

Topic: Linking digital assessment of mobility to clinical endpoints to drive regulatory acceptance and clinical practice

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Topic details

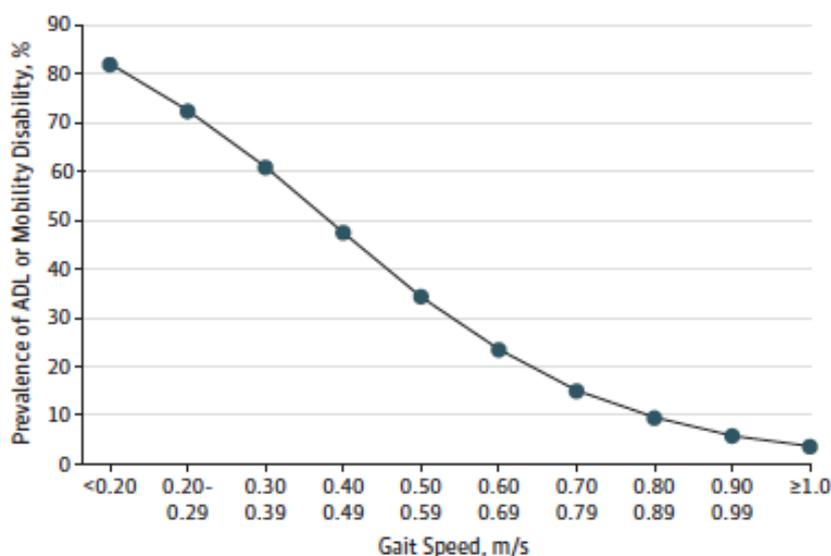
Action type Research and Innovation Action (RIA)

Submission & evaluation process 2 Stages

Specific challenges to be addressed

Loss of mobility is a growing unmet medical need, driven by chronic illness and frailty in the elderly and by injury in the young (Figure 1). Loss of mobility is a key morbid effect of diseases of various organ systems, including Chronic obstructive pulmonary disease (COPD), heart failure, multiple sclerosis, neurodegenerative diseases, etc. New therapeutic approaches target restoration of function and mobility in patients with degenerative diseases, acute injuries, and age-related disabilities, such as muscle anabolic drugs, cartilage regeneration approaches, and other therapies targeting the musculoskeletal system.

Figure. Prevalence of Either Disability for Activities of Daily Living or Mobility Disability by Usual Gait Speed Among Men Aged 80 Years (N=6534)



However, current primary endpoints that measure mobility are either based on patient reported outcome or performance testing, both of which have significant shortcomings. Emerging digital technologies can now measure many aspects of mobility in the “real world” on a long-term basis. Preliminary results suggest that those technologies have the potential to fundamentally change clinical trials across the development pathway and

eventually, medical practice, much the way that Holter monitoring revolutionised the assessment of cardiac arrhythmias decades ago. However, full acceptance and integration of digital mobility assessment into clinical trials and utilisation as primary or secondary endpoint requires rigorous validation and linkage to clinically relevant “hard” endpoints, such as death, disability, falls, or other complications.

The DIAMOND programme will validate digital mobility assessment, focusing on “real world walking speed” (RWS) as a primary endpoint for a more sensitive, objective measurement in patients’ native environment over longer periods of time and with greater granularity than is currently feasible. RWS is chosen because it requires shorter periods of observation (and lower patient compliance) than 24-hour step counts, fall detection, etc.; and because observed gait speed is already linked to mortality, falls, and hospitalisations in multiple populations. Emerging data suggest that RWS can be detected using digital inertial sensors, with or without global positioning (GPS) capability, using centre of mass (i.e., belt or skin-worn) devices. Secondary outcomes of additional digital mobility assessment (walking parameters including total time, step counts, gait characteristics, gait cadence, estimated energy expenditure of physical activity, etc.) should be assessed as well.

