German Registry for Hidradenitis Suppurativa

HSBest

Registry protocol

Version 1.1, 31.10.2025

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Content

1. HSBest Organisation

Study sponsor and data owners

CVderm at IVDP/UKE Hamburg	Prof. Dr. med. Matthias Augustin
Board of study centers	To be elected
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Collaborating partners	Prof. Dr. med. Prof. hon. Dr. h.c. Christos C. Zouboulis Städtisches Klinikum Dessau Hochschulklinik für Dermatologie, Venerologie und Allergologie, Immunologisches Zentrum Auenweg 38, 06847 Dessau-Roßlau Dr. med. Dagmar Presser Universitätsklinikum Würzburg Klinik und Poliklinik für Dermatologie, Venerologie und Allergologie Josef-Schneider-Straße 2, Haus D8, 97080 Würzburg Prof. Dr. med. Lars French Ludwig-Maximilians-Universität München Klinik und Poliklinik für Dermatologie und Allergologie Frauenlobstraße 9-11, 80337 München Dr. med. Andreas Pinter Universitätsklinikum Frankfurt Klinik für Dermatologie, Venerologie und Allergologie Theodor-Stern-Kai 7, 60590 Frankfurt Prof. Dr. med. Falk Bechara St. Josef-Hospital Klinikum der Ruhr-Universität Bochum

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	CVderm, Dr. Stephan Rustenbach
Technical IT solution	Vahid Djamei (Swiss4Ward Germany)

Scientific Advisory Board To be nominated

Operation Institute CVderm Germany

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Dr. med. Frenz Ohm (Coordinator)

Dr. phil. Stephan J. Rustenbach, PhD (consulting head methodology and statistics)

Cooperations

Future cooperations with other evolving European or international HS registries are intended.

2. Summaries

2.1. German short summary

Titel	**Deutsches Hidradenitis Suppurativa Register (HSBest)**
Indikation	Klinisch diagnostizierte Hidradenitis Suppurative (Akne inversa) mit dem Bedarf einer topischen oder systemischen Behandlung
Ziel des Registers	Ziel des aktuellen Projekts ist die Entwicklung des Registers für HS-Patienten in Deutschland. Das Register soll alle Patienten mit HS rekrutieren und einschließen, die in den teilnehmenden Zentren diagnostiziert und behandelt werden. Das Register wird Konsensberichte, Expertenempfehlungen und jährliche Aktualisierungen aus dem Register liefern. Ein Kerndatensatz von wichtigen Variablen, die sowohl vom Arzt als auch vom Patienten bewertet werden, wird zu bestimmten Zeitpunkten gesammelt.
Hauptzielkriterien (Primary Objectives)	1. Wirksamkeit von Therapien (topisch und systemisch) bei Patienten mit Akne inversa unter Alltagsbedingungen
Nebenzielkriterien (Secondary Objectives)	2. Patientenseitige Nutzen und Versorgungsbedarf 3. Wirksamkeit im Langzeitverlauf über Jahre 4. Die optimalen Erhaltungsdosierungen Sicherheit und Nebenwirkungsprofile unter Alltagsbedingungen 5. Zuverlässige Prädiktoren für das Ansprechen („responder“) 6. Die Nutzen und Wirksamkeiten etwaiger Kombinationstherapien oder alternierender Anwendungen von zugelassenen systemischen antientzündlichen Therapien bei chronischer Prurigo.

Patientenauswahl	Männer und Frauen ab 18 Jahren mit einer klinisch diagnostizierten Hidradenitis Suppurativa (Akne inversa)	
Anzahl der Patienten	(mindestens) 1000 Patienten bis Studienende, wobei die Patientenzahl nach oben nicht begrenzt wird, da es sich um eine Registerstudie handelt.	
Studien-Leitstelle	Institut für Versorgungsforschung in der Dermatologie und bei Pflegeberufen (IVDP), CVderm	
Register-Zentren	Erfahrene dermatologische Praxen und Kliniken in Deutschland	
Zeitplan:	First Patient in:	01.11.2020
	Last Patient in:	31.10.2030
	Last Patient out:	nicht anwendbar
	Datenmanagement und Auswertung:	01.11.2020 bis 31.10.2030
	Berichtsentwurf (First Draft):	30.11.2029
	Biometrischer Abschlussbericht (Final Draft):	31.03.2030 (wobei jährliche Berichte und Auswertungen erstellt werden)

