ARGENTINEAN REGISTER OF ADVERSE EVENTS WITH INNOVATIVE BIOLOGIC THERAPIES, BIOSIMILARS, SMALL MOLECULES AND GENERIC SMALL MOLECULES IN RHEUMATIC DISEASES

(Phase III)

Sociedad Argentina de Reumatología
(Argentinean Society of Rheumatology)

STUDY PROTOCOL

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CONTENT

RATIONALE AND JUSTIFICATION

Rheumatic Diseases - Disease Burden and Socio-Economic Impact

Rheumatic diseases affect more than 10% of the general population (1). The prevalence of rheumatoid arthritis (RA) in Argentina is 0.33%, being more frequent among females, and the incidence rate is 25.2 and 8.8 per 100,000 person-year for female and male respectively (2). Additionally, RA shows a high disease burden and socio-economic impact, with 70% of the patients developing irreversible structural damage over the first years after diagnosis (3), and 80% of the adults of working age with incapacitating pain, rigidity, and functional capacity reduction (4), which restricts their activities and social life (5,6). In our country, up to 20% of early arthritis patients developed work disability, and this was comparable between RA and undifferentiated arthritis (7). Regarding the socio-economic impact, in this same cohort, Waimann and col, described that patients in high disease activity entail a disease burden of 0.28 quality-adjusted life-years (QALYs) after one year of follow-up. They also showed that the total annual cost per patient with early arthritis in Argentina was between 2630 and 3740 USD (8).

Spondyloarthropathies are a heterogeneous group of rheumatic inflammatory diseases that share clinical, radiological and immunogenic features, such as the presence of the HLA-B27 haplotype. The prevalence of this group of diseases ranges between 0.1% and 2.5% of population, presenting marked differences according to race and geographic area (9–13). The most prevalent spondyloarthropathies in Argentina are psoriatic arthritis (PsA) (46.7%), Ankylosing spondylitis (AS) (30.3%), undifferentiated spondyloarthritis (12.4%), reactive arthritis, and entheropatic arthritis (in association with inflammatory bowel diseases: Crohn´s disease, and ulcerative colitis) (14). Spondyloarthropathies' clinical evolution often shows a tendency to ankylosis, disability, and impaired quality of life, leading to permanent disability in 20% of patients (15). Similar to RA, 26.2% of patients with ankylosing spondylitis in Argentina presented work disability (16).

Psoriatic Arthritis (PsA) is a frequent disease in Argentina, with a prevalence of 74 per 100,000 persons and an incidence rate of 6.26 cases per 100,000 person-year (17). PsA presents an aggressive phenotype in 40-60% of the patients (18), with a burden of physical disability and pain comparable to RA (19,20). Regarding the economic impact of PsA, direct annual health costs in the US were estimated to be over $ 1.9 billion, and indirect costs are estimated to be 52-72% of total costs. Both direct and indirect costs of PsA increase when physical function gets worse and there is an increase of the disease activity (19).

Systemic Lupus Erythematosus (SLE) is a complex systemic autoimmune disease (21) with a prevalence rate in Argentina of 84.1 cases per 100,000 inhabitants, being more frequent in female, and an incidence rate of 6.8 cases per 100,000 person-year (22). Although patients with SLE can present a wide spectrum of clinical manifestations and a variable course, SLE is associated with a mortality rate 2.6 times higher than in the general population, mainly due to higher rates of cardiovascular disease, renal disease and infections (23). The estimated economic burden of SLE in the US is 39.021 USD for patients with moderate/severe SLE and 23.519 USD for mild SLE (24).

The aforementioned diseases, RA, PSA and SLE, are the most prevalent rheumatic diseases included in the Argentinean Register of Adverse Events with Biologic Therapies, Small Molecules and Biosimilars in Rheumatic Diseases (acronym BIOBADASAR).

Therapeutic Management of Chronic Inflammatory Diseases

The treatment of these diseases is complex and requires a tailored strategy. The standard of care requires multidisciplinary management including non-pharmacological measures (physical, occupational, and psychological therapies), analgesics and corticosteroids, and early administration of disease modifying anti-rheumatic drugs (DMARDs) such as methotrexate, sulfasalazine, or leflunomide, and in case of treatment failure, biologic DMARDs or small molecules (25–28). Products currently used in biologic therapy have diverse mechanisms of action, routes of administration, and pharmacokinetic and pharmacological properties that anticipate specific safety-related aspects.

Numerous clinical trials have proved the effectiveness and safety of biologic therapies; however, long-term follow-up and real life evidence is limited. For this reason, it is necessary to conduct evaluations in real scenarios, and for this purpose, different registers have been carried out in several countries. This evaluation is not redundant due to the demographic, socio-economic, and medical care and epidemiological differences among different countries. This type of register has proved to be useful in proactively monitoring potential safety problems with biologic therapies (29).

