INTRODUCTION TO THE REMOTE ASSESSMENT OF DISEASE AND RELAPSE (RADAR) PROGRAMME

All information regarding future IMI Call topics is indicative and subject to change. Final information about future IMI Calls will be communicated after approval by the IMI Governing Board.

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Programme background and problem statement

With rising health-care costs, all health care stake-holders (payers, physicians, patients) are shifting the onus from a 'pay for intervention' to a 'pay for performance' model. This change in focus towards overall outcomes will drive a paradigm shift towards disease interception, i.e. move from a 'diagnose and treat' to a 'predict and pre-empt' approach. In this model, pre-emption, i.e. intervening early enough in the disease process to prevent serious effects of the disease associated with progression, becomes a critical component of managing chronic disease. Additionally, as the trajectory of chronic diseases is often cyclical, this offers multiple interception opportunities to prevent serious decline — for example, predicting and pre-empting recurrence/suicidality in severe depression, hypoglycaemic event in diabetes, or exacerbations in multiple sclerosis (MS), Chronic Obstructive Pulmonary Disease (COPD) or asthma.

Measuring physiological and activity-based parameters remotely and continuously via unobtrusive on-body sensors or smartphones has the potential to revolutionise our ability to predict and pre-empt harmful changes in disease trajectory. Developing methods for real-time identification of behavioural and physiological patterns (bio-signatures) that culminate in relapse is of great importance: early detection and communication of "red flags" to both patients, care-givers and providers can prompt help-seeking behaviour and deployment of just-in-time interventions that may prevent relapse episodes, effectively altering one's clinical trajectory.

A platform to acquire data in a real world setting would also enable the development of measures of real world effectiveness of medicines.

RADAR is a multi-topic programme in IMI2 that aims to overcome three key bottlenecks in developing such methods: 1) a lack of fundamental disease understanding into the signals and fluctuations in disease state and 2) the lack of clear policy, guidelines and pathways to develop and license "pre-emptive" therapeutic strategies that use such digital monitoring and remote assessment technology. 3) the maturity of the technology platforms including sensors technology, data exchange standards and the analytical methodology that mean that research is hampered by ad-hoc solutions that are not suitable to develop healthcare product.

Need and opportunity for public-private collaborative research

The RADAR programme aims to test if new pre-emptive therapeutic strategies based on remote continuous monitoring are both scientifically feasible and also practically feasible as part of a wider healthcare system.

Scientific feasibility will be performed via the individual topics of the RADAR programme to focus on the specifics of different disease areas. The first topic, published as part of IMI2 Call 3, will study the fluctuation of the chronic diseases of depression, MS and epilepsy using remote monitoring technology to provide a foundation for developing a novel paradigm based on prediction and pre-emption. The current topic launched as part of IMI2 Call 9 will study the development and validation of technology enabled, quantitative and sensitive measures of functional decline in people with early stage Alzheimer's disease.

In the future, we intend to add other diseases to the CNS topic, such as pain and schizophrenia, and also add further topics in other disease areas such as airways disease and diabetes. Research in these areas needs to bring together physicians, patient groups, sensor manufactures, ICT providers, data management and analyst specialists with the pharmaceutical industry.

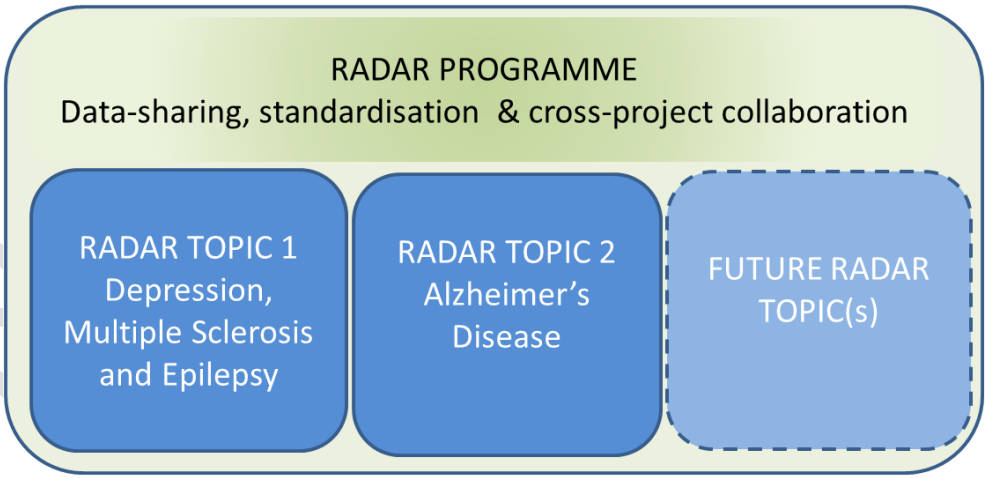
Introducing a therapeutic strategy based on such science and technology requires a second type of public private research to be undertaken to 1) develop policy for the regulatory and licensing pathways to deliver a digital intervention 2) understand and develop a framework to support new digital based interactions between patients and health care providers. This will require key stakeholders such as patient groups, regulators, healthcare providers, communications organisations, device manufactures and infrastructure providers to understand and develop a roadmap of how such interventions can be deployed effectively and safely.