English summary following proposal

Short title	HSBest
Authors	Prof. Dr. Matthias Augustin
Project Leads	Prof. Dr. Matthias Augustin, Hamburg Frenz Ohm (coordination), Hamburg Prof. Dr. med. Prof. hon. Dr. h.c. Christos C. Zouboulis, Dessau
Collaborating partners	Dr. med. Dagmar Presser, Wurzburg Prof. Dr. med. Lars French, Munich Dr. med. Andreas Pinter, Frankfurt Prof. Dr. med. Falk Bechara, Bochum Prof. Dr. med. Petra Staubach-Renz PD Dr. med. Maurizio Podda Dr. Bechara, Bochum Prof. Dr. French, München LMU PD Dr. Gerdes, Kiel Dr. Kirsten, Hamburg PD Dr. Kokolakis, Berlin PD Dr. Pinter, Frankfurt Prof. Dr. Podda, Darmstadt Dr. Dagmar Presser, Würzburg Dr. Florian Schenck, Hannover Prof. Dr. Staubach, Mainz Prof. Dr. Thaci, Lübeck PD Dr. Volz, München TU Prof. Dr. Zouboulis, Dessau
Main project associates	German Psoriasis Registry PsoBest German Platform on Patient Registries in Dermatology DermBest German Society for Dermatology (DDG) German Association of Dermatologists (BVDD)
Summary	This proposal summarizes the concept of a joint project on the development of the German National Registry of hidradenitis suppurativa (HSBest). In consecutive phases, this registry can be extended to an international EU registry for hidradenitis suppurativa (HS-EU-Best) based on the identical IT solution. The objective of the registry is to assess and analyze clinical types, disease burden and patient needs in the real-world care for HS and to investigate the current treatment standards and outcomes. As a further option, the effectiveness and safety of current and upcoming drugs for HS can be explored. An upgrade to a pharmacovigilance registry is possible.

	The overall project consists of two phases: Phase I: Development, installation, and validation of the registry database, including set-up of a governance structure. Phase II: Initiation and operation of the registry in 30-50 leading German centers for overall 5 years, including 2 years observation time per patient. This proposal is related to both phases in order to develop a governance structure, an administrative basis and a fundament of methods followed by the set-up of the electronic database and the operation in Germany. The Hamburg IVDP group will provide all methodological knowledge, medical surveillance, advise and the statistical components of the project. The IT technology will derive from Swiss4Ward, a specialist in IT solutions for dermatology including several online registries. All study procedures follow the international standards of methodology for registries, including the German registry guidance (Müller 2010). Specific task shares and responsibilities will be defined in a separate study protocol.
Mission	The mission of the current program is to gain knowledge of clinical types and real-world care for HS as well as to establish a uniform long-term disease registry in Germany and consecutively in Europe. Worldwide there is high need for real-world data by HCPs, decision makers in politics, payers, the patients and the public. Using registry data will enlarge the knowledge and the velocity of analyses of real-world data on HS, to emphasize the impact and burden of the disease. However, routine data are currently rarely used in a systematic and logic way for comprehensive analyses. Thus, the data integration from different centers specialized in dermatology care for HS will provide high added value. For such, this advanced technology of data generation and integration as well as analysis of multisource data is needed. Furthermore, an administration and governance structure is to be established and an electronic database to be started which is the goal of this first project series.
Objectives	1. To conceptualize, develop, install and validate a web-based electronic solution for an integrated disease registry on HS 2. To establish an administrative body and found a governance structure for the project 3. To define standards of data fields, documentation and outcomes measurement 4. To run a uniform database integrating routine and/or research registry data 5. Mid-term: To extend the registry continuously to other countries in Europe and beyond
Project design	This project includes a series of subprojects (work packages, WP), which meet the project goals including: WP 1: Study set-up, constitution of project partners and organization, development of study protocol WP 2: Founding an administrative structure, legal affairs (including Ethics) and a coordinating function WP 3: Development of standard data sets and outcomes based on the international collaboration group for HS WP 4: Preparing, testing and validating the electronic database WP 5: Center recruitment, pre-study meetings, initiation procedures WP 6: Operation of the database in routine care including routine baseline and outcomes reporting.
Patients	A total of n=3000 patients will be recruited within 5 years and each patient observed for 2 years (prolongation to 5 years possible). The patient basis will involve the HS patients routinely documented in the single centers after informed consent has been obtained. All data from these centers will be completely worked up and used for analysis.
Data set	Clinical data, history and patient-reported outcomes will be obtained in regular visits during routine treatment of the patients.

	The data sets will be used for descriptive and confirmative analyses on a regular basis following the study protocol.
Observation period	Each patient included will be observed for 2 years in routine treatment regardless of therapy applied. Time points of measurement will be 0-6-12-24 months.
Center honoraria	The honorarium to the center for each patient is 50 EUR for the initial visit and 30 EUR for consecutive visits, adding up to a total of 140 EUR.
Statistical analyses	All statistical analyses will be planned in a statistical analysis plan (SAP) presenting the specific research questions. Data cleaning and descriptive analyses of the data will be conducted and quality assured at any time point. The statistical planning and analysis will be conducted by the statistical expert group of the CVderm/IVDP institute at the University Medical Center of Hamburg. The analyses follow the guidance of the registry steering group (to be announced).
Publications	A series of peer-review publications will be prepared. Moreover, submissions to congresses will be performed.
Quality assurance and data protection	All processes of the study are subject to quality management and current European data protection acts. Validated, recognized methods according to international standards will be applied in all phases. The IVDP institute at the University Medical Center of Hamburg is certified by DIN ISO 9001:2008. It works according to the centre's own SOPs. The study's methodology and quality (design, patient selection, data collection, and organization) have been reviewed and reaffirmed in preliminary studies. The development project will be executed according to the criteria of "Good Epidemiological Practice" and specific SOPs shared between the project partners. A notification will be sent to the ethics committee of the state chamber of medicine in Hamburg and to any other region if needed.
Legal affairs	The project governance and overall lead is based in the HSBest steering group and a selected group of international experts. Administration will be settled to a convenient place. Complete members and responsibilities will have to be defined.
Time planning	The overall project can be started at any time point in 2020.The registry operation is planned for five years, observing each patient for at least two years. The consecutive phases will be started as needed.

