# PREDIRA (PRediction mEdical DevIce for Rheumatoid Arthritis): Scale-up of unique predictive online platform highly improving the quality of life of Rheumatoid Arthritis' patient by personalized and efficient biotherapies prescription

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# Abstract

Background: Rheumatoid arthritis (RA) is one of the leading chronic inflammatory rheumatism. First-line therapy with synthetic disease modifying anti-rheumatic drugs (sDMARD) is insufficiently effective in 40% of cases and these patients are treated with biotherapies. The increases use of these drugs each year is becoming a public health issue with considerable economic burden. This cost is 20 times higher than that of sDMARD. However, among patients treated with biotherapies, clinical practice shows that about one-third will not respond to the selected drug. In non-response cases, practitioners currently have no choice but to perform an empirical switching between different treatments, because no tool capable of predicting the response or non-response to these molecules is currently available.

Methods : The study is a prospective, phase III, controlled, multicenter, and randomized, single-blind (patient) clinical trial, including RA patients with a previous failure to anti-TNF therapies. The main objective is the analysis of the clinical and pharmacoeconomic impact after 6 months of treatment. Intervention arm: Prescription of biotherapy (rituximab, adalimumab, abatacept) using SinnoTest® software, a prediction software based on proteomic biomarkers. Control arm: Prescription of biotherapy based on current practice, without the SinnoTest® software (any biotherapy). In addition, a sub study will be carried out within this trial to generate a biobank and further analyze the proteomic profile of the patients and their modification throughout the study.

Discussion : This clinical trial study will be the first validation study of a biotherapy response prediction software, bringing personalized medicine into the management of RA. We expect that the findings from this study will bring several benefits for the patient and the Health Care System. Trial registration : The study was registered at clincaltrials.gov (NCT04147026). Registered on 31 October, 2019.


# Introduction

### Background and rationale {6a}

Rheumatoid arthritis (RA) accounts for a large proportion of chronic inflammatory rheumatism (CIR) with a prevalence of 0.4% in the Caucasian population (1) and an incidence of 9/100 000 (2). Chronic inflammation is clinically manifested by pain and morning stiffness and can lead to joint destruction, often leading to a major functional disability in the medium term (3). RA is the result of genetic determinism and environmental factors leading to increased circulating levels of many cytokines. Inhibition of these cytokines, such as Tumor Necrosis Factor (TNF-α), interleukin (IL) -6, is a logical approach that has allowed a disruption of the treatment of these pathologies. Gradually since the 2000s, biological Drug Modifying the Activity of the Rheumatic Disease (bDMARDs) were added to the existing therapeutic arsenal. There are currently different bDMARDs including TNF-α antagonists, anti-IL-6 receptor, IL-1, a T cell anti-activator and a B-CD20 + anti-lymphocyte. But several molecules among the bDMARDs are still ahead and may complicate therapeutic strategies in RA.

However, practitioners currently have no alternative but to make an empirical choice between different biological treatments, as no tool is able to predict the response or non-response to these molecules. In case of nonresponse of their patient, the practitioners thus perform an empirical rotation between the different treatments. This vision of the choice of bDMARDs or tsDMARDs (targeted synthetic DMARDs) has led to practices such as “switching of biotherapies".

In fact, the personalized and early management/care of the patient requires not only the development of new tools to improve the diagnosis and the severity of the pathology to better identify patients at risk of structural progression or complications (Personalized management), but also by prediction tools allowing an adapted AND early treatment (early management of the patient).

Indeed, the demonstration of the superiority of early treatments and the provision of close monitoring of disease activity in order to regularly readjust the therapeutic strategy have been demonstrated in numerous studies cited in the synthesis of Combe's literature and al. (4). It is now established that the prognosis of the disease is in part determined by the "tight" control of rheumatism activity guided by frequent assessment of activity of rheumatism, keystone of optimization of the management of the patient of patient (5). The goals of RA treatment are the control of joint pain and inflammation, the prevention or limitation of structural lesions, the maintenance of life quality and socio-occupational integration.

The international recommendations of learned societies of rheumatology for the treatment of RA suggest 3 phases in its treatment with the consideration of factors predictive of radiological evolution. The therapeutic choice in phase I does not pose too many problems. However, in case of inadequate response to a first synthetic treatment, phases II and III are much more open with a large number of therapeutic options. The choice between the bDMARDs and tsDMARDs (6) is made empirically and based on subjective parameters such as the patient's preference, that of the doctor, most comfortable pharmaceutical form, patient profile, etc.

The switching between biological treatments is currently the recommended strategy in case of inadequate response to a bDMARD. However, selection of the new therapeutic option is not well-defined when managing bDMARD failure.

Rheumatologists now have access to a broad range of bDMARDs beside anti-TNFa reported to be as effective (5). For unknown reasons, around 30%-50% of patients fail to respond to bDMARDs (3,4). The reason why some patients respond to TNFi and others respond better to non-TNFi biotherapy remains elusive. In the absence of well-defined international recommendations, the available data favour a personalized approach, tailoring treatment to each individual patient. Thus, currently rheumatologist does not have evidence-based knowledge to choose the most suitable bDMARD for his patients and these biologics are often prescribed in a ‘trial-and-error’ manner. From this situation non-responders are unnecessarily exposed to undesired side-effects along with the worsening of their physical condition. Furthermore, the ineffective use of biologics has a dramatic burden on the medico-economic resources regarding the important cost of these treatments (5). Thus the major current challenge in RA therapy is

being able to predict drug responsiveness prior to treatment initiation (7) mainly by identifying relevant predictive biomarkers. Such tool capable of providing a probability score of response or non-response to specific treatment would be an important benefit for the clinician and patients.

