Project Protocol

1. Title

Reuma.pt/myositis – the Portuguese registry of inflammatory myopathies.

2. Abstract

Inflammatory idiopathic myopathies (IIM) are a heterogeneous group of disorders. Geographical factors significantly influence IIM epidemiology, and the Portuguese population has never been characterised. Clinical features and autoantibody expression can influence treatment responsiveness and prognosis. Fully characterising a patient ensures that all the information regarding treatment responsiveness and prognosis is available to the assisting Rheumatologist. Reuma.pt/Myositis is a great tool to systematically evaluate IIM patients and expand our current knowledge on these systemic rheumatic diseases. We intend to present the Reuma.pt/Myositis protocol to the scientific community and characterise its IIM cohort.

3. Background

Idiopathic inflammatory myopathies (IIM) are a heterogeneous group of disorders in which chronic inflammation of the skeletal muscle, leading to muscle weakness, is a common feature[1]. Other organs are frequently affected, such as the skin, joints, lungs, gastrointestinal tract, and heart[1]. It affects both children and adults and can frequently be a paraneoplastic manifestation in the adult population.

Muscle weakness is typically proximal, and the *Manual Muscle Testing of a Subset of Eight Muscles* (MMT8) is a validated muscle strength test[2]. Myalgia is also a frequent feature. Dysphagia and dysphonia occur often and can be severe, whereas the involvement of respiratory muscles can be fatal[1]. Muscle enzymes, including creatinine kinase (CK), aldolase, myoglobin, aspartate transaminase (AST), alanine transaminase (ALT), and lactate dehydrogenase (LDH), are typically elevated[1]. Muscle biopsy is the gold standard for muscle involvement characterisation. However, it is not essential for diagnosis. Electromyography (EMG) can show myopathic features, and T1 and short tau inversion recovery (STIR) magnetic resonance imaging (MRI) sequences can detect muscle oedema reflecting myositis[1]. Muscular ultrasonography is another imaging tool with good potential [3].

Skin manifestations may include Gottron's sign and papules, heliotrope erythema, linear erythema, V-shaped erythema, the shawl sign, periungual telangiectasias, calcinosis, mechanic's hands, and hiker's feet[1,4–7]. As active skin lesions resolve, patients are frequently left with poikiloderma (areas of hypopigmentation and hyperpigmentation), telangiectasias and skin atrophy[1].

Interstitial lung disease (ILD) is a severe feature associated with some of the IIM subtypes[8]. The three main presentations are (i) acute and rapidly progressive ILD, (ii) subacute or chronic ILD corresponding to organising pneumonia (OP) or overlap of OP and non-specific interstitial

pneumonia (NSIP), usually with an excellent response to corticosteroids, and (iii) chronic progressive fibrosing ILD, corresponding to fibrotic NSIP or usual interstitial pneumonia (UIP), which tends to respond poorly to steroids and other forms of immunosuppressive therapy[1,8].

Raynaud's phenomenon (RP), arthritis, fever and gastrointestinal involvement are also frequent[1]. Myocarditis is a rare but potentially severe manifestation[1].

Myositis-specific and myositis-associated antibodies (MSA and MAA, **Table 1**) are associated with distinct clinical features. They can help identify subsets of IIM in which extra-muscular symptoms might be the presenting or predominant feature, especially when muscle symptoms are mild or absent[1,9]. Of note, MSA may be undetected in HEp-2 IIFA-screening, i.e., patients may be anti-nuclear antibodies (ANA) negative.

Table 1 - Myositis-specific and myositis-associated antibodies.

