



RheumaMap

A Research Roadmap
to transform the lives of
people with Rheumatic and
Musculoskeletal Diseases

Prepared by a
European League
Against Rheumatism
Taskforce

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Key purpose

To provide a concise overview of the unmet needs that require research in Rheumatic and Musculoskeletal Diseases (RMDs) in Europe. RheumaMap aims to inform policy makers, funding institutions, the broad scientific community and stakeholders about the exciting challenges and opportunities in RMD research.

Overview – key points

- RMDs comprise one of the major challenges to human health across Europe and on a global basis, particularly with the changing demographics of an ageing population.
- RMDs can affect people of all ages from early childhood to old age and thereby impact health across the entire life span.
- The consequences of RMDs include chronic pain, disability, reduced quality of life, social exclusion, loss of employment and reduced productivity, together with increased financial burden on the individual, their families and society.
- In the last decade there has been remarkable progress in understanding the biological processes that lead to several RMDs. Critically, however, the precise causes of RMDs are not yet known, making prevention challenging.
- Although biological discoveries have yielded new therapies that have brought significant improvements for some RMDs, they are expensive; many unmet clinical needs remain, and no cures exist. The costs of ongoing treatment, while reducing for some of the older biologic drugs coming off patent, remains significant. With their use starting earlier in the disease process and the necessity for the patient to take them over the course of many years, overall their cost is rising for both the individual and society.
- An innovative research programme ranging from the molecule to the population is urgently required to inform the next steps in transforming the lives of people with RMDs. Engagement of and participation by, a broad range of experts, will be critical with patients included at all stages.
- EULAR now presents a ‘research roadmap’ that defines the key issues which relate to the most common RMDs, and which should receive priority for intellectual and funding resources over the next decade. They should also contribute to social policy decisions across the health care spectrum.

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Introduction

Rheumatic and musculoskeletal diseases (RMDs) are among the most prevalent, disabling and burdensome, non-communicable diseases in Europe eliciting high costs for European healthcare and social security budgets. The causes of more than 200 RMDs (including a number of rare diseases) are unknown. Although there are still no cures current treatments allow for a significant improvement in clinical manifestations and disability prevention.

Research and innovation are crucial for improving our understanding of the causes and characteristics of RMDs and to develop better prevention strategies and therapies. Research into RMDs, however, while focussing successfully on some conditions, lacks coordination and integration with respect to long-term planning in many major areas. Research in Europe remains dispersed; scientific institutions are willing to cooperate, but depend on short-term project funding, limiting them to collaboration often in rather narrow areas. EU Member States and other European countries are promoting research into these diseases to very different degrees, and without sufficient cooperation, while priorities are often defined in total isolation across distinct states or regions.

Scarcity of funding resources and the need to foster scientific excellence throughout the continent, leads to the conclusion that strategic coordination for a field as important as RMDs would be of great added value. Furthermore, long-term strategic coordination will provide both the scientific community and funding organisations at international, EU and national levels with orientations for long-term investment – and inspire strategic prioritisation during the next decade.

In order to contribute to the development of the strategic coordination, the European League Against Rheumatism (EULAR) has proposed the European Roadmap for Research in Rheumatic and Musculoskeletal Diseases (RheumaMap) initiative. EULAR represents scientific societies, patient organisations and health professional associations from all European countries. This document has been developed in close collaboration with all EULAR stakeholders to include the range of relevant perspectives. This document presents the second version of RheumaMap, which will be further developed in the coming months and years, thereby serving as a 'living document' to serve the dynamic and emerging needs of people with RMDs.

The roadmap identifies unmet needs and main challenges in research and innovation in RMDs, proposing key areas where long-term strategic efforts should focus over the mid-term in order to help reduce the enormous burden of these conditions in Europe. In this sense, the aim of RheumaMap is to guide scientific and policy efforts and investment in order to achieve substantial policy goals.

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RheumaMap goals

- To increase the **visibility and recognition** of RMDs in patients, healthcare providers, and policy makers.
- To prevent the onset of RMDs
- To improve levels of early diagnosis of RMDs and secondary prevention (or mitigation of impact once established) of RMDs thereby reducing morbidity and mortality in people with RMDs.
- To achieve the above objectives through:
 - Performing research that will move towards the cure of those with RMDs (ideally drug-free or otherwise drug-maintained)
 - Maximising strategies to reduce the impact of RMDs on quality of life, working across the entire societal spectrum.
 - Ensuring outstanding, equitable outcomes through delivery of state-of-the-art care.
 - Generating cost-effective models for delivery of RMD care that can be applied across the EU and other European countries.
 - Enhancing the relationship between the management of RMDs and employability, social inclusion and participation, thereby reintegrating individuals into society.
- To enhance patient education and provision of information, extending this to inclusion of family members.

RheumaMap is expected to serve as a foundation for communicating with decision makers, the broad scientific community, funding institutions and key stakeholders on what to prioritise in order to significantly reduce the burden of RMDs in Europe.

About RMDs

Rheumatic and Musculoskeletal Diseases (RMDs) cover a wide range of painful medical conditions, affecting joints, bones, cartilage, tendons, ligaments, nerves and muscles. RMDs are typified by pain and a consequent reduction in the range of motion and function in one or more areas of the musculoskeletal system, which provides form, support, stability and movement to the body. In addition, RMDs can also affect internal organs. They range from those that arise suddenly and are short-lived such as acute back pain and gout attacks to life-long disorders such as osteoarthritis, rheumatoid arthritis, osteoporosis, fibromyalgia and the systemic autoimmune diseases such as systemic lupus erythematosus and vasculitis.

RMDs pose a further significant risk to the population by virtue of accelerating many **co-morbidities** including increased rates of some cancers, cardiovascular disease, gastrointestinal disease, diabetes and increased rates of mental health disorders. As such RMDs comprise a major part of the rapidly increasing emergence of **multi-morbidity** whereby people present with more than one chronic illness, each impacting on the treatment and outcome of the other.

While RMDs occur at all ages, including in children and young adults, some RMDs such as rheumatoid arthritis and especially osteoarthritis preferentially appear in older people. RMDs affect both genders although the prevalence in women is generally higher, particularly in diseases such as osteoarthritis or osteoporosis.

Many risk factors for RMDs are common for all chronic diseases. Obesity is known to increase the risk and progression of RMDs. Smoking, dietary factors and physical inactivity have been shown to be major preventable risk factors for several RMDs. Genetics often play a significant role in disease development and progression. Increasingly there is evidence for a role of the microbiome in the gut and the lung in RMD initiation and propagation. Moreover, there is evidence that RMDs can be caused or aggravated by work-related risk factors, such as repetitive movements, shifting heavy loads and prolonged standing or walking.