Biologic and Biosimilar Therapy for the Control of Rheumatic Diseases in Argentina

The Argentinean Regulatory Agency for Drugs, Food and Medical Technology (ANMAT) has approved to October 2020 fifteen innovative biologic drugs for rheumatic diseases (http://anmatvademecum.servicios.pami.org.ar/index.html). Five of these drugs are Tumor Necrosis Factor (TNF) antagonists (infliximab, etanercept, adalimumab, certolizumab pegol, and golimumab); one fusion protein that modulates T cell activation (abatacept); two monoclonal antibodies that block the interleukin 6 receptor (tocilizumab and sarilumab); one anti-CD20 monoclonal antibody (rituximab); one anti-Interleukin 17 (secukinumab); one anti-Interleukin 12-23 (ustekinumab); two anti-interleukin 23 (guselkumab and risankizumab); one anti interleukin-1 monoclonal antibody (canakinumab); and one monoclonal antibody directed against B-cell activating factor (BAFF) (belimumab). In addition, the rheumatologist's pharmacological arsenal was enlarged with the approval of small molecules such as tofacitinib, baricitinib, upadacitinib and apremilast, and the recent approval of biosimilars and generic of small molecules.

A biosimilar is a biologic drug developed to be similar to an already existing biologic drug (the reference medicinal product), and although there may be minor differences due to production methods, there must be no clinically significant differences (30). For a biosimilar to be authorized there is need to prove that variability and differences between the biosimilar and its reference medicinal product do not affect safety or effectiveness. Currently, there are 7 biosimilars approved in Argentina (2 biosimilars of infliximab, 1 of etanercept, 2 of adalimumab, and 2 of rituximab) and 4 generics of small molecules (2 generics of tofacitinib and 2 of apremilast).

The BIOBADASAR registry was launched in 2010 with the objective of monitoring the safety of innovative biologic drugs for rheumatic diseases under real conditions, identify adverse events, estimate the risk of adverse events, and estimate effectiveness by using drugs survival as a surrogate marker (31). In response to the development of new treatments, the third phase of the BIOBADASAR was launched in 2018, and updated the inclusion criteria to patients treated with innovative biologic drugs, biosimilars, small molecules or generic of small molecules. Up to date, November 2020, there are 5884 patients included in BIOBADASAR, being 3196 (58.5%) under treatment with biologic drugs or small molecules. The most frequently used drugs are etanercept (19.7%), adalimumab (11.5 %), abatacept (5.9%), certolizumab (5.1%) and rituximab (4.5%).

Justification

The effectiveness of biologic therapies and patients' acceptance is a fact. However, there is a need for further studies on long-term safety for non-selected populations, mainly regarding the most recent products on the market. According to the legislative framework about pharmacovigilance of medicinal products for human use and guidelines of Good Clinical Practice (GCP), there is a need for strategies for close surveillance of the potential development of adverse reactions regarding innovative biologic drugs, and biosimilars and small molecules that are used for rheumatologic diseases.

The implementation of registers is the best strategy regarding proactive surveillance of potential safety problems with biologic therapies. This kind of register is essential to establish the probability of a specific adverse event occurring outside clinical trials. In addition, registers also provide valuable information from the real world regarding drug effectiveness and survival, particularly of those patients that according to their comorbidities and disease characteristics are not included in clinical trials. For this reason, we believe that it is necessary to give continuity to the third phase of the BIOBADASAR project, which is updated with technological developments and regulatory changes, to continue providing the best information on drug safety, survival and efficacy in a real world setting.

OBJECTIVES

Objectives for BIOBADASAR phase III are as follows:

- To identify significant adverse events occurring during treatment of rheumatic diseases with innovative biologic therapies, biosimilars, innovative small molecules, and generic drugs of the innovative small molecules, and estimate their frequency of occurrence.
- To identify unexpected adverse events.
- To identify significant adverse events occurring after discontinuation of treatment.
- To evaluate, under non experimental conditions, the elapsed time until discontinuation of biologic therapies in patients suffering from any rheumatic pathology, as well as the reasons for this interruption (secondary effects, ineffectiveness or loss of the biologic effectiveness, remission, or death).
- To evaluate changes in disease activity of patients who are included in the register.

METHODOLOGY

Design

The BIOBADASAR is a prospective case-control study on patients with rheumatic diseases (Appendix II) under treatment with innovative biologic drugs, biosimilars, small molecules or generic of small molecules (Appendix I), the cases, and patients with matching disease treated with conventional DMARDs, the controls. Patients are included when they start with a target treatment, and controls are included simultaneously to the inclusion of a case. The included patients need to be evaluated at least once a year and their clinical data

updated. Since it is unknown if exposure to biologics has long-term effects, patients are considered to be exposed indefinitely, and are followed-up continuously, even after having suspended biologic therapy, or until the withdrawal of consent, loss of follow up or death.

