Specific Operationnal Criteria - Monogenic Connective Tissue Disorders

The requested information will be used to define the specific criteria for our project proposal for a European Reference Network (ERN) for Rare and Undiagnosed Skin Disorders. Please note that, each health care provider member of our ERN will have to fulfil these criteria. These criteria have to be realistic/reasonable while ensuring a high level patient management. These criteria have to be based on the evidence and consensus of the scientific, technical and professional community.

NB: A sample of healthcare providers will be selected for on-site audits to validate the information.

Monogenic Connective Tissue Disorders

Rare Diseases(s)	Short description of the rare disease	Code/ ICD/ Orphacode	Epidemiology	Incidence	Prevalence
1. Ehlers-Danlos syndrome (EDS)	EDS is a group of heritable connective tissue disorders, characterized by joint hyperlaxity and skin manifestations, including a stretchable and fragile skin with atropic scarring. Depending on the subtype systemic involvement, often reflecting organ fragility, may be present. Most of the know defects in EDS affect the synthesis of collagen fibers or glycosaminoglycans.	ICD-10: Q79.6 / ORPHA98249 / OMIM 130020, 615349, 130000, 615539, 225400, 612350, 225410, 130070, 225320, 130060, 601776, 130050, 614557, 229200, 606408, 300049, 614170	n/a	n/a	1-2/ 10 000
2. Cutis laxa (CL)	CL is a group of inherited connective tissue disorders, all characterized by loose redundant skin folds and variable systemic involvement. Most known defects genetic defects affect the assembly and maintenance of elastic fibers.	ICD-10: Q82.8 / ORPHA209 / OMIM 614438, 613177, 219200, 219150, 612940, 613075, 304150, 219100, 123700, 614437, 616603, 278250, 208050, 231070	n/a	n/a	Unknown (only around 200 families being reported in the literature to date.)

3. Pseudoxanthoma elasticum (PXE)	PXE is a progressive connective tissue disorder characterized by the triad of skin (yellowish papular lesions), ocular (mainly angiod steaks) and cardiovascular involvement (mainly accelerated atherosclerosis). This autosomal recessive recessive disorder shows enhanced mineralisation of elastic fibers due to mutations in ABCC6, encoding a transporter for which the substrate is still debated.	ICD-10: Q82.8 / ORPHA758 / OMIM 264800, 177850, 610842, 208000	n/a	n/a	1/40 000 in Europe (population dependent)
4. Buschke-Ollendorff syndrome	BOS is a autosomal dominant connective tissue disorder characterized by connective tissue nevi and osteopoikilosis due to mutations in the LEMD3 gene	ICD-10: Q78.8/ ORPHA1306 / OMIM 166700	n/a	n/a	<100 families reported to date

Rare Diseases(s)	**Specific challenges associated with the recognition of the condition**	**Specific challenges associated with the diagnosis**	**Specific challenges associated with the treatment**	**Specific challenges associated with care of these patients over their lifespan - Quality of life issues - Gaps accross the care**

1. Ehlers-Danlos syndrome (EDS)	Overlapping phenotypes between the subtypes of EDS. Mildest form merge with normality in the general population	detailed clinical phenotyping - genetic testing - no clear diagnostic guidelines	lack of strict guidelines - mainly expert opinion. Treatment is mainly symptomatic and the number of RCT trials is limited (except for the use of celiprolol in	Joint pain, complications of fragility of organs and vasculature, lack of natural history studies, mainly in the rare entities of EDS. Some patients may worry about the esthetic aspects of the disease.
2. Cutis laxa (CL)	All entities are rare, and show considerable overlap	detailed clinical phenotyping - genetic testing - no clear diagnostic guidelines	lack of strict guidelines - mainly expert opinion	Joint pain, complications of fragility of organs and vasculature, pulmonary, gastro-intestinal and genitourinary complications. Lack of natural history studies, since all entities within the cutis laxa spectrum are rare. Some patients may worry about the esthetic aspects of the disease

3. Pseudoxanthoma elasticum (PXE)	Detection of the triad of skin (papular lesions in flexural areas), ocular (angioid streaks with a propensity for subretinal neovascularization and hemorrhage), and cardiovascular (occlusive peripheral vessel disease) symptoms that can vary significantly in severity. Many related phenotypes and phenocopies (Beta-thalassemia)	detailed clinical phenotyping - genetic testing	longterm follow-up necessary for ophthalmological and cardiovascular complications. Control of cardiovascular risk facors, need for specialized retinal imaging techniques (blue light autofluorescence , near-infrared confocal reflectance imaging, high resolution optical coherence tomography, fluorescein and indocyanine green (ICG) angiography)	Risk for severe ophthalmological complications including retinal hemorrhages and vision loss - risk for cardiovascular complications of accelerated atherosclerosis (coronay artery disease, peripheral artery disease, stroke). Some patients may worry about the ethetic aspects of the disease.
4. Buschke-Ollendorff syndrome (BOS)	rare disorder charaterized by connective tissu naevi that may appear aspecific. Need for radiogrpahic imaging if the diagnosis is suspected	Due to is rarity and the variability of the clinical symptoms it remains underrecognized	There is currently no treatment nor guidelines for treatment	The disease is mostly benign, but some patients may develop joint pain. Patients may worry about the esthetic aspects of the disease

