Universitätsklinikum Jena

Zentrum für Klinische Studien

Registry Protocol

Sepsis-Associated Purpura Fulminans International Registry - Europe

SAPFIRE

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Principal Investigator:
Prof. Frank M. Brunkhorst, MD
Jena University Hospital
Center for Clinical Studies
Department of Anesthesiology and Intensive Care Medicine
Salvador-Allende-Platz 27, 07747 Jena

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Table of contents

1. Signature page

The signatories confirm herewith their approval of the present Registry Protocol.

Name: Prof. Frank M. Brunkhorst, MD **Principal Investigator**	**Date** 18.07.13	**Signature**
Name: Thomas Lehmann, PhD **Biometrician**	**Date** 18.07.13	**Signature**

2. List of abbreviations

AE	Adverse Event
APACHE II	Acute Physiology and Chronic Health Evaluation (Version II)
aPTT	activated Partial Thromboplastin Time
CK	Creatine kinase
ECMO	Extracorporeal Membrane Oxygenation
eCRF	electronic Case Report Form
GCP	Good Clinical Practice
GEP	Good Epidemiologic Practice
ICU	Intensive Care Unit
IRB	Institutional Review Board
ISF	Investigator Site File
PELOD	Pediatric Logistic Organ Dysfunction
PF	Purpura fulminans
PRISM III	Pediatric Risk of Mortality (Version III)
PT	Prothrombin time
SAE	Serious Adverse Event
SAPF	Sepsis-associated Purpura Fulminans
SAPS II	Simplified Acute Physiology Score (Version II)
SOFA	Sequential Organ Failure Assessment
TATc	Thrombin-Antithrombin Complex

3. Responsible parties

Project leader Principal investigator	Prof. Frank M. Brunkhorst, MD Jena University Hospital Center for Clinical Studies Salvador-Allende-Platz 27, 07747 Jena Tel.: +49 3641-9-323381 E-Mail: frank.brunkhorst@med.uni-jena.de
Project Management	Dr. Wibke Wetzker Jena University Hospital Center for Clinical Studies Salvador-Allende-Platz 27, 07747 Jena Tel.: +49 3641-939 66 99 E-Mail: wibke.wetzker@med.uni-jena.de
Biometrics	Thomas Lehmann, PhD Jena University Hospital Center for Clinical Studies Salvador-Allende-Platz 27, 07747 Jena Tel.: +49 3641-9-396678 E-Mail: thomas.lehmann@med.uni-jena.de
Data Management	Cornelia Eichhorn Jena University Hospital Center for Clinical Studies Salvador-Allende-Platz 27, 07747 Jena Tel.: +49 3641- 9-396653 E-Mail: cornelia.eichhorn@med.uni-jena.de

Advisory Committee	***Voting members*** Jan Hazelzet, MD, PhD, FCCM Erasmus Medical Center Rotterdam, The Netherlands Prof. Paul Knöbl, MD Medical University of Vienna Vienna, Austria Simon Nadel, MRCP St Mary's Hospital, Imperial College London, United Kingdom Michael Sasse, MD Hannover Medical School Hannover, Germany Owen Smith, MD Our Lady's Children's Hospital Dublin, Ireland

4. Abstract

Title	Sepsis-Associated Purpura Fulminans International Registry - Europe
Short title (Acronym)	SAPFIRE
Rationale and background	*Purpura fulminans* is the clinical manifestation of disseminated thrombosis in dermal and systemic microcirculation. This rare disease is frequently associated with multiple organ failure and represents a life-threatening condition with mortality exceeding 50 %. Apart from isolated idiopathic cases, deficiency of Protein C, a major intrinsic anti-coagulant, is considered the leading cause of *Purpura fulminans*. In the vast proportion of cases, the condition has been shown to emerge secondary to acquired Protein C deficiency associated with severe sepsis, mostly of meningococcal or pneumococcal origin. A consistent therapeutic approach to sepsis-associated *Purpura fulminans* (SAPF) has not been established yet. With exaggerated pro-coagulant activity being confirmed as the key pathogenic aspect, several treatment modalities aiming at the balance restoration in the coagulation cascade have been considered. Based on the experience gathered in patients with inherited Protein C deficiency, supplementation with Protein C formulations has been used as adjuvant therapy in SAPF. Most of the information on SAPF incidence and therapy has been obtained before 2004. Meanwhile, lack of comprehensive data poses considerable difficulties with regard to its diagnosis and treatment. SAPF causality might have been substantially altered in the wake of widespread meningococcal vaccination. There are neither evidence-based treatment guidelines nor comparative evaluation of the efficacy of different therapeutic approaches. Therefore there is a pronounced need of systematic data collection and evaluation covering several aspects of SAPF, such as epidemiology, causality, morbidity and therapy.
Research question and objectives	• Systematic acquisition, analysis and dissemination of information on incidence and prehospital/inhospital course of *Purpura fulminans*, (possible long-term follow up) and its relation to infectious agents (e.g. meningococcemia, streptococcus etc.) • Systematic acquisition, analysis and dissemination of information on current management of PF (sepsis bundles and replacement strategies – protein C, AT, etc.) • Systematic acquisition, analysis and dissemination of information on outcomes (morbidity, mortality) of PF with current management strategies, stratified for use or non-use of protein C
Design	Prospective multicenter registry derived from systematic data collection on the incidence and treatment of sepsis-associated *Purpura fulminans*
Population	Patients diagnosed with *Purpura fulminans* associated with severe sepsis