Myositis-specific antibodies (other than anti-synthetase)	**Myositis-specific anti-synthetase antibodies**	**Myositis-associated antibodies**
Anti-SRP	Anti-Jo1	Anti-Pm/Scl
Anti-HMGCR	Anti-PL7	Anti-U1RNP
Anti-Mi2	Anti-PL12	Anti-Ku
Anti-MDA5	Anti-EJ	Anti-Ro52
Anti-TIF γ	Anti-OJ	Anti-mitochondrial antibody
Anti-NPX2	Anti-Zo	
Anti-SAE	Anti-YRS/Ha	
Anti-CN1A	Anti-KS	

Different phenotypes have been identified within the IIM spectrum, based on the muscle involvement characterisation, extra-muscular findings, and immunology. Dermatomyositis (DM) generally includes the classic skin and muscle involvements of IIM. Clinically-amyopathic dermatomyositis (CADM) is a recently created term that includes both amyopathic dermatomyositis (ADM) and hypomyopathic dermatomyositis (HDM)[1]. CADM represents a clinical phenotype with typical DM skin manifestations and may include internal organ involvement but not significant muscle weakness. A notable example includes anti-MDA5 CADM, in which rapidly-progressive ILD is a prominent feature. Polymyositis is a term that has been gradually abandoned. Patients with typical DM muscle biopsy without skin involvement are now classified as having non-specific myositis (NSM)[1]. Other patients previously categorised as having polymyositis are now classified as having antisynthetase syndrome (ASSD), immune-mediated necrotising myopathy (IMNM) or overlap syndromes with other connective tissue diseases. ASSD is characterised by myositis, ILD, mechanic's hand, hiker's feet, arthritis or Raynaud phenomenon in the presence of an anti-synthetase antibody. IMNM is histologically characterised by necrotic muscle fibres and scarce or no inflammatory cell infiltrates. IMNM patients present with markedly high levels of serum CK and may present positive anti-SRP or anti-HMGC-R. If both these MSA are negative, the patient is classified as having seronegative IMNM. Anti-HMGC-R is frequently associated with statin-induced myositis. Inclusion body myositis (IBM) is suggested on the basis of three main features: (i) finger flexor or quadriceps weakness, muscle biopsy showing (ii) the presence of rimmed vacuoles, and (iii) endomysial inflammation and invasion of non-necrotic muscle fibres.

Adult patients with IIM are at increased risk for cancer[10,11]. Older age, male gender, the DM phenotype, rapid onset of the disease, distal muscle weakness, dysphagia, asymmetric Raynaud's phenomenon, cutaneous vasculitis, skin necrosis, elevated CK, C-reative protein (CRP), or erythrocyte sedimentation rate (ESR), and ANA-negativity are risk factors for concomitant or underlying malignancy[11,12]. Additionally, in adults anti-MDA-5, anti-TIF-1γ, and NXP-2 have been associated with higher neoplasia risk[11]. Risk factors for malignancy according to the muscle disease phenotype include older age and low serum levels of CK for patients with DM[13] and male sex and low serum levels of CPK for patients with PM[13].

The 2017 European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) classification criteria were published in 2017[14] but have since then been highly discussed[15–18]. Despite its high specificity, there is low sensitivity due to the exclusion of autoantibodies (other than anti-Jo-1) and high reliability in muscle biopsy, which is frequently not performed in clinical practice[19]. The inclusion of MRI and autoantibodies in classification criteria would increase sensitivity without compromising specificity[20]. The nonrecognition of ASSD as an individual condition has also been pointed out[16] and has led to the creation of the EULAR/ACR Classification Criteria for ASSD (CLASS) Project, which is currently underway[21].

Even when considered as a group of diseases, IIM is rare[22]. Geographic factors seem to influence its incidence and prevalence[22], specifically latitude[23]. However, the Portuguese population of IIM has never been characterised.

In conclusion, IIM is a heterogeneous group of disorders in which different clinical features and autoantibody expression influence treatment responsiveness and prognosis. With the current inconsistencies in IIM subgroup classification, the complete characterisation of a patient is the only way to ensure that all the information regarding treatment responsiveness and prognosis is available to the assisting Rheumatologist. Reuma.pt/Myositis is a great tool to systematically evaluate IIM patients and expand our current knowledge on these systemic rheumatic diseases. We intend to present the Reuma.pt/Myositis to the scientific community and characterise its Portuguese IIM cohort.

