Global Innovator's Briefing: Rare Diseases

Systemic Sclerosis

Not every rare disease is necessarily inherited

Systemic Sclerosis

- A chronic autoimmune rheumatic disease impacting multiple organs
- Characterised by blood vessel disease (vasculopathy), skin and internal organ fibrosis (caused by excessive collagen production).
- Classified into two distinct subtypes
    - limited systemic sclerosis
    - diffuse systemic sclerosis
- Morbidity and severe, often irreversible organ damage in SSc can occur early within the first two years of disease onset.

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Main abbreviations used (all others explained in text)

HCP: healthcare professional N/AV: not available SSc: Systemic Sclerosis

cite: Dando JS. Systemic Sclerosis: Rare Disease Innovators Briefing: Last updated Oct 2022. Accessed from: www.echino.eu/knowledge

About Echino Innovator Briefings: Rare Diseases,

These briefings are designed as introductions for **early-stage innovators, covering a range of diverse rare diseases**. They are based upon freely available peer reviewed and referenced or professional information, that have been designed as a 'cog' between the two worlds of healthcare need and innovation implementation. Six are planned: some core sections will be identical throughout.

To stimulate or aid the innovator in any global geography, these introduce the state-of-the-art, the stakeholders and their interactions to anyone or any entity that is interested in innovating a solution (interventional, diagnostic, med tech, med device, digital health, healthcare process, occupational and physical therapy, patient support globalisation) for a Rare Disease, whether its social entrepreneurship, charitable or for-profit.

Why Innovator focused specific communication:
There is a knowledge gap with specific relevance to Rare Diseases between innovators and the stakeholder communities that play a pivotal and critical role in making sure innovations deliver real benefit, that has greater pertinence than more frequent diseases due to patient numbers and product development costs. It can be baffling to know where to start.

I have participated in sufficient investment committee review meetings with presentations focusing on rare diseases, often with a feeling of that only one or two stakeholders or issues have been truly considered: this makes the transition of the idea to a beneficial product or solution much more difficult.

Inversely, for an innovator to identify and understand the spectrum of knowledge needed is daunting: a significant amount of the information is very technical in content, with a broad spread across many sources and often focused on the authors immediate communities.

I have not tried to simplify the knowledge (except when it is very clinical terminology, specifically on symptoms), and always provided references. References are provided according to the schedule of people who work in innovation, where possible next to the pertinent information being discussed. For purposes of brevity, I have only indicated the first author et al, in most cases with the link (mainly to PubMed). I know this not the normal standard, but this is tailored for the audience.

References are not designed to favour any given stakeholder or KOL, nor are they are substitutes for digging much deeper if the innovator is serious. If, any KOL has felt they have been left out, this was not the intention (apologies): many more publications were read than referenced (the ones indicated by the book symbol  are *suggested introductory starting points and are technical/specialised in most cases*)

The briefings were started over summer 2022, with the aim to be globally focused and comprehensive… like all knowledge exploration exercises, the more you discover the more you realise you don't know... so they are not necessarily brief.

They do not include any references to standards or regulations applied in the different geographies for product development, manufacture and validation... for the innovator, this information is widely available and for you to find. They also do not include market valuations: there is sufficient information present in these briefs including the supplementary material of references, plus easily available online price catalogues for you to do the calculation yourself

Sometimes only specific stakeholders and single geographies are prioritised with a focus on bottom-line returns, this is somewhat understandable but as a general principle Rare Disease focused work is a long-haul and avoiding care disparity is a major goal. This may require a global approach to innovation in solution pricing, and reflection on strategies related to the orphan drug legislation and designation, to make sure investment is not diluted too much on competing too-similar initiatives. A forward movement without balance between all stakeholders is a movement backwards

Many patients with all types of rare diseases have stepped up and got involved, knowing full well that their involvement will likely not generate a benefit for them in their lifetime or of the ones they care for, but may help the next generation. I don't think very many of them made that decision with another entities financial ROI as their main objective.

What these are not:
They are unfortunately not multilingual: I also only had the time to write them in English. If anyone is interested in generating multilingual/multicultural sensitive versions, please reach out and I am happy to provide the original word doc. for translation.

These are **not adverts**: i.e., after reading, if stimulated, further detailed reading that is needed first: following which the innovators next point of contact should be a KOL: Patient Association or a Medical/Researcher.

Declaration:
I have no conflict of interest with any entity (public or private), I represent no faith or faith associated body, I represent nor am paid by any entity: non-profit, pharmaceutical or biotech, for these briefings.

And I am enormously grateful to the vast array of open-source publications, and authors, databases, charities, associations and NGOs that are making the knowledge and information for these long briefings freely available.

Systemic Sclerosis: Risk factors

- **Age**: onset between ages of 30–50.
- **Gender**: ratio of disease: Average of 4:1 ratio, Female to Male.
- **Family history**: if sibling has it, high risk other siblings will develop it (familial clustering), but inheritance rare.
- **Genetic variants**: Person has specific genetic variant that potentially predisposes disease.
- **Environmental factors**: Exposure to silica.

Abbot S, et al. Risk factors for the development of systemic sclerosis: a systematic review of the literature. Rheumatol Adv Pract. 2018;2(2):rky041. **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6649937/

Ota Y, Kuwana M. Updates on genetics in systemic sclerosis. Inflamm Regen. 2021;41(1):17. **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8204536/

Kassamali B, et al. Geographic distribution and environmental triggers of systemic sclerosis cases from 2 large academic tertiary centers in Massachusetts. J Am Acad Dermatol. 2022;86(4):925-927. **Link:** https://pubmed.ncbi.nlm.nih.gov/33771593/

Global incidence and prevalence

Table 1: 2021 single source global figures

Location	Incidence per 100,000 person years	Prevalence per 100,000	Continent population (Global cancer obs. data)	Est.number of total prevalent patients	Est. number of prevalent female patients	Est. number of prevalent male patients
Africa (Botswana)	0.2	N/AV	1 340 598 088	N/AV	N/AV	N/AV
Asia	0.9	6.8	4 639 847 464	315 509	252 408	63 101
Europe	1.6	14.8	748 843 410	110 829	88 663	22 166
North America	2	25.9	368 869 643	95 537	76 430	19 107
Oceania	1	23.8	42 677 809	10 157	8 126	2 031
South America	1.5	24.8	653 962 327	162 182	129 746	32 436

Source: Bairkdar M, et al. Incidence and prevalence of systemic sclerosis globally: a comprehensive systematic review and meta-analysis. Rheumatology. 2021;60(7):3121-3133. **Link:** https://pubmed.ncbi.nlm.nih.gov/33630060/

Accurate numbers, especially in locations with non-optimal access to informed HCPs and diagnostic procedures is a common problem in rare diseases: additional concepts and reading to consider:

SSC studies in Africa:

Erzer JN, et al. Systemic sclerosis in sub-Saharan Africa: a systematic review. Pan Afr Med J. 2020;37:176. **Link:** https://pubmed.ncbi.nlm.nih.gov/33447331/

Sibanda EN, et al. Systemic Sclerosis in Zimbabwe: Autoantibody Biomarkers, Clinical, and Laboratory Correlates. Front Immunol. 2021;12:679531. **Link:** https://pubmed.ncbi.nlm.nih.gov/34858387/

Ilovi S and Oyoo GO. Characteristics of systemic sclerosis patients in Nairobi, Kenya : a retrospective study, Afr J Rheumatol 2013; 1(1): 8-12 **Link:** https://profiles.uonbi.ac.ke/csilovi/files/characteristics_of_systemic_sclerosis_patients_in_nairobi.pdf

Adelowo O, et al. Rheumatic diseases in Africa. Nat Rev Rheumatol. 2021 Jun;17(6):363-374. **Link:** https://pubmed.ncbi.nlm.nih.gov/33850309/

Prevalence in Japan 2022

Kuwana M, et al. Incidence Rate and Prevalence of Systemic Sclerosis and Systemic Sclerosis-Associated Interstitial Lung Disease in Japan: Analysis Using Japanese Claims Databases. Adv Ther. 2022 ;39(5):2222-2235. **Link:** https://pubmed.ncbi.nlm.nih.gov/35316503/

- Prevalence SSc 37/100,000, prevalence SSC-ILD 13.9/100,000
- Incidence SSc 6.6/100,000 person years, SSC-ILD 1.9/100,000 person years

Japanese population demographics: Worldometer number of 125 603 826 people = 46 473 prevalent cases, *implying (but possibly wrong)* that 15% of all prevalent SSC patients from Asia, reside in Japan, and its incidence there is twice as high as the continent average.

This has ramifications for innovation possibilities in ways to generate accurate indication related data sets.

What symptoms do patients with SSc experience

Table 2: Non-exhaustive list of the symptoms experienced by patients diagnosed with SSc. Major healthcare focuses and cost/burden drivers are highlighted in red.

Frequency (%)	Description
80–99	Raynaud Phenomenon (fingers turn different colours in response to triggers that decrease blood flow) Muscle aches and pains Joint stiffness Gastrointestinal abnormalities ANA positivity (antibody mediated autoimmunity) Thickened skin
30–79	***Biochemical***: elevated serum CK, anticentromere and topoisomerase antibody positivity **Cardiovascular:** dilated blood vessels near skin surface ***Dermatological:*** ulcers on finger tips, skin tightening, skin colour changes ***Gastrointestinal:*** abnormal oesophagus morphology ***Kidney:*** Renal abnormality ***Musculoskeletal:*** muscle weakness, joint swelling, finger joint changes ***Pulmonary***: fibrosis, interstitial abnormalities (interstitial lung disease ILD)
5–29	***Biochemical:*** proteinuria, albuminuria ***Cardiovascular:*** interstitial cardiac fibrosis, myocarditis, fainting episodes, pericarditis, blood vessel dilation ***Dermatological:*** sweat gland damage, hair loss, skin infections, facial soft tissue abnormality ***Gastrointestinal:*** Acid reflux damage to oesophagus, small and large intestinal abnormalities incl. bleeding, bowel incontinence ***Kidney:*** Severe forms of kidney damage (acute and chronic), renal insufficiency, damage to kidney microfilters ***Musculoskeletal:*** arthritis, joint inflexibility, bone infections ***Pulmonary:*** shortness of breath, Pulmonary Arterial Hypertension (PAH)
1–<4	Gangrene

Source: Data obtained from Orphanet 'rare diseases: clinical signs and symptoms'. For purpose of brevity, symptoms summarised and indicated by organ. The complete list can be found at the original source https://www.orpha.net/consor/cgi-bin/Disease_HPOTerms.php?lng=EN with a detailed explanation of the data.

What do these symptoms mean?

The experience of living with scleroderma is complex; patients experience the following:

- Limitations in mobility and hand function,
- Pain
- Fatigue
- Difficulty breathing
- Gastrointestinal problems
- Sleep disturbance
- Depression
- Sexual dysfunction
- Itchy skin
- Body image distress from disfiguring changes in appearance, concerns with physical appearance
- Emotional distress, including depression, low self-esteem,
- Uncertainty about future outcomes,
- Significant disruptions in their social lives, a burden considered by many as the worst consequence of their disease.

Extracted from 'section 3.3 humanistic burden of SSc' of *Fischer A, et al. Humanistic and cost burden of systemic sclerosis: A review of the literature. Autoimmun Rev. 2017;16(11):1147-1154 (see next page for link).*

After SSc onset:

Risk factors for renal damage development: corticosteroid exposure, tendon friction rubs, skin thickness

Gordon SM, et al. Risk Factors for Future Scleroderma Renal Crisis at Systemic Sclerosis Diagnosis. J Rheumatol. 2019;46(1):85-92. **Link:** https://pubmed.ncbi.nlm.nih.gov/30008456/

Risk factors for interstitial lung disease development: alveolar damage, gender males>females, ethnicity, biochemical and clinical changes

Distler et al. Predictors of progression in systemic sclerosis patients with interstitial lung disease. Eur Respir J. 2020;55(5) **Link:** https://pubmed.ncbi.nlm.nih.gov/32079645/

Risk factors for PAH: late diagnosis, longer duration of disease, age, biochemical and clinical changes

Jiang Y, Turk MA, Pope JE. Factors associated with pulmonary arterial hypertension (PAH) in systemic sclerosis (SSc). Autoimmun Rev. 2020 Sep;19(9). **Link**: https://pubmed.ncbi.nlm.nih.gov/32659476/

What does it mean to live with SSc: the patient and caregivers voice, in their own words

Any innovator with any intention to create a real benefit needs to understand the patient and the caregiver: the healthcare community has published their voice and the voice of the caregiver, whether it's an HCP, a neighbour, a friend or a family member.