The burden of RMDs

It is now broadly recognised that RMDs represent one of the more burdensome chronic conditions affecting European societies. The high prevalence of RMDs as well as their disabling consequences impose an enormous burden not only on individuals and families, but also on our societies as a whole, particularly in terms of work, productivity loss, health care costs and challenges to social security systems.

RMDs affect around **25 percent of the overall EU population** (that is more than 120 million citizens) and a third of all people will be affected at some point during their lifetime.

As a consequence, **RMDs are the number one cause of disability in Europe**. According to the Global Burden of Disease Study, RMDs are responsible for almost 30 percent of Years Lived with Disabilities (YLDs) in Europe (see figure 1).

The burden of RMDs

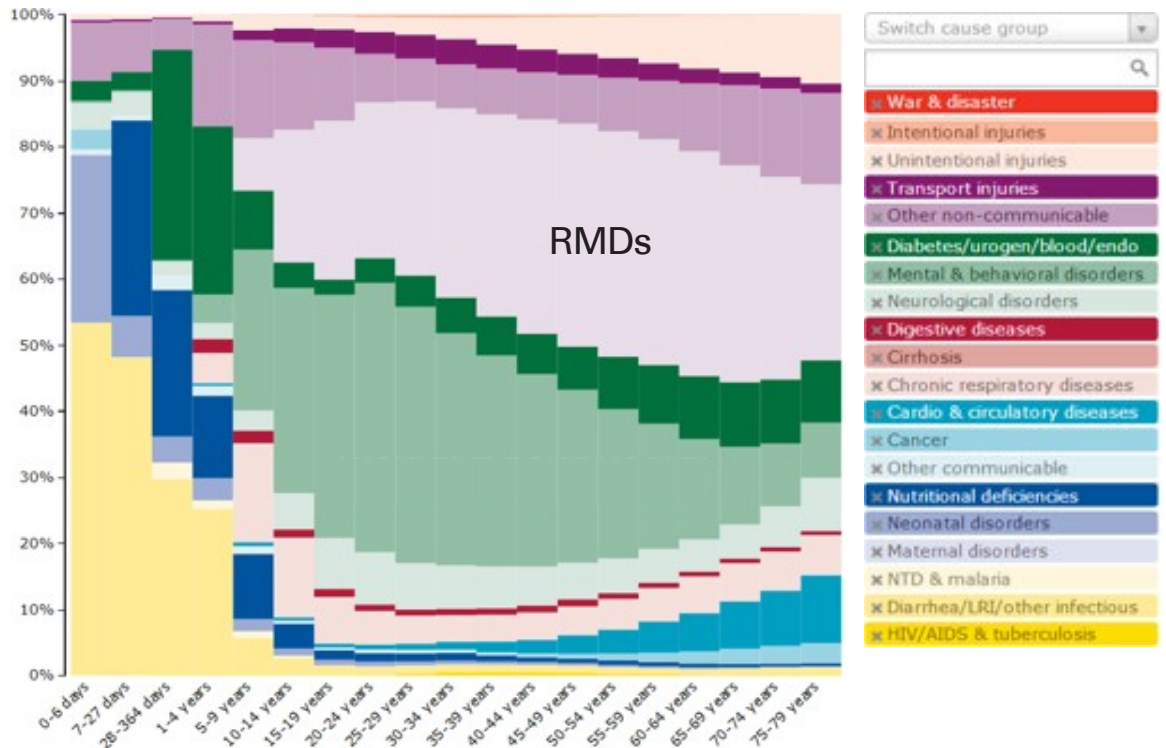


Figure 1 Years Lived with Disability (YLDs) in percent: EU & EFTA countries by cause (Murray, et al., 2010)

At the level of the individual, many RMDs pose severe limitations on activities of daily living for a significant proportion of the population. RMDs are often long-term persistent or remitting and relapsing conditions, bringing high direct and indirect costs to individuals and their families (including medical care, extra transportation or adjustments to the home environment, but also work loss or a need to change jobs to adapt to loss of function). In addition, RMDs often have an impact on emotional wellbeing and mental health, causing significant intangible costs. Commensurate with the co-morbidities described above, the prevalence of clinical anxiety and clinical depression in those with RMDs is about twice that seen in the general population. Despite this impact, the psychosocial aspect of RMDs is often overlooked when assessing the burden on patients and drawing up a tailored care plan.

Beyond the impact on individuals and families, RMDs impose an enormous burden on European societies, particularly in terms of productivity loss as well as in terms of health care and social security costs. RMDs currently represent a burden of EUR240 billion to European countries every year, while direct costs are estimated to represent 2 percent of the gross domestic product. The increasing number of older people and other changes in lifestyle across the age spectrum mean that the burden on people and society is set to increase dramatically.

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In terms of productivity, RMDs can lead to significant work loss and inability to participate in preferred activities, thereby creating substantial indirect costs. RMDs are a major cause of productivity loss according to the European Agency for Health and Safety at Work (EU-OSHA),¹ either due to presenteeism (lost productivity while at work because of diminished capacity), absenteeism (time off work due to sick leave), work disability (permanent partial or complete disablement for work purposes), early retirement, premature death (income loss and reduced taxation revenue) as well as compensation for household work performed by others. The following exemplars depict the impact of RMDs on work and productivity loss:

RMDs are the most prevalent occupational diseases at the European level, representing 38 percent of all occupational conditions.

RMDs are the most common medical cause of long-term sickness absence and the second only to respiratory disorders as a cause of short-term sickness absence (less than two weeks).

The percentage of sick leave days attributed to RMDs ranges from 19 percent in Slovenia (2006) to 40 percent in Belgium (2008).

Up to 60 percent of people taking early retirement or long-term sick leave in Sweden claimed RMDs as the reason.

Within 10 years of RA disease onset, a significant percentage of patients are unable to maintain a full-time job; patients who develop RA at a younger age (before 45) are more likely to become severely disabled than those who develop RA at a later stage (over 70).

In Germany the total productivity loss as a result of RMDs stands at EUR8.5 billion, which represents 0.4 percent of Germany's gross national product.²

With the increasing likelihood of later retirement (healthy aging) the economic impact of RMDs is likely to increase.

