

Topic: Development of sensitive and validated clinical endpoints in primary Sjögren's Syndrome (pSS)

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 Actions (RIA)
Submission & evaluation process	2 Stages

Specific challenges to be addressed

Unmet medical need: Primary Sjögren's syndrome (pSS) is a common systemic autoimmune disease affecting as a hallmark exocrine glands leading to sicca symptoms of the eyes and the mouth [1]. Systemic and extra-glandular manifestations can often develop as well. A negative impact on quality of life (QOL) is prominent, mainly due to the disabling fatigue as the most important factor in loss of work productivity [1,2]. Moreover, pSS patients have 9-fold higher risk of developing B cell lymphomas [1]. Only symptomatic treatments are available for commercial use. Given the significant heterogeneity in the clinical presentation and course of patients with pSS, success in therapeutic trials will depend on a better understanding of disease phenotypes to drive patient selection and stratification [3]. There are no treatments for systemic correlates of the disease and there have been no industry sponsored studies that have been able to show a disease modifying effect.

Challenges for medicines development: Currently, published data from placebo-controlled and adequately powered clinical trials in pSS are scarce [3]. Although specific novel, validated treatment outcome measures have been developed recently, e.g. European League against Rheumatism (EULAR) Sjögren's syndrome disease activity index (ESSDAI) and EULAR Sjögren's syndrome patient reported index (ESSPRI) [4,5], their recent use in clinical trials has yielded mixed results [6,7]. Important features of pSS such as swallowing difficulties, dietary problems, mental health challenges, sexual dysfunction, dental problems (including tooth loss and decay) are not (adequately) captured. Overall, the utility of the currently available measures (including sensitivity to change in Patient Reported Outcomes (PROs) and in various ESSDAI domains) in assessing efficacy and disease-modifying potential of an investigational drug is still to be determined. Moreover, no objective validated measure or functional marker of disease activity for assessing therapeutic benefits of improvement is currently available. Sensitive and validated endpoints including objective measures/biomarkers of improvement are needed to increase the likelihood of success of drug development in pSS [8].

Scientific opportunities to address the challenge: With the growing number of clinical trials testing different treatment modalities, there is an emerging opportunity for comprehensive, integrated analysis of the data generated in the past combined with data analysis of future results from pSS clinical trials. Such a 2-tiered approach offers an unprecedented opportunity to identify additional or improved outcome measures that are sensitive, reflect the disease biology and are most suitable as endpoints for clinical trials of new drug development or may confirm the utility of the currently available pSS endpoints.

Need and opportunity for public-private collaborative research

The ability to measure and monitor clinically relevant endpoints in pSS populations to enhance clinical development and to generate payer relevant evidence of real world impact of therapeutic interventions is an early need in the field of drug development in pSS prior to the existence of proven disease-modifying therapies, and therefore well suited for a public-private consortium.

The ability to measure and monitor clinically relevant endpoints in pSS populations is an early need in the field of drug development in pSS prior to the existence of proven disease-modifying therapies. Furthermore, enhancing clinical development and generating payer relevant evidence of real world impact of therapeutic interventions will be important. This effort is well suited for a public-private consortium.

The identification, development and validation of clinical endpoints in pSS will benefit most from public-private collaboration between pSS clinical sites/ centers, academic and industry experts and regulatory authorities. In addition, the value and impact of the proposed project will be further enhanced by a collaborative partnership with patient advocacy groups, the care-giver community, and privacy and bioethics experts to ensure that the solutions developed can be adopted in the real world.

While outcome measures have been recently proposed and introduced into clinical trials by efforts of the academic community, large, randomized placebo-controlled clinical trials applying and validating these endpoints are lacking. There are regulatory uncertainties with respect to the best registration endpoints for pSS. Involvement of health authorities, patient groups and the pharmaceutical industry can help cover further aspects of and needs for these outcome measures, and generate larger datasets –those can be a challenge if handled by the academia alone.

Clinical parameters as well as novel biomarkers (including laboratory and imaging tools) would help better characterise this heterogeneous population, allowing to link the mechanisms of the disease with clinical manifestations, disease severity and progression. A better patient phenotyping will also be beneficial in the understanding of the clinical endpoints behaviour and response to therapy.

Scope

The overarching objective of this proposal is to develop sensitive and validated clinical endpoints for use in future clinical trials of pSS.