2.2. Executive summary

Background

There is still lack of systematic research on long term outcomes of hidradenitis suppurativa (HS) in dermatology routine care. Patient registries are the state of methodology to observe and analyze long courses of real-world outcomes in medicine.

Objectives

To establish and conduct a patient registry on hidradenitis suppurativa in Germany according to international high-scientific standards. Here the module for HS is reported.

Methods

The patient registry is designed as a non-interventional, prospective cohort study conducted over a period of 60 months of observation period plus 12 months final data management, analysis and reporting. The inclusion period is planned for 60 months, and each patient is observed for 60 months. In the observation period of 0 to 60 months, data are obtained in intervals of six months. This includes physician visits at month 0 – 6 – 18 – 30 and direct patient contacts at month 12 and 24.

The study is conducted in volunteering German dermatological clinics and practices based on an electronic data capturing provided by Swiss4Ward (head: Vahid Djamei) and on standardized electronic CRFs. A minimum of n=1000 patients is expected to be recruited within 12 months. Registration will be consecutively for patients freshly starting a HS treatment recommended by guidelines.

Inclusion criteria: Adult patients (minimum age of 18 years) diagnosed with clinically diagnosed HS.

Exclusion criteria: Lack of informed consent, participation in a clinical trial at baseline, patients who show any medical or non-medical reasons that interfere with participation in an observational study of HS treatment.

Outcomes: include 1) clinical scores, 2) patient-reported outcomes, 3) safety and tolerability outcomes.

Methodology, biometric planning and statistical analyses are provided by CVderm, Hamburg (Director: Prof. Dr. Matthias Augustin), a health services research institute with international high-rank reputation.

Charter and quality assurance

All structures, processes and procedures of registry conductance will be defined in a charter to be released by the scientific board and to be approved by center board. The registry was planned and will be executed according to international guidance of patient registries. All methods and processes involve high levels of quality assurance and will be well controlled during registry conductance.

Reporting

The reporting schedule follows differentiated target groups, timing and contents of regular data reporting.

Data analysis

Data analysis will follow a specific statistical analysis plan per objective. This includes application of standard methods of analysis for cohorts from non-interventional trials. Beside of descriptive crude analysis, appropriate methods (e.g. propensity scoring) will be considered for adjustment and/or control in order to balance for potential inhomogeneities between cohorts compared.

Data ownership and Publications

Data are owned by the Board of Study centers and the registry lead. All use of data will be regulated by the principle investigator and the scientific board.

3. Research objectives, specific aims and rationale

3.1. Research objectives

To establish and conduct a patient registry on hidradenitis suppurativa treatment in Germany according to high methodological standards.

The objective of the registry is to generate empirical evidence on long-term real-world effectiveness and safety of treatments of patients with hidradenitis suppurativa. The primary objective is clinical response to treatments. Secondary objectives are patient relevant response to treatments (patient reported outcomes and benefit) and treatment safety. Additional objectives are the exploration and description of the natural course of hidradenitis suppurativa, patient needs for care and standards and patterns of hidradenitis suppurativa care in Germany.

3.2. Aims

The registry aims at investigating

- the long-term effects of listed treatment options for HS including clinical and patient-reported outcomes
- the tolerability and safety of treatments for HS
- the real-world treatment behaviour of German dermatologists

in order to get valid data for future health care planning and optimizing. The following questions have been defined:

a. How effective is the treatment of hidradenitis suppurativa with listed treatments under everyday conditions?

b. Which are the usual treatment choices and which are the standards of care of HS in Germany?

c. Which health care needs and benefits do patients report?

d. What is the health-related quality of life in a HS patient?

e. Does treatment of HS change the health-related quality of life?

f. How safe are the treatments in long-term and what are the side effects profiles of treatments?

g. Do treatment options show differences in recurrence and progression rates?

h. Which treatment patterns are observed over the time?

i. Can predictors of “response” be found in the long-term course?

j. What are the benefits and how effective are observed combinations or alternating schedules of treatments?

k. How long do treatment effects last?

l. How does the treatment of HS and outcomes vary long-term over a period of years? What types of therapy withdrawals or changes are necessary?

m. What are the optimal therapy modalities?

3.3. Rationale

Clarification of the objectives and questions named above are of primary importance for three reasons:

1. In Germany, there are still huge unmet needs in quality of health care for patients with hidradenitis suppurativa and the optimum treatment modalities. Scientifically sound data on the long-term outcomes will help to meet the need for better, more efficient care.

2. In the forthcoming years, increased regulation of supply with innovative drugs is anticipated from the instrument of "benefit evaluation" in the sense of a "fourth hurdle". Regulatory bodies use "patient-relevant benefits" as the primary evaluation criterion, which can be only inadequately depicted from the Phase II and III studies currently available, while a patient registry will provide more comprehensive and valid data.

