Brussels, 23 June 2017

COST 021/17

DECISION

Subject: **Memorandum of Understanding for the implementation of the COST Action "Maximising Impact of research in NeuroDevelopmental DisorderS" (MINDDS) CA16210**

The COST Member Countries and/or the COST Cooperating State will find attached the Memorandum of Understanding for the COST Action Maximising Impact of research in NeuroDevelopmental DisorderS approved by the Committee of Senior Officials through written procedure on 23 June 2017.

MEMORANDUM OF UNDERSTANDING

For the implementation of a COST Action designated as

COST Action CA16210
MAXIMISING IMPACT OF RESEARCH IN NEURODEVELOPMENTAL DISORDERS (MINDDS)

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);
b. "COST Action Proposal Submission, Evaluation, Selection and Approval" (COST 133/14);
c. "COST Action Management, Monitoring and Final Assessment" (COST 134/14);
d. "COST International Cooperation and Specific Organisations Participation" (COST 135/14).

The main aim and objective of the Action is to create a collaborative network to enhance identification of patients carrying genetically penetrant pathogenic Copy Number Variants (CNV) which are rare cases and present a unique opportunity to understand neurodevelopmental disorders (NDD), standardise research methodologies and facilitate exchange of information for the benefit of clinicians, researchers and patients. 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 48 million in 2016.

The MoU will enter into force once at least five (5) 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.

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.

TECHNICAL ANNEX

OVERVIEW

Summary
This Action focuses on patients with rare neurodevelopmental disorders (NDD) whose study have the potential for major impact on our understanding and treatment of NDD in general, including schizophrenia and Autism Spectrum Disorder (ASD). NDD affect 1 in 25 individuals in Europe, and have high impact on healthcare systems, economic development and society. Lack of mechanistic knowledge hampers development of improved treatments. New knowledge from psychiatric genomics provides for the first time a route to identify neurobiological mechanisms underlying NDD. The key challenge is to link genetic risk to altered brain biology.

Although highly informative, substantial variability and severity of psychiatric symptoms means that genomic studies based on the general NDD patient population experience significant difficulties in assigning individual gene mutations to clinical phenotype. A solution to this challenge is the study of subgroup of NDD patients where deletions or duplications of DNA segments (Copy Number Variants, CNV) alter gene dosage and have a strong causal relationship with NDD. These pathogenic CNV present a major opportunity to establish mechanistic understanding and develop new therapies. However, NDD patients with these CNV are rare and require a coordinated, international collaboration to find and study them in large numbers.

MINDDS will create a pan-European network of clinical scientists, preclinical researchers and patient representatives to advance studies of NDD patients for these pathogenic CNV. It will create a legal and ethical framework for effective transnational NDD patient cohort building; develop standardized protocols and establish effective mechanisms for effective data sharing and knowledge exchange.

Areas of Expertise Relevant for the Action	**Keywords**
● Clinical medicine: Psychiatric disorders	● Neurodevelopmental disorders (NDD)
● Basic medicine: Genetic epidemiology	● Autism Spectrum Disorders (ASD)
● Basic medicine: Neuropsychology	● Schizophrenia
● Basic medicine: Stem cell biology	● Psychiatric genomics
	● Copy Number Variants

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

Research Coordination
● A pan-European framework for NDD patient cohorts: The Action will establish a single framework for transnational patient recruitment, incorporating regulatory, legal and ethical requirements.
● Standardization of protocols and methodologies: It is important to maximize the utility and quality of the resultant research data outputs. The Action will agree on standardized research protocols for the major study regimes, including clinical phenotyping, brain imaging and patient-derived cell studies.
● Integration of information: The Action will develop an over-arching platform, including prototype database, to support NDD patient research.

Capacity Building
● Training and Knowledge Exchange: Research conferences, training schools and workshops will form an education programme.

● Leading on standardization and SOPs: The Action will establish working groups, which will create, review and publish standardized protocols, experimental methodologies and best practice.
● Data sharing and knowledge exchange: The Action will establish optimal methods to collate and share our expanding knowledge, via a “knowledge nexus”.

1) S&T EXCELLENCE

A) CHALLENGE

I) DESCRIPTION OF THE CHALLENGE (MAIN AIM)

This COST Action aims to maximise research impact of the study of the neurodevelopmental disorders (NDD) such as schizophrenia and the overlapping triad of Autism Spectrum Disorder (ASD), developmental delay (DD) and intellectual disability (ID) by focussing on the unique opportunity offered by patients carrying rare genetically penetrant chromosomal micro-deletions or duplications (pathogenic Copy Number Variants; CNV).

Mental wellbeing is an important contributor to health and prosperity of all European citizens. Maintenance of good mental health and effective treatment of mental disorders are key societal challenges. Neurodevelopmental disorders (NDD) are a major class of mental health conditions, and arise when disruption of brain development leads to neuropsychiatric impairments of learning, memory, executive function, emotion and social interaction. NDD affect approximately 18 million European citizens per year, nearly 4% of the population [1]. Their effects arise during childhood, adolescence, or early adulthood but are usually life-long. NDD include childhood-onset disorders (ASD, DD, and ID), and schizophrenia, the onset of which peaks in late adolescence to early adulthood. At present, current therapies, when available, are at best palliative, treating symptoms not fundamental pathophysiological causes. Consequently, the persistence and severity of NDD impart a disproportionally high burden on European healthcare services, with an estimated socio-economic impact of ~€180 Billion per year [1]. To meet this challenge, it is essential to identify the pathophysiological mechanisms that lead to NDD, as these provide the route to effective therapeutic strategies, accurate diagnosis and improved patient benefit.