'A Patient's View

*One always tries to understand '**How could this happen to me?"***

Extracted from: Cossu M, et al. Clin Rev Allergy Immunol. 2018;55(3):312-331.

Recommended reading

1.'A Patient's view' sections from:

Unmet Needs in Systemic Sclerosis Understanding and Treatment: the Knowledge Gaps from a Scientist's, Clinician's, and Patient's Perspective

Cossu M, et al. Unmet Needs in Systemic Sclerosis Understanding and Treatment: the Knowledge Gaps from a Scientist's, Clinician's, and Patient's Perspective. Clin Rev Allergy Immunol. 2018;55(3):312-331.

Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6244948/

2. Patients' point of view

Living with systemic sclerosis: the point of view of patients

Ilaria Galetti

Galetti I. Living with systemic sclerosis: the point of view of patients. Curr Med Res Opin. 2021 Nov;37(sup2):1-4.

Link: https://pubmed.ncbi.nlm.nih.gov/34726111/

3.Patient's and caregivers survey

How do systemic sclerosis manifestations influence patients' lives? Results from a survey on patients and caregivers

Galetti I, et al. How do systemic sclerosis manifestations influence patients' lives? Results from a survey on patients and caregivers. Curr Med Res Opin. 2021;37 (sup2):5-15.

Link: https://pubmed.ncbi.nlm.nih.gov/34726112/

4. Humanistic and cost burden

Humanistic and cost burden of systemic sclerosis: A review of the literature

Fischer A, et al. Humanistic and cost burden of systemic sclerosis: A review of the literature. Autoimmun Rev. 2017 Nov;16(11):1147-1154.

Link: https://pubmed.ncbi.nlm.nih.gov/28899803/

5. CDER/FDA: The voice of the patient

The Voice of the Patient

A series of reports from the U.S. Food and Drug Administration's (FDA's) Patient-Focused Drug Development Initiative

Systemic Sclerosis

Public Meeting: October 13, 2020
Report Date: June 30, 2021

Link: https://www.fda.gov/media/150454/download

6. Patient interviews on pulmonary issues

Expert opinion and patients' in-depth interviews on the impact of pulmonary complications in systemic sclerosis

Antonella Caminati[a,*], Barbara Vigone[b,c,*], Sergio Cozzaglio[d], Paola De Nigris[e], Ilaria Galetti[d], Sara di Nunzio[f], Viviana Verzeletti[f], Jennifer Cighetti[f], Carla Garbagnati[d], Laura Paleari[d], Erminio Tabaglio[g] and Salvatore Pirri[h]

Caminati A, et al. Expert opinion and patients' in-depth interviews on the impact of pulmonary complications in systemic sclerosis. Curr Med Res Opin. 2021;37(sup2):17-26.

Link: https://pubmed.ncbi.nlm.nih.gov/34726093/

Additional reading

SSC and employment/work productivity: (1) Xiang L, et al. Arthritis Care Res (Hoboken). 2022;74(5):818-827. (2) Lee JJY, et al. Best Pract Res Clin Rheumatol. 2021;35(3):101667. (3) Morrisroe K, et al. Rheumatology (Oxford). 2018;57(1):73-83.

Evidence from LMIC: Kakade G, Samant R, Mahashur A, *et al* SAT0278, Study of quality of life in patients with systemic sclerosis- a cross-sectional study, *Annals of the Rheumatic Diseases* 2019;78:1215-1216. **PLUS,** publications on page 3 above on SSc in Africa

Takeaways:

Obtaining correct healthcare:

- First symptoms not easily recognised by the family doctor
- Disease complexity means HCP understanding of all components of disease can result in misdiagnosis
- Time (years) between presentation of first symptoms and correct diagnosis
- Different perspectives on correct medicine or intervention to take and its availability

Personal impacts: obtaining accurate diagnosis representing a 'watershed' moment for the patient, as 'shocking and tragic'. Every aspect of life impacted:

- Gastro-intestinal dysfunction preventing normal life
- Social life and parenting capacity diminished
- Loss of self-recognition, feeling of shame and self-isolation, psychological stress due to physical disease manifestations
- Burden for family to provide care and cost of travel to different specialists and costs of treatment
- Anxiety and depression present in almost every patient
- Work absenteeism, employment opportunities reduced or eliminated (early retirement)

Note: the precise emphases of each are influenced by type of available healthcare provision (private, universal, hybrid), HCP human resource availability, socioeconomic status of the patient and social determinants of health

Clinical benefit, Health Related Quality of life (HRQoL), and Patient reported outcome measures (PROMs)

- Connecting a change in a specific clinical outcome to a change in QoL adds definition to the benefit of the solution.
- QoL changes applies to the patient and the caregiver.
- Depending on the clinical symptom being targeted and its severity, QoL changes may occur in the short term or over a longer period; or clinical symptom alleviation may not result in an identifiable change in QoL.
- In rare diseases late-stage diagnosis can mean each individual patient can present with their own specific spectrum of clinical symptoms and HRQoL/ QoL needs.
- Without a large evidence base of 'similar cases' that can be found in frequent diseases, that supports decision making, assessing QoL benefit in rare diseases can be challenging.
- PROMs design and complexity can vary between use as *patient monitoring tools* such as in daily patient care, to larger scale multi-dimensional tools used in complex case management and clinical trials.

Introduction to PROMs:

Patient-reported outcome measures (PROMs) as proof of treatment efficacy

Kluzek S, et al. BMJ Evid Based Med. 2022 Jun;27(3):153-155.

Link: https://pubmed.ncbi.nlm.nih.gov/34088713/

Patient reported outcomes in Systemic sclerosis: introductory reading

Common measure of quality of life for people with systemic sclerosis across seven European countries: a cross-sectional study

Ndosi M, et al. *Annals of the Rheumatic Diseases* 2018;77:1032-1038.
Link: https://ard.bmj.com/content/77/7/1032.citation-tools

Presents an essential concept of cross cultural QoL measurements for SSc, that enables care standardization, but also reassures innovators on solution design and larger patient benefit: a concept applicable across all continents

A rare disease patient-reported outcome measure: revision and validation of the Germ version of the Systemic Sclerosis Quality of Life Questionnaire (SScQoL) using the Rasch model

Kocher A, et al. Orphanet J Rare Dis. 2021;16(1):356
Link: https://pubmed.ncbi.nlm.nih.gov/34372892/

Introduces an essential concept of how SSc PROMs need to be adapted even between cultures that speak the same language to account for subtleties in understanding that can influence reporting

Development and validation of a patient-reported outcome measure for systemic sclerosis: the EULAR Systemic Sclerosis Impact of Disease (ScleroID) questionnaire

Becker MO, et al. Ann Rheum Dis. 2022;81(4):507-515.
Link: https://pubmed.ncbi.nlm.nih.gov/34824049/

Presents PROM design as a function of interactions with patients with SSc, to determine which health dimensions they thought impacted their QoL the most.

Introduces the idea of ensuring that new concepts align with existing ones, to permit evaluation within an existing healthcare process and infrastructure

Patient-reported outcome instruments in clinical trials of systemic sclerosis

Pauling JD, et al. J Scleroderma Relat Disord. 2020;5(2):90-102.
Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8922614/

Provides the innovator with as close to possible list of PROMs used during clinical trial validation of solutions, that they would need to consider during any study to align clinical symptom alleviation with the patients' QoL

Patient-reported outcome measures in systemic sclerosis–related interstitial lung disease for clinical practice and clinical trials

Saketkoo LA, et al. J Scleroderma Relat Disord. 2020;5(2 Suppl):48-60.
Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7243660/

Introduces several key concepts in PROMs for enabling healthcare:

- *Symptomatology*
- *The behavioural aspects of symptom-related impacts and how they are perceived by the clinician*
- *How PROMs change with disease progression and severity*

Health-related quality of life in patients with systemic sclerosis: evolution over time and main determinants

van Leeuwen NM, et al. Rheumatology (Oxford). 2021;60(8):3646-3655.
Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8328503/

8–year (median 3.4 years) longitudinal study of HRQoL changes in a 202-SSc patient cohort

Study limitations and strengths section illustrates the 'rare-disease' wide issues of evaluating HRQoL and issues of agreement amongst diverse specialists and low patient number.

Additional information: EULAR listed validated PROs (typically for clinical trials) – https://oml.eular.org
Search term: systemic sclerosis

Patient Associations, public/non-profit organisations and open-source specialists: Entities supporting patients with Systemic Sclerosis

In Rare Diseases, indication focused Patient Associations and public organisations are The essential '***central cog***' and **they work hand-in-hand with HCPs**. Each other stakeholder has a spectrum of focuses, agendas and motivations, for these entities, the specific indication itself or elevation of awareness and knowledge of Rare diseases as a whole is the motivation.

They exist as global networks, international publishers, national bodies, local organisations, groups of friends and family of those affected: they liaise between every stakeholder, provide information to policy makers and collaborate with payment bodies to provide the voice of the patient at time of review of new solutions.

For patients with Systemic Sclerosis the following (non-exhaustive) organisations and bodies exists.

These types of organisations move mountains. The innovator should take time to explore everything they have done, their outputs and what they continue to do, during their own reflections on the benefits they think they can provide.

Table 3: patient associations, organisations and bodies providing support and information

Name	Location	Geographic focus	Website	Languages
Patient associations				
The World Scleroderma Foundation	Switzerland	Global	https://worldsclerofound.org	English
Federation of European scleroderma associations (FESCA)	Belgium	Europe/Global	https://fesca-scleroderma.eu	English (links to multilingual national organisations)
Scleroderma & Raynaud's UK	UK	UK	https://www.sruk.co.uk	English
National Scleroderma Foundation	US	US	https://scleroderma.org	Chinese, English, French, Hindi, Portuguese, Spanish
Scleroderma Research Foundation	US	US	https://srfcure.org	English
Scleroderma Australia	Australia	Australia/global	https://www.sclerodermaaustralia.com.au	English
Scleroderma Canada	Canada	Canada	https://www.scleroderma.ca	French/English
Spin	Canada	Global	https://www.spinsclero.com	French/English
Scleroderma Manitoba	Canada	Canada	https://sclerodermamanitoba.com	English
Scleroderma India	India	India	https://www.facebook.com/ScleroIndia/	English
Clinical organisations/networks				
Rheumatologic dermatology society	US	US	https://www.rheumaderm-society.org/systemic-sclerosis-information-for-patients/	English
European Reference Network: Systemic Sclerosis	Europe	Europe	https://reconnet.ern-net.eu/disease-ssc/	English
Rare Disease organisations				
Orphanet	Europe	Europe/Global	https://www.orpha.net/consor/cgi-bin/index.php	English
Eurordis	Europe	Europe/Global	https://www.eurordis.org	English
US National organisation for rare diseases	US	US/Global	https://rarediseases.org	English
NIH Genetic and rare diseases information center	US	US/Global	https://rarediseases.info.nih.gov	English
RarediseasesIndia	India	India	http://www.rarediseasesindia.org/about	English
Information disseminators				
ProjectScleroderma	online	online	https://www.projectscleroderma.com/about/	English
Orphanet Journal of Rare Diseases	online	online	https://ojrd.biomedcentral.com	English
Scleroderma news	online	online	https://sclerodermanews.com	English

Each entity has created and implemented **at least one unique global enabler (in most cases many more)**, and numerous national ones, from tool kits, research programmes, education to patient registries: combined, expanded and translated….the global impact and benefit would be huge.

What are the healthcare costs to the system (patient and healthcare provider)?

Healthcare costs increase dramatically with disease progression and the transition to more severe pathologies:

Table 4 Overall total annual medical costs for SSc across different continents

Continent or location	Currency reported	value
Canada	CAD	10,673–18,453
USA	USD	14,959–23,268
Europe	Euro	4,607–30,797
Oceania	AUD	7,060–11,607
Asia	USD	1,005–1,440
South America	N/AV	N/AV

Source: Martin Calderon L, et al. Healthcare utilization and economic burden in systemic sclerosis: a systematic review. Rheumatology (Oxford). 2022 Aug 3;61(8):3123-3131. **Link:** https://pubmed.ncbi.nlm.nih.gov/34849627/

If the disease progresses from SSc to **SSc with ILD**, increase in annual hospitalisations can occur: in Australia the annual average increases from 2.8 to 3.9 hospitalisations, that becomes a major healthcare cost driver. This cost impact has been reported globally with healthcare costs (excluding medicines) increasing by up to 60%.