3. The cost-benefit ratios of HS therapeutics have not yet been adequately investigated neither internationally nor for the German health system. Allocation of future health expenses will have to be based on robust data derived from naturalistic registry studies. In routine care, valid evidence will rest on the results of long-term trials, as well as on data for possible combination therapies and predictors of response.

In light of this, long-term documentation of hidradenitis suppurativa therapy with lots of patients is mandatory in order to clarify the stated questions on safety and effectiveness with high methodical rigor. Excellent experience with such a database has been obtained for psoriasis therapy PsoBest, which was set up as a nation-wide registry at the DDG/BVDD (German Societies of Dermatology and Venereology), in cooperation with the pharmaceutical industry.

The present study protocol summarizes the required steps to establish and maintain a registry of long-term courses in hidradenitis suppurativa therapy.

The following have especially been used for implementation[123]:

- Gliklich R, Dreyer N, Leavy M, eds. Registries for Evaluating Patient Outcomes: A User's Guide. Third edition. Two volumes. (Prepared by the Outcome DEcIDE Center [Outcome Sciences, Inc., a Quintiles company] under Contract No. 290 2005 00351 TO7.) AHRQ Publication No. 13(14)-EHC111. Rockville, MD: Agency for Healthcare Research and Quality. April 2014. http://www.effectivehealthcare.ahrq.gov/registries-guide-3.cfm.
- Müller D., Augustin M., Banik N., Baumann W., Bestehorn K., Kieschke J., Lefering R., Maler B., Mathis S., Rustenbach S., Sauerland S., Semler S.C., Stausberg J., Sturm H., Unter C., Wiesel A., Neugebauer E.A.M.: Memorandum Register für die Versorgungsforschung. Gesundh.wes., 2010, 72: 824-839.
- Guideline on good pharmacovigilance practices (GVP) Module VIII – Post-authorization safety studies. European Medicines Agency and Heads of Medicines Agencies, 2012.

For further Guidance and quality Standards see quality assurance and quality control.

4. Study tasks milestones and timelines

4.1. Registry preparation

The registry preparation follows the detailed work plan presented in attachment 2.

The goal is a rapid and efficient establishment of a patient registry to observe long-term effectiveness, patients need for and benefit of care, maintenance treatment patterns, treatment safety and predictors of response in patients treated with hidradenitis suppurativa.

4.2. Registry set-up

The registry will start in November 2020 (First Patient In). Last Patient In is expected in October 2025. Accordingly, First Patient Out will be in October 2025. The final study report will be finished in March 2028. However, annual interims reports will be submitted.

The registry will provide regular reports on patient characteristics and periodic safety reports during the entire period of 60 months of observation.

4.3. Registry start

Recruitment of centers participating (dermatological practices and hospitals):

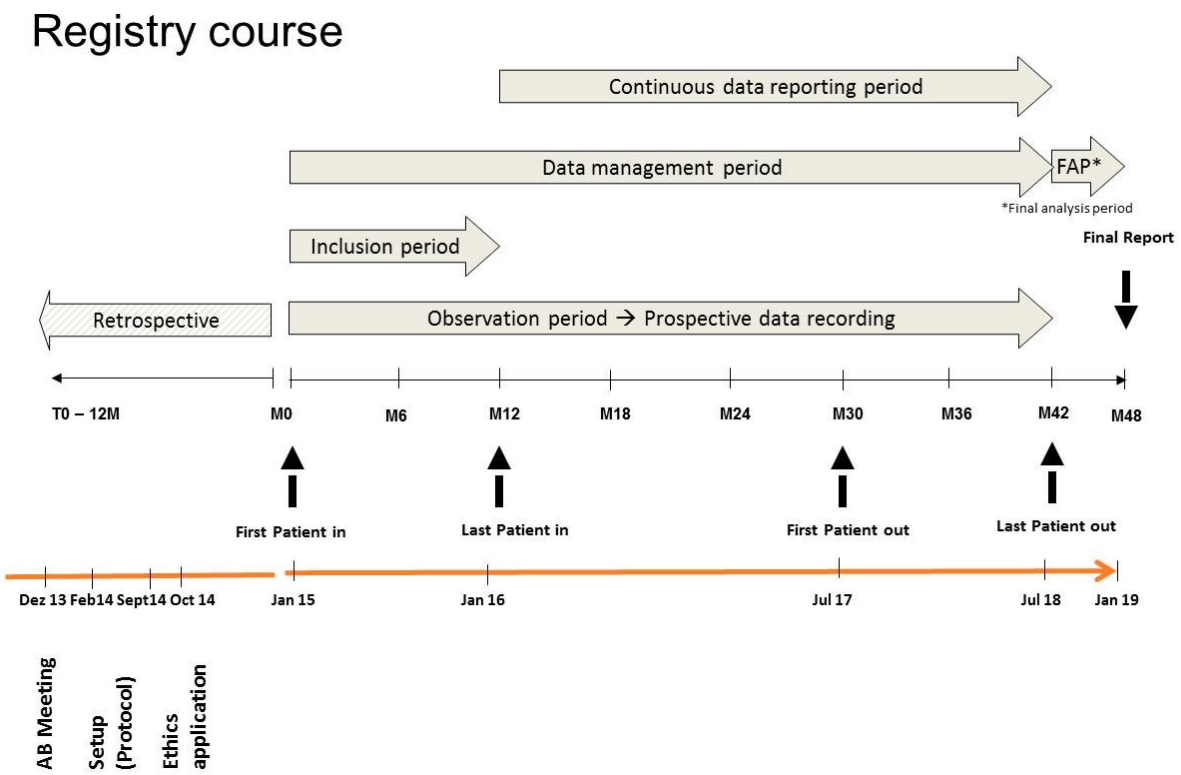
Total centers targeted:	min. 60
Total University Hospitals targeted:	10
Total leading hospitals targeted	10
Total dermatologist in private practice targeted	60