The DIAMOND project is envisioned as having two parts: **Part A**, a 1-2 year technical validation part that will develop an algorithm for quantifying RWS in relevant population of slow walkers; and **Part B**, a 3-year validation programme that will demonstrate that the algorithm predicts relevant clinical outcomes (e.g., falls, injurious falls, hospitalisations, disability, and mortality). The successful applicant consortium will include academic centres and private entities that have expertise in development of digital sensor solutions. The consortium will identify and engage existing longitudinal cohort studies in several relevant populations (e.g., heart failure, multiple sclerosis, Parkinson Disease, COPD, frailty/sarcopenia, post-hip fracture) and support application of digital sensors to the participants with ongoing follow-up for key regulatory endpoints (death, falls, hospitalisations, institutionalisation, loss of activities of daily living [ADLs]) over several years. Linkage of these novel digital methods and readouts to clinically relevant outcomes is mandatory for uptake of these methods by the medical community, regulators, and payers. If successful, the results will be used to support an application for recognition of RWS or other mobility endpoints as surrogate endpoints for clinical trials by European Medicines Agency (EMA), US Food and Drug Administration (FDA), and other Health Authorities. In addition to the primary outcome of RWS, additional digital mobility measurements should be collected and compared (or combined) with RWS to identify outcomes of maximum predictive power¹. These secondary measurements could include step counts, gait characteristics, cadence, time sitting/standing/walking, estimated energy expenditure of physical activity, etc.

More background information is available in the following list of publications:

[1][2][3][4][5][6][7][8][9][10][11][12][13][14][15][16][17][18][19][20][21][22][23][24].

Need and opportunity for public-private collaborative research

Most pharmaceutical companies are grappling with how to apply emerging digital technology to clinical development programmes and post-marketing authorisation assessment of drug efficacy or safety. However, for digital endpoints to truly transform research, regulatory recognition is required. In addition, expertise from pharmaceutical companies and partners with expertise in digital data collection and analysis, use of wearable devices, “big data” handling and analysis, and data privacy will be required. This expertise is not prevalent among EFPIA partners and will require engagement of companies that are already experienced in the field of continuous monitoring. We believe that physical activity monitoring using inertial sensors is the most advanced technology relevant to pharmaceutical development, and that RWS is the most advanced endpoint that could be validated within a 2-3 year period. By achieving surrogate endpoint qualification, DIAMOND will harmonise the approach to digital endpoint development, create a powerful regulatory precedent, drive innovation in both pharmaceutical and technology markets, and potentially transform clinical practice relating to frail, elderly, and chronically ill populations. Such an approach can only be done by multiple companies, working with governmental, academic, and patient advocacy groups, to create a harmonised approach.

¹ [http://www.oarsijournal.com/article/S1063-4584\(17\)30253-4/abstract](http://www.oarsijournal.com/article/S1063-4584(17)30253-4/abstract)

Scope

The purpose of the DIAMOND consortium is to measure in three chronically ill or frail populations,:

- As a primary outcome, real world walking speed (RWS);
- As secondary outcomes, additional digital mobility assessment (step counts, time walking, gait characteristics, cadence, estimated energy expenditure of physical activity, etc).

We will demonstrate that RWS or one of the other gait parameters predicts relevant medical outcomes (falls, injurious falls, hospitalisations, loss of ADLs, death), and achieve regulatory recognition of RWS as a surrogate endpoint independently of underlying disease diagnosis.

The specific aims are to develop and apply algorithms that will subsequently become publicly available to any users, so that the validated endpoint consists of the measurement algorithm, the analytic method, and the range of normal or abnormal results that predicts relevant clinical outcomes. This construct should support a variety of wearable hardware and inertial sensor types, and provide design-control characteristics that allow any manufacturer to receive medical device approval by demonstrating comparable performance characteristics to the tested device (i.e., a CE mark and reimbursement approval in the EU or 510(k) process in the USA). For the purposes of DIAMOND, however, the successful consortium will only be asked to demonstrate the validity of a single device-algorithm pairing; expansion to subsequent devices will be outside the scope of DIAMOND.

For simplification, the following parameters are recommended, although arguments in favour of alternative approaches may be made:

- Devices that capture data from the body centre of mass or lower extremities are preferred to those positioned at the wrist;
- Preference will be given to medical-grade devices over consumer-grade devices, although consumer-grade devices that have adequate documentation of performance characteristics, can meet clinical data quality standards and make raw data available (x, y, z accelerations) in addition to summary outcomes provided by the device firmware, are acceptable;
- The technical specifications of the device – hertz rate of signal acquisition, battery life, presence or absence of feedback to subject – should be described;
- The device must be able to accurately record wear-time to get an estimate of compliance;
- The algorithm to be developed should include step detection, gait speed assessment, and other relevant parameters; any information relating to detection thresholds should be described;
- The method for capturing reference data, i.e. ground truth and other annotations, for Part A (algorithm development) should be stated (e.g., GaitRite, observed 6 minute walk, 400 m walk, etc.), preference will be given to references which provide granular and real-world relevant information;
- The development population must be clinically relevant (i.e., gait speed 0.4-1.0 m/s, not only healthy volunteers, although early testing in healthy adults is acceptable). Consideration may be given to remote (internet-based) recruitment and/or follow-up of subjects, with appropriate consent and tracking procedures;
- Once a beta-version of the algorithm-device pair is available, human factor and wearability testing should be performed in a relevant population. Wearability should be tested for at least 7 days, and reliability of measurements when data are collected for fewer days should be assessed to determine the minimal number of days of wear that would constitute adequate collection. In addition, usability testing by patient interview should be conducted.

In addition, important confounding variables should be considered. A key decision is how much gait asymmetry will be acceptable in the study populations, and how much the algorithm can accept without excessive error. In general, the goal of DIAMOND is to validate low gait speed and/or inadequate walking as a whole-body function, rather than gait asymmetry due to arthritis, neurological deficits (stroke, etc.) that affect primarily one limb or joint. However, these are not always clear distinctions, and some overlap is expected, especially in elderly populations. In addition, environmental factors limit physical activity to different extents in

different geographical locations, depending also on the patient's medical condition (ability to go outside, etc.). Applicants should describe their approach to these confounding variables, including but not limited to:

- a. Postural stability
- b. Balance
- c. Dizziness
- d. Symmetry of gait
- e. Medications
- f. Comorbid conditions
- g. Weather/external conditions/location.

The regulatory approach, already under discussion with EMA, will be analogous to multi-indication approval for drugs, where demonstration of efficacy in two or more populations can lead to a broad approval for an indication. Engagement of EMA (and FDA) by the successful consortium will be a key aspect of the plan. The output of the consortium will be validation of RWS or other endpoints with cut-offs for predicting increased risk of the clinical endpoints for 1) surrogate primary or secondary endpoints for clinical trials carried out under EMA, FDA, or other competent authorities; 2) recognition by payers and health technology assessment (HTA) bodies of the validity of RWS and application of cut-offs to support pharmacological or other interventions; 3) clinical decision making outside of clinical trials.

Sustainability of the project beyond the 5-year period should also be considered (see "Indicative Duration" below). Additional work to validate, promulgate, and expand on the use of the algorithm(s) developed during the project period may be considered for separate funding. While detailed proposals are beyond the scope of this Call, applicants should indicate which activities might fall in the scope of sustainability work beyond Year 5.

Expected key deliverables

The key deliverables for the DIAMOND project include:

Part A:

- Development of the appropriate algorithm and one (or more) digital mobility assessment devices to use in the subsequent validation studies. Assessment of algorithm precision and accuracy should be carried out using a reference method (wheel-based speed assessment, video step analysis, GaitRite analysis, shoe insole systems, etc.) in a relevant population of slow walkers (gait speed approximately 0.4-1.0 m/s). The algorithm must be able to function across the relevant range of gait speeds associated with poor clinical outcomes (e.g., 0.4-1.0 m/s). The sensitivity and specificity of the algorithm to detect bouts of purposeful walking should be assessed;
- Human factors and wearability testing in a relevant population;
- Consensus on data collection, database structure, data quality, and analysis algorithms that will be publicly available and can function across multiple devices;
- Ongoing collaboration with and submission of algorithm validation for mobility assessment to health authorities and HTA bodies.

Part B:

- Identification of ongoing longitudinal cohort studies in relevant populations, in which the outcome measures are being or can be collected;
- Digital mobility and clinical outcome assessment over 2-3 years in each of three populations (COPD, heart failure, multiple sclerosis, neurodegenerative diseases, sarcopenia/frailty, hip fracture recovery, etc.). Define the duration and frequency of digital gait assessment needed (e.g., one week every six months?) to successfully predict the endpoints;

- Analysis of the predictive capacity and thresholds for increased risk of clinical outcomes (falls, hospitalisations, loss of ADLs, death) in multiple populations Definition of what constitutes a meaningful change (e.g., responder definition or minimum clinically relevant difference) in gait parameters in each population studied – e.g., is 0.1 m/s the smallest difference that represents a meaningful change in how the patient feels, functions or survives? ;
- Meta-analysis of mobility across populations as a predictor of adverse clinical outcomes. Does RWS or a secondary endpoint predict outcomes equally across all three populations? Are meaningful differences of the same magnitude? What is the minimal device wear time that gives a stable estimate of each predictive parameter? ;
- Submission of data to health authorities and HTA bodies for consideration as a surrogate endpoint for clinical trials, and for payer recognition of the endpoint for clinical use, respectively.

