SRUK Research Strategy

Introduction

Scleroderma is a rare, chronic auto-immune condition affecting connective tissue and blood vessels. In the UK there are around 12,000 people diagnosed with the condition. The cause is unknown, and prognosis is poor, often leading to multi-organ dysfunction and premature death. Research is urgently needed to understand the cause of the condition and to improve treatment.

Primary Raynaud's phenomenon is common and usually symptoms are mild and manageable. Over-sensitivity of peripheral small blood vessels to temperature change leads to characteristic attacks with blood vessel constriction, loss of blood and oxygen from the exposed tissue (fingers, toes or other extremities) followed by excessive blood vessel dilation on warming. Attacks can very be painful.

Secondary Raynaud's phenomenon, which is more serious and can lead to ulceration and calcification, is associated with the presence of an auto-immune connective tissue disease and can often be the first indication for the disease. Almost all patients diagnosed with scleroderma have secondary Raynaud's phenomenon. Treatment, other than to relieve symptoms, is relatively ineffective.

To improve the lives of patients and to work towards better treatment or prevention, SRUK awards small grants to carry out research into the causes or treatment of Raynaud's phenomenon, scleroderma and the associated complications of the diseases.

Purpose of the research strategy

Supporting research is one of the key aims of SRUK as it is vitally important to improve treatment, increase quality of life and ultimately find a cure. This requires us to have a focused research strategy based on a clear understanding of the areas where our funding can have the greatest impact. We work in partnership with people affected by scleroderma and Raynaud's to inform, develop and deliver our work, ensuring that people affected by scleroderma and Raynaud's have a strong voice and play an integral part in the development of SRUK's services.

This research strategy is based on the research topics that were prioritised by people with scleroderma and Raynaud's, researchers and clinicians in 2017 to consider how the charity can best focus its resources for patient benefit. Research priority areas as well as the overall research strategy are reviewed every 3-5 years in consultation with people with scleroderma and Raynaud's, researchers and clinicians.

As part of development of a research strategy, it is necessary to conduct a priority-setting exercise with key stakeholders, including patients, carers, researchers and health professionals.

Who we are

Scleroderma & Raynaud's UK (SRUK) is the only UK charity dedicated to improving the lives of people affected by scleroderma and Raynaud's. We exist to improve awareness and understanding of these conditions, to support those affected, and ultimately to find a cure.

We are a new charity formed by the merger of the Raynaud's & Scleroderma Association (RSA) and the Scleroderma Society. SRUK officially launched on 31st March 2016. By bringing the support, expertise and passion of the two organisations together, we have a strong new organisation focused on supporting people with scleroderma and Raynaud's, funding and campaigning for research into the conditions and dedicated to building better understanding and treatment for everyone affected by them.

Improving the lives of people with scleroderma and Raynaud's is central to everything we do. We want everyone with the conditions to live as full and unlimited a life as possible, until we find a cure.

Being there for our community when it needs us is paramount – we do this through our helpline, local support contacts, support groups and our online forum. We also run regular educational events and have a yearly conference to bring people together.

We also make our voices heard with decision-makers and politicians, pushing scleroderma and Raynaud's up the health and social care agenda.

We are driven to make real progress towards more effective treatments and a cure. We invest in innovative research projects at the forefront of the field.

In the 2015–16 financial year, the charity's expenditure on medical research in the UK was £749,809. Spending on other charitable activities (patient information and support) was £559,266. SRUK's average annual expenditure on medical research from 2012–17 was £500,000. The charity's anticipated spend on medical research in the UK for the current financial year is £815,000. There are 13 currently active SRUK grants, inclusive of ongoing grants awarded by the RSA and Scleroderma Society. SRUK has one or two grant rounds each year, depending on the level of financial reserves.

Our vision

Our vision is a world where no-one has their life limited by scleroderma and Raynaud's.

Our Mission

Our mission is to improve the lives of everyone affected by scleroderma and Raynaud's. We do this by investing in research, improving awareness and understanding of the conditions and providing information and support to all those affected.