4. Objectives

Primary objective

- To describe the Reuma.pt/Myositis protocol and highlight its potential for both daily clinical management of patients and clinical research
- To characterise the Portuguese inflammatory myopathies cohort, regarding:
    - Disease phenotypes (DM, JDM, CADM, NSM, IMNM, ASSD, IBM, overlap syndromes)
    - Clinical characteristics
    - Immunological profile
    - Muscle biopsy, EMG and MRI features
    - Treatment history

Secondary objectives

- Describe the proportion of patients that can be classified as having an IIM according to the 2017 EULAR/ACR classification criteria[14]

- Associate the expression of MSA and MAA autoantibodies with specific disease phenotypes (DM, JDM, CADM, NSM, IMNM, ASSD, IBM, overlap syndromes) or specific clinical features

5. Methods

Type of study

Multicentre prospective open cohort study

Inclusion criteria

- Patients clinically classified as having myositis by their assisting physician
- Patients registered in Reuma.pt/Myositis[24], with at least a clinical characterisation
- Patients of all ages will be included

Data collection

- Data collection will start with exportation and subsequent exploratory analysis of the current data in Reuma.pt/Myositis. An anonymised Microsoft Excel document will be created and sent to every participating centre, highlighting the Reuma.pt missing information.
- In the first phase of data completion, the centre's designated local investigators will fill in the missing information in Reuma.pt/Myositis and include every patient followed in the centre fulfilling inclusion criteria, inserting in Reuma.pt/Myositis every variable required for this study.
- After the first phase of data completion is concluded, exportation and exploratory analysis of the Reuma.pt/Myositis data will be performed again. A new Microsoft Excel document will be created based on the exportation document.
- If any missing information persists after this phase, the Microsoft Excel document will be sent to every participating centre indicating the incomplete data. At this stage, the centre's designated local investigators are expected to fill in the missing information both in Reuma.pt/Myositis and directly in the Microsoft Excel document of the study.

Variables to be collected

- Age (continuous variable)
- Gender (dichotomic variable: female=0; male=1)
- Date of loss of follow-up (date)
- Cause of loss of follow-up (categorical variable)
- Type of myositis (categorical variable: dermatomyositis, juvenile dermatomyositis, amyopathic/ hypomyopathic dermatomyositis, non-specific myositis, polymyositis, mixed connective tissue disease, immune necrotising myositis, inclusion bodies myositis, overlap syndrome[1])
- 2017 EULAR/ACR criteria (dichotomic variable: no=0; yes=1)
- Date of first symptom (date)

[1] Including anti-synthetase syndrome

- Date of diagnosis (date)
- Disease manifestations:
    - Myalgia/ myositis (dichotomic variable: no=0; yes=1)
    - Gottron's papules (dichotomic variable: no=0; yes=1)
    - Heliotrope rash (dichotomic variable: no=0; yes=1)
    - Raynaud's phenomenon (dichotomic variable: no=0; yes=1)
    - Digital ulcers (dichotomic variable: no=0; yes=1)
    - Oedema (dichotomic variable: no=0; yes=1)
    - Calcinosis (dichotomic variable: no=0; yes=1)
    - Periungual changes (dichotomic variable: no=0; yes=1)
    - Lipoatrophy (dichotomic variable: no=0; yes=1)
    - Arthralgia/ arthritis (dichotomic variable: no=0; yes=1)
    - Oesophageal involvement (dichotomic variable: no=0; yes=1)
    - Gastric involvement (dichotomic variable: no=0; yes=1)
    - Intestinal involvement (dichotomic variable: no=0; yes=1)
    - Heart involvement (dichotomic variable: no=0; yes=1)
    - Lung involvement (dichotomic variable: no=0; yes=1)
- Myositis-specific and myositis-associated antibodies:
    - Anti-nuclear antibodies (dichotomic variable: negative=0; positive=1)
    - Anti-Mi2 (dichotomic variable: negative=0; positive=1)
    - Anti-TIF1γ (dichotomic variable: negative=0; positive=1)
    - Anti-MDA5 (dichotomic variable: negative=0; positive=1)
    - Anti-NPX2 (dichotomic variable: negative=0; positive=1)
    - Anti-SAE1 (dichotomic variable: negative=0; positive=1)
    - Anti-Ku (dichotomic variable: negative=0; positive=1)
    - Anti-Pm/Scl (dichotomic variable: negative=0; positive=1)
    - Anti-PL7 (dichotomic variable: negative=0; positive=1)
    - Anti-PL12 (dichotomic variable: negative=0; positive=1)
    - Anti-EJ (dichotomic variable: negative=0; positive=1)
    - Anti-OJ (dichotomic variable: negative=0; positive=1)
    - Anti-RNP (dichotomic variable: negative=0; positive=1)
    - Anti-SSA/SSB (dichotomic variable: negative=0; positive=1)
    - Anti-Jo1 (dichotomic variable: negative=0; positive=1)
    - Anti-SRP (dichotomic variable: negative=0; positive=1)
    - Another positive autoantibody (dichotomic variable: negative=0; positive=1)
    - Another positive autoantibody (categorical variable)
- Other exams:
    - Muscle biopsy with myositis evidence (dichotomic variable: no=0; yes=1)
    - Elevated muscle enzymes:
        - ⇨ CK (dichotomic variable: no=0; yes=1)
        - ⇨ LDH (dichotomic variable: no=0; yes=1)
        - ⇨ Aldolase (dichotomic variable: no=0; yes=1)
        - ⇨ AST (dichotomic variable: no=0; yes=1)
        - ⇨ ALT (dichotomic variable: no=0; yes=1)
    - Myopathic alterations in EMG (dichotomic variable: no=0; yes=1)
    - MRI with myositis evidence (dichotomic variable: no=0; yes=1)