Major advances in genomics have identified several hundred genetic loci that contribute to risk for NDD, particularly ID, ASD, and schizophrenia [2,3]. Some risk genes conform to our current clinical knowledge. For example, the dopamine D2 receptor (*DRD2*) is both a schizophrenia-associated risk gene and is targeted by anti-psychotic medication. However the majority of risk genes fall within biological pathways outside those targeted by current drug treatments, associating with the glutamate signalling pathway, GABA receptors, ion channels, neuronal plasticity, neuronal transcription factors and epigenetic regulators. An important discovery is a significant genetic overlap between the different NDDs, suggesting common biological origins to aspects of these conditions. Furthermore, comorbidity seen between different psychiatric conditions and apparently unrelated, non-psychiatric conditions such as epilepsy and cardiac malformations, presents difficulties for diagnosis as well as treatment. This argues for more genetic driven criteria for clinical assessment.

Unfortunately, the genetic architecture of NDD is complex and the current picture is incomplete. It is clear for ASD and schizophrenia, where most data are available, that both individual and population risk is conferred by multiple alleles at many loci; in other words, these are polygenic disorders [4]. There is also considerable phenotypic variability for all of the major NDD, so that individuals with similar polygenic load differ in psychiatric symptoms and their severity. This high polygenicity and clinical heterogeneity makes direct correlation between specific pathogenic gene mutations and patient phenotype very difficult, and challenges our

ability to translate genetic knowledge into understanding of biological mechanism and subsequent healthcare improvement.

MINDDS (Maximising Impact of research in NeuroDevelopmental DisorderS) addresses this challenge by focussing on patients with pathogenic Copy Number Variants (CNV) that are associated with high risk of neuropsychiatric psychopathology. Although these can be considered as distinct rare diseases, individuals who possess one or more of these CNVs are at very high risk (up to 60%) of developing a NDD. Hence studying carriers of the CNVs offers a unique opportunity to increase our understanding of the relationship between genotype and clinical phenotype. These high-risk, pathogenic CNV are rare, because their deleterious nature affects the reproductive fitness of carriers. However, they are maintained in the population because they tend to originate in chromosomal regions subject to high mutation rates. For example, 22q11.2 Deletion Syndrome (22q11.2DS), which occurs at a rate of ~1 in 3,000 life births. It is caused by the deletion of ~60 genes and is associated with mild to moderate intellectual disability (60%), whilst 55% of cases have at least one psychiatric diagnosis, including ADHD (41%) and ASD (26%) [6]. Lifetime prevalence of schizophrenia in 22q11.2DS is estimated to be 25%, compared to the 1% in the general population [7]. To spearhead research into these rare CNV, collaboration across multiple sites is necessary. The MINDDS network aims to substantially accelerate research progress via a Europe-wide framework for the identification of individuals who possess pathogenic CNV, and subsequently maximize the research value by the creation of standardised protocols for systematic clinical evaluation, and the facilitation of data sharing and knowledge exchange.

II) RELEVANCE AND TIMELINESS

Rare highly penetrant CNV offer an important route to insights into the biological underpinnings of psychiatric disorder, and will lead to major innovations in diagnosis, drug development and therapeutics. The Action has already identified the following patient cohorts (Table 1).

Table 1: Patient numbers with pathogenic CNV associated with NDD currently available within MINDDS

Chromosomal region	One of the genes in the region	Deletion	Duplication	Combined
1q21.1	*GJA5*	41	79	120
2p16.3	*NRXN1*	63	9	72
7q11.23	*GTF21*	16*	318	334
15q11.2	*CYFIP1*	91	64	155
15q11-13	*SNRPN*	44**	24	68
15q13.3	*CHRNA7*	47	30	77
16p11.2	*KCTD13*	118	161	279
16p13.11	*MYH11*	24	107	131
17q12	*LHX1*	15	38	53
22q11.2	*COMT*	910	99	1009
22q11.2 distal	*CRKL*	44	54	98
Other				691
TOTAL				**3087**

*Williams-Beuren syndrome
** Prader-Willi & Angelman syndrome

Coordinated research activity has delivered significant advances in the understanding of genetic risk [2-5], but this is only the beginning. A key limitation to progress is the need to greatly expand the cohort sizes. Europe possesses world-leading research strengths across all aspects of mental health disorder and has highly advanced provisions for mental healthcare. It is ideally placed to create large, pan-European patient cohorts and coordinate standardized working protocols.

MINDDS will form a **partnership of preclinical scientists, clinical researchers, rare disease registry/research database specialists and patient representatives** to deliver: 1) a pan-European framework for building patients cohorts with NDD due to CNV; 2) standardisation of research protocols and data collection; and 3) design of an integrated platform for knowledge and data sharing. A recent EU FP7 project ROAMER (ROAdmap for MEntal health research and well-being Research in Europe) defines the key priorities for success in mental health research for the next 5-10 years [10]. MINDDS aims to directly contribute to the priority areas of building research capacity and facilitating future research to improve mental health care for all.
In summary, Europe has the potential to deliver rapid and major progress in the understanding and treatment of NDD, but in order to achieve this an adoption of a pan-European strategy to build highly powered patient studies, standardization of research protocols and data sharing, are needed.

B) SPECIFIC OBJECTIVES

I) RESEARCH COORDINATION OBJECTIVES

MINDDS has three interlinked objectives to build clinical research capacity, improve data quality and promote data sharing and knowledge exchange.

A pan-European framework for NDD patient cohorts: The Action will establish a single framework for transnational patient recruitment, incorporating regulatory, legal and ethical requirements. This will be accompanied by gold standard assessment criteria specific for each pathogenic CNV, based on recently gained genetic knowledge. This will generate a minimum of 5 position papers or published guidelines.

Standardization of protocols and methodologies: Given the high research value of patient cohorts, it is important to maximize the utility and quality of the resultant research data outputs. The Action will agree on standardized research protocols for the major study regimes, including clinical phenotyping, brain imaging and patient-derived cell studies. For each regime (>3) protocols will be published in academic or professional journals.

Integration: The Action will develop an over-arching platform to support NDD patient research. This will comprise three separate components: 1) a European registry for NDD patients that includes permission for participation in future research; 2) a database to collate research outputs, including capacity for inter-operability with existing and future patient studies; and 3) delivery of knowledge exchange (KE) for clinicians/caregivers, patients/parents and other stakeholders. At least one position paper will be generated for each component.