RMDs also represent one of the greatest risks to the sustainability of health care and social security systems:

RMDs are a major cause of disability and therefore lead to significant costs in terms of disability pensions and benefits. Disability pensions and allowances granted to people with RMDs are the most important ones (e.g. 35 percent in Austria in 2003; 30 percent in the Netherlands in 2010).³

In the EU 24 percent of people report long-term treatment as a result of longstanding troubles with muscles, bones and joints.⁴

RMDs are in the top 5 diagnostic groups in Europe in terms of healthcare costs.

RMDs rank second as most common reason for consulting a doctor and for most countries they correspond to 10-20 percent of primary care consultations (In the UK, in 2003, the estimated cost of GP consultations for diseases of the musculoskeletal system was the third-highest of all disease groups at GBP - 1,340 million).

1. European Agency for Health and Safety at Work (EU-OSHA) (2010): OSH in figures: Work-related musculoskeletal disorders in the EU - Facts and figures, Luxembourg: Publications Office of the European Union.

2. Ibid

3. eumusc.net (2010)

4. European Commission (2007): Special Eurobarometer. Health in the European Union.

Roadmap for Research in Rheumatic and Musculoskeletal Diseases

RheumaMap defines the key unmet needs across all RMDs – rigorous attention to this research agenda will provide for amelioration and eventually prevention of RMDs to the benefit of individuals and society at large. Below is a series of key point summaries defined within the major RMDs that highlight their compelling unmet needs and research priorities.

Current unmet needs (applicable to all ARDs)

Disease modifying therapies that can reduce the clinical burden across a wide range of tissues are currently absent or sub-optimal

There is an urgent need for improved imaging and biochemical diagnostic biomarkers

There is need for better phenotyping of the various ARDs to allow a more pathogenesis-focussed approach to their treatment.

There is an urgent need for optimal networks across Europe and beyond that are best equipped to address the needs of people with RMDs across the research spectrum

There is the need to translate research findings into educational materials for people with RMDs and their carers to support the expected outcomes.

Osteoarthritis

Osteoarthritis (OA) is the most prevalent chronic joint disease. The incidence of osteoarthritis is rising due to ageing populations, the epidemic of obesity and cardiometabolic syndrome. Pain and loss of function are the main clinical features that prompt treatment, including non-pharmacological, pharmacological, and surgical approaches. Osteoarthritis is a disorder involving movable joints characterised by cell stress and extracellular matrix degradation initiated by micro- and macro-injury that activates maladaptive repair responses including pro-inflammatory pathways of innate immunity. The disease manifests first as a molecular derangement (abnormal joint tissue metabolism) followed by anatomic, and/or physiologic derangements (characterized by cartilage degradation, bone remodelling, osteophyte formation, joint inflammation and loss of normal joint function) that can culminate in illness that is clinically obvious.

Current unmet needs

- There are no effective disease-modifying treatments
- Imaging and biochemical diagnostic and prognostic biomarkers are sub-optimal
- Better phenotyping of OA patients to implement a precision medicine approach is required.
- Improved implementation of non-pharmacological interventions

Recommended research focus areas

Identify and elucidate

- The role of genetic variants and epigenetics in OA phenotypes
- The role of epidemiologic factors including lifestyle, occupational and other modifiable risks
- The markers for early OA, OA phenotypes, disease activity, disease progression, and of therapeutic response
- The targets for therapy (to ameliorate pain and structure loss and improve function).

Understand

- Tissue communication in OA (between cartilage, subchondral bone, synovium, blood vessels, adipose tissue)
- Non-cartilage pathology in OA
- The mechanisms of mechanical joint injury and the translation to inflammation and repair
- The relationship between synovitis, radiographic progression and pain
- The relationship between ageing, gender and OA
- The impact of physical activity and lifestyle changes on the progression of OA.

Osteoporosis

Approximately 30% of all postmenopausal women have osteoporosis in Europe making it a major public health concern. At least 40 percent of these women and 15 – 30% of men will sustain one or more fragility fractures in their lifetime¹. There will be an increase as European populations age. Osteoporosis may be a primary or a secondary form. Osteoporosis is defined as low bone mass with micro architectural alterations in bone leading to fragility fractures. Primary osteoporosis is age related and occurs in post- menopausal women and in men in the absence of an underlying disease. Secondary osteoporosis occurs in the presence of an underlying disease and/ or medication. Glucocorticoid-induced osteoporosis (GIOP) is the most common form of secondary osteoporosis, most commonly seen in patients treated with these drugs for inflammatory disorders.

Current unmet needs

- Novel improved treatments
- Improved screening and treatment strategies
- Patient education

Recommended research focus areas

Identify and elucidate

- Reliable biomarkers and better technical measurements for diagnosis and assessing response to therapy of osteoporosis
- The interactions between immune system and bone, and anti-rheumatic treatments and bone quality/quantity/microarchitecture and osteoporosis.

Understand

- Disease pathogenesis, especially that of secondary osteoporosis forms including that arising from glucocorticoids
- Long-term outcome of patients with rheumatic diseases with regard to bone/osteoporosis
- The declining pattern of osteoporosis testing and treatment
- The need for patient education.

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¹ <http://www.iofbonehealth.org>

Inflammatory arthritis

There are many causes of inflammatory arthritis that can occur across the age groups, described in their distinct diagnostic categories below. They are unified by the common theme of the inflammatory/immune system attacking musculoskeletal tissues leading to pain, damage and loss of function.

Crystal Arthropathies

The two main crystal arthropathies are gout and calcium pyrophosphate crystal deposition (CPPD) which mimics gout. Gout is highly prevalent, associates with multiple comorbidity, and is potentially “curable”. Chronic elevation of uric acid above the saturation point for sodium urate crystal formation is the main cause of gout. Gout is the most common form of inflammatory arthritis worldwide, and its incidence and prevalence are rising, largely due to increased longevity and the increased prevalence of cardiometabolic syndrome, of which hyperuricaemia is an integral part. Gout affects 1 – 2.5 percent of the population within Europe. The unique characteristic of this RMD is that it is fully reversible by reducing serum urate levels to normal using currently available drugs and by addressing modifiable risk factors for hyperuricaemia. Gout associates with, and is a risk factor for, both cardiovascular disease and chronic kidney disease. An acute attack of gout requires prompt anti-inflammatory management, but in the long-term chronic patient urate-lowering treatment (ULT) is the challenge, since this is offered to the minority of people with gout, often at an insufficient dose, and without adequate explanation which results in poor adherence and lifelong suffering from gout (only <1 in 10 people with gout are “cured”).

