Specific Operationnal Criteria - Autoimmune Bullous Diseases & Severe 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. 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.

Autoimmune Bullous Diseases & Severe Drug Reactions

Rare Diseases(s)	Short description of the rare disease - Code/ ICD/ Orphacode	Epidemiology	Prevalence &Incidence
2.Stevens-JohnsonSyndrome and Toxic epidermal necroylsis	ORPHA537- SJS and TEN are considered variants of epidermal necrolysis. They occur 4-28 days after drug exposure. For about 30% of the cases (SJS/TEN), no causative drug is identified, and, for 15%, drug responsibility is deemed unlikely. Mycoplasma pneumoniae has been associated with SJS/TEN in children. General physical deterioration, fever, flu-like syndrome, ocular and ear, nose and throat (ENT) events and skin pain frequently precede dermatological manifestations, and are key points contributing to early diagnosis. Initially, the eruption is distributed on the face, upper trunk and proximal extremities, while distal portions of upper and lower limbs are relatively spared. Initial lesions are characterized as erythematous, dusky–red macules, irregularly shaped. Atypical target lesions with dark centers may often be observed without the typical three concentric rings of erythema multiforme major. Necrotic lesion confluence leads to extensive erythema, flaccid blisters and large epidermal sheets, revealing areas of red dermis. Nikolski's sign, ie, epidermis sloughs off under lateral pressure, is positive on erythematous areas. Clinical classification is defined by the extent of body surface area skin detachment: <10% SJS, ≥30% TEN and in between overlap SJS/TEN. Two or more mucous membranes are involved in 80% of the cases, often preceding skin lesions. Erythema, blisters or erosions involve nasopharynx, oropharynx, eyes, genitalia and/or anus mucous membranes, and occur during the early stage associated with pain and dysfunction. When the lips have a vermillion border and oral-cavity hemorrhagic erosions are coated by grayish–white pseudomembranes, crusts are the main lesions. Conjunctival lesions, including hyperemia, erosions, chemosis, photophobia and tearing comprise eye involvement. Severe forms lead to corneal ulceration, anterior uveitis, purulent conjunctivitis and synechiae. Disease progression is time-limited (7 to 10 days). SJS/TEN visceral involvements include transient liver and/or renal enzyme increases or bronchial and digestive tract epithelial necroses. Although rare, specific acute visceral failures in SJS/TEN must be suspected and documented after eliminating bacterial or viral superinfection. No specific score or diagnostic test is available for SJS/TEN diagnosis. The diagnosis mainly relies on a broad spectrum of clinical signs/symptoms and histological tests. Full-thickness epidermal necrosis and negative direct test are mandatory. Less sensitive indirect immunofluorescence assays are mainly helpful to assess alternative diagnoses. Differential diagnoses include erythema multiforme major, linear IgA bullous dermatosis ((spontaneous or drug-related), generalized FDE, superficial burns, cytotoxic drugs eg methotrexate, toxicity, acute graft vs host disease. TEN-like histological and clinical features were recently described with	The incidence of SJS/TEN is estimated at 2/million inhabitant	cf. Epidemiology

