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Remote Assessment of Disease and Relapse– Central Nervous System-RADAR-CNS

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ABSTRACT

Remote Assessment of Disease and Relapse in Central Nervous System Disorders (RADAR-CNS) is a major international research project. It aims to develop new ways of measuring major depressive disorder, epilepsy and multiple sclerosis (MS) using wearable devices and smartphone technology. RADAR-CNS aims to improve people's quality of life and change how depression, epilepsy and MS are managed and treated. Data from mobile devices can give a full picture of a person's condition at a level of detail which was previously impossible. This offers the potential to detect changes in behavior, sleep, or mood before the individual themselves is aware of it. This could help them to predict or even avoid a relapse. To achieve this, we are creating a pipeline for developing, testing and implementing remote measurement technologies for depression, multiple sclerosis (MS) and epilepsy. Depression, multiple sclerosis and epilepsy are all disorders of the central nervous system. While the symptoms and disability experienced by individuals with each condition are different, they all have a significant effect on people's wellbeing. For doctors and people with these long-term or chronic conditions, understanding how their disease changes over time can help with its management. But in chronic conditions most of the symptoms and episodes happen outside of the health care environment. Measuring individuals' symptoms, mood and daily function continuously, could help people gain better insight into their condition. RADAR-CNS receives funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 115902. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation program and EFPIA.

Keywords: Central Nervous System Disorders, Depression, Multiple sclerosis and epilepsy

1 Introduction

Remote Assessment of Disease and Relapse in Central Nervous System Disorders (RADAR-CNS) is a major international research project. It aims to develop new ways of measuring major depressive disorder, epilepsy and multiple sclerosis (MS) using wearable devices and smartphone technology.

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or mood before the individual themselves is aware of it. This could help them to predict – or even avoid – a relapse.

RADAR-CNS brings together clinicians, researchers, engineers, computer scientists and bioinformaticians from all over the world. It is jointly led by King's College London and Janssen Pharmaceutical NV. The project is funded by the Innovative Medicines Initiative a Public Private Partnership set up between the European Federation of Pharmaceutical Industries and Associations (EFPIA) and the European Union. It includes 23 organizations from across Europe and the US.

2 Strategy

RADAR-CNS aims to transform patient care through remote assessment using wearable technologies such as smartphones or fitness trackers. The project will develop the technology to identify which clinical or physiological biosignatures can be measured remotely to predict relapse or deterioration.

To achieve this, we are creating a pipeline for developing, testing and implementing remote measurement technologies for depression, multiple sclerosis and epilepsy. Patients will be involved at each stage of development. It will include a generic data management and modelling infrastructure applicable to other mental and physical disorders. It will be designed with the flexibility to be sustainable alongside future technological developments.

We will anticipate and solve any potential problems with using these technologies by consulting patients, clinicians, regulators and healthcare providers throughout the project.

We bring together an international consortium of academic and EFPIA members who are leaders in the fields of depression, multiple sclerosis and epilepsy. We also deliver clinical expertise and access to patient cohorts in each disease area. This is combined with leading technical and methodological expertise in the disciplines required to develop and implement remote measurement technologies.

3 Conditions

Depression, multiple sclerosis and epilepsy are all disorders of the central nervous system. While the symptoms and disability experienced by individuals with each condition are different, they all have a significant effect on people's wellbeing. For doctors and people with these long-term or chronic conditions, understanding how their disease changes over time can help with its management. But in chronic conditions most of the symptoms and episodes happen outside of the health care environment. Measuring individuals' symptoms, mood and daily function continuously, could help people gain better insight into their condition.

3.1 Major Depressive Disorder

Major depressive disorder, sometimes called "clinical depression" or "depression", can be triggered by a life event, or result from stress, or happen without a specific cause. It is the most severe form of depression where people exhibit a sense of hopelessness and despair along with low mood and negative thoughts. This can affect the way people eat, sleep, feel about themselves, and think about things. Without treatment, the symptoms can last for weeks, months, or even years.

People with depression can lose interest in activities they once enjoyed, withdraw socially, and have trouble concentrating or making decisions, and may experience changes in eating and sleeping patterns.

Physical symptoms of depression can include fatigue, weight change, a feeling of being slowed down, headaches, digestive disorders, or chronic pain.

At its worst, people with depression can feel like they want to harm themselves, and experience or act on thoughts of suicide. There are several different types of depression, and RADAR-CNS focuses on Major Depressive Disorder, which affects approximately 7% of adults in Europe. Depression is thought to affect over 30 million people in the European Union [1].