Patients

Target Population

Patients diagnosed with any of the rheumatic diseases listed in the Appendix II who are being treated with any of the innovative biologic drugs, biosimilars, small molecules or generic of small molecules listed in Appendix I.

Accessible Population

Patients treated with innovative biologic drugs, biosimilars, small molecules or generic of small molecules (Appendix I) due to any of the listed rheumatic diseases (Appendix II) that followed by the rheumatology department of any of the centers registered in the third phase of BIOBADASAR.

Sample

Patients suffering from any of the listed rheumatic disease (Appendix II) who are under treatment with innovative biologic drugs, biosimilars, small molecules or generic of small molecules (Appendix I), and who are recruited by any of the participant centers of BIOBADASAR III and sign an informed consent.

Recruitment

The the Argentine Society of Rheumatology [Sociedad Argentina de Reumatología (SAR)] will establish strategies in order to obtain maximum publicity for this phase, noting the interest and responsibility of health professionals who are attending patients under treatment with biologic drugs or small molecules. The strategies to publish the third phase of the register will be conducted through the usual information channels of SAR: a) Letter to partner, b) Web page, c) SAR's bulletin, d) Email notification to the SAR's affiliates, e) Revista Argentina de Reumatología, and f) Congreso Nacional de Reumatología (National Congress of Rheumatology).

Criteria for Center Selection

The centers selected for BIOBADASAR II remain active as long as they adequate to updated requirements of the register, and centers that voluntarily request to participate in phase III will be considered. Currently, 54 centers distributed in all the regions of the country collaborate with the BIOBADASAR. The centers are subject to 3 virtual evaluations and 1 on site evaluation each year to guarantee the quality of the data.

Criteria for Patients Selection

Patients suffering from any of the listed rheumatic diseases (Appendix II) will be eligible as long as they meet the following criteria:

1. Patients followed in any of the participant center that start treatment (or are under treatment) with an innovative biologic therapy, biosimilar or small molecule listed in the appendix I. These patients are considered cases.
2. Patients followed in any of the participant center that have a matching disease with a patient listed as case that start treatment (or are under treatment) with a conventional DMARD. These patients are considered controls.
3. Patients who have stopped a treatment with biologic drugs or small molecules, regardless of the cause, as long as the last dose was received during the last year and all the required data for the register is available (patient, treatment, and adverse events).
4. Patients who authorize prospective data collection according to the procedure set out in the informed consent.

ETHICAL ASPECTS

General Considerations

This study must be developed in accordance with the protocol and standards of Good Clinical Practice (GCP). Each investigator will ensure that the study is carried out in full conformity with the ethical principles laid down in the Declaration of Helsinki regarding medical investigation in human beings ("Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects"). A copy of the Declaration of Helsinki is in the Appendix IV of this protocol, and can be accessed on the World Medical Association website: http://www.wma.net/e/policy/b3.htm.

The researcher agrees to accept, by signing this protocol, the instructions and procedure described in this protocol, and hence, to comply with principles of the GCP on which this protocol is founded.

Informed Consent

The investigator must explain to each patient (or legally authorized representative) the nature of the study, objectives, procedures, planned duration, and potential risks and benefits regarding his/her participation in the study, as well as any inconvenience this study may cause. Each patient must be advised that his/her participation in the study is voluntary and that he/she can drop out of the study at any moment, without affecting further treatment or relationship with the physician who is treating him/her .

The informed consent (IC) must be written in terms that participants can understand, and must be printed and handed to the patient who must have enough time to read it and evaluate it. Upon consent to participate, the patient must write his/her name, the informant doctor´s name, and the date in their own handwriting. Patients must also sign the document and will receive a copy of the signed document. The IC used in Phase III presents some changes in respect to the one used in Phase II (Appendix V). The IC copy must be kept by each center and must be available for the monitor and health authorities upon request.

If the subject cannot read or sign the documents, there may be an oral presentation, or the signature of his/her legal representative may be required as long as a witness not involved in the study is present and as long as this is mentioned in this document and/or the clinical records.

A patient will not be included in the study without having previously presented their IC.

Confidentiality

Confidentiality of Information

By signing the protocol, the researcher pledges to keep all the information provided by the Sponsor in strict confidentiality and to encourage his/her team and Clinical Research Ethics Committee (CREC) to do the same. The documents provided by Sponsor must be securely kept to assure confidentiality. The information provided to the researcher by the Sponsor cannot be disclosed to third parties without the Sponsor´s direct authorization in writing, except to obtain the IC from patients who want to take part in the study .