II) CAPACITY-BUILDING OBJECTIVES

To deliver our Research Coordination Objectives, the Action will pursue three capacity-building objectives.

Training and Knowledge Exchange: Research conferences, training schools and workshops will form an education programme. Four training schools (1 each year) will train clinicians and clinical researchers in the identification and responsible recruitment of eligible patients. Two workshops for researchers (Year 2 and 3) will disseminate knowledge of research outputs, assessment criteria, standard operating procedures (SOPs) and best practice.

Leading on standardization and SOPs: The Action will establish working groups, which will create, review and publish standardized protocols, experimental methodologies and best practice; each leading to position papers and KE activities.

Data sharing and knowledge exchange: The Action will establish optimal methods to collate and share our expanding knowledge, via a “knowledge nexus”. This will comprise the design of prototype databases using a set of common data elements in existing databases of network participants and web-based knowledge exchange procedures for patients / parents,

clinicians and researchers, to be developed in collaboration with experts in e-health, informatics, secure-by-design e-infrastructures and data protection safety/security.

C) PROGRESS BEYOND THE STATE-OF-THE-ART AND INNOVATION POTENTIAL

I) DESCRIPTION OF THE STATE-OF-THE-ART

Genotype-phenotype studies of cohorts selected by clinical diagnosis are difficult to interpret due to the polygenic nature of NDD and the over-representation of more severely affected patients. Samples selected for the presence of a pathogenic CNV offer much stronger linkage between genotype and phenotype, but the lack of sizeable, phenotypically well-characterized cohorts is a major limitation. Current recruitment and assessment of patients with pathogenic CNV relies heavily on local collaboration between researchers and regional healthcare services within different European countries. The advantages of a large collaborative resource are evident, however there are many barriers to consider. Study designs based on highly specific research objectives and variation in assessment criteria across sites complicates data integration. Furthermore, phenotyping poses challenges because of the complex patterns of co-occurrence between different psychiatric conditions and a range of other problems, such as seizures, and motor, immunological, cardiac, renal, and gastrointestinal dysfunction. Furthermore, this complex presentation may change over the life course. For example, ASD becomes evident in early childhood and continues to persist in adulthood, the rate of ADHD declines in adolescence, whilst schizophrenia becomes manifest in late adolescence/ early adulthood, although subtle preclinical symptoms can be present years earlier. Even when these methodological disparities are overcome, regional and international differences in regulatory and legal policies and ethical review criteria can still hinder, or even prevent, collaboration and data integration.

Critical to effective collaborative studies is the use of universal, **objective measures for detailed clinical phenotyping.** Advances in our knowledge have highlighted the need for capturing a broad range of quantitative data associated with each NDD. For example, neurocognitive tests, such as the Cambridge Neuropsychological Test Automated Battery (CANTAB) battery are providing insights into the neural and genetic basis of neuropsychiatric disorders. These studies can be carried out in parallel with brain imaging methodologies. Structural magnetic resonance imaging, such as diffusion tensor imaging (DTI), functional magnetic resonance imaging (fMRI) and magnetic resonance spectroscopy (MRS) are now achieving high resolution structural, functional and in some cases biochemical data from patients. Initiatives such as Research Domain Criteria (RDoC) [11] aim for a more flexible approach for patient assessment that better captures traits that are shared across disorders than the traditional clinical criteria.

In addition, **induced pluripotent stem cells (iPSC) and new post-genomic sequencing technologies** are now close to implementation for patient studies. Technologies to generate patient iPSC offer a powerful new research interface for clinical studies via in vitro differentiation into neurons and glial cells, and may deliver cell-based assays to directly examine neurodevelopment, neurophysiology and preclinical pharmacology [12]. These studies will reveal underlying mechanism and act as patient-specific cell platforms for drug development in precision medicine approaches. To date, patient cell studies have been limited to a few randomly selected schizophrenia and ASD patients, and a small number with pathogenic CNV, such as Rett, Timothy and Phelan-McDermid Syndromes [13-15]. Emerging technologies are likely to be more applicable to rapid and high throughput analysis, such as direct cell reprogramming [16]. Similarly, technology developments in DNA sequencing are impacting on the cost, speed and quality of DNA sequencing and enabling higher content genotyping and clinical phenotyping by transcript and epigenetic profiling [12].

The value gained from CNV patient studies will only be truly realised if data can be **integrated within a coherent body of knowledge**. This necessitates careful consideration of how data is collected, stored and assessed. Lack of data type and repository consistency is often a limiting factor in collaborative studies, requiring new methodologies in health and medical

research informatics, and often challenges regulatory, legal and ethical frameworks. Europe has strengths in neuroscience and behavioural research at all levels from human psychology to animal models and cell systems. New technologies, such as CRISPR-Cas9, are accelerating the speed of the generation of genetic models in rodents whilst other advances are facilitating the study of gene function in whole animals. However, alignment between these neuroscience efforts and patient studies is needed to fully understand disease mechanism. Finally, a key question is how pathogenic CNV relate to the NDD phenotype seen in the general patient population. Current data for 22q11.2DS indicates that this is the case for schizophrenia [17], but further research is required.