- MMT8[2]
    - Worse MMT8 (continuous variable)
    - Most recent MMT8 (continuous variable)
- CMAS[3]
    - Worse CMAS (continuous variable)
    - Most recent CMAS (continuous variable)
- Joint count (number of painful joints)
    - Worse count (continuous variable)
    - Most recent count (continuous variable)
- Joint count (number of swollen joints)
    - Worse count (continuous variable)
    - Most recent count (continuous variable)
- Patient's global visual analogue scale
    - Worse (continuous variable)
    - Most recent (continuous variable)
- Modified DAS skin
    - Worse DAS (continuous variable)
    - Most recent DAS (continuous variable)
- Muscular involvement characterisation[4]
    - Proximal muscle weakness (dichotomic variable: no=0; yes=1)
    - Other muscle weakness (dichotomic variable: no=0; yes=1)
- Skin involvement characterisation
    - Heliotrope rash (dichotomic variable: no=0; yes=1)
    - Gottron's sign or papules (dichotomic variable: no=0; yes=1)
    - Periungual capillary changes (dichotomic variable: no=0; yes=1)
    - Lipodystrophy (dichotomic variable: no=0; yes=1)
    - Calcinosis (dichotomic variable: no=0; yes=1)
    - Digital ulcers (dichotomic variable: no=0; yes=1)
    - Generalized subcutaneous oedema (dichotomic variable: no=0; yes=1)
    - Periorbital subcutaneous oedema (dichotomic variable: no=0; yes=1)
    - Malar/ facial rash (dichotomic variable: no=0; yes=1)
    - Shawl sign (dichotomic variable: no=0; yes=1)
    - Mechanic's hands (dichotomic variable: no=0; yes=1)
    - Alopecia (dichotomic variable: no=0; yes=1)
    - Vasculopathy lesions (dichotomic variable: no=0; yes=1)
    - Photo-sensitivity (dichotomic variable: no=0; yes=1)
    - Livedo reticularis (dichotomic variable: no=0; yes=1)
    - Panniculitis (dichotomic variable: no=0; yes=1)
    - Other skin involvement (dichotomic variable: no=0; yes=1)
    - Other skin involvement (categorical variable)
- Organ involvement characterisation
    - Musculoskeletal involvement (dichotomic variable: no=0; yes=1)
        - ⇨ Arthritis (dichotomic variable: no=0; yes=1)

[2] For adults
[3] For children
[4] MMT8 will also be evaluated, but in its specific menu

