CoReumaPt Protocol: the Portuguese Cohort of Rheumatic Diseases

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ABSTRACT

Introduction: Rheumatic diseases (RD) are conditions with a variety of clinical manifestations and prognosis influenced by several factors. Cohorts and registries have been already established in some countries and have contributed to important knowledge about the disease course and the long-term outcomes of RD. This paper introduces the CoReumaPt project and sets the first step towards the creation of a prospective cohort study including the main RD occurring in the Portuguese population. CoReumaPt will allow outcomes research of chronic RD and the assessment of factors influencing the development and progression of RD. It will also allow to further evaluate the economic impact and the burden of RD in Portugal. CoReumaPt will be linked to Reuma.pt, the National Register of Rheumatic Diseases from the Portuguese Society of Rheumatology.

Methods: An open cohort will be created, initially composed by the randomly selected population of the cross-sectional National Epidemiological Rheumatic Diseases study (EpiReumaPt) and afterwards by other sources, namely through self- and physician's referral. Follow--up with annual self-administered questionnaires will be performed, in order to systematically collect and analyze outcomes of interest, mainly patient-reported outcomes. Data concerning less frequent assessments, such as radiographs and biomarkers, will also be assembled.

Conclusions: CoReumaPt will be a valuable resource for scientific research and will deliver pivotal information to improve public health policies concerning the prevention and the management of RD in Portugal.

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Keywords: Rheumatic Diseases; Cohort Studies; Outcome Assessment; Epidemiologic Studies.

INTRODUCTION

Rheumatic diseases (RD) are complex conditions characterized by a variety of clinical manifestations and prognosis. Cohort studies are one of the best ways to assess and understand the course of these diseases. To complement information obtained from randomized clinical trials, various cohorts and registries of patients with specific RD or other exposures have been established in the last decade (for instance, the Consortium of Rheumatology Researchers of North America [CORRONA] and the British Society for Rheumatology Biologics Register [BSRBR]). Thus, large prospective cohorts have increasingly contributed to pivotal research in the field of RD, which would have been difficult to obtain from other data sources. Actually, they constitute one of the major sources of clinical research publications and communications in rheumatology. Prospective cohort studies describe the disease course and management strategies and record long--term outcomes of the disease. Moreover, they contribute substantially to better understand the pathogenesis and the mechanisms underlying the disease progression. Prospective cohorts also enable the study of associations between disease and treatment interventions. In fact, information derived from such studies can guide the design of future drug trials[1].

Cohorts are organized around conditions or exposures, such as a particular disease, a health care service (e.g. a new medical procedure), or a product (including medical devices). In fact, registries of cohorts are mainly either drug based (e.g. patients enrolled after starting a particular medication) or disease based (e.g. patients enrolled after being diagnosed with a particular disease, such as a certain RD)[1]. They can vary in complexity, from simply recording a product use, as a requirement for reimbursement, to more systematic efforts to collect prospective data on several treatments, risk factors and clinical events in a defined population. Therefore, prospective cohorts allow complete data collection in a deliberate attempt to gather relevant information (i.e. aiming at maximizing measured covariates and minimizing missing information)[4]. The duration of follow-up can range from days (e.g. hospital admission registry) to decades (e.g. orthopedic implant registry or rheumatoid arthritis cohorts)[1].

The Portuguese Society of Rheumatology (SPR) already detains a national register (Reuma.pt) for several rheumatic diseases [rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA) and juvenile idiopathic arthritis (JIA)], but so far no further registries of patients with other relevant chronic RD have been undertaken in Portugal, such as, osteoporosis (OP), osteoarthritis (OA), systemic lupus erythematosus (SLE), polymyalgia rheumatica (PMR), fibromyalgia (FM), gout (GO), periarticular diseases (PD) and non-specific low-back pain (LBP). Several outcome research projects on these RD have been published based on European and North American cohorts. However, different populations have diverse genetic and environmental backgrounds that influence outcomes, such as morbidity and mortality rates. Furthermore, patient's access to healthcare services and the economic burden of these diseases in Portugal have clearly very specific patterns that need to be identified, namely by measuring the healthcare resources consumption and by assembling data concerning absenteeism and presenteeism (loss of productivity). This effort will define the precise social and economical impact of RD, allowing the adaptation of future policies by our National Healthcare System to the identified needs.