Endpoints	• All-cause in-hospital mortality • Morbidity at defined post-diagnosis intervals and over 7 consecutive days - Mean total SOFA score (age ≥ 16) - PELOD score (age < 16) - ΔSOFA or dPELOD score for day-to-day comparisons • Extent and severity of Purpura lesions • Need for reconstructive surgery (amputations, skin grafts) • Length of ICU stay (days) • Length of hospital stay (days) • Changes in hematological parameters - WBC count - Thrombocyte count - Hemoglobin • Changes in coagulation parameters - Prothrombin time (PT) - Activated partial thromboplastin time (aPTT) - Fibrinogen - D-dimers - Thrombin-antithrombin complex (TATc) - Protein C activity - Antithrombin III activity • Changes in inflammatory parameters - C-reactive protein (CRP) - Procalcitonin (PCT) - Interleukin 6 (IL-6) • Changes in organ dysfunction parameters - Glucose - Lactate - Creatine kinase (CK) • Duration of mechanical ventilation (days) • Duration of renal replacement therapy (days) • Vasopressor use (days/doses) • Sepsis-inducing pathogen • Adverse event related to PF treatment (reporting as per decision of the investigator) - Bleeding - Thrombotic events
Inclusion criteria	- Diagnosis of severe sepsis and *Purpura fulminans* - Signed informed consent (according to local legal regulations)
Exclusion criteria	- premature neonates (< 36 gestational week)
Centers	Approx. 30 participating centers in Germany, Austria, Ireland, UK, Italy, Spain, Netherlands (selected centers)

Timetable	First patient in	Q3 2015
	Registry duration	3 years, with an option of prolongation
	Estimated enrolment	Approx. 50 patients/year
	Interim Analysis	Biannually

5. Amendments and updates

Number	Date	Section of registry protocol	Amendment or update	Reason
01	30.9.2015		Update	• Flowchart optimization • Staff change • ADR reporting
02	31.08.2017		Update	•
03	11.07.2019		Update	• Staff change • Milestones delete

6. Rationale and background

Purpura fulminans is a life-threatening and highly disabling condition characterized by rapidly evolving thrombosis in the dermal and systemic microcirculation. The estimated incidence of the disease is 0.1 per 100,000 inhabitants [Nicolas and Debonne, 2002]. It is associated with high mortality (above 50 %), owing to progressive cutaneous hemorrhage and multiple organ dysfunction. Profound tissue lesions and grave disturbance in numerous vital functions also determine a considerable long-term morbidity and disability.

Apart from a few cases of idiopathic origin, the etiology of *Purpura fulminans* is ascribed to either congenital abnormality or acquired deficiency of Protein C-operating anticoagulant pathways. The latter condition is in the vast majority secondary to an acute severe infection, thus coining the term sepsis-induced or sepsis-associated *Purpura fulminans* (SAPF) [Betrosian et al., 2006]. Several bacterial pathogens can induce SAPF, with meningococcal and pneumococcal infections accounting for the majority of cases. Causal involvement of viral and protozoan pathogens also has been described [Betrosian et al., 2006].

