Behavioural Model of Factors Affecting Patient Adherence

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.

Topic details

Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages
IMI2 Strategic Research Agenda - Axis of Research	Patient-tailored adherence programmes.
IMI2 Strategic Research Agenda - Health Priority	Other

Specific challenges to be addressed by public-private collaborative research

Patient non-adherence to prescribed treatment is an issue that affects patient health outcomes and healthcare system costs worldwide. It is estimated that it contributes to 200 000 premature deaths in the EU each year [1]. The annual costs in Europe of avoidable hospitalisations, emergency care and adult outpatient visits are assessed at EUR 125 billion[1] and there are similar figures in the US [2]. In addition, poor patient outcomes and resulting lower productivity affect the wider society, estimated in the US as 2.3 times direct healthcare costs [2]. Addressing the issues of adherence would significantly improve both individual patient outcomes and reduce societal costs.

Reported adherence rates for on-market drug products vary from 7% to 87% [3] and average 50% [4]. Non-adherence may also include non-pharmaceutical treatments (e.g. digital therapeutics, non-pharmaceutical respiratory devices, lifestyle changes) and over-use of medication, for example, patients are known to increase their intake of pain relief medication above their prescribed dose [5].

Many researchers have approached the topic of adherence[3] but insights have necessarily been limited to specific sub-topics due to the breadth of the field. Consequently, whilst there are pockets of knowledge, both published and unpublished, there are also areas and interactions that are not fully understood. Although a number of app-based solutions for non-adherence have been developed, their effectiveness is highly variable [6]. Unless the underlying problem is well-defined and understood, the probability of developing effective solutions with broad and consistent impact is low. In addition, for a solution to be effective, it must be used. Therefore, the patient burden must be minimised and the solution must be simple to apply to ensure broad implementation. An optimised solution is

required balancing personalisation (complexity) and simplicity of use. This may include population segmentation according to behavioural phenotypes [7].

A disease-agnostic solution has the potential to achieve the necessary simplicity. Although there are some factors which appear to be disease-specific (e.g. stigma of the disease) these may exist more generally in the population and merely be weighted more strongly in specific conditions. There are also many significant factors which are not associated with any single disease state and which vary minimally between them, such as a patient's health beliefs, need for control, social environment or education level. This indicates the potential for a disease-agnostic baseline model.

Consequently, there is a need to generate a more comprehensive theoretical and empirical understanding of the underlying causes of these patient behaviours and any interactions. This topic proposes the creation of a generalised model, grounded in behavioural theory, which integrates significant factors affecting non-adherent behaviour. Factors should include patient motivation, which is critical to adherence [8], and is particularly under-represented in the literature compared to more quantitative factors such as education level. This would provide a robust definition of the problem – a foundation for understanding and predicting patient behaviour – and guidance to develop and implement cost-effective tools and solutions for patients, healthcare professionals (HCPs) and other healthcare stakeholders which directly target the causes of non-adherence and, ultimately, improve patient outcomes and reduce health system costs.

As medication adherence includes three distinct elements: 1) initiation of therapy, 2) implementation of the dosing regimen, and 3) persistence with treatment **Error! Reference source not found.**, it is anticipated that these three issues can be addressed by the proposed model.

Creating the necessary understanding for an effective model will require broad engagement and skills, particularly since we are targeting a disease agnostic model. The perspectives of patients, healthcare providers, academic experts, behavioural scientists, digital and data analytics experts and regulatory bodies will be essential to maximise the benefits and ensure all sectors of society are well served.

The establishment of a public-private partnership offers the opportunity to generate the necessary breadth of data and bring together the breadth of expertise needed to address these challenges.

Scope

The aims of the Call topic are to:

- develop a comprehensive understanding of the factors which affect patient needs and adherence, independently from the therapeutic area (i.e. generic or disease-agnostic), in a real-world context (as opposed to clinical setting);
- identify the most significant factors;
- evaluate existing models and then either create an open access behavioural model or further develop an existing model;
- collect additional real-world data to refine the model;
- provide tools that will enable healthcare stakeholders to cost-effectively develop and implement solutions to address patient needs and improve adherence rates.

The project will require a phased approach as the results of earlier activities may influence the focus and definition of later stages.

The scope of the project will include a definition of adherence and collate the factors affecting adherence. The relative impact and significance of factors shall be assessed and a gap analysis performed against theory to identify areas for research during the project. The review stage should therefore include an evaluation of available models of non-adherence behaviour. One potential model identified during the development of this text is the Subjective Experienced Health Methodology (SEHM) [10]. The evaluation of models should consider the extent to

which significant factors are included and the applicability and availability of models for ongoing development to achieve the project aims.