The major scope of this effort will be the identification, development and validation of pSS-related outcome measures including clinical, PRO, laboratory, bio-behavioural activity and imaging parameters (biomarkers), applying the following step-wise approach:

- Data generation and review. Existing data including published epidemiology data, results from interventional and non-interventional studies, and from pSS registries will be reviewed and analysed. As a key contribution to this step, data from prospective, randomized, controlled clinical trials comprising baseline data and longitudinal data from the control (placebo) groups in Phase 2 (or Phase3 if available) trials from the participating industry partners will be made available.
- Development of new outcome measures based on the review and analysis activities.
- Application and validation by prospectively testing of these proposed new pSS outcome measures, as well as existing ones, in (at least one) dedicated, prospective clinical trial. It is anticipated that this future clinical study will be an interventional clinical trial adequately designed to determine if the endpoint model is sensitive to detect treatment differences for use in registration trials.
- Analysis of the outcome of the validation trial and validation of the new endpoint(s). The performance of the new outcome measures or scoring systems will be compared to that of the existing ones, with the purpose to select the most promising outcome measures for future validation.

It is anticipated that the scoring system(s) will require a combination of objective and subjective outcome measures to improve upon existing scoring systems (e.g., selected, core set of ESSDAI domains combined with ESSPRI fatigue or other key PRO items).

If industry sponsored, large e.g. Phase 3 trial(s) are conducted for novel therapies in parallel with (but independently of) the validation trial during the project, the proposed new endpoint(s) may be included as exploratory endpoints in the Phase 3 trials to increase power and robustness of the validation. The analysis of these trials may, however, occur after this IMI project.

Health technology Assessment (HTA) and payer views and expectations will be integrated in determining the endpoints for regulatory approval and market access requirements. Input from patient groups will also be sought and considered in the analyses to capture relevant and currently underestimated or ignored disease aspects.

Expected key deliverables

Expected deliverables will be a set of sensitive and validated pSS outcome measures with potential regulatory and market access consensus.

The project is also expected to provide evidence for the characterization and usefulness of the currently available outcome measures (e.g. ESSDAI or ESSPRI).

The following deliverables are anticipated from the project:

- (i) Identification and characterization, (ii) prospective qualification and (iii) regulatory acceptance of disease scoring tools to assess key features of pSS including disease activity, organ specific improvement and reduced damage under therapy.
- Identification and validation of a biomarker or sets of prognostic markers that could be used as a surrogate endpoint(s) in Phase II trials, and which would be early predictors of long-term organ specific changes or adverse systemic outcomes, for example lymphoma development.
- Development of an endpoint model to determine what the patient- (and payer-) relevant endpoint measures are, independent of where treatments have an effect. The endpoint model will be used to develop a relevant patient reported outcome measure that can be deployed in future clinical trials.
- Development of a suitable methodology to capture semi-continuous bio-behavioural activity data in pSS patients by exploring activity patterns and features which are specific to pSS fatigue symptomatology.
- Patient phenotyping to characterize different subgroups of pSS (being a heterogeneous disease). For this, clinical data as well as established and novel biomarker data will be used that could identify commonalities and differences across subgroups as well as response to therapies.

Expected impact

This project is expected to enhance the development of new systemic treatments in pSS and influence the regulatory guidelines. It is expected to result in more efficient clinical trial designs that will minimize the number of subjects required to be able to detect statistically significant and clinically meaningful differences between treatments. The optimal duration of clinical studies required to demonstrate these differences will also be characterized. Furthermore, new relevant outcomes will have potential to optimise pSS patients' management, and large data sets about the natural history of the disease will provide information about the clinical utility of new and innovative diagnostic and treatment interventions in pSS. Engagement of important stakeholders including regulators, payers and patient advocacy groups will help capture all aspects of pSS.

Consequently, improved and innovative therapies are expected to emerge and be available to pSS patients whose health-related quality of life and productivity will eventually improve. Selection of the optimal treatment for the right patient in a clinically and molecularly heterogeneous disease will be made possible in pSS.

Overall, the project goals and expected impact are in line with the predefined IMI2 Goals (Article 2 of the IMI2 Council regulation, points i. through iv.) in the following aspects:

- the success rate in clinical trials for pSS is expected to increase;
- time to reach clinical proof of concept in medicine development is expected to be reduced for pSS;
- new therapies for pSS for which there is a high unmet need would be developed;
- diagnostic and treatment biomarkers would be developed for pSS.

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 .

Projects and initiatives that may be considered for collaboration by the applicants are:

HarmonicSS (http://cordis.europa.eu/project/rcn/207205_en.html), a Horizon 2020 ongoing project. One of the goals of HarmonicSS is the “Data generation and review”, that is very similar to the scope of this topic. Thus, a collaboration with this project would allow a more rapid progression and a more thorough and extensive data analysis. The synergy of the two initiatives would therefore be of mutual benefit. The prospective validation trial may also be done in collaboration.

PRECISESADS (www.precisesads.eu), a IMI ongoing project that aims to molecularly reclassify Systemic Autoimmune Diseases.

