Specific Operational Criteria -Autoimmune bullous diseases and severe cutaneous drug reactions

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.

Autoimmune bullous diseases and severe cutaneous drug reactions

Rare Diseases(s)	Short description of the rare disease Code/ ICD/ Orphacode - 704	Epidemiology	Incidence	Prevalence
1. Pemphigus	704 - Pemphigus is a rare acquired autoimmune bullous disease due to the production of auto-antibodies directed against desmoglein 1 and 3 that are adhesion molecules of desmosomes of the skin and mucosae respectively. Binding of auto-antibodies on desmogleins lead to disruption of desmosome and intra-epithelial separation. This is responsible for the formation of blisters and large erosive areas on the skin and mucous membranes; oral, genital, ocular, anal, oesophageal and sometimes ENT mucosae can be involved. Erosions of the skin and mucous membrane are painful and lead to dysphagia, weight loss and infection. Two clinical and histological main subtypes of pemphigus have been described: pemphigus vulgaris which is characterized by mucosal and skin involvement, and pemphigus foliaceus , characterized by excusive skin involvement. Treatment of pemphigus is based on corticosteroids, conventional immunosuppressive drugs and more recently biologics targeting B lymphocytes, IVIG and immunoadsorption of pathogenic antibodies .	Most cases of pemphigus are sporadic but endemic forms have ben described especially in South America and in North Africa. Pemphigus vulagris represents 80% of sporadic cases in Europe and the US, whereas Pemphigus foliaceus corresponds to 70-80% of endemic cases. Some cases of pemphigus can be induced by drugs. A rare particular subtype called paraneoplastic pemphigus has been recently described in patients with lymphoproliferative disorders or Castelman's disease. The mortality rate of pemphigus is estimated between 5-15% one year after the diagnosis, and between 10-25% two years after the diagnosis. Infections are the most frequent cause of death.	The incidence of pemphigus in Europe is estimated at between 1 to 4 new cases per million inhabitants per year. A higher incidence has been described in Israel (16 new cases per million inhabitant per year) and in Tunisia (7 new cases per million inhabitant per year).	The prevalence is not very well known .It can be estimated in Europe at between 60 000 and 80 000 patients.

2.Bullous Pemphigoid	703 - Bullous pemphigoid (BP) is a subepidermal autoimmune bullous disease, affecting mostly elderly patients. It is pathogenetically linked to autoantibodies directed against the 180 kD (BP180) and the 230 kD (BP230) antigens, two hemidesmosomal proteins promoting dermo-epidermal cohesion. BP typically presents with severe pruritus, preceding for several weeks the development of urticarial plaques and tense, mostly clear, blisters commonly on the flexural aspects of the limbs and the abdomen. Oral mucosal lesions are present in 10-20% of patients.Other clinical variants of BP are: prurigo-like BP, dyshidrosiform-like BP, erythroderma-like BP, ecthyma gangrenosum-like BP and localized (pretibial) BP. BP lesions in untreated patients may result in multiple erosions and crusts and pruritus may become torturous. Treatment of bullous pemphigoid is based on topical use of very potent steroids (clobetasol propionate), systemic steroids, dapsone, doxycycline, IVIG and more recently rituximab and immunoadsorption of pathogenic antibodies .	BP cases are sporadic with an increasing incidence due to the increasing age of the general population and the availability of more sensitive and specific diagnostic assay systems. BP generally presents in patients above 70 years of age and rarely occurs in individuals younger than 50 years. Few cases in infants, children, and adolescents have been reported. There is a strong association of BP with major cognitive impairment, Parkinson's disease, stroke, epilepsy, and multiple sclerosis. Recently there is a high index of suspected BP induction by dipeptidyl peptidase-4 inhibitors in elderly diabetic patients. 1-year mortality for patients with BP ranges from 20% to 40%, which is about 2-3 times higher than that of age -matched and sex-matched controls. Age, widespread disease, low Karnofsky score and high doses of oral steroids are major risk factors.	There is a wide range among BP incidence reported in different European countries. 12.1 new cases per 1 million people per year have been calculated in Switzerland, 13.4 in Germany, 14 in Scotland, 21.7 in France and 66 new cases per 1 million people in the UK.	Prevalence of BP in Europe?