The pathogenesis of SAPF exemplifies the induction of a coagulopathy by the intertwined action of extrinsic bacterial (e.g. endotoxins) and intrinsic (e.g. vascular, inflammatory and hematologic) factors. The decay of endogenous anti-coagulant systems has a decisive contribution to the imbalance of clotting in sepsis and the presence of a consumptive coagulopathy is a distinct feature of infection-associated *Purpura fulminans* [Darmstadt, 1998]. Extensive similarities with clinical and pathological characteristics of *Purpura fulminans* in congenital Protein C deficiency have brought this endogenous anti-coagulant into focus with regard to the pathogenesis of SAPF [Francis, 1990]. Indeed, SAPF reflects an exaggerated pro-coagulant response resulting from decreased abundance/activity of endogenous anticoagulants, such as antithrombin and Protein C [Dempfle,

2004]. Meanwhile, ample evidence has accumulated in support of the view that circulating Protein C concentrations markedly decline in severe sepsis, due to both, suppressed biosynthesis and increased consumption/degradation [Fourrier et al., 1992; Leclerc et al., 1992; Borgel et al., 2006; Shorr et al., 2006].

The emergence of SAPF lesions is considered a localized manifestation of the Shwartzman phenomenon [Francis, 1990]. Bacterial endotoxin-triggered endothelial damage, inflammatory cytokine release and tissue factor production, in conjunction with continuous thrombin generation and breakdown of the regulatory feedback exerted by natural anti-coagulants, lead to multiple intravascular coagulation, perivascular infiltration and extravasation, which become manifest as cutaneous lesions. The latter evolve rapidly from scattered erythema to petechiae and ecchymoses, and ultimately to necrosis of the skin and subcutaneous tissue. As intravascular coagulation occurs simultaneously in visceral organs as well, signs of multiple organ dysfunction and failure are integral parts of the clinical presentation [Francis, 1990].

Although several therapeutic interventions have been employed in the past, currently there are no evidence-based medical management guidelines for SAPF. Pathogenesis-targeting approaches generally aim at the restoration of balance of pro- and anti-coagulation pathways, thereby curtailing intravascular clotting. The broad array of such disease-modifying options [Darmstadt, 1998] has been narrowed over time to the supplementation of essential endogenous anti-coagulants as either whole plasma products (fresh frozen plasma, cryoprecipitate, and plasmapheresis) or single-protein formulations (Protein C concentrate, recombinant activated Protein C, antithrombin III, tissue plasminogen activator). The therapeutic experience with these products has been described in several studies [Cobcroft et al., 1994; Ettingshausen et al., 1999; Rintala et al., 2000; White et al., 2000; de Kleijn et al., 2003; Dhainaut et al., 2004; Zenz et al., 2004; Vincent et al., 2005; Schellongowski et al., 2006; Nadel et al., 2007; Veldman et al., 2010; Donati et al., 2013] and numerous case reports.

Gaps in knowledge and controversial study results constitute the major difficulties in establishing compelling recommendations for the treatment of SAPF. The longstanding concept that meningococcal infections are the principal cause of SAPF might need reconsideration in view of the broad introduction of meningococcal vaccination [Maat et al., 2007]. The evaluation of the importance of this factor is far from accomplished. The limited endurance of immunity achieved with the quadrivalent vaccine (Vu et al., 2006), and insufficient data on the epidemiological consequences of the recently introduced vaccines against meningococcal serotypes B (Martin and Snape, 2013), C and Y (Perry, 2013) pose difficulties in establishing a comprehensive overview. Suboptimal performance of certain protein products with regard to general sepsis outcomes (Marti-Carvajal et al., 2012; Nadel et al., 2007) has generated doubts as to their applicability and led to market withdrawal and corresponding changes in sepsis treatment guidelines [Dellinger et al., 2012]. Apart from a few experimental reports [Aoki et al., 2000], head-to-head comparisons of the efficacy of individual treatment modalities in SAPF have not been performed. Finally, systematic collection and evaluation of information on the epidemiology, causality, course, morbidity, comparative efficacy of therapeutic approaches, as well as effects of co-medication and outcomes of SAPF remains to be implemented.

7. Research questions and objectives

Clinical registries are valuable instruments for the continuous collection and assessment of information on the epidemiology and outcomes of rare diseases as well as for usage of drugs and medicinal products.

Registries are highly relevant pertaining to issues of quality assurance. They permit the evaluation of clinical benefit and general performance of the therapeutic approach/product under real-life conditions and large-scale application, and foster the usage of accumulated knowledge for the generation of performance benchmarks.