Table 5: Available data for annual healthcare costs for patients specifically with SSc-ILD

Continent or location	Currency reported	Value	Source
USA	USD	31,285–55,446	Calderon et al (link above)
France	Euro	21,539	Cottin et al. **Link:** https://pubmed.ncbi.nlm.nih.gov/34552943/
Denmark	Euro	17,666	Knarborg et al. **Link:** https://pubmed.ncbi.nlm.nih.gov/35224821/
Denmark	Euro	17,480.57	Davidsen et al. **Link:** https://pubmed.ncbi.nlm.nih.gov/33156462/
Portugal	Euro	8696.84	
Greece	Euro	6191.34	*Diagnosis was reported to be between 5–10% of the costs*
Netherlands	Euro	10,751.4	
Belgium	Euro	9293.58	
Norway	Euro	16,333.22	
Finland	Euro	13,857.6	
Sweden	Euro	25,354.25	

Table 6: Complete annual healthcare costs for SSc patient cohorts with and without ILD in Denmark.

Category	Subcategory	Non-SSc-ILD costs €	SSC-ILD cost €
Healthcare costs	Outpatient services	4433	5398
	Inpatient admissions	5435	11215
	Prescription drugs	975	1384
	Primary health sector	746	917
	Psychiatric outpatient services	35	37
	Psychiatric inpatient services	96	98
	Sub total	11719	19050
Homecare	Home care-care	914	1007
	Home care-practical help	206	218
	Sub total	1120	1225
Earned income*	Earned income	15111	14922
Public transfer income	Unemployment insurance	266	237
	Social security benefit	1043	1318
	Age pension	5370	4782
	Early retirement	974	1307
	Disability pension	4518	4931
	Housing benefits	541	551
	Child benefits	733	280
	Sub total	13864	14097
	Total	**41814**	**49294**

*This is the presented average across age ranges. Compared to case controls patients with SSc has up to 50% reductions in earned income. Source: Knarborg et al, link above.

Patients with SSc-PAH incur significantly higher costs that are linked to both hospitalisation costs and treatments: In Spain, for all Group 1 PAH subtypes, of which SSc-PAH is one, (but responds to the same treatment as the others), costs increase based on functional class (FC-I, no impediment to FC-IV, very high impediment). There is a logic to identify patients when FC levels are lower, and at time of incidence to reduce healthcare related costs and patient burden.

FC class	Incident patient costs €/yr	Prevalent patient costs €/yr	Source
FC I-II	25,666	65,233	Zozaya et al. The economic burden of pulmonary arterial hypertension in Spain. *BMC Pulm Med* 22, 105 (2022). **Link:** https://pubmed.ncbi.nlm.nih.gov/35346140/
FC III	44,667	103,736	
FC IV	95,188	208,821	

In the USA, the annual costs over a 5-year period for Incident SSc-PAH were US$44,454 to US$63,320

Fischer A, et al. All-cause Healthcare Costs and Mortality in Patients with Systemic Sclerosis with Lung Involvement. J Rheumatol. 2018 Feb;45(2):235-241. **Link**: https://pubmed.ncbi.nlm.nih.gov/29142033/

From the cumulative information in this briefing, and reading these articles plus supplementary material provides more details on costs from which, the estimated market value, cost effectiveness and budget impact can be easily calculated by the innovator for their own solutions.

HCP Care pathways

Healthcare has to be regulated, while evidence-based solution development needs a lot (a lot!) of capital

Innovators have to generate solutions that fit into existing care pathways and resolve an outstanding issue: either through identifying existing ones and modifying/repositioning them (applicable to all types of solution in healthcare) or the creation of new ones. This requires extensive and high-risk typically low-return investment to generate products that need to be highly regulated through standards and laws.

To enable this, rare disease guidelines for standardized of patient care ideally need to be as homogenised as possible, throughout the whole patient journey, in every location:

- From initial symptoms, through primary care to tertiary care and post hospital release
- Accounting for healthcare reimbursement models
- Integrating in the different healthcare resources and infrastructures in different geographies
- Generating solutions and alternatives that work throughout all income settings
- While addressing the patients' and caregivers' requirements

Given the low number of patients, this is a huge bottleneck for innovation in rare diseases, but if resolved will enable the innovator to design and potential investors reassured so that the solution could be used in as many locations as possible.

Solution development should not be hinged on repositioning one solution across multiple indications: while an ideal scenario it does not happen that frequently, and the evidence generation behind it still incurs extra costs.

If innovators are forced to focus on bottom line ROI, then logically only the most lucrative geographies, that are either private or publicly funded will be targeted. This may increase the generation of very similar solutions, even with orphan drug laws, that could dilute investment unnecessarily and leave the great majority of global patients without any help at all.

For SSc, patient care guidelines have been migrating towards a common approach over at least the previous 5 years:

Kowal-Bielecka O, Fransen J, Avouac J, et al. Update of EULAR recommendations for the treatment of systemic sclerosis. Ann Rheum Dis. 2017;76(8):1327-1339. **Link:** https://pubmed.ncbi.nlm.nih.gov/27941129/

Smith V, Scirè CA, Talarico R, et al. Systemic sclerosis: state of the art on clinical practice guidelines. RMD Open 2019;**4**:e000782. **Link:** https://rmdopen.bmj.com/content/rmdopen/4/Suppl_1/e000782.full.pdf

de Vries-Bouwstra JK, Allanore Y, Matucci-Cerinic M, Balbir-Gurman A. Worldwide Expert Agreement on Updated Recommendations for the Treatment of Systemic Sclerosis. J Rheumatol. 2020 Feb;47(2):249-254. **Link:** https://pubmed.ncbi.nlm.nih.gov/31043545/

Hachulla, *et al.* French recommendations for the management of systemicsclerosis. *Orphanet J Rare Dis* **16** (Suppl 2), 322 (2021) **Link:** https://ojrd.biomedcentral.com/articles/10.1186/s13023-021-01844-y

Saketkoo LA, et al. A comprehensive framework for navigating patient care in systemic sclerosis: A global response to the need for improving the practice of diagnostic and preventive strategies in SSc. Best Pract Res Clin Rheumatol. 2021;35(3):101707. (Future of SSc care section). **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8670736/

It is unclear how far this is applied amongst the actual HCPs given their low numbers and workload

Pope JE. Recommendations for the Treatment of Systemic Sclerosis: Agreement May Not Translate into Uptake. J Rheumatol. 2020 Feb;47(2):164-165. **Link:** https://pubmed.ncbi.nlm.nih.gov/32007942/

From this commentary:

'Agreement with guidelines does not necessarily translate into practice. For instance, only about half of the guidelines are routinely followed… A further lag occurs before there is translation into practice because that requires access to medications…. Agreement by experts does not generalize to the majority of practicing rheumatologists and may far overestimate actual care through practice audits.'

It is also unknown how these compare to guidelines written from the perspective of a HCP in a LMIC setting, where most of the SSc patients may be, with their available infrastructure and resources.

Midhuna PV, Thappa DM. Simplified guidelines for the management of systemic sclerosis. CosmoDerma 2021; 1:24. **Link:** https://cosmoderma.org/simplified-guidelines-for-the-management-of-systemic-sclerosis/

Adelowo O, Mody GM, Tikly M, Oyoo O, Slimani S. Rheumatic diseases in Africa. Nat Rev Rheumatol. 2021;17(6):363-374. **Link**: https://pubmed.ncbi.nlm.nih.gov/33850309/

To stimulate innovation that extends beyond experimental design in to practice, in rare diseases these differences need to be built in to the design of the innovation. This may also mean the innovator aligning all the stakeholders to provide care provision at fair pricing strategies, accounting for low global patient numbers, diverse healthcare markets, high development costs and the need for development sustainability.

A significant component of feedback on Systemic Sclerosis throughout all the cited articles is the need for education and training tools for HCPs, especially at the earliest stages, to correctly identify and understand the disease.. that need to be culturally sensitive, multilingual and HCP level tailored

The patient journey: pathogenesis, diagnosis, treatment and care

In most cases the evidence below is based on countries with developed healthcare infrastructures, and there is still a long way to go..but ... try to keep what it would also mean in a country where these do not exist .. do you have a solution, could you design one, would it work there?

An introduction to SSc pathogenesis: what is happening inside the patient

Figure 1: Overview of biological pathways involved in the pathogenesis of SSc

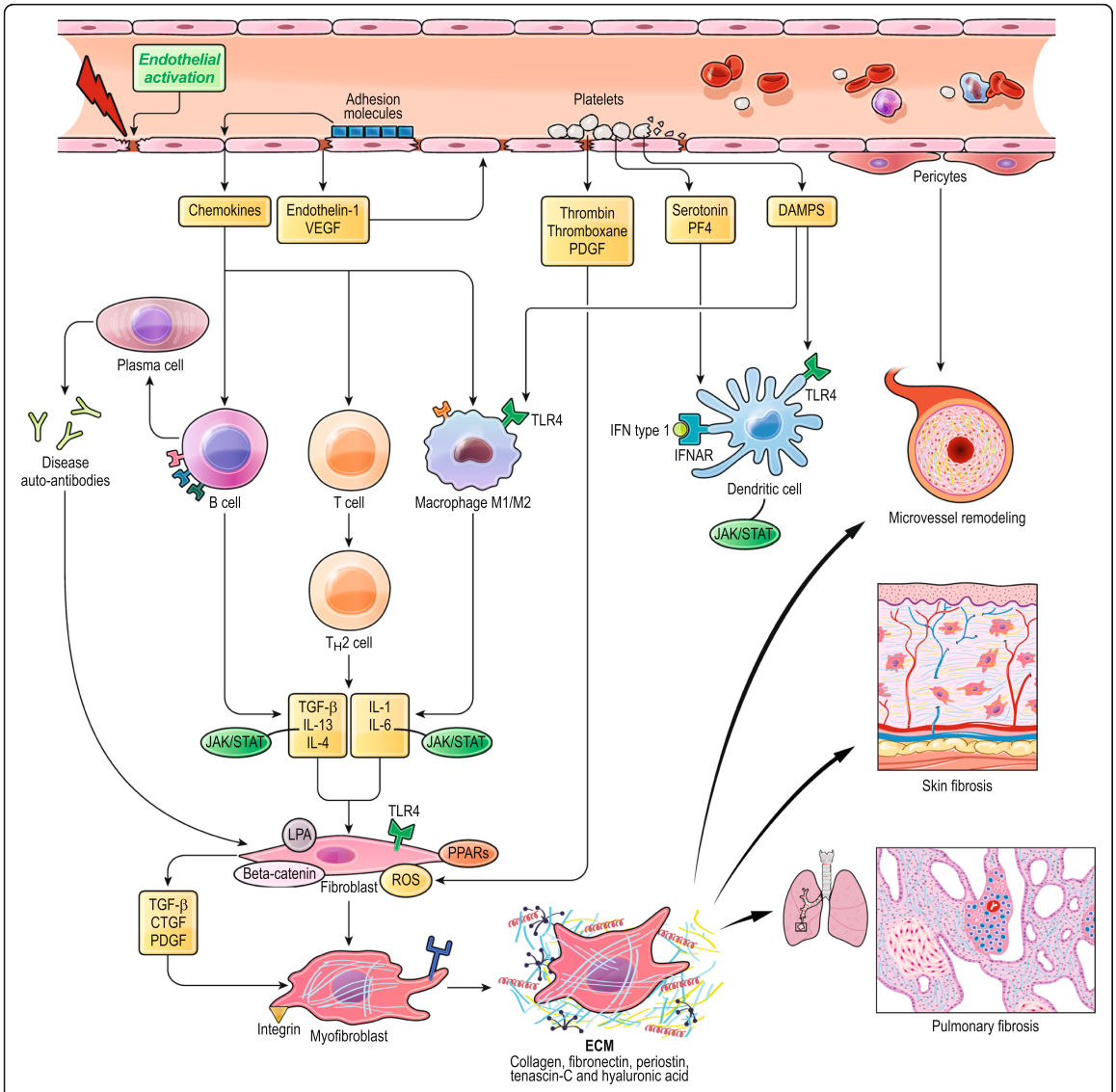


Fig. 1 The pathogenesis of systemic sclerosis. The highly specific mesenchymal cell activation and related fibrosis underlying systemic sclerosis are thought to be induced by vascular injury and endothelial activation leading to an uncontrolled inflammatory/immune reaction. The main actors and players are indicated in the cartoon together with the targets of recently performed clinical trials. VEGF = vascular-endothelial growth factor. PF4 = platelet-factor 4. DAMPS = damage-associated molecular patterns. TLR4 = toll-like receptor 4. IFNAR = interferon receptor. JAK = Janus kinase. PPAR = peroxisome proliferator-activated receptor. LPA = lysophosphatidic acid receptor. ROS = reactive oxygen species. TGF = tissue growth factor. CTGF = connective tissue growth factor. PDGF = platelet-derived growth factor. ECM = extracellular matrix

Figure adapted from Campochiaro C, Allanore Y. An update on targeted therapies in systemic sclerosis based on a systematic review from the last 3 years. Arthritis Res Ther. 2021, ;23(1):155, following the Creative Commons license http://creativecommons.org/licenses/by/4.0/. Adaptations made were removal of drugs in development: the original article can be found at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8168022/

Cutolo M, et al. Pathophysiology of systemic sclerosis: current understanding and new insights. Expert Rev Clin Immunol. 2019 ;15(7):753-764. **Link** https://pubmed.ncbi.nlm.nih.gov/31046487/

Asano Y. The Pathogenesis of Systemic Sclerosis: An Understanding Based on a Common Pathologic Cascade across Multiple Organs and Additional Organ-Specific Pathologies. J Clin Med. 2020;9(9):2687.**link** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7565034/

Rosendahl, A-H, et al. Pathophysiology of systemic sclerosis (scleroderma). *Kaohsiung J Med Sci.* 2022; 38: 187– 195. **Link** https://onlinelibrary.wiley.com/doi/full/10.1002/kjm2.12505

Diagnosis and treatment

Early/Very Early SSc

'Shortening the time needed for a diagnosis is crucial to help patients avoid a "diagnostic odyssey," drifting from one center to another while experiencing the progression of the disease.'