3. Mucous Membrane Pemphigoid	ICD-10: L12.1 Orpha46486 - Mucous membrane pemphigoid (MMP) is the subgroup of pemphigoid (see above) affecting the mucous membranes. Several subtypes are classified based on clinical symptoms/membranes involved and target antigens, such as ocular MMP, localized vulvar pemphigoid, anti-laminin-332 MMP. Autoantibodies are directed against different structural proteins in the skin basement membrane zone, with BP180 as the main target antigen. Other antigens such as laminin-332, BP230, a6B4 can also be targeted by autoantibodies. Clinically MMP is characterized by erosions and blistering of the oral mucosa (85%), conjunctiva (65%), and, less frequently, the nose (20-40%), oesophagus (5-15%), pharynx (20%), larynx (5-10%), and genitals (20%). Clinical severity is highly variable between the different subtypes of MMP. Progressive scar formation is a severe complication in active disease in ocular MMP and anti-laminin-332 MMP, resulting in blindness or upper airway obstruction when not treated fast and accurately. Anti-laminin 332 MMP is associated with an increased risk for malignancy, especially adenocarcinoma. Previously, the term cicatricial pemphigoid (CP)was used synonymously for MMP. However, at present, the term CP refers to the rare clinical subtype with scarring skin lesions. Patient´s and doctor´s delay is frequently seen in MMP. For accurate diagnosis, DIF and detection of circulating autoantibodies in serum is mandatory. Management and prognosis of MMP depends on the severity and extent of the disease and involves local and oral corticosteroids, and (adjuvant) immunosuppressive drugs, and more recently rituximab..	See also Incidence and Prevalence in the following columns. MMP is a sporadic disease. It seems that women are affected twice as often as men. The mean age of diagnosis is 60-70 years of age. MMP in children is extremely rare, localized vulvar pemphigoid can be seen in children. No racial difference have been observed. Mortality rate of MMP is unknown.	1.3-2.0 per million people per year (France, Germany)	Prevalence unknown, estimations can be made: for Europe between 40.000-60.000 patients

4. Epidermolysis bullosa acquisita	46487 - Epidermolysis bullosa acquisita (EBA) is subepidermal autoimmune blistering disease in which blisters on skin as well as on mucous membranes develeop due to binding of IgG autoantibodies to type VII collagen (structural component of anchoring fibrils) in upper dermis. EBA hes two major clinical subtypes - mechanubullous and inflammatory variants. Mechanobullous variant present with skin fragility, blisters, scarring, milia, dystrophic changes on trauma-prone areas and can resemble features seen in DEB, inflammatory variants resembel other AIBD as BP-like, MMP-like and Brunsting Perry pemphigoid like as well as LABD like disease which is most common in children. Diagnosis is based on clinical picture, histology and direct immunofluorescence which can be very similar to BP. In salt split skin immunofluorescence finding in patients with EBA deposits are found on the dermal side of the blister. Comercial anti col VII ELISA kits are available. Therapeutically disease can be very resistant. Treatment options are systemic corticosteroids, IVIg, colhicin, dapsone, rituximab.	EBA is rare, sporadic disease disease, that has no racial predominance. It can appear in any age, although more commonly in adults. When appears in childhood it has better prognosis regarding therapy.	The incidence of EBA in Western europe is 0.17-0.26 new patients per 1 milion inhabitants per year	Prevalence unknown?