Based on this research, a behavioural model will be created or selected and refined. In parallel, adherence modules will be added to existing patient studies to fill identified gaps in the data.

While disease-agnostic, the model should be able to increase the prediction power and accuracy when applying additional, disease-specific inputs. The model should be sufficiently flexible to allow future development as population needs change.

It is envisaged that there will be a strong data analysis component (e.g. through Machine Learning (ML) or Artificial Intelligence (AI), if applicable) in the evaluation of data and generation of tools to assess the proposed model. This will identify any factors not demonstrated in the literature and identify patterns within the data. The model should clearly indicate the primary causes of patient motivations and should provide guidance for aligning patient needs with solutions. Feedback from this activity will be used to develop and optimise the model.

Given the quantity of data that will be collected or generated, consideration will be required for data storage and management solutions.

Once developed or refined, the model will be validated for multiple ages (including paediatric), ethnicities and conditions. It is anticipated that this shall be achieved using the following therapeutic areas, dependent on access to patients provided by members of the consortium:

- Cardiovascular;
- Oncology;
- Immunology;
- Neurology;
- Endocrinology and
- Rare Disease.

It should be noted that this list is not exhaustive. Where opportunities arise to validate in other additional therapeutic areas, these should be explored. The objective of this phase is to demonstrate the consistency and effectiveness of identifying patient needs and predicting adherence rates.

Finally, an implementation strategy of this model will be determined (e.g. guidelines for use, Application Programming Interface or API approach). To ensure that any future tools generate genuine benefit for both patients and HCPs, a phase of work is required to assess how the interface could be simplified for patients, potentially sharing common data between companies or a common interface framework to engage with patients in a single location.

The implementation of stand-alone, patient-facing solutions (e.g. digital platforms) is out of scope of this Call topic. Modelling the behaviour of HCPs is also out of scope.

During the funded action, members of the industry consortium plan to contribute scientifically relevant pre-existing data and/or data from prospective studies including activities for generating such data that are part of broader industry clinical trials and/or patient studies and making such data fit for purpose.

Expected key deliverables

- Searchable database of published and available (to the consortium) unpublished sources of data on treatment adherence causes;
- Definition of adherence and methodology for assessing data, including consideration of bias;
- Statistical analysis and prioritisation of relative significance of factors on treatment adherence and persistence;

- Evaluation of available treatment adherence models, assessing strengths and weaknesses of selected models, considering the balance between personalisation and simplicity of implementation. This deliverable will then be used by the consortium to choose one model to refine/build a new model for validation;
- Methods to measure key factors and adherence levels which can feasibly be used with patients, considering minimum burden to patient;
- Disease-agnostic model of patient behaviour considering all factors identified above;
- Development of tools to collect data from patients and to quantify behavioural factors, for use in validating the model and in future applications of the model;
- Evaluation of trends within the data which indicate population sub-groupings with similar causes of non-adherent behaviour, and which could be used to cost-effectively identify suitable support types for patients;
- Model validation to demonstrate effective understanding of patient needs and prediction of adherence rates;
- Guidance on applying the model to develop solutions to address patient needs and, hence, adherence rates;
- Educational tools for patient organisations and support groups, pharmacies and healthcare providers;
- Requirements assessment for data-sharing solutions to minimise patient burden and data entry duplication. Potential proof-of-concept solution to demonstrate how a single patient input can be shared with multiple companies.

Expected impact

The model and supporting guidance developed under the project have the potential to transform the way healthcare stakeholders engage with patients to optimise their understanding of their condition and their adherence levels throughout their healthcare journey.

In their proposals, applicants should describe how the outputs of the project will contribute to the following impacts and include wherever possible baselines, targets and metrics to measure impact:

- Positive impact on healthcare at a societal level through enhanced adherence, targeted use of resources, and improved overall patient outcomes;
- Validated foundation to compile and understand factors affecting patient non-adherence to treatment regimens and the relative weighting of these factors;
- Identification of sub-groups of the population with similar causes of non-adherent behaviour such that solutions can be tailored to population needs and applied in a cost-effective manner to multiple treatment conditions;
- Model for the basis of a consistent approach to non-adherence across the industry; a framework for future development of patient-centric solutions, with the capacity for the model to evolve with the future needs of patient populations;
- Guidance, based on the validated model, for identifying patient needs and tailoring support tools for patients and HCPs which most closely address patient adherence needs and improve patient outcomes and quality of life;
- The data collected during the project will provide a broad and deep resource for future understanding of adherence.