Caminati et a, 2021 (reference below: https://pubmed.ncbi.nlm.nih.gov/34726093/)

- Most known signs and symptoms are absent at earliest stage of SSc.
- GPs are not familiar with the first manifestations of SSc and symptoms
- Risk of patients having permanent functional damage if correct diagnosis not made quickly
- Diagnosis and care are heavily influenced by distance from specialised centres
- First accurate understanding of manifestations occurs more frequently by a rheumatologist, than a GP
- The more disparate the population density, the further patients have to go to specialist centres, or for HCPs to visit them.
- Very Early Diagnosis of Systemic Sclerosis (VEDOSS) criteria used for initial diagnosis

Diagnosis:

- **Experts needed:** GP, nurse, rheumatologist, dermatologist
- **Clinical assessments**: Raynauds phenomenon (painful cold sensitivity, numbness in hands and/or feet), puffy fingers, skin tightening, potential digital ulcers
- **Biochemical**: Antinuclear antibodies (ANA)
- **Imaging**: Nailfold videocapillaroscopy (NVC)

- 95% of SSc patients have Raynauds phenomenon (RP) as first symptom: (RP not exclusive to SSc)
- Median time to SSc diagnosis after onset of RP: 2.8 years
- RP +ANA and/or typical capillaroscopic abnormalities have been linked to a 60-fold higher prevalence of definitive SSc vs. other RP patients
- Early SSC may present with asymptomatic organ involvement: the combination of which organ, skin and level of vascular involvement defines the clinical phenotype and which treatment approach to follow. This requires a close follow-up of the patients to monitor for organ damage.

Bellando-Randone S, et al. Very early systemic sclerosis. Best Pract Res Clin Rheumatol. 2019 Aug;33(4):101428. Link: https://pubmed.ncbi.nlm.nih.gov/31810547/

Lepri G, et al. Early diagnosis of systemic sclerosis, where do we stand today? Expert Rev Clin Immunol. 2022 Jan;18(1):1-3. Link: https://pubmed.ncbi.nlm.nih.gov/35023438/

Blaja E, et al. The Challenge of Very Early Systemic Sclerosis: A Combination of Mild and Early Disease? J Rheumatol. 2021 Jan 1;48(1):82-86. Link https://pubmed.ncbi.nlm.nih.gov/32173655/

Delisle VC, et al. Sex and time to diagnosis in systemic sclerosis: an updated analysis of 1,129 patients from the Canadian scleroderma research group registry. Clin Exp Rheumatol. 2014;32(6 Suppl 86):S-10-4. Link: https://pubmed.ncbi.nlm.nih.gov/24144459/

International consensus criteria for the diagnosis of Raynaud's phenomenon

Maverakis E, et al. International consensus criteria for the diagnosis of Raynaud's phenomenon. J Autoimmun. 2014 Feb-Mar;48-49:60-5. Link https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4018202/

Table 7**:** Treatments used for treating RP and fingertip lesions

Abnormality	Medication	Strength of recommendation
Raynaud's phenomenon	Calcium channel antagonists (dihydropyridine derivatives) such as nifedipine	A
	Phosphodiesterase type 5 inhibitors – sildenafil	A
	Iloprost (i.v. infusions/p.o.)	A
	Alprostadil (i.v. infusions)	A
	Fluoxetine	C
Fingertip lesions	Iloprost (i.v. infusions)	A
	Phosphodiesterase type 5 inhibitors – sildenafil, tadalafil	A
	Endothelin receptor antagonist – bosentan	A

Table adapted from table 2 of: Sobolewski P, et al. Systemic sclerosis - multidisciplinary disease: clinical features and treatment. Reumatologia. 2019;57(4):221-233.following the Creative Commons license http://creativecommons.org/licenses/by/4.0/. Adaptations made were removal of treatments for more severe symptoms: original article can be found at**:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6753596/

SSc-ILD

'Interstitial lung disease (ILD) is the leading cause of mortality in systemic sclerosis…With the exception of autoantibodies, there are no routinely measured biomarkers in SSc-ILD and reliable validation of the many potential biomarkers is lacking.'

> Cole, A., Denton, C.P. Biomarkers in Systemic Sclerosis Associated Interstitial Lung Disease (SSc-ILD). *Curr Treat Options in Rheum* (2022). Link: https://link.springer.com/article/10.1007/s40674-022-00196-3

'On average, it can take a patient with SSc up to 7 months to be referred after onset of ILD symptoms. In a survey evaluating the diagnostic experiences of 600 patients with ILD (of whom approximately one-third had an autoimmune disease), nearly all participants initially consulted a primary-care physician; however, only 28% were referred to a specialist after their first visit.

For 88% of respondents, the final diagnosis was made by a pulmonologist, with 35% reporting diagnosis by physicians from expert ILD centers. '

> Cheema TJ, et al. Patient and Physician Perspectives on Systemic Sclerosis-Associated Interstitial Lung Disease. Clin Med Insights Circ Respir Pulm Med. 2020;14:1179548420913281. Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7081464/

'All patients with systemic sclerosis should be screened for systemic sclerosis-associated ILD using high-resolution CT (HRCT); HRCT is the primary tool for diagnosing ILD in systemic sclerosis; pulmonary function tests support screening and diagnosis; systemic sclerosis-associated ILD severity should be measured with more than one indicator'

> Hoffmann-Vold et al. The identification of interstitial lung disease in systemic sclerosis: evidence based European consensus statements. Lancet Rheumatol. https://www.thelancet.com/pdfs/journals/lanrhe/PIIS2665-9913(19)30144-4.pdf#seccestitle10

Diagnosis/screening:

- **Experts needed:** Pulmonologist, rheumatologist, dermatologist, nurse (in-care and at-home), GP, social workers
- **Biochemical**: Antinuclear antibodies (ANA), complete blood count, hepatic profile, ACE, urinalysis, CPK, sputum assessment
- **Imaging**: HRCT, chest X-ray, CT pulmonary angiogram
- **Pulmonary function tests**: FVC (forced vial capacity), DLCO (diffusion capacity for carbon monoxide)
- **Exercise stress test:** six-minute walk test, but opinion of use of this varies between specialists due to absence of longitudinal studies.
- **Invasive procedures**: Transbronchial biopsy, bronchoalveolar lavage, bronchoscopy
- **Hospitalisation**: required

Cole, A., Denton, C.P. Biomarkers in Systemic Sclerosis Associated Interstitial Lung Disease (SSc-ILD). *Curr Treat Options in Rheum* (2022). **Link**: https://link.springer.com/article/10.1007/s40674-022-00196-3

Distler O, et al. Predictors of progression in systemic sclerosis patients with interstitial lung disease. Eur Respir J. 2020;55(5):1902026. **Link:** https://pubmed.ncbi.nlm.nih.gov/32079645/

DeMizio DJ, Bernstein EJ. Detection and classification of systemic sclerosis-related interstitial lung disease: a review. Curr Opin Rheumatol. 2019;31(6):553-560. **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7250133/

Bonhomme O, et al. Biomarkers in systemic sclerosis-associated interstitial lung disease: review of the literature. Rheumatology (Oxford). 2019;58(9):1534-1546. **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6736409/

Cottin V, Brown KK. Interstitial lung disease associated with systemic sclerosis (SSc-ILD). Respir Res. 2019;20(1):13. **Link:** https://pubmed.ncbi.nlm.nih.gov/30658650/

Table 8: Treatments routinely used for SSc-ILD

Agents for maintenance of Disease	Limited SSc-ILD		Extensive SSc-ILD	
	Number of panellists using the drug, (%)	% of patients using the drug (weighted by the number of patients indicated by the panellist)	Number of panellists using the drug, (%)	% of patients using the drug (weighted by the number of patients indicated by the panellist)
No treatment (watch and see)	16 (40)	26.1	8 (20)	5.5
Mycophenolate Mofetil	20 (50)	35.4	33 (82.5)	64.5
Systemic corticosteroid	14 (35)	10.6	24 (60)	30.5
Cyclophosphamide	10 (25)	9.1	31 (77.5)	27.7
Azathioprine	7 (17.5)	3.4	15 (37.5)	10.3
Hydroxychloroquine	7 (17.5)	4.7	3 (7.5)	2.0
Rituxumab	7 (17.5)	3.8	19 (47.5)	13.1
Methotrexate	4 (10)	5.0	4 (10)	2.8
Toclizumab	0 (0)	0	3 (7.5)	0.4
Tacrolimus	0 (0)	0	1 (2.5)	0.3

Panellists: 32 Pulmonologists, 8 Rheumatologists. 37.5% had between 5–20 years' experience, 25%> 20 years' experience: all worked in public hospitals. All drugs were used either as monotherapy or in combination.

Table adapted from table 3 of: Davidsen JR, et al. Economic Burden and Management of Systemic Sclerosis-Associated Interstitial Lung Disease in 8 European Countries: The BUILDup Delphi Consensus Study. Adv Ther. 2021;38(1):521-540. **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7854393/ following the Creative Commons license https://creativecommons.org/licenses/by/4.0/

Information for diagnosis and treatment obtained from across 8 EU countries *(From an innovator insight perspective the detail the authors present with regard to healthcare usage in tables 1 through 4, are incredibly detailed)*:

Davidsen JR, et al. Economic Burden and Management of Systemic Sclerosis-Associated Interstitial Lung Disease in 8 European Countries: The BUILDup Delphi Consensus Study. Adv Ther. 2021;38(1):521-540. **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7854393/

Systematic review of existing pharmacological treatments (includes recently approved treatments)

Vonk MC, et al. Pharmacological treatments for SSc-ILD: Systematic review and critical appraisal of the evidence. Autoimmun Rev. 2021;20(12):102978. Link: https://pubmed.ncbi.nlm.nih.gov/34718159/

HCP choice of treatment has significant impact on the use of any innovative healthcare product. Fundamentally, the HCP community define the utility of the solution and its prescription: is the patient benefitting, clinically and from a quality-of-life outcome? How much does it cost and is it cost-effective? Are there side effects?

When converting an idea into a health-care product this is something that should always be kept in mind by the innovator.

SSc-PAH

'Given such poor long-term outcomes, it is logical to aim to detect early disease manifestations before the onset of symptoms.

There is a delay of 2–4 years between the onset of symptoms and diagnosis of PAH, underscoring the need to also consider PAH and establish the diagnosis expediently once those symptoms arise.

Unfortunately, the most recent studies from European PAH registries still observe that 72–85% of patients are in Functional Class III or IV symptoms at diagnosis, which is unchanged from the National Institutes of Health registry cohort published over 30 years ago.

Furthermore, most patients still present with severe haemodynamics with right heart dysfunction or right heart failure at the time of PAH diagnosis.

Therefore, earlier detection of PAH during a milder, asymptomatic period could allow early intervention and the opportunity to improve outcomes.'