II) PROGRESS BEYOND THE STATE-OF-THE-ART

First, there is a strong need for an effective approach to **expand the size of our existing rare CNV patient cohorts**, via enhanced recruitment and pooling of patient data collected at sites throughout Europe. As population structure, clinical practice and research culture varies a consensus approach is required for patient selection and recruitment across sites. In addition, there is a need to **define the legal and ethical frameworks** for secure exchange of phenotypic data and distribution of biological samples. This requires agreement on transnational processes for pre-recruitment, informed consent, patient involvement, making research results or incidental findings available to participants, and data sharing in accord with national and EU regulations, and ethical guidelines. To be effective, patient recruitment should follow **standard clinical assessment criteria** designed to capture the full and complex range of features associated with each pathogenic CNV of high NDD risk. By necessity, these must go beyond conventional psychiatric assessments and include neuro-cognitive impairments, motor dysfunction and physical health problems including seizures and congenital abnormalities and be appropriate for capturing changing profiles across the life course and variation due to gender and environmental influences, including socio-economic class. Advances in genetic knowledge will be taken into account in the selection of our measures.
Second, to maximise the utility of pan-European cohorts, the Action will **standardise the approaches to patient studies and clinical phenotyping**. These need to be measureable and sufficiently robust to allow direct comparison between different testing sites. SOPs need to be agreed for both current research activities, e.g., cognitive testing and brain imaging, but also to **incorporate new and emerging technologies** for cell phenotyping, patient iPSC and genomic based analyses. There is currently no consensus phenotype for NDD patient iPSC, with key issues to be resolved concerning biological variation due to polygenic background and variation introduced during iPSC production and in vitro neuronal differentiation due to differences in technical approach. All outputs from these patient iPSC studies need to be quantitative, and back translatable to align with mechanistic hypotheses arising from the basic research enterprise as well as comparable to studies of NDD populations and animals.
Third, the Action will find **methodologies to collate and share knowledge** gained from cohort studies. To achieve integration, the Action will develop shared semantics and ontologies that will ensure inter-operability and quality of data from different cohorts and research sites. In parallel, strategies need to be devised for the exchange of knowledge across all sectors of stakeholders, with key questions concerning how changes in biological understanding affect healthcare and societal provision, as well as the consequences for healthcare planning and public perception. MINDDS will set up mechanisms in line with existing recommendations for high quality rare disease registries issued by RD-Connect and IRDiRC consortia to monitor the impact of its activities on patients/research participants.

III) INNOVATION IN TACKLING THE CHALLENGE

The MINDDS network (Figure 1) will create **a partnership between researchers and patient organisations** to establish a single framework for building and sharing pan-European patient cohorts for pathogenic CNV associated NDD. This will go beyond simply delivering governance policies and will incorporate draft **legal and ethical frameworks to support transnational cooperation**. The legal and ethical protocols will take into account specific issues arising from the rarity of these conditions, such as potential compromised patient confidentiality.

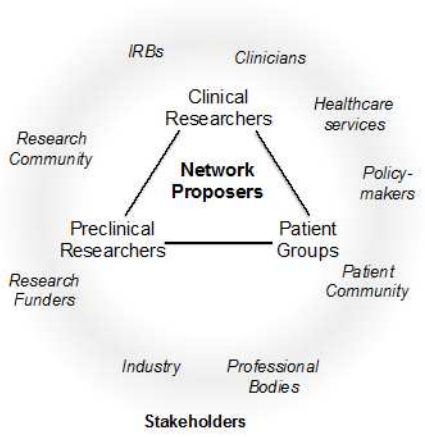


Figure 1: The **MINDDS Network**

The **MINDDS framework will facilitate the establishment of patient cohorts of a size not previously possible** by establishing a common procedure for all participating centres, compliant with Institutional Review Boards (IRBs) and national regulation.

To ensure cohort quality, the Action will develop **gold-standard assessment criteria** to ensure uniform patient selection across all sites. Based on our genetic knowledge, these will be designed to assess a range of traits, including physical health, psychiatric disorder and IQ and other neurocognitive measures, including attention, memory, social cognition and executive function. An effective means of patient registration with full consent and in accordance with an ethical and legal framework will be devised and include longitudinal follow-up and obtaining of biological samples, including for genotyping, gene expression and iPSC generation. This will include protocols for continued communication with patients and making research findings available to participants.

MINDDs will review current methodologies and derive **standardised clinical phenotyping protocols**. Based on current genetic knowledge, assessments will focus on objective measures such as neurocognitive testing, motor function, and brain imaging. MINDDS will also **review new and emerging and cell-based technologies** and develop standardised protocols for cell re-reprogramming and neuro-differentiation, including criteria for quality control. Similar consideration will be undertaken for cell and patient phenotyping based genomic applications. MINDDS will ensure that its standard protocols **maximise the integration with other research strategie**s, such as animal and cell-base experiments. In addition, it will reverse this process to create recommended experimental guidelines to maximise the compatibility of preclinical models for understanding patient biology. Further, MINDDS will establish a standing review process to validate and integrate clinical phenotypic data.

MINDDS will establish **methodologies for data integration and sharing** via three prototype health and research informatics projects: 1) the development of a **specific NDD registry**; 2) the design of a **research database** and; 3) the establishment of a **web-based knowledge exchange "nexus"**. To avoid variation due regional differences, such as language, culture and local healthcare provision, common data elements will be established to ensure inter-operability and harmonisation of phenotype data. Infrastructural requirements, such as data storage capacity, security and procedures for data sharing compliant with ethical and regulatory requirements will be taken into consideration, and recommendations made for the benefit of future projects.

D) ADDED VALUE OF NETWORKING

I) IN RELATION TO THE CHALLENGE

MINDDS requires networking to achieve its three objectives:

A framework for building patient cohorts: As patients with pathogenic CNVs are rare, a European-wide research network is necessary to build an effective cohort size and allow wide coverage; this requires cooperation across all nations. A network will create a research framework to inform, educate and train clinicians and researchers across Europe for patient identification.

Standardization of protocols and methodologies: Key researchers in each of the study regimes and activities will work together to draw up common guidelines and protocols for data collection, standardized methodologies, quality assurance and clinical practice.

Integration and Knowledge exchange: This requires wide-ranging legal agreement for common formats for data collection, access management, analysis and dissemination that

are accessible to researchers, health professionals and patient groups. As health practice and societal understanding may differ across Europe, common agreement must be made across network partners for consistent approaches and guidelines for clinical practice, policy and ethics and patient ownership, whilst respecting European geographical and population diversity.