Overall objectives of the RADAR Programme

The key objective of the RADAR programme is to develop the foundational components to "Improve patient outcomes through remote assessment". These components will be split into several topics with some cross-cutting themes co-ordinated across all topics. Considering the overall objective of the RADAR programme, the actions stemming from the different topics will be deemed to be complementary to each other. Consequently, the selected consortia will have to conclude collaboration agreements to coordinate their work under the different Grant Agreements.

RADAR Programme Architecture

The full RADAR programme will consist of several topics that are resourced and managed independently but will collaborate in key areas such as technological approach and data sharing. Applicants must reserve some resources to facilitate this cross-project collaboration. The RADAR-CNS topic covering depression, MS and epilepsy was launched under IMI2 Call 3. Under IMI2 Call 9, one additional topic will be launched in Alzheimer's Disease.



Future RADAR Topics

At a later stage, the IMI2 JU may publish additional topics which will become part of the RADAR programme. In that respect, potential applicants must be aware that all or some of these additional topics, if so foreseen in

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the applicable annual work plan, may be restricted to those projects already selected under this call in order to enhance their results and achievements by extending their duration and funding. Consortia will be entitled to open to other beneficiaries as they see fit to fill critical skills gaps in the consortia that reflected the extensions in these work plans.

General Principles for all Projects Conducted under the RADAR Programme

Data Sharing

Data sharing is paramount to the success of the RADAR programme. The framework supporting this data sharing (i.e., the type of data to be shared and the access governing data sharing) will be fully established during the preparation of the full proposals in line with IMI2 IP policy and considering the overall approach agreed upon in the other RADAR projects. EFPIA members and consortia partners will be committed to sharing all data (clinical, bio-sensor etc.) available to, or generated by the RADAR program amongst all members of a RADAR topic, and across topics as required. In addition to data, RADAR constituents will also share code, technology, learning and expertise developed in IT architecture, data management, usability, regulatory and policy pathways etc. across the RADAR program and externally as required by IMI policy and procedures. It is expected that any system built within the RADAR programme adheres to well accepted data standards, where applicable, to ensure compatibility with other systems both within the RADAR programme and more widely.

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Topic: Development and validation of technology enabled, quantitative and sensitive measures of functional decline in people with early stage Alzheimer's Disease (RADAR-AD)

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Topic details

Action type	Research and Innovation Actions (RIA)
Submission & evaluation process	2 Stages

Specific challenges to be addressed

Alzheimer's today is the leading cause of dementia and one of the most common causes of disability and loss of independence among the elderly. The World Health Organization estimates the cost of dementia disorders in the European Union alone to be more than 160 Billion Euros per annum. This cost will continue to rise dramatically as the numbers of people with dementia in European Union are projected to nearly double every 20 years, due to Europe's aging demographic.

Early stages of Alzheimer's are associated with cognitive and memory decline, overlapping with increasing functional decline (impairments in the ability to perform daily activities of living), leading to progressive loss of independence and escalation of caregiver burden and medical costs. While much effort has gone into developing sensitive measures of cognition, today there do not exist similar measures of subtle functional changes in early AD subjects which have direct impact on disease burden.

Recent data from long-term clinical studies have begun to delineate cognitive domains and functional tasks that are most affected by AD pathology. These include cognitive domains related to episodic memory, spatial orientation, processing speed and functional read-outs such as changes in ability to perform simple financial calculations, ability to use phone/computer, gait speed, driving performance, and ability to adhere to medications, amongst others. In addition, AD and related co-morbidities also have an effect on stress, mood and sleep. Impairment of these cognitive domains, functional capabilities and mood and sleep can be captured by new technology methods such as wearables, mobile devices and home based sensor technologies.

The overall goal of RADAR AD would be to track functional decline/deficits in Alzheimer's patients using a robust, scalable technology enabled system that can be deployed in real world settings to monitor and improve real world outcomes that are relevant to patients and their care-givers.