Over the last 15 years, considerable progress has been made in the management of RA treatment and clear data on treatment response rates are now available (7). Matrices model the risk of short-term radiological progression to predict the severity of disease (8). The combination of 12 serum biomarkers has led to a composite score, MBDA (Multiple Biomarker Disease Activity), which is associated with disease activity, structural progression, and risk of relapse in some patients (9). However, these data are not applied to the current therapeutic response (10).

As a result, the problem of nonresponse remains unresolved, especially since about 60% of patients will be non-responders or partial responders to certain biotherapies.

In order to improve the response rate to bDMARDs, research for predictive biomarkers of the therapeutic response has been active for more than 15 years (11) and falls within the scope of personalized medicine. Personalized medicine aims to optimize preventive, diagnostic, prognostic and therapeutic management at the individual level in order to choose the therapeutic options that are likely to give the best results in terms of efficacy and tolerance for a given patient.

Biomarkers use molecular biology and biochemistry. If the quest for “The" marker to predict "The" response to a biological treatment in RA is an illusion, the association of several biomarkers in intelligent algorithms seems to be a relevant solution.

In this perspective, genomics, transcriptomics, epigenetics and proteomics are complementary and non-redundant pillars allowing this search for predictive biomarkers. However, not all of these strategies have contributed benefits at present. Indeed, in genomic (12), the search for candidate genes and the replication of results on different cohorts is fragile and tedious. The hypothesis of several associated genes each having a low impact is preferred over that where few genes each with a significant effect would be involved. Its routine use remains complex. Similarly, epigenetics has provided very preliminary data for the time being (13,14). Finally, the study of the transcriptome makes it possible to identify a certain number of genes but its use is difficult on a daily basis (15) and the study of the serum metabolome remains complicated (16).

The proteomic approach, on the other hand, is innovative and simpler to use in routine: it is focused on proteins which are the terminal elements of cellular actions. It has been emerging in research for about 10 years in rheumatology for the theranostic side (17,18) but clinical applications are not routine. The latest developments in this area, especially in our laboratory, could change the management of these patients (17,19,20). These studies have made it possible to characterize biomarkers differentially expressed at baseline in patients who respond to a bDMARD compared to weak or non-responders, hoping to optimize a targeted prescription of bDMARDs (17,18,21). In order to allow a rapid translation to clinical practice,

our approach prioritizes the selection of biomarkers for which validated diagnostic assays exist, are routinely used and commercially available.

Based on identified biomarkers and predictive algorithms (17,19,20), an application called SinnoTest® has recently been validated (22,23) to determine a priori the most appropriate treatment for the patient with RA according to its clinical context (bDMARD's naïve patients or rotating patients), depending on its specific proteomic profile (predictive and personalized medicine). This medical device has also been CE marked/approved since August 2018.

The Hospital Clinical Research Program (HCRP) BIORI program of 2004 (04PHR06) was initiated to provide predictive models of anti-TNFa efficacy in first-line bDMARD patients with RA and ankylosing spondylitis (AS). The three main anti-TNFa drugs (infliximab, etanercept and adalimumab) were studied. The results of this study allowed to build an algorithm combining 3 biomarkers (pre-albumin, platelet factor 4 and S100A12) to predict the therapeutic response to the anti-TNFa class with a sensitivity of 78%, a specificity of 77%, and a positive predictive value of 72% and a negative predictive value of 82%. This study validated the proof of concept and was published in the "Joint Bone Spine" (22).

We next focused our investigation on RA patients who failed to respond to a first-line bDMARDs most frequently anti-TNFa. This patient's population correspond to a large percentage of patients admitted to rheumatology and are in urgent need of alternative treatment. Identifying the right bDMARD for each patient is critical given that, for patients who have already been exposed to TNFi, the likelihood of a response to subsequent treatment with biologics declines as the number of previous TNFi treatments increases (24).

In addition to TNFi (infliximab, etanercept, adalimumab, golimumab, and certolizumab pegol), rheumatologists now have access to a broad range of bDMARDs targeting different immune cell types or molecular mechanisms involved in immunology – such as CD20+ B cells (rituximab), activation of T cells (abatacept), IL6 receptors (tocilizumab and sarilumab). These new molecules are reported to be as effective as TNFi (5). We developed predictive algorithms covering 3 classes of bDMARDs: Anti-TNFa: adalimumab; Inhibitor of costimulation of T cells: abatacept; Anti-B-cell antigen CD20: rituximab.

In practice, from a simple biological sample of a patient, such as blood (plasma or serum), specific protein biomarkers are assayed/quantified using routine techniques, allowing after combination through an algorithm, to associate the Patient's profile at a personalized response or nonresponse status for these biotherapies rotational patients. An online interface allows the rheumatologist to access, for each patient, the results of biomarker analysis, as well as the probability of response to different biotherapies available on the market.

The societal cost of RA has been estimated in Europe at 45.3 billion (25). A study by Meissner and colleagues (26) shows a greater overall economic impact on the health system of patients who changed bDMARD following failure of a first biological compared to those who did not change. This economic burden is even greater when the patient has to change his treatment for a second time. This phenomenon

seems difficult to reverse in case of initial misdirection since the probability that the patient who has already received an anti-TNF to respond to another biological treatment decreases gradually according to the increasing number of failures of previous treatments (27).

We hypothesize that the SinnoTest® software, a predictive algorithm for responding to bDMARDs, offers real-world medical-economic and clinical benefits by integrating the main biotherapies currently available. This study will target patients with RA in rotation of a first biotherapy due to inefficiency or toxicity. This population corresponds to a very large majority of patients admitted to rheumatology consultations.