The EpiReumaPt survey, is an ongoing Portuguese epidemiologic cross-sectional study (2011-2013) and it has the main aim of estimating the prevalence of different RD in Portugal. The 10000 participants in this project (a random sample of the Portuguese population) will be invited for a long-term follow-up, during which they will be integrated into the CoReumaPt cohort.

This article presents the CoReumaPt study and sets the first step towards the creation of a prospective cohort for the main RD occurring in the Portuguese population.

OVERVIEW OF COREUMAPT

The overarching principle of the CoReumaPt Project is to improve public health through the knowledge and prevention of RD in Portugal. In order to achieve this, a cohort will be created, including chronic RD patients (namely OP, OA, RA, AS, SLE, PMR, FM, GO and LBP) and "non-RD" subjects. This large cohort might be afterwards divided in specific cohorts according to the future development of this project. The link with Reuma.pt will be done; patients with a confirmed diagnosis of RA, spondyloarthritis (SpA, including AS and

PsA) or JIA will be also invited to enroll the ongoing register of patients with these diseases, in case they are not already participating.

OBJECTIVES OF COREUMAPT

PRIMARY OBJECTIVE

To establish open cohorts to further explore outcomes research of chronic RD and the risk factors for the development of RD.

SECONDARY OBJECTIVES

1. To estimate the incidence of health outcomes in different RD according to clinical and socio-demographic characteristics.
2. To evaluate prospectively the impact of different RD at the individual (clinical and humanistic consequences) and social level (including economic consequences).
3. To estimate the contribution of prognosis factors to the progression of RD in the Portuguese population.
4. To determine the burden of different RD on the functional capacity and work participation of the Portuguese population.
5. To monitor the effectiveness and safety of current RD treatments in a "real-world" setting.
6. To identify regional differences across the country for the abovementioned endpoints.
7. To compare the incidence of relevant outcomes with other countries.

METHODOLOGY OF COREUMAPT

STUDY DESIGN

Population-based multi-disease, multipurpose cohort study.

STUDY POPULATION

The study population source is described in more detail elsewhere[7] and is composed by Portuguese non-institutionalized adults (≥ 18 years old) randomly selected in the EpiReumaPt study and who voluntarily agreed to participate by signing a written Informed Consent. In parallel, other sources of patients might be used, for instance, physician's referral or patient's self-referral, as long as validation by a rheumatologist occurs prior to the inclusion in the cohort (Figure 1).

All enrollees must also be mentally competent, as defined by the opinion of the investigator or rheumatologist, in order to be able to participate in all study required assessments and procedures. Subjects unwilling to sign the Informed Consent, unable to speak Portuguese or with an inability to answer the questionnaire will be excluded.

PRIMARY OUTCOMES

This study will be designed to systematically collect and analyze longitudinal outcomes. Herein is the list of the "core" outcomes of interest a priori targeted for this cohort. Later, specific domains will be addressed for particular groups of subjects (e.g. specific measures of disease activity and physical function). These specific domains will be detailed in future publications.

Thus, a core set of outcome measurements (clinical, laboratory and imaging) will be assembled at baseline and follow-up. Questionnaires will be designed to be mainly self-administered by the participants (i.e. patient-reported data) and cover most of the outcomes outlined in Figure 2. Questionnaires will also address socio-demographic factors, life-style factors and exposure variables.