EULAR (www.eular.org) task force responsible for classification guidelines and EULAR sponsored EU pSS registries, e.g. Big Data Sjogren Project (EULAR-SS Task Force International Network) and Systemic Involvement at Diagnosis Evaluated by the ESSDAI in 3314 Patients with Primary Sjögren Syndrome [9]

In addition, collaborations with transatlantic projects and initiatives such as ones by the American College of Rheumatology (www.rheumatology.org) and/or by the Sjögren's Syndrome Foundation (<https://www.sjogrens.org>) may also be considered.

Industry consortium

The industry consortium will contribute the following expertise and assets:

- Program management to oversee budgets, timelines, and administration of all uniform processes and procedures including confidentiality agreements, master contracts, budget templates, and institutional review board/ethics committee processes
- Clinical trial design including adaptive design and the use of modelling/simulation and predictive analytics for determination of dose selection, sample size, and other parameters
- Clinician, clinical pharmacologist, statistician or clinical scientist from each company to act as a company network champion and facilitate company communication and participation with the network.
- Clinicians for communication, on-site visits, and other interactions with academic medical centres, investigators, and advisory boards
- Biostatistical/ data management expertise to co-lead central network data coordinating centre, co-maintain central organization website, and co-lead installation of needed performance monitoring tools and procedures at all participating sites
- Regulatory expertise in interacting with the European Medicines Agency EMA, and other regulatory health authorities
- Clinical operations including feasibility assessment, Informed consent forms and assents, recruitment and retention of subjects, clinical trial monitoring, and assessment of trial performance metrics
- Business planning and development; contractual agreements
- Financial planning and implementation
- Legal counselling
- Industry-sponsored clinical trials and the data generated from such clinical trials to test the viability of the network.

Studies will be sponsored and 100% funded by the respective company including the cost of full time equivalents and other expenses to run the studies, including but not limited to clinical research organisation CRO costs, laboratory costs, investigator and institutional costs. For sites belonging to the network and for other network related services, payments will be based on respective agreements with network related sites and/or network scientific advisory groups.

Indicative duration of the project

The indicative duration of the project is 72 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 expertise and resources:

- Experience and know-how in conducting clinical trials in Sjogren's;
- Expertise in the science of drug development including all aspects of clinical pharmacology and study design and conduct;
- Access to a large representative pSS population(s);
- Expertise in patient reported outcomes, development and validation;
- Physicians and other health care providers covering the spectrum of clinical manifestations of pSS (rheumatologists, dental care etc);
- Patient advocacy organisations able to actively contribute to development and standardisation of study procedures and processes, to assess feasibility, clinically meaningful endpoints, and risk-benefit;
- Expertise in developing regulatory guidelines and in interacting with EMA or national regulatory authorities
- Expertise in interacting with national payers (e.g. the National Institute for Health and Care Excellence) will be also important to success;
- Information technology/ data management;
- Expertise in legal and clinical compliance aspects (International Conference of Harmonization) and Good Clinical Practice;
- Strong project management and communication expertise;
- Office administration and website management.

Efforts should be made to include organisations in as many European countries as possible from the outset as part of the applicant consortium. Small–Medium Enterprises (SME) are also welcome to join this consortium to bring value from a complementary perspective to the academic organisations.

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 participation including their contributions and expertise.

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

In the spirit of the partnership, and to reflect how IMI2 Call topics are built on 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 and required agreements.

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

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

Sustainability

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

Work Package 1: Project Management and Oversight of IMI project

Objective: to establish a framework for collaboration and ensure minimisation of duplicative work and maximisation of sharing across the various work packages as well as to ensure strategic alignment of efforts. Specific activities include:

- project design and charters with clear accountabilities;
- set-up of joint governance structure
- provide coordination and support to work package teams
- define work expectations of different work streams, deliverables, dates, activities and review progress regarding adherence to budget, timelines and quality
- ensure key cross-functional partners are engaged
- define project interdependencies, stakeholders and risks
- ensure meetings and interactions between work packages, sub-groups, and consortium governance bodies to coordinate and follow-up on work effort

Industry contribution

- Project Management support with project design and day-to-day operation,
- Legal expertise, Clinical Operations, Data Management, and Clinical expertise to support regular review of deliverables regarding quality and operational ability
- Industry co-leads to contribute to consortium governance structure and meetings
- Ensuring the implementation and maintenance of ethical requirements, e.g. patient informed consent forms, data anonymization etc.

Expected Applicant consortium contribution

- Ensuring the implementation of the coordinating tasks and running the day-to-day operation, such as project tracking and reporting, meetings, internal communication, budget management, etc.
- Ensuring the implementation and maintenance of ethical requirements, e.g. patient informed consent forms, data anonymization etc.

Work Package 2: Understanding of pSS disease mechanisms and outcomes

Objective: to evaluate currently available evidence as well as prospective clinical trial data to set up the scientific consensus necessary to support designing for outcome measures.