The model and associated tools and guidance will provide open access resources that healthcare stakeholders can use to independently:

- Collect a minimum dataset from patients e.g. via questionnaire or online tool;
- Use data and the model to estimate risk of patient non-adherence;

- Use data and the model to identify patient needs for good adherence – potentially linked to a sub-group of similar patients;
- Use as a baseline to create their own specific toolkits;
- Create support solutions for delivery to patients or patient sub-groups, based on patient needs e.g. patient education, practical tools such as dose histories, links to HCPs or patient groups for emotional support. Potential to create multiple tools or resources but only deliver those that are most valuable to the individual patient;
- Repeat assessments to identify changing patient attitudes and needs

In their proposals, applicants should outline how the project plans to leverage the public-private partnership model to maximise impact on innovation, research & development, as well as regulatory, clinical and healthcare practices, where relevant. This could include a strategy for engagement with patients, healthcare professional associations, healthcare providers, regulators, Health Technology Assessment (HTA) agencies, payers etc., where relevant.

In addition, applicants should describe how the project will impact the competitiveness and growth of companies including SMEs.

In their proposals, applicants should outline how the project will:

- Manage research data including use of data standards;[1]
- Disseminate, exploit, and sustain the project results. This may involve engaging with suitable biological and medical sciences Research Infrastructures;[2]
- Communicate the project activities to relevant target audiences.

In addition, the following additional exploitation[3]/dissemination[4] obligations must be considered to maximise impact:

It is expected that the model, guidance and any development tools will be made available through an open source process to achieve the aims of maximising the number of patients receiving support.

Potential synergies with existing consortia

Synergies and complementarities should be considered with relevant national, European and non-European initiatives (including suitable biological and medical sciences research infrastructures**Error! Bookmark not defined.**) in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap, and duplication of efforts and funding.

Industry consortium

The industry consortium is composed of the following EFPIA partners:

- Pfizer (lead)
- Astellas
- Janssen
- Merck KGaA

[1] Guidance on data management is available at http://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/open-access-data-management/data-management_en.htm
[2] http://www.corbel-project.eu/about-corbel/research-infrastructures.html
[3] Article 28.1 (Additional exploitation obligations) of the IMI2 Grant Agreement will apply
[4] Article 29.1 (Additional dissemination obligations) of the IMI2 Grant Agreement will apply

- Novonordisk
- Resmed
- Servier
- Takeda

In addition, the industry consortium includes the following IMI2 JU Associated Partner:

- Link2Trials

The industry consortium (EFPIA and Associated Partner) plan to contribute the following expertise and assets as in-kind contributions:

- Curation and re-analysis of existing in-house study data or data summaries to show adherence rates and links to causes of non-adherence;
- Expertise in behavioural science to support model development/refinement;
- Development of methods to collect and assess treatment adherence rates;
- Study design, planning and management experience;
- Access to planned patient studies for data generation, model development, testing and validation activities. Identification of planned industry-sponsored phase 4 or other planned real-world studies to which an adherence module could be appended. Industry studies will provide access to patients for the selected medical conditions as a minimum. Further assessment areas may be added depending on the availability of suitable studies. Studies will be sponsored and funded by the respective company including the cost of full-time equivalents (FTEs) and other expenses to run the studies, including but not limited to contract research organisations (CRO) and investigator costs;
- Data analysis, including statistical analysis of study results and advanced analytics/machine learning expertise to identify trends;
- Project leadership and programme oversight;
- Regulatory, General Data Protection Regulation (GDPR), legal and medical expertise.

Indicative duration of the action

The indicative duration of the action is 60 months.

This duration is indicative only. At stage 2, the consortium selected at stage 1 and the predefined industry consortium may jointly agree on a different duration when submitting the stage 2 proposal.

Indicative budget

The financial contribution from IMI2 JU is a maximum of EUR 5 950 000.

The indicative in-kind contribution from EFPIA partners and IMI2 JU Associated Partner is EUR 5 950 000. This contribution comprises an indicative EFPIA in-kind contribution of EUR 5 700 000 and an indicative IMI2 JU Associated Partner in-kind contribution EUR 250 000.

Due to the global nature of the participating industry partners and IMI2 Associated Partner it is anticipated that some elements of the contributions will be non-EU/H2020 Associated Countries in-kind contributions.

Expertise and resources expected from applicants at stage 1

The stage 1 applicant consortium is expected, in the submitted short proposal, to address all the objectives and key deliverables of the topic, taking into account the expected contribution from the industry consortium, which will join at stage 2 to form the full consortium.