The selection of primary outcomes for measurement in this study has been accomplished considering the

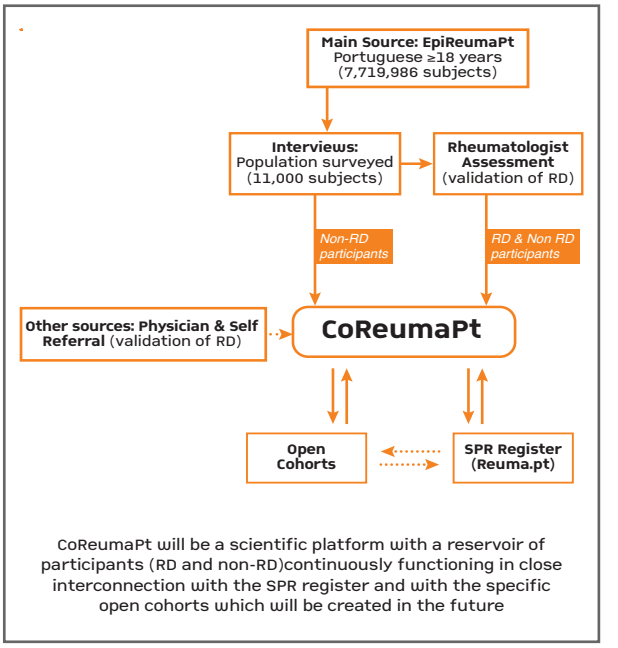

Figure 1. CoReumaPt study population and due participants' flow

RD: Rheumatic Diseases

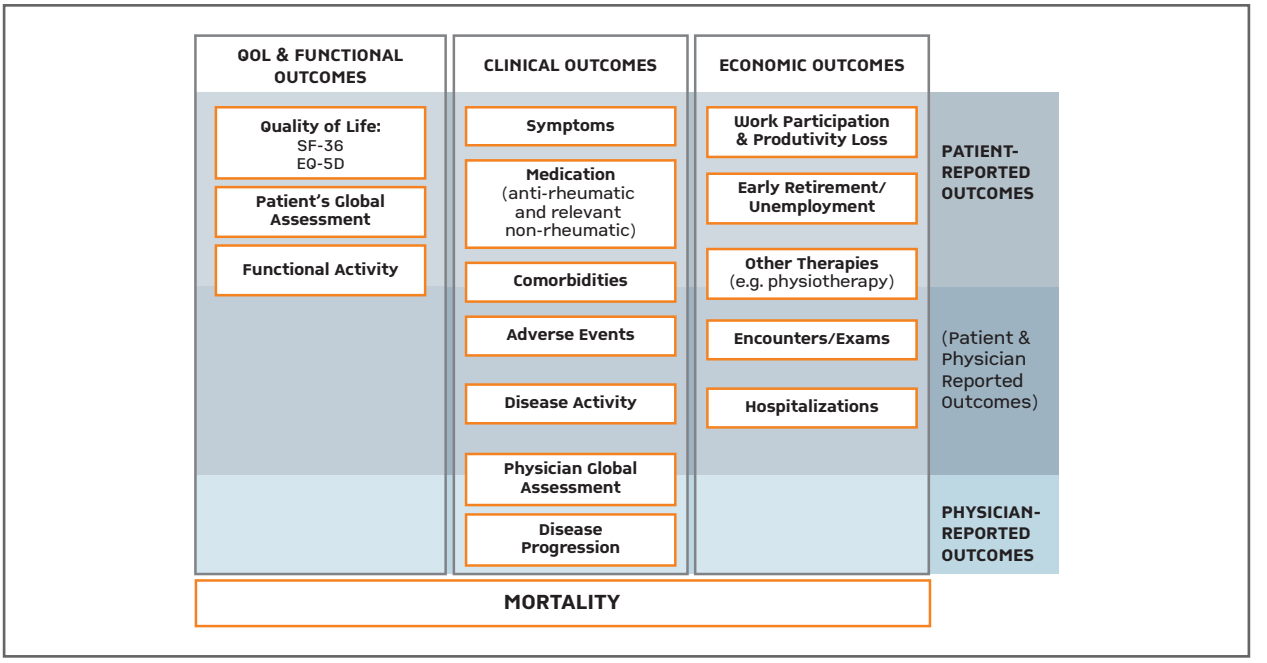

Figure 2. Primary Outcomes to be addressed in the CoReumaPt study

QoL: Quality of Life; SF-36: Short Form (36) Health Survey; EQ-5D: EuroQol-5D

OMERACT (Outcome Measures in Rheumatology Clinical Trials) consensus process.

STUDY PROCEDURES

INITIAL PATIENT ENROLLMENT AND PHYSICIANS' PARTICIPATION

Following each subject's selection and participation in the EpiReumaPt cross-sectional study, an assessment of the willingness to be followed-up and due involvement in the subsequent cohort phase will be done, which includes an Informed Consent and collection of information contact. Within 3-6 months, the participant will be contacted again by the study staff via phone call in order to confirm willingness to be followed-up and to obtain additional data. The enrollee will also be inquired about his preferred method of contact (phone, paper-based or web-based). Repeated unsuccessful contacts may lead to the participant's dismissal from the cohort.

In this first assessment, the participant will be given details to access a web-based platform (including a username and a password), which is meant to be the preferred method for patient-data collection during the follow-up period. Phone calls and questionnaires sent by post during follow-up will be alternative ways to collect data if requested by the participant or to complete information provided via online questionnaires (Figure 3).