What we have achieved so far

Research we've funded has led to breakthroughs in our understanding of Raynaud's and scleroderma, leading to earlier diagnosis, better monitoring and the identification of various genes involved. To date, the RSA, Scleroderma Society and SRUK have spent £10.1 million on research being carried out into Raynaud's phenomenon and scleroderma in the UK. The RSA started awarding research grants in 1985 and the Scleroderma Society's first grants were allocated in 1990. Since its creation in 2016, SRUK has awarded four grants totalling £145,000 for projects investigating aspects of scleroderma. Details of these grants have been published on our website. In total, the charities have awarded over 200 grants.

Over half of grants awarded have been for research aiming to improve the understanding, characterisation and treatment of scleroderma, with approximately one-sixth of grants covering both conditions, such as funding for specialist nurses, and one-fifth being for research into Raynaud's. There have also been several projects focusing on rarer but related conditions including erythromelalgia (a condition primarily affecting the extremities characterised by intense burning pain, redness and increased skin temperature) and morphoea (a form of localised scleroderma). The severity of scleroderma in comparison to Raynaud's, the link between scleroderma and secondary Raynaud's, and the limiting side-effects of many available treatments explain the bias towards financing scleroderma research.

Many projects supported are pilot studies. The results of these small studies provide the basis on which larger studies receive funding. As such, the charities have invested in grass roots research to maximise the long-term impact of their investment and outcomes for people living with scleroderma and Raynaud's. The results of these studies have been presented to the research and healthcare community at conferences and meetings as talks, abstracts and posters. Over 100 papers have also been published in recognised and respected journals focusing on rheumatology, such as *Arthritis and Rheumatology*, *The British Journal of Dermatology* and *Clinical Rheumatology* and *Rheumatology (Oxford)*, and related fields, such as *Thorax*, *The American Journal of Pathology* and *The Journal of Biological Chemistry*.

Collaboration and career development

Collaborative working is an important aspect of research the charities have funded as it increases the available skill base, provides access to specialist equipment and increased numbers of patients that can be drawn from, as scleroderma is a rare condition. Groups or

individuals awarded grants have often worked with professionals from at least one other institution and several large grants have been awarded as a result of joint applications, such as the award to the Royal Brompton and Royal Free Hospitals for research into the pathogenesis and clinical manifestations of pulmonary fibrosis in scleroderma. Funding from the Scleroderma Society and RSA enabled the European Scleroderma Observational Study to run for an extra year, enabling more patients to be enrolled to study the effectiveness of immunosuppressant therapies in diffuse cutaneous systemic sclerosis.

Fellowships and PhD funding have enabled professionals such as Professor Jill Belch at the University of Dundee and Dr John Pauling, consultant at the Royal National Hospital for Rheumatic Diseases, to develop their careers in scleroderma and Raynaud's research. In the longer term, various grants have supported the work of researchers such as Professor Ariane Herrick at the University of Manchester and Professor Christ Denton at UCL, enabling them to carry out breakthrough research and us to build stronger relationships with the research community through them. Funding of nursing posts has enabled nurses to develop new skills, advance their careers, educate healthcare professionals about Raynaud's and scleroderma, and reach out to patients and their supporters. Their work has encompassed patient recruitment, project administration, ethical approval and clinical research in addition to running clinics and helplines, counselling patients and their families. The RSA invested about £1 million in specialist and research nurses. One such nurse was Sue Brown, who was promoted to senior sister and obtained a bursary for an MSc in Health Care Practice during the grant period, and went on to become the first consultant nurse specialising in connective tissue diseases.

Development of technology, techniques, treatments and markers

Projects funded by the RSA and Scleroderma Society have led to the development and testing of techniques, treatments and technologies for both Raynaud's phenomenon and scleroderma. Examples include:

- *Novel drug therapies:* In 2015 Professors Richard Winpenny and Ariane Herrick at Manchester University were awarded a grant to develop novel therapies for scleroderma-related calcinosis (painful calcium lumps that form on the hands or near joints). Their research assesses how well calcinosis lumps are broken down by various treatments that are coupled with molecules that can cross the skin.
- *Imaging techniques:* Over the past decade, Professor Herrick and her colleagues at Manchester University have, in collaboration with Dr Marina Anderson at the University of Liverpool, developed and validated a computerised nailfold capillaroscopy system that can monitor changes in nailfold capillaries over time in people with primary and secondary Raynaud's phenomenon. The initial grant enabled the system to be developed, and follow-on grants enabled it to be evaluated and automated.
- *Genetic markers*: In 2010–14 Professors David Abraham and Chris Denton and their colleagues at the Royal Free and Royal Brompton Hospitals studied genetic markers in scleroderma to see if they could be related to rates of disease progression and

- outcomes. They found nearly 1,000 genes were abnormally regulated in scleroderma. Many of these genes were involved in inflammation, host defence, immune response and scar formation. Genome-wide association studies identified several genes in previously unknown pathways that may explain the development of particular subtypes of disease, such as fibrosis (gene CD226), anticentromere antibody (SOX5 and NOTHCH4 genes) and limited cutaneous disease (IRF8, GRB10 and SOX5).
- *Protein and gene markers:* A 2007–9 project run by Dr Gisela Linhdhl and David Abraham at the Royal Free hospital studied the regulation of CCN2 (connective tissue growth factor), which is not normally secreted in the body but is secreted by activated fibroblast cells. CCN2 has a role in fibrosis as the production of CCN2 protein by the CCN2 gene leads to the overproduction of extracellular matrix proteins by fibroblasts. A region within the CCN2 gene was studied as it is a target for Sp1/Sp3 proteins that block the production of CCN2, and a TGFβ receptor inhibitor was found to stop Sp1/Sp3 binding to CCN2, and so stop protein production. CCN2 is therefore a clinical biomarker of fibrotic scleroderma and the Sp1/Sp3 pathway is a promising target for therapeutic development.
  Technology: Since 2012, Dr Maya Buch at the University of Leeds has been studying the use of implantable loop recorders to identify scleroderma patients at risk of life-threatening arrhythmias. Such patients need an implantable cardioverter-defibrillators. This pilot study uses novel methods to study the structure, small vessels and electrical activity of the heart. Within the first year, data recorded by the implantable loop recorders from 20 patients revealed that one patient needed an implantable cardioverter-defibrillator and one had previously undiagnosed arrhythmia. The results support the need for a larger trial of implantable loop recorder use.

Where we are headed

As part of our research strategy, we have established the priorities of our stakeholders so that we can make informed choices about how we spend our limited funds. Details of the research priorities survey, which was distributed via *SRUK News* magazine, the e-magazine, e-newsletter and a link on the website, have been published on the SRUK website. Having been informed by the survey, the four main areas of research we will be funding in 2017–22 are:

- finding a cure
- improving treatments
- working towards an earlier diagnosis
- improving the care and services that people with scleroderma and Raynaud's receive.

Research area 1: Finding a cure

We will support research into finding a cure for scleroderma and Raynaud's. This includes understanding the causes and underlying mechanisms of both conditions and may include looking into the genetic and environmental factors contributing to the development of scleroderma and Raynaud's. Identifying risk factors that may predict whether a person is likely to develop one or both conditions and finding ways to prevent an outbreak are also important aspects of this area of research.

Research area 2: Improving treatments

Improving the treatment of scleroderma and Raynaud's may slow down progression and prevent further damage to the organs that are involved. Slower progression and improved tolerance towards the treatment may lead to a significant increase in quality of life. Moreover, if, for example, issues like fatigue could be addressed, this may enable people to take part in social activities and hold a job, both of which could greatly improve people's wellbeing.

Research area 3: Working towards an earlier diagnosis

Earlier diagnosis of the conditions may have a significant impact on their progression. We will therefore encourage research into finding better methods by which to detect the onset of the conditions, which may include research into biomarkers and imaging methods. This research area also includes increasing awareness of both conditions, so healthcare professionals are better able to diagnose the complex symptoms and early signs of scleroderma and Raynaud's.

Research area 4: Better provision of care and services

Supporting this area will lead to new insights into how the special needs of people affected by scleroderma and Raynaud's can be met by means other than just medical treatment. This may include providing psychological support and information, assessing and meeting the special and individual needs of people affected by the conditions. The overall aim is to encourage research into relieving the symptoms of scleroderma and Raynaud's with methods other than medical treatment.