For guidance regarding timing, it is suggested that Years 1-2 (Part A) may consist of algorithm and device selection, algorithm validation, development of clinical protocols and consent forms, coordination with clinical study sites, etc. Years 3-4 may be focused on validation data collection; Year 5 on data analysis, and regulatory and HTA submission. Applicants are free to modify this suggestion as they think best. It is recognised that HA and HTA review and feedback will probably continue after the end of the project, and results exploitation will be part of the planning in Year 5. As RWS is already in use with pilot data in multiple populations, and several pharmaceutical companies have already initiated discussions with EMA and FDA, the goal of full surrogate endpoint validation should be realistic.

Expected impact

The mission of IMI is to improve health by speeding development of, and patient access to, innovative medicines, particularly in areas of high unmet medical or social need. As the fastest-growing population in Europe is that of people over 80 years of age, and many previously fatal illnesses have been converted into chronic diseases, mobility disability is going to continue to grow in the 21st century. The first step in treating loss of mobility and preventing disability is detecting it effectively, with methods that do not require highly complex, hospital-based solutions. By making mobility assessment feasible, and indeed an integral part of medical care, the DIAMOND consortium could enable development of novel solutions (pharmacological, digital, nutritional, exercise-based) to a major public health problem – the increasing prevalence of mobility disability due to the aging of the population and chronic diseases. The digital assessment of mobility is such a method, and has the potential to revolutionise the care of frail populations and of the development of drugs to treat them.

Successful demonstration that digitally-detected low mobility predicts relevant clinical outcomes will have major impact on drug development and clinical care of the target populations. We anticipate that many additional projects will emerge if DIAMOND is successful, for example, demonstration of RWS predictive power in additional populations; further studies required for surrogate endpoint recognition; applications to clinical settings in various national health care system contexts, etc.

Potential synergies with existing Consortia

Applicants should take into consideration, while preparing their short proposal, relevant national, European (both research projects as well as research infrastructure initiatives), and non-European initiatives. Synergies and complementarities should be considered in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap and duplication of efforts and funding.

Applicants should consider any relevant related projects from IMI, FP7, Horizon 2020 and other relevant initiatives outside the EU.

Because DIAMOND does not focus on a single clinical disease, there is great potential for synergy with existing IMI projects in:

- **COPD (PRO-Active)** (www.imi.europa.eu/content/pro-active)
- **U-BIOPRED** (www.europeanlung.org/en/projects-and-research/projects/u-biopred/home)

- multiple sclerosis **RADAR-CNS** (www.radar-cns.org)
- and age-related sarcopenia **SPRINTT** (www.mysprintt.eu).

Conversely, there is potential synergy with other IMI projects that focus on digital medicines (e.g., **EMIF** - www.emif.eu , **eTRIKS** - www.etriks.org , **EHR4CR** - www.ehr4cr.eu), especially in regard to learnings about data management, privacy, transfer, and analysis; and capture of clinical outcomes. Such agreements would enhance the ability of various types of digital data to be captured, analysed, and shared with greater efficiency, and would be an additional boon to the field.

Industry Consortium

EFPIA participants are already working with actimetry in their own clinical trials, and are working on analysis and measurement algorithms to various extents. DIAMOND will utilise this expertise through close collaboration with EFPIA participants, both directly and in a Scientific Advisory Board that will meet regularly throughout the study. EFPIA members may also offer in-kind contributions of expertise and analysis capacity based on their internal research experience with digital devices in general and mobility assessment in particular. Technology companies, as EFPIA Partners in Research, are expected to bring additional and greater expertise in the data handling and analysis aspects.

Indicative duration of the action

The indicative duration of the action is 60 months.

Future Project Expansion

Potential applicants must be aware that the Innovative Medicines Initiative 2 (IMI2) Joint Undertaking may, if exceptionally needed, publish at a later stage another Call for proposals restricted to the consortium already selected under this topic, in order to enhance and progress their results and achievements by extending their duration and funding. The consortium will be entitled to open to other beneficiaries as they see fit.