Confidentiality of Data

The identity of patients cannot be disclosed or disseminated. Patient data collected in the DCL during the study must be anonymously linked to a code (patient number). This way, only the researcher will be able to link the data to an identifiable person.

If, by way of exception, due to legal reasons, or if an audit to evaluate data quality takes place, and it is mandatory to know the identity of the patient, the Sponsor must always respect rules of confidentiality as prescribed by the law of Personal Information Protection (Law n° 25.326).

The database containing that data that this study would generate will not contain any reference to the identity of the patient except for the numeric code which does not allow anyone to know the identity of the patient. The identity of the patient is just known by his/her doctor, and cannot be obtained without the consent of both the patient and his/her doctor.

DEFINITIONS AND VARIABLES

Operational Definitions

Adverse reaction: It is any not intended noxious responses to a drug, included adverse reactions in relation to any usage outside the terms of the marketing authorization, abuse, and errors in medication.

Serious adverse event (SAE): It is any unfavorable effect, that, irrespective of dose:

- causes death,
- endangers life,
- requires admission to the hospital or extends hospital stay,
- leads to persistent or significant disability,
- leads to congenital malformations.

Significant medical events not being immediate life-threatening or causing death, but that are dangerous or require intervention in order to prevent some of the results listed above, are also considered significant adverse events.

Biologic therapy: It is that therapy that uses modified proteins that are normally produced by the immune system to treat inflammatory diseases such as: monoclonal antibodies and fusion proteins. An innovative biologic drug is a new medical product which has to demonstrate in clinical trials that it is safe and effective for the treatment of a disease before it is approved by the health regulatory agencies. A biosimilar drug is a biologic drug developed to be similar to an already existing biologic drug (the reference medicinal product), and although there may be minor differences due to production methods, there must be no clinically significant differences (30). For a biosimilar to be authorized, there is need to prove that variability and differences between the biosimilar and its reference medicinal product do not affect safety or effectiveness. See Appendix I for the list of drugs considered innovative biologic drugs and biosimilar drugs.

Small Molecules: They are a group of synthetic agents designed to selectively block the pathophysiological mechanisms of rheumatic diseases. It may be considered as a biologic therapy by use of a broader definition. See Appendix I for the list of drugs considered small molecules and generics of small molecules.

Comorbidity: It is the presence of pathologies that accompany the rheumatic disease, which is considered as primary, before the start of the biologic therapy treatment, treatment with biosimilars, or small molecules. All health problems occurring after the start of treatment, whether they are or not associated with the medicinal product are considered adverse reactions.

The **Naranjo algorithm** is proposed to evaluate the adverse reactions causality with biologic therapy, biosimilars and small molecules (32). These methods are generally accepted and are the most commonly used in evaluating causality in clinical practice, since they offer a simple methodology to differentiate comorbidity from any adverse reactions, reducing to a minimum, or even suppressing, the measurement bias.

	YES	NO	UNKNOWN	SCORE
Are there any conclusive previous reports on this adverse reaction?	+1	0	0	
Has the adverse reaction occurred after the drug administration?	+2	-1	0	
Did the adverse reaction improve with drug suspension or by administering a selective antagonist?	+1	0	0	
Did adverse reaction reappear with the re-administration of the drug?	+2	-1	0	
Are there any alternative causes (apart from the drug) that could have caused the adverse reaction?	-1	+2	0	
Did the adverse reaction reappear due to the re-administration of the drug?	-1	+1	0	

Was the drug confirmed in sample of blood or other biologic fluids?	+1	0	0	
Did the reaction get worse by increasing dose, or did it improve by reducing dose?	+1	0	0	
Did the patient have a similar reaction to similar drugs in any previous exposures?	+1	0	0	
Was the undesirable effect confirmed by any objective evidence?	+1	0	0	
Final score: definitive ≥ 9; probable 5-8; possible 1-4; doubtful ≤ 0				

The inclusion of the **Charlson Comorbidity Index (CCI)** (33) is proposed to reduce variability during the collection of information on comorbidity at the beginning of treatment. This index assigns a given weight (score 1-6) to each process according to the relative risk of death, and a global score is obtained by calculating the sum of all weights.

Ineffectiveness: Lack of response to treatment with a biologic drug, biosimilars or small molecule in the conditions of habitual clinical practice. It is defined and measured through the rheumatic disease activity indexes for the three most prevalent pathologies (DAS28 for RA, BASDAI for AS, and DAS28 for PsA), which are registered before the biologic treatment starts and at least once a year from the beginning of treatment.