Patient recruitment:

Minimum number of patients for each University Hospital:	n=50
Minimum number of patients for each Regional Hospital:	n=20
Minimum number of patients for each private practice:	n=15

Number of patients targeted: at least n=3000

4.4. Course of the registry



Quality control

Training of study center personal

First training of all study center personnel: 11/2022 via web training

Targeted training per year: 1

- individual trainings will be organized by request
- Number and content of queries will serve as an indication for additional trainings of centers

Monitoring of study centers

First monitoring all study centers starts in 12/2022

Targeted monitoring (online or presence) is planned during the entire study period

A monitoring plan will be developed in advance

Data management and analyses

Follow SOP and is based on ISO certified processes

4.5. Registry closure

Start final data analysis: 03/2030

Final Report: 03/2031

6. Critical review of the literature to evaluate pertinent information and gaps in Knowledge

Current status of evidence for HS treatments in clinical trials and in patient registries

1) Clinical trials

In the protocol-guided literature search dated 12.10.2022, a total of 173 hits on clinical trials in hidradenitis suppurativa were found (Fig. 1).

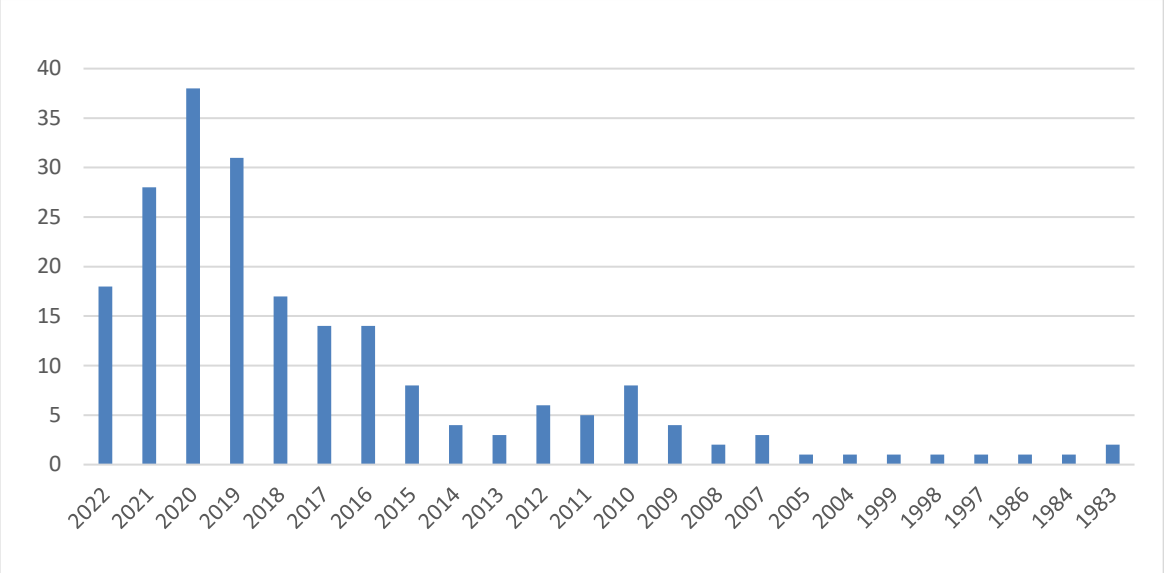


Fig 1: Results of literature search for clinical trials on hidradenitis suppurativa AND treatment: In total, 173 hits were identified.

In most trials, systemic drug treatments were investigated. All of these treatments published in peer-review journals were considered target therapies in the HSBest registry. The major clinical outcomes measures beyond histology were as follows: 1) Improvement of PGA, 2) Clearance/reduction of overall number of lesions, 3) severity of target lesions, 4) tolerability of treatment, 5) quality of life, 6) patient satisfaction.

2) Patient registries

Among the overall number of publications on hidradenitis suppurativa (k=3.928), 92 hits on the combination with “Patient registr*” were found. Only a few active registries worldwide were identified (review publication in process).

In sum, there is a lack of long-term data on hidradenitis suppurativa treatment and there are only a few studies which compare different drugs against each other and show a follow up of the results but there`s no German registry for hidradenitis suppurativa and observation for all possibility of therapies to date. So it will be the first time for a whole country get comprehensive, robust and long-term evidence on the treatment of this disease.

7. Methods

7.1. Design

The registry is designed as a prospective open cohort study.