5. Linear IgA Disease	ICD-10: L13.8 - Linear IgA disease (LAD) constitutes a heterogeneous group of chronic, subepidermal, blistering mucocutaneous autoimmune diseases featuring an immune response to hemidesmosomal proteins solely driven by IgA. Autoantigens in LAD are LAD-1 and LABD-97, which are both cleavage products of the extracellular domain of BP180, as well as BP180 itself. In another subtype of LAD, type VII collagen serves as autoantigen. In addition to a spontaneous emergence of disease, LAD can also be drug-induced. LAD exhibits a bimodal peak of onset and predominantly emerges in children 4-5 years old and in adults in the 5th decade of life. LAD typically presents with grouped, tense skin blister (“string of pearls”) on urticarial, erythematous patches. Most LAD patients suffer from severe itch.80% of patients in addition show erosions on mucous surfaces, which can cause scarring. LAD with predominant disease manifestation on mucous membranes is clinically indistinguishably from mucous membrane pemphigoid. LAD has been associated with a number of cancers and other inflammatory diseases, especially with colitis. LAD is diagnosed based on the clinical presentation, histopathology, direct and indirect immunofluorescence as well as detection of autoantibodies by Western blot utilizing recombinant proteins as antigens. LAD is of recalcitrant to treatment. The treatment of first choice is dapsone.	LAD exhibits a bimodal peak of onset and predominantly emerges in children 4-5 years old and in adults in the 5th decade of life.	Estimated as approx. 1/million/year	unknown
	LAD clinically resembles other pemphigoid diseases as well as dermatitis herpertiformis Duhring, from which it was distinguished as separate disease in 1979, which complicates early diagnosis.			

6. Dermatitis Herpetiformis	1656 - Dermatitis herpetiformis (DH) is and uncommon subepidermal blistering dermatosis, currently regarded as the cutaneous manifestation of celiac disease (CD). The leading theory for DH is that a genetic predisposition (association with HLA-B8, HLA-DR3, and HLA-DQw2) for gluten sensitivity, coupled with the dietary gluten, leads to the formation of IgA antibodies against gluten-tissue transglutaminase (t-TG), a cytosolic enzyme found in the gut. Anti t-TG antibodies cross-react with epidermal transglutaminase (e-TG) which is highly homologous with tTG. Deposition of IgA and epidermal TG complexes in the papillary dermis triggers an immunologic cascade, resulting in neutrophil recruitment and complement activation resulting in subepidermal separation. Clinically, DH is characterized by polymorphic itchy cutaneous eruption, consisting of consisting of erythema, urticarial papules and plaques, and herpetiform vesicles followed by excoriations, crusted erosions and residual hyper-, or hypopigmentations. The eruption is with a typical symmetrical distribution on the extensor surfaces, including elbows, knees, shoulders, and buttocks. Morbidity is mainly related to the intense pruritus, scratching, discomfort, and insomnia. Systemic complications consist mainly of the symptoms of the associated gluten-sensitive enteropathy (GSE), which is generally mild or clinically completely absent. However, inflammatory small bowel changes can often be found by histological examination even in the absence of clinical findings. The diagnosis of DH isbased on clinical, histological and immunological features and presence of GI disease.	DH is more common among individuals of Northern European descent, it is extremely rare in Orientals and is uncommon in Asians and Afro-Caribbeans. This uneven geographic distribution of the disease may be dependent both on the immunogenetic and environmental factors, such as high or low consumption of wheat and related cereal products. Onset lies most frequently between the second and the fourth decade, but it may occur at any age, including childhood, usually after the age of 5 years. Men are more often affected than women, whereas the opposite is true for CD. In patients with DH younger than 20 years, however, women tend to outnumber men.	An annual incidence of 1.05 and 1.13 per 100 000/year has been reported in South Sweden (1986), 2.6 and 0.4/100 000/year in Northern and Southern Ireland, respectively (1972 and 1983), and 3.5/ 100 000/year in Finland (2011).	The prevalence of DH has been reported to be 1.2 per 100,000 population in Great Britain (1971), 39.2 per 100,000 population in central Sweden (1984) and 75.3 per 100 000 in Finland (2011).