The stage 1 submitted short proposals should include suggestions for creating a full proposal architecture (which could be in line with the suggested architecture described below, though this architecture is only a suggestion.)

This may require mobilising, as appropriate the following expertise:

- Published expertise in patient experience, factors which affect treatment adherence, e.g. scientific and research organisations;
- Expertise to provide insight across countries and therapeutic areas as well as insight from different HCPs (e.g. physicians, pharmacists, nurses) and stakeholders (e.g. patients, healthcare providers, healthcare policy makers, and pharmaceutical researchers);
- Academic and commercial expertise in building and evaluating behavioural models and frameworks and the factors which drive treatment adherence behaviour;
- Reporting capabilities in agreement with the ABC taxonomy and the EMERGE guidelines;
- Study design and management expertise;
- Expertise in the use and analysis of real-world data on treatment adherence to contribute to and validate the model, including machine learning to identify data patterns and trends;
- SMEs with implemented solutions (i.e. hardware and software) to measure and manage medication adherence, ideally with own datasets and published evidence;
- Experience of patient communication, patient interfaces and app development for individualisation of therapies and patient empowerment;
- Legal and data privacy (e.g. GDPR) expertise;
- Access to health authorities, healthcare professionals, patients, patient advocacy groups and policy makers for their input into the implementation of the model, either as partner of the consortium or seeking advice;
- Information technology, data management, website management expertise;
- Expertise in clinical compliance/ICH GCP (International Council for Harmonisation – Good Clinical Practice) aspects;
- Project management, project administration/coordination, budget management and communication expertise;

NB It is not a requirement that public partners recruit patients unless it is for patient studies to which they have access.

It may also require mobilising, as appropriate, the following resources:

- Evidence-based digital tools to systematically collect adherence factors and dosing rate data from all participants included in studies and to identify relevant patterns in the adherence data.

Considerations for the outline of project work plan:

In their stage 1 proposals applicants should

- Give due visibility to data management; dissemination, exploitation and sustainability; and communication activities. This should include the allocation of sufficient resources for these tasks which will be further developed in stage 2 proposal;
- Consider including a strategy for ensuring the translation of the project results to drug development, regulatory/ HTA settings (e.g. through scientific advice/qualification advice/opinion, etc.), clinical and healthcare practices and/or decision-making processes.

Suggested architecture

Work package 1 – Review of existing data and state of the art

The goals of this work package are to:

- Agree on a definition of adherence;
- Collate published adherence work and unpublished data from members of the consortium demonstrating significant factors that impact patient behaviour with respect to treatment adherence. The work should consider medical, psychological and social factors, variation during the patient journey, and both over- and under-utilisation;
- Create a searchable database of data on treatment adherence causes;
- Carry out statistical analysis and prioritisation of relative significance of factors on treatment adherence and persistence;
- Identify published and unpublished models of patient behaviour with respect to treatment adherence and adherence levels;
- Evaluate available adherence models, assessing strengths and weaknesses of selected models. This deliverable will then be used by the consortium to choose one model to refine/build a new model for validation;
- Perform gap analysis against behavioural theories to identify factors that are missing or not well substantiated.

Work package 2 – Model Development / Model Refinement

The goals of this work package are to:

- Develop a disease-agnostic model of patient behaviour considering all factors identified in WP1;
- Refine the model using the additional data collected in WP3 and any data analysis techniques to identify trends, patient groupings or surrogate measures for adherence;
- Develop methods to measure key factors and adherence levels that can feasibly be used with patients, considering minimum burden to patient.

Work package 3 – Generation of additional data

The goals of this work package are to:

- Generate additional data to fill the gaps identified in WP1 and contribute to WP2 for the model refinement;
- Develop tools to collect data from patients and to quantify behavioural factors and potential solution types, for use in refining and validating the model and future model implementation;
- Use existing industry-sponsored real-world studies and append a module on adherence factors and measurement to generate a breadth of data across different conditions.

Work package 4 – Model validation

The goals of this work package are to:

- Identify suitable studies (e.g. existing Phase 4 clinical studies, real-world studies) to test the model predictions of patient needs and adherence rates;
- Validate the behavioural model for at least six therapeutic areas covering the most significant medical, psychological and social factors identified in WP1;
- Develop prototype solutions as required to support validation activities.

Work package 5 – Implementation strategy

The goals of this work package are to:

- Develop guidance on how to apply the model to develop solutions to address patient needs and, hence, adherence rates, for use by industry partners, academia or healthcare practitioners;
- Consider how patients with multiple conditions may interact with likely adherence solutions. Consider concepts for future tools that could share data or interfaces to minimise the burden on the patient. Determine the requirements for such tools, including the needs of patients, healthcare providers, regulators and industry;
- Prepare a proof of concept of such tools.