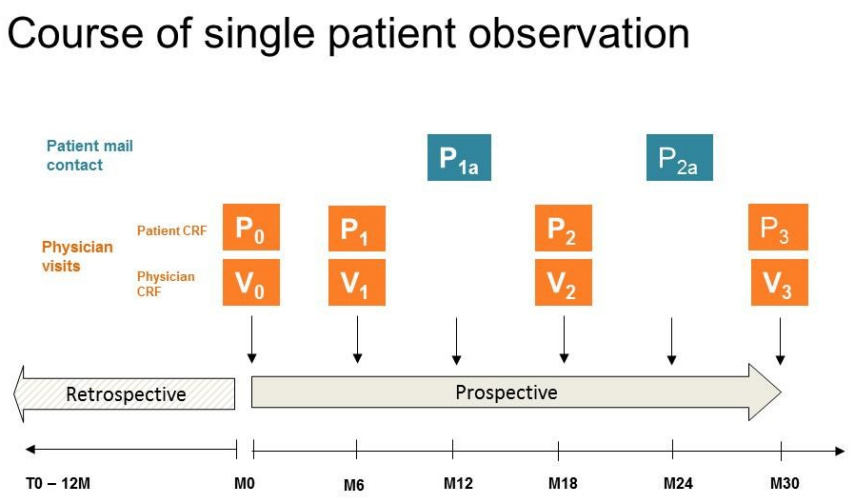
The prospective cohort study design allows for the calculation of incidence rates, thus relative risks (RR) can be estimated as measures of association. Furthermore, reasons for choosing the cohort design were to obtain complete and nearly unbiased information on exposure (treatments) and to study multiple effects of multiple treatments.

The study group consists of several treatment cohorts, according to all licensed and guideline-recommended interventions for the treatment of hidradenitis suppurativa in Germany, substantially comparing patients and/or patient years of exposure from each treatment cohort to a comparator cohort with similar characteristics but exposed to other treatments or to any pooled group of treatment cohorts.

Additionally, the patient registry analyses will allow for nested case-control studies, i.e. “cases” with a certain outcome of interest can be compared with regard to differences in exposures variables (treatments) to matched “controls” in which this outcome hasn’t occurred.

The set-up and conduct of HSBest was planned to meet the requirements for pharmacovigilance of the pharmaceutical companies holding licenses of HS treatments.

The observation of patients and treatment will be kept in the form of a patient-related database, as a “registry”. The data will be analyzed descriptively and reported as sequential time point data and by subgroup tabulations. Reports on effectiveness and safety will be generated at regular intervals.



Adult patients are consecutively recruited in the participating study centers and registered to HSBest if a treatment of a “target lesion” of HS freshly started. Patients remain registered regardless of treatment switches or withdrawals for 30 months of observation. In this time interval, follow-up visits in the study centers are planned at 6, 18 and 30 months. Additionally, standardized paper CRFs are sent directly to patients at months 12 and 24.

A prolongation of the observation period up to 60 months is explicitly considered. The initial target is the inclusion of n= 1000 patients. At study center visits data from both, the dermatologist and the patients are collected in a standardized electronic case report form (eCRF). The case report forms are standardized in the same way for both CRF and eCRF, the content is described in section 6.3.

7.2. Registry population

The target population are adults with a diagnosed HS in Germany. The intended population is defined as the subset of the target population that seeks treatment in Germany.

Patients will be selected from the target population by a two-stage cluster sampling procedure. At the first stage of sampling, study centers are recruited. Within the participating study centers, patients seeking treatment (accessible population) are consecutively asked for written informed consent to participate. Patients giving written informed consent will be the actual population registered in HSBest. The treatment decision will be driven by indication.

7.2.1. Definition of population

Study Centers

Dermatological practices and hospital outpatient departments are the providers of care in Germany. All University hospitals, regional hospitals and all dermatological practices known to DDG/BVDD will be contacted, informed and asked for voluntary participation in HSBest by DDG/BVDD.

Patients

Patients seeking treatment for HS in Germany build the accessible population. This population is sparsely confined by following in- and exclusion criteria.

Inclusion criteria

- Diagnosis of hidradenitis suppurativa by a dermatologist,
- Age >18,
- Sufficient language skills (German or English) for the informed consent to participate
- Written and informed consent to participate

* Fresh beginning does NOT imply treatment naïve (i.e. no lifetime exposure to a specific treatment). A former lifetime exposition of the patient is possible.

Exclusion criteria

- Lack of informed consent
- Patients being participants of clinical trials on hidradenitis suppurativa at the day of admission to the registry (if a patient is included into a clinical trial during the registry follow-ups, the patient data will be recorded, but analyzed separately)
- Patients who show any medical or non-medical reason that interferes with participation in an observational study

Note: unlike in other registries, •Fresh beginning* (i.e. no continuation, no restart of short term withdrawal) of a specific treatment is not required.

Treatments

Treatments licensed in Germany and recommended by the European S1 guideline on hidradenitis suppurativa treatment will be observed. The indication for treatment is decided by the dermatologist only. The registry simply observes the routine care in a non-interventional way, and thus no further limitations to treatments are defined.

