network to cover the current challenges that this new field faces. It is the right time to successfully face this challenge because: 1) the impressive amount of scientific evidence from neuroscience, neurology, and genetics on brain disease can now be interpreted with the help of CKD models and known MCI-CKD uremic toxins; 2) new drugs for dementia and novel dialysis regimens are available and their effects on MCI and on MCI-CKD await to be understood, and 3) new research tools (including 2-photon microscopy, omics, fMRI, tractography) have become available, that can be used to identify the mechanisms of MCI and of MCI-CKD. In addition, the original COST Action network proposed here can build on extensive current networks in kidney and brain research (see also Section 2.1.1) to create awareness and mobilize a larger range of stakeholders.

1.2 PROGRESS BEYOND THE STATE-OF-THE-ART

1.2.1 APPROACH TO THE CHALLENGE AND PROGRESS BEYOND THE STATE-OF-THE-ART

The novelty of CONNECT is to gather preclinical and clinical researchers with expertise in neurology and nephrology within one network. Because these fields have made tremendous progress in the

previous 15 years in their individual domains of research, exchange of knowledge, strategies, and building a joint research agenda for MCI-CKD will advance this new interdisciplinary field. The CONNECT Action will advance the current state of the art by:

Establishing and fostering preclinical research across different fields: Over the past years, preclinical research in nephrology focused mostly on systemic effects of CKD, including bones and anemia, with little attention to cognitive functions. Most recent results derive from a single laboratory, which showed specific functional alterations of the brain in animal models of CKD[17], though it received little attention from both the neuroscience and the nephrological communities. In neuroscience, the lack of familiarity of neuroscientists with the animal models of CKD has greatly limited their analysis on these models. Very few advances have been made in preclinical MCI-CKD research, even though significant progress has been made in the understanding of kidney and brain function in health and disease separately. This COST Action will perform the mapping and sharing of preclinical models and new technologies amongst researchers. Thereby, new research lines can be set up and the network will establish a new interdisciplinary research field from currently separated expertise.

Enabling clinical research and clinical trials: Very few clinical trials have been conducted at the interface of CKD and cognitive impairment. Current clinical trials have mainly focussed on 1) risk factors for CKD, 2) brain function in the general population, 3) or brain function in MCI-CKD patients. As a result, there is currently very limited knowledge on what the exact risk factors and causes are for MCI-CKD, and if and how they differ from MCI in the general population. This COST Action will: 1) analyse the problems in this type of clinical research/clinical trials to identify cofounders that play a role, 2) define methodological strategies for MCI-CKD cohorts and clinical trials, and 3) harmonize protocols, guidelines, and best practices between countries. Guidelines will be compiled according to ERBP-guidelines, i.e. a rigorous Cochrane-like methodology with systematic reviews. Any guideline to be developed will also align with AGREE II (the standard to assess the methodological quality of a practice guideline). Together, this will stimulate preclinical and clinical research in this field and reduce inequality between countries. Moreover, transferability of studies and study protocols will increase the comparative strength between studies and this strong evidence will enable updating of guidelines.

Improving beyond state-of-the-art diagnosis and treatment: Very few advances have been made in the past decades in the diagnosis and treatments for patients with MCI-CKD. This is mainly attributable to the focused clinical practice that is split between different health care professionals with their own expertise. By sharing clinical practice and insights through the CONNECT Action, clinical doctors will gain access to the tools to make diagnoses beyond their primary expertise. Thereby, patients with early CKD will be assessed for cognitive function, and patients with MCI will be assessed for kidney function in an early phase. Moreover, the CONNECT Action will develop and publish guidelines according to ERBP-guidelines. Developed guidelines will align with AGREE II. When insights into the causal links and treatments for MCI-CKD become available by clinical and preclinical research, health care professionals will also be better equipped to treat MCI-CKD patients to halt cognitive decline or improve cognitive functions.

Facilitate bioinformatics: Analysis of kidney-brain relation requires awareness of bioinformatical challenges and techniques. The CONNECT COST Action will address how to analyse data gathered in ongoing and new research lines. There are three main bioinformatics approaches, which should be shared by the clinicians and scientists of the consortium to understand the results:

1. Network medicine approach analyses all the data gathered by looking at their relationship and thereby identifying “hubs” that are elements (brain regions, proteins, metabolites, etc.) with a central role in the functioning of the system[18].
2. Data enrichment methods analyses the elements (brain regions, genes, proteins, etc.) associated with the disease phenotype looking at their common “function”, by interrogating available databases with gene-, protein- or brain region- function data[19].
3. Machine learning (also referred to as deep learning) uses a specific mathematical technique called “neuronal networks” to recognize patterns in complex datasets[20].

The consortium should be made aware of these bioinformatic approaches, their strengths and limitations, and the interpretation of the results to avoid falling into the classical “one protein-one disease” analytical approach. To accomplish this aim, clinicians and scientists will share their high-throughput data (“big data”) and discuss these with reference analytical centres (available among the participants). Specific training schools for junior researchers and early career investigators (ECIs) and round tables will be organized to address this aim.