	Histopathological findings are characterized by subepidermal blisters with predominantly neutrophil infiltrates in the papillary dermis. Direct immunofluorescence (DIF) reveals pathognomonic granular deposits of IgA and C3 in the papillary dermis, more pronounced at the tips of dermal papillae which is the key diagnostic criterion for DH. Serum antibodies against tissue transglutaminase (anti-tTG), more precisely against t-TG2 and t-TG3 and several other circulating autoantibodies have been shown to be specific and sensitive serologic indicators of both CD and DH. Several other autoimmune diseases, including thyroid abnormalities, type I diabetes mellitus, connective tissue disorders, etc., are associated with DH. A gluten-free diet (GFD) is the cornerstone of DH therapy, while pharmacological treatment consists of peroral dapson.				
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 across the care continuum**	
1. Pemphigus	Mean delay to diagnosis of pemphigus is between 6 months to 2 years. The disease is often misdiagnosed as oral ulcers, oral allergy, genital ulcers, conjonctivitis. Patients are often initially referred to odontologists, stomatologists, ENT, or ophthalmologists for months and months before the diagnosis is made by dermatologists. This delay of misdiagnosis leads to complain, psychological trauma and a long-lasting resentment of patients.	The diagnosis of this rare autoimmune blistering disorders needs the confrontation of clinical and histological features, and immunological exams performed both on patient's skin and mucosa. Precise recognition of the different pemphigus subtypes is necessary for proposing an adequate treatment.	High doses of systemic corticosteroids (CS) are considered the standard treatment for patients with pemphigus, most often associated with conventional immunosuppressants. Long term CS treatment is responsible for severe and even life-threatening side effects in patients with pemphigus. There is a high need for new treatments in order to improve the prognosis of pemphigus patients and to decrease treatment adverse effects.	Optimal management of pemphigus patients needs the involvement of both highly specialized dermatologists, stomatologists, ophtalmologists and in some cases gynecologists ENT, and GP. Other specialists can be involved in the managment of corticosteroid- side effects: rheumatologists, endocrinologists... Nurses are particularly involved during the acute phase of the disease to achieve disease control and epithelialisation of skin and mucosal erosions. They have a major role in patients educational programs. Many patients complain of long-lasting symptoms or psychological troubles, that frequently needs the intervention of psychologists.	Pain - disphagia - itch - weight loss - denutrition - psychological trauma - sexual disconfort, resulting in a major alteration of quality of life.

2. Bullous Pemphigoid	Mean delay in diagnosis of bullous pemphigoid is about 6 months. Main causes of delay are the lack of bullous lesions and the localization on one anatomic area. Almost 20% of patients present with non bulllous lesions, mimicking forms of eczema. This delay is associated with torturous pruritus and severe impact on patients' quality of life.	Diagnosis of bullous pemphigoid is based on the combination of clinical, histopathological and immunological criteria. Atypical clinical variants, especially those with intense pruritus and non bullous lesions, should be investigated with immunofliuorescence techniques.	Although the use of super potent topical steroids are recommended as first line therapy (EADV /EDF Consensus), this therapeutic option has the disadvantages of poor practicality in bedridden patients, high rates of incompliance and poor accessibility in many countries.The main challenge in the treatment of BP remains the dose and duration of oral steroid treatment. Elderly patients, who are the majority of BP patients, suffer from steroid - induced side effects (uncontrolled diabetes, osteoporosis myopathy, cataract, glaucoma). New therapeutic options are needed. Drug induced BP remains also a challenge, in terms of recognition of the causatiive agent and of management	Optimal management of bullous pemphigoid patients require a multidisciplinary approach by highly specialized dermatologists, internists, neurologists and general practitioners. Other specialists who can be involved in the management of corticosteroid- side effects are rheumatologists, endocrinologists and ophtalmologists. Nurses are particularly involved during the acute phase of the disease to achieve disease control and epithelialisation of skin and especially, when the topical application of high potency steroids is selected as monotherapy. Nursing staff play also a major role in patients' educational programs. Many patients complain of long-lasting symptoms or psychological troubles, that frequently needs the intervention of psychologists.