Specific areas of activity may include additional meta-analyses across the study populations; longer follow-up beyond the initial study period; secondary data analyses for additional endpoints; exploratory analyses of subpopulations, etc. Additional activities for further publication of the results, dissemination of the algorithm, and application to additional digital devices may also be in scope for sustainability.

Applicant Consortium

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

The applicant consortium is expected to address all the research objectives and make key contributions to the defined deliverables in synergy with the industry consortium. Relevant technology companies, in particular Small- and Medium-sized Enterprise, should be part of the successful consortium, along with academic medical centres that have access to ongoing longitudinal cohort studies of the patient populations of interest (geriatrics, heart failure, COPD, MS, Parkinson Disease, or other populations with high event rates for mortality, serious morbidity/complications, and falls). It is imperative that at least one technology company with expertise in wearable technologies for activity monitoring be part of all applicant consortia. Experience with medical device registration is also an advantage. Additional technology partners may be part of the EFPIA consortium and participate on the Scientific Advisory Board (SAB) of the final project. It is envisioned that regulatory and HTA bodies will be engaged in an advisory capacity, rather than as consortium members. Patient advocacy groups should be included in within the consortium work packages as appropriate. A work package directly related to these activities should be included in consortium applications. The exact number and nature of other work packages are left to the discretion of the applicants.

Suggested architecture of the full proposal

The applicant consortium should submit a short proposal which includes their suggestions for creating a full proposal architecture, taking into consideration the industry contributions and expertise provided below.

The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 JU rules and with a view to the achievement of the project objectives.

In the spirit of the partnership, and to reflect how IMI2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme and project leadership as well as project financial management. The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed project leader from among EFPIA beneficiaries/large industrial beneficiaries shall facilitate an efficient negotiation of project content and required agreements. All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

The below architecture for the full proposal is a suggestion; different innovative project designs are welcome, if properly justified.

The consortium is expected to have a strategy on the translation of the relevant project outputs into regulatory practices, regulatory, clinical and healthcare practice. A plan for interactions with Regulatory Agencies/health technology assessment bodies with relevant milestones and resources allocated should be proposed to ensure this, e.g. qualification advice on the proposed methods for novel methodologies for drug development, qualification opinion.

A plan for aspects related to sustainability, facilitating continuation beyond the duration of the project should also be proposed.

Work package 1 – Project Management and Oversight

This work package will address the strategy, management, and implementation of the project. Work package 1 (WP) will create regular meetings and interaction between sub-groups and teams, to coordinate and follow up on the work effort. This WP will also be responsible for post-project result sustainability and exploitation planning.

Industry contribution:

- Support for project management, including planning, budgeting, follow up and tracking, and consolidation of work package reports to IMI. Project risk management and comprehensive communication and dissemination of its progress and its milestones are important additional elements of EFPIA contribution. In-kind contribution of legal support as feasible for IP discussions.

Expected Applicant consortium contribution:

- Providing detailed follow up and tracking, via regular work package reports, early report of any unexpected organisational or structural issue or delay with respect to the project deployment and intermediate objectives. This WP will also organise a Scientific advisory board (SAB) and a Data monitoring committee (DMC) (if needed) to review and support the studies and give advice to the project. The WP should also engage with patient support groups and ensure patient input to the development and validation process.
- In addition, this WP will ensure that intellectual property (IP) of participants is respected and that dissemination of results is not prevented by IP disputes. Primary legal support will be from the Principal Investigator's institution, with input from the EFPIA lead. Pre-existing IP of each participant should be clearly described at the beginning of the project, and IP developed during the programme will become publicly available, either through publication or licensing, within IMI and EU regulations.

Work package 2 – Algorithm development and technical validation

Academia, EFPIA, Technology Partners in Research, and Small-Medium Enterprises will collaborate to select a digital activity detection device, develop or obtain an algorithm for step detection, purposeful walking detection, and walking speed measurement, and pursue technical validation against a reference method.

Industry contribution:

- The industry partners will work closely with the consortium to assist in the steps above, and provide research expertise and in-kind contributions to support data capture, analysis, and interpretation.