The expected economic impact is multiple: Change in the use of care: hospitalizations, medicines, regular biological controls, outpatient stays, consultations, nursing, surgery, transportation, etc.; Reduction of the costs related to the losses of production (reduction of the incapacities at work inducing absenteeism, long-term work stoppages, putting in disability ...); Reduction of intangible costs, the assessment of which is difficult but which represents an expected social benefit of such a care strategy. In addition, we will try to show that SinnoTest® also has a strong clinical impact in terms of early adapted management via the responder rate.

### Objectives {7}

The primary objective of this clinical trial is to study the clinical and pharmacoeconomic impact after 6 months of the use of the SinnoTest® predictive tool in patients with rheumatoid arthritis who have failed to a first anti-TNF biologic agent compared to usual care. The secondary objectives will be medical-economic: budget impact analysis (BIA) at 6 and 12 months and clinical objectives as describe the performance of the software's predictive model on new clinical data from the 6-month trial.

We will also carry out a proteomics substudy with the objectives of compare the variation of the proteomic profile between the M0 (date of inclusion) and the M6 (end of study date). The achievement of this objective will be based on the constitution of a bio-bank, which will serve as a basis for future studies focused on the therapeutic management of these patients.

### Trial design {8}

This project is a prospective phase III randomized clinical trial in 2 parallel groups, multicentre, controlled (prescription of bDMARD with or without the SinnoTest® software), single-blind (the patient will not know if his bDMARD treatment has been prescribed with or without the help of SinnoTest® software). The inclusion period will be 12 months. Each patient will be followed up to 6 months (clinical evaluation) and up to 12 months (for the analysis of the budgetary impact at 12 months).

## Methods: Participants, Interventions And Outcomes

### Study setting {9}

The population studied concerns patients with rheumatoid arthritis who have failed a first anti-TNF (including inefficiency or adverse events). This situation corresponds to a very large majority of patients admitted to rheumatology consultations.

### Eligibility criteria {10}

Patients meeting the criteria below will be eligible in the study: Patients over 18 year old and under 70 years old with RA, defined according to the ACR / EULAR 2010 or ACR 1987 criteria; Patients failing a first anti-TNF, defined as ineffectiveness (which is defined as a DAS28-ESR ≥3.2 and an inadequate response to iTNF according to the usual rheumatologist, which generally includes one or more of the following conditions: persistent swollen and tender joints, persistence of disease activity according to the overall evaluation of the patient, high levels of acute phase reactants and/or dependence of analgesics, nonsteroidal anti-inflammatory drugs or corticosteroids) or toxicity(defined as the appearance of any adverse event that the habitual rheumatologist relates to the medication and requires discontinuation); Effective contraception for patients of childbearing potential; Patients able to read and understand the modalities of the protocol; Patients who have dated and signed the informed consent form of the trial; Stability of treatments (immunosuppressants, corticosteroids, nonsteroidal anti-inflammatory drugs) between the selection visit and the inclusion visit (M0).

The exclusion criteria will be; Patients who do not meet the criteria below will be eligible in the study; Patients with a contraindication to a bDMARD or methotrexate: Patients included in another therapeutic evaluation trial during the trial; surgical intervention programmed during the test; Patients with difficulties in understanding the Spanish language; Patients cannot be followed up at 12 months; Psychosocial instability incompatible with regular monitoring (homelessness, addictive behaviour, antecedent of psychiatric pathology or any other comorbidity that would make it impossible for free and informed consent or limit adherence to the protocol); Breastfeeding, pregnancy, although there are bDMARD that can be used in pregnancy, since SinnoTest can recommend one that discourages this condition, it is decided to exclude the inclusion of pregnant.

### Who will take informed consent? {26a}

The Investigator will be responsible for providing each patient with an information sheet about the trial and the objectives, methods, foreseeable benefits and potential risks of the study, which should be read by the patient. The investigator must explain to the patients that they are totally free to refuse their participation in the study or to abandon it at any time and for any reason. The researcher will be responsible for obtaining the written informed consent of each of the participating patients before proceeding with any medical procedure of the study. The investigator will be responsible for not involving any patient in the study without having previously obtained their voluntary consent in writing.

### Additional consent provisions for collection and use of participant data and biological specimens {26b}

In addition, for the proteomics sub study, a second independent informed consent will be collected, which will also include the possibility of storing the samples not used in the present study in the biobank of the center where it is carried out in the study and in the Biobank of the Center Hospitalier Universitaire Grenoble Alpes (France).

## Interventions

### Explanation for the choice of comparators {6b}

### Intervention description {11a}

The patients will be randomized to an intervention group (SinnoTest®) or a control group (placebo). Patients allocated to the intervention arm will receive the prescription of bDMARD (rituximab, adalimumab, abatacept) using SinnoTest® software. While those allocated to the control arm will receive the prescription of bDMARD without the SinnoTest® software which corresponds to current practice (all bDMARDs).

### Innovative procedure.

***Innovative Medical Device (IMD): SinnoTest® Software.*** SinnoTest® is a therapeutic guidance device for patients suffering from chronic inflammatory rheumatism, in particular RA. SinnoTest® consists of the following three elements: "routine" biological assay of biomarkers from a blood sample, calculation algorithm and graphical user interface (software and online application). This device was designed by the company Sinnovial. The assessment of its conformity was carried out by SurgiQual Institute.