Unlike randomized controlled trials, registry data allow the identification of subcategories of patients, who display exceptionally pronounced or insufficient benefit of the treatment.

Ultimately, clinical registries are a powerful medium for the transfer of innovative therapy approaches into the clinical routine.

The present registry aims at

- Large-scale data accumulation and comprehensive evaluation of the incidence, causality and current treatment strategies of SAPF
- Comparative assessment of treatment strategies including or not including protein C supplementation
- Identification of patient subgroups of particular eligibility for Protein C treatment, as judged by established criteria of disease severity assessment
- Feedback of aggregated data to registry contributors, thus permitting quality management and standard updates
- Dissemination of data evaluation summaries and recommendations for the use of Protein C formulations in clinical routine
- Elaboration of a framework for SAPF treatment recommendations and guidelines

8. Research methods

8.1. Study design

The registry comprises prospective, open-label data collection on the current state of incidence and management of SAPF, regardless of the etiopathogenic background. Using appropriate statistical techniques, specific emphasis will be laid on the comparison of outcomes in therapeutic approaches including or avoiding supplementation with Protein C formulations.

8.2. Setting

The registry will include comprehensive records on diagnosis, morbidity and management of SAPF, supplied in the form of eCRFs by the participating centers over a period of three years.
The provision of informed consent by the patient or patient's legal guardian will be required for inclusion in accordance with local legal regulations.
The causal SAPF-inducing pathogen will be identified by microbiological examination.
The presence of Protein C deficiency and its contribution to the clinical manifestations of SAPF will be examined upon enrolment by determinations of Protein C concentration and activity, and subsequently documented in the eCRF. Changes in Protein C levels resulting from supplementation will be monitored as well.
The registry will also compare data on the efficacy of therapeutic approaches including or omitting Protein C supplementation.
A further aspect of specific interest is the stratification of outcomes by demographic (e.g. age, sex) and clinical criteria (e.g. morbidity at admission, causal pathogen), in order to identify subgroups of patients with above-average or marginal responsiveness to Protein C supplementation.
The contribution of supportive measures (e.g. assisted ventilation, renal replacement therapy, fluid resuscitation) and co-medication (e.g. vasopressors, corticosteroids, heparin etc.) will be evaluated as well.

Flowchart

Activity / Endpoint	Baseline[1)]	Post-diagnosis period (days)					
		1	3	5	7	ICU discharge or death on ICU after day 7	End of study at hospital discharge or in-hospital death after ICU discharge
Confirm inclusion criteria	x						
Provision of informed consent [2)]	x						
Demographic data collection (incl. ethnic origin)	x						
Risk factors (vaccination status, asplenia) and comorbidities	x						
Estimated time of SAPF onset (hours)	x						
Mortality prediction (APACHE II /SAPS II[3)] or PRISM III[4] score)	x						
Morbidity assessment (SOFA[3]/PELOD[4] score)	x	x	x	x	x		
Laboratory parameters (hematology, coagulation, inflammation)	x	x	x	x	x		
Purpura lesion assessment (c.f. eCRF)	x	x	x	x	x		
Vasopressor use record	x	x	x	x	x	x	
Site, source and origin of infection (including viral)							x
Concomitant causal, supportive and adjunctive treatment (c.f. eCRF)		x	x	x	x	x	
Cumulative dose of blood products and anti-coagulant treatment		x	x	x	x	x	
Antimicrobials		x	x	x	x	x	
Days in ICU							x
Days on mechanical ventilation							x
ECMO and circulatory support systems		x	x	x	x	x	
Days/type on renal replacement therapy							x
Purpura-related surgery (fasciotomy, debridement, amputation)							x
In-hospital mortality assessment		x	x	x	x	x	x
Days in hospital							x
Adverse drug reactions							x

[1)] admission at ICU;
[2)] according to local regulations
[3)] APACHE II/SAPS II and SOFA scores will be used in patients aged above 16
[4)] PRISM III and PELOD scores will be used in patients aged below 16

8.3. Variables

The selection of the endpoint all-cause in-hospital mortality is justified, in view of the exceptional severity of the disease *per se* and considerable risk associated with the subsequent management of its late sequelae (e.g. reconstructive surgery). On a case-by-case basis, a comparison with the probability of a lethal outcome, as defined by the APACHE II/ SAPS II or PRISM III score, will be made.

