Topic: Optimising Future Obesity Treatment

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

Specific challenges to be addressed

The prevalence of obesity is increasing and affects more than 650 million people of all ages to become one of the foremost global health threats [1]. It is a complex disease and we only have a crude understanding of its underlying causes and biology, how to best describe and define it. Obesity can be preventable, but once it has occurred it is considered a chronic disease for which treatments are often inadequate. Currently we have no way of predicting who will respond to or benefit from what kind of treatment [2][1].

Obesity can seriously impair health through a broad range of complications such as cardiovascular disease, type 2 diabetes (T2D), cancer, musculoskeletal disorders, psychosocial imbalances, and reduced quality of life, and impacts the treatment of other conditions, e.g. type 1 diabetes (T1D) [3]. Weight reduction has been shown to have a positive effect on these co-morbidities and may increase the effectiveness of treatments specific for other co-morbidities. Lifestyle modification is an integral part of the weight management journey, but is often insufficient on its own, and should be complimented by pharmacological and surgical add-on treatments to achieve greater and more sustainable weight loss. It is likely that there are subgroups of patients that are more suited to certain types of treatment and results risk dilution of perceived efficacy unless these groups are identified and treatment is personalised. People with T1D have traditionally been thought to have low body mass index (BMI), but current research has shown otherwise [4]. The obesity prevalence in T1D is increasing faster than in the general population [5].While intensive insulin therapy, lack of physical activity, and so called double diabetes (T1D and T2D) are some of the mechanisms for weight gain in people with T1D, little is known about effective weight management in this population.

This topic focuses on multifaceted profiling of patients with obesity in order to define clinically meaningful and relevant subgroups as a premise for optimising future prevention and treatment of obesity and its complications. Stakeholders are expected to pool pre-existing observational and/or clinical data to establish a database with enough phenotypic granularity for a data-driven stratification of obesity into subgroups based on a set of operational parameters including subject characteristics, biomarkers and questionnaires. The outcome of this proposal should work towards a common understanding and an aligned vocabulary among stakeholders to facilitate scientific, medical and political acknowledgement of obesity as a disease and the importance of weight loss and weight maintenance.

Need and opportunity for public-private collaborative research

[1] In the context of this proposal, treatment refers in a broad sense to a variety of different interventions for patients with obesity including lifestyle advice on appropriate diet and exercise alone or in combination with drugs or obesity surgery.

This initiative, based on a public-private partnership, provides a unique scientific opportunity to address the challenges of maximising the efficacy of preventing and treating obesity. The major advantages of using the IMI platform are the ability to address these challenges in an independent effort, to engage with multiple stakeholders that otherwise might not interact in this context such as academia, patient organisations, pharma, food, diagnostic companies including small and medium-sized enterprises (SMEs) with knowledge and interest in obesity and its complications. Internationally recognised academics and a range of companies with expertise in obesity and its complications approaching this topic from each their own individual angle would be needed to optimally analyse and interpret the large pool of data and impact the obesity landscape. The industry partners contribute with the necessary expertise to ensure that the scope of the analysis is fit for the purpose of developing innovative treatment paradigms and medicines. The participation of patient organisations will ensure the relevance for patients and they should be actively consulted as a source of unique knowledge. Therefore to ensure success of the action, it is important to engage with a broad range of stakeholders including patients, clinicians and decision makers.

Scope

The scope of the topic is to identify pathophysiologically and clinically meaningful subgroups of obesity that will allow for optimisation of prevention and treatment of obesity and its complications. Establishing (or revisiting) a robust sub-classification may include the current use of body mass index as the best anthropometric measure, or alternatively waist circumference or waist to hip ratio; it may include a direct or indirect measure for the duration of disease (e.g. acknowledging the difference between paediatric onset obesity and decades of metabolic insult); genetics and epigenetics, to name a few.

More specifically the objectives of the topic are to:

- Establish a federated database by pooling of the baseline data from pre-existing cohorts from observational or interventional studies to achieve as broad and detailed information on patients with obesity as possible, including sufficient clinical phenotyping and multi-omics data.
- Perform data driven analysis of the federated database to identify and characterise patient subgroups and potential biomarkers for diagnosis, prediction of the development of complications, and potentially inform on appropriate type of and response to treatment.
- Fill the gaps of information regarding selected biomarkers by reanalysing pre-existing biobank samples. Such biomarkers should be affordable and operational in the context of real world clinical practise and clinical development of innovative medicines and other treatments.
- Address specifically type 1 diabetes (T1D) as an example of a co-morbid condition in which both clinical phenotype and treatment is influenced by obesity in an intricate manner, including public education about obesity in T1D. As part of this, datasets from the T1D Exchange programme will be available.
- Collect and integrate patient perspectives in relation to diagnosis and treatment of obesity to understand the need, perceived barriers and value of determining medical treatment for patients with obesity.
- Conduct a shared value analysis among key stakeholders reflecting values and challenges within the obesity landscape for optimising treatment and prevention. Engagement of external stakeholders is encouraged to generate educational material to support a common understanding of obesity. The content could include determinants and consequences of obesity including weight management.
- Establish a Patient Advisory Board including representatives from patient organisations in order to ensure that patient-driven research and insights relevant for the project are identified and considered within and across the different work packages.