Biomarkers are detected and quantified in blood samples of patients, using commercial tests aimed at determining the levels of these molecules. These results are sent to the SinnoTest® secure server. These data are processed by algorithms to determine the probability of response to the treatments available in the therapeutic arsenal (biological therapies). This data is sent to a secure server. The graphical user interface is an independent software, accessible through a web platform, which allows authorized health professionals to access the results of the analysis of individual patients. SinnoTest® is a stand-alone IMD-MD software, accessible via a web platform (see fig 2, 3, 4 and 5 below). Rheumatologists from the different centers will be contacted by email to register for the SinnoTest® online platform. A link in this email will provide access to the registration part of the application. The rheumatologists will then be able to connect to the SinnoTest® platform thanks to their personal identifiers.

***Process of the innovative procedure.*** The selection of the bio-drug is carried out based on the recommendations of SinnoTest®. This test categorizes bDMADR based on the probability of response. It will allow to prescribe both original molecules, as well as biosimilars, in an equivalent way. In the SinnoTest® arm, the investigator prescribes the treatment defined as the most effective by SinnoTest®, except in case of contraindication. If contraindicated, the investigator prescribes the second-choice treatment (if any) of SinnoTest® in terms of efficacy.

The bDMARDs possibly recommended by SinnoTest® are: adalimumab, rituximab, abatacept. Not being exhaustive in terms of biotherapies, it is possible that the SinnoTest® cannot recommend any bDMARD. In this case, the rheumatologist may prescribe one of the following other bDMARDs: etanercept, adalimumab, infliximab, certolizumab, tocilizumab, sarilumab, abatacept, anakinra, golimumab, o rituximab.

**Reference procedure.**

There is currently no evidence of treatment response in RA. The choice of rheumatologist is therefore empirical. In order to simplify the process and favoring blinding, regardless of which arm the patient is randomized to, the usual rheumatologist will record two treatment proposals in the clinical history. On the one hand, the treatment that he would prescribe if the patient was randomized to the control arm. On the other hand, the one that would prescribe if the patient was randomized to the intervention arm and if SinnoTest® did not recommend any treatment (therefore, the proposed treatment in this case cannot be any of the 3 potentially recommended by SinnoTest®).

At the successive visit after 6-10 days in which the bDMARD will be scheduled, if the patient was randomized to the control arm, or was randomized into an intervention group, but SinnoTest® did not recommend any bDMARD, the medication previously registered by the usual rheumatologist

***Process of the reference procedure.*** This is the current management of patients with RA, based on the EULAR recommendations. In case of rotation of biotherapy after prescription of a first biotherapy, the rheumatologist may prescribe the following bDMARDs: etanercept, adalimumab, infliximab, certolizumab, tocilizumab, abatacept, anakinra, golimumab, rituximab. All these bDMARDS can be prescribed as well as their biosimilars. In case of remission of more than 6 months, a reduction (dosage or spacing of the catch) of the biotherapy can be considered.

***Concomitant medications authorized with anti-TNFα, anti-Il-6R and CTLA-4.***

Any conventional synthetic DMARD that the patient was previously taking before being included in the study and that his rheumatologist deems necessary to continue. Oral corticosteroids at dose ≤ 15mg / day, intravenous corticosteroids, intra-articular and peri-articular local injections of corticosteroids, salicylates, non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, drugs necessary for the treatment of comorbidities, concomitant treatment with corticosteroids, NSAIDs and analgesics showed no effect on the pharmacokinetics of these biotherapies.

**Criteria for discontinuing or modifying allocated interventions {11b}**

The discontinuing or modifying allocated interventions for a given trial participant in the study will be: Lack of response to medication in the intermediate visit (3 months after inclusion) using the EULAR response criteria; Occurrence of adverse events, including malignancy; Loss of patient follow-up; Withdrawal of consent by the patient; Decision of the investigator (Inadequate follow-up of the instructions of the doctor or study staff); The rheumatologist or the promoter (medical monitor) decides

that continuing the study can be harmful to the patient; In case of pregnancy (only if the patient is under treatment with a therapy that does not recommend pregnancy, in the event that the medication is compatible with the pregnancy, the patient can still be included in the study); In case the patient needs a treatment or has received some treatment not allowed in the study; Erroneous inclusion in the study; Circumstances not foreseen; Cancellation of the study.

No treatment / procedure prohibited during the study.

**Strategies to improve adherence to interventions {11c}**

Not applicable.

**Relevant concomitant care permitted or prohibited during the trial {11d}**

Not applicable.

**Provisions for post-trial care {30}**

Not applicable

**Outcomes {12}**

**Primary Outcome Measures.**

Incremental Cost Utility ratio at 6 months (Time Frame: 6 months). This outcome will be calculated as the average differential cost per patient between both study arms (mean costs of the Sinnotest® Arm - mean costs of the Control Arm) divided by the diference in effectiveness between both study arms measured in the number of years of life weighted by the quality of life (QALY: quality-adjusted life year) generated by each of the strategies (mean QALY of the Sinnotest® Arm - mean QALY of the Control Arm).

QALY will be measured using the EuroQol-5D. Cost will be considered from a Societal perspective, including both direct and indirect costs The ratio will be expressed in cost (2019 Euros) per QALY earned, which represents the additional cost that will have to be spent to earn a healthy year of life.

**Secondary Outcome Measures.**

**Budget impact analysis at 6 and 12 months (Time Frame: 12 months).**

A budget impact analysis will be carried out if the innovation is deemed efficient.

This budget impact analysis will describe the resources consumed and the expenses generated by each scenario, a scenario with the use of SinnoTest® and a scenario without SinnoTest®.

**Software's predictive model performance (Time Frame: 6 months).**

Sensitivity, specificity, positive and negative predicted values of the predictive models using the biomarkers will be assessed on the new clinical data from the 6-month trial.