        - ⇨ Contractures (dichotomic variable: no=0; yes=1)
    - Gastrointestinal involvement (dichotomic variable: no=0; yes=1)
        - ⇨ Dysphagia (dichotomic variable: no=0; yes=1)
        - ⇨ Dysphonia (dichotomic variable: no=0; yes=1)
        - ⇨ Abdominal pain or gastrointestinal ulcers (dichotomic variable: no=0; yes=1)
    - Lung involvement – interstitial lung disease (dichotomic variable: no=0; yes=1)
    - Heart involvement (dichotomic variable: no=0; yes=1)
    - Constitutional involvement characterisation
        - ⇨ Fever, as temperature > 38ºC (dichotomic variable: no=0; yes=1)
        - ⇨ Weight loss (dichotomic variable: no=0; yes=1)
        - ⇨ Fatigue (dichotomic variable: no=0; yes=1)
        - ⇨ Raynaud's phenomenon (dichotomic variable: no=0; yes=1)
    - Neoplasia (dichotomic variable: no=0; yes=1)
        - ⇨ Specific neoplastic diagnosis (categorical variable)
        - ⇨ Date of onset (date)
        - ⇨ Date of outcome (date)
        - ⇨ Treatments (categorical variable)
        - ⇨ Outcome (categorical variable: cure, remission, in treatment, persistent, death, unknown)
- Pharmacological treatments (previous)
    - Intravenous glucocorticoid pulses (dichotomic variable: no=0; yes=1)
    - Oral glucocorticoids (dichotomic variable: no=0; yes=1)
    - Hydroxychloroquine (dichotomic variable: no=0; yes=1)
    - Methotrexate (dichotomic variable: no=0; yes=1)
    - Azathioprine (dichotomic variable: no=0; yes=1)
    - Mycophenolate mofetil (dichotomic variable: no=0; yes=1)
    - Mycophenolic acid (dichotomic variable: no=0; yes=1)
    - Cyclosporine (dichotomic variable: no=0; yes=1)
    - Tacrolimus (dichotomic variable: no=0; yes=1)
    - Oral cyclophosphamide (dichotomic variable: no=0; yes=1)
    - Intravenous cyclophosphamide (dichotomic variable: no=0; yes=1)
    - Intravenous immunoglobulin (dichotomic variable: no=0; yes=1)
    - Rituximab (dichotomic variable: no=0; yes=1)
    - Others (dichotomic variable: no=0; yes=1)
- Pharmacological treatments (current)
    - Intravenous glucocorticoid pulses (dichotomic variable: no=0; yes=1)
    - Oral glucocorticoids (dichotomic variable: no=0; yes=1)
    - Hydroxychloroquine (dichotomic variable: no=0; yes=1)
    - Methotrexate (dichotomic variable: no=0; yes=1)
    - Azathioprine (dichotomic variable: no=0; yes=1)
    - Mycophenolate mofetil (dichotomic variable: no=0; yes=1)
    - Mycophenolic acid (dichotomic variable: no=0; yes=1)
    - Cyclosporine (dichotomic variable: no=0; yes=1)
    - Tacrolimus (dichotomic variable: no=0; yes=1)
    - Oral cyclophosphamide (dichotomic variable: no=0; yes=1)
    - Intravenous cyclophosphamide (dichotomic variable: no=0; yes=1)

- Intravenous immunoglobulin (dichotomic variable: no=0; yes=1)
- Rituximab (dichotomic variable: no=0; yes=1)
- Others (dichotomic variable: no=0; yes=1)

Variables to be created (transformed)