II) IN RELATION TO EXISTING EFFORTS AT EUROPEAN AND/OR INTERNATIONAL LEVEL

MINDDS addresses a unique health research challenge, but fits within an overall European and international landscape of activity from which it will benefit, and to which, in turn, it will contribute. Overlap between MINDDS and the activities below will ensure **strong linkage and durable synergistic interactions**.
The international **Psychiatric Genetic Consortium** (**PGC**; http://www.med.unc.edu/pgc) has driven a step change in size and scope of meta-analyses and genomic analysis for NDD, but members are also pioneering activity to convert this genetic knowledge into biological understanding and therapy. MINDDS will have a close linkage with RaDiCo, the French national platform for rare diseases cohorts (www.radico.fr) that will provide the experience of transnational cohort building for rare disease and an interface, including direct participation, with five infrastructures of the **European Strategy Forum on Research Infrastructures** (ESFRI): BBMRI-ERIC (biobanks and biomedical resources), ECRIN-ERIC (multinational clinical research), ELIXIR (research data integration), Euro-BioImaging (Biomedical imaging and the cluster project CORBEL (Bridging Research Infrastructure). The Action envisage strong interaction with the FP7 project RD-Connect (http://rd-connect.eu), which aims to create an integrated platform connecting databases, registries, biobanks and clinical bioinformatics for rare disease research. Other key international projects relate to semantics and human phenome ontologies (HIBPI-RD); infrastructures for data exchange (BioMedBridges, EXCELERATE); and the Action will continue to engage with activities aligned with the RD-European Reference Networks (ERNs) priority on rare diseases [18]. With regard to the patient partnership, MINDDS will be well connected to **Eurordis** (www.eurordis.org) and **EGAN** (www.egan.eu). The latter has established patient advisory boards for numerous European projects (FP7: CONSERT, PatientPartner, GenCodys, CLOSED, GRIP, ECRIN-IA, ASTERIX. H2020: COSYN, PedCrin, IMI: Eupati, Interreg: EMRaDi). For an alterative perspective, MINDDS has input from a patient-lead social network and registry, Gen1DA (https://genida.unistra.fr). In addition, MINDDS will have a strong expertise in patient ethics (previous H2020 project overlapping advisory role in other EU funded projects, such as **IMI-EPAD** (http://ep-ad.org/) and **COSYN)**. For real time research input, including provision of data, MINDDS has good overlap with the UK-wide ImagineID study (http://imagine-id.org/), EuroStemCell and particularly COSYN [19], the first H2020 project on NDD patient cell phenotyping in the Personal Medicine Societal Challenge. Finally, MINDDS will be well placed for stakeholder engagement via collaboration with national health authorities (drug safety agencies, ministries) and the **European Medicines Agency**, and contact with a number of Innovative Medicines Initiatives (IMI), EU-AIMS, EBiSC, STEMBANCC and the previous NEWMEDS.

2) IMPACT

A) EXPECTED IMPACT

I) SHORT-TERM AND LONG-TERM SCIENTIFIC, TECHNOLOGICAL, AND/OR SOCIOECONOMIC IMPACTS

Mental health is a major societal challenge, as recognized by the European Pact for Mental Health and Well-being (2008) [20]. Addressing this need reduces the negative health, economic and societal impact, and can contribute to economic growth through commercialization of new drugs, diagnostics and intervention strategies. With a focus on NDD,

MINDDS will deliver short and long-term impacts that address a number of immediate and future objectives identified in Table 2.

Table 2 Short and long-term impacts

Objective	Short-term Impact	Long term Impact
1. Patient Cohorts		
Framework for cohort building	Regulatory, legal and ethical framework for cohort building, acceptable to IRBs, facilitating rapid implementation of studies.	Establish best practise for the benefit of future cohort projects.
Consent for re-contacting	Facilitates longitudinal follow-up and biological sampling, including iPSC.	Availability of closely linked life course data and biological samples.
Gold standard clinical assessments	Standardisation of patient assessment based on our new genetic insights. Improved understanding of population profiles of NDD patients with pathogenic CNV.	Facilitate personalized medicine strategies for the NDD. Improved patient characterisation and stratification beyond DSM – based classifications.
Ethical and societal impacts	Establish a responsible basis for NDD research based on patient and societal needs.	Provide evidence-based guide lines for future policy making.
Training of clinical research teams	Build leadership and skills for patient recruitment, assessment and sample collection. Increase social, geographical and cultural diversity of patient recruitment activity.	A new generation of European clinical researchers with embedded knowledge and skills. Expand research base to ensure research outputs reflect diversity within Europe.
2. Standardisation		
Clinical Phenotyping	Establish clinical guidelines and SOPs for clinical researchers.	Best practice for future clinical assessments, improving future patient care and clinical trials.
Compatibility with other research strategies	Maximise value of research outputs by ensuring capacity for cross comparison with other research approaches, e.g. animal and cellular studies.	Validation of model systems and clinical phenotyping for future mechanistic studies, diagnostics and drug discovery programmes.
New and emerging technologies	Agreement on best use and procedures for new and emerging technologies, particularly use of patient iPSC.	Improvements to cell-based testing for drug development. A route to cell-based diagnostic tests for precision medicine.
Ethics	Establish an ethics framework for the use of new technologies in patient research.	Guidelines for new technologies for future diagnostics.
3. Integration		

NDD patient registry	Larger samples of NDD patients to allow better study of the effects of pathogenic CNV.	Understanding of patient population structure and diversity, informing patient stratification for personalised medicine.
Design of a research database	Framework for improved interaction between researchers and patients, facilitating engagement in future research.	Model for improved capacity for health informatics projects and research programmes.
Knowledge exchange	Disseminating of new knowledge from patient studies to key stakeholders, particularly researchers, clinical practice and policy, and patients.	Evidence-based knowledge for all stakeholders informing future translational research and policy decisions. Greater understanding of NDD for patients and society.

B) MEASURES TO MAXIMISE IMPACT

I) PLAN FOR INVOLVING THE MOST RELEVANT STAKEHOLDERS

MINDDS will primarily form a partnership between researchers (preclinical and clinical) and patient organisations, however the network will also benefit from the input of key stakeholders (see Table 3). Furthermore, representative stakeholders are also included amongst the secondary proposers of this application.