Principal Variables

For the Descriptive Objective

The **significant adverse event (AE)** is the primary outcome variable of this study, and it is collected in two ways: through open question, and through a term based on the MedDRA (Medical Dictionary for Drug Regulatory Activities). Afterwards, through this variable the following will be created:

- A nominal variable (yes/no) that in general identifies the incidence of adverse events.
- Categorical variables of events through organs or systems, based on the SOC (superior order classification) of MedDRA regarding the chosen term.

The following information will be collected from all patients presenting a significant adverse event:

- Date when the adverse event appears.
- Comorbidities for the Charlson index calculation (33) at the start of treatment with biologic drug or with biosimilar.
- Concomitant treatments the patient was receiving when the adverse event appears.
- Severity of the event. The different categories of this ordinal variable are the following:
  - Serious
  - Non serious
  - Fatal

- Outcome of the event. They are classified as follows:
- Unknown.
- Recovered with no sequels.
- Recovered with sequels.
- Not yet recovered.
- Death due to AE.
- Death. The drug may have contributed.
- Death. Not related to the drug.
- Congenital malformation at the moment of birth of descendants of patients included in BIOBADASAR.

For the objective of assessment of duration of treatment

The principal variable will be time in treatment. It will be measured in days from start of treatment until dose change or interruption. This variable will be calculated using the date when the treatment starts, the date of dose modification, and the date when the treatment ends. It will be considered interruption of treatment when there has not been administration for a period equal to four times the maximum time between doses. The reason for the treatment modification is also recorded:

- The main reason for interruption will be the most compelling one: a) ineffectiveness, 2) adverse event, and 3) others.
- Other reasons to interrupt treatment must be specified, and may include patient´s decision, problems supplying the product, or desire for pregnancy. Stopping treatment due to “medical decision” is not an admissible reason.

DATA COLLECTION

The time for data collection on adverse events is not be established by protocol, but notifications will take place as these events occur, or as a part of the patient´s routine consultation used for the control of the disease.

Data is entered in an online application designed ad hoc and it is monitored by a person specifically hired and trained to do this. In addition, these data must be downloaded to a relational database that will make possible to perform queries in order to conduct the analysis.

The following data will be entered in the application (accessed via a personalized password):

- Center, and department/unit identification data (included the person responsible for communication with BIOBADASAR)
- Patients:
  - Gender

  - Date of birth
- Diagnosis, and date of diagnosis
- Comorbidities to calculate the Charlson index
- Disease activity at the beginning of treatment with biologic or biosimilar and at least once a year from the start of a treatment and at any time there is suspicion of lack of effectiveness:
  - For RA and PsA: Number of swollen joints (28), number of tender joints (28), visual analogic scale (VAS) and ESR. DAS28 recorded in medical history if the above information is not available
  - For AS: BASDAI
- Treatment data: Conventional DMARDs, biologic treatments, biosimilars or small molecules: As many as the patient uses during the follow-up. The following information will be compiled:
  - The trade name of biologic, its active ingredient
  - The start and the end dates
- Reasons for interruption
- Concomitant treatments
- History of pulmonary tuberculosis
- Data on significant adverse events:
  - Type, according to MedDRA
  - Severity
  - Outcome
  - Biologic, biosimilar or small molecule lot number (if fatal or serious adverse event)
  - Specified infections

BIOBADASAR CODING

Each patient is given a unique numeric code that cannot be changed even if the patient changes centers. If this happens, the attending doctor will notify the person responsible in the new center of the change and notify the BIOBADASAR as soon as possible, thereby avoiding patient´s numeric code changes due to this new situation.

QUALITY CONTROL

Inclusion of patients, changes in treatment, and adverse events, will be noted as they happen. In addition, once a year —or every six months for recently approved drugs— the following controls to validate data will be performed:

- Online monitoring three times per year, performed by personnel with experience in pharmacovigilance, to detect any abnormalities in entered data and discuss these abnormalities with the clinicians who entered the data, to perform a control of quality. A report on detected incidences and suggestions to improve data entry will be sent to researchers.
- In situ monitoring. The clinical research associate will visit each center to verify that collected data match the patient´s medical history on an annual basis.

PERIODIC REPORTS

There will be an annual report on the following information:

- Number of participant centers.
- Number of patients under treatment who have been included as well as their description:
  - Gender
  - Age at the beginning of treatment
  - Diagnoses
  - Disease duration at the beginning of treatment
- Treatments being received
- Information on treatment interruptions:
  - Absolute and relative frequency of interruptions
  - Survival curve until interruption
  - Absolute and relative frequency of interruption due to ineffectiveness
  - Absolute and relative frequency of interruptions due to adverse events
  - Absolute and relative frequency of interruptions due to other reasons
- Information on adverse events:
  - Absolute and relative frequency of adverse events during treatment:
    - In total
    - Sorted by tracts and systems
    - Specific
  - Absolute and relative frequency of adverse events after treatment suspension

These reports will be uploaded to the project website. Other fast communication channels may be used if deemed necessary.