**Description of the variation of the proteomic profile between M0 (biotherapy start date) and M6 (6 months visit) (Time Frame: Inclusion and 6 months)**

Based on shotgun and semi quantitative proteomics, the differences between the proteomic profile at baseline and at M6 will be analyzed

**Other Outcome Measures.**

Incremental Cost Effectiveness ratio at 6 months (Time Frame: 6 months)

This outcome will be calculated as the average differential cost per patient between both study arms (mean costs of the Sinnotest® Arm - mean costs of the Control Arm) divided by the difference in effectiveness between both study arms measured as the percentage of patients achieving a good clinical response in each study arm (% in the Sinnotest® Arm - % in the Control Arm).

Good clinical response will be measured using the EULAR criteria of Good clinical response Cost will be considered from a Societal perspective, including both direct and indirect costs The ratio will be expressed in cost (2019 Euros) per increase in 1% of subjects achieving a Good Clinical Response, which represents the additional cost that will have to be spent to earn a healthy year of life rates of treatment-response patients associated respectively with the usual strategy without SinnoTest® and with the strategy with SinnoTest®

**Participant timeline {13}**

This study will be conducted by rheumatologists who have the opportunity to follow patients with RA and to conduct this study in good conditions and in accordance with regulatory and legal recommendations. The only difference in follow-up between the 2 groups is the addition of the "SinnoTest® Protein Biomarker" assay and the use of the results of this assay for therapeutic management.

Patients will be seen as part of their follow-up consultation in the Rheumatology department:

- Screening: verification of the eligibility criteria.

- Inclusion or M0 visit: after information and signature of informed consent. All patients will have a SinnoTest® blood sample. At the end of this visit, the patient is randomized to the SinnoTest® group or the control group. In the control group the SinnoTest® sample is kept but not analysed.

- 6-10 days after the consultation, the prescription of the biotherapy recommended by the rheumatologist is sent by post. This prescription uses SinnoTest® results in the SinnoTest® arm.

-Followed quarterly: M3 and M6.

As part of the proteomics sub study, for those patients who agree to participate, blood samples will be collected from the 2 groups in the M0 and in the M6 to study the variations in the proteomic profile of the patients. In addition, the remaining samples will be deposited in a biobank (in the recruitment center and in the Biobank of the Center Hospitalier Universitaire Grenoble Alpes, France). The participant timeline is presented in Figure 1.

### Sample size {14}

To re-evaluate the metrological properties of SinnoTest®, including 90 patients per group will highlight a differential response rate between the software arm and the control arm of more than 18%; considering a current response rate of 65% with conventional care (control arm). The number of subjects required was estimated considering a bilateral alpha risk at 5% and a power of 90%. In total 180 patients will be the estimated number of participants needed to achieve study objectives.

### Recruitment {15}

Recruitment will be done among patients coming for rheumatology consultations in the 5 centers participating in the study. Potentially eligible patients will be identified in the everyday clinical practice of the research staff, or referred to them for assessment of eligibility having been identified by rheumatologist who are not research staff. Medical records will be checked to identify any other potentially eligible patients. The patient's eligibility will be confirmed by the responsible researcher. After confirmation, any patient who agrees to participate in the research must sign the inform consent to begin participation.

### Assignment of interventions: allocation

### Sequence generation {16a}

### Concealment mechanism {16b}

### Implementation {16c}

The eligible patient will be randomized via an internet server (access by secure code 24/24) in one of two groups: SinnoTest Group or Control Group. A randomized patient in the software arm will receive a blood sample for the determination of selected biomarkers for the use of SinnoTest®. A randomized patient in the control arm will benefit from the same blood sample (but this one will not be analysed) so that the two arms are identical and to maintain the blind for the patient.

The coordinating centre will manage its development and its availability on the internet. It will only be done after informing the patient and signing the consent. The randomization will be individual with blocks of random size, stratified by centre. The investigator or CRA will connect to the server after confirming that the patient meets all the inclusion / exclusion criteria. The server will assign a randomization number to the patient that will be used to connect the patient to a random block.

The involvement of 5 centers in this study allows individual randomization without fear of the existence of a contamination bias. Indeed, investigators may change their empirical management under study because of patient outcomes previously included with SinnoTest®, but the relatively low inclusion counts per centre suggest that this bias will be negligible. In addition, in the control arm the treatments will be prescribed by the rheumatologist who usually treat the patient, so the number of patients with whom will have the opportunity to "learn" is even lower, because it is shared among all doctors that include patients in the study.

This design also neutralizes the disappointment bias of investigators who can all use the innovation under study.

### Assignment of interventions: Blinding

### Who will be blinded {17a}

### Procedure for unblinding if needed {17b}

This is a single blind study (single blind). Only the doctor knows the details of how to prescribe treatment (ie the doctor knows if the patient is in the control group or the group using the SinnoTest® software). Lifting of the blind is not applicable.

### Data collection and management

### Plans for assessment and collection of outcomes {18a}

The use of the SinnoTest® V1 device is reserved for hospital rheumatologists. A training in the use of the graphical interface will be dispensed. In addition, manuals have been created for the use of the device and for the collection, processing and delivery of samples.

### Plans to promote participant retention and complete follow-up {18b}

Not applicable.

### Data management {19}

Electronics Case report forms (eCRFs) will be used that complies with the general and specific good practice standards, as well as the highest requirements for computer validation, with restricted access at the user level, provided with inconsistency detection filters and with traceability of all the information until the final closing of the study. CRFs must be completed for each subject screened/enrolled in this study. This also applies to patients who do not complete the full follow-up planned in the trial.