7.2.2. Recruitment and Retention

Study Centers

The goal is to recruit in parallel a total of about 20 clinics (10 university, 10 non-university regional hospitals) and 60 private practices. All University hospitals, and all dermatological practices known to

DDG/BVDD will be contacted, informed and asked for voluntary participation in HSBest by DDG/BVDD. A letter signed by the presidents of DDG/BVDD will be sent.

Interested practice willing to participate in the registry send back a return e-mail with a written consent. The coordinators at HSBest will send per e-mail the study material to the practice, including:

- Study protocol
- CRFs
- Patient information and patient consent form

The participating centers will be contacted at regular intervals by the coordination center at HSBest with a newsletter (by e-mail). Newsletters are planned for issue initially at 8-week intervals, and later at 6-month intervals.

The continuous motivation for the participating centers will be an enhanced image and publicity due to their participation, leading to greater visibility in the health market. Inclusion rates will be published by newsletter and on the HSBest-Website.

Patients

Patients will be informed about HSBest at the study center. The patient information sheet and the informed consent form are handed out to the patient and explained by the dermatologist. After the patients voluntary decision for participation, the informed consent form is signed by both.

The consecutive enrolment of eligible patients without further limitations will guarantee that the treatment group in the registry comes as close as possible to the actual population of patients seeking HS treatment.

7.3. Strategies and data sources for determining exposures, health outcomes, other characteristics, potential confounder and effect modifier

Organisational forms and forms containing personal information will be sent to the coordination center by fax. This includes participation contracts, informed consent forms, and adverse event forms.

Registry data will be obtained from the patient and dermatologist at study visits directly by standardized electronic questionnaires (eCRF). At interim months 12 and 24, patients will be contacted by the coordination center with a letter asking to complete an analogous paper-CRF.

Documentation will be carried out according to international standards for epidemiological studies ("Good Epidemiological Practice"), the requirements of the Pharmacovigilance (EMA/827661/2011, EMA/813938/2011 Rev. 1) the usual outcome parameters for chronic pruritus/prurigo and in compliance with the AWMF-Guideline for Recording Quality of Life in Dermatology.

7.4. Operational definitions

Standardized items of following domains/areas will be collected at the start and during the course of the registry (for more details see CRF):

Dermatologist eCRF:

- Clinical characteristics of HS and target lesion(s), e.g. localization, phenotype, severity
- Treatment characteristics per target lesion, e.g. intervention, begin and end dates, dosage, application schedule
- Comorbidities, especially skin malignancies and their respective treatments
- Systemic comedications and their indications and characteristics

- Response status (not at baseline), for definition see below
- AE/SAE forms of German medic (not at baseline)

Patient eCRF and pCRF:

Only at baseline:
- Socio-demographic Characteristics, Sex and Age
- Medical Characteristics, weight, height
- Anamnestic information on HS and respective treatments

All Patient eCRFs and pCRFs:
- Patient reported outcomes:
  - Health-related quality of life
    - DLQI (dermatology specific)

All Patient follow-up eCRFs an pCRFs:
- Quality of care
  - Patient-reported treatment characteristics (intervention, duration)
  - Patient-reported benefit of treatment (global assessment)

The status of "response" to treatment will be defined by the scientific advisory board in detail.

The following definitions were considered for statistical planning:

1. Clinical scores

The status of disease severity is defined with the help of different scores.

1.1 Hurley-Score:	O Stage I	Abscesses, no tunnels, no cicatrization
	O Stage II	Recurrent abscesses with tract formation and cicatrization
	O Stage III	Multiple interconnected tracts and abscesses

1.2 IHS4-Score:

Outcomes can be:	O mild	≤ 3 points
	O moderate	= 4-10 points
	O severe	≥ 11 points

1.3 HS-PGA-Score:	0)	Clear
	1)	Minimal
	2)	Mild
	3)	Moderate

4) Severe

5) Very severe

If needed by single centers, the Sartorius score can additionally be used.

2. Health-related quality of life

The classification follows the manuals of the instruments:

2.1 DLQI:	0-1	no impact on QoL
	2-5	mild impact
	6-10	moderate impact
	11-15	severe impact
	>15	very severe impact

3. Patient needs

The PBI (Patient benefit index) technology can be used but is not obligatory in the study. If used, the patient needs questionnaire will be obtained before/at start of the patient in the registry and the patient benefit questionnaire been applied along the treatment course in intervals as needed.

4. Further patient-reported outcomes (PROs)

A set of specific PROs will be optionally available, including instruments for assessing fatigue, depression, anxiety, wellbeing and further outcomes needed in certain treatment situations. For further information see: https://www.dermavalue.com/de/home.html

7.5. Projected study size, statistical precision and the basis for their determination

The sample size of a minimum of 1000 patients was estimated for the given population of patients in Germany (prevalence) and the achievable number of patients to be registered within 12 months inclusion time. This minimum sample size is needed for descriptive data analysis and the exploration of differences in response rates defined with acceptable precision for trend identification.