STATISTICAL CONSIDERATIONS

The following aspects of the project can be distinguished: a) descriptive, b) study treatment duration.

Descriptive aspects of the BIOBADASAR study will be carried out in compliance with the sections above. Collected data will be compiled using indexes (means ± standard deviation, frequencies, medians), and in survival curves where sensing variable is the treatment interruption or the adverse event, dependent on the objective. Outcomes will be reported in absolute and relative frequencies and in incidence-density (patients/year).

Particular adverse events can occur in patients who have received more than one biological agent. The attribution to a particular drug depends on the type of AE: AE of rapid development, such as infusion reaction, is clearly attributed to the drug being received, while AE of slow development, such as a neoplasm, would be attributed to all previous immunosuppressive therapies. When periods of exposure to more than one biologic are analyzed, a new period of exposure called “combined exposure” will be assigned, and AE will be attributed to both combined treatments.

OTHER ASPECTS

Notification of Suspicion of Adverse Reactions to the Argentinean System of Pharmacovigilance

The notification of a serious adverse event to BIOBADASAR, under no circumstances, replaces the requirement to notify the corresponding regional pharmacovigilance center of this adverse event any time the doctor suspects that there is a causal connection (suspicion of adverse reaction).

Sponsors

BIOBADASAR is a study that depends of the Argentinean Society of Rheumatology and it is sponsored by pharma companies.

Responsible Scientists of BIOBADASAR

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BUDGET

The budget for this project is $ 120.000 (US Dollars, one hundred and twenty thousand).

It has been divided into 5 main items:

- Data base maintenance.
    - UNISAR will be in charge of paying the Spanish society of Rheumatology for the web-based database. The cost for maintenance will be 5000 US dollars per year.
- Study coordinator
    - Will be responsible of the conduction of the study, coordinate the centers, answer centers queries.
- Study Monitors

  - Will oversee the accuracy, the consistency, and data completeness.
- Recruiting centers
  - Recruiting centers are those that belong to BIOBADASAR and include and follow up the patients in the database.
  - Recruiting Centers will be payed per new or follow up visits included with complete data peer year.
- Investigation Unit
  - Will be the ultimate responsible of the Study.
  - Will Oversee the data base.
  - Will hold the data and provide the interim analysis and the final reports.
  - Will Answer the sponsors queries and provide them with the reports.
  - Will conduct all the secretary work.

The maximum budget is based on performance of all Services described in this Scope of Services. The budget is further itemized in the table which follows:

	2021			2022			Total Period
Items	Cost per unit ($)	Total Units	Total cost	Cost per unit ($)	Total Units	Total cost	
Data base maintenance	5.000	1	5.000	5.000	1	5.000	
Study coordinator	12.000	1	12.000	12.000	1	12.000	
Study Monitors	9.000	2	18.000	9.000	2	18.000	
Recruiting centers	15	5.000	7.500	15	5.000	7.500	
Investigation Unit	17.500	1	17.500	17.500	1	17.500	
Total cost			60.000			60.000	120.000

FINANCIAL ASPECTS

Support requested to PFIZER is: $ 120.000 (US Dollars, one hundred and twenty thousand).

Billing: SAR will send 2 (two) invoices to PFIZER after contracts/legal documents has been approved and signed following payment schedule:

- August 2021: $60,000
- August 2022: $60,000

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APPENDIX

<u>Appendix I.</u> List of the included innovative biologic drugs, biosimilars, small molecules and generic of small molecules

Innovative Biologic Drugs	Biosimilars	Innovative Small Molecules	Generic Small Molecules
- Humira (Adalimumab)	- Abrilada (Adalimumab)	- Xeljanz (Tofacitinib)	- Tofax (Tofacitinib)
	- Amgevita (Adalimumab)		- Terfanib (Tofacitinib)
- Remicade (Infliximab)	- Remsina (Infliximab)	- Olumiant (Baricitinib)	
	- Inflectra (Infliximab)	- Rinvoq (Upadacitinib)	
	- Ixifi (Infliximab)	- Otezla (Apremilast)	- Apremax (Apremilast)
- Enbrel (Etanercept)	- Enerceptan (Etanercept)		- Facemil (Apremilast)
- Cimzia (Certolizumab)		- Ofev (Nintedanib)	
- Simponi (Golimumab)		- Pirfenidone	
- Orencia (Abatacept)			
- Actemra (Tocilizumab)			
- Kevzara (Sarilumab)			
- Cosentyx (Secukinumab)			
- Stelara (Ustekinumab)			
- Taltz (Ixekizumab)			
- Tremfya (Guselkumab)			
- Skyrizi (Risankizumab)			
- Benlysta (Belimumab)			
- Mabthera (Rituximab)	- Novex (Rituximab)		
	- Rixathon (Rituximab)		
- Ilaris (Canakinumab)			
- Kineret (Anakinra)			
- Prolia (Denosumab)			
- Nucala (Mepolizumab)			
- Ocrelizumab			