Source: Weatherald J, et al. Screening for pulmonary arterial hypertension in systemic sclerosis. Eur Respir Rev. 2019 Jul 31;28(153):190023. **Link**: https://pubmed.ncbi.nlm.nih.gov/31366460/

And as indicated in costs section, earlier detection should result in lower healthcare costs

Diagnosis/screening:

- **Experts:** GP, nurse, specialists (pulmonologists, cardiologists, rheumatologists, radiologist, orthopedist, ophthalmologist)
- **Biochemical test:** NT-pro BNP (useful when used in combination with other tests), antibody tests
- **Pulmonary function tests**: FVC (forced vial capacity), DLCO (diffusion capacity for carbon monoxide)
- **Imaging**: chest X-ray, CT angiogram (needs dedicated specialized infrastructure and available radiologists)
- **Exercise stress test:** six-minute walk test, but opinion of use of this varies between specialists due to absence of longitudinal studies.
- **Invasive procedures**: right heart catheterization is conclusive test to detect mean pulmonary arterial pressure elevation
- **Hospitalisation**: required

Approach used in SSc but yet to be integrated into SSc-PAH diagnostic algorithms.

Nailfold videocapillaroscopy (NVC):

'Unequivocal associations were found between (incident) SSc-PAH and capillary density and NVC pattern'.

Smith V, et al. Nailfold Videocapillaroscopy in Systemic Sclerosis-related Pulmonary Arterial Hypertension: A Systematic Literature Review. J Rheumatol. 2020 1;47(6):888-895. **Link:** https://pubmed.ncbi.nlm.nih.gov/31416927/

Screening:

Algorithms including combinations of diagnostic/screening tests have been developed, but utility and cost effectiveness not demonstrated in remote or resource stretched settings.

'As described in the 2015 ESC/ERS guidelines, a screening method should use tools that are noninvasive, reproducible, cost-effective and associated with a high NPV for the condition. In our opinion, an additional criterion for a good screening tool is the fast availability of the test result,

Echocardiography, safe, noninvasive and with immediate availability of the test result, may remain a major, first-step screening tool for PAH in unselected SSc patients. Other screening tools used by the DETECT algorithm are useful, particularly to detect borderline PAP. '

Vandecasteele E, et al. Screening for pulmonary arterial hypertension in an unselected prospective systemic sclerosis cohort. Eur Respir J. 2017 11;49(5):1602275. **Link** https://pubmed.ncbi.nlm.nih.gov/28495691/

Giucă A, et al. Screening for Pulmonary Hypertension in Systemic Sclerosis-A Primer for Cardio-Rheumatology Clinics. Diagnostics (Basel). 2021 Jun 1;11(6):1013. **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8229459/

Humbert M, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2022;43(38):3618-3731. Link: https://pubmed.ncbi.nlm.nih.gov/36017548/

SSc-PAH Treatments:

Table 9: Drugs used to treat SSc-PAH, their unit consumption, annual cost (incl. administration) and use by FC

Drug	Admins. route	Posology	Unit consumption	Total cost excl. adm. (patient/ year)	Admin.cost (patient/ year)	Total cost (patient/ year)	Distribution of drug's use			
							FC I-II (%)	FC III (%)	FC IV (%)	Total (%)
Sildenafil	O	20 mg, 3×/ day	60 mg/day	€3,732.86	€0	€3,732.86	9.6	8.2	11.1	9.1
Tadalafil	O	40 mg, 1×/ day	40 mg/day	€4,229.83	€0	€4,229.83	29.4	30.0	22.2	29.6
Riociguat	O	1–2,5 mg, 3×/ day	3 tablets/day	€32,797.44	€0	€32,797.44	0.0	2.7	0.0	1.2
Bosentan	O	125 mg, 2×/ day	250 mg/day	€1,626.86	€0	€1,626.86	14.7	6.4	0.0	10.7
Ambrisentan	O	5-10 mg, 1×/ day	1 tablet/day	€10,451.65	€0	€10,451.65	15.4	9.1	11.1	12.6
Macitentan	O	10 mg, 1×/ day	10 mg/day	€29,760.64	€0	€29,760.64	21.3	26.4	22.2	23.7
Selexipag (prevalents)	O	200–1,600 mcg, 2×/day	2 tablets/day	€45,225.54	€0 €	€45,225.54	2.9	8.2	0.0	5.1
Selexipag (incidents)			2,6 tablets/day	€59,102.97		€59,102.97				
Iloprost	Inh	5 mcg, 6–9×/ day	37,5 mcg/day	€18,920.38	€65.00	€18,985.38	2.2	0.9	0.0	1.6
Treprostinil	IV	(1,5 vials 5 mg/ml) 1×/ month	7,5 mg/ml/ month	€91,698.05	€195.00	€91,893.05	2.2	0.9	0.0	1.2
Epoprostenol	IV	0,5 mg (9 vials 0,5 mg) 1×/48 h	4,5 mg/48 h	€103,465.67	€4,403.54	€107,869.21	2.2	7.3	33.3	5.1

(1) * EUR per mg. or EUR per tablet. (2) For selexipag, maintenance doses were assumed for prevalent patients. For incident patients, a titration period of 8 weeks was assumed, until reaching the maximum dose of 1,600 µg, 2 times a day. (3) Laboratory sale prices were considered, with official deductions and VAT. (4) O: oral. IV: intravenous route. Inh.: inhalation route. ×/day: times per day

Table adapted from table 2 of: Zozaya N, Abdalla F, Casado Moreno I, Crespo-Diz C, Ramírez Gallardo AM, Rueda Soriano J, Alcalá Galán M, Hidalgo-Vega Á. The economic burden of pulmonary arterial hypertension in Spain. BMC Pulm Med. 2022 Mar 26;22(1):105. following the Creative Commons license http://creativecommons.org/licenses/by/4.0/. Adaptations made were removal of pack cost, pack presentation, unit cost: original article can be found at https://pubmed.ncbi.nlm.nih.gov/35346140/

Treatments and pricing indicated above may not be applicable in all geographies, or be on the approved reimbursement list of healthcare payors. Innovators are encouraged to search for regulatory and reimbursement approvals through national health body and insurance company databases.

Almaaitah S, et al. Management of Pulmonary Arterial Hypertension in Patients with Systemic Sclerosis. Integr Blood Press Control. 2020 Mar 23;13:15-29. **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7125406/

Argula RG, et al. Therapeutic Challenges And Advances In The Management Of Systemic Sclerosis-Related Pulmonary Arterial Hypertension (SSc-PAH). Ther Clin Risk Manag. 2019 Dec 13;15:1427-1442. **Link:** https://pubmed.ncbi.nlm.nih.gov/31853179/

Non-pharmacological requirements in SSc

Nutritional needs

Recasens MA, et al. Nutrition in systemic sclerosis. Reumatol Clin. 2012;8(3):135-40. **Link:** https://pubmed.ncbi.nlm.nih.gov/22197834/

Burlui AM, et al. Diet in Scleroderma: Is There a Need for Intervention? Diagnostics (Basel). 2021;11(11):2118. **Link**: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8620611/

Kaminski L et al, eating well with scleroderma. Scleroderma foundation, January 2019. Accessed from: https://national.scleroderma.org/site/DocServer/NUTRITION_FINAL.pdf?docID=1462

Dental/oral needs

Zhang S, Zhu J, Zhu Y, Zhang X, Wu R, Li S, Su Y. Oral manifestations of patients with systemic sclerosis: a meta-analysis for case-controlled studies. BMC Oral Health. 2021 May 10;21(1):250. **Link**: https://pubmed.ncbi.nlm.nih.gov/33971854/

Smirani R, Truchetet ME, Poursac N, Naveau A, Schaeverbeke T, Devillard R. Impact of systemic sclerosis oral manifestations on patients' health-related quality of life: A systematic review. J Oral Pathol Med. 2018 Oct;47(9):808-815. **Link:** https://pubmed.ncbi.nlm.nih.gov/29855076/

Suggested reading for aligning innovation design with current approaches, HCP identified unmet needs and patient need across the spectrum of Systemic Sclerosis

Bruni C, et al. Patient preferences for the treatment of systemic sclerosis-associated interstitial lung disease: a discrete choice experiment. Rheumatology (Oxford). 2022 Oct 6;61(10):4035-4046. **Link:** https://pubmed.ncbi.nlm.nih.gov/35238334/

CDER/FDA: the voice of the patient: Systemic Sclerosis. Report data: June 30, 2021. **Link:** https://www.fda.gov/media/150454/download

Caminati A, et al. Expert opinion and patients' in-depth interviews on the impact of pulmonary complications in systemic sclerosis. Curr Med Res Opin. 2021 Nov;37(sup2):17-26. **Link:** https://pubmed.ncbi.nlm.nih.gov/34726093/

Fischer A, et al. Humanistic and cost burden of systemic sclerosis: A review of the literature. Autoimmun Rev. 2017 Nov;16(11):1147-1154. **Link**: https://pubmed.ncbi.nlm.nih.gov/28899803/

Galetti I, et al. How do systemic sclerosis manifestations influence patients' lives? Results from a survey on patients and caregivers. Curr Med Res Opin. 2021 Nov;37(sup2):5-15. **Link:** https://pubmed.ncbi.nlm.nih.gov/34726112/

Cossu M, et al. Unmet Needs in Systemic Sclerosis Understanding and Treatment: the Knowledge Gaps from a Scientist's, Clinician's, and Patient's Perspective. Clin Rev Allergy Immunol. 2018 Dec;55(3):312-331. **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6244948/

El Aoufy K et al. Patient preferences for systemic sclerosis treatment: A descriptive study within an Italian cohort. J Scleroderma Relat Disord. 2021 Jun;6(2):165-169. Link: https://pubmed.ncbi.nlm.nih.gov/35386742/

McMahan ZH, Volkmann ER. An update on the pharmacotherapeutic options and treatment strategies for systemic sclerosis. Expert Opin Pharmacother. 2020 ;21(16):2041-2056. Link: https://pubmed.ncbi.nlm.nih.gov/32674612/

Saketkoo LA, et al. A comprehensive framework for navigating patient care in systemic sclerosis: A global response to the need for improving the practice of diagnostic and preventive strategies in SSc. Best Pract Res Clin Rheumatol. 2021 Sep;35(3):101707. **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8670736/

Hoffmann-Vold AM, et al. Identifying unmet needs in SSc-ILD by semi-qualitative in-depth interviews. Rheumatology (Oxford). 2021;60(12):5601-5609. **Link:** https://pubmed.ncbi.nlm.nih.gov/33587103/

Molecular diagnostics

Development of precisely a new diagnostic, especially if it is based on molecular signals for a rare disease needs to be carefully considered. The overriding point is that the final product used to measure the molecular signal must:

- Integrate into the existing care pathway and make diagnosis more accurate
- Be easy to use within the actual infrastructure, with little or no specialisation required
- It must also have sufficient patient specific statistical evidence to prove sensitivity and specificity.

Statistics/Biostatistics measurements:

You need to to identify the solutions diagnostic yield: basically, does the diagnostic provide the info needed.

1) Sensitivity and specificity: you must be able to differentiate patients. This is typically done comparing the existing gold standard with your innovation (high false signals stop development)

	Subjects with the disease	Subjects without the disease
Positive	True positive	False positive
Negative	False negative	True negative

2) Predictive values: measuring probability of having the disease in a defined population.
3) Accuracy measurements: this data is essential and ideally should be stratified for the relevant populations

- Likelihood ratio: best used for clearly identifying if a disease is actually present, so fundamentally diagnostic accuracy
- Receiver Operating Characteristic: every patient tested has a range of potential diagnostic scores, withcut off values, which are then plotted on a specificity vs sensitivitycurve, to see how the tests differentiates patients.
- Diagnostic odds ratio and Youden's index: two different methods that compare two or more diagnostic tests

Data management is also a critical consideration: Numerous diagnostic products have been sent back to drawing board by regulatory authorities following due diligence of data management processes and methods that have not adhered to all the standards used for quality control (these are different standards to those for medicines).

For rare diseases the low patient number and therefore statistical relevance with regard to sensitivity and specificity becomes a significant bottleneck. Companion diagnostics are not advisable due to therapeutic response heterogeneity, that can make a molecular signal seem irrelevant.

A potential starting point for innovators is to approach molecular signals in rare diseases as possible 'patient management/monitoring' tools.

If the patient has this molecular signal, could this be used as a more routine and regular approach to address the number of at-risk patients within a broad population that should then be transitioned into the approved diagnostic pathway.

Noviani M, et al. Toward Molecular Stratification and Precision Medicine in Systemic Sclerosis. Front Med (Lausanne). 2022;9:911977. **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9279904/

Mehta BK, et al. Molecular "omic" signatures in systemic sclerosis. Eur J Rheumatol. 2020;7(Suppl 3):S173-S180. **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7647683/

Zhang T, et al. Salivary anti-nuclear antibody (ANA) mirrors serum ANA in systemic lupus erythematosus. Arthritis Res Ther. 2022;24(1):3. Link: https://pubmed.ncbi.nlm.nih.gov/34980255/

Integrating new insights with existing Point-of-Care solutions

The implication, reviewing existing solutions, future plans and unmet needs, therefore becomes reflections on potential integrations of: Existing Point-of-care solutions (med devices mainly – spirometry, handheld echocardiography, hand held NVC), molecular signals (preferably totally non-invasive: a blood draw needs specialised personnel and resources) and Digital healthcare solutions

That could enable the HCP to rapidly identify a possible incident patient to transition them into the approved pathway. These same solutions may also provide global wide data on epidemiology, disease influencing factors and changes to care processes as a function of available HCPs and infrastructure.