All CRFs must be filled out by the personnel duly authorized to do so, who will have access codes to the application for entering personal and non-transferable data. The investigator will keep the records and data during the trial in compliance with all legal and regulatory provisions in force. All data must be

supported by original documents in the test center. Any record or document used as a source of information (which will be called the "original data of the subject") will be kept for review by authorized representatives of the promoter or regulatory bodies. The CRFs will be filled in as soon as possible after the evaluation has been carried out.

All the dates that appear in the CRFs referring to analytical tests and other data must coincide with the dates in which the samples were obtained or the procedures were performed.

**Study database.** To facilitate the statistical analysis, a computerized database will be created in which the integrity of the data from the CRFs will be recorded, so that an exact replica of the information contained in them is created.

A data management plan will be made before the beginning of the definition of the database in which the recording process and the errors and consistency controls that will be performed on the recorded data will be detailed. A dictionary of variables will be generated in which the correspondence between the data contained in the CRFs and the variables of the database will be detailed, as well as the codifications used and the meaning of the recorded values.

In the event of inconsistencies or errors in the data, requests for clarification will be generated for the researchers for their verification or correction, which will be treated in an equivalent way to the CRFs. Access to the database will be restricted to the Data Manager (design, input and data cleansing) and the personnel in charge of data transcription (data entry).

Prior to the declaration of the definitive database, a verification of the consistency of the values of the inclusion / exclusion criteria, of the clinical evaluations, of the results of complementary explorations, of the dates of the visit, of the compliance, of the medication received, adverse events, information about dropouts and evaluation of effectiveness.

A definitive database will be declared that will be registered with signature and date. Two protected copies of the same will be kept, and paper lists of the variables contained in the database will be generated for archiving. The final database will be used for statistical analysis.

**Registry and file maintenance.** All the essential documentation of the clinical trial will be filed in a master file of the study, whose safe and complete conservation will be ensured for the time required according to the legislation in force and at the disposal of the authority that requests it. This documentation will include: Work protocol (final version) and amendments; Models of all the employed versions of information sheet and informed consent form; CREC permits; Authorizations of the Health Authorities; Curriculum vitae of all the personnel participating in the study; Random assignment list and treatment allocation codes; Individual Data Collection Notebooks; Documentation related to the study monitoring procedures; Documentation of the study database and definitive database; Documentation of data management and clarification requests; Statistical analysis; Adverse Event Notifications; Final report;

Certificates of audits; Standardized Work Procedures applied in the study; Study financing and payments; Correspondence.

### Confidentiality {27}

The investigator will ensure the right to privacy of patients and must protect their identity against unauthorized third parties. The study monitor may have access to the patient's identity and data in relation to the study's monitoring procedures.

The investigator will keep a patient identification list updated with the correspondence between the name, clinical history number and the patient's identification number or code for the clinical trial, which will be kept together with the patients' informed consent forms in a file unique in the centre. The full name of the patient should not appear in any other section of the data collection notebooks or study documentation. At the end of the study a copy of the list in which the names of the patients will be hidden will be included in the file of the researcher of the study.

In case that an audit of the study is conducted, the auditors who perform it, as well as the health authorities that may require it for regulatory purposes related to the study, may also have access to patient data.

All participants in this research project expressly commit themselves not to disclose the identity of the treated patients and to respect the rules of confidentiality regarding the data and information to which they have access when participating in the trial. The personal data collected and stored for the purpose of this study will be treated in accordance with the provisions of the General Data Protection Regulation (GPDR: Regulation EU 2016/679).

### Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

In the case a subject agrees to participate in the Proteomics Substudy, after carrying out the planned experiments during the trial, the remaining biological samples will be donated to the biobanks belonging to the corresponding ISCIII Biobank Network of each participating center and the Biobank of the Center Hospitalier Universitaire Grenoble Alpes (France). These samples may be transferred to other researchers, in accordance with current regulations (Biomedical Research Law 14/2007 and Royal Decree 1716/2011), to carry out studies related to their disease. Any project for which samples are used will be previously approved by an accredited Ethics Committee.

### Statistical methods

### Statistical methods for primary and secondary outcomes {20a}

**Description of the population studied.** The study population will be described by a flow diagram according to the CONSORT recommendations (CONsolidated Standards Of Reporting Trials). The

different variables (demographic and biological) will be described, for each pathology, and each biotherapy through the descriptive statistics: For quantitative variables: number of data analysed, mean, and standard deviation, Q1, Q3, minimum, maximum and median. For qualitative variables: number of analysed data, absolute frequencies and percentage.

The statistical analysis will proceed as follows:

1. Calculating the 6-month incremental cost-utility ratio from the community perspective using the following parameters: Differential of the total cost of care and difference in the number of QALYs generated by the strategies on both study arms.
2. Sensitivity analysis: Deterministic sensitivity analysis: it allows to take into account the uncertainty on certain parameters that can influence the cost of the strategies. This analysis will take into account in particular the impact of the cost of SinnoTest®, the impact of a change in the cost of treatments through biotherapy, the impact of the cost of work stoppages and the time of the caregivers and probabilistic sensitivity analysis: it will include the calculation of the confidence intervals of the cost-utility ratio by the non-parametric Bootstrap method and the plot of the associated acceptability curve.
3. In addition to the cost-utility ratio, differences in cost and utility will be analyzed separately: Comparison of the cost of the two strategies: the difference in costs between the groups will be tested by a Student test or a non-parametric test (Mann-Whitney tests) in case of non-Gaussian distribution. The choice of the test will be made with regard to the distribution of costs in each group (Shapiro-Wilk test, on raw data or, if necessary, on transformed data). The construction of the average cost confidence interval will be based on the nonparametric Bootstrap method and comparison of the Utility: The number of QALYs will be calculated taking into account the time elapsed between two successive measurements. If the initial utility level between the groups differs, a comparison of the number of QALYs between the groups will be made from a linear model to adjust for this level of utility (Manca, 2005). Given the time horizon, no updates will be made, those of the inclusion visit (M0) will be taken.
4. Multivariate regression method to determine the explanatory factors of the average cost per patient of the strategies (i.e. age, sex, socio-professional category ...).