Expected key deliverables

The ambition is that the proposed topic should lead to:

- A federated database of pre-existing phenotypic characterisation that can be used for the funded action and sustained for future analysis (see below on estimate on size of database).
- A set of operational variables that can be used for stratification of obesity into clinically meaningful patient subgroups, i.e. subgroups that may require different or respond differently to treatment of obesity and its complications.
- A detailed description of the clinical characteristics and manifestations of the identified patients subgroups, and wherever possible any existing or expected differences in treatment preference, effect, size, and sustainability of the effect and safety.
- An algorithm based on the set of operational variables that can be used to identify subjects that require and respond differently to prevention and/or treatment of obesity in clinical practice.
- Description of the impact of obesity on T1D in terms of patient characteristics, clinical manifestation, treatment and outcomes, whether similar or different from non-obese patients with T1D. Use of corresponding data from the federated database is expected to be very useful to contrast or balance these findings.
- Documentation of patient preferences regarding diagnosis and treatment of obesity.
- A shared value analysis among key stakeholders and the establishment of a common understanding and vocabulary about obesity as a disease. These activities should be carried out throughout the project from the initiation of the project, to interim and final learnings.

Expected impact

Paving the way for an optimised and more personalised future obesity treatment, the identified patient subgroups should, where data are available, be analysed for treatment results, including weight loss and weight maintenance, and prevention and/or development of complications. Importantly, novel ways of defining and diagnosing obesity may also develop and detail the classification of obesity, and contribute to improving prevention, personalising health and lifestyle interventions, and weight management as well as the precision of evidence-based medicine and development of novel treatments. Deciphering the heterogeneity of obesity and the potentially differential effect of weight loss and weight maintenance should lead to:

- Novel ways of describing and defining the obesity disease;
- Potential for novel and innovative diagnostics for classification and evaluation of the obesity disease;
- Increased understanding and respect for obesity as a chronic disease entity;
- Increased potential to develop targeted delivery of safe and effective treatments to clinically meaningful subgroups of patients with obesity;
- Reducing the barrier of entry for innovative translational research and commercial development;
- Improved clinical trial design and increased precision of evidence based obesity medicine;
- Better understanding of how to design effective measures to prevent and treat obesity based on its stratification into patient subgroups;
- Increased understanding of the effect or lack of effect of weight loss on a broad range of obesity related complications;
- Increased understanding of how obesity impacts other diseases as exemplified by impact on incidence, characteristics, treatment and outcomes of T1D.

Applicants should also demonstrate how their proposal will impact on the competitiveness and industrial leadership of Europe by, for example, engaging suitable SMEs.

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, duplication of efforts and funding.

In particular, the action generated by this topic should, among others, consider initiatives such as previous IMI projects that have addressed the compilation of cohorts from legal/ethical and technical/analytical perspectives such as:

EMIF (European Medical Information Framework) http://www.emif.eu/,

DIRECT (Diabetes Research on patient stratification) https://www.direct-diabetes.org/

RHAPSODY (for precision therapy and prevention of diabetes) https://imi-rhapsody.eu/

This knowledge is based on common data standards that promote the sustainability of the project and should be taken into account. Data from these projects within the obesity and diabetes areas could also be of importance for the current proposal.
In order to have the same federated database platform, the applicants should also consider interacting with the future IMI2 JU project resulting from the topic European Health Data Network (EHDN) IMI2 – Call 12, which will deliver an operational, federated network in order to have direct access to RWD for developing new or incremental services in healthcare area http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2Call12/IMI2_Call12_CallText.pdf;
Likewise, IMI2 PREFER project should be considered regarding patient preference for preventive measures and treatment https://www.imi-prefer.eu/**.**

Industry consortium

The industry partners will bring in-depth knowledge in the fields of clinical pharmacology and translational medicine, clinical data management, bioinformatics analysis, and of obesity. The industry partners will also provide know-how and means to support the establishment of the federated database including legal advice, setting up the database, and making analysis feasible, accessible and sustainable over time.

Limited supplementary funding could be made available for supporting further analysis of biobanked samples and development of digital tools to assist physicians in subgrouping of patients based on the outcome of the analysis (to be discussed by the full consortium).

