European clinical trials: the example of the NECESSITY project

The French Sjögren association AFGS is a partner in the European research project on primary Sjögren's disease, NECESSITY (necessity-h2020.eu), which has three objectives:

- NECESSITY aims to develop new evaluating scores based on clinical or biological elements of the disease, with the ambition of providing **new clinical endpoints** to best assess the effect of treatments in future clinical trials for primary Sjögren's disease (Objective 1).
- NECESSITY aims to discover and validate discriminating **biomarkers** for the **stratification** of patients with primary Sjögren disease (Objective 2).
- Finally, these new clinical endpoints and biomarkers will be validated in an original **clinical trial** evaluating several combinations of treatments (objective 3).

Here are some explanations on these complicated concepts to better understand the objectives of NECESSITY.

Conduct of a clinical trial in Europe

In the NECESSITY project, the planned clinical trial (objective 3) is used to validate the work carried out in the first two stages (objectives 1 & 2). In order to understand fully the reason for this research and its development, it is necessary to know the procedures to which any clinical research project must adhere.

What is a clinical trial?

A **randomised clinical trial** is a scientific study used to assess the efficacy and safety of a treatment (can be a new molecule or a known molecule being applied to a disease that is not currently approved for its treatment). It works like this: first, participants are selected by healthcare professionals in accordance with specific criteria called **inclusion criteria**, which ensure that the included patients have the right characteristics for participating to the study. They are provided a patient information sheet with the study details for them to choose to participate or not. They then give their informed consent. After this, participants are randomly assigned (like a coin toss, this is called **randomisation**) into two or more groups or 'arms'. One group receives a placebo (an inactive treatment) known as the control group, and the other group or groups receive active molecule treatment(s), known as active group. Neither the patients nor the clinical team in charge of the study know which treatment is being given to which group (this is known as **'double blinding'**). This makes it possible to compare the effects of the treatments objectively without bias and to ensure that the results are reliable. The aim is to determine which treatment is most effective and safest for patients. In the NECESSITY trial, there are 3 arms, one placebo and two with two different active arms.

Application for authorisation of a clinical trial.

Any **clinical trial** involving a medicinal product taking place in Europe must be submitted via the **European CTIS portal** (Clinical Trial Information System; Regulation (EU) no. 536/2014). A single application for authorisation, covering all the countries involved in the trial, is submitted in English via this portal. Among other things, the sponsor submits the protocol and the information notice and informed consent documents for participants and proposes a Member State to act as rapporteur for all the countries involved (called reporting Member State).

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For the trial to be authorised, the sponsor must obtain the favorable opinion from two types of official bodies:
Firstly, the favorable opinion of the Medicines Agencies in each concerned Member State, which perform an analysis of the scientific aspects of the trial and come to an agreement on a unified final protocol;
Secondly, the favorable opinion of the Ethics Committee of each concerned Member States, which review more specifically all the documents sent to the participants and issue their opinion country by country.
The Medicines Agency of the reporting Member State is responsible for issuing the final opinion. If a country's Medicines Agency is not in favour, the trial is not authorised in that country. For a country involved in a trial, even if the reporting Member State, on behalf of the participating States, and this country's Medicines Agency issue a favorable opinion, if this country's Ethics Committee issues an unfavourable opinion, the trial cannot be carried out in this Member State.

The NECESSITY clinical trial has obtained the joint favorable opinion of the Medicines Agencies and the respective favorable opinions of the Ethics Committees of the 8 concerned Member States. As France is the reporting Member State, the final opinion was issued by the ANSM (French Medecines Agency) on behalf of all the other Member States involved. The NECESSITY trial has started in all participating countries, and almost all centres have begun enrolling patients (a participant in the trial is said to be 'included' after having consented to participate in the clinical trial).

Analysis of the results of the clinical trial.
To assess the efficacy of a drug tested in a clinical trial, objectives are set:
Primary objective and secondary objectives. These **objectives correspond to primary endpoints** (usually only one primary endpoint) **and secondary endpoints**. If the primary endpoint is not satisfied, the primary objective is said not to have been achieved and the trial is said to be negative. The secondary objectives also count, but they are not what will qualify the trial as positive in order to authorise the marketing of a drug. For this to happen, the primary endpoint must be imperatively met.

The example of NECESSITY

The title of the NECESSITY project - NEw Clinical Endpoints in primary Sjögren's Syndrome: an Interventional Trial based on stratifYing patients - shows that the aim of this project is to find new endpoints and new patient stratification to be used in clinical trials.
Up to this moment in time, clinical trials on Sjögren's disease have not been able to prove the efficacy of a drug to treat the disease. The existing primary endpoints that are used by the scientific community in the field of rheumatology for evaluating a clinical trial have not shown positive results (the often used endpoint: ESSDAI - EULAR Sjögren Syndrome Disease Activity Index). On the other hand, if we analyse the secondary endpoints, some have been met for certain populations in certain trials. It is therefore necessary **to define a new primary endpoint and stratify the participants to evaluate efficacy of a clinical trial**. This is why the NEVCESSITY project was initiated, in order to develop a new primary endpoint, which was developed by researchers and patients in 2022. We called it STAR - **S**jögren **T**ool to **A**ssess **R**esponse - (the opinion of Sjögren's patients was taken into account during the development phase of STAR). It is being gradually used in clinical trials by the scientific community. Some of the trials that have used STAR show its ability to capture efficacy of a molecule at improving

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patients health state as compared to ESSDAI. The NECESSITY clinical trial has been developed to validate the capacity of STAR to capture the efficacy of treatment in Sjogren's patients, it is currently in stage of active inclusions.
In most of the trials conducted to date, the participants included had significant systemic organ involvement from their Sjogren's disease, and patients with only symptoms were not included. The NECESSITY trial includes a group of patients with severe symptoms but little systemic organ involvement and a group with significant systemic organ involvement and few or no symptoms. This study design will make it possible to assess the response to treatment in these two groups. **STAR evaluates both systemic and symptomatic responses to treatment.**
As far as **stratification** is concerned, new biomarkers are being studied by the project's researchers (objective 2) and will make it possible to establish patient profiles that can be used to better identify patients for inclusion in future trials.

Would you wish to participate to the trial, please contact **your** physician.

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