1.2.2 OBJECTIVES

This COST Action will set up an interdisciplinary network combining preclinical brain and kidney research, clinical knowledge in nephrology and neurology, epidemiology, and bioinformatics. The Action is organised around 5 highly collaborative Working Groups which relate to the main challenges identified: 1) Pre-clinical research, 2) Clinical research and clinical trials, 3) Clinical practice, 4) Bioinformatics, and 5) Inclusiveness and dissemination (Figure 2). To achieve CONNECT's aims, the Action formulates a series of research-coordinating and capacity-building objectives.

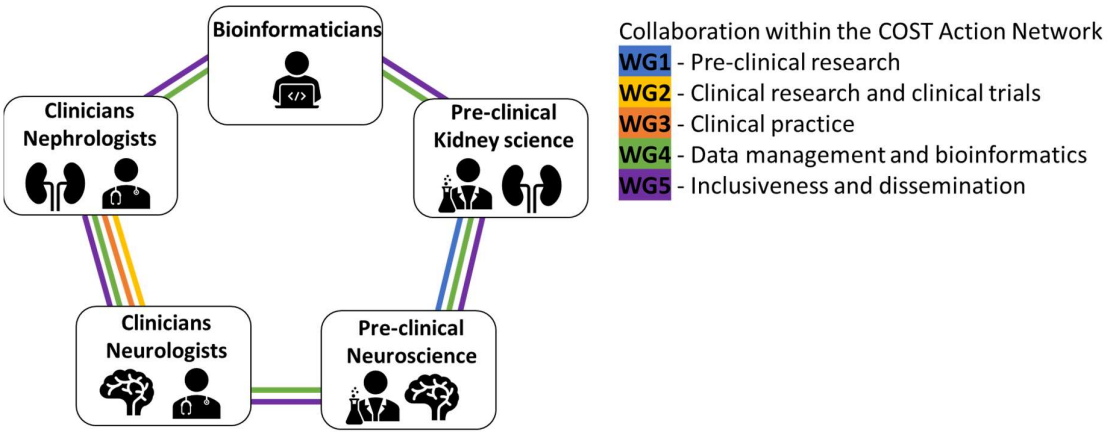


Figure 2. The highly collaborative nature of the CONNECT Action disciplines within the CONNECT Working Groups.

1.2.2.1 Research Coordination Objectives

The main aim is to build the CONNECT Action network among already existing research groups to leverage currently funded research. The Action has identified research coordinating objectives for each working group. The research coordination objectives are:

- Gain understanding of the current state-of-the-art CKD and cognitive animal models available, imaging tools available for animal models (WG1).
- Coordination of pre-clinical research efforts on MCI-CKD (merge currently separated research lines, WG1). Publication of state-of-the-art review on putative mechanisms of MCI in CKD and open questions as evident from preclinical models.
- Define the needs for clinical research and clinical trials to be conducted (WG2).
- Development and publication of MCI-CKD clinical trial guidelines and/or best practices (WG2)
- Coordinate clinical cohort and trial data collection (WG2).
- Define methodological challenges in clinical trials (WG2).
- Develop a common clinical understanding of MCI-CKD (WG3).
- Develop and publish guidelines for testing for – and/or treatment of – MCI-CKD (WG3).
- Map the software and analytical needs of preclinical and clinical researchers (WG4).
- Disseminate CONNECT outcomes and guidelines to relevant stakeholders from health care professionals, researchers, pharmaceutical industry, politics and the public to ensure uptake by the broader scientific and clinical community and general public (WG5)

1.2.2.2 Capacity-building Objectives

CONNECT will increase the capacity for MCI-CKD research through capacity-building objectives, which is largely supported by the research coordination objectives. This Action will bring together the different stakeholders to have an adequate capacity to undertake research for the link between MCI and CKD. By connecting them, the Action will build a new platform for this research by bridging the fields of kidney disease and cognitive research. The capacity-building objectives are:

- Bridge the preclinical MCI and CKD fields to form an interdisciplinary field (WG1).

- Exchange knowledge of existing and new clinical cohorts and clinical trial conduction in MCI-CKD. (WG2).
- Involve clinical researchers currently not conducting clinical trials within MCI-CKD (WG2).
- Foster knowledge exchange: a) Educate nephrologists on tests used for cognitive impairment and its treatment, and b) Educate neurologists on the diagnosis and role of CKD in MCI and its treatment (WG3).
- Develop a joint research agenda to investigate MCI-CKD (WG3).
- Train researchers in the use of bioinformatic tools for big data (WG4).
- Create an international platform for MCI-CKD research to ensure active participation of clinicians and scientists to ensure growth of the field during, and after completion of, the COST Action (WG5).

2 NETWORKING EXCELLENCE

2.1 ADDED VALUE OF NETWORKING IN S&T EXCELLENCE

2.1.1 ADDED VALUE IN RELATION TO EXISTING EFFORTS AT EUROPEAN AND/OR INTERNATIONAL LEVEL

Interdisciplinary research has been minimal in the field of MCI-CKD, which is the result of the absence of efforts that connect the brain and kidney research fields and their respective research lines. In contrast, the individual fields have made major progress in the past 15 years. Major networking efforts to share knowledge and to collaborate have been undertaken in both the individual fields of neurology and nephrology. These efforts have paid off and greatly advanced these fields by understanding brain function and transforming kidney disease into a more treatable chronic disease. Therefore, the time is now to start such efforts for a network that will advance research for MCI secondary to CKD. By interdisciplinary research, information, data, techniques, tools, perspectives and theories from both fields can be merged to solve urgent clinical and preclinical research objectives.