Work package 6 – Project management, incl. sustainability plan, regulatory, legal & data privacy

The goals of this work package are to:

- Ensure alignment between the beneficiaries as well as smooth internal and external communication;
- Monitor compliance with the work plan;
- Monitor planned resources and time schedule;
- Coordinate fulfilment of all administrative milestones;
- Prepare a sustainability plan for the deliverables that shall be maintained and/or developed after the completion of the project. The plan shall be produced in parallel with model development;
- Ensure legal and data privacy requirements are met during the project lifetime.

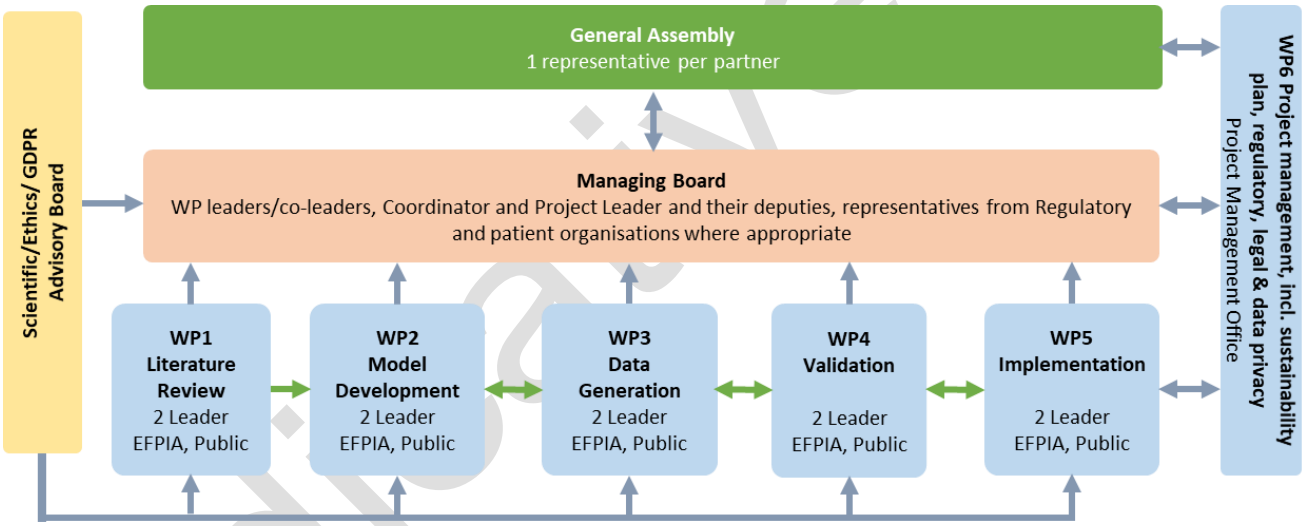

Figure 1 – Suggested WP architecture

Additional considerations to be taken into account at the stage 2 full proposal

At stage 2, the consortium selected at stage 1 and the predefined industry consortium jointly submit the full proposal developed in partnership. The full proposal is based upon the selected short proposal at stage 1.

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.

Data management

In their stage 2 proposal, applicants should give due visibility to data management including use of data standards. A full 'data management plan' (DMP) as a distinct deliverable must be delivered within the first six months of the project. The DMP needs to be kept up to date with the needs of the project and as such be updated as necessary during its lifetime.[5]

Dissemination, exploitation and sustainability of results

In their stage 2 proposal, applicants must provide a draft plan for dissemination and the exploitation, including sustainability of results. A full plan as a distinct deliverable must be delivered within the first six months of the project.[6], and updated during the project lifetime and could include identification of:

- Different types of exploitable results;
- Potential end-users of the results;
- Results that may need sustainability and proposed sustainability roadmap solutions.

Sufficient resources should be foreseen for activities related to dissemination and exploitation, including the plan for the sustainability of the project results. This may involve engaging with suitable biological and medical sciences Research Infrastructures (RIs).[7]

Communication

The proposed communication measures for promoting the project and its findings during the period of the grant should also be described and could include a possible public event to showcase the results of the project.

[5] Guidance on data management is available at http://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/open-access-data-management/data-management_en.htm
[6] As an additional dissemination obligation under Article 29.1 of the IMI2 Grant Agreement will apply
[7] http://www.corbel-project.eu/about-corbel/research-infrastructures.html

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