Current unmet needs

- Failure to detect gout
- Poor adherence and implementation of guidelines

Recommended research focus areas

Identify and elucidate

- Those genetic and epigenetic factors involved in the development of gout.

Understand

- Disease pathogenesis thereby developing novel therapeutic leads to initiate preventative medicine approaches
- When best to treat asymptomatic hyperuricaemia
- The pathogenesis (and best treatment options) of the acute gout attack
- The interaction between gout, uric acid and cardiovascular disease and whether ULT improves cardiovascular and CKD outcomes, and reduces mortality.

Further development and continuous improvement of diagnostic and treatment algorithms as listed in the EULAR Recommendations.

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Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an inflammatory arthritis that may affect people from childhood to old age. Its prevalence is around 1 percent and thus it is the commonest inflammatory cause of disability. Whereas its precise causes are not yet known, it is associated with a strong genetic component, reflected in a frequent family history of disease, particularly implicating genes of the immune system. Environmental factors also increase risk particularly smoking and related lung diseases, and changes in the microbial make-up of mucosal surfaces. Other lifestyle factors include obesity, vitamin D deficiency, lower educational attainment; lower alcohol consumption is also implicated. The last two decades have seen remarkable progress in several key areas. *First*, we have developed several new 'biologic' (targeted) therapies based on our increased understanding of the pathogenesis of disease – key exemplars include inhibitors of TNF and IL-6 receptor, together with drugs targeting key cells of the immune response such as B and T cells. More recently new small molecule (oral) drugs have been developed that offer significant benefits. *Second*, we have established that regardless of drug choice the key strategies of treating early and with a defined disease activity target will significantly improve outcomes. It is therefore imperative to make an early diagnosis and to suppress inflammation rapidly thereby reducing the risk of damage that typically ensues without such an approach. Joint damage in turn leads inexorably to loss of function and long-term disability. Finally, it is widely accepted that RA is associated with other co-morbidities particularly those that affect the vascular system (heart attacks and strokes are more common), the brain (increased rates of depression), bone (increased osteoporosis and fracture risk) and to increased rates of some cancers (especially lung and lymphoma).

Current unmet needs

New therapeutics/approaches that produce improved outcomes: more generalised responses and ideally treatment-free remission, ie. a cure for RA.

Repair of damage to joints, ligaments and tendons caused by RA.

Tailoring treatment to the individual: Providing the right care for the right individual, at the right time.

Recommended research focus areas

Identify and elucidate

- The role of genetic variants and epigenetics in RA phenotypes
- Markers for early RA – extending to better definition of pre-RA.
- Prognostic markers for treatment response or toxicity,
- New targets for inflammatory disease based on improved pathogenesis understanding, especially in those not responding to existing therapeutics
- The key pathways that drive co-morbidities such as fatigue in RA
- The best means of delivery of emotional and psychological support
- The potential for regenerative medicine for reparative purposes in joints, ligaments and tendons.

Understand

- How epidemiologic and lifestyle factors promote onset and perpetuation of RA
- The molecular and cellular basis of remission when it is achieved, and flare when that occurs
- Inflammatory and non-inflammatory causes of pain in the context of RA.

Develop

- Improved imaging modalities for the characterisation of RA
- Medicines capable of resetting immune function and thereby leading to ‘cure’ those already with disease
- Effective patient education / self-management programmes.

The Spondyloarthritides

Spondyloarthritis (SpA) describes a group of chronic inflammatory diseases with a heterogeneous presentation. They may mainly affect the spine, associated with inflammatory back pain or peripheral joints leading to arthritis, enthesitis and dactylitis. In severe cases, this may result in a complete fusion of the spine. Frequently, SpA is associated with symptoms in the skin (psoriasis), gastrointestinal tract (inflammatory bowel disease) or eye (acute anterior uveitis). These distinct pathologies can be present in various combinations. There is a strong genetic relationship with immune genes, particularly HLA-B27. These diseases usually develop in early adulthood and affect males more frequently than females. The prevalence is around 1 percent. This places a major burden on patients, their families and societies.

Current unmet needs

- Pathogenesis understanding remains poor, including particularly the relationship between inflammation and bone remodelling
- Novel diagnostic tests are urgently required
- Long-term outcome for patients without structural damage are not clear
- Treatments inhibiting bone formation are lacking
- Treatment strategies especially personalised therapy require to be defined to optimise care.

Recommended research focus areas

Identify and elucidate

- Disease pathogenesis including understanding of discrete tissue manifestations (including eye, skin and gut) and the role of contributing genetic and epidemiologic factors
- Mechanisms of bone proliferation and bone loss, even occurring in the same patient
- The effect of early treatment and better referral strategies on long-term outcome.

Understand

- The impact of physical activity and lifestyle changes on the progression of SpA.

Develop

- Optimal use of imaging techniques (MRI, CT-scan) for diagnosis, outcome assessment and monitoring
- Better diagnostic tests and markers for different types of SpA to guide treatment or assess the risk of toxicity and predict disease progression, organ involvement and remission
- Novel diagnostic tests and diagnostic algorithms
- Treat-to-target strategy trials including various biologicals and new, emerging oral therapeutics
- Long-term cohorts that start with sufficiently early disease as to be informative to all stakeholders.

Psoriatic Arthritis

Up to one third of people with psoriasis also develop a chronic, potentially disabling arthritis—termed psoriatic arthritis (PsA). PsA presents with symptoms of pain and swelling in peripheral joints, but also may involve tendon insertions, spinal joints and whole digits (dactylitis). PsA may be associated with severe nail disease and comorbidities including obesity, depression, heart disease and diabetes. In addition to high levels of pain and reduced mobility, patients with PsA experience poor quality of life, high rates of healthcare utilisation and significantly reduced work productivity. PsA pathogenesis is characterised by several genetic factors and immune system disturbance, with increased activation of inflammatory pathways specifically relating to T-cells and associated cytokines e.g. IL17, in addition to TNF. Blood vessel function and growth is also significantly disrupted. Physical and psychological stress also appear to be significant factors.

Current unmet needs

- Over 50 percent of sufferers are unrecognised and untreated
- High levels of progressive disease go unchecked
- Personalised medicine strategies are not available
- Poor understanding of disease pathogenesis remains a block to new therapeutic developments
- High levels of comorbidities are especially troublesome and impact significantly on quality of life
- It remains unclear why some patients given biologic drugs show improvement in their rash or joints, or both, whereas others show no response at all.