Existing efforts in nephrology
Existing efforts of networking in the field of nephrology are well established. These are best exemplified by the ERA-EDTA (European Renal Association – European Dialysis and Transplant Association – 11,000 members), ISN (International society of Nephrology – 10,000 members), the American Society of Nephrology (ASN, 16,000 members), and the Asian Pacific Society of Nephrology (APSN). These associations organise annual conferences, provide education, and maintain guidelines for clinical practice. However, whilst some awareness has been raised on MCI as a result of CKD, nephrologists have not been mobilised yet to start collaborative research with neurologists and neuroscientists to investigate the causes and effects of MCI-CKD. Therefore, nephrologists should be encouraged to initiate such collaborations in the brain-kidney field.

Existing efforts in neurology
Existing efforts of networking in neurology and neuroscience are well established. These are best exemplified by the Society for Neuroscience (SfN, 37,000 members), the Federation of the European Neuroscience Societies (FENS), American Academy of Neurology (AAN, 36,000 members), European Academy of Neurology (EAN, 45,000 members) and the International Society of Cerebral Blood Flow and Metabolism (ISCBFM). These organizations are responsible for management and updating of treatment guidelines, educational resources, sharing of clinical and pre-clinical research results, and exchange of current best practices. This has pushed the boundaries of clinical neurology, but the neurological societies have not yet recognized the effects of CKD on cognitive function – and cognitive impairment. Therefore, neurologists and neuroscientist should be encouraged to undertake collaborations in the field of brain-kidney research.

Added value of networking
There are currently no existing efforts with the primary goal of improving MCI-CKD patient care or investigating causative relations of MCI-CKD in a patient or preclinical setting. Even with strong networking within the fields of nephology and neurology there is currently no cross-communication between these specialties. The challenges in MCI-CKD research cannot be undertaken by the separate fields of nephology and neurology because knowledge and efforts from both fields needs to be brought together. This COST Action will be an accelerator in brain-kidney research by - for the first time - combining this expertise within one network. The CONNECT Action will organize networking activities,

conference satellite events, including courses, workshops, Short Term Scientific Missions (STSMs), and a dedicated CONNECT conference, to facilitate exactly this exchange of knowledge. This will ensure timely achievement of CONNECT's deliverables. CONNECT will extend the reach of the proposed COST Action network by partnering with existing networks and conferences of the ERA-EDTA. The Action will do this by organizing satellite events to leverage the current reach of these organizations (11,000+ nephrologists and 45,000+ neurologists). This will ensure the CONNECT Action will move the field of MCI-CKI beyond state of the art in: 1) preclinical research, 2) clinical trials, and 3) diagnosis and treatment. Finally, the CONNECT Action will involve European/national patient organizations, to give high attention for patient perspective.

2.2 ADDED VALUE OF NETWORKING IN IMPACT

2.2.1 SECURING THE CRITICAL MASS AND EXPERTISE

The success of CONNECT relies on the partners involved in the network. The network has both the critical mass and the expertise available to reach the defined objectives. This COST Action network has a critical mass of 55 proposers from as many different centres and/or departments in 22 countries. Their expertise covers partners who are experts in the interdisciplinary field of MCI-CKD or are experts within their respective neurological and nephrological fields. Partner expertise covers all Working Groups, namely:

1. Pre-clinical research
2. Clinical research and clinical trials;
3. Clinical practice ;
4. Data management and bioinformatics;
5. Inclusiveness and dissemination (This is the responsibility of all 55 proposers. Special attention will be given by the WG leaders in collaboration with the dedicated dissemination manager that will be appointed at the start of the Action).

The distribution of the participants will ensure that the newly developed research lines and interdisciplinarity of the field will be taken up extensively. The network consists of 52,4 percent Inclusiveness Target Countries (ITCs), 11 percent early career investigators (ECI) and 32,7 percent women. Junior researchers and ECIs from currently included centres will be stimulated by more senior participants to join STSMs and training schools to ensure their involvement after the action has started. Moreover, the Action will actively monitor gender and geographical balance throughout the COST Action (task 5.1) and boost participation of ITCs by including them in key management positions (task 5.2). In addition, the CONNECT Action will include 13 partners from 11 ITCs. One partner from the USA will join this COST Action to ensure global reach and connection to research efforts beyond the European network. Additional focus will be on inclusion of more International Partner Countries and Near Neighbour Countries where relevant.

2.2.2 INVOLVEMENT OF STAKEHOLDERS

All stakeholders in MCI-CKD will be involved into the Action. Involvement of these stakeholders will be the responsibility of WG5: Inclusiveness and dissemination. For each stakeholder group the WG5 managing committee will appoint an explicit liaison. The stakeholders include:

The **scientific community** within the current network and beyond. This includes both clinical- and preclinical research, and data scientists. The network and its reach will be expanded through the professional networks of the current participants and will encourage additional scientists to also join the CONNECT COST Action. These will include the aforementioned networks of ERA-EDTA, ISN, ASN, APSN, SfN, FENS, AAN, EAN and ISCBFM.