Identified physicians clinically in charge for a given participant will also be invited to participate in this study; thereby receiving details for the access to the web-based platform, and also getting their patients' identification codes. Physicians will be requested to complete some baseline information (e.g. disease activity) and also yearly updates on other relevant clinical information, complementary to the patient-reported data (see below Annual Questionnaire). Physicians will also be requested to validate some patient-reported outcomes (PRO) (e.g. hospitalizations and serious adverse events).

FIRST CONTACT - BASELINE ASSESSMENT

The majority of the baseline data will be provided by the EpiReumaPt study, however CoReumaPt baseline assessment will collect more detailed medical history, such as past hospitalizations, past and current comorbidities, medications and adverse events. Any hospitalization occurring within the past 12 months and self-reported by the participant should be validated through medical records or by contacting the respecti-

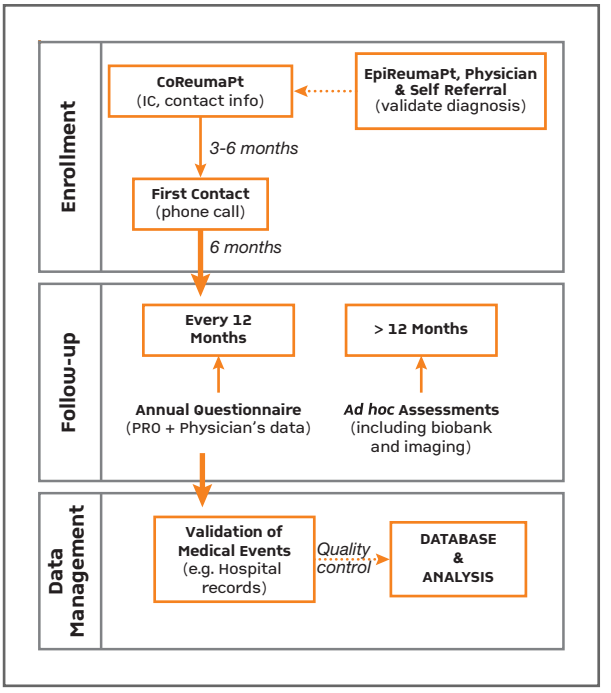

Figure 3. Flow diagram of CoReumaPt processes and follow-up assessments

IC: Informed Consent; PRO: Patient-Reported Outcomes

ve hospital or the physician. Other up-to-date PRO will be addressed, such as health-related quality of life, functional status and work disability. For further economic analysis, healthcare resources utilization (such as medical encounters and exams) should be registered at the baseline assessment. After finishing this contact, scheduling of the next one will be done (Figure 3).

