Specific Operationnal Criteria

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

ERN Skin / ALLOCATE

Rare Diseases(s)	Short description of the rare disease	Code/ ICD/ Orphacode	Epidemiology	Incidence	Prevalence
1. Hidradenitis suppurativa / acne inversa (familial form)	Hidradenitis suppurativa / acne inversa (HS) is a chronic, inflammatory, recurrent, debilitating skin disease of the hair follicle that usually presents after puberty with painful, deep-seated, inflamed lesions in the apocrine gland-bearing areas of the body, most commonly the axillae, inguinal and anogenital regions. The familial cases may present mutations at the nicastrin gene of the gamma-secretase complex (chrom. 19p13).	ICD-10: L73.2 / Orphacode: 387	Male : female ratio 1:2-1:5. Disease onset peak at the 3rd decade of life.	6.0 / 100 000 inhabitants per year (spontaneous disease)	0.27-5 / 10 000 (familial disease), 5.3-100 / 10 000 (spontaneous disease)

2. PAPA syndrome	PAPA syndrome is an acronym for pyogenic arthritis, pyoderma gangrenosum and acne. It is a rare genetic disease inherited in an autosomal dominant fashion. Recently, the responsible gene, PSTPIP1, has been identified on chrom. 15q24-q25.1. Two mutations have been found in a protein called CD2 binding protein 1 (CD2BP1). This protein is part of an inflammatory pathway.	ICD-10: M14.8 + L88 + L70.9 / Orphacode: 69126	Extremely rare disease, a few families have been reported.	unknown	unknown
3. PAPASH syndrome	The PAPASH syndrome (pyogenic arthritis, pyoderma gangrenosum, acne, hidradenitis suppurativa / acne inversa) has recently been described in few unrelated patients as a new entity within the spectrum of hidradenitis suppurativa / acne inversa syndromes. PAPASH syndrome is similar to PAPA syndrome but differs insofar as it includes hidradenitis suppurativa / acne inversa. Mutations of the PSTPIP1 gene have been detected in some cases.	ICD-10: M14.8 + L88 + L70.9 + L73.2	Extremely rare disease, a few patients have been reported.	unknown	unknown

4. PASH syndrome	The PASH syndrome (pyoderma gangrenosum, acne, and hidradenitis suppurativa / acne inversa) has recently been described in few unrelated patients as a new entity within the spectrum of hidradenitis suppurativa / acne inversa syndromes. PASH syndrome is similar to PAPA syndrome but differs insofar as it lacks the associated arthritis and has a different genetic basis, since no mutations have yet been detected in PASH syndrome.	ICD-10: L88 + L70.9 + L27.2 / Orphacode: 289478	Extremely rare disease, a few patients have been reported.	unknown	unknown
5. PASS syndrome	PASS syndrome is a rare inflammatory disease characterized by a chronic-relapsing course of pyoderma gangrenosum, acne vulgaris, hidradenitis suppurativa and ankylosing spondylitis.	ICD-10: L88 +L70.9 + L73.2 + M45	Extremely rare disease, a few patients have been reported.	unknown	unknown

6. SAPHO syndrome	SAPHO syndrome (acronym for synovitis, acne, pustulosis, hyperostosis and osteitis) is an auto-inflammatory disease, mainly characterized by the association of neutrophilic cutaneous involvement and chronic osteomyelitis. The etiology is unknown.	ICD-10: M86.3 / Orphacode: 793	Rare disease.The age of onset ranges from childhood to late adulthood, with a median age between 30 and 40 years. Sporadic cases have been reported.	unknown	unknown
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 continuum**	
1. Hidradenitis suppurativa / acne inversa (familial form)	The disease is not recognised when mild, despite the existence of clinical diagnostic criteria been considered as recurrent bacterial follicultis / recurrent abscesses and been treated repeatedly by short-term antibiotics / incisional surgery. There is a critical worldwide delay of diagnosis of 7.2 years. Still unknown molecular and immunological background, no biomarker available.	The entity is unknown in several medical specialties.	Optimum treatment requires a wide expertise.	Chronic, initially recurrent, later scarring disease. Long-term follow-up and repeated treatment in specialised centers is required. No widespread experience, since dermatologists only examine 4 pts/year, surgeons 2 pts/year and general practitioners 0.5 pts/year (spontaneous disease). The ambulatory follow-up of wound healing is unsatisfactory even in the vicinity of specialosed centers. Strongest influence on the quality of life among all dermatological diseases. Great reduction of workability.	