Health care professionals, including hospital staff (medical doctors, nurses) and the organisations responsible for updating of treatment guidelines. These stakeholders will go hand-in-hand: experienced health care professionals have to design and reach agreement on guidelines to be updated. Next, the guidelines can be updated by responsible organizations and subsequently disseminated with an extensive reach of nephrologists and neurologists. The current network covers the clinical expertise well and organizations that update the guidelines will be added to the CONNECT Action by through the professional network of current participants.

Patients and laypersons, including patient families and the general public. MCI-CKD patients and their caregivers will highly benefit from more scientific research because it will lead to improved diagnosis and improved treatments when these become available through the concerted action of the newly established field of brain-kidney interactions in MCI-CKD. CONNECT will also involve European and national patient organizations to increase the attention for patient perspective. Current participants have long-standing relationships with patients and national patient organizations and will involve these and the general public in the CONNECT Action.

Policy makers and Healthcare payers, including national and regional governments, national health care systems and insurance companies. These stakeholders will be involved in an early stage of the CONNECT Action by participants from every participating country. The CONNECT participants will devise a plan in the first year to involve policy makers and healthcare payers from minimum of 10 countries by the start of year 3 of the Action. This will facilitate reimbursement of novel MCI-CKD diagnosis and treatments when these become available and are taken up into updated clinical guidelines.

Industrial partners, including major pharmaceutical and biotechnological companies will be involved and further engaged for the duration of CONNECT. These companies will be invited to join CONNECT Action activities to exchange knowledge and establish new collaborations. At the kick-off meeting, the CONNECT participants will devise a plan to involve a minimum of 5 industrial participants by the start of year 2 of the Action. Thereby, engagement with industrial partners in an early phase will boost the uptake of new research findings and increase likelihood for valorisation of novel diagnostics and treatment options.

2.2.3 MUTUAL BENEFITS OF THE INVOLVEMENT OF SECONDARY PROPOSERS FROM NEAR NEIGHBOUR OR INTERNATIONAL PARTNER COUNTRIES OR INTERNATIONAL ORGANISATIONS

The University of Virginia from the USA will join the CONNECT Action as an International Partner Country (IPC). This participation will be arranged according to mutual benefit for all partners. The University of Virginia will strengthen the European Action by adding knowledge currently not yet available in Europe and by connecting these fields internationally. The University of Virginia will benefit from the European interdisciplinary CONNECT Action by transferring knowledge directly to their own university and gain insights into how to introduce an interdisciplinary kidney brain field in the USA.

3 IMPACT

3.1 IMPACT TO SCIENCE, SOCIETY AND COMPETITIVENESS, AND POTENTIAL FOR INNOVATION/BREAK-THROUGHS

3.1.1 SCIENTIFIC, TECHNOLOGICAL, AND/OR SOCIOECONOMIC IMPACTS (INCLUDING POTENTIAL INNOVATIONS AND/OR BREAKTHROUGHS)

The CONNECT Action is the very first network that will bring the divergent fields of nephrology and neurology together to resolve the outstanding questions on cognitive decline in CKD. The biggest breakthrough would be, in the short term (1-5 years), that CKD not only is a risk factor for cognitive decline, but the fundamental mechanisms for this decline are also involved in other neurodegenerative diseases. In the longer run (20 years), nephrologists can share with neurologists their therapeutic options to eliminate large and small toxins from the bloodstream, thus opening the field to new therapeutic possibilities. This type of interdisciplinary research has been very successful in other fields. For instance, recent interdisciplinary collaborations have demonstrated how intestinal health influences Type 2 diabetes and heart disease, how the immune system affects cancer therapy, and how personalised health prognosis can be made with use of big data. Given the success in other interdisciplinary fields, the CONNECT Action will set up network for brain-kidney research to make sure that this field seizes the current opportunity.

Expected impact on science: In the short term, CONNECT will 1) found a new interdisciplinary field of research, 2) enable scientists with the tools to perform this type of research, and 3) enable efficient clinical research and clinical trials within this new field. Starting this interdisciplinary field now will in the long term enable scientists to uncover the cause for MCI-CKD and start research on prevention and treatment. To this end strong involvement of ECIs is crucial to make the new field of MCI-CKD

sustainable. Therefore, additional ECI participants are especially encouraged to join the CONNECT Action and summer schools, training schools, and STSMs will be prioritized for their participation. Once the field of MCI-CKD has been established and made sustainable, both clinician scientists, biotech and big pharmaceutical companies will be aligned to develop new diagnostic tests and treatments to bring technological and social economic impact.

Expected impact on technology: For the first time, already existing technologies that are currently used for brain or kidney research will be more widely used for research on MCI-CKD. These include recent and validated technological advances in: 1) Human functional brain imaging; 2) Animal models for functional (brain) imaging and cognitive decline: 3) Animal models for kidney physiology such as 5/6th nephrectomy; 4) Human & animal cognitive tests; and 5) Omics tools. In the long term, these tools will be more specifically developed and adopted for MCI-CKD research and may be technologically tailored to facilitate this research. Moreover, scientific findings on the cause and treatment of MCI-CKD will enable new technological advances to help research efforts and patient treatments, which may include new tests based on novel biomarkers.