### Clinical Primary objectives.

Criteria for disease activity, therapeutic response to CJP assessment and quality of life scores at 6 months.

The activity of the PR will be evaluated by the DAS28 score and will define the rate of responder, moderate responder and non-responder. To determine the metrological properties of SinnoTest®, the response rate will be described through descriptive statistics in the "software" arm and in the "control"

arm. It will then be compared between the two arms, using a chi-square test (or Fischer if necessary). This comparison will be carried out globally by pathology (independently of biotherapy), and for each of the biotherapies.

Scores and clinical criteria from the DAS 28 (VS and CRP) and HAQ scales will describe the quality of life. For quantitative variables: number of analysed data, mean, standard deviation, Q1, Q3, minimum, maximum and median. Then comparison via the Student test (or non-parametric tests if necessary). For qualitative variables: number of analysed data, absolute frequencies and percentage. Then compare the two arms, using a chi-square test (or Fischer if necessary).

**Clinical Secondary Objectives.** Diagnostic performance indices at 6 months: sensitivity, specificity, positive and negative predictive values, likelihood ratio will be described. The performance of the SinnoTest® will be calculated in the "SinnoTest®" arm by comparing the response predicted by the software and the response observed at 6 months. It will be searched globally, and for each of the biotherapies.

**Medico-economic primate and secondary objectives.** The incremental cost effectiveness ratio at 6 will be calculated from the cost differential of the strategies and the efficiency differential defined by the rate of responder patients in each group. The ICER and the 6 month ICUR will be subjected to a deterministic and probabilistic sensitivity analysis.

**Statistical analysis of the proteomic sub study.** The biomarkers of the proteomic profile will be compared between the Inclusion visit (M0) and the 6-month visit, as well as the differences in both the M0 and M6 visits between the two treatment arms.

The comparison will be done by biomarker. The biomarkers will be described at each time (indicators and boxplot) globally, as well as by observed response group. The risk of the first species α is fixed, by convention, at 5% for the different comparative analyses.

### Interim analyses {21b}

Not applicable.

### Methods for additional analyses (e.g. subgroup analyses) {20b}

Not applicable.

### Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

Analyzes will be carried out by intention to treat (ie, each patient will be considered to belong to the group to which they were randomized, regardless of the intervention they receive).

For each patient that leaves the study before its completion, the cause will be collected, which will be classified as: Lack of response to biotherapy; occurrence of adverse events; loss of follow-up; withdrawal of consent; the investigator's decision; use or need for medication not allowed; erroneous inclusion in the study; unforeseen circumstances; or cancellation of the study.

Following the advice of Little et al (28), for the management of lost data multiple imputation techniques will be carried out, in addition to sensitivity analysis with the object to check that the assumptions made in the imputation and check whether the conclusions of the study are modified, or not, according to the analysis strategy adopted. There will also be an analysis per protocol, of those patients with all the data collected.

### Plans to give access to the full protocol, participant level-data and statistical code {31c}

Not applicable.

### Oversight and monitoring

### Composition of the coordinating centre and trial steering committee {5d}

Not applicable.

### Composition of the data monitoring committee, its role and reporting structure {21a}

Not applicable.

### Adverse event reporting and harms {22}

In each study visit, the presence of the most common adverse events related to the study medication will be actively inquired by the blind investigator.

Regarding the notification of severe adverse events, we will follow the definitions and guidelines of the document MEDDEV 2.7/3 review 05/03/2015 “Guidelines on medical devices: Clinical investigations: Serious adverse event reporting under Directives 90/385/EEC and 93/42/EEC”.

All adverse events will be followed until its resolution, subjects death or lost of follow-up.

### Frequency and plans for auditing trial conduct {23}

Not applicable.

### Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

The principal investigator (PI) will notify the sponsor of this project of any changes to the protocol and will submit the changes for review to the local CREC. The PI will notify the clinical Research centre (study

site) of any protocol changes and will update the protocol in the clinical trial registry.

### Dissemination plans {31a}

During and after the study, the ClinicalTrials.gov database will be replete with data. After completing the research and processing the data, an article will be written for later publication in an international journal for the dissemination of data and results.

## Discussion

This single-blind controlled multicentre clinical trial study is the first validation study of a bDMARD response prediction software, bringing personalized medicine into the management of inflammatory rheumatism. This interest is also shared by pharmaceutical companies who wish to improve the stratification of patients and thus offer more targeted treatments.

We believe that the findings from this study will bring several benefits for the patient and for the health system as reducing patient exposure to ineffective and potentially poorly tolerated bDMARDs, control of RA activity. The SinnoTest® will maximize the chances of successful treatment with biotherapy, the patient will benefit from the most appropriate treatment at the right time, which will improve its quality of life.

For public health, the short-term benefit will focus on optimizing the management of RA, improve and adjust the SinnoTest® predictive software, thanks to the clinical results obtained. Data from clinical validation studies will be used to validate and improve the existing algorithm for performance, ergonomics and functionality. Anticipate access to the market by collecting medico-economic data and pursuing the search for partners to allow rapid deployment of the test in clinical practice. The SinnoTest® will allow physician optimize the selection of the biotherapy in real time.