ANNUAL QUESTIONNAIRE – PRO AND PHYSICIAN-REPORTED DATA

At 12-month intervals, CoReumaPt participants will be surveyed by a self-administered questionnaire. This questionnaire shall bring together information regarding PRO and the clinician-reported data (Figure 3).

All physicians will be reminded to include data concerning the closest visits of their patients. Physicians will be requested to revise all patient-reported fields (including medication and adverse reactions) and, more importantly, will be asked to fill in clinical data related with the physician's evaluation (including disease activity). Both patients and physicians (if applicable) will also be requested to record all hospitalizations, medical encounters and other relevant healthcare resource consumption occurred in the past 12 months.

New RD cases among the "non-RD" participants will be captured through self-report of RD diagnosis or rheumatic symptoms. This must be further validated by a rheumatologist.

>12-MONTHS ASSESSMENTS (BIOBANK AND IMAGING EXAMS)

In order to address some outcomes of interest and to further assess the evolution of RDs, some exams will be periodically required (e.g. radiographs to assess structural damage, BMD as measured by DEXA, and laboratory tests). These assessments are disease-specific and their periodicity will depend on the outcomes selected for each specific cohort, which will be described in more detail in dedicated publications. Moreover, for future genetic and biomarkers analysis, blood samples will be drawn at baseline from participants during the EpiReumaPt procedures and afterwards at different time-points along their follow-up. All these samples will be stored at the Biobank of Instituto de Medicina Molecular, Lisbon.

OTHER ASSESSMENTS

Patients and physicians might be asked by the CoReumaPt staff to send the results of some exams with the purpose of validating outcomes of interest (for example, radiographic evidence of OP fractures). This will be done *ad hoc* and driven by the Steering Committee of the CoReumaPt team (see below Steering Committee section). Other data might be requested upon a new scientific question requiring additional data not captured in the original questionnaires. This should also be previously approved by the Steering Committee.

DEFINITION OF RHEUMATIC DISEASES

The participant's exposure to any RD will be assessed by the rheumatologist who will validate the final diagnosis of each participant. This diagnosis of a given RD, either active or in remission, will be based on the internationally accepted classification criteria of that RD and should be aligned with the EpiReumaPt study[7].

INTERNAL/EXTERNAL VALIDITY AND QUALITY CONTROL

An essential requirement for the use of a longitudinal dataset is the internal and external validity of the cohort. Patients without RD should be representative of

the population from which they are drawn, using a random sampling and avoiding selection bias. This issue has been carefully handled in the EpiReumaPt study, which is the primary source of the CoReumaPt, and thus representativeness of the Portuguese Population is expected to be maintained concerning that source of participants. This will be tested by comparing the demographic characteristics of the overall EpiReumaPt population versus the Portuguese population, according to the National Institute of Statistics (INE). Nevertheless, CoReumaPt is an open cohort which will allow further entry of new enrollees. Therefore it is possible that selection bias occurs along the project. This bias and any other eventual deviation will be handled *ad hoc* by the Steering Committee.

In an attempt to avoid any bias based on socioeconomically status, paper-based questionnaires will be sent to those participants without phone or computer devices or; for those who simply prefer to send their responses by post (free-of-charge).

In order to increase internal validity and to provide complete and accurate data, the methods of observation will be clearly defined and the measurement tools will be valid and reliable. All procedures will be standardized and properly documented. The activities designed to achieve proper quality control will encompass all aspects of the study, including: clear, pretested data collection forms; measurements that are validated; central and local training of staff; monitoring of recruitment and retention; surveillance and evaluation of data quality as it is collected. Supervision and ultimate responsibility of quality assurance will rest with the Steering Committee.