3.2 Multiple Sclerosis

Multiple sclerosis is a condition in which the body's immune system has an abnormal reaction to the central nervous system (CNS, made up of the brain, spinal cord and optic nerves). The immune system attacks elements of the CNS, disrupting the transmission of nerve signals and producing the symptoms that characterize MS. The exact cause is unknown, but is thought to be triggered by a combination of environmental and genetic factors.

MS can be mild, moderate or severe, and can show different patterns of symptoms over time. Most people (85%) with the disease have the relapsing remitting form, which involves clearly defined attacks of neurological symptoms followed by periods of partial or complete recovery. Some people experience progressive MS where symptoms and disability worsen over time. For many people with MS, as time goes on their symptoms do not resolve completely, resulting in gradually worsening illness and disability.

Treatments for MS involve disease modifying drugs which slow the progression of the disease and reduce the frequency of the attacks. There is no cure for MS and the challenge lies in managing the disease as best possible to continue to live a normal life. MS affects around 700000 people in Europe.[2], [3]

3.3 Epilepsy

Epilepsy is one of the most common serious neurological conditions in the world, affecting around 6 million people in Europe. Epilepsy affects the brain, causing seizures. A seizure is caused by a sudden burst of intense electrical activity in the brain, temporarily disrupting its normal function.There are many different seizure types. In some seizures the person remains alert, but experiences altered sensations and perceptions. In others they lose consciousness, and their muscles may stiffen and jerk.

Epilepsy is usually diagnosed after someone has more than one seizure, and there is considered to be a high probability that they will have further seizures. Some types of epilepsy last for a limited time and the person eventually stops having seizures, but for most people, epilepsy is a life-long condition.

Epilepsy has no cure, but taking anti-epileptic drugs (AEDs) helps people to prevent or reduce the frequency of seizures. AEDs do not work for everyone, so other treatments may include brain surgery, vagus nerve stimulation or a special diet.[4], [5]

4 Governance & Funding

The Figure. 1 shows the overall organizational structure of RADAR-CNS, and the bodies responsible for specific aspects of project management.

To ensure that the views of people with conditions are incorporated into RADAR-CNS we have set up a Patient Advisory Board that includes people with depression, epilepsy and multiple sclerosis along with representatives from relevant support organizations. Their role is to provide feedback on the layout and

content of research materials and provide expert opinions on important decisions to be made in the design of studies.

RADAR-CNSis a large and complex project, involving collaborators from diverse disciplines and 23 partner organizations from across Europe and the US. To ensure the project is conducted efficiently and thoroughly, the project's research program is arranged into 11 work packages. Work packages are arranged into three clusters – Clinical Disorders, Translational Pathways, and Technical Platforms – with the Central Management cluster providing support for the project as a whole. Membership between work packages is strongly overlapping, and many centers and investigators contribute to multiple work packages.

4.1 Central Management

This cluster provides project management, data management and communications support for the RADAR-CNS project as a whole.

Project Management (Work Package 1)

Provides overall management of the project, ensures that its contractual duties are carried out, and establishes and maintains effective communication within the project.

Dissemination, Exploitation and Communication (Work Package 11)Deals with the dissemination, communication and exploitation of the results generated in RADAR-CNS. This includes raising public and scientific awareness of the project and managing processes for the capture and protection of intellectual property.

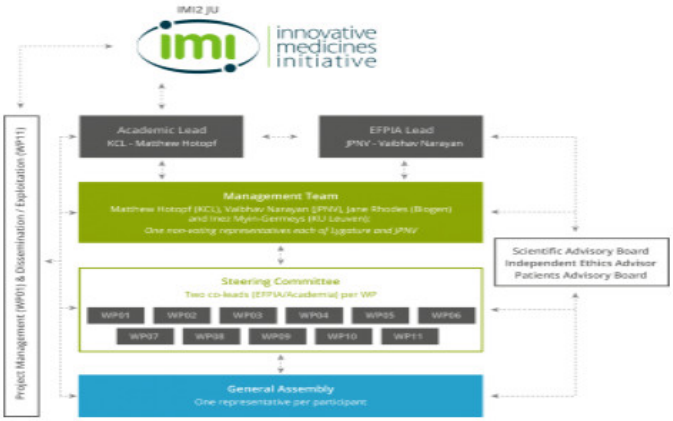

Figure 1overall organizational structure of RADAR-CNS, and the bodies responsible for specific aspects of project management.[7]

4.2 Clinical Disorders

This cluster brings together clinical expertise across RADAR-CNS relating to our three focus conditions: depression, epilepsy and multiple sclerosis. This cluster focuses on evaluating the feasibility, adherence and personal satisfaction with remote measurement technologies in people with different conditions. It also addresses the clinical harmonization required to assess sleep, physical activity, speech, mood, and cognition in everyday life across clinical disorders.