Expected Applicant consortium contribution:

- Should include a strong technology company participant that is capable of carrying out the technical validation procedures and providing the raw digital data; identify a patient population of slow walkers in whom the initial validation can be carried out; develop the study protocols for initial algorithm development (method development) and subsequent initial method validation. Human factor and wearability/usability testing as described above should be included in the development plan. This will be the bulk of Part A of the project.

Work package 3 – Database development and data management

Academic investigators will develop and host the clinical and technical database to support the Project and provide access to all consortium members.

Industry contribution:

- Advice and oversight based on member companies' expertise with database development and function, including privacy assurance and data anonymization experience.

Expected Applicant consortium contribution:

- Server hosting, database development and maintenance; creation of processes for data security, privacy, and transfer; provision of data anonymization procedures when necessary, definition of data standards that can be used for capture of raw and processed data from a range of inertial sensor types and sensor positioning.

Work package 4 – Validation of RWS vs. Clinical Outcomes and definition and validation of RWS/mobility clinical endpoints

Academia, EFPIA, Patient & Carer Representatives and Health Care Professionals will jointly identify at least three (3) clinical populations to study; identify the existing longitudinal cohort studies that are available to the consortium to carry out Part B of the study; and develop the protocol for Part B.

Industry contribution:

- Making fully available the member companies' expertise in clinical study initiation and conduct, providing oversight over the study management, the accomplishment of overall objectives. EFPIA members will also support study monitoring and participate in data interpretation.

Expected Applicant consortium contribution:

- Coordinate with existing longitudinal cohort studies to incorporate the digital device into their procedures; agree on a common set of procedures, endpoints, and analytical approaches; develop the data structures and transfer specifications to support digital data analysis; create the appropriate database structures for Part B; develop endpoint definitions and their measures of meaningful change; lead the analysis of the data and report the results in collaboration with WP 6.

Work package 5 – Regulatory and Payer Consensus over Operational Definitions

Regulators, EFPIA, Academia, and Patient Representatives will jointly contribute to the overall evaluation of evidence and results from WP 2 and WP 4. This WP will engage with EMA and FDA, as well as with relevant HTA bodies, to develop the administrative and regulatory pathways for digital mobility analysis in parallel with the development of the data to support submissions. EMA should be invited to participate in the consortium under the IMI framework, to the extent feasible.

Industry contribution:

- Planning, hosting and organising workshop(s) with regulators and payers, contributing to discussion of available evidence (including unpublished data), literature analysis, publication support, co-authoring of reviews and white paper(s).

Expected Applicant consortium contribution:

- Participate, actively contribute to constructive discussion with regulators and payers to promote and achieve consensus over operational definitions. (Co-)author reviews and white paper(s).

Work package 6 – Statistical analysis, evaluation of results, and data availability

Academia, Regulatory Authorities and specifically the European Medicines Agency and its Experts, EFPIA via the member companies will collaboratively review the trial results in order to draw the necessary clinical and regulatory conclusions. This WP will also be responsible for creating the project databases, including those which will become publicly available at the conclusion of the project.

Industry contribution:

- Planning, hosting and organising workshop(s) with regulators; contributing to results discussion via its Experts (including biostatisticians); providing technical support (translations, etc.); (co-) authoring of reviews and white paper(s).

Expected Applicant consortium contribution:

- Analyse the data and collaborate with EFPIA sponsors on data interpretation and publication. Contribute to constructive discussion with regulators to achieve scientific and regulatory agreement over the interpretation of study results. Co-author primary papers, reviews, and white paper(s). Support consolidation of the scientific consensus necessary to achieve project aims.

Work package 7 – Stakeholder information and results dissemination

Academia, Regulatory Authorities, EFPIA, healthcare professionals, patient representatives will contribute over the 5-year project duration to drive public awareness of the project, including presentation to stakeholders and media as appropriate. In collaboration with WP 6, this WP will develop methods for external researchers to access project results at the end of the project period.

Industry contribution:

- Logistics and organisational support; contribution of EFPIA experts as appropriate; providing technical support (translations, etc.); this will include a dedicated website and organisation of milestone workshops for stakeholders (and the general public as appropriate).

Expected Applicant consortium contribution:

- Provide the scientific and medical content for building, consolidating and updating information about digital mobility assessments over the project duration; provide personal and collegial contribution to the dissemination programme implementation; support publication of papers in peer reviewed scientific journals.

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