How are we going to achieve this?

All grant applications will be assessed as to whether they comply with the overall research strategy and priorities of SRUK (as part of our peer review process), making sure we fund research that our supporters have identified as their key priorities. Also, the rigorous peer review process will ensure that we only fund the best research projects and researchers.

As we are keen to achieve the biggest impact with our limited funding, grants of two types are prioritised. First, those exploring novel science with a view to providing pilot data for future larger applications to other funding bodies. Second, those adding value to the clinical diagnosis of disease classification or progression with a view to providing results that can be applied more widely for patient benefit. Applications are invited from tenured staff in any university or recognised research centre in the UK and we support the AMRC's position statement to support UK research universities.

To assess the outcomes of our research funding, we will regularly monitor the progress of the projects we are funding. The principal investigator is required to submit a final report within 2 months of the completion of a research project and, if longer than 12 months, an annual report outlining progress to date, presentations given and publications prepared/submitted and future plans. These reports consist of two parts: a technical summary containing details of presentations and publications submitted and/or accepted for publication, and a lay summary. Additional interim reports may be required, depending on the nature and progress of the individual award. Through monitoring of funded research, we will be able to see which priorities have been met and which are not attracting funding.

We offer a range of funding streams in order to maximise the outcomes of our research funding. The funding schemes include:

- PhD studentship (3 years, maximum £100,000)
- Small project grant for preclinical research, maximum of 2 years and £100,000
- Grant for a small clinical study, maximum of 2 years and £100,000
- Equipment grants of up to £50,000 and requiring matching funding from other sources
- Travel grants to attend scientific meetings

Research grants are awarded on an annual basis following a call for applications on the SRUK website and via direct email circulation to the research community. The grant will be awarded following external peer review and a meeting of the scientific advisory committee to discuss the merits of each application. The decision to award the grants will be made by the board of trustees following the recommendations of the scientific advisory committee. This should happen in a period of within 6 months of the application deadline, as the trustees meet every 3 months. Funding will become available as soon as the administrating authority has accepted the grant following an award letter being sent and the signed terms and conditions being returned to SRUK. Payment will be made every 3 months in arrears following the submission of an invoice to SRUK. Work on the project should start within 6 months of the grant application being authorised or the trustees may require re-application.

Travel grants

Applications for travel grants to attend and/or present at scientific meetings do not need to go through the standard application and review process as they are for much smaller sums of money. Decisions to award travel grants will be made by the trustees on a case-by-case basis based on the merit of the application.

Application process

After receiving research grant applications, SRUK sends these out for peer review by at least two independent experts in the field, who may be outside the UK. Their reports are then discussed by the Scientific Advisory Committee, which will review the application and give a recommendation to the Board of Trustees, which makes the final decision.

Animal use in medical research

Scleroderma & Raynaud's UK will only fund animal-based work when there is no alternative to address the research questions posed by the study. Any animal use must be fully justified in an application; comply with a stringent procedure to ensure that animal work is only supported when absolutely necessary and conforms to strict regulations on the treatment of the animals involved. Scleroderma & Raynaud's UK, as a member of the Association of Medical Research Charities, would adopt and adhere to the AMRC Statement on animal research. This can be found at www.amrc.org.uk.

Beyond grants: Supporting researchers

SRUK supports researchers by publicising their work and that of the institutions they work for through both internal and external channels. The award of grants and results of studies are published on the SRUK website, shared at key events throughout the year, such as our annual conference, and featured in our e-newsletter and *SRUK News* magazine.

Each quarterly *SRUK News* magazine features an article written by a researcher at a key specialist centre in the UK. Here the researcher answers questions about projects, introduces the team of researchers and discusses specialist support provided by their institution. Research summaries are produced annually and upon on conclusion of the research project, which are then published on the website.

Going forward, technical and simplified 'lay' summaries will be used to produce news articles and press releases to increase engagement and awareness within the wider medical community (e.g. news pieces in journals) and general public (e.g. newspapers and magazines featuring personal interest stories that can be related back to breakthroughs in research).