Changes in morbidity (as assessed by the SOFA or PELOD indices) will be presented by the difference between scores measured at admission and after 1, 3, 5 and 7 days upon being diagnosed with SAPF (ΔSOFA, dPELOD), as well as by the mean total score (SOFA, PELOD) recorded over the observation period of 7 days.

Records will also include description of imminent surgical interventions (during the SAPF treatment), as well as reconstructive measures (skin grafting, amputation).

The sepsis-inducing pathogen and the primarily affected organ will be identified by the results of microbiological examinations and in accordance with clinical manifestations.

Further endpoints comprise the length of stay in the ICU and the total duration of hospitalization (including time of post-SAPF therapy).

Changes in hematological, coagulation and inflammatory parameters will be monitored at selected intervals across the treatment and serve as biomarkers of treatment efficacy or surrogate endpoints, as follows:

- Thrombocyte counts
- Leukocyte counts
- Hemoglobin
- Prothrombin time (PT)
- Activated partial thromboplastin time (aPTT)
- Fibrinogen
- D dimers
- Thrombin-Antithrombin complex (TATc)
- Protein C activity
- Antithrombin III activity
- C-reactive protein (CRP)
- Procalcitonin (PCT)
- Interleukin 6 (IL-6)

Several of these parameters have been used in clinical studies and shown significant changes in the course of therapeutic interventions in sepsis and Purpura fulminans [Bernard et al., 2001; de Kleijn et al., 2003; Schellongowski et al., 2006; Shorr et al., 2008].

Laboratory indices of organ dysfunction are confined to measurements of

- Glucose
- Lactate
- Creatine kinase

Recording of adverse events related to the treatment of SAPF is left at the discretion of the local site investigator (c.f. comment in *9.9. Limitations of research methods*); the emphasis is laid on

- bleeding incidents
- thrombotic events

8.4. Data sources

Registry subjects will be identified by the participating centers. The recruitment will be primarily based on the concomitant presence of clinical signs of sepsis and *Purpura fulminans*. Clarification of the underlying etiopathogenesis will be performed *post hoc*, upon collection of additional clinical and laboratory data.

Data capture comprises assessment at baseline and at several intervals of 24 (initially) and 48 (subsequently) hours for an overall period of 7 days, while in ICU. A final appraisal of the patient's status will take place at the time point of discharge from the hospital.

The exposure to individual therapeutic agents will be deduced from doses and frequency of application during the period spent in ICU.

The influence of potential confounding variables and effect modifiers (e.g. concomitant anticoagulant medication, fluid resuscitation, renal replacement therapy etc.) will be extrapolated from the corresponding specific entries in the eCRF.

The outcome indicators have been previously validated and are routinely used.

8.5. Study size

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Earlier reports on the incidence of SAPF [Darmstadt, 1998; Nicolas and Debonne, 2002] were based on the association of the condition with meningococcal sepsis. Conceivably, these data hardly permit extrapolation to the contemporary situation, which has substantially changed after the introduction of meningococcal vaccination [Maat et al., 2007]. Depending on the number of participating centers, a realistic forecast envisages the recruitment of 50 to 70 adult and pediatric patients during the first year of the registry, with subsequent possible increase to 100 per year. In view of the spread of meningococcal vaccination among children and adolescents, the expected proportion of adult patients might eventually exceed 50 %.
With regard to the relatively limited projected study size, and with regard to the lack of a uniform treatment concept for SAPF, demonstration of differences between individual treatment paradigms might require dichotomization (e.g. use vs. omission of Protein C supplementation) and could be applicable only to selected endpoints.

8.6. Data management

Individual data will be collected in accordance with the flowchart by means of electronic Case Report Forms (eCRF) and transmitted by remote data entry to the server of the Center for Clinical Studies of the Jena University Hospital. The local user authentication is ensured by password-protected logins. A role-based hierarchical security structure warrants multi-tier prevention of unauthorized access. The communication between the participating site's workstation and the server is encrypted. Data processing employs the software OpenClinica, which fulfils the regulatory requirements (GCP, 21 CFR Part 1).
Data management will resort to electronic applications. The anonymity of data is warranted in the course of evaluation. A first plausibility check will take place during raw data input in the eCRF at the investigator site, with missing or implausibly aberrant values signaling imminent correction requirement. A further verification of plausibility and consistency will be conducted by applying a controversy-detection algorithm. Permission for data corrections will be conferred to a restricted number of authorized study personnel (e.g. site investigator, study nurse, data manager). A final plausibility check will take place upon receipt of the reply to queries and the eCRFs bearing all annotated modifications.