- Death (dichotomic variable: no=0; yes=1)
  - =0 if "cause of loss of follow-up" and "date of loss of follow-up" are missing
  - =1 if "cause of loss of follow-up" = death
  - =9 if "cause of loss of follow-up" ≠ death
- Muscle involvement (dichotomic variable: no=0; yes=1)
  - =1 if "Myalgia/ myositis" =1 in "Disease manifestations" or if "Muscle biopsy with myositis evidence" or "MRI with myositis evidence" =1 in "Other exams" =1 or if "Proximal muscle weakness" in "Muscular involvement characterisation" =1 or if "Dysphagia" or "Dysphonia" in "Gastrointestinal involvement" =1
  - MMT8, muscle enzymes elevation and EMG will not be considered to score "Muscle involvement" =1 because of their assumed lack of specificity
- Articular involvement (dichotomic variable: no=0; yes=1)
  - =1 if "Arthralgia/ arthritis" =1 in "Disease manifestations" or if "Arthritis" in "Musculoskeletal involvement characterisation" =1 or if "Worst swollen joint count" >0
- Skin involvement (dichotomic variable: no=0; yes=1)
  - =1 if "Gottron's papules", "Heliotrope rash", "Calcinosis", "Oedema", "Periungual changes" or "Lipoatrophy" =1 in "Disease manifestations" or if "Worse DAS skin" > 0 or if at least one variable =1 in "skin disease characterisation"
- Gastrointestinal involvement (dichotomic variable: no=0; yes=1)
  - =1 if "Oesophageal involvement" =1 in "Disease manifestations" or if "Gastric involvement" =1 in "Disease manifestations" or if "Intestinal involvement" =1 in "Disease manifestations" or if "Gastrointestinal involvement" in "Organ involvement characterisation" =1
- Lung involvement (dichotomic variable: no=0; yes=1)
  - =1 if "Lung involvement" =1 in "Disease manifestations" or if "Lung involvement – interstitial lung disease" in "Organ involvement characterisation" =1
- Heart involvement (dichotomic variable: no=0; yes=1)
  - =1 if "Heart involvement" =1 in "Disease manifestations" or if "Heart involvement" in "Organ involvement characterisation" =1
- Gottron's papules or sign (dichotomic variable: no=0; yes=1)
  - =1 if "Gottron's papules" =1 in "Disease manifestations" or if "Gottron's sign or papules" in "skin disease characterisation" =1
- Heliotrope rash (dichotomic variable: no=0; yes=1)
  - =1 if "Heliotrope rash" =1 in "Disease manifestations" or if "Heliotrope rash" in "skin disease characterisation" =1
- Subcutaneous oedema (dichotomic variable: no=0; yes=1)

    - =1 if “Oedema” =1 in “Disease manifestations” or if “Generalized subcutaneous oedema” in “skin disease characterisation” =1 or if “Periorbital subcutaneous oedema” in “skin disease characterisation” =1
- Calcinosis (dichotomic variable: no=0; yes=1)
    - =1 if “Calcinosis” =1 in “Disease manifestations” or if “Calcinosis” in “skin disease characterisation” =1
- Periungual changes (dichotomic variable: no=0; yes=1)
    - =1 if “Periungual changes” =1 in “Disease manifestations” or if “Periungual capillary changes” in “skin disease characterisation” =1
- Digital ulcers (dichotomic variable: no=0; yes=1)
    - =1 if “Digital ulcers” =1 in “Disease manifestations” or if “Digital ulcers” in “skin disease characterisation” =1
- Raynaud’s phenomenon (dichotomic variable: no=0; yes=1)
    - =1 if “Raynaud’s phenomenon” =1 in “Disease manifestations” or if “Raynaud’s phenomenon” in “constitutional involvement characterisation” =1

Variables to be created (calculated)

- Age at disease onset (continuous variable)
    - (“Date of first symptom” – “Date of birth”) in days / 365
- Age at diagnosis (continuous variable)
    - (“Date of diagnosis” – “Date of birth”) in days / 365
- Diagnostic delay in years (continuous variable)
    - (“Date of diagnosis” – “Date of first symptom”) in days / 365
- Disease duration in years at the time of death (continuous variable)
    - (“Date of loss of follow-up” – “date of first symptom”) in days / 365, if “cause of loss of follow-up” = death
- Disease duration in years up to the last follow-up (continuous variable)
    - (“Date of the last appointment” – “date of first symptom”) in days / 365, if “cause of loss of follow-up” ≠ death

Statistical analysis

The data will be analysed using SPSS version 26.0 (SPSS, Inc., Chicago, IL, USA).

Descriptive statistics will be presented as mean ± standard deviation for continuous and normal variables, as median (interquartile range) for continuous non-normal variables, and as absolute and relative frequencies for categorical variables.