3. Mucous Membrane Pemphigoid	Mucous membrane pemphigoid with exclusive oral, genital of ocular lesions is often unrecognized in the early inflammatory stage and often misdiagnosed for other diseases such as lichen planus, lichen sclerosis, Behcet, aphtosis, or infections. The delay of diagnosis is usually 6 months to years, and sometimes exceeds many years. Difficult to treat complications of scarring can be the result.	Diagnosis of MMP is based on the combination of careful clinical examination of skin and all mucous membranes, and histopathology and direct immunofluorescence of affected mucous membrane and healthy skin. Indirect immunofluorescence and immunoblot are necessary to subtype the MMP. Precise recognition of the different subtypes and autoantigens is necessary for adequate treatment and prognosis.	MMP is known to be therapy resistant. Fast and aggressive treatment is necessary to prevent the sequelae of scarring in certain types of MMP. First choice treatment modalities consist of dapson, cyclophosphamide, and oral corticosteroids with a steroid sparing adjuvant. Refractory cases may be treated with rituximab (anti-CD20). Moderate to potent topical corticosteroids may aid in treatment effect. A challenge is the formulation of optimal treatment in a stepwise approach for the different types of MMP. Because of the rarity of the disease it is difficult to include large groups of patient to investigate the effectivity of different treatment modalities.	Intake of nutrition and/or fluids can be reduced with weight loss and denutrution as a result. Pain is a prominent feature. Other problems with the several forms of MMP may include bleeding, dysphagia, shortness of breath, hoarseness/loss of voice, dyspareunia, dysuria, caries, poor mouth hygiene, vision problems and even blindness. Scarring as a result of the damage of inflammation is a major problem when the disease is not treated adequate in time. Psychological problems due to above mentioned problems is frequently observed. A multidisciplinary approach with multiple disciplines as mentioned below in this table is very important.

4. Epidermolysis bullosa Acquisita	EBA can be misdiagnosed as BP according histopathology and DIF if salt splited skin is not performed. As it usually do not respond well to the therapy with corticosteroids, additional laboratory investigations are perfomed. So delay of diagnosis can be 6 months or more.	Diagnosis of EBA is based on the combination of careful clinical examination of skin and all mucous membranes, and histopathology, direct and indirect immunofluorescence of affected mucous membrane and healthy skin. Indirect immunofluorescence (on salt splitted skin). Comercial ELISA as well as immunoblot are available and useful for final diagnosis.	EBA can be therapy resistand disease. Although it is known that oral corticosteroids are not very effective in this disease, patiens are often treated with CS as a first line treatment. According to the literature colchicine or dapsone could be treatment of choice. If this therapy doesn't give results, immunosuppressants, IVIg or rituximab should be tried.	Optimal management of EBA patients require a multidisciplinary approach by highly specialized dermatologists, as well as specialists of other specialities as well as general practitioners. Specialists who can be involved in the management of corticosteroid- side effects are rheumatologists, endocrinologists and ophtalmologists. Nurses are also involved in the therapy. Nursing staff play also a major role in patients' educational programs. Many patients complain of long-lasting symptoms or psychological troubles, that frequently needs the intervention of psychologists.	
5. Linear IgA Disease	Rare disease, often misdiagnosed as Dermatitis herpertiformis Duhring, BP or MMP	Histopathology is unspecific, closely resembling other pemphigoid diseases. Indirect immunofluorescence on monkey esophagus is often negative. Frequently, Western blotting is required to detect antibodies, which requires specialized autoimmune labs.	Disease is of recalcitrant under treatment. There are no controlled trials evaluating treatments. Standard treatment is dapsone, which is only rarely used by most dermatologists but requires some experience in its use. Pediatric expertise is required when children are affected.	The disease requires treatment by specialized dermatlologists often over many years. Specialists from other disciplines (e.g., ophthalmologists, gastroenterologists) are especially required when mucous membranes are involved.	Itch, pain, blindness, dysphagia, colitis