Seetharam K, et al. Application of mobile health, telemedicine and artificial intelligence to echocardiography. Echo Res Pract. 2019;6(2):R41-R52. **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6432977/

Berks M, et al. Comparison between low cost USB nailfold capillaroscopy and videocapillaroscopy: a pilot study. Rheumatology (Oxford). 2021;60(8):3862-3867. Link: https://pubmed.ncbi.nlm.nih.gov/33232464/

Chanprapaph K, et al. Nailfold Capillaroscopy With USB Digital Microscopy in Connective Tissue Diseases: A Comparative Study of 245 Patients and Healthy Controls. Front Med (Lausanne). 2021;8:683900. **Link:** https://pubmed.ncbi.nlm.nih.gov/34422857/

Digital health solutions: linking diagnosis with patient monitoring and management

1. Gender and digital health: SSc has a significant gender dimension - 4:1 ratio of female to male patients.

Female healthcare and diagnosis disparity is documented:

Balla et al, Disparities in cardiovascular health and outcomes for women from racial/ethnic minority backgrounds. Curr Treat Options Cardiovasc. Med. 2020; 22(12):75). **Link**: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7669491/

Digital health developers should therefore also verse themselves with the GMSA publication on the **gender gap in mobile usage** with regard to study designs for evidence generation and validation for the indication.

https://www.gsma.com/mobilefordevelopment/blog/the-mobile-gender-gap-report-2022/

2. Guidelines for development

Both professional associations and regulatory bodies have generated evidence frameworks that they consider essential for development of such solutions, that the innovator needs to be profoundly aware of. The European Alliance of Associations for Rheumatology (EULAR) published its opinion of digital health solution development for aiding patients self-manage rheumatic diseases.

Table 1 of Najm A, et al. EULAR points to consider for the development, evaluation and implementation of mobile health applications aiding self-management in people living with rheumatic and musculoskeletal diseases. RMD Open. 2019 Sep 13;5(2):e001014.**Link:** https://pubmed.ncbi.nlm.nih.gov/31565245/

Professional Association requirements should be used in conjunction with **national based evidence requirements for digital health solutions**, of which the following are only some examples.

-Australian Therapeutic Goods Administration: https://www.tga.gov.au/sites/default/files/how-tga-regulates-software-based-medical-devices.pdf
-FDA software as a medical device: https://www.fda.gov/media/100714/download
-UK NICE: digital health evidence standards framework: https://www.nice.org.uk/corporate/ecd7

3. Telehealth: brought into focus during recent pandemic

Similar to many indications, the pandemic brought the concept of telemedicine: care at distance into focus. Widely used for some time now within the healthcare field, its use for reducing patient and caregiver burden and the unnecessary burden of time, costs and absenteeism has also been reported for SSc, especially if combined and extended with home spirometry solutions.

Saketkoo LA, et al. A comprehensive framework for navigating patient care in systemic sclerosis: A global response to the need for improving the practice of diagnostic and preventive strategies in SSc. Best Pract Res Clin Rheumatol. 2021;35(3):101707. (Future of SSc care section). **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8670736/

Cuomo G, et al. AB1412 Importance of telemedicine in systemic sclerosis during the COVID-19 pandemic. *Annals of the Rheumatic Diseases* 2022;81:1811-1812. **Link:** https://ard.bmj.com/content/81/Suppl_1/1811.2

4. SSc focused or designed Patient monitoring solutions

i.VersusArthritis sponsored development of app for finger ulcers in SSc: Versusarthritis is supporting Prof. A. Herrick to develop an app to better assess healing of finger ulcers in SSc

https://www.versusarthritis.org/research/our-current-research/our-current-research-projects/scleroderma-developing-a-smartphone-app/

ii.Project Scleroderma Patient support app (launched in conjunction with FESCA): The app allows patients to track and chart symptoms on a daily basis and keep a running diary of notes to share with their physicians. It offers a space to interact privately and securely with other scleroderma patients, and will serve as a hub for patient resources and educational videos.

https://fesca-scleroderma.eu/scleroderma-app-now-available-for-download/

iii.Scleroderma and Raynauds UK: STAR ResearchApp: Symptom Tracking App for Raynaud's, ResearchApp

https://www.sruk.co.uk/research/symptom-tracking-app-raynauds-star-researchapp/

iv.Self-manage Scleroderma: taking chart of Systemic Sclerosis – an internet self-management program
This web based self-management program was designed to help you learn about scleroderma, manage your symptoms and learn strategies to help you advocate for yourself.

https://www.selfmanagescleroderma.com/index.html

5. Chronic illness and mental health management
Similarly, many generic chronic illness, nutritional management, quality of sleep and mental health management apps have been developed. However, their direct relevance to SSc is unclear.

Global healthcare infrastructure availability (personnel and beds)

Personnel (numbers per 10,000 population)

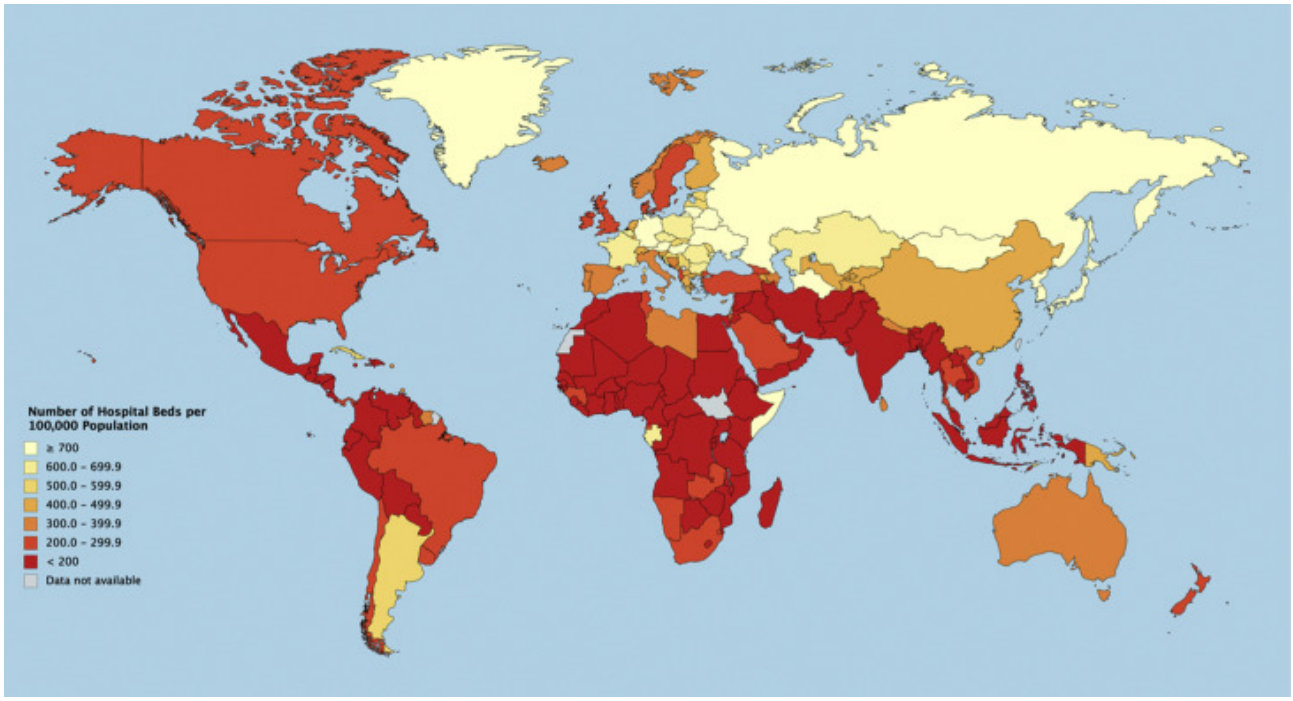
WHO region	Medical doctors	Nursing/midwifery	Dentistry	Pharmacists
Africa	2.62	12.89	0.33	0.8
Americas	24.5	81.63	5.84	5.08
South-East Asia	7.66	20.41	1.49	6.55
Europe	36.61	83.41	6.2	6.47
Eastern Mediterranean	11.17	16.49	2.65	3.3
Western Pacific	20.98	39.91	4.55	4.42

Source: WHO Global Health Workforce Statistics
Medical and Pathology lab staff, physiotherapy personnel and community health worker total number statistics available by country level only.
See: https://www.who.int/data/gho/data/themes/topics/health-workforce

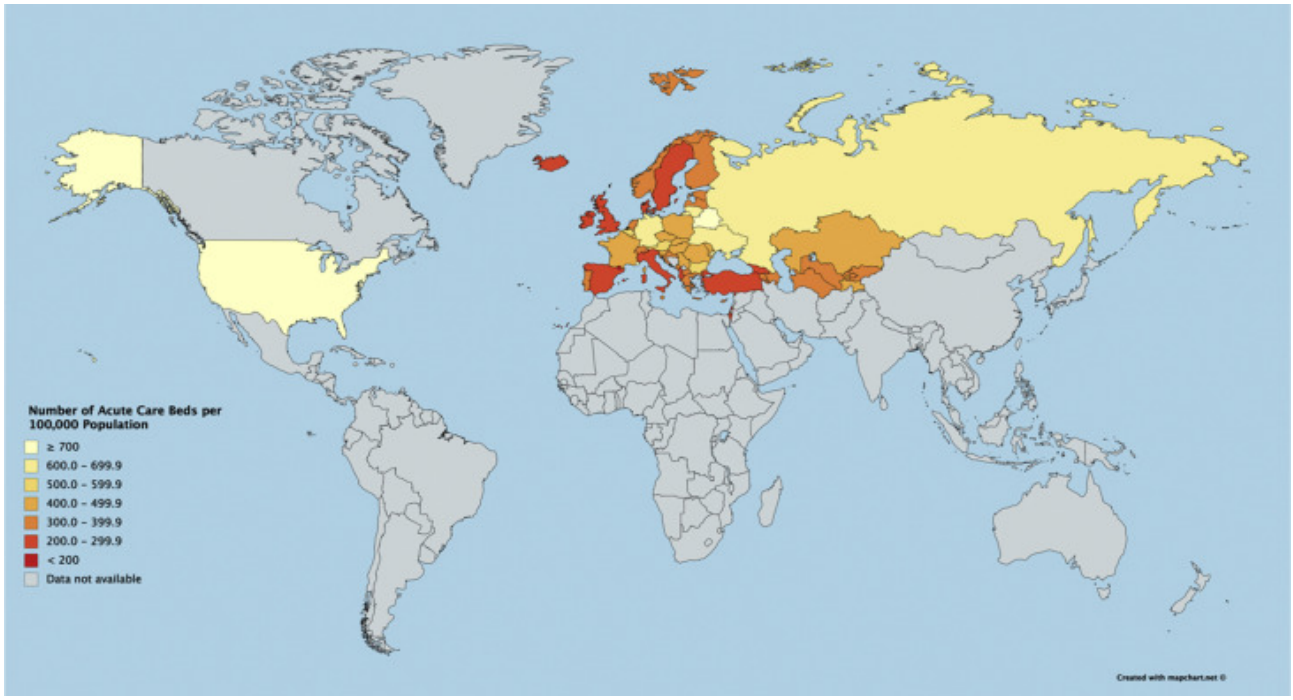
Available beds

Source of following charts: Sen-Crowe B, et al. A Closer Look Into Global Hospital Beds Capacity and Resource Shortages During the COVID-19 Pandemic. J Surg Res. 2021;260:56-63. **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7685049/ (Reproduced following the copyright and license information published on Elsevier connect)