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	
2. Toxic epidermal necrolysis	Case-assessment relies on the eruption's clinical appearance, eg, potentially virus- or drug-related, duration and associated symptoms (eg, fever, pruritus, lymphadenopathy) and the time elapsed between drug intake and sevre cutaneous adverse reactions (SCAR) onset. Physical examination includes the description of SCAR-specific lesion distributions. For orifices, the cutaneous or mucous membrane indicating a severe reaction (external or internal) must be specified. Photos and clinical signs should be collected as often as possible to enable retrospective expert SCAR validations. Skin biopsy, including direct immunofluorescence of blistering eruptions and some biological tests are strongly recommended. If confirmed, SJS/TEN management by a referral center or specialized intensive care unit is strongly recommended. A better survival rate is associated with SJS/TEN diagnosis within 7 days after onset.	No specific score or diagnostic test is available for SJS/TEN diagnosis. The diagnosis mainly relies on a broad spectrum of clinical signs/symptoms and histological tests. Full-thickness epidermal necrosis, and negative direct test are mandatory.6 Less sensitive indirect immunofluorescence assays are mainly helpful to assess alternative diagnoses. Differential diagnoses include erythema multiforme major, linear IgA bullous dermatosis (spontaneous or drug-related), generalized fixed drug eruption, superficial burns, cytotoxic drugs eg methotrexate, toxicity, acute graft vs host disease. TEN-like histological and clinical features were recently described with Coxsackievirus A6 infection. Diagnostic tests may easily discard differential diagnoses. Drug-causality assessment considers	For all patients, culprit-drug identification and its early withdrawal are the first mandatory steps. During the acute stage, SCARs may require intensive care because of multiorgan failure and fluid loss. Supportive care consists of hemodynamic equilibrium and prevention of life-threatening complications.Patients with erythroderma and/or epidermal detachment are exposed to increased fluid loss, hypovolemia, renal insufficiency, thermal dysregulation and sepsis. Fluid replacement must be started as soon as possible and adjusted daily. Environmental temperature should be raised to 28°C. Nutritional hypercaloric and hyperprotidic enteral feeding of SJS/TEN patients is systematically discussed and often initiated through a nasogastric tube.Central venous lines are placed, when possible, in a region of uninvolved skin. For SJS/TEN, opioid agonists are used to limit the pain and/or stress inherent in mucosal or skin-debris removal. 70sitating respiratory	SCARs, mainly SJS/TEN and DRESS, are life-threatening and carry a non-negligible risk of severe sequelae. During SJS/TEN acute stages, visceral involvement (eg, renal failure, intestinal, ocular-specific pulmonary lesions and/or sepsis) represents the main complication. Respiratory insufficiency may result from specific involvement or misswallowing with superinfection, severe ENT lesion defined by laryngeal lesion being significantly associated to pulmonary infection. Sepsis is the predominant	See. Specific challenge. At the population level, avoiding SCARs as much as possible should be considered an "active" public health and drug policy SJS/TEN organizing experts and referral centers to improve SCAR management and outcomes; patients' viewpoints and associations, such as Amalyste (French Lay Group of patients having had TEN).

Rare Diseases(s)	Key Diagnostic Tests		Key Treatment, Resources or Procedures
2. Toxic epidermal nerolysis	Express histological examination. Histologic examination of a skin biopsy, direct immunofluorescence performed on the skin.		Multidisciplinary team: Intensive Care Unit or Burn Unit, Wound Care, Dermatologists, Ophthlamologists, Pneumologists, Urologists, Gynecologists, Otorhino-Laryngologists , management of pain, psychological trauma, follow-up of sequelae.

Please state the minimum/optimum thresholds that Healthcare Providers within the network will need to meet to maintain competence and expertise. List the					
Rare Diseases(s)	**Minimum Number of patients treated per year at each HCP**			**Minimum Number of new patients**	
	Adults	Paediatric*	Rationale for the threshold	Adults	Paediatric*
1. Toxic epidermal necrolysis	10	2	Incidence is around 2 per million of inhabitants	10	2

Please list the necessary human resources and the profesional qualifications essential to the quality of patient care within the Network's area				
Rare Diseases(s)	**Health Care Professional (type)**	**Training & Qualifications**	**Minimun of number of procedures per patient per year**	**Rationale**
2. Toxic epidermal necrolysis	Dermatologist	2-3 years experience	10 patients	Managment of the different localisation of the disease and the complication and sequelae.
	ICU or Burn Unit Doctor	2-3 years experience	10 patients	
	ENT	2-3 years experience	2 patients	
	Ophthalmologist	2-3 years experience	10 patients	
	Dentist / Stomatologist	2-3 years experience	5 patients	
	Gynaecologist	2-3 years experience	2 patients	
	Urologist	2-3 years experience	2 patients	
	Pain physician	2-3 years experience	3 patients	
	Dietetician	2-3 years experience	10 patients	
	Specialized nurse	2-3 years experience	10 patients	
	Psychologist	2-3 years experience	10 patients	

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**		
2. Toxic epidermal necrolysis					
2.	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		

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
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 diseasesi 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.