2. PAPA syndrome	Clinical features along with the familial tendency may suffice to make a diagnosis.	No genetic test widely available yet.	No drug registered. No clinical studies performed.	Skin scarring due to severe acne and pyoderma gangraenosum is prominent. With repeated episodes of arthritis, the joints become damaged with multiple joint replacements required.
3. PAPASH syndrome	Clinical features may help to make a diagnosis.	No genetic test widely available yet. Mutations have not been detected in all cases.	No drug registered. No clinical studies performed.	Skin scarring due to severe acne, pyoderma gangraenosum and hidradenitis suppurativa / acne inversa is prominent.
4. PASH syndrome	Clinical features may help to make a diagnosis.	Unknown genetic etiology.	No drug registered. No clinical studies performed.	Skin scarring due to severe acne, pyoderma gangraenosum and hidradenitis suppurativa / acne inversa is prominent.
5. PASS syndrome	Clinical features may help to make a diagnosis.	Unknown genetic etiology.	No drug registered. No clinical studies performed.	Skin scarring due to severe acne, pyoderma gangraenosum and hidradenitis suppurativa / acne inversa is prominent.

6. SAPHO syndrome	Diagnosis, suspected upon clinical examination, must be confirmed with imaging procedures (X-rays, CT, MRI) showing a combination of osteolysis and osteosclerosis with secondary hyperostosis, bone marrow edema, endosteal-periosteal inflammation, perifocal myositis, and adjacent arthritis.	Multifactorial triggering of unknown genetic etiology.	Multimodal treatment of uncertain efficacy.	The disease usually has a chronic evolution, with alternating periods of remission and relapse, sometimes with the appearance of new osteosclerotic lesions. Spontaneous resolution can occur. Complications include impairment of bone and joint function, vascular compression, chronic pain syndrome, and progression towards classical spondyloarthritis.

Rare Diseases(s)	**Key Diagnostic Tests**	**Key Treatment, Resources or Procedures**
1. Hidradenitis suppurativa / acne inversa (familial form)	Clinical diagnosis. Mutations at the nicastrin gene of the gamma-secretase complex possible.	Proper administration of antibiotics, immunoregulators / antinflammatory compounds, minor and radical surgery. S1 guidelines of treatment have been published by the group. Currently, adalimumab has been the first registered drug for active moderate to severe disease.
2. PAPA syndrome	Clinical diagnosis. Mutations in the PSTPIP1 gene.	Off label treatments: IL-1beta antagonists may be appropriate, adalimumab, infliximab (TNF inhibitors) and tetracyclines may improve the disease.
3. PAPASH syndrome	Clinical diagnosis. Mutations in the PSTPIP1 gene possible.	Off label treatments: IL-1beta antagonists may be appropriate, adalimumab, infliximab (TNF inhibitors) and tetracyclines may improve the disease.

4. PASH syndrome	Clinical diagnosis. No diagnostic test	Off label treatments: IL-1beta antagonists may be appropriate, adalimumab, infliximab (TNF inhibitors) and tetracyclines may improve the disease.
5. PASS syndrome	Clinical diagnosis. No diagnostic test	Off label treatments: IL-1beta antagonists may be appropriate, adalimumab, infliximab (TNF inhibitors) and tetracyclines may improve the disease.
6. SAPHO syndrome	Clinical and radiological diagnosis. No diagnostic test	Symptomatic treatment (NSAIDS) or corticosteroids. In resistant cases methotrexate. I.v. biphosphonates can alleviate bone pain. Azithromycin or TNF-inhibitors may control both osteoarticular and cutaneous manifestations. Acne treatment with systemic doxycycline. Palmoplantar pustulosis / pustular psoriasis responds to topic corticosteroids or PUVA therapy. Physiotherapy is recommended.