Recommended research focus areas

- Identify and elucidate
 - The key immune system dysfunctions
 - Biomarkers of disease and response to therapy and potential toxicities
 - The role and impact of imaging in the treatment of PsA including MRI and ultrasound.

Understand

- The pathogenesis including role of genetic factors.

Develop

- Better health care programmes to combining the expertise of rheumatologists and dermatologists in the management of the disease to provide integrated decision making.
- Precision medicine strategy, which drugs for which aspects of psoriatic arthritis

Juvenile Idiopathic Arthritis (JIA)

JIA is the most common childhood chronic rheumatic disease. It is one of the most common chronic diseases in childhood, leading to significant morbidity and long-term disability. In Western countries, it has an incidence varying from 2 to 20 and a prevalence between 16 to 150 per 100,000. JIA represents a group of diseases and remains classified based on general clinical features. A pathophysiology-based classification system is not yet in place. JIA has obvious similarities with adult Rheumatoid Arthritis in some cases but not in others. Critical differences exist not only in clinical expression, but also in genetic susceptibility and inheritance, prognosis, presence and absence of autoantibodies and treatment response. To date, treatment of JIA is based on therapies developed for adult RA. However, based on the striking differences between them it is unlikely that the optimal treatment of both diseases is the same. The need to develop innovative therapies in JIA remains. Despite increased efforts, the effect of new anti-inflammatory, disease-modifying medicines may be disappointing. Even successful interventions with key inflammatory pathways with biological agents fails to restore the immune balance, permanently necessitating life-long treatment. Such life-long treatment may interfere with growth and development in children and represents a significant risk of long-term, as yet unknown adverse events. Biomarkers that could help to mitigate these risks through prediction of disease course, response to therapy and potential side effects of treatment are lacking.

Current unmet needs

- The interplay of genetic and environmental factors in disease pathophysiology is poorly understood
- Biomarkers to predict disease prognosis, true (biological) disease remission and long-term side effects are lacking
- A pathophysiology-based classification system is required
- Network of expertise and information in JIA throughout Europe is not optimally established.

Recommended research focus areas

Identify and elucidate

- The potential for psychosocial support systems for the patient and the family in addressing chronic disease in young people
- Optimal mechanisms to ensure education attainment and subsequent lifelong productive employment
- Biomarker development for different subtypes of JIA and for disease trajectory prediction
- Strategies to ensure optimal growth and achievement of developmental milestones.

Understand

- The optimal approach to physical activity maintenance.

Develop

- Strategies and methodologies to share information (registries & best practices) throughout Europe
- An immune pathophysiology-based new classification system of JIA.
- Precision medicine strategy

Systemic Autoimmune Diseases – including autoimmune rheumatic diseases (ARD) and connective tissue diseases

These comprise a range of inflammatory disorders that have the capacity to target a variety of tissues which may lead to a very wide range of symptoms and signs. Consequently, their impact can be very profound and diverse, for example, involving major organs such as the heart, kidney and/or brain and leading to rapid onset of disability and premature death.

Collectively they pose significant unmet needs defined as follows:

Systemic Lupus Erythematosus

Epidemiological data estimate a prevalence of Systemic Lupus Erythematosus (SLE) in the range – 40 (in Caucasians) to – 200 (Afro-Caribbean) per 100,000; 90% of patients are female and there is an 85% 15-year survival rate. Many tissues are targeted by the disease including the skin, joints, kidneys brain nerves, heart, blood vessels and lungs. With the exception of Belimumab and rituximab, recent advances in targeted therapies have been of little benefit.

Current unmet needs

The interplay of genetic and environmental factors in disease pathophysiology is poorly understood

Biomarkers to predict disease prognosis, true (biological) disease remission and long-term side effects are lacking

Effective therapeutics beyond glucocorticoids, some cytotoxic and early biologic interventions are limited.

Recommended research focus areas

Identify and elucidate

Epidemiology studies across different ethnic backgrounds to understand better the polygenic basis and environmental influences on disease phenotypes

Clarify more precisely the factors that conspire to cause lupus to facilitate earlier diagnosis and limit its progression.

Understand

Immunopathogenic aspects of distinct genetic backgrounds including deep sequencing, immunologic and serologic characteristics of clinical subgroups

The mechanisms and optimal treatment of comorbidities in SLE.

Develop

Treatment guidelines for best use of currently available therapeutics

New drugs in defined SLE sub-groups on a smaller scale and using surrogate end-points. Such work will likely require further outcome measure developments

Trial immunosuppressive drugs previously not tested in SLE (e.g. repository trials)

The management of common, hard-to-treat manifestations, such as fatigue and depression in SLE.

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Antiphospholipid Syndrome

An autoimmune disease with high health economic burden related to acquired thrombo-embolic events and obstetric complications, i.e. recurrent abortions (about 20–% of all recurrent abortions). This syndrome may be primary but also complicates 10–15% of SLE patients, is a key example that a distinct pathophysiology, such as hypercoagulation, results in a distinct clinical entity with defined clinical treatment consequences – this syndrome responds to anticoagulation but not to immunosuppression.

Current unmet needs

- The pathophysiology is poorly understood
- Biomarkers to predict disease prognosis and treatment response are lacking
- Effective therapeutics beyond anticoagulation are limited.

Recommended research focus areas

Identify and elucidate

- Immunopathogenic aspects including genetic predisposition and environmental influence of leading to arterial, venous occlusions versus obstetric complications

Understand

- The role of endothelial activation in APS
- Why some patients develop the obstetric complications and others the thromboembolic ones.

Develop

- Trials assessing safety and efficacy of antiplatelet therapy versus oral anticoagulation with vitamin K antagonists and newer oral anticoagulants for the treatment of cerebrovascular and venous thromboembolic events
- Prospectively evaluation of the risk of antiphospholipid antibody-positive individuals to develop blood vessel and/or obstetric complications
- Epidemiology studies assessing the prevalence of APS as cause of acute myocardial infarctions, cerebrovascular events and venous thrombosis/lung embolism among the overall entities.