The industry consortium will provide access to the following observational cohorts:

Gutenberg Health Study (Univ. Med. Center Mainz, Germany)

The Gutenberg Health Study (http://www.gutenberg-gesundheitsstudie.de/ghs/willkommen.html) [9] is a population-based, prospective, single-center cohort study including more than 15.000 subjects with 5-(completed) and 10 year (planned) follow-up that started in 2007 at the University Medical Center Mainz and is supported by Boehringer Ingelheim. Approximately 3.500 subjects with a BMI >30 kg/m^2 at baseline have been included. The Study focuses on cardiovascular diseases, cancer, eye diseases, metabolic diseases, diseases of the immune system and mental diseases. The study aims at improving the individual risk prediction for diseases, and includes a comprehensive data set comprising anthropomorphic characteristics, general health status, disease status, and clinical chemistry parameters. In addition, DNA, citrate/EDTA plasma samples, serum and urine samples have been banked and are available for -omics analyses. Access is granted to the Gutenberg Health data after review of specific research studies proposed by the selected Consortium and release by the GH Steering Committee. Support for data analysis of the Gutenberg Health

Study, as well as further biomarker research/validation by omics methods analysis of bio-banked samples, will be provided by Boehringer Ingelheim.

The T1D Exchange database

The T1D Exchange clinical registry comprises data from about 35.000 children and adults with T1D in the U.S; about 2/3 of adults and close to half of youth being overweight or obese. There is prospective 5-year follow up data and biosamples are available for a subset of the subjects [10][11]. The registry's aim is to characterise the population of adults and children with T1D in the U.S. with respect to diabetes history and medical history and includes a comprehensive data set of anthropomorphic characteristics, general health status, disease and treatment status, and clinical chemistry parameters.

Diogenes (Diet, Obesity and Genes) and Ottawa cohorts

The Diogenes comprises about 1.000 obese subjects without T2D who participated in a meal replacement weight loss and weight maintenance study aimed at identifying biomarkers for prediction of successful weight loss and mechanisms for differential treatment response [12]. The database includes detailed phenotypic characterisation and multi-omics data (i.e. genomics, transcriptomics, metabolomics, lipidomics, and proteomics). The Ottawa cohort comprises about 2.000 patients recruited through Ottawa obesity clinic within the Nestlé Optifast weight loss programme with the aim of identifying biomarkers for differential treatment response. The database includes detailed phenotypic characterisation and multi-omics data (i.e. genomics, plasma micro-RNA, proteomics).

Anonymised data from clinical trial cohorts from industry partners can be made available supplementing the academic cohorts, e.g. for validation of findings or addressing specific research questions.

Indicative duration of the action

The indicative duration of the action is 60 months.

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, which will join the selected applicant consortium in preparation of the full proposal for stage 2. This may require mobilising, as appropriate, the following:

- existing research activities either within public health or clinical services in the field of obesity treatment with interests in better defining phenotypes of obesity and their responses to treatment, and;
- expertise in e.g. anthropology, epidemiology, public health, data management and harmonisation, bioinformatics, systems medicine or multi-omics analysis, lifestyle treatment, and public relations;
- access to pre-existing clinical cohorts (expected total number from public and private datasets n=50.000) with as broad and detailed relevant phenotyping as possible and access to biobanked specimens for selected biomarker analysis wherever available (including documented informed consent).

The involvement of patient organisations is imperative to make findings relevant. They should be involved at least as advisors to the analysis and interpretation, and as advocates for the community outreach. Although it is not expected that the patient subgroups or biomarkers should obtain regulatory acceptance within the scope of the funded action, dialogue with regulators should be considered.

Relevant SMEs with relevant proven expertise are encouraged to participate in the applicant consortium. SMEs can be of great benefit to IMI projects and, inter-alia strengthen the competitiveness and industrial leadership of Europe. Their involvement might offer a complementary perspective to industry and academia, and strengthen the long-term impact of the project. For these reasons, applicants should consider engaging

SMEs throughout the proposal. Under this topic, the contribution of SMEs could be considered in providing expertise and activities such as data and knowledge management; project management with expertise and experience relevant to IMI2 JU/H2020 projects.

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.

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 architecture of the full proposal should be designed to fulfil the objectives and key deliverables within the scope of this proposal. However, there are already from the participating partners some cohorts and data available that the applicants may want to consider how to include and analyse.. A plan for aspects related to sustainability, facilitating continuation beyond the duration of the action should also be proposed.

In addition to being an active contributor to the key deliverables of the relevant work packages, the participating patient organisations will support communication internally and help disseminate information externally. The Patient Advisory Board is expected to meet with work package leads four times a year, either in person or via teleconference. Both industry and academic partners are expected to contribute to Patient Advisory Board activities, and thus funds should be reserved for this purpose.