Need and opportunity for public-private collaborative research

The ability to track and measure functional decline in AD populations to shorten clinical development and generate payer relevant evidence of real world impact of therapeutic interventions is a precompetitive need in the field of Alzheimer's drug development, and therefore well suited for a public-private consortium.

The development and validation of technology enabled functional endpoints in AD will require public-private collaboration between AD clinical sites, home based care-givers, sensor manufacturers, analytics experts and software developers. In addition, RADAR AD will also require a collaborative partnership with AD patient advocacy groups, the care-giver community and privacy and bioethics experts to ensure that the technology solutions developed in RADAR AD can be adopted in the real world.

Scope

The main goal of RADAR AD is to develop valid and meaningful smartphone, wearable and home sensor based measures that can detect early and subtle functional decline in early Alzheimer's patients.

The following activities will be within the scope of RADAR AD to achieve its goal:

1) analysis of existing longitudinal AD datasets to identify functional domains that are specific and sensitive to early stages of Alzheimer's progression and most predictive of deleterious long-term outcomes such as loss of independence and nursing home entry. We expect such functional domains to include real-world activities such as ability to perform financial calculations, utilize the phone, navigate around the house/neighbourhood, and adhere to medication schedule and other everyday tasks that require episodic memory and executive function. The RADAR AD program will identify and gain access to the appropriate longitudinal datasets that allow retrospective analysis of cognition, function and care-giver/payer relevant long-term outcomes;
2) obtain and incorporate feedback from regulators regarding potential use of technology enabled functional end-points in registration studies of drugs;
3) obtain and incorporate feedback from care-givers and payers to ensure that functional domains being measured are relevant and meaningful;
4) implement a technology enabled system to measure identified functional domains via smartphone, wearable and fixed home based sensors. These measures can be passive (e.g. ability to use phone or computer key-board, gait speed etc.), or active (a challenge task requiring financial calculations etc.);
5) validate the technology enabled function assessment system in a real world clinical setting. This validation study will require short-term (~ 3 months) assessment of function using the built sensor based system in cognitively normal, MCI and AD cohorts. The technology enabled functional measures will be optimized for the following:
    - ability to best differentiate different stages of the Alzheimer's disease (cognitively normal vs. MCI vs. AD). Main focus will be to identify functional measures that best separate cognitively normal from early MCI patients;
    - correlation with cognitive domains known to be effected in Alzheimer's (e.g. episodic memory);
    - correlation with known biomarkers of pathology, such as PET and CSF measures;
    - correlation with care-giver burden and health care utilization costs;
    - ease of use and adherence by users in real world clinical settings.

Expected key deliverables

1) Prioritized list of functional domains relevant to early Alzheimer's disease progression (based on analysis of existing datasets and input from experts, payers, patient and care-giver advocacy groups);
2) prioritization of pre-existing wearable/home based sensors and computerized functional tasks that would best measure the prioritized functional domains in early AD populations;

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3) implementation of the RADAR AD system to collect, transmit, store, analyse and visualize prioritized functional measures;

4) deployment of RADAR AD system in clinical cohorts (normal, MCI, AD) to gather validation data and further refinement of RADAR AD system based on the deployment;

5) finalized version of RADAR AD system ready for deployment in pragmatic clinical trials, real world evidence gathering studies and elder/dementia care facilities.

Expected impact

Development of objective and sensitive functional measures will enable potential dementia therapies to demonstrate functional impact and clinical meaningfulness of early intervention without requiring long follow-on studies thus reducing time and cost required to bring Alzheimer's disease modifying drugs to market.

An objective, scalable, technology enabled functional assessment system will also allow measurement of real world impact of disease trajectory on individual patients in home and care-giver settings and help direct scalable and customized interventions that target specific functional deficits that promote independent living thus reducing cost and care-giving burden.

Furthermore, adding AD to the RADAR CNS system will make the entire system more attractive to professionals involved in dementia care, thus helping with the dissemination and adoption of the entire RADAR platform.

To maximise impact, it is expected that the system built within the RADAR-AD project will adhere to well accepted data standards, where applicable, to ensure compatibility with other systems both within the RADAR programme and more widely. For example, many patients with Alzheimer's disease also have depression as a co-morbidity, the facility to deal with many diseases will make the entire system more attractive to professionals involved in elder care, thus helping with the dissemination and adoption of the entire RADAR platform.