Frau Sabine Barta

8.7. Data analysis

A binary logistic regression model will be fitted for the all-cause in hospital mortality to compare the efficacy of the different treatments (e.g. with or without Protein C supplementation). To adjust for confounders, causal pathogen, baseline Apache II (PRISM III) score, laboratory parameters, age, sex, co-medication etc. can be included as covariates in this model.

Consecutive changes in SOFA or PELOD scores (ΔSOFA, dPELOD) at individual post-diagnosis intervals and their mean values calculated for the observation period of 7 days will be compared to the scores determined on admission (baseline). Changes in these organ failure indices will be examined by means of

- Paired samples T-test
- Linear model with morbidity score baseline adjustment and alternative co-variables (e.g. hematological, coagulation or inflammatory parameters)

Explorative analysis without correction and with a pre-set level of significance of 0.05 will be conducted as well.

All endpoints will be subjected to descriptive statistical analysis with determination of 95-percent confidence intervals. Between-group comparisons will be preceded by distribution analysis (Shapiro-Wilk Test of normality). Depending on the data distribution, *post hoc* processing will involve either parametric (one-way ANOVA, T test) or non-parametric (Kruskal-Wallis, Mann-Whitney U-test) approaches.

8.8. Quality control

Quality control measures encompass activities aiming at the preclusion of protocol violations and erroneous data capture and transmission. They include

- surveillance of collection of data within the specified window of time
- verification of accuracy, consistency and plausibility of eCRF data feeds
- consistent use of pre-programmed inherent data range and plausibility checks enabling prompt feedback and clarification of aberrant records
- strict assignment of roles and data access rights, thus ensuring the compliance with requirements of privacy and data protection

Monitoring site visits are not envisaged by default.

8.9. Limitations of the research methods

The selected endpoints are routinely used and the methodologies for their assessment have been comprehensively verified and proved to display predictive strength. However, it should be taken into consideration that the inherent high mortality risk might compromise the validity of mortality as a major endpoint. Simultaneous use of composite outcomes is deemed to ameliorate the assessment of the effects of therapeutic interventions [Goldstein et al., 2005; Nadel et al., 2007].

The current approach to scoring the severity of purpura-associated lesions employs arbitrary statements, which reflect the investigator's day-to-day impression [de Kleijn et al., 2003]; accordingly, large variations and limited possibility for quantitative comparisons should be expected. A descriptive lesion grading of the external appearance based on pictorial reference examples in the eCRF it is expected to provide at least a uniform description.

The endpoint 'length of hospital stay' will conceivably display large inter-individual variability, due to varying length of post-ICU recovery and immediately adjacent reconstructive surgical interventions. Nonetheless, this variable is expected to deliver important information on the economic burden of SAPF and its direct sequelae.

Despite encouraging evidence, the relevance of biochemical markers of inflammation in monitoring the effects of therapeutic interventions in sepsis remains ambiguous, mainly due to issues of sensitivity and specificity [Goldstein et al., 2005]. Still, in view of the undisputed role of inflammatory mediators in the pathogenesis of SAPF [Darmstadt, 1998], their measurement is justifiable.

The therapy of SAPF involves multi-pronged measures, which may obscure the "net effect" of an individual therapeutic agent. Thus, efficacy aspects of a given treatment have to be evaluated in conjunction with the co-medication used in the individual case; this circumstance, as well as the influence of concomitant medication, will be taken into consideration while designing the eCRF.

9. Protection of human subjects

The Registry protocol is subject to approval by the IRB of the Friedrich Schiller University, Jena, which will serve as the supervisory ethic institution in charge. Approval of the Registry protocol by the responsible regional or national authorities will be sought after by participating centers which are outside of the jurisdiction of the IRB in charge.

Eligibility for an individual treatment modality will be defined by the responsible physician by fulfillment of the criterion "manifest clinical signs of sepsis-associated *Purpura fulminans*". The probability of inclusion into the Registry will not influence the physician's decision on the use of a selected medication.

An informed consent, signed by the patient or his/her legal representative, also comprising collection and use of medical data, will be sought for before enrolment into the Registry. However, in view of the rarity of the disease and the high mortality, usage of deviant regional and national regulations will be considered where appropriate and legally acceptable.