Expected impact on social economy:

Impact on health: investigating and resolving cognitive impairment secondary to CKD will have major impact on CKD patient health. 30-60% of patients receiving invasive kidney replacement therapies have been diagnosed with cognitive impairments. Neurological and cognitive impairments, and depression weigh heavily on the QoL of these patients. For these patients and their caregivers, the QoL is markedly reduced to similar levels as observed in patients with metastatic breast cancer[21]. The patient perspective can only be improved by performing research in the interdisciplinary field of brain-kidney. By more targeted research interdisciplinary collaborations will be enabled to 1) diagnose and 2) treat MCI-CKD in an early phase. By early diagnosis and better treatments, the QoL of patients and their caregivers will drastically improve beyond the current standard of care. Indeed, the reduced QoL in CKD and dialysis patients derives from a reduction in physical functioning, physical role functioning and in the physical component summary, particularly in individuals with higher educational level who were professionally active. Furthermore, mental health significantly impinges upon the patient's autonomy. Clearly, by improving cognitive functions, regained autonomy, and self-esteem, (former) CKD patients can continue to carry out their work with better performance.

Health economics: Patients with CKD present with MCI that is characterized by impairment in several key cognitive domains, including memory, processing and emotion-depression. In addition to a reduced QoL, this also represents an economic burden on patients and their caregivers. For patients in the working population, cognitive impairment signifies a direct loss in employment and productivity. The most adequate figures are available for the USA, and European nephrologists confirm these numbers translate to the EU. 67-80% of working age patients with CKD are unemployed (compared to about 1% in the USA population), with even higher percentages in the case of dialysis[22]. Most of the patients entering in dialysis give up their job, even if they are still able to work[23]. It is at present unclear how much cognitive impairment affects this decision. In other diseases, such as Systemic Lupus Erythematosus, the appearance of cognitive impairment decreases the employment percentage by 20%[24]. For both CKD patients that are in the working-age population and elderly CKD patients that are not, economic burden also lies at caretakers, including family and professional care. Where the economic costs of caregiver burden are not well-assessed in MCI-CKD, they are in caregiver burden with late-life depression. For instance, depressed elders receive up to three additional hours of informal care weekly compared to those without depression, representing a yearly cost of approximately EUR 1,200 per person[25]. Thereby, when interdisciplinary research enables early diagnosis and treatment of MCI-CKD, CKD patients will be more independent and both primary economic burden and caregiver burden will be reduced.

3.2 MEASURES TO MAXIMISE IMPACT

3.2.1 KNOWLEDGE CREATION, TRANSFER OF KNOWLEDGE AND CAREER DEVELOPMENT

Knowledge creation: by enabling interdisciplinary research in the new field of cognitive impairment in CKD patients the scientific community will acquire new knowledge from clinical and pre-clinical research. To extend the reach beyond the current COST Action network the topic of MCI-CKD will be made future-ready by preparing a brain-kidney joint research agenda, which will be updated at least once a year.

Transfer of knowledge: It is of great importance that new knowledge from the COST Action will become available to the appropriate stakeholders. To this end, a targeted dissemination plan for newly obtained knowledge is described in 3.2.2 and will be further updated during the COST Action. New knowledge

will become publicly available by publishing these in appropriate scientific journals and, whenever possible, on the COST Action website. These will include:

- A white paper on MCI-CKD;
- Reports and publications in scientific journals on: 1) available pre-clinical animal models, research tools and technologies, 2) data management and available bioinformatic tools, 3) best practices in MCI-CKD clinical trials, and 4) CONNECT Action effectiveness. Additional scientific papers on the topic of MCI-CKD from CONNECT Action participants will also be endorsed;
- Publishing of guidelines for testing for – and/or treatment of – MCI in CKD patients and vice versa;

CONNECT deems it of vital importance that the network will become sustainable beyond the current Action. This will ensure that the developments in the brain-kidney field will deliver maximum impact. To this end, the Network will investigate alternative arrangements for network formalization and investigate alternative funding beyond the COST Action (See also Section 4).

Career development: junior researchers and ECIs will be engaged in the CONNECT Action from currently and newly participating institutes. They will be engaged in summer schools and educated cross-topic at the interface of brain-kidney physiology and research. This will open new career perspectives for these ECIs as it enables them to start at the forefront of new brain-kidney developments and strengthen their own research lines. To ensure sustainability of the new interdisciplinary field the CONNECT Action will actively explore and pursue future funding for training efforts such as the Erasmus+ programme, Marie-Curie Innovative Training Networks, and other training networks for junior researchers and ECIs.

3.2.2 PLAN FOR DISSEMINATION AND/OR EXPLOITATION AND DIALOGUE WITH THE GENERAL PUBLIC OR POLICY

Dissemination of results: Appropriate dissemination of CONNECTs results is essential for the effectiveness and sustainability of the Network and the continued establishment of novel brain-kidney research lines. Therefore, CONNECT will develop a detailed dissemination plan for each relevant group of stakeholders (Table 1). The detailed dissemination plan will include the message, platforms (Table 2), frequency of the messages, assess efficacy of the dissemination activities, and update the plan where needed. To ensure these tasks are met the CONNECT Action will appoint a dedicated dissemination manager within the Working Group Inclusiveness and dissemination (WG5) and dedicated communication liaisons for each stakeholder group.