4.2.1 Major Depressive Disorder (Work Package 6)

At the heart of this work package is a multicenter observational cohort study following patients with recurrent depressive disorder. Participants will use remote measurement technologies whilst being followed for clinical outcomes (particularly, though not exclusively, recurrence and relapse) over the course of 12 months. This study will be complemented by learning from the ORBIT [6]and, although not identical in design, the two studies will be sufficiently close to allow us to test whether findings from one generalize to the other. The project lead of the Orbit study is a participant of this work package and will provide the full support and experience required.

4.2.2 Epilepsy (Work Package 4)

We are initiating a set of studies into remote measurement technologies across a range of parameters. We aim to determine the feasibility, acceptability of, and adherence to, remote measurement technologies in people with epilepsy to provide real-time objective, multidimensional indications of seizure occurrence and clinical state in epilepsy. We are also exploring whether the trajectory of non-seizure-related aspects (e.g. stress, mood) associate with, and predict/anticipate, changes in the trajectory of frequency of seizure occurrence.

4.2.3 Multiple Sclerosis (Work Package 5)

Exploring whether remote measurement technologies can be used to characterize two important features of clinical presentation, depression and gait disturbance in people with multiple sclerosis. We are determining whether remote measurement technologies can detect mood changes in MS patients in the early stages of their condition, and exploring whether they can reliably assess the clinical disability of MS patients. We are also investigating these technologies' sensitivity in detecting state changes and disability progression over time, evaluating the interaction among fatigue, depression and sleep disorder and sensory-motor dysfunction, including gait.

4.2.4 Clinical Harmonisation (Work Package 3)

Providing an overarching assessment and analysis scheme to assess sleep, physical activity, speech, mood, and cognition in everyday life across clinical disorders. We are focusing on variability in sleep quality, levels of activity, social interactions, mood, cognitive performance and stress as possible predictors of clinical course. We are also examining how remote measurement technologies can monitor and improve quality of life and psychological well-being for people with depression, epilepsy, or multiple sclerosis.

4.3 Technical Platforms

This cluster provides the technical and computing knowledge required to bring the RADAR-CNS project to clinics. As well as producing a flexible, reusable platform that can be used across numerous conditions and scenarios, the cluster also provides the data analysis expertise required to understand the data collected and how they relate to clinical outcomes.

4.3.1 Devices and Platform (Work Package 7)

Building an end-to-end system to support passive and active remote measurement and feedback using mobile and web technologies. We expect emerging monitoring technologies to continue to evolve rapidly at unpredictable rates. As such, the generic architecture of the RADAR platform is intended to assist incorporation of new technologies in the short term for RADAR-CNS, but will also form a reusable, flexible

architecture that can power future RADAR projects (e.g. RADAR-DIABETES). A technology steering committee will ensure the close working between the clinical, patient engagement and technology Work Packages.

4.3.2 Data Analysis & Biosignatures (Work Package 8)

Enabling data collected as part of the project to be analyzed. We aim to understand the association between these data and the remission, relapse, and recurrence of the conditions being studied, and to classify and predict the disease status. Requires the creation and refinement of algorithms for data extraction and filtering; analysis of the collected data to create models of diseases and its fluctuations; and finally the generation of data to enable patient and clinician engagement tools.

4.4 Translational Pathways

This cluster ensures that findings from the RADAR-CNS Clinical Disorders and Technical Platforms clusters are translated efficiently and effectively into real-world clinical applications. We aim to have workable clinical devices entering health services by 2020. To achieve this, we need to understand and learn from the needs of patients, clinical services and regulators.

4.4.1 Patient Involvement (Work Package 2)

Works with patient stakeholders to understand issues such as privacy, usability, and acceptability of remote measurement technologies. Also works to identify clinical endpoints which are most relevant to patients, and identify facilitators and challenges for engagement and adherence that can be further tested in this project.

4.4.2 Clinical Pathways (Work Package 9)

Identifies the requirements of clinical stakeholders (healthcare professionals, managers, commissioners and payers) for integrating remote measurement technologies into care pathways for depression, epilepsy, and multiple sclerosis in different European healthcare systems. Provides a structure so that these requirements form a coherent contribution to the project system specification to ensure its maximum applicability, acceptability and adoption in healthcare systems.

4.4.3 Regulation (Work Package 10)

Works with EU medical device and product regulators to understand their requirements in this field. Provides a structure to ensure that the regulatory learning during the project is collected and integrated to ensure its maximum applicability, acceptability and adoption. This work package will provide a framework for the classification of remote measurement technologies as medical devices or otherwise, and will also identify what kind of information is needed for regulatory approval.

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