Vasculitis

Vasculitis, immune mediated inflammation of the blood vessel wall, can occur independently, (e.g. granulomatosis with Polyangiitis, Giant Cell Arteritis) or as part of another ARD, such as rheumatoid arthritis or SLE. The aetiology of vasculitides is unknown, but is clearly multifactorial, including ethnicity, genes, gender, and environmental factors. Vasculitis might be localised to a single organ but it is more often generalised. Location of the vasculitis determines its symptoms. The systemic vasculitides are a heterogeneous group of relatively rare conditions (less than 3 per 1000 persons) involving blood vessels of various size, from the aorta and its branches (as seen in giant cell arteritis – GCA) to small vessels as the primary site of inflammation. Related to GCA is polymyalgia rheumatica, that is characterised by pain, aching and morning stiffness in the shoulder girdle, pelvic girdle and neck; incidence increases with age (up to 1 percent in those over 60 years of age) and, as in most ARDs, women are more often affected than men. The different forms of vasculitis may be organ or even life threatening, and intensive immune suppression is warranted in order to prevent permanent disability and death. Glucocorticoids are still widely used in treating vasculitis; in spite of their significant side-effects. Classic immunosuppressive drugs, and increasingly biologicals, notably Rituximab, are used to reduce the burden caused by steroids.

Current unmet needs

- The pathophysiology is incompletely understood

- Biomarkers to predict disease prognosis and treatment response are lacking

- Effective therapeutics have brought about significant improvements in recent years but remain potentially toxic and are non-curative. Relapse remains problematic.

Recommended research focus areas

Identify and elucidate

- Delineate genetic and epigenetic factors involved in the development of the different forms of vasculitis

Understand

- Disease pathogenesis, thereby developing novel therapeutic leads to initiate preventative and precision-based medicine approaches

- The factors which would enable an early diagnosis of vasculitides.

Develop

- Investigation of potentially triggering bacterial and virus infections and their interaction with the Immune system

- Novel therapeutic approaches and treatment strategies for both induction and maintenance therapy of vasculitides to reduce the adverse event burden of standard treatment (e.g. glucocorticoids, cyclophosphamide, mycophenolate)

- Early detection of polymyalgia rheumatica and giant cell arteritis in order to save sight and prevent (other) ischemic complications

- Improve the diagnostic and treatment algorithms as per the EULAR Recommendations; develop care strategies involving different medical disciplines and health professions.

Autoimmune Myositis

Polymyositis and dermatomyositis together with inclusion body and necrotic myositis (less frequent), carry a substantial burden of co-morbidities and increased mortality. They manifest as weakness of major proximal muscle groups and can be complicated by skin, joint, lung and nervous system abnormalities.

Current unmet needs

- The pathophysiology is poorly understood

- Diagnosis is often challenging

- Biomarkers to predict disease prognosis and treatment response are lacking

- Effective therapeutics beyond glucocorticoids and broad-spectrum immune suppressants are limited.

Recommended research focus areas

Identify and elucidate

- Genetic and immunopathogenic differences of the four distinct clinical entities

- The epidemiology of the prevalence, clinical characteristics including comorbidities of autoimmune myositis subtypes and support international registries of these rare entities.

Understand

- Identify the key pathogenetic effector pathways by studying human disease ex vivo and in refined model systems of disease.

Develop

- Trials assessing safety and efficacy of new immunosuppressive and biologic agents

- Treatment algorithms utilizing EULAR recommendations

- Further assessment of the (numerous) myositis specific autoantibodies with the various clinical disease subtypes.

Primary Sjögren's Syndrome

The hallmark primary Sjögren's syndrome (pSS) is a generalized dryness of the eyes and mouth, skin and vagina, which is known as sicca syndrome. It can also affect other organs of the body, including the muscles, peripheral nervous system, kidneys and lungs. Patients with pSS have a notably higher risk (x 40) of non-Hodgkin's lymphoma. The most commonly reported problem by patients is, however, a substantial and overwhelming fatigue. pSS is a common rheumatic condition with an estimated prevalence of 0.5 percent. There is a female prevalence of 9:1. The cause of pSS is unknown but it is clear that genetic and epigenetic factors are implicated. There is no effective therapy for pSS and trials are hampered by a lack of robust response criteria reflecting disease response in all its facets.

Current unmet needs

- The pathophysiology is poorly understood
- Biomarkers to predict disease prognosis and treatment response are lacking
- Effective therapeutics are limited.

Recommended research focus areas

Identify and elucidate

- Genetic and epigenetic factors involved in the development of pSS
- The understanding of disease pathogenesis thereby developing novel therapeutic leads to initiate preventative medicine approaches
- The earliest molecular changes in the blood and exocrine glands in pre-clinical disease (non-Sjögren's sicca) leading to autoimmune exocrinopathy (gland disease).

Understand

- The cause of fatigue and tissue dryness in pSS patients.

Develop

- Novel treatment strategies.
- Biomarkers for the identification of early disease opening avenues for disease facilitating early intervention
- Biomarkers for disease progression and/or complications most specifically to identify those patients at risk for developing malignancy
- Further improvements in the diagnostic and treatment algorithms as per the EULAR Recommendations.
- New therapeutic agents that will effectively prevent glandular loss and functional failure.

Systemic Sclerosis

Systemic sclerosis (SSc) is an autoimmune fibrotic disorder where a multitude of genetic and epigenetic as well as environmental factors lead to disease. The earliest phase of SSc is typified by ongoing inflammation and microvascular remodelling (resulting in progressive loss of capillaries) culminating in fibrosis of skin, lungs, heart and other organs. Sinister complications are pulmonary arterial hypertension, renal crisis and pulmonary fibrosis that account for most SSc related deaths. SSc still has a 10-year survival of only ± 50 percent. Although SSc is a rare condition affecting 0.01 percent of the population with a clear predominance for females (9:1), it is seen as an exemplar fibrotic condition that if understood, could lead to clear insights into other fibrotic conditions. As SSc is usually preceded by the presence of Raynaud's phenomenon, this provides the opportunity to investigate the earliest effects on the microvasculature (endothelial cell damage) together with immunological changes (specific autoantibodies) leading to full-blown disease.

Current unmet needs

The pathophysiology is increasingly emerging, but is too incompletely understood to allow formal therapeutic developments

Biomarkers to predict disease prognosis and treatment response are lacking

Effective therapeutics across the range of target organs are limited.

Recommended research focus areas

Identify and elucidate

Genetic and epigenetic factors leading to disease development from the earliest phases of pre-clinical disease and what distinguishes those patients with 'skin only' disease from those with internal organ involvement.

Understand

Disease pathogenesis thereby developing novel therapeutic leads to initiate preventative medicine approaches.

Develop

Biomarkers and test new diagnostic tools that investigate the early microvascular damage for the identification of early disease opening avenues for disease interception (preventative medicine)

Biomarkers for disease progression and/or complications and prognosis.

