Lay summary of research project grant application

1. **Objective of the project**

The global aim of this project is to determine which aspects of spondyloarthritis are treatable (or not) with anti-TNF versus anti-IL17A therapy and to use this information to determine which treatment should be given to which patient. The specific research questions are:

- What is the impact of IL-17A and TNF blockade on pathways of inflammation and structural damage in SpA patients?
- Can we identify "pathogenic pathways" that are modulated by one but not the other treatment?
- Can the information in these pathways define criteria ("biomarkers") to decide if SpA patients will benefit from one but not the other treatment?

2. **Background**

Anti-TNF is a powerful treatment for patients with spondyloarthritis, including ankylosing spondylitis and psoriatic arthritis. Anti-TNF, however, is not effective for all aspects of disease (for example: it does not halt ankylosis) and for all patients. Anti-IL17A, recently approved by EMA, is now appearing as a second good treatment option for patients with spondyloarthritis. We do not know, however, which patient or which disease manifestation will benefit most from treatment with one versus the other biologic drug. A first step towards 'tailored' treatment is to understand better which cellular and molecular processes involved in the disease are differentially modulated by one versus the other treatment. This 'biologic' profile could then be matched to a specific patient subset, which would optimally benefit from the treatment with either anti-TNF or anti-IL17A. In other words: understanding how exactly these two powerful treatments work is a first but crucial step to determine who should benefit most from the treatment.

3. **Methods and approach**

In a collaborative effort between 4 centers in 3 countries we will use 'high-tech' approaches to measure how anti-TNF and anti-IL17A modulate key features of SpA. We will include patients in 4 small studies where we measure biologic features of the disease before and after treatment. All studies will be aligned in terms of inclusion criteria, treatment protocols, and standard clinical assessments, sticking as closely as possible to standard clinical use of these treatments. As the purpose is to compare anti-IL-17 with anti-TNF, all patients will receive active treatment (no placebo groups) and the number of patients remains small (n=20 per group, as the primary aim is not to assess differences between patients in on single treatment arm). Whereas the study design is thus simple and patient-friendly, the baseline and post-treatment measurements themselves are high-tech. They include: biopsies from the inflamed joints, peripheral blood sampling, and CT imaging.

4. **Primary and secondary outcome measures**

   The primary outcomes of the 4 studies are the 'biologic' measurements. Obviously, classical safety and efficacy data will be collected as well.

5. **Recruitment of participants**

   The patients will be recruited from the outpatient clinics based a clinical indication (according to registration and guidelines) to start a biologic. Patient organizations, such as the 'Bechterew stichting' in the Netherlands are actively involved to help for recruitment.

6. **Expected benefits for patients**

   For the participating patients, there is no direct benefit from the studies except from being treated with a powerful biologic drug.

7. **Expected benefits for society**

   The studies will yield important information for our understanding of response or non-response of specific disease characteristics to the initiated treatment and may thus help to better tailor the treatment to specific patients in the future.

8. **Burden for patients participating in this study**

   Patients will be treated with either anti-TNF or anti-IL17A based on a clinical indication for these treatments (in other words: they would also receive this treatment if they were not participating to the studies). So the treatment itself is not a burden but a benefit for the patient. The extra-investigations in the different studies are: synovial biopsies, peripheral blood sampling, PET-CT of the spine, or high resolution CT of the hands. We know from previous studies that the burden of these investigations (when performed in experienced centers) is much lower than generally assumed. For example, synovial biopsy sampling is considered less 'stressful' than MRI by our patients.

9. **Patient involvement in the design and conduct of the study**

   Patients and patient organizations will be involved at two crucial stages of the project. First, they will actively contribute to promote recruitment. Second, a lay advisory board of patients will be instrumental in the interpretation of the data, in particular in addressing the question if and how the anticipated biologic profiles can be applied in a useful way to stratify individual patients or patient groups to anti-TNF versus anti-IL17A treatment.