Appendix II. List of included rheumatic diseases

- Enteropathic Arthritis
- Juvenile Idiopathic Arthritis
- Psoriatic Arthritis
- Reactive Arthritis
- Rheumatoid Arthritis
- Autoinflammatory diseases
- Behcet's disease
- Still's disease
- Epidermolisis Bullosa
- Juvenile Spondyloarthritis
- Undifferentiated Spondyloarthropathy
- Juvenile Undifferentiated Spondyloarthropathy
- Ankylosing Spondylitis
- Scleroderma
- Eosinophilic Fasciitis
- Hidradenitis Suppurativa
- Systemic Lupus Erythematous
- Chronic Seronegative Oligoarthritis
- Pioderma Gangrenoso
- Chronic Seronegative Polyarthritis
- Relapsing Polychondritis
- Polymyalgia Reumatica
- Polymyositis / Dermatomyositis
- Psoriasis
- Sarcoidosis
- Overlap Syndrome
- Felty's Syndrome
- SAPHO's Syndrome
- Primary Sjögren's Syndrome
- Uveitis
- Vasculitis

Appendix III. List of Variables in BIOBADASAR

- General Variables
  - Age
  - Sex
  - Weight
  - Height
- Clinical information
  - Diagnosis of Rheumatic Disease
  - Date of diagnosis
  - Specifications:
    - If Psoriatic Arthritis, specify: Oligoarticular, polyarticular, Axial, Mutilans, Distal Interphalangeal joint affection
    - Others: Axial involvement, Peripheral involvement, Amyloidosis, Seronegative Rheumatoid Arthritis, Lupus Nephritis, Interstitial Lung Disease, Nodular disease, Secondary Sjögren's disease, uveitis
  - Rheumatoid Factor
  - Titer of Rheumatoid factor
  - ACPA antibodies
  - Titer of ACPA
  - HLA-B27
  - AntiNuclear Antibodies
  - Swollen Joint Count
  - Tender Joint Count
  - Patient's Global Visual Analogue Scale
  - Erythrocyte Sedimentation Rate
  - C Reactive Protein
  - DAS-28
  - For patients with Ankylosing Spondylitis or Psoriatic Arthritis with axial manifestations:
    - BASDAI
    - ASDAS CRP
  - For patients with SLE:
    - SLEDAI
- Comorbidities:
  - Cancer
  - Ischemic Cardiopathy
  - Hypercholesterolemia
  - Arterial hypertension

- Smoking habits
- Interstitial lung disease
- Osteoporosis
- Infection with EBV
- Infection with Hepatitis B Virus (HbSAg, HbSAc, HbCAc)
- Infection with Hepatitis C Virus

- Charlson Comorbidity Index
- Treatment
  - Treatment
  - Start date
  - Stop date
  - Administration route
  - Dose
  - Frequency of administration
  - Reason for treatment interruption
  - Tuberculosis
    - Personal history of TB
    - Contact with patients with TB
    - TB prophylaxis
    - Vaccination with Calmette-Guerin bacillus
    - Findings in chest X-Ray
    - Result of test with tuberculin
    - Result of test with tuberculin booster
    - Result of Quantiferon
  - Concomitant treatments
    - Methotrexate
    - Hydroxychloroquine
    - Azathioprine
    - Cyclophosphamide
    - Cyclosporine
    - Denosumab
    - Corticosteroids
    - Leflunomide
    - Mesalazine
    - Mycophenolate
    - Sulfasalazine
    - Tacrolimus

Appedix IV. Helsinki Declaration of the World Medical Association. Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th World Medical Assembly Helsinki, Finland, June 1964,

amended by the 29th World Medical Assembly Tokio, Japan, October 1975

35th World Medical Assembly, Venice, Italy, October 1983

41st World Medical Assembly, Hong Kong, September 1989

48th General Assembly Somerset West, South Africa, October 1996

52nd General Assembly, Edinburgh, Scotland, October 2000

53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)

55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)

59th WMA General Assembly, Seoul, Republic of Korea, October 2008

64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions

(methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimizes possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimize the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific requirements and investigation protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorized representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention.

The patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

<u>Appendix V.</u> Patient Information Sheet and Informed Consent

Consentimiento Informado

Título del Estudio: Registro Argentino de Eventos Adversos ocasionados por el uso de Agentes Biológicos. (BIOBADASAR)

Investigador:

Ud. ha sido invitado a participar en una investigación. Antes de poder decidirse, es importante que Ud. lea y comprenda el motivo de esta investigación, y lo que ella implica. Este documento describe el propósito del estudio, quiénes son las personas que están llevando a cabo la investigación, los procedimientos del estudio, los beneficios, los riesgos y las molestias que pueden presentarse por participar.

Propósito del estudio

Ud. tiene una enfermedad reumática y su médico le indico un tratamiento que incluye diversos medicamentos, con la finalidad de controlar la actividad de su enfermedad. Como Ud. sabe estos medicamentos pueden generar reacciones adversas que pueden variar de intensidad y severidad.

El propósito de este estudio es reportar la aparición de eventos adversos ocasionados por el uso de terapia biológica. Su médico reportará el evento adverso en una base de datos que será confeccionada a este fin. Dicha base permitirá conocer cuál es la frecuencia de eventos, si existen factores que predispongan a los mismos, si se asocian a otras enfermedades como por ej.diabetes, hipertensión, etc, y también permitirá conocer si los mismos son más comunes de ver en los pacientes que reciben algunas drogas en particular.

Investigadores

El proyecto de investigación está siendo conducido por.....
.....Los co-investigadores son .....
.....
.....

El estudio cuenta con el aval y soporte científico de la Sociedad Argentina de Reumatología (SAR), PANLAR (Congreso de la Liga Panamericana de Asociaciones de Reumatología) y la Sociedad Española De Reumatología, esta última aporto su base como modelo y participo en el entrenamiento de los coordinadores de cada uno de los países participantes en este proyecto .....
.....

Explicación de los procedimientos del estudio

Si Ud. accede a participar de este proyecto, su médico le realizara algunas preguntas para conocer las características de su enfermedad, tiempo de evolución, tratamientos que recibe, y si Ud. tiene otras enfermedades asociadas. Cada vez que Ud. concurra a la consulta su médico le preguntara si Ud. tuvo algún evento adverso nuevo o si se empeoro alguno preexistente y revisara sus análisis de laboratorio para ver si tiene algún hallazgo relevante.

Además su médico podrá contactarlo telefónicamente para conocer su estado, si continua recibiendo la medicación y si apareció algún evento adverso que Ud. no haya comunicado.

Beneficios de participar en el estudio

No hay beneficios directos por participar en este estudio. No obstante, se espera que esta investigación aporte conocimiento sobre los diferentes acontecimientos adversos que puedan aparecer, los cuales podrán ser utilizados para mejorar el control de los pacientes con enfermedades reumáticas, tomar decisiones en base a los datos aportados y crear guías locales que permitan una mejor utilización de las diferentes terapias disponibles.

Riesgos de participar en el estudio

Ud. no está expuesto a riesgo físico o psicológico, la visita a su médico será similar a las previas y no se espera que experimente molestias por responder a las preguntas que le realice su médico.

Confidencialidad

Toda la información que se obtenga durante el estudio permanecerá confidencial. Al momento de su ingreso se le asignara un código numérico que será único y solo para Ud. Su identidad como participante no será revelada, y solo su médico podrá conocer la misma. .

Incentivos para participar

No hay incentivos especiales ofrecidos a los voluntarios por participar en este estudio

Financiación

Este estudio es llevado a cabo por la Sociedad Argentina de Reumatología (SAR).

Naturaleza voluntaria de la participación

La participación en este estudio es voluntaria. Su decisión de participar o no, no tendrá ninguna influencia en los resultados del estudio..... Si Ud. decide participar, será libre de retirar su consentimiento y suspender su participación en cualquier momento sin ninguna consecuencia para Ud.

Preguntas sobre este estudio

Si Ud. tiene alguna pregunta sobre este estudio o sobre sus derechos como participante, podrá llamar al investigador.....TE:....., o podrá escribir al Comité de Ética....., Dirección..... y teléfono .....

Si Ud. firma debajo significa que ha leído la información contenida en este documento y tuvo la oportunidad de realizar todas las preguntas que creyó necesario sobre el estudio. Su firma también indica que está de acuerdo en participar en este estudio, y que se le ha dicho que puede cambiar de opinión y retirar su consentimiento en cualquier momento. Se le entrega una copia de este consentimiento informado. También se le ha dicho que por firmar este consentimiento Ud. no resigna ninguno de sus derechos legales.

Nombre del participante: ……

…….. ……

Firma del participante Fecha

Nombre del investigador: ……

…….. ……

Firma del Investigador Fecha