The protection of participant's privacy will be warranted by ***a)*** pseudonymization of patient personal data at the participating center for the duration of the clinical observation period, ***b)*** data transmission using a secure password-protected login and ***c)*** ultimate anonymization of the collected information upon verification of data consistency and plausibility. The pseudonymous ID list will

assign a four-digit-number to each participant and contain a pre-defined minimum of personal information considered essential for the processing of queries pertaining to accuracy, plausibility and consistency. For the communication with the Data Management, only the assigned four-digit-numbers will be used. The identity a patient can be disclosed only to the authorized study team members at the participating sites. Personal identity data (i.e. the pseudonymous ID record) are subject to transformation upon confirmation of the completeness of relevant information by the Registry Data Management. Numbers assigned in the process of pseudonymization will be replaced by the Data Management, in order to abrogate the possibility of tracking back patient's identity, while retaining the possibility to allocate data to the center of origin. The primary ID lists at the participating sites will be stored for at least 10 years in a mode, which precludes access of non-authorized persons. Compliance with this requirement will be verified in the course of monitoring site visits.

The sovereignty over the Registry data is exerted by the Advisory Committee. Documentation will take place at the Center for Clinical Studies of the Jena University Hospital. Registry data will be processed automatically, with scheduled regular backups. Registry data are accessible to a limited number of staff members, who are directly involved in this project. Data media are stored in a secured space on the premises of the Center for Clinical Studies, with access permitted only to the system administrator.

Publication of Registry data will occur only in aggregated form, without disclosure of details of subjects and participating investigation sites. These conditions also apply to the dissemination of Registry data, e.g. on request of external investigators. In the latter case an approval of the IRB will be solicited.

The regulations pertaining to patients' welfare and privacy protection comply with the international and national norms and legislation (Helsinki Declaration, GCP, GEP national regulations of participating countries).

10. Management and reporting of adverse events/adverse reactions

Considering the critical condition of patients with Purpura fulminans and their high disease-related mortality, the documentation and reporting of all adverse events (AE) and serious adverse events (SAE) occurring in these patients is beyond the scope of this registry.

In view of the complex pathology and the multitude of concomitantly used therapeutic agents in SAPF patients, registration of treatment-emergent adverse drug reactions (ADR) will be confined to those, which denote pathological alteration of the coagulation status. In this context, ADR of specific interest include

- bleeding (especially intracranial and in visceral organs)
- thrombotic events

Occurrence of adverse drug reactions (ADR) will be recorded by the study teams at the participating centers in the eCRF, with the local investigator being responsible for the assessment of the ADR. Severity of ADR will be assessed by means of a three-grade-scale (mild-moderate-severe). In view of the severity of the condition, however, it is predictably difficult to discern ADR of mild and moderate intensity.

Additionally an ADR Report Form for these assessments will be distributed to the local investigators as a part of the Investigator Site File (ISF). Documented treatment-related ADR or other safety

concerns (regardless of the expectedness or causality) will be forwarded by the local investigator by his own responsibility to the Marketing Authorization Holder of the presumably involved product and the Advisory Committee of the registry within 24 hours of awareness.

11. Plans for disseminating and communicating study results

A major objective of the Registry consists in accumulation and systematic evaluation of etiology, clinical course and treatment approaches of SAPF. The individual aspects of knowledge encompass (but are not restricted to):

- Gaining new insight into the causality of SAPF
- Comparative evaluation of currently used treatment strategies, especially those comprising use of anti-coagulant proteins
- Identification of patient clusters (e.g. by age, initial morbidity score, Purpura etiopathogenesis, concomitant therapy etc.) which display above-average responsiveness to anti-coagulant protein supplementation
- Disclosure of biomarkers which are particularly suitable for outcome prediction and dynamic monitoring of therapy
- Disclosure of unacquainted side-effects of therapeutic interventions

Registry data will be systematically scrutinized with regard to the above-listed issues and the results will be disseminated in aggregated form as

- Periodical (biannual) reports
- Hot-topic updates
- Safety information
- Publications
- Recommendations for the elaboration of uniform guidelines for SAPF

As improvement of quality aspects of treatment quality form a key objective of the Registry, the participating centers will be entitled to access their retrospective data in individual or aggregated form (before or upon completion of anonymization, respectively), and receive biannual summaries collating their performance to the average of all participants.