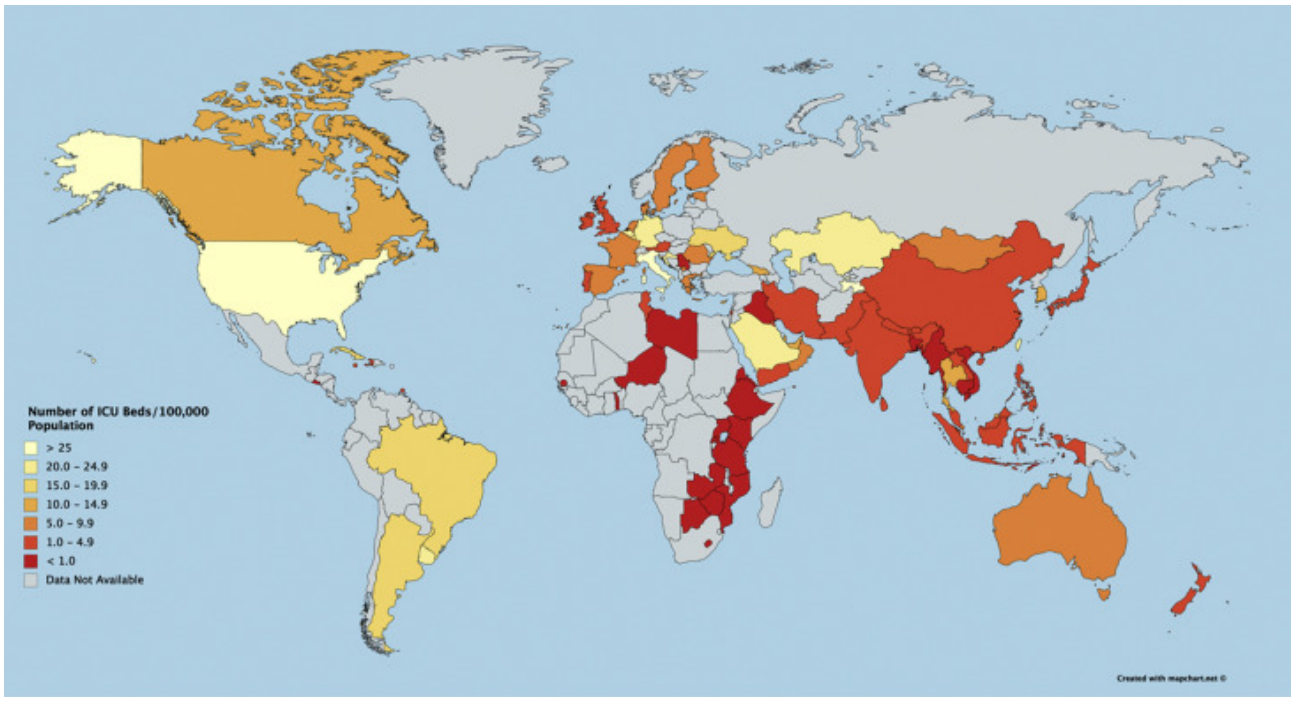
1) Number of hospital beds per 100,000 population



2) Number of acute care beds per 100,000 population



3) Number of ICU beds per 100,000 population



Some final considerations for the innovator:

Join the dots: before designing, consider the whole ecosystem and the actors in it. Look at solutions that have been designed and rolled out, but maybe not expanded. If innovations are combined, and those opportunities definitely exist for SSc based on the work that has been done already by all the stakeholders; don't forget it still needs validation in a clinical setting.

PICO: Patient population, Intervention(product), Comparator, Outcome, should be applied to every type of product. The broader the impact the product, the more data and sensitivity you will need, especially if it's anything non-interventional that potentially results in a medical intervention. Rare disease patient populations are heterogeneous: their low number means precise pathogenesis is often incomplete, and as indicated above pathogenesis greatly impacts the type of innovation and its design.

Factor that in: you may consider your innovation to be applicable to a whole Rare Disease patient population, but often solutions are applicable to specific symptoms, age groups, phases or stages and underlying morbidities, or other SDOH related risks that the patient may be exposed to, some of which may be responsible for idiopathic occurrence.

There is always a comparator, even in Rare Diseases, where interventions do not currently exist. In addition to direct clinical impacts, is your planned product reducing caregiver related burdens and costs, does it reduce burden on HCPs and/or processes, or will it increase the needs for more specialists and dedicated facilities, is your solution equitable, are you addressing the needs of one stakeholder, many or all of them?

Health Economic and Outcomes Research (HEOR): the aspect a lot of Innovators think about too late, it is not the same as clinical outcome, take a short online course on it or HTA to introduce it to yourself. While review and approval bodies are not always national or centralized, the economic evidence assessments they use tend to be based on the same concepts and then adjusted locally. Note that perspectives and calculations of value differ between locations (QALYs vs DALYs, differing PROMs, accepted outcomes).

The ISPOR US Healthcare System Overview-Decision makers and influencers gives a good illustration of what is needed from the pharmacoeconomic angle: https://www.ispor.org/heor-resources/more-heor-resources/us-healthcare-system-overview

While global country information, where available, can be found at their around the world section https://www.ispor.org/heor-resources/more-heor-resources/pharmacoeconomic-guidelines

Note that most of these only apply to therapeutic application, med tech, diagnostics, healthcare process, and now digital health, have differing requirements and are often not nationally homogenous.

Social determinants of health and wealthy countries vs. LMIC

Many available existing sources of information do not include every stakeholder or perspective, and some innovators may not know where to look, to complete the picture. Especially when evidence is generated in different geographies with different healthcare infrastructures e.g., Universal healthcare vs private or hybrid, timing and location of evidence generation and influence of Social Determinants of Health (SDOH) on the patient, their journey, quality of life, available care or infrastructure and epidemiological data.

This is relevant for all countries irrespective of overall recognised income status. With this perspective, it may make the identification and development of innovative solutions for Rare Diseases global by design: solutions designed for wealthy countries (even if incidence and prevalence maybe influenced by socioeconomic status, ethnicity and gender within them), where available specialised Rare Disease healthcare is sparse, and SDOH and lifestyle risks can symptoms, may with partnering and redesign be applicable for patients with Rare Diseases in Low- and Middle-Income Countries, where resources are even more stretched, and *vice versa*.

Appendix 1: What's been recently developed and reviewed or being clinically tested:

Targeted therapies review

An update on targeted therapies in systemic sclerosis based on a systematic review from the last 3 years

Campochiaro C, Allanore Y. Arthritis Res Ther. 2021;23(1):155.
Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8168022/

In clinical trials at time of writing (October 2022)

Search location: clinicaltrials.gov
Condition or disease: systemic sclerosis

Filters:

- **Recruiting** (not yet recruiting, recruiting, enrolling by invitation, active not recruiting)
- **Age and sex**: all
- **Study type**: all
- **Study phases**: early phase 1, phase 1, phase 2, phase 3, phase 4, not applicable (includes devices and behavioural interventions)

NCT Number	Status	Phases	Interventions	Enrollment
NCT04380831	Recruiting	Early Phase 1	Procedure: Allogeneic Hematopoietic Stem Cell Transplantation|Drug: Cyclophosphamide|Radiation: Intensity-Modulated Radiation Therapy|Procedure: Total-Body Irradiation	15
NCT05085444	Recruiting	Early Phase 1	Biological: Assigned Interventions CD19/BCMA CAR T-cells	9
NCT04368403	Active, not recruiting	Phase 1	Drug: KHK4827	8
NCT05298358	Not yet recruiting	Phase 1	Biological: RIC alloBMT w PTCy in refractory SSc	30
NCT04948554	Not yet recruiting	Phase 1	Biological: MK-2225|Biological: Placebo	48
NCT05016804	Recruiting	Phase 1	Biological: AlloRx	20
NCT05462522	Recruiting	Phase 1	Drug: RO7303509|Drug: Placebo	100
NCT04478994	Recruiting	Phase 1	Biological: TEPEZZA|Other: Placebo	25
NCT03816345	Recruiting	Phase 1	Biological: Nivolumab	312

NCT05098145	Recruiting	Phase 1|Phase 2	Biological: FCR001	18
NCT03211793	Recruiting	Phase 1|Phase 2	Drug: Mesenchymal stromal cells|Other: Placebo	20
NCT03222492	Recruiting	Phase 1|Phase 2	Biological: Brentuximab Vedotin|Biological: Placebo	24
NCT04356287	Not yet recruiting	Phase 1|Phase 2	Biological: UCMSC|Other: Placebo	18
NCT05214014	Enrolling by invitation	Phase 1|Phase 2	Biological: Autologous Regulatory –¢-cells|Other: Standard treatment according to the clinical protocols	30
NCT04680975	Active, not recruiting	Phase 2	Drug: Belumosudil	10
NCT04683029	Active, not recruiting	Phase 2	Drug: Guselkumab Dose 1|Drug: Guselkumab Dose 2|Drug: Placebo	56
NCT03919799	Active, not recruiting	Phase 2	Drug: Belumosudil (KD025)|Drug: Placebo	60
NCT01413100	Active, not recruiting	Phase 2	Biological: Anti-Thymocyte Globulin|Procedure: Autologous Hematopoietic Stem Cell Transplantation|Drug: Cyclophosphamide|Biological: Filgrastim|Other: Laboratory Biomarker Analysis|Drug: Mycophenolate Mofetil|Procedure: Peripheral Blood Stem Cell Transplantation|Drug: Plerixafor|Other: Quality-of-Life Assessment|Other: Questionnaire Administration	21
NCT01895244	Active, not recruiting	Phase 2	Drug: Autologous stemcell transplantation with CD (cluster of differentiation) 34 selected stem cells	44
NCT04647890	Active, not recruiting	Phase 2	Drug: FT011|Drug: Placebo	30
NCT03221257	Active, not recruiting	Phase 2	Drug: Pirfenidone (PFD)|Drug: Placebo (Plac)|Drug: Mycophenolate Mofetil (MMF)	51
NCT04118699	Active, not recruiting	Phase 2	Drug: Rifaximin oral tablet|Drug: Placebo oral tablet	12
NCT03616184	Active, not recruiting	Phase 2	Drug: Ruxolitinib	49
NCT04789850	Not yet recruiting	Phase 2	Drug: Itacitinib|Drug: Placebo	74
NCT04986605	Not yet recruiting	Phase 2	Device: Extracorporeal Photopheresis (ECP)|Drug: UVADEX	15
NCT05559580	Not yet recruiting	Phase 2	Drug: BI 685509|Drug: Placebo	200
NCT05149768	Not yet recruiting	Phase 2	Drug: Brentuximab vedotin	10
NCT05339087	Not yet recruiting	Phase 2	Drug: Riociguat Oral Tablet|Other: Placebo	70
NCT03844061	Recruiting	Phase 2	Drug: Belimumab|Drug: Rituximab|Other: Placebo Subcutaneous Injection|Other: Placebo Infusion|Drug: MMF	30
NCT04927390	Recruiting	Phase 2	Drug: Mycophenolate Mofetil 500mg	120
NCT05214794	Recruiting	Phase 2	Drug: nemolizumab	8
NCT04166552	Recruiting	Phase 2	Drug: Patients will be randomized to receive EHP-101 or Placebo	36
NCT03198689	Recruiting	Phase 2	Drug: Brentuximab Vedotin	11
NCT04440592	Recruiting	Phase 2	Drug: MT-7117|Drug: Placebo	72

NCT04781543	Recruiting	Phase 2	Drug: HZN-825 BID|Drug: Placebo|Drug: HZN-825 QD	300
NCT04356755	Recruiting	Phase 2	Procedure: Adipose tissue harvest|Drug: Autologous ASC|Drug: Placebo	32
NCT05270668	Recruiting	Phase 2	Drug: PRA023 IV|Device: Companion diagnostic (CDx)|Drug: Placebo	100
NCT04200755	Recruiting	Phase 2	Drug: Dupilumab 300Mg Solution for Injection|Other: Placebo	45
NCT03630211	Recruiting	Phase 2	Drug: Cyclophosphamide|Drug: Mesna|Drug: Rituximab|Drug: Alemtuzumab|Drug: Thiotepa|Drug: GM-CSF|Drug: Intravenous immunoglobulin|Radiation: Total Body Irradiation|Drug: Anti Thymocyte Globulin	8
NCT04797286	Recruiting	Phase 2	Drug: Sildenafil|Other: Placebo	30
NCT02682511	Recruiting	Phase 2	Drug: Oral Ifetroban|Drug: Oral Placebo	34
NCT04837131	Recruiting	Phase 2	Drug: Ixazomib	12
NCT05029336	Recruiting	Phase 2	Biological: Depletion of CD3/CD19 in an autologous stem cell transplant	20
NCT03582800	Recruiting	Phase 2	Drug: STS	40
NCT05000216	Recruiting	Phase 2	Biological: Moderna mRNA-1273|Biological: BNT162b2|Biological: Ad26.COV2.S|Drug: IS (MMF or MPA)|Drug: IS (MTX)|Biological: IS (B cell depletion therapy)	2340
NCT05098704	Recruiting	Phase 2|Phase 3	Drug: clopidogrel treatment|Drug: Placebo	90
NCT05236491	Recruiting	Phase 2|Phase 3	Biological: COVID-19 vaccine	287
NCT03957681	Active, not recruiting	Phase 3	Drug: KHK4827|Drug: Placebo	100
NCT03313180	Active, not recruiting	Phase 3	Drug: Nintedanib	444
NCT05148598	Not yet recruiting	Phase 3	Device: ADRCs|Other: Standard Care|Other: Placebo	174
NCT05416697	Not yet recruiting	Phase 3	Drug: CBD oil|Drug: Placebo	40
NCT05198557	Recruiting	Phase 3	Drug: Inebilizumab|Drug: Placebo	80
NCT04464434	Recruiting	Phase 3	Procedure: Upfront autologous HSCT	120
NCT05300932	Recruiting	Phase 4	Drug: Baricitinib|Drug: Cyclophosphamide	60
NCT05505409	Recruiting	Phase 4	Drug: Pirfenidone|Drug: glucocorticoid and immunosuppressant	120
NCT04928586	Recruiting	Phase 4	Drug: Pirfenidone|Drug: DMARDs	200
NCT04491396	Active, not recruiting	Not Applicable	Behavioral: Gentle Yoga and Yogic Breathing	30
NCT04908943	Recruiting	Not Applicable	Behavioral: RENEW	168
NCT04246528	Recruiting	Not Applicable	Behavioral: SPIN-SELF Program	524