6. Dermatitis Herpetiformis	The diagnosis of DH can be delayed for several months or years due to the polymorphic nature of the cutaneous eruption, the lack of vesiculo-bullous lesions which are often excoriated due to the severe pruritus. In these cases, DH might not be suspected due to clinical similarity to atopic dermatitis, insect bites, neurotic excoriations, or prurigo-like eruptions. The delay in recognizing DH has severe impact on patients' quality of life.	A definitive diagnosis of DH cannot be made without this diagnostic DIF finding. A potential cause for its delay is a false negative result from the DIF, which can occur if lesional skin is biopsied because the inflammatory infiltrate can destroy the IgA. The optimal biopsy site for DIF testing is normal-appearing skin immediately adjacent to a lesion. In cases of clinical signs suggestive of DH and negative DIF, serial sections of the biopsy should be performed and if negative a second biopsy should be taken from surely uninvolved skin and checking that the patient is not on a GFD. DIF testing must be performed in experienced laboratories to minimize both false-positive and false-negative results.	The treatment of DH includes avoidance of gluten, and suppressive treatment with dapsone (diamino-diphenyl-sulfone, DADPS) at a dosage of 100 to 200 mg per day. In patients intolerant to dapsone, who are glucose-6-phosphate dehydrogenase deficient, or who have cardiac disease, a second line pharmacological treatment with sulfasalazine (1-2 g/daily) or sulfapyridine (0.25 - 1.5 g/daily) can be considered. Regular screening for dapsone-induced side effects is needed. Strict GFD can clear cutaneous lesions and reverse underlying GSE. Upon reintroduction of gluten the eruption recurs. Although GFD offers many benefits in the management of DH, it is not easy to realize by many DH patients. A GFD requires scrupulous monitoring of all ingested foods; it is time-consuming and socially restricting. Strict adherence to a GFD requires extensive knowledge of foods and diet, thus consultation with a dietician and involvement in DH support groups are strongly encouraged. In general, patients following a GFD are advised to read carefully all food labels and to avoid products with unfamiliar ingredients since many of them (i.e. additives, cereal grains, colourings, emulsifiers, excipients, flavourings, malts, hydrolysed plant and vegetable proteins, etc.) may be derivatives of gluten-containing products.	Optimal management of DH patients requires a multidisciplinary approach by highly specialized dermatologists, gastroenterologists and dieticians for evaluation of GSE and formulation of a GFD to help alleviate future symptomatology, and GPs. Other specialists who can be involved are hematologists in the management of dapsone side effects but also to rule out potential lymphoma, endocrinologists in the diagnosis of frequently associated autoimmune diseases (thyroid disease, insulin-dependent diabetes, Addison’s disease, etc.), and neurologists for diagnosis and management of neurologic disease if present. Nursing staff plays also a major role in patients' educational programs. Dieticians are of outmost importance in the adherence to a strict GFD and alleviation of malabsorption symptoms. Many patients complain of long-lasting symptoms or psychological troubles that frequently needs the intervention of psychologists. Considering the increased incidence of immunomediated diseases and associated conditions, several screening tests should be performed in patients with dermatitis herpetiformis. Nonspecific antibodies, such as antithyroid peroxidase, antigastric parietal cells, antinuclear and anti-Ro/SSA antibodies, should be tested in both DH and CD patients. The presence of such antibodies correlates with autoimmune predisposition of CD/DH patients. Furthermore, testing for thyroid disease (TSH, T3 and T4) and for diabetes (glucose) should be performed	Intense pruritus, malabsorption, difficulties in following GFD, resulting in impaired quality of life.

Rare Diseases(s)	Key Diagnostic Tests	Key Treatment, Resources or Procedures
1. Pemphigus	Histologic examination of a skin biopsy, direct immunofluorescence performed on the skin and/or the mucous membranes, and serum examination using different techniques: indirect immunofluorescence, immunoblotting and ELISA assays.	Multidisciplinary team. Wound care. Management of pain, pruritus, psychological trauma, and transient or long-lasting treatment side effects (medical and/or surgical management). Oncology.
2.Bullous Pemphigoid	Histologic examination of a skin biopsy, direct immunofluorescence performed on the skin and/or the mucous membranes, and serum examination using different techniques: indirect immunofluorescence, immunoblotting and ELISA assays.	Multidisciplinary team. Wound care. Management of pruritus, psychological trauma, and transient or long-lasting steroid treatment side effects (medical and/or surgical managment).
3. Mucous Membrane Pemphigoid	Histologic examination of a skin/mucous membrane biopsy, direct immunofluorescence performed on the skin and/or the mucous membranes, and serum examination using different techniques: indirect immunofluorescence, immunoblotting and ELISA assays.	Multidisciplinary team. Wound care. Mouth and other mucous membrane care. Management of pain, scars and the complications arising from the scars, psychological trauma, and transient or long-lasting treatment side effects (medical and/or surgical management). Oncology (increased risk in anti-laminin 332 MMP)
4. Epidermolysis bullosa acquisita	Histologic examination of a skin biopsy, direct immunofluorescence performed on the skin and/or the mucous membranes, and serum examination using different techniques: indirect immunofluorescence, immunoblotting and ELISA assays.	Multidisciplinary team. Wound care. Management of pruritus, psychological trauma, and transient or long-lasting steroid treatment side effects (medical and/or surgical management).
5. Linear IgA Disease	Histopathology, direct immunofluorescence, indirect immunofluorescence on salt-split skin, immunoblot	Multidisciplinary team. Management of pruritus and pain, Wound care, management of scars, psychological trauma, monitoring and management of drug side effects. Pediatrician if children are affected
6. Dermatitis Herpetiformis	Histologic examination of a skin biopsy, direct immunofluorescence performed on perilesional skin and serum examination using different techniques: Indirect immunofluorescence, immunoblotting and ELISA assays.	

