Second workshop sharing opinions of patients, experts and health authorities on Patient Reported Outcome Measures in primary Sjögren's syndrome

Several members of the NECESSITY Patient Advisory Group (PAG) participated to a workshop organized on January 21st 2022 by the NECESSITY consortium.

This document is a summary of the workshop intended for the Sjogren's patients.

1. Objectives

This workshop was organized in the context of Work Package 8 (WP 8) which aims at reaching consensus with key stakeholders regarding the use of current and new measurement tools in clinical trials.

That event was focused on Patient Reported Outcomes Measures.

Specifically, our goals were to:

1) Gather expectations from patients, regulators and payers on existing and new Patient Reported Outcome Measures (PROMs),

2) Determine how to translate improvement in PROMs into Health Economics benefit.

2. Participants

This workshop brought together 23 participants representing the NECESSITY consortium (academia and industry), Health Technology Assessment experts (approving new drugs for market), payers (setting the level of reimbursement of drugs), and patient representatives.

3. Progress report on NECESSITY: the STAR index

NECESSITY aims at developing new tools (endpoint, biomarkers) to improve the design of clinical trials in Sjögren's Syndrome and speed up the discovery of new therapeutic options.

The NECESSITY consortium has developed a new score called the 'Sjögren's Tool for Assessing Response' (STAR). The STAR is a composite responder index. "Responder" means that it determines

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whether a patient responded to a treatment or not. "Composite" means that it combines different domains to measure the effect of the drug on all the important aspects of the disease.

The STAR has five domains: systemic activity, symptoms as reported by the patient, lachrymal gland function, salivary gland function and biological markers. These five domains were identified as very important to be improved by 76 experts in rheumatology, internal medicine, oral medicine and ophthalmology, and by 20 patients. For each patient, we look at the clinical and biological data and determine if each domain has improved, or not. If the domain has improved, the patient gets the points for that domain. The points are then added up. If the total score is 5 or more, the patient is considered as responding to the drug.

The intent is for the STAR to be used as an efficacy endpoint in clinical trials to speed up the discovery of new effective drugs in pSS. Because STAR allows the identification of patients responding to a treatment by looking at improvement of all aspects of the disease, this new tool allows a global evaluation of the effect of the drug, contrary to current tools used in trials, which are more restrictive. Moreover, this also allows the STAR to be used on all types of patients: those with symptoms only, and those with systemic activity and symptoms.

After this preliminary validation, the STAR will go through two more rounds of validation such as during the NECESSITY clinical trial, opening in April 2022.

The development process including experts and patients ensured that the tool was relevant for the clinician and the patients. It is also important that this tool be recognised as important by the entities who have the authority for marketing of new drugs. Consequently, the team sought advice to the EMA (European Medicines Agency) on the STAR and next steps for validation. The EMA has written a letter of support for STAR to encourage others to use it in future clinical trials.

4. Expectations on Patient Reported Outcome Measures (PROMs)

The Patient Related Outcomes (PRO) are directly reported by the patient without interpretation of the patient's response by a clinician or anyone else. The PROs relate to the patient's health, quality of life, or functional status associated with health care or treatment. The Patient Related Outcome Measures (PROMs) are the tools or instruments used to measure PROs.

Presentation of the PEPSS webapp, developed by NECESSITY

The NECESSITY consortium has developed a web application called PEPSS. The patients access this tool through an online secure website on their computer, tablet or smartphone. The patients fill in questions about the level of dryness, pain, fatigue and the number of eye drops used. The tool

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allows self-reporting of symptoms on a daily basis and in an "ecological" setting, in other words in an environment that is part of the daily routine of the patients. This aspect is important because visits at the hospital can be stressful and may influence the score given by the patient at the time of the hospital visit. Also, it is reported that symptoms are very variable from one day to another so the scientists wonder if measuring symptoms at specific time points in a clinical trial is really representative of what the patient feels on a daily basis. This tool will be evaluated during the NECESSITY trial to determine how useful it is for assessing the efficacy of a new drug in clinical trials.

Presentation of the results of the patient survey on PROM

Ahead of this workshop, a survey was organised to collect the opinion of the patients on the "conceptual coverage" of the PROs used in the NECESSITY trial, in other words whether the patients think that the PROs do include all the symptoms or impact of their disease on their daily life. The online survey was disseminated among the NECESSITY Patient Advisory Group.

In that survey, the patients reported that dryness is the most bothersome symptom and they found fatigue to be the symptom most in need of improvement. The patients indicated that physical wellbeing is the most important aspect of Health Related Quality of Life (HRQoL) they would like to see improved. In conclusion, the PROs used in the NECESSITY Trial cover both important aspects for the patients: the most bothersome symptom and the one patients would like to be improved the most. The PROs capture the most relevant patient burdens reported by the patients (dryness, pain, fatigue, physical wellbeing). The PRO instruments need to be used in combination to cover most of the patient needs.

Some useful suggestions have been provided by the patients which can be explored further. For example, they suggested adding questions to compare symptoms perceived by the patients at the time of the hospital visit to 1 month, 1 year, 3 years ago, to understand the evolution of the disease from a patient perspective as the disease gets slowly worse over time.

Group discussion on PROMs – key points raised by the patient representatives

- The patients agreed that a combination of PROMs would cover most needs, but they advised to consider the burden for the patients.
- They noted that paper questionnaires are more suited to Sjögren's Syndrome patients than online tools (eye dryness/screen).

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- They stressed that brain fog is not covered by the PROs in NECESSITY, however it is an important aspect of physical well-being for the patients.
- They advised to cover both mental and physical fatigue separately as patients may report different level on both.

5. Translation of improvement in PROM in Health economics benefit

Many countries consider the value for money when deciding on market authorisation and reimbursement price for new drugs. To that end, Health Economics analysis measure and compare costs and outcomes to assign a perceived value to that intervention. To define the overall value, the efficacy, safety and Quality of Life are combined. Quality Adjusted Life Years (QALYs) are used in Cost Utility analysis. The QALYs combine two attributes (length of life i.e. mortality, and quality of life i.e. morbidity) into a single number.

The NECESSITY trial will include the EQ-5D-5L questionnaire for collecting health-related quality of life data which can be derived to determine utility. The NECESSITY trial will not collect cost data so it will not be possible to provide Cost Utility data from this study. If the active arms demonstrate benefit then improvement in QALYs can be determined.

One goal of NECESSITY is to provide advice on Health Economics aspects in a guidance, published by the project participants, that will set out the unmet need, the scientific validity of the outcome measures and how improvement can translate into improvement in Health Related Quality of Life, Quality Adjusted Life Years and economic benefit based on a similar process in other disease(s).
A draft text of the planned document will be discussed as one of the objectives of a final Workshop planned towards the end of the NECESSITY IMI study once the outcome of the NECESSITY clinical trial is available.

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