Associations between the different categorical or dichotomic variables will be tested using Chi-Square Test or Fischer’s Exact Test, as appropriate. For statistically significant associations, the odds ratio will be calculated as a measure of the effect size of the association. The associations of continuous variables with categorical or dichotomic variables will be tested using Student’s t-Test or Mann-Whitney Test, as appropriate (normality and variance homogeneity will be calculated). Cohen’s D will be used as a measure of the effect size of the differences.

Statistical significance will be set at $p < 0.05$.

6.1. Expected results

The main objectives of this study are to present the Reuma.pt/Myositis protocol to the scientific community and to clinically and immunologically characterise the patients of its cohort. We expect to create awareness of the available data and hope to foster further clinical research work based on this cohort. In terms of clinical subtypes and autoantibodies prevalence, we expect our cohort to be similar to international cohorts of similar latitudes (i.e., Southern European cohorts).

6.2. Possible limitations

Internal and external validity

Since this study focuses on a specific cohort (Reuma.pt/Myositis) and it will potentially include the whole target population, we do not expect major issues with external validity. Only patients registered in Reuma.pt/Myositis that do not have a clinical charaterisation will be excluded. Therefore, we expect that most patients within our target population will be included in this study. Moreover, we will ask all participating centres to complete the missing information to avoid the exclusion of any patient. However, our results may not generalizable to other cohorts with a different genetic background.

In order to get maximum representativity, we expect not only tertiary but also secondary centres to participate in this project. Centres that actively collaborate in the project may designate project co-authors, irrespective of the number of eligible patients.

Sample size

IIM is a very rare group of diseases, and therefore data sets tend to be small. To maximise our sample size, we will try to include as many centres as possible. Besides, we will use measures of effect size to better interpret statistically non-significant results.

Missing data

To overcome this problem, we will ask all participating centres to complete the missing information with data from patients' medical records whenever such information is available.

Typing errors

To minimise the influence of typing errors, we will make an exploratory evaluation of the data extracted from Reuma.pt. Outlier cases will be individually analysed.

Publication bias

We expect to publish the results of our study, irrespective of the significance of our results.

7. Calendar of tasks

- Literature review, study design and elaboration of research protocol: April – May 2021
- Submission of research protocol to Reuma.pt and Ethics Commission: May 2021
- Invite all national centres to participate in the project: June – July 2021
- Exploratory data extraction and first Microsoft Excel document compilation: July 2021
- Data completion by all participating centres: August – October 2021
- Data extraction and second Microsoft Excel document compilation: November 2021
- Data completion by participating centres with missing information: December 2021
- Data analysis: January – February 2022
- Final report and abstract submissions for presentation at national/international congresses as well as publication: February – June 2022

8. Ethical considerations

The study will be conducted according to the principles of the Declaration of Helsinki (revised in Fortaleza – 2013)[25] and will be submitted for evaluation and approval to the Ethics Committee of *Centro Académico de Medicina de Lisboa (CAML*) and the Reuma.pt National Committee.

This work's databases and all steps of the research process will be fully anonymised.

All patients must have signed the Reuma.pt informed consent to be included.

9.1. Proponent

Eduardo Dourado[1,2], Rheumatology resident.

9.2. Research team

Eduardo Dourado[1,2], Ana Teresa Melo[1,2], and Patrícia Martins[1,2], Rheumatology residents.

João Eurico Fonseca[1,2], and Raquel Marques[1,2], Rheumatologists.

9.3. Institutions

The project will be coordinated by the proponent (first author) and the senior author (last author), with the following affiliations:

1. Rheumatology Department, CHULN, Centro Académico de Medicina de Lisboa (CAML);
2. Rheumatology Research Unit, Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, CAML.

The project is open to all national centres willing to participate.

9.4 Co-authorship

Clinicians who actively collaborate in the project will be co-authors, according to the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (Vancouver Convention)[26], with a maximum of 2 co-authors per participating centre (+1 author for each 10 patients included without major missing data after the 20th patient).

10.1. Budget

Reuma.pt data exportation (to be defined).

10.2. Conflicts of interest

There are no conflicts of interest to be declared.

References

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