Exploitation of results: the aim of the CONNECT Action is to merge the currently separate fields of neurology and nephrology into a new research field fostering inter- and transdisciplinary MCI-CKD research. To ensure that results will reach the patient as new diagnostics or treatment options for MCI-CKD the CONNECT participants recognize that biotech and major pharmaceutical companies need to be involved in an early phase.

Dialogue with the general public: the general public will be involved in the CONNECT dialogue by communicating with them through social media and traditional media outlets. In addition, CONNECT COST Action participants have long standing relationships with their national patient organizations and local popular science festivals and will disseminate knowledge to the general public to raise awareness of cognitive impairment in CKD patients.

Table 1. Targeted dissemination strategies of identified stakeholders.

Stakeholders	Motivation	Intended effect	Means of communication
 **Patients**	Better care for MCI-CKD patients	Awareness and enrolment in interdisciplinary studies	Website, social media, newsletter, brochures, patient organizations, public lectures, science festivals
 **Scientific community**	Advance clinical and preclinical MCI-CKD research	Establishment of interdisciplinary collaborations and research lines	Publications, reports, conferences and satellite events, social media (LinkedIn)

	Medical professionals	Offer standardized treatments to MCI-CKD patients	Awareness and contribution to the COST Action	Publications, guidelines, conferences and satellite events, social media (LinkedIn)
	Policy makers and healthcare payers	Cost-effectiveness of MCI-CKD treatments	Awareness and timely reimbursement of new diagnostics and treatments	Ad hoc meetings, brochures, conferences, website, social media (LinkedIn)
	Industry	Development of new products	Knowledge exchange, new collaborations and increased likelihood for valorisation	Ad hoc meetings, joining COST Action activities, website, social media (LinkedIn)
	General public	Improved healthcare	Awareness and motivation of other stakeholders	Social media, traditional media outlets, patient organizations, public lectures

Table 2. CONNECT dissemination channels

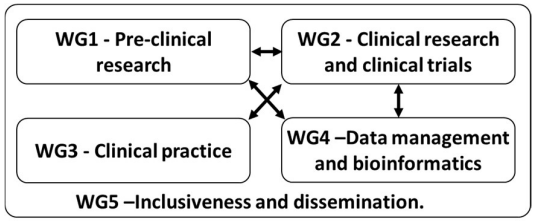
Channel	Frequency
Website	Updated at least 4x per year and information for the general public translated into major the European languages
Social media (including LinkedIn)	Post and updates at least 4x per year
Newsletter	At least 2x per year
Brochure	2 brochures: one for patients and one for policy makers and healthcare payers. Brochures will be distributed through the European and the national nephrology societies at annual meetings
Public lectures and science festivals	Yearly public lectures in countries of COST Action participants, always in the language of the respective country. This will be achieved by teaming up with national science festivals (e.g. Bergamoscienza in IT, Weekend of Science in NL, Berlin Science Week in DE)
Scientific publications and reports	At least 5 during the CONNECT COST Action: 1) MCI-CKD white paper; 2) available pre-clinical animal models, research tools and technologies, 3) data management and available bioinformatic tools, 4) best practices in MCI-CKD clinical trials, and 5) CONNECT Action effectiveness. These will be published in high impact-international journals. Additional scientific papers on the topic of MCI-CKD will also be endorsed
Conferences and satellite events	At least 2 by partnering with for instance the ERA-EDTA, SfN and the National Nephrology meetings (e.g. the Italian Society of Nephrology)
Guidelines	At least 2 guidelines for testing for – and/or treatment of – MCI-CKD patients will be published in international journals.

4 IMPLEMENTATION

4.1 COHERENCE AND EFFECTIVENESS OF THE WORK PLAN

4.1.1 DESCRIPTION OF WORKING GROUPS, TASKS AND ACTIVITIES

CONNECT has 5 working groups that each contribute to tackling a specific challenge of CKD-induced MCI. Management and alignment of the working groups will be ensured by cross communication through the kick-off meeting, CONNECT website, collective meetings, and communication by the WG leaders.



Working Group 1 (WG1) - Pre-clinical research.
The main objective of WG1 is to strengthen collaboration on pre-clinical models for kidney disease and brain research. This main objective will be reached by achieving below RCO's and CBO's: Objectives RCO1.1 Gain understanding of current state-of-the-art animal models and imaging tools available for these animal models; RCO1.2 Coordination of pre-clinical research efforts on MCI-CKD (merge currently separated research lines). CBO1.1 Bridge the preclinical MCI and CKD fields to form an interdisciplinary field.
Tasks T1.1 Review state-of-the-art animal models and technology available T1.2 Provide interdisciplinary training on brain-kidney interaction Milestones (month of achievement) M1.1 WG1 meetings (M6, 12, 18, 24, 30, 36, 42, 48) M1.2 STSM for preclinical scientists to visit other institutions and exchange technologies and models (M13-48) M1.3 Scientific papers published (M19-48)