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

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. Pemphigus	10		The incidence of pemphigus is about 3 new cases per million inhabitants per year	2	

2.Bullous Pemphigoid	20		The incidence of BP is 12.1 to 66 new cases per million per year in epidemiological studies from different European countries		
3. Mucous Membrane Pemphigoid	7	na	The incidence of MMP is: ~1 case per million inhabitants per year, the prevalence is: per million inhabitants	2	na
4. Epidermolysis bullosa acquisita	03-mai				
5. Linear IgA Disease	5		The incides is 1 case/million/year		
6. Dermatitis Herpetiformis	10	3	An incidence of about 11 and 13 cases/million/year is found in Sweden in Finand, respectively but it tends to decrease with the decades.		

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

Rare Diseases(s)	Health Care Professional (type)	Training & Qualifications	Minimum of number of procedures per patient per year	Rationale
1. Pemphigus	Dermatologist	2-3 years experience	10 patients	Management of the different localisation of the disease and the complication and sequelae of treatment. Patients educational programs.
	ENT	5 years experience	2 patients	
	Ophthalmologist	2-3 years experience	2 patients	
	Dentist / Stomatologist	2-3 years experience	8 patients	
	Gynaecologist	2-3 years experience	2 patients	
	Rheumatologist	2-3 years experience	4 patients	
	Cardiologist	2-3 years experience	4 patients	
	Endocrinologist	2-3 years experience	5 patients	
	Pain physician	2-3 years experience	3 patients	
	Dietician	2-3 years experience	10 patients	
	Specialized nurse	2-3 years experience	10 patients	
	Psychologist	2-3 years experience	6 patients	
	Physiotherapist	2-3 years experience	5 patients	
2. Bullous Pemphigoid	Dermatologist	2-3 years experience	20 patients	
	Internist	5 years experience	10 patients	
	Ophthalmologist	2-3 years experience	5 patients	

	Rheumatologist	2-3 years experience	5patients
	Cardiologist	2-3 years experience	5 patients
	Endocrinologist	2-3 years experience	5 patients
	Dietician	2-3 years experience	10 patients
	Specialized nurse	2-3 years experience	10 patients
	Psychologist	2-3 years experience	10 patients
	Physiotherapist	2-3 years experience	10 patients
3. Mucous Membrane Pemphigoid	Dermatologist	5 years experience	5 patients
	ENT	5 years experience	5 patients
	Ophthalmologist	2-3 years experience	5 patients
	Dentist / Stomatologist	2-3 years experience	5 patients
	Gynaecologist	2-3 years experience	2 patients
	Rheumatologist	2-3 years experience	2 patients
	Cardiologist	2-3 years experience	2 patients
	Endocrinologist	2-3 years experience	2 patients
	Pain physician	2-3 years experience	3 patients
	Dietician	2-3 years experience	5 patients
	Specialized nurse	2-3 years experience	5 patients
	Psychologist	2-3 years experience	5 patients
	Physiotherapist	2-3 years experience	2 patients
4. Epidermolysis bullosa acquisita	Dermatologist	5 years experience	5 patients
	ENT	5 years experience	5 patients
	Ophthalmologist	2-3 years experience	5 patients
	Dentist / Stomatologist	2-3 years experience	5 patients
	Gynaecologist	2-3 years experience	2 patients
	Rheumatologist	2-3 years experience	2 patients
	Cardiologist	2-3 years experience	2 patients
	Endocrinologist	2-3 years experience	2 patients
	Pain physician	2-3 years experience	3 patients
	Dietician	2-3 years experience	5 patients
	Specialized nurse	2-3 years experience	5 patients
	Psychologist	2-3 years experience	5 patients