Follow-up maintenance is crucial for the success of any cohort study[10], therefore attrition bias will be avoided by using reminders for scheduled visits and implementing specific activities to motivate participation (e.g. periodic newsletters and reminders sent to participants). A specific task-force reporting to the Steering Committee will deal with this bias and will be responsible for activities designed to increase participants' retention in this study. Non-respondents will be tracked in order to ascertain reasons of discontinuation and to fill, whenever possible, a short "end-of-study" questionnaire. Lost to follow-up population will be characterized to detect eventual factors asymmetrically prevalent when compared with more adherent participants. If possible, death records will be consulted for all participants to whom long-term unsuccessful contacts have occurred.

All assessment dates will be reminded to patients and physicians upfront and missing assessments will be followed-up via phone directly by a member of the CoReumaPt staff. Missing data within one assessment will generate automatic reminders both to patients and physicians so that completion could be fulfilled.

Concerning the quality of the database, its content will be audited visually by a person trained to process the forms and a web-based platform will be designed to detect out-of-range values, inconsistencies and missing data, thereby triggering alerts to the CoReumaPt staff.

Any event that results in hospitalization or any critical medical event will be validated by obtaining medical confirmation. Exposure variables will be subject to frequent validation by the Steering Committee of the CoReumaPt, namely the RD exposure. Primary Outcomes will also be subject to the Steering Committee's evaluation, especially those requiring radiographic confirmation.

REGISTRY SIZE AND DURATION

There is no limit set regarding the cohorts' size. For the time being, size will depend on the EpiReumaPt participants' willingness to be followed-up. Since this is a multipurpose cohort study there is no a priori definition for its duration. It will depend on several factors, including funding and enrollees' availability and willingness to persist on study.

ETHICAL CONSIDERATIONS

This project was approved by Comissão Nacional de Protecção de Dados, the Portuguese data protection authority (in accordance with the Portuguese law number 67/98, October 26th, regarding protection of personal data) and was submitted to the Ethics Committee of the Faculty of Medical Sciences from the Universidade Nova de Lisboa. The study will be conducted in accordance with the applicable laws and regulations including, but not limited to, the Guideline for Good Clinical Practice (GCP) and the ethical principles stated in the Declaration of Helsinki.

Participants' confidentiality will be safeguarded by the nonexistence of identifiers on the database (only unique ID participants' codes). Their names and contacts will be stored separately from study data trans-

mitted to the coordinating center (based on the headquarters of the SPR). Thus, all data for future analysis will be kept anonymously and securely by the CoReumaPt authorized staff.

All participants will sign an Informed Consent before enrollment, thereby authorizing further follow-up for collection of personal and clinical data. For the Biobank future research purposes, a specific Informed Consent will also be signed by those accepting to participate in this part of the CoReumaPt study.

For all paper-based questionnaires, transcription for the electronic system will be done by authorized personnel complying with all confidentiality procedures of the study. The electronic dataset will then be associated with the participants' ID code.

There will be absolutely no disclosure of individual health information to the general public. Thus, publications will be strictly confined to aggregated data.

STEERING COMMITTEE

The Steering Committee will be the primary governing body of the study and provides its scientific leadership. It will have responsibility for the overall study design, policy decisions and operations of the CoReumaPt study. As abovementioned, the Steering Committee might decide upon the request of additional data (e.g. laboratory exams, imaging) as needed. Members of this Steering Committee will include national rheumatologists, epidemiologists and statisticians, as well as international consultants thoroughly experienced with previous cohort studies.

Among the Steering Committee there will be investigators responsible for future specific cohorts. Thus, a given leading coordinator will be accountable for the oversight and the selection of the outcomes assigned to each specific cohort. Nominations for this coordination and all changes in the protocol will be subject to majority vote of the Steering Committee. This Steering Committee will be chaired by the SPR board and a record of changes and decisions will be maintained by SPR.

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