Working Group 2 (WG2) - Clinical research and clinical trials
The main objective of WG2 is to disseminate knowledge on clinical research and clinical trials on cognitive impairment in CKD. Thereby, more, and more successful clinical trials can be conducted on the prevalence, risk factors, and best treatments of MCI-CKD. This main objective will be reached by achieving below RCO's and CBO's: Objectives RCO2.1 Define the needs for clinical research and clinical trials to be conducted; RCO2.2 Development and publication of MCI-CKD clinical trial guidelines and/or best practices; RCO2.3 Coordinate clinical cohort and trial data collection; RCO 2.4 Define methodological challenges in clinical trials. CBO2.1 Exchange knowledge of existing and new clinical cohorts and clinical trial conduction in MCI-CKD; CBO2.2 Involve clinical researchers currently not conducting clinical trials within MCI-CKD.
Tasks T2.1 Identify challenges in current clinical trials T2.2 Identify focus areas for new clinical trials together with gap analysis from T3.5 T2.3 Provide training on establishment of new clinical trials Milestones (month of achievement) M2.1 WG2 meetings (M6, 12, 18, 24, 30, 36, 42, 48) M2.2 STSM for clinical researchers to centres that have successfully conducted clinical trials (M13-48) M2.3 Scientific papers published (M19-48)

Working Group 3 (WG3) - Clinical practice.
The main objective of WG3 is to strengthen collaborations between nephrologists and neurologists to ensure they speak a common language. When their knowledge is up to date on MCI-CKD, clinicians will be able to cross-diagnose beyond their own expertise and refer patients to neurologists or nephrologists for further diagnosis and treatment when appropriate. This main objective will be reached by achieving below RCO's and CBO's: Objectives RCO3.1 Develop a common clinical understanding of MCI-CKD; RCO 3.2 Develop and publish guidelines for testing for – and/or treatment of – MCI-CKD. CBO3.1 Foster knowledge exchange: a) educate nephrologists on tests used for cognitive impairment and its treatment, and b) educate neurologists on the diagnosis and role of CKD in MCI and its treatment; CBO3.2 Develop a joint research agenda to investigate MCI-CKD.
Tasks T3.1 Review current state of the art diagnosis and treatments for MCI and CKD T3.2 Identify minimal clinical understanding on kidney (dys)function that neurologists should have T3.3 Identify minimal clinical understanding on cognitive impairment that nephrologists should have T3.4 Provide training for clinicians on the minimal understanding defined in T3.2 and T3.3 T3.5 Perform gap analysis in current clinical research to develop a joint research agenda

T3.6 Share best practices among health institutions and countries by updated guidelines. This will be done according to ERBP-guidelines, i.e. a rigorous Cochrane-like methodology with systematic reviews. Any guideline to be developed will align with AGREE II (the standard to assess the methodological quality of a practice guideline).
Milestones (month of achievement)
M3.1 WG3 meetings (M6, 12, 18, 24, 30, 36, 42, 48)
M3.2 2 White papers published (M18, M48)
M3.3 Updated clinical guidelines available in accordance with ERBP principles (M48)

Working Group 4 (WG4) – Data management and bioinformatics.

The main objective of WG4 is to exchange knowledge on big data management and bioinformatics among researchers for omics, imaging, and epidemiology. This main objective will be reached by achieving below RCO's and CBO's:

Objectives
RCO4.1 Map the software and analytical needs of preclinical and clinical researchers. CBO4.1 Train researchers in the use of bioinformatic tools for big data.

Tasks
T4.1 Identify types of big data and current data management in clinics and preclinical research
T4.2 Identify topics that should be covered by training sessions/summer schools
Milestones (month of achievement)
M4.1 WG4 meetings (M6, 12, 18, 24, 30, 36, 42, 48)
M4.2 Training schools for data management and bioinformatics (M18, M36)

Working Group 5 (WG5) –Inclusiveness and dissemination.

The main objective of WG5 is to involve diverse stakeholders and disseminate CONNECT Action knowledge to the research and clinical communities. This main objective will be reached by achieving below RCO's and CBO's:

Objectives
RCO5.1 Disseminate CONNECT outcomes to relevant stakeholders to ensure uptake by the broader scientific and clinical community, and guidelines. CBO5.1 Create an international platform for MCI-CKD research to ensure active participation of clinicians and scientists to ensure growth of the field during, and after completion of, the COST Action.

Tasks
T5.1 Monitor gender and geographical balance throughout the COST Action
T5.2 Boost participation of ITC countries by including them in key management positions
T5.3 Support organization of events organized by the other WGs
T5.4 Organize online internal and external communication through the website and social media
T5.5 Optimize, realize, and monitor the dissemination strategy
Milestones (month of achievement)
M5.1 Kickoff meeting (M1)
M5.2 Action website online (M6)
M5.3 Organize satellite events with current conferences and meetings (M12, M24, M48)
M5.4 Brain-kidney joint research agenda published (M18, M40)
M5.5 Brain-kidney COST Action international conference (M36)
M5.6 Interdisciplinary summer schools (M12, M24, M36, M48)