Trial modalities that can optimise new therapeutic development

Soft tissue rheumatic diseases

Typically, the term soft tissue RMDs (STRMD) is applied to a group of conditions that are not marked by systemic disease but with a local or regional presentation involving muscles, tendons, ligaments or bursae. Typical STRMDs include mechanical back pain, tendinitis and bursitis, peripheral regional presentations such as regional pain syndrome, and conditions related to specific activities such as sports or occupational participation. Often linked to these conditions, though with more diffuse consequences, are Benign Joint Hypermobility Syndrome and Fibromyalgia which can cause many diverse and chronic symptoms. The impact of soft tissue rheumatic diseases can be profound, both in terms of the significance to the individual but also in terms of workplace injuries and disabilities with a high prevalence of these conditions in the population. Furthermore, it is important to consider the relationship between STRMD conditions and the multiple comorbidities that often co-exist.

Local soft tissue disorders result in significant demand in primary and secondary care services. This group of conditions is characterised by features that require special consideration in research planning. There are important risk factors for these disorders including mechanical exposure and workforce demands (repetition, high workplace demands with poor control and support). Over 40 million workers in Europe are affected by musculoskeletal conditions attributed to their work. Despite the great burden imposed on the health economy they are often associated with poor clinical definition and diagnostic criteria, resistance to objective measurement and require treatments that are often physical in nature and therefore susceptible to bias in the conduct of randomized clinical trials.⁵

Current unmet needs

- Effective treatments for most STRMDs are lacking
- There is little understanding of the underlying pathology of these conditions
- There is often a fractured approach to their diagnosis and management between primary and secondary care and across health professional groups.

Recommended research focus areas

Identify and elucidate

- The factor genetic and environmental which contribute to the development of these conditions.

Understand

- The pathogenesis including neurocognitive aspects
- The pathogenesis of common soft tissue rheumatic disorders at a cellular or molecular level.
- Health economic and cost effectiveness in clinical trials to capture the scale of these conditions in the population
- Effective outcome measurements that capture the benefits of new therapeutics
- Specific and non-specific treatment effects of given interventions
- Intervention models that curtail the natural history of common RMDs.

5. *Fit for work? Musculoskeletal disorders in the European workforce*; Bevan S, Quadrello T, Mc Gee R, Mahdon M, Vavrovsky A, Barham L (2009)

<http://www.theworkfoundation.com/Reports/224/Fit-for-Work-Musculoskeletal-Disorders-in-the-European-Workforce>

Pain

1 in 5 people throughout Europe have persistent moderate or severe pain. Around half will be in constant pain. Few are managed by pain specialists and a sizeable minority (40 percent) have inadequate management of their pain. Most of pain reported is musculoskeletal in origin, notably in the low back, shoulder/neck, hips and knees pain. However, pain is a common feature of almost all RMDs and (together with fatigue) is a crucial determinant of patients' quality of life, function and the ability to remain in work. Outcome of patients presenting to general practice with pain, is most strongly influenced by psychosocial factors.

Current unmet needs

Most patients with chronic pain do not have access to pain management specialists

Chronic regional pain especially of the neck can be associated with an additional burden arising from consequent neurological and neuromuscular symptoms

Interventions are often complex, targeting components of the musculoskeletal system, the neurological system and less well understood pain sensitisation pathways

Pharmacological management for chronic pain generally results in modest improvements and patients will often experience important, quality of life influencing side-effects

Non-pharmacological management for example cognitive behaviour therapy is equally important but even those demonstrated to be effective, although leading to increased quality of life, result in relatively modest improvements in pain.

Identify and elucidate

Those patients that benefit most from behavioural therapies. Can behavioural therapies be delivered at lower cost either through training of non-specialist staff, delivered in new ways (e.g. online) and/or delivering to groups of patients?

Whether combined pharmacological and non-pharmacological approaches to management are more effective than single modality management.

Understand

The prescribing patterns of opioid therapy improve the medical and social consequences associated with these drugs and determine effective ways to reduce or stop opioids in such patients.

Develop

Tailor-made management according to patient characteristics and likely prognosis or therapeutic response patterns

Assessments of those aspects of a healthcare system optimise outcome for patients with complex chronic pain conditions.

Given its importance in most patient surveys, and omnipresence in the majority of RMDs, we offer regional dissection of the major impact of pain as follows:

Mechanical back and neck disorders

Non-specific back pain (as opposed to inflammatory back pain) affects approximately one third of the adult population each year, and approximately 1 in 15 people access public health care as a consequence. Standardised pathways exist for the management of mechanical back pain and in the first instance are directed at stratifying risk and directing patients toward self-management or more interventionist approaches. Self-mediated exercise and activity, accompanied by behaviour modification are known to be helpful in a large proportion of cases. This can be supplemented by physical therapy intervention although the effect of 'dose' is poorly understood and is often impacted by pressures within the health care system. Braces and splints are generally not well-tolerated and other device-based interventions such as laser, TENS and h-wave have yielded conflicting evidence of effectiveness. Direct injection can provide short-term relief and there is a growing body of evidence around the use of pharmacological agents that act on the pain pathways. Invasive options vary and are associated with generally similar long-term outcomes to non-surgical interventions.

Identify and elucidate

- Those factors genetic and environmental leading to these problems.

Understand

- The role of supported self-mediated exercise and activity in low risk mechanical back pain
- Investigate the health and economic benefits of stratified back care pathways.

Develop

- The dose-response relationship for physical therapies
- The effectiveness of invasive procedures such as facet joint injection
- The trials comparing the effects of manipulation, anti-inflammatory drugs and injections in neck pain
- Pan-European approaches to delivering programmes to reduce injury and reduce recurrent absences from work.

Foot pain

Foot pain has a similar level of impact as does hip and knee pain although there are fewer definitive treatment options. Footwear advice and modification is of demonstrated benefit in some presentations and provision of insoles, orthoses or specialist footwear may also help in some cases. Physical therapies can be of some benefit. Injectable and surgical interventions for non-specific soft tissue foot pain are of variable efficacy.

Identify and elucidate

- Those factors genetic and environmental leading to these problems

Understand

- The effectiveness of insoles in the management of non-specific foot pain

- The role of footwear in management (risk factor, prognostic factors, and possible treatment)

- The value of early footwear assessment and management in reducing referrals for knee replacement surgery.

Develop

- An optimal role for exercise and other interventions for heterogeneous foot presentations

- The role of the multi-disciplinary team in the targeted regional management of foot pain.