Work package 1 – Project Management

The goal of this work package is the overall project coordination including:

- Financial management and monitoring of deliverables and milestones;
- Legal and contractual management;
- Ethics management.

Work package 2 – Data Federation and Database Management

- Provision of pre-existing observational and/or clinical data from obese cohorts;
- Provision of multi-omics data, where possible;
- Converting data from different cohorts into a standard format;
- Harmonisation of anonymised and converted data into a common structure to be able to be pooled;
- Making data accessible to database for analysis;
- Database construction of pooled data and establishment of suitable database analysis tools;

- Database management and administration of users, permissions and security;
- Ensure legal issues including data sharing agreements;
- Develop plan for sustainability of database and ways to ensure creation of value from the project results beyond the project period

Work package 3 – Systems Biology and Data Analysis

- Setup of a web portal and tools enabling analysis and visualisation of data and including an Application Programming Interface (API) for programmatic access for data analysis;
- Perform integrative analysis across datasets and cohorts to identify the patient sub-groups;
- Comparison of patient cohorts and identify relevant gaps and biosamples for analysis;
- Perform additional biomarker analysis in bio-banked samples for relevant gaps identified;
- Identify and/or establish assays for analysis of biosamples.

Work package 4 – Analysis of T1D and Obesity

- Epidemiology: Determine prevalence of overweight/obesity among people with T1D in general population, by demographic group (age, income, ethnicity), by lifestyle (diet, exercise frequency, etc.);
- Characterisation of the obese phenotype in T1D;
- Determine how obesity and its converse, weight loss, affect T1D disease characteristics, treatment effectiveness, clinical outcomes;
- Identify mechanisms underlying the effect of obesity on T1D metabolism and outcomes toward the goal of developing improved treatments in the future;
- Assess the effects of long-term obesity in people with T1D, and “metabolic memory” phenotypes conferred by obesity that may persist even after weight loss;
- Assess whether any of the above is distinct for T1D due to the autoimmune milieu and whether specific therapeutic strategies should be targeted or not;
- Weight management in T1D: determination of effective therapeutic and lifestyle interventions for obesity prevention and weight loss in people with T1D;
- Communication of findings to the public to educate all customers about T1D and obesity.

Work package 5 – Patient Preferences

- Collection and generation of information on patient preferences in relation to the need, value and assessment of obesity treatment;
- Apply an analytic mind-set and tools to synthesise a patient perspective to ensure the relevance and value to patients across the project. Liaise and collaborate with patients and key stakeholders to facilitate outcomes and learnings including educational material with relevant patient organisations.

Work package 6 – Shared Value Analysis and Communication

- Establish a network consisting of key internal and external stakeholders to engage in collaboration around obesity from a public health perspective;
- Conduct a shared value analysis to extract common values and challenges. Based on this analysis generate a shared value package/communication to reflect current thinking among stakeholders;

- Engage across work packages to shape communication and deliverables as relevant to address public health perspectives and support knowledge about obesity, prevention and treatment opportunities.

Industry contribution

In summary, the industry consortium will provide the following to the project:

- Access and support for analysis of the Gutenberg Health Study;
- Access to the T1D Exchange data;
- Access to the Diogenes and Ottawa cohorts;
- Anonymised data from clinical trial cohorts from industry partners supplementing the academic cohorts;
- In-depth knowledge in the fields of clinical pharmacology and translational medicine, clinical data management, bioinformatics analysis, and of obesity;
- Know-how and means to support the establishment of the federated database including legal advice, setting up the database, and making analysis feasible, accessible and sustainable over time;
- Limited supplementary funding for supporting further analysis of biobanked samples;
- Limited supplementary funding of development of digital tools to assist physicians in subgrouping of patients based on the outcome of the analysis;
- Management of the consortium incl. the Patient Advocacy Board.

Expected Applicant consortium contribution:

In summary the applicant consortium is expected to provide the following:

- Pre-existing cohort data from patients with obesity;
- Biobanked samples for analysis;
- Data-driven analysis tools and expertise;
- Follow-up analysis of data and definition of further biomarker analysis needs;
- Generation of a subgrouping tool, e.g. an application based on a diagnosis algorithm including a measure of the confidence level of the suggested subgroup;
- Bioinformatic expertise;
- Public-health and public relations skills;
- Capability of omics analysis;
- Access to validated platforms for analysis of bio-samples;
- Assay development;
- Data reformatting and harmonisation.

References

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[8] Corbin et al. Obesity in type 1 diabetes: pathophysiology, clinical impact and mechanisms. Endocr Rev. 2018; doi: 10.1210/er.2017-00191.

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