II) DISSEMINATION AND/OR EXPLOITATION PLAN

Conference and conference-based workshops: MINDDS will hold specific "kick-off" and "closing" research conferences to bring network participants and stakeholders together to finalize objectives and outputs. These will be an important mechanism to identify all actions and priorities; recruit expertise to the network; support the integration outputs and engage stakeholders. In addition, MINDDS will support themed workshops within related conferences (target of 1 per year). Possible conferences will include ones organised by the International Society for Stem Cell Research (ISSCR); and the Psychiatric Genome Consortium and Neurosciences Societies (SfN, FENS).

Short-Term Scientific Missions (STSMs): Creation of standardised protocols and methodologies will be augmented by short scientific visits between sites to share and record best practise.

Training Schools: A major objective is training of clinicians and clinical researchers in the identification and assessment of patients for cohort building. This will primarily be undertaken via Training Schools, held regularly and in different geographical locations for maximum coverage.

Internal Work Group Meetings: Each work group will meet physically and virtually for strategic planning, to produce guidelines and standardised protocols. Outcomes will include position papers, protocols and wherever possible dissemination via academic and professional publications.

Web-based database and information exchange tool – a "knowledge nexus": The Action will design web-based communication tools with the following functions: 1) secure patient registry; 2) secure research database; 3) online training courses for clinical research teams; 4) repository of standardised protocols and guidelines; 5) public facing web sites, with tailored content to specifically target; healthcare professionals and policymakers; the patient community.

Position papers, published guidelines and policy papers, newsletters, research publications: Members of the Working Groups (WGs) will publish the conclusions of their Tasks in appropriate format to disseminate their outputs and retain a legacy beyond the lifetime of the initial network.

Table 3: Stakeholder Dissemination Plan

Stakeholders	Examples		Dissemination Channel	Desired outcome
	National	EU/international		
Research Community	Universities and research institutes.	H2020 projects (COSYN), IMIs, PGC.	Conferences, workshops, training schools, publications, STSMs.	Research collaboration, data sharing, better resource usage.
Patient Community	VSOP (NL), Genetic Alliance (UK), Mind(UK), Unique, Genetic Rare Disorders Organisation (IRL)	EGAN, Eurordis.	Online resources, patient newsletters, conferences and workshops.	Patient empowerment, improved ethics & guidelines.
Clinicians, Health Service & Policy makers	NHS (UK), HSE Ireland	European Medicines Agency (EMA).	Position papers, training school.	Better patient assessments and diagnosis.
Institutional review boards	Local institutions.	Idem.	Position papers, Guidelines for best practice, conferences and workshops.	Guidelines uniformity, best practice and streamlining of reviews.
Industry	SMEs (Cambridge Cognition (UK), LIFE & BRAIN GmbH (D)	Multinational pharmaceutical companies (AZ, GSK, Merck).	Conferences and workshops; publications.	Identification of drug targets, assays and screening platforms.
Research Funders	MRC (UK), DFG (D), INSERN (F), Science Foundation Ireland	EU (H2020, ERC).	Conferences and workshops.	Identification of research priorities.
Professional bodies	BMA (UK), Royal College of Psychiatrists, Irish College of Psychiatrists	European Psychiatric Association(EPA).	Conferences, workshops, training schools; newsletters and position papers.	Knowledge exchange, improvements in best practice.

C) POTENTIAL FOR INNOVATION VERSUS RISK LEVEL

I) POTENTIAL FOR SCIENTIFIC, TECHNOLOGICAL AND/OR SOCIOECONOMIC INNOVATION BREAKTHROUGHS

MINDDS addresses the specific challenges of building a large patient cohort for rare pathogenic CNV groups of NDD patients. A database with information on large numbers of these rare patents will constitute an extremely valuable and unique resource and spearhead future NDD research. MINDDS will deliver this by creating an enhanced framework for patient recruitment, assessment and engagement; as well as developing standardized protocols, improving data quality and unique resources for data sharing and knowledge exchange. Table 4 summaries risks and mitigation.

Table 4: Risks & Mitigation

Identified Risks	Level	Potential Impact	Possible Mitigation
Failure to agree a universal framework	Medium	A single framework may be impractical due to national ethics, regulations and legal requirements.	Create flexibility, insertion of national appendices to adapt framework for local conditions. Work via local representatives to gain acceptance in IRB.
Low rates of patient consent for re-contacting	Low	Limited utility of patient registry.	Work with local clinics and patient groups for good patient engagement.
Failure to train sufficient clinical research teams	Medium	Poor geographical coverage/numbers in cohorts.	Work directly with national biomedical contacts to engage with local research teams.
Patient registry & research database integrity	Medium	Data quality or security issues.	Ensure independent review, scrutiny and auditing by database/e-health experts.
Public fear and stigma	Low	Poor representation of patients from some countries or cultures.	Public engagement to increase understanding of NDD and value of research.
Poor engagement with industrial and health policy Stakeholders.	Low	Failure to achieve full impact from network outputs.	Undertake a "needs analysis" and report outputs in a form appropriate to stakeholder needs.

3) IMPLEMENTATION

A) DESCRIPTION OF THE WORK PLAN

I) DESCRIPTION OF WORKING GROUPS

MINDDS will support 4 overlapping interdisciplinary Work Groups feeding into the three objectives of a framework for patient cohort building (WG1), standardisation of methodologies (WG2/ 3) and data integration and knowledge exchange (WG4). WG5 coordinates the network and outputs.

WG1. Framework for cohort building. This will establish a framework for the building of trans-European patient cohorts for each pathogenic CNV based NDD, incorporating regulatory, legal, ethical and patient governance, and patient selection criteria.

Tasks 1: Framework for NDD patient cohort building: This will consider clinical, regulatory, legal and ethical requirements for NDD patient cohort building to create a framework for use in current and future projects. It will have a strong input from patient representatives, and initial mapping of ethical and legal issues relating to patient recruitment, sampling, re-visits and

sharing of data and biological samples, including cell banking for iPSC production. This task will work closely with Task 2. **Deliverable:** A single framework for new cohort building and patient recruitment across Europe.