Rare Diseases(s)	**Key Diagnostic Tests**	**Key Treatment, Resources or Procedures**

1. Ehlers-Danlos syndrome (EDS)	Genetic testing. History taking, physical examination, family history,	symptomatic treatment and management
2. Cutis laxa (CL)	Genetic testing. Personal history, physical examination, family	symptomatic treatment and management
3. Pseudoxanthoma elasticum (PXE)	Personal history taking, physical examination, family history, histological analysis, cardiovascular imaging studies,	symptomatic treatment and management
4. Buschke-Ollendorff syndrome (BOS)	Personal history taking, physical examination, family history, histological analysis, skeletal survey (Rx), genetic testing	symptomatic treatment and management

Please state the minimum/optimum thresholds that Healthcare Providers within the network will need to meet to maintain competence and expertise.

Rare Diseases(s)	**Minimum Number of patients treated per year at each HCP**			**Minimum Number of new**	
	Adults	Paediatric*	Rationale for the threshold	Adults	Paediatric*
1. Ehlers-Danlos syndrome (EDS)	10	5	based on overall frequency	3	1
2. Cutis laxa (CL)	1	2 (in life or 'telemedicine')	very rare disorder, many patients die during childhood	1	1 (including telemedicine)
3. Pseudoxanthoma elasticum (PXE)	10	2	based on overall frequency, disease is often not manifest in children and thus underdiagnosed	3	n/a (rarely diagnosed in childhood)
4. Buschke-Ollendorff syndrome (BOS)	n/a	n/a	n/a	n/a	n/a

Please list the necessary human resources and the profesional qualifications essential to the quality of patient care within the Network's area of expertise.

Rare Diseases(s)	**Health Care Professional (type)**	**Training & Qualifications**	**Minimun of number of procedures per patient per year**	**Rationale**

1. Ehlers-Danlos syndrome (EDS)	Geneticist, dermatologist, ophthalmologist, cardiologist, radiologist, orthopedist/reumatologist, pediatrician, physiotherapist, pathologist	high with specific expertise in the disorder	1	n/a
2. Cutis laxa (CL)	Geneticist, dermatologist, ophthalmologist, cardiologist, pulmonologist, radiologist, neurologist, paediatrician, urologist, physiotherapist, pathologist	high with specific expertise in the disorder	1	n/a
3. Pseudoxanthoma elasticum (PXE)	dermatologist, ophthalmologist, cardiologist, radiologist, pathologist	high with specific expertise in the disorder	1	n/a
4. Buschke-Ollendorff syndrome (BOS)	Geneticist, dermatologist, orthopedist, radiologist, pathologist	high with specific expertise in the disorder	1	n/a

Please list the specialised equipment, infrastructure, and information technology required to support the rare or complex disease(s), condition(s) or highly specialised intervention(s) and describe the importance of each

Rare Diseases(s)	**Specialised equipment, infrastructure, and information technology**	**Threshold**	**Rationale**
1. Ehlers-Danlos syndrome (EDS)	Genetic testing facility using next-generation sequencing (can be done in collaboration with other labs). Multidisciplinary clinic with all specialist as decribed above. Need for telemedicine.	high	n/a

2. Cutis laxa (CL)	Genetic testing facility using next-generation sequencing (can be done in collaboration with other labs). Multidisciplinary clinic with all specialist as decribed above. Need for telemedicine.	high	n/a
3. Pseudoxanthoma elasticum (PXE)	Genetic testing facility using next-generation sequencing (can be done in collaboration with other labs). Multidisciplinary clinic with all specialist as decribed above.	high	n/a
4. Buschke-Ollendorff syndrome (BOS)	Genetic testing facility using next-generation sequencing (can be done in collaboration with other labs). Multidisciplinary clinic with all specialist as decribed above. Need for telemedicine.	high	n/a

Please provide a summary explaining the approach or plans your group will undertake to produce good practice guidelines and implement outcome
1) detailed recording of clinical data and follow-up data 2) submit clinical data to international registries once available 4) publication of clinical series 3) join consortia to establish and implement guidelines