4.1.2 DESCRIPTION OF DELIVERABLES AND TIMEFRAME

- D1.1 Report on available pre-clinical animal models, research tools, technologies (M18, M40)
- D1.2 Scientific papers (M18-M48)
- D1.3 Conference, poster presentations (M12, M24, M36, M48)
- D2.1 Best practices in MCI-CKD clinical trials (M18)
- D2.2 Scientific papers (M18-48)
- D3.1 MCI-CKD white paper (M18)
- D3.2 Guidelines for testing for – and/or treatment of – MCI in CKD patients and vice versa (M48)
- D3.3 Ranking what knowledge nephrologists should have to identify MCI, and neurologists to identify CKD, for them to speak the same language (M12)
- D4.1 Report on data management and available bioinformatics (M18, M40)
- D4.2 (content for) Training school (M18, M36)

- D5.1 CONNECT Action website (M6)
- D5.2 (content for) Interdisciplinary summer school (M12, M24, M36, M48)
- D5.3 Joint research agenda (M18, M40)
- D5.4 Report on Action effectiveness (M48)

4.1.3 RISK ANALYSIS AND CONTINGENCY PLANS

RISKS RELATED TO WG1:

- Risk 1.1: Researchers do not work together. Mitigation: Identify blockers and solutions for better knowledge exchange. Identify additional centres as new collaborators.
- Risk 1.2: Insufficient funding for preclinical research. Mitigation: Identify foundations that could support large, international research consortia beyond EU.

Risks related to WG2:

- Risk 2.1: Clinicians, clinical researchers, and epidemiologists do not reach consensus on best practices. Mitigation: Describe gaps in knowledge and approaches how to identify best practice.

Risks related to WG3:

- Risk 3.1: Clinicians do not work together. Mitigation: Identify blockers and solutions for better knowledge exchange. Identify additional centres as new collaborators.
- Risk 3.2: Updated guidelines are not supported in all countries. Mitigation: Initiate discussion on reasons why guidelines are not supported and identify challenges/necessities that help to accept guidelines.

Risks related to WG4:

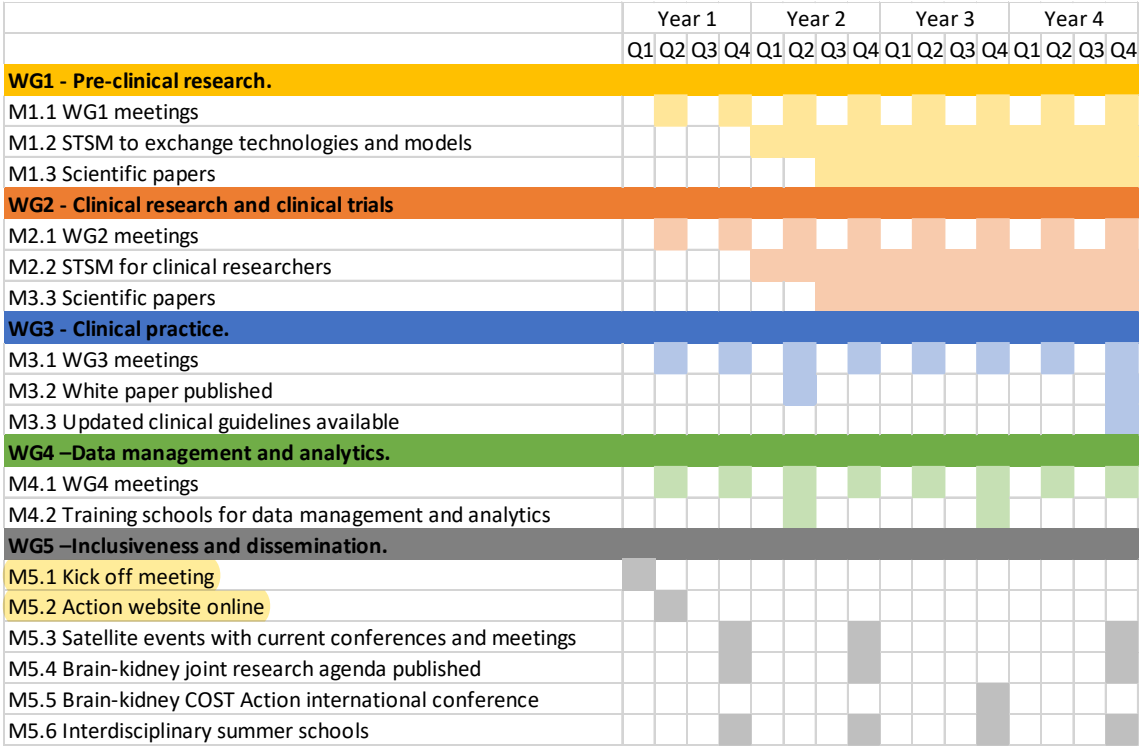
- Risk 4.1: Uncertainty on bioinformatic tools to be included require training schools. Mitigation: Map available tools and bioinformatics needs and include several diverse tools for training.

Risks related to WG5:

- Risk 5.1: Lack of broad stakeholder engagement. Mitigation: Broaden approach to stakeholders, identify reasons for scepticism and address open issues.

4.1.4 GANTT DIAGRAM

CONNECT tasks are highly interconnected and run for the duration of the COST Action. Working group milestones are depicted below.



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