T**ask 2: Standard Clinical assessment criteria:** This will apply our current knowledge, derived mainly from the new genetic insights, to generate gold standard clinical assessment criteria for patient selection. It will include estimation of required cohort sizes (statistical power), decisions of which patient data to collect and patient inclusion rules. **Deliverable:** Standard assessment criteria for patient selection for NDD patients with pathogenic CNV.

Task 3: Mapping ethical and societal issues associated with MINDDS: To outline and address ethical and societal issues associated with the MINDDS project and its key objectives, including pre-recruitment, mechanisms for privacy protection, informed consent, the return of individual research results and incidental findings, the impact of genetic diagnosis on patients, and the benefits, risks and implications of participation in MINDDS. **Deliverable:** report/scientific paper on ethical and societal issues in MINDDS plus a patient information leaflet based of this paper.

Task 4: Training research teams: Training for clinical researchers in new assessment criteria for patient recruitment, including appropriate patient and ethical considerations. This WG will select training course content, and ensure numbers recruited and geographical distribution will reflect good European coverage. National leads will play a crucial role in delivering Task 4, supported by an online learning resource (WG4, task3). **Deliverable**: A cadre of trained European research team leaders with a pan-European geographical distribution.

WG2: Standardisation of clinical phenotyping protocols: To maximize the utility of patient research data, the Action will promote standardization of protocols and research outputs, for clinical testing and brain imaging. These protocols will be designed so that data collected in different geographical locations, gender and age groups, and research projects produces compatible outputs for further data integration.

Task 1: Define standards and quality control for patient studies: This will select appropriate modes of clinical phenotying, such as cognitive testing and brain imaging, and define key research objectives, data collection methods and formats, quality control and assessment, and best practice. **Deliverables:** Generate SOPs, guidelines, and content for training schools.

Task 2: Review of CNV patient data: A standing expert review will examine how data from pathogenic CNV patients compares to patients in the general population without pathogenic CNVs. This will ensure good concordance with the network's high-level objective of using pathogenic CNV data as the basis for understanding the general NDD. **Deliverable:** Validation of assessment criteria and guidelines.

Task 3: Cross-compatibility between human and animal systems: Review clinical and imaging data in comparison to data generated using cell and animal model systems. This will advise on how best to seek convergence between these different models. Establishing equivalent assays for both patient and model systems will better inform design of preclinical testing in basic research and drug discovery (linked with WG3, task 2). **Deliverable:** Guidelines, publications and workshop sessions to ensure maximum data convergence with other experimental systems.

WG3: New and emerging technologies. New technologies, such the use of patient derived stem cells and direct cell reprogramming, offer huge potential. As these currently still mostly reside in the preclinical research arena and need careful translation to the clinical context, they require their own WG. This WG will consider how best to translate to the clinical level and how new technologies can retain back-translatability.

Task 1: Standardize protocols for iPSC reprogramming and neuronal differentiation. This is one of the most developed new technologies and forms a discrete Task to review options and establish a standard set of protocols for cell collection, iPSC reprogramming and cell differentiation. In addition, establishing standardized protocols for storage of differentiated neurons and their distribution would greatly aid transnational research. **Deliverable:** Generate guidelines and publication for standard operating procedures (SOPs).

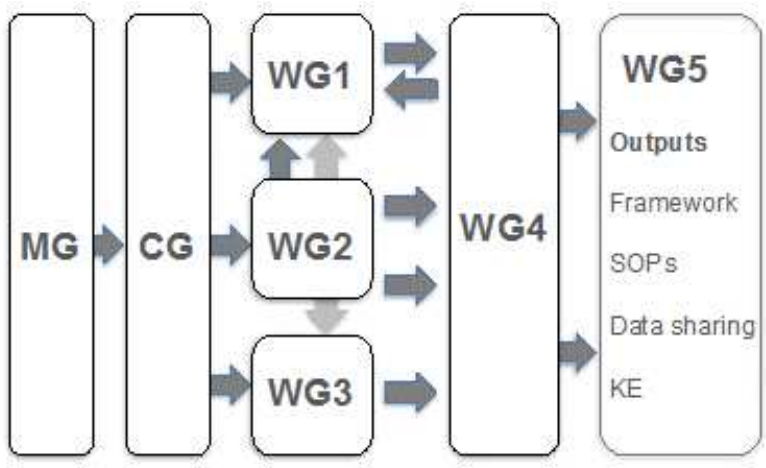
Task 2: Cell based assays: Review options, and establish agreement on common cell assays aimed to standardize and assess patient cell phenotyping between sites (linked with WG2, task3). **Deliverable:** Guidelines and publication for SOPs.
Task 3: Review alternative technologies: Advances in technology, such as direct cell reprograming, genomic sequencing and informatics, which may offer alternatives to the deep phenotyping strategies currently under development. The Action will conduct a standing review to assess their future potential for NDD patient research. **Deliverable:** Publication of position papers, and if appropriate, guidelines.
Task 4: Explore ethical issues surrounding iPSC and emerging technologies: The mapping of ethical issues associated with the introduction of new technologies, especially patient-derived stem cells, in research and preclinical pharmacology, and the establishment of ethics guidance their use. **Deliverable:** Position paper on ethics guidelines for research.
WG4: Data sharing and knowledge exchange. A key output of MINDDS is the integration of patient data into common databases, capability to share data and dissemination of information to stakeholders.
Task 1: Patient registry: Establish methodologies for patient registration, considering different models from clinical based to patient self-registration. Mechanisms for integration between multiple sites and with existing cohort data, and future inter-operability will be investigated. **Deliverable:** Guidelines for a specific registry and a prototype database.
Task 2: Design of a Research Database: This will define the specifications of a research database, including control semantics and ontologies for multiple site inputs, access, confidentiality and data outputs. The database design will be prototyped using existing cohort data. **Deliverables:** Guidelines and SOPs for data collection and access; prototype database.
Task 3: Knowledge Exchange: Major outputs (SOPs, guidelines, data resources, etc) will be made available via online resources, the "knowledge nexus". This will comprise of 3 domains written and populated appropriately for the following stakeholders: patients; clinicians and policymakers; and researchers (preclinical, clinical and industrial). The clinical domain will support online learning resources (WG1 task3). **Deliverable**: Web-based knowledge dissemination.
WG5: Delivery, Networking and Public awareness. Lead by a Core Group (CG), this is an internally focussed WG to support network infrastructure and delivery.
Task 1: Coordination: Liaison with Management Committee (MC) and coordination of activities. **Deliverable:** intermediate and final reports.
Task 2: Supporting knowledge exchange: Initial entry and updating of data and online content. **Deliverable:** Curation of the Knowledge Nexus and research databases.
Task 3: Network coordination: Ensuring coordination within and between WGs and network participants. **Deliverables:** Facilitation of virtual and face-to-face work grouping, training schools and international conferences.