We believe that RADAR AD has the potential to become a widely used tool to measure and improve quality of life in elder care homes and assisted living facilities that focus on dementia and other age related causes of functional decline.

Potential synergies with existing consortia

The RADAR-AD project is expected to actively seek synergies with existing IMI projects in the AD field such as:

- **RADAR CNS**[1]: to ensure interoperability of the device, software and analytical system developed in RADAR CNS;
- **EMIF**[2]: to explore collaborations with EMIF to obtain the datasets required to evaluate functional domains in AD patients. The RADAR AD consortium should seek to utilize the output of IMI EMIF to acquire longitudinal datasets for evaluation of functional changes in AD subjects;
- **BD4BO ROADS**[3]: RADAR AD will strive to form a collaboration with the ROADS consortium to obtain input from regulators and payers which will be important in developing valid and meaningful functional measures and can be obtained via mechanisms developed in ROADS;

[1] See the topic description in the IMI2 Call 3 topic text: http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2Call3/IMI2Call3_TopicTextWebFINAL.pdf
[2] http://www.emif.eu/

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- **EPAD**[4]: to explore the possibility of deploying the system developed in RADAR-AD in forthcoming clinical studies run by EPAD to accurately measure longitudinal changes in function and to correlate these to changes in cognitive scores, PET/CSF markers and drug treatment. This will provide the necessary validation for the RADAR-AD output to be accepted by regulators as a valid and qualified measure of function in AD patients.

Synergies with other relevant initiatives should also be explored.

Indicative duration of the project

The indicative duration of the project is 24 months.

Applicant consortium

The applicant consortium will be selected on the basis of the submitted short proposal.

The applicant consortium is expected to address all the research objectives and make key contributions on the defined deliverables in synergy with the industry consortium which will join the selected applicant consortium in preparation of the full proposal for stage 2.

This is the second topic in the RADAR programme, as such, applicants should make themselves aware of the requirements to interact with RADAR-CNS and future RADAR consortia, as described in the introduction to the RADAR programme, above.

Given the focused nature of this project is to rapidly test and validate in a cross sectional study fine grained functional assessment of early stage Alzheimer's dementia. The applicant consortium must demonstrate that:

1) they have required constituents to deliver the AD specific elements of this study. This would the ability to design the clinical validation study, recruit and consent the required Alzheimer's patient cohorts and the operational expertise to execute the clinical validation study in a well-controlled manner;
2) they have a functional and production ready technology platform for conducting research studies in dementia cohorts as most (~80%) of the funding of this should be dedicated to research and validation of the dementia related study.

The applicant consortium must also reserve sufficient budget to enable cross consortium collaboration and harmonisation with the RADAR-CNS project to ensure synergy of the technology platforms and reduce the risk of multiple overlapping investments by the IMI.

Beyond the structural elements of the consortium described above, the applicant consortium must demonstrate the following requirements:

- provide expertise and capability in running clinical studies in AD patients;
- provide smart-home technology or other biosensors that may be particularly well suited for measuring functional changes in AD patients;
- provide the IT expertise and infrastructure required to collect biosensor/wearable data from in AD clinical studies

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[3] See the topic description in the IMI2 Call 6 topic text: http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2Call6/IMI2_Call6_FINAL.pdf
[4] http://ep-ad.org/

- provide expertise in modelling and analytics of clinical, biomarker, cogntion and function data from longitudinal AD cohorts.

Suggested architecture of the full proposal

The final architecture of the full proposal will be defined together with the industry consortium in observance of IMI2 rules and in consideration of the project objectives.

In the spirit of the partnership, and to reflect how IMI2 Call topics are built upon identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, it is envisaged that IMI2 proposals and projects may allocate a leading role within the consortium to an EFPIA beneficiary/large industrial beneficiary. Within an applicant consortium discussing the full proposal to be submitted at stage 2, it is expected that one of the EFPIA beneficiaries/large industrial beneficiaries may elect to become the coordinator or the project leader. Therefore to facilitate the formation of the final consortium, all beneficiaries are encouraged to discuss the weighting of responsibilities and priorities therein. Until the roles are formally appointed through a Consortium Agreement the proposed project leader shall facilitate an efficient negotiation of project content.

Glossary

AD	Alzheimer's disease
CNS	Central Nervous system
COPD	Chronic Obstructive Pulmonary Disease
CSF	Cerebrospinal Fluid
ICT	Information and Communication Technology
MCI	Mild Cognitive Impairment
MS	Multiple Sclerosis
PET	Positron Emission Tomography
RADAR	Remote Assessment of Disease and Relapse

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