Please state the minimum/optimum thresholds that Healthcare Providers within the network will need to meet to maintain competence and expertise. List the measure, threshold, and rationale for this threshold

Rare Diseases(s)	**Minimum Number of patients treated per year at each HCP**			**Minimum Number of new patients diagnosed per year at each HCP**	
	Adults	Paediatric*	Rationale for the threshold	Adults	Paediatric*
1. Hidradenitis suppurativa / acne inversa (familial form)	50 patients with spontaneous disease, among them 5 patients with familial disease	Not relevant	Rare disease. Expertise due to the complex character of the disease and the surgical resources is required.	10 patients of any age	Not relevant

2. PAPA syndrome	1 patient of any age	Not relevant	Very rare disease	0 to 1 of any age	Not relevant
3. PAPASH syndrome	1 patient of any age	Not relevant	Very rare disease	0 to 1 of any age	Not relevant
4. PASH syndrome	1 patient of any age	Not relevant	Very rare disease	0 to 1 of any age	Not relevant
5. PASS syndrome	1 patient of any age	Not relevant	Very rare disease	0 to 1 of any age	Not relevant
6. SAPHO syndrome	1 patient of any age	Not relevant	Very rare disease	0 to 1 of any age	Not relevant

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. Hidradenitis suppurativa / acne inversa (familial form)	Dermatologist / Dermatosurgeon or surgeon (occasionally gastroenterologist / radiologist)	Experience in skin and perianal / proctologic surgery	25	Complex skin surgery may be required.
2. PAPA syndrome	Dermatologist / Radiologist	Specialization in rare skin disorders	1	Dermatological manifestations are the leading signs. Radiology may be required.
3. PAPASH syndrome	Dermatologist / Radiologist / Dermatosurgeon or surgeon	Specialization in hidradenitis suppurativa / acne inversa and rare skin disorders	1	Dermatological manifestations are the leading signs. Radiology may be required. Compex surgery may be required (similar with hidradenitis suppurativa / acne inversa).

4. PASH syndrome	Dermatologist / Dermatosurgeon or surgeon	Specialization in hidradenitis suppurativa / acne inversa and rare skin disorders	1	Dermatological manifestations are the leading signs. Compex surgery may be required (similar with hidradenitis suppurativa / acne inversa).
5. PASS syndrome	Dermatologist / Radiologist / Dermatosurgeon or surgeon	Specialization in hidradenitis suppurativa / acne inversa and rare skin disorders	1	Dermatological manifestations are the leading signs. Radiology may be required. Compex surgery may be required (similar with hidradenitis suppurativa / acne inversa).
6. SAPHO syndrome	Dermatologist / Radiologist (occasionally orthopaedic surgeon)	Specialization in rare skin disorders	1	Dermatological manifestations are the leading signs. Radiology may be required. Orthopaedic surgeon may become involved.

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. Hidradenitis suppurativa / acne inversa (familial form)	Center with inpatient department and access to experienced dermatosurgery or surgery and wound healing	Specialized inpatient and outpatient departments / wound healing clinics	Clinical and surgical experience		
2. PAPA syndrome	Center with clinical expertise and access to molecular diagnosis	Specialized outpatient clinics	Clinical experience		

3. PAPASH syndrome	Center with clinical expertise and access to experienced dermatosurgery or surgery and molecular diagnosis	Specialized inpatient and outpatient departments / wound healing clinics	Clinical and surgical experience
4. PASH syndrome	Center with clinical expertise and access to experienced dermatosurgery or surgery	Specialized inpatient and outpatient departments / wound healing clinics	Clinical and surgical experience
5. PASS syndrome	Center with clinical expertise and access to experienced dermatosurgery or surgery	Specialized inpatient and outpatient departments / wound healing clinics	Clinical and surgical experience
6. SAPHO syndrome	Center with clinical expertise	Specialized outpatient clinics	Clinical experience

undertake to produce good practice guidelines and implement outcome measure and		
1. For hidradenitis suppurativa / acne inversa guidelines already exist at European level (work of our group) and harmonization of treatment, especially of surgical treatment, is necessary at the EU level. There is a need to standardize severity grading of the disease for registered treament and for future clinical trials. Ressources concerning molecular diagnosis need to be shared at the EU level. Increasing awareness will speed up diagnosis and increasing experience and advanced surgical skills will improve the treatment of difficult cases. The European Hidradenitis Suppurativa Foundation e.V. is established (work of our group) and an EU registry is under preparation and has received an implementation grant from the European Academy of Dermatology and Venereology (work of our group). - 2. The diagnosis and treatment of the very rare syndromes PAPA, PAPASH, PASH. PASS and SAPHO should be performed in differential diagnosis to the classical hidradenitis suppurativa / acne inversa cases. - 3. Close cooperation with patient associations has been established.		