Industry contribution:

- clinical trial data (prospective clinical trials considered from the start of the project as well as existing data from clinical industry sponsored clinical trials)
- clinical, medical and drug safety expertise;
- expertise in Health Economics and Outcomes Research (HEOR), epidemiology, and translational science;
- medical writing and medical communication expertise;
- biomarkers operational deployment;
- specific expertise, investigational/diagnostic products, related centralised bioanalytical facilities, operations to deliver results and reports.
- work package co-chairs.

Expected Applicant consortium contribution:

- expertise in conducting literature reviews and on determining relevant outcomes in collaboration with multiple stakeholders including academic environment, regulatory agencies, HTAs, payers, clinical research organisations, patient organisations and advocacy, and cooperative international groups.
- expertise in developing and validating new patient reported outcome measures
- data management and statistical programming expertise
- expertise in medical research
- scientific clinical expertise in biomarkers
- biomarker assay implementation per protocol

Work Package 3: Generation of novel endpoints, design and execution of clinical trial to validate pSS endpoints

Objective: to plan and conduct dedicated clinical trial(s) including novel as well as conventional endpoints based on data generated in WP2

Industry contribution:

- providing expertise in randomized clinical trial initiation and conduct
- oversight over the study management, and the accomplishment of overall objectives

- technical and logistic assistance for the meetings of the study committees, etc.

Expected Applicant Consortium:

- experience and expertise in conducting clinical trials including clinical and care facilities and adequate trained physicians and specialised personnel to implement the clinical trial protocol;
- state-of-the-art expertise in the field of primary Sjögren's syndrome;
- efficient patient recruitment capacity by using territorial network

Work Package 4: Evaluation of validation trial results

Objective: To evaluate clinical trial data, with special attention to the outcome measures in order to draw the necessary clinical and regulatory conclusions regarding their future use in trials (with potential regulatory and market access consensus).

Industry contribution:

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

Expected Applicant consortium:

- data analysis
- active contribution to constructive discussion with regulators and payers to achieve scientific and regulatory agreement over the interpretation of study results.
- consolidation of the scientific consensus to support sound operational definitions in terms of use of clinical trial
- co-authoring of reviews and white paper(s).

Work Package 5: Engagement with key stakeholders including health authorities and payers

Objective: consensus with health authorities and payers regarding the use of new endpoints for regulatory approvals and reimbursement, respectively, in the management of primary Sjögren's syndrome

Industry contribution:

- expertise in developing proposals and recommendations to gain regulatory acceptance, including writing of briefing books as well as presentations of positions and supporting arguments
- regulatory, and reimbursement expertise;
- partnerships with relevant stakeholders based on common goals;
- editorial support;

Expected Applicant consortium contribution:

- medical/scientific community: establish link between clinical outcomes and value creation (for individuals and society); insights on future developments in diagnostics and therapeutics;
- regulatory, reimbursement, HTA bodies and patient organisations: healthcare delivery needs, gaps and opportunities; insight into policy evolution and potential changes;
- patients' advocacy and representative groups: provide point of view of patients in terms of relevant outcomes and current challenges within healthcare delivery.

Work Package 6: Legal and ethical compliance

Objective: Develop and maintain ethical and legal framework to provide guidance on patient confidentiality and data sharing and ownership throughout the project

Industry contribution:

- Expertise in legal, ethical, compliance, communication.

Expected Applicant consortium contribution:

- Expertise in legal, ethical, compliance; patient advocacy, and technical writing support

Work Package 7: Communication

Objective: to define and execute overall communication strategy for the project including internal as well as external publications, dissemination of results, web postings, repository of key documents, and quality assessment of documents.

Industry contribution:

- medical communication;
- media interactions;
- medical writing;
- contact with healthcare provider professional organisations and their communication groups,
- contact with patient organisations.

Expected Applicant consortium contribution:

- pharma communication and/or media expertise;
- Health care professional organisations
- clinical expertise in the key diseases areas;
- guideline commissions;
- expertise on payers / healthcare provider financing;
- market research organisation

Currently, Novartis, as the initiator of this call, is being proposed to assume the role of the co-ordinator/project lead. In order to facilitate the formation of the final consortium, all beneficiaries will be encouraged to discuss the weighting of responsibilities and priorities therein. Until the roles are formally appointed through a

Consortium Agreement, the proposed project leader facilitates an efficient negotiation of project content and required agreements.

Glossary

EMA	European Medicines Agency
ESSDAI	EULAR Sjögren's syndrome disease activity index
ESSPRI	EULAR Sjogren's Syndrome Patient Reported Index
EULAR	European League against Rheumatism
HTA	Health Technology Assessment
NICE	The National Institute for Health and Care Excellence
PRO	Patient reported outcome
pSS	primary Sjögren`s syndrome
RCT	Randomized controlled trial
QOL	quality of life

Indicative text