External interested parties may receive on demand and on condition of approval by the Advisory Committee and the IRB excerpts from Registry data pertaining to a previously defined topic.

Based on the results of biannual Registry evaluations and safety records, the Advisory Committee will compile and update recommendations for SAPF therapy, which will be distributed to the participating centers and interested external parties.

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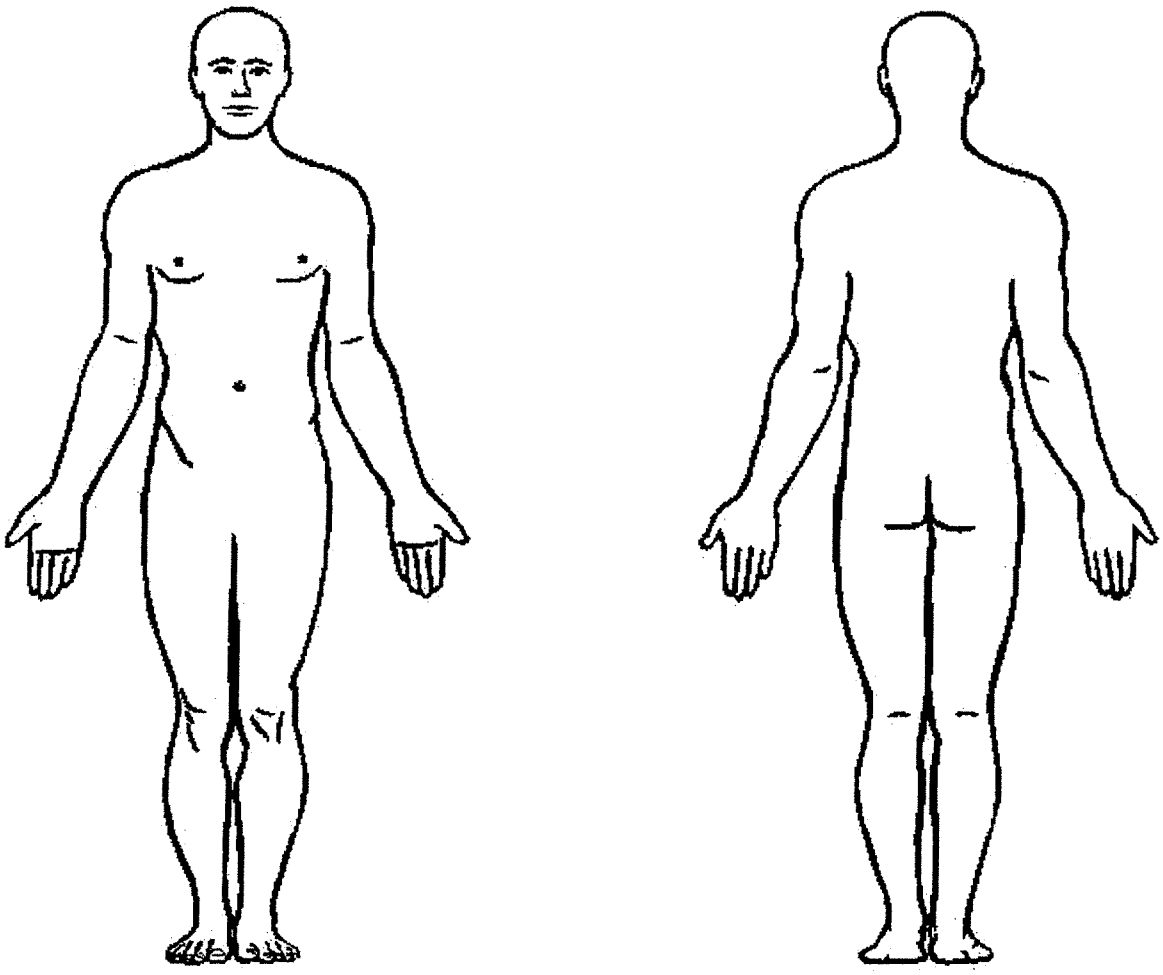
13. Annex

Proposed scheme of localization mapping and severity assessment of Purpura fulminans lesions



Symbol	Lesion description	Severity		
		low	moderate	severe
▲	Petechiae			
■	Ecchymosis			
O	Bullae			
✖	Necrosis/Gangrene			

Frau Sabine Barta