	Physiotherapist	2-3 years experience	2 patients	
5. Linear IgA Disease	Dermatologist	5 years experience	5 patients	
	ENT	5 years experience	5 patients	
	Ophthalmologist	5 years experience	5 patients	
	Pediatrician	5 years experience	5 patients	
	Dentist / Stomatologist	2-3 years experience	5 patients	
	Gynaecologist	2-3 years experience	2 patients	
	Rheumatologist	2-3 years experience	2 patients	
	Cardiologist	2-3 years experience	2 patients	
	Endocrinologist	2-3 years experience	2 patients	
	Pain physician	2-3 years experience	3 patients	
	Dietician	2-3 years experience	5 patients	
	Specialized nurse	2-3 years experience	5 patients	
	Psychologist	2-3 years experience	5 patients	
	Physiotherapist	2-3 years experience	2 patients	
6. Dermatitis Herpetiformis	Dermatologist	2-3 years experience	10 patients	Management of the skin rash, gluten enteropathy and potential associated disease, including prevention of malignancies, as well as management of complications and sequelae of treatment. Patients educational programs.
	Gastroenterologist	2-3 years experience	10 patients	
	Endocrinologist	2-3 years experience	5 patients	
	Hematologist	2-3 years experience	5 patients	
	Neurologist	2-3 years experience	3 patients	
	Dietician	2-3 years experience	10 patients	
	Specialized nurse	2-3 years experience	10 patients	
	Psychologist	2-3 years experience	10 patients	
	General practitioner	2-3 years experience	3 patients	

Rare Diseases(s)	**Specialised equipment, infrastructure, and information technology**	**Threshold**	**Rationale**
1. Pemphigus	Out-patient clinic and in-patient beds, immunology laboratory familiar with immunoblotting and ELISA assays.	4 clinics per year and as required admissions	Minimal experience
2.Bullous Pemphigoid	Out-patient clinic and in-patient beds, immunology laboratory familiar with immunofluorescence, immunoblotting and ELISA assays.	2 clinics per month and as required admissions	Minimal experience

3. Mucous Membrane Pemphigoid	Out-patient clinic and in-patient beds, close collaboration with ENT specialist, ophthalmologist, gynaecologist, immunology laboratory familiar with immunofluorescence, immunoblotting and ELISA assays.	1 clinic per month and as required admissions	Minimal experience
6. Dermatitis herpetiformis	Out-patient clinic and in-patient beds, immunopathology laboratory familiar with direct and indirect immunofluorescence, and immunoserology laboratory familiar with immunoblotting and ELISA assays.	4 clinics per year and as required admissions	Minimal experience

Please provide a summary explaining the approach or plans your group will undertake to produce good practice guidelines and implement outcome measure and quality controls
PEMPHIGUS : Clinical practice guidelines for pemphigus have been done by the EADV/EDF task force and published in the Journal of the European Academy of Dermatology in 2014. These guidelines will have to be updated to take into account major advances in the treatment of pemphigus (especially the first line use of rituximab). The French study group on autoimmune blistering skin diseases has proposed specific guidelines for the management of oral lesions and dental care in pemphigus patients. These guidelines will have to be discussed by the European group.
BULLOUS PEMPHIGOID: EADV/EDF Consensus recommendations have been published in the British Journal of Dermatology in 2015. EADV study on the 0.5mg/kg BW in BP treatment (co ordinated by Prof Joly) will add useful data. Also, discussion on newer targeted therapies will be continued. Use of quality of life outcome measures (ABQOL, TABQOL) in all centres will help improving physician's concept about the impact of BP on patient's quality of life.
MUCOUS MEMBRANE PEMPHIGOID: In 2002 the first and only consensus on diagnosis and treatment of MMP has been published in the Archives of Dermatology. Definitions and outcome measures for MMP have been published in the Journal of the American Academy of Dermatology 2015. A new consensus/guidelines, especially on the treatment of MMP, is necessary. Studies comparing dapson and cyclophosphamide to rituximab will be performed.