The combination of SinnoTest® algorithms will optimize the selection of biotherapy for RA patients and given the minimal risk for patients and the expected collective benefit, the benefit-risk ratio is very favourable.

### Trial status

The study is in the data collection phase. Recruitment started in December 2019 and is predicted to end in January 2021. The current protocol is version 1.0, created in March 2019 and approved the Clinical Research Ethics Committees (CREC) of the participating centers, as well as the approval of the Spanish Agency of Medicines and Health Products in December 2019 before starting the study. Registered at Clinicaltrials.gov, identifier: NCT04147026. Registered on 31 October, 2019.

## Abbreviations

Rheumatoid arthritis (RA). Chronic inflammatory rheumatism (CIR). Synthetic disease modifying anti-rheumatic drugs (sDMARD). Tumor Necrosis Factor (TNF-α). Biological Drug Modifying the Activity of the Rheumatic Disease (bDMARDs). Targeted synthetic DMARDs (tsDMARDs). The European League against Rheumatism (EULAR).The Hospital Clinical Research Program (HCRP). Ankylosing spondylitis (AS). Quality-adjusted life year (QALY). Innovative Medical Device (IMD). Electronics Case report forms (eCRFs). Clinical Research Ethics Committees (CREC). Principal investigator (PI). General Data Protection Regulation (GPDR). CONsolidated Standards Of Reporting Trials (CONSORT)

# Declarations


### Acknowledgements

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### Authors’ contributions {31b}

PG and LRR were responsible for the study concept and definition of the scope. DF, LRR, IG, JLP, AB, MV, PG and BFG were involved in abstract and full-text screening. LRR and DF were responsible for drafting of the manuscript. DF, LRR, IG, JLP, AB, MV, PG and BFG were responsible for critical revision of the manuscript. All authors read and approved the final manuscript.


### Funding {4}

This work is supported by the European Institute of Technology and Innovation (EIT-Health) (#19577). All the funding sources are not involved in the study design and data collection, and will not be involved in the analysis and interpretation of data.


### Availability of data and materials {29}

Not applicable.

### Ethics approval and consent to participate {24}

This study will be carried out strictly respecting the ethical principles of biomedical research and current legislation in Spain. All personnel participating in this study agree to follow, during the performance of the study, the Standards of Good Clinical Practice (Guideline for good clinical practice E6 R2: https://bit.ly/2VuHzVD).

The approval of the Clinical Research Ethics Committees (CREC) of the participating centers will be obtained and documented, as well as the approval of the Spanish Agency for Medicines and Health Products before starting the study. The local approvals corresponding to the participating centers will be obtained and documented before starting the study in the centers. The responsible researcher of each center will be the interlocutor of the CREC corresponding to its center in everything related to the present study. It will keep the CREC informed of the evolution of the study in the center and of the possible incidents and minor modifications that may occur. Any relevant modification to the protocol after its approval must receive express approval from the reference CREC and the Spanish Agency for Medicines and Health Products before its implementation, unless there are risk circumstances for the participating subjects, in which case they will be implemented the precise measures to ensure the integrity of the patients immediately awaiting the corresponding approvals.

A signed informed consent will be obtained from all study participants before any study-related procedures are undertaken.

## Consent for publication {32}

Not Applicable.

## Competing interests {30}

The authors declare that they have no competing interests.

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Not applicable.

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## Note About Figures

Figures 2, 3, 4 and 5 are mentioned in the text on page 14, but were omitted by the authors in this version of the manuscript.

## Figures

| Visits | Selection | Inclusion[1] M0 | M3 ± 2 weeks | M6 ± 2 weeks | M12 ± 2 weeks |
|---|---|---|---|---|---|
| Information[1] | ✓ | | | | |
| Information and consent[2] | | ✓ | | | |
| Confirmation of eligibility | | ✓ | | | |
| Clinical/physical examination, Rheumatoid | | ✓ | ✓ | ✓ | |
| Routine blood analysis | | ✓ | ✓ | ✓ | |
| Questionnaire EQ5D | | ✓ | ✓ | ✓ | |
| Questionnaire HAQ | | ✓ | ✓ | ✓ | |
| Biomarkers[3] | | ✓ | | | |
| Patient booklet[4] | | ✓ | ✓ | ✓ | ✓ |
| Administration / Dispensation of Biotherapy | | ✓ | | | |
| Bio-bank [6] | | ✓ | | ✓ | |
| Concomitant treatments | | Collection throughout the study | | | |
| Adverse Effects Collection | | Collection throughout the study | | | |

**Figure 1**

Schedule of enrollment, interventions, and assessments. 1 Inclusion: the inclusion visit should be done in 2-3 weeks. 2 Information and Informed Consent: The patient will sign informed consent for the main study and additional consent (optional) if they accept 6-month and 1-year inclusion samples, which will be retained for the creation of bio-bank. 3 Biomarkers: a blood sample will be taken for the determination of SinnoTest® biomarkers in the intervention arm patients. 4 Patient booklet: the rheumatologist or CRA investigator will deliver the booklet to the patient at the inclusion visit. The patient will visit each follow-up visit with his notebook and will carry it with him after the visit. At the end of the follow-up, he will return his completed patient booklet to the CRA / TEC of the Investigator Center by mail using the envelope provided with the notebook. 5 Administration / Dispensation of Biotherapy: Patients in the control group will receive their biotherapy prescription in current practice. For patients in the intervention group, the rheumatologist will prescribe the biotherapy selected by SinnoTest®. The results of the pregnancy test should be negative. 6 Bio-bank: a blood test will be carried out in all included patients who signed the additional consent for the creation of a bio-bank.

# Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SPIRITChecklistPREDIRA.doc