Shoulder pain

Shoulder pain interventions are often complex, combining elements of strength, mobility, neuromuscular control, behavioural change as well as directly targeted invasive interventions such as manipulation under anaesthetic, injections with agents such as corticosteroid or platelet rich plasma, and lithotripsy for calcific tendinitis. Surgical options are numerous with approaches including tenoplasty, patch grafting and joint reconstruction.

Identify and elucidate

- The pathogenesis of the variety of causes of shoulder pain e.g. tendinopathy
- The use of ultrasound and MRI to improve diagnosis and surgical interventions.

Understand

- The need to develop targeted care pathways.

Develop

- Collaborations between research groups to ensure larger trials with wider applicability to clinical practice
- Direct comparison of glucocorticoid injection, or other locally injected therapeutic entities or cell-based preparations and physical therapy interventions.
- Novel therapeutic targets to define more appropriate medical interventions.

Carpal tunnel/wrist pain

Carpal tunnel syndrome (CTS) is a nerve entrapment syndrome affecting the wrist and hand and is often associated with local as well as radiating pain and symptoms. It may be associated with workplace activities. CTS affect between 1 – 3 people per 1000 per year and may be difficult and costly to treat. There is controversy over the effectiveness of surgical intervention compared to conservative care although surgery is becoming more widely accepted. Existing studies into the conservative management of carpal tunnel/hand/wrist pain can be grouped into four main areas: behaviour, education and exercise (with limited evidence); physical devices for which there is some supportive evidence; pharmacological (including injections), which are advocated prior to any surgical intervention; and other (including complementary therapies). Carpal Tunnel release is the most common surgical intervention for CTS, performed either through an open incision or endoscopically.

Identify and elucidate

- The basic pathogenesis of CTS

Understand

- The decision to refer patients to rheumatologists/orthopaedic surgeons/neurologists.

Develop

- Collaboration between research groups to ensure larger trials
- Investigation of workplace options for modification of activity.

Fibromyalgia

Fibromyalgia syndrome is characterized by chronic widespread pain and a variety of associated symptoms. The precise pathogenesis is not known but altered pain system function has been shown in some patients. The healthcare utilisation by patients with FMS is high (EUR2,000 per patient per year). Existing EULAR guidelines recommend combined approaches of behaviour/activity modification with additional psychological input. Some physical therapies (for example, heated pool) have been shown to be effective. Direct interventions using device-mediated (electrical and magnetic) interventions are of unknown benefit. There is some evidence of benefit of pharmacological interventions targeting pain pathways and anxiety.

Current Unmet Needs

- Getting more rheumatologists to develop an interest in this condition
- Optimizing an agreed definition and therapeutic strategy
- A better understanding of the long-term outcome.

Identify and elucidate

- The pathogenesis of fibromyalgia including what triggers it.

Understand

- The extent of contribution of CNS dysfunction
- The bio /psycho/ social interactions that may contribute to the disorder.

Develop

- Multi-system interventions including activity, behavioural and pharmacological approaches.

Conclusion – RheumaMap

Rheumatic and musculoskeletal diseases (RMDs) place an enormous burden on European society. 120 million people are already affected, a number that will rise sharply as populations age. Those afflicted suffer pain, disability and socioeconomic deficit as individuals. The collective impact of RMDs challenges the sustainability of health care and social security systems whilst hindering the productivity of European economies.

Furthering research and innovation in the field of RMDs is therefore crucial. We urgently require evidence-based policies, such as improving access to timely, high quality health care and improvement in working conditions, if we are to improve treatment and eventually prevent RMDs. People with RMDs deserve to lead independent lives, remain active in the labour market and fully participate in society. There is thus both a duty and an overwhelming business case for supporting the economic and social participation of people with RMDs. However, the impact of these policies will be limited without a better understanding of the aetiopathogenesis of RMDs, more accurate diagnostic tools, more effective therapies to limit and prevent their disabling consequences and, eventually, a pathway to a cure. Active participation of people with RMDs in the prioritisation of research topics and the design and conduct of research, will facilitate achieving these goals. Novel approaches using social media and the development of apps to engage younger patients in particular will be needed.

Research in the field of RMDs, particularly in Europe, has advanced significantly in recent years. Substantial unmet needs in the area of research, highlighted in the RheumaMap, will however require an altogether higher level of commitment and innovation. Implementation of the distinct elements contained in RheumaMap will rely on scientists, patients and health professionals. Equally, it will require an unwavering, strong commitment from policy makers across Europe and at the national level, as well as the support of international organisations, industry and other stakeholders.

The good news is that the means to success are clearly laid out before us. A multi-faceted approach that includes a clear policy dimension can, if properly implemented, generate a positive evolution in the management of RMDs along the entire pathway, from therapeutic innovation to treatment and rehabilitation to prevention.

Prioritising the unmet research needs for RMDs as laid out in the RheumaMap will require a long-term perspective. The tremendous potential for benefit will only be realised when Member States of the EU, other European countries, and European institutions develop new ways of working together to address the challenge of RMDs. All parties now have the opportunity to develop a jointly owned, long-term strategy to extend the level and effectiveness of RMD research and to ensure that outcomes translate into societal benefit at scale. A new form of co-operation is therefore required to maximise cost effectiveness whilst increasing equality of outcomes for citizens.

With RheumaMap, EULAR and the RMD community anticipates and stands ready to support such commitments and collaboration.

RheumaMap

—
Research Roadmap
to transform the
lives of people
with Rheumatic and
Musculoskeletal
Diseases

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and the many other individuals involved in
this project for their contributions.*

Rheumatic and Musculoskeletal Diseases (RMDs)

Rheumatic and musculoskeletal diseases (RMDs) are a diverse group of diseases that commonly affect the joints, but can also affect the muscles, other tissues and internal organs. There are more than 200 different RMDs, affecting both children and adults. They are usually caused by problems of the immune system, inflammation, infections or gradual deterioration of joints, muscle and bones. Many of these diseases are long term and worsen over time. They are typically painful and limit function. In severe cases, RMDs can result in significant disability, having a major impact on both quality of life and life expectancy.

About EULAR

The European League Against Rheumatism (EULAR) is the organisation which represents the people with arthritis/rheumatism, health professional and scientific societies of rheumatology of all the European nations.

The aims of EULAR are to reduce the burden of rheumatic diseases on the individual and society and to improve the treatment, prevention and rehabilitation of musculoskeletal diseases.

To this end, EULAR fosters excellence in education and research in the field of rheumatology. It promotes the translation of research advances into daily care and fights for the recognition of the needs of people with musculoskeletal diseases by the governing bodies in Europe.

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