II) GANTT DIAGRAM

Year:	Year1				Year2				Year3				Year4			
Quarter:	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
MC meetings	M		M		M		M		M		M		M		M	M
CG Meetings	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Research Conference		C													C	
WG1		G		T		W		T		W		T		W		T
WG2				G				G				G				G
WG3		V				S				G				G		
WG4: Databases				Design						Build				Pilot		
WG4: KE		WEB								Build content						
WG5:						Report								Report		

M: Meeting C:Conference G: Publish Guidelines T: Training Course
W: Workshop V=STSM

III) PERT CHART



IV) RISK AND CONTINGENCY PLANS

Risk	WG	Contingency
To Network:		
Smaller network membership than expected	**All**	Run an active recruitment (WG5) with set target numbers for gender, geographical coverage and ECI. The "kick off" research conference offers a good opportunity early in the network to attract members.
Turnover of network members	**All**	Targeted recruitment of network members with key backgrounds to ensure depth of knowledge within the network.
Poor patient engagement	**WG1**	Encourage and support network members to conduct local public engagement activates, e.g. patient information days.
Stakeholder disinterest	**WG4, 5**	Conduct active dialogues with stakeholders.
Workloads and Task completion rates	**All**	WG5 to monitor workloads and delivery.
To Science/Technology (S&T):		
Sub-optimal coverage of patient cohorts	**WG1, 2,4**	Expand recruitment outside Europe; Consider focus on selected CNV types.
Failure to agree consensus cohort recruitment framework	**WG1**	Agree minimum workable framework for compliance and criteria; reduce geographical coverage to achieve compliance.
Failure to agree consensus for standard protocols	**WG2, 3**	Agree minimum criteria for recruitment to patient registry, with options for recording extra data.
Overtaken by new technologies	**WG3**	Use additional STSM to gain experience with new methodologies prior to assessment incorporation.
Lack of compatibility with other research strategies	**WG2**	Adjust parameters of assessment and studies if necessary to allow cross-comparisons.
Data compliance & scrutiny	**WG4**	Establish an independent data quality and security review board to audit and scrutinise databases.
Knowledge exchange database	**WG4**	Use and review ethics to consider impact of public release of data and /or advice.

B) MANAGEMENT STRUCTURES AND PROCEDURES

MINDDS will be coordinated by a Management Committee (MC) formed in accordance with the COST action “Rules for Participation and Implementation of COST Activities”, which will meet in person once a year, coinciding with the MINDDS annual conference, and virtually every 6 months. At the 1st MC meeting, the MC will appoint a Chair, Vice Chair, leaders of the five Working Groups (WGs), a Training Co-ordinator (responsible for co-ordinating the Training Schools and STSMs), an early-stage researcher representative and an equality and diversity officer. The MC will be responsible for setting and monitoring the Action strategy; strategic decisions, the establishment and over-arching management of the 4 WGs (and coordinating WG5: Delivery, Networking and Public awareness), approval of the work and budget plan for Grant Periods, new countries joining the Action (when required), and preparation of the Action reports. Each annual conference (and thus MC) will be held in a different COST Action country. To facilitate the day-to-day management, a Core Group (CG) of the MC will be convened, consisting of the MC Chair, Vice Chair, WG leaders and the Training Co-ordinator. Each WG will appoint a leader (and deputy), who in collaboration with the MC will plan and coordinate tasks and delivery, and when necessary appoint Task Coordinators (TCs). WG meetings will be organised appropriate to their tasks (eg. regular teleconference and meetings in person). Early career researchers, female researchers and members from ITC countries will be encouraged to take up these positions. Each working group will submit an annual report of the progress, deliverables and impact of the WG activities ahead of the annual conference, thereby facilitating annual MC discussions and the planning of the annual work programme.

C) NETWORK AS A WHOLE

MINDDS is a multidisciplinary European network comprising three constituency groups: preclinical and clinical researchers and patient groups, and has a combined interest in NDD. The starting group of proposers has strong representation from major research centres with track records in NDD research, encompassing psychiatric genetics, psychiatry and clinical medicine; epidemiology; neuroscience, stem cell biology and brain imaging. It also includes patient group representatives, an ethicist and representatives of both SME and a large pharmaceutical company. A number of the partners have existing local, small-scale pathogenic CNV patient cohorts, data from which will be available to the network. In addition, the close relationship with a number of proposers and other H2020 projects, particularly COSYN, will provide access to unpublished data of clinical phenotype and patient iPSC-based studies. Similarly, the familiarity of some proposers with creating transnational patient cohorts, clinical database and secure methods for data sharing is of major benefit to the network. A key aim will be to expand the network to increase coverage of expertise and geography, and the Action expects to involve many Early Career Investigators (ECI).

The network will provide gender and national balance. Leadership of WGs and Task activities will be shared across senior researchers, experts in their field and ECI. Representatives from industry and interest groups in rare diseases will ensure consideration of all stakeholders. Working within the network will strengthen existing collaborations and build new ones moving forward. A particular objective is to build critical mass in this major area in need of increased research activity and clinical provision.

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