NCT04212247	Recruiting	Not Applicable	Behavioral: Well-Being Therapy|Behavioral: Control condition	60
NCT01776398	Recruiting	Not Applicable	biobank	2000
NCT03473912	Recruiting	Not Applicable	Biobank	500
NCT01931644	Recruiting	Not Applicable	Biobank, mobile health, patient registry	20000
NCT04244916	Recruiting	Not Applicable	Biological: AUC of MPA measure	50
NCT03575156	Active, not recruiting	Not Applicable	Biological: blood sample|Biological: urine sample	208
NCT04265144	Recruiting	Not Applicable	Biological: Blood samples|Other: Biopsy|Other: Bronchoalveolar samples	500
NCT05251415	Recruiting	Not Applicable	Biological: Blood sampling	3000
NCT04746313	Recruiting	Not Applicable	Biological: blood test	200
NCT03800017	Not yet recruiting	Not Applicable	Biological: Hyperoxia	40
NCT01884051	Recruiting	Not Applicable	biomarker	1899
NCT03268330	Recruiting	Not Applicable	Biomarker	40
NCT02422875	Enrolling by invitation	Not Applicable	Biomarkers	1050
NCT02062125	Active, not recruiting	Not Applicable	Calcinosis risk factors	300
NCT02450396	Recruiting	Not Applicable	CTD in pregnant women	5000
NCT04223817	Not yet recruiting	Not Applicable	Device: 7.0 T RMI	50
NCT04854850	Active, not recruiting	Not Applicable	Device: Apollo	27
NCT04971018	Recruiting	Not Applicable	Device: Auricular vagus nerve stimulation|Device: Sham Auricular vagus nerve stimulation	20
NCT05181644	Recruiting	Not Applicable	Device: EmoLED treatment|Procedure: current Standard of Care	72
NCT04567537	Recruiting	Not Applicable	Device: Laser Treatment	20
NCT04627857	Recruiting	Not Applicable	Device: Manual toothbrush|Device: Manual toothbrush and water flosser (Philips Sonicare AirFloss)|Device: Sonic toothbrush|Device: Sonic toothbrush (Philips Sonicare) and water flosser (Philips Sonicare AirFloss)	100
NCT04922736	Enrolling by invitation	Not Applicable	Device: UVA-1 Phototherapy	30
NCT04875078	Recruiting	Not Applicable	Device: UVA-1 Phototherapy	30
NCT04650659	Active, not recruiting	Not Applicable	Diagnostic Test: 6-minute walk test part one|Diagnostic Test: 6-minute walk test part two|Diagnostic Test: 1-minute sit-to-stand test|Diagnostic Test: 4-meters gait speed test|Diagnostic Test: Nailfold videocapillaroscopy|Diagnostic Test: HR-pQCT|Diagnostic Test: Hand x-ray|Diagnostic Test: DEXA	83
NCT03438032	Recruiting	Not Applicable	Diagnostic Test: Bronchoscopy with lavage	20
NCT05482594	Recruiting	Not Applicable	Diagnostic Test: ELISA|Diagnostic Test: Videocapillaroscopy	65
NCT05205239	Recruiting	Not Applicable	Diagnostic Test: Endoluminal image analysis by capsule endoscopy	20

NCT04535245	Recruiting	Not Applicable	Diagnostic Test: LCI testing	50
NCT05204355	Recruiting	Not Applicable	Diagnostic Test: MRI|Drug: Hyperpolarized Xe129|Diagnostic Test: HRCT	42
NCT05365009	Recruiting	Not Applicable	Diagnostic Test: Multidisciplinary aproach	1000
NCT04532151	Active, not recruiting	Not Applicable	Diagnostic Test: Non-invasive skin imaging assessment	60
NCT05215431	Recruiting	Not Applicable	Diagnostic Test: periodontal examination's and determination of salivary antioxidants	20
NCT04630782	Recruiting	Not Applicable	Diagnostic Test: PET-MRI scan	70
NCT04095351	Recruiting	Not Applicable	Diagnostic Test: Pulmonary function test|Diagnostic Test: Imaging|Biological: Blood sampling	120
NCT04966416	Not yet recruiting	Not Applicable	Dietary Supplement: Pyrophosphate|Dietary Supplement: Placebo	60
NCT05168215	Recruiting	Not Applicable	digital ulcer diagnosis	300
NCT04515706	Not yet recruiting	Not Applicable	Drug: Iguratimod|Drug: Placebo	20
NCT04325217	Recruiting	Not Applicable	Drug: Nintedanib	600
NCT04334031	Recruiting	Not Applicable	Genetic: Biobanking with genetic analysis|Other: SF-12 questionnaire	2200
NCT05482607	Not yet recruiting	Not Applicable	HRCT patterns in SSc-ILD	100
NCT04996082	Not yet recruiting	Not Applicable	Imaging diagnosis	60
NCT04986514	Not yet recruiting	Not Applicable	Other: Bio-banking without genetic analysis	1000
NCT04206644	Recruiting	Not Applicable	Other: biological analysis	180
NCT05007340	Recruiting	Not Applicable	Other: Blood draws|Other: Other biological samples to biobank (skin, lung and muscle biopsies; bronchoalveolar lavage (BAL fluid)|Other: Clinical data collection|Other: Genetic data/DNA/RNA	252
NCT05532865	Not yet recruiting	Not Applicable	Other: Blood samples|Other: Stool samples|Other: Skin swab samples|Other: Questionnaires on quality of life, pain and disability	100
NCT05528809	Not yet recruiting	Not Applicable	Other: Blood sampling	40
NCT05273138	Recruiting	Not Applicable	Other: Blood sampling and skin biopsy	40
NCT04995588	Recruiting	Not Applicable	Other: Blood test	180
NCT05453071	Active, not recruiting	Not Applicable	Other: Cognitive Exercise Therapy Approach (BETY)	40
NCT04917705	Recruiting	Not Applicable	Other: Collection of biological samples	55
NCT04301596	Recruiting	Not Applicable	Other: Collection of data	150
NCT05351060	Not yet recruiting	Not Applicable	Other: Custom Fabricated Splint	10
NCT05234671	Recruiting	Not Applicable	Other: Exercise programme	180
NCT05078749	Recruiting	Not Applicable	Other: Exercise training group|Other: Control training group	26
NCT04563481	Not yet recruiting	Not Applicable	Other: Hand Therapy via Telerehabilitation|Other: Hand Therapy by Physiotherapist	32

NCT03271333	Recruiting	Not Applicable	Other: lung function tests	70
NCT01808937	Recruiting	Not Applicable	Other: Morphea	500
NCT05297474	Recruiting	Not Applicable	Other: MRI	95
NCT05462574	Not yet recruiting	Not Applicable	Other: No Intervention	75
NCT03459716	Recruiting	Not Applicable	Other: No intervention	56
NCT03269630	Recruiting	Not Applicable	Other: No intervention. Biospecimen collection only	450
NCT04401943	Active, not recruiting	Not Applicable	Other: online fatigue intervention	12
NCT05103553	Not yet recruiting	Not Applicable	Other: Outpatient Clinic	250
NCT05533034	Not yet recruiting	Not Applicable	Other: Rehabilitation	15
NCT04917146	Recruiting	Not Applicable	Other: Self-administered questionnaires for relatives (caregivers=CG)	50
NCT05505617	Recruiting	Not Applicable	Other: Single-breath nitric oxide lung diffusing capacity measurements according to type of device in random order.	23
NCT05105217	Not yet recruiting	Not Applicable	Other: Slit2 biomarker	85
NCT04132206	Recruiting	Not Applicable	Other: stool sampling	60
NCT05041868	Recruiting	Not Applicable	Other: Treatment	104
NCT03819777	Recruiting	Not Applicable	PAH biomarker	150
NCT04610788	Recruiting	Not Applicable	PAH BP diagnosis	100
NCT03446339	Recruiting	Not Applicable	PAH screening	1800
NCT01656447	Recruiting	Not Applicable	Patient registry	300
NCT01793168	Recruiting	Not Applicable	Patient registry	20000
NCT03840928	Recruiting	Not Applicable	Patient registry	9867
NCT04402086	Recruiting	Not Applicable	Patient registry	5000
NCT05445817	Recruiting	Not Applicable	Patient registry	150
NCT03276923	Recruiting	Not Applicable	Patient registry maternal health	1000
NCT05108857	Enrolling by invitation	Not Applicable	PET Imaging agents	10
NCT04752397	Recruiting	Not Applicable	phototherapy response assessment	10
NCT04363021	Recruiting	Not Applicable	Preeclampsis and SSc history	378
NCT02298777	Recruiting	Not Applicable	Procedure: - Skin biopsy - Urine sample - Blood sample	140
NCT04148716	Recruiting	Not Applicable	Procedure: additional biopsies	18

NCT04746599	Recruiting	Not Applicable	Procedure: Autologous Fat Grafting	20
NCT03444805	Recruiting	Not Applicable	Procedure: Autologous HSCT	60
NCT04303208	Not yet recruiting	Not Applicable	Procedure: Blood sample	80
NCT04791280	Recruiting	Not Applicable	Procedure: Faeces collection	200
NCT05177380	Not yet recruiting	Not Applicable	Procedure: Personalized rehabilitation program of facial involvement in systemic sclerosis|Other: Delivery of a standard prescription for facial rehabilitation	60
NCT04804930	Recruiting	Not Applicable	Procedure: picture	200
NCT05204784	Recruiting	Not Applicable	Procedure: Rheopheresis treatment|Drug: Intravenous Infusion	30
NCT03559465	Recruiting	Not Applicable	Procedure: skin biopsy|Other: Blood punction	71
NCT05450276	Enrolling by invitation	Not Applicable	PROM study	56
NCT04954573	Recruiting	Not Applicable	Radiation: infrared-A (wIRA)	22
NCT05177471	Recruiting	Not Applicable	Retrospective response	20
NCT04335396	Recruiting	Not Applicable	Screening at risk patients	150
NCT05345795	Not yet recruiting	Not Applicable	SSc-ILD progression	600
NCT05455437	Enrolling by invitation	Not Applicable	Telemedicine	200

Appendix 2: Innovation development costs (ball park figures: US marketplace) and pricing considerations for rare diseases

- Rapid POC diagnostic development: 1.4 million USD
- Standard in vitro diagnostic development: 2.5 to 2.8 million USD
- App or Wearable technology development: 425,000 to 500,000 USD
- Electronic Healthcare Record: 150,000 USD
- Health Tracker: 200,000 USD
- Imaging agent: 100 to 150 million USD
- New software solution for imaging platform: 50,000 to 400,000 USD
- Orphan drug (chemical entity/new molecular entity type) 250 million USD (*see Berdud et al, Jayasundara et al refs below*). This changes as a function of whether:
    - the drug is a biologic (antibody, peptide) or an advance therapy medical product (gene therapy, bioengineering)
    - If the rare disease is oncology focused or not (rare oncological diseases have similar patient number requirements as frequent oncological, whereas on average for orphan drugs 2 to 5 fold lower requirement in patient number based on phase of development)

Ball Park figures excludes costs of:

- Multiple clinical trial requirements within and across geographies
- Level of uniqueness of solution (costs can significantly increase to address statistical relevance, long-term impact and evidence requirements if significantly different to existing standard-of-care)
- Post approval studies can cost approximately a further 6 million USD.

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