Power analysis was based on the primary outcome of response to treatment of the target lesion. A two-sided Fishers exact test and the assumptions of power at $\beta=0.8$ and a type I error at $\alpha=.05$ were chosen for estimation of differences in response rates between the treatment starter cohorts (i.e. the width of the 95%-confidence interval) to estimate expected lower limit of precision. For this lower limit, the expected response rate of one cohort was fixed at 50%, since power raises for more extreme expected rates in both directions. Bonferroni-adjustment to control for each set of multiple comparisons (familywise) was applied for sensitivity analyses. A dropout-rate of 5% from the total sample size was assumed, leading to a sample size of n=950 at month 30. Patient inclusion and dropout was assumed to be equally distributed among the cohorts.

Eleven treatment starter cohorts (each of endpoint sample size of n=86) were considered for comparison of response rates:

Topical: Topical steroids (TCS), topical antibiotics (TCI), other

Systemic: Steroids, Methotrexate, Antibiotics, Biologics (Adalimumab, Secukinumab, Ustekinumab), other Immunosuppressants

Surgery: Deroofing, Radical excision

Two test scenarios for response rates were considered: Pairwise comparison of cohorts and each cohort against all other cohorts

Pairwise comparison of cohorts

For each pairwise comparison between the treatment starter cohorts a difference in response rates of 0.5 - 0.2825475 = 0.2174525 or more extreme will be significant under the assumptions given above. Corrected for all 66 pairwise comparisons possible, the difference in rates would be 0.5- 0.1896636= 0.3103364 or more extreme for a nominal type I error of α=.05.

Each cohort against all other cohorts

For each comparison of a treatment starter cohort to all other treatment starter cohorts, a difference in response rates of 0.5-0.3399=0.1601 or more extreme will be significant under the assumptions given above. Corrected for all 11 comparisons possible, the difference in rates would be 0.5-0.2940036= 0.2059964 or more extreme for a nominal type I error of α=.05.

7.6. Governance

The registry follows a governance structure which includes the registry directors, the registry operating center CVderm, the board of study centers, the scientific ad board and the collaborating bodies. Details are defined in a separate registry charter.

7.7. Methods used in assembling the study data

All registry data will be assembled via a web-based data capturing system provided by Swiss4Ward. It consists of two parts, a management system (AMS) and the capturing system openclinica. Data are stored in a postgre database (more detail are given in the data protection plan).

The web-frontend at the study centers shows the standardized eCRFs for the dermatologist and the patient at each visit. As an emergency option, all eCRFs can be printed and serve as paper CRFs. These pCRFs are in the same way standardized as the pCRFs that are sent directly to patients at interim intervals. The items, forms and questionnaires included, are described below.

The web-frontend at the coordination center CVderm shows all entry directly and allows for further quality assurance and data management.

7.7.1. Research Instruments and IT solution

Since many dermatologists do use internet-connected personal computers for their practice, the initial data assembling consists of an inclusively electronic data based collection. All CRFs and questionnaires used in the registry are standardized, have been pre-tested in pilot studies and/or taken from other registries and studies of CVderm. Standardized questionnaires and scales were developed and evaluated

according to internationally accepted methodological standards of psychometrics by CVderm or taken from the literature.

The CRF-Questions and data collection procedures have been adapted in accordance to the experiences with the eCRFs of patient registries at CVderm, e.g. PsoBest and PSOBEST. References to the standardized and evaluated scales and questionnaires are given above at (Operational definitions).

7.7.2. Personnel

At study centers, dermatologists document their professional decisions and observations on the eCRF. In some centers, the documentation will be delegated to qualified study nurses. Concerning registry-specific procedures a training program for participating physicians and their assistant medical personnel will be provided, including an online platform describing the use of registry-instruments. For more details see "Quality standards at the centers"

The patient's eCRF and pCRF were designed to allow the patient to be "the expert" of his health and care. Standards of Patient reported outcomes (PRO) are incorporated and well tested.

Staff at CVderm is skilled for epidemiological, observational and clinical research by profession. The personnel is qualified for all procedures of registry execution, since this is their daily routine.

Data entry, management and coding personnel is trained regularly see CVderm"

7.8. Procedures for data management

All data are stored via the web-based data capturing system AMS and Openclinica into the relational database Postgre. The inbuilt features of Openclinica will be used for routine data management.

OpenClinica is powerful, industry leading web-based software for capturing and managing clinical trial data. Therefore, it allows to build up studies, design electronic Case Report Forms (eCRFs), and conduct a range of clinical data capture and clinical data management functions.

OpenClinica supports Good Clinical Practice (GCP), regulatory guidelines such as 21 CFR Part 11, and is built on a modern architecture using leading open standards. OpenCinica includes tools to

- Submit Data: Intuitive interface for subject enrollment, clinical data capture, validation, and query management.
- Monitor and Manage Data: Tools for data cleaning, clinical data management, and site monitoring. Extract Data: Custom define and obtain clinical datasets in real-time, and in a variety of formats.
- Study Build: Design tools for configuring your study protocol: sites, eCRFs, edit checks/rules, users, and study event definitions. It allows for dynamic generation of web-based CRFs for electronic data capture with validation logic defined in reusable templates.
- Management of User Roles: Designate appropriate access for both site-level and study-level users.
- Administration: Tools for overall system oversight, auditing, configuration, and reporting.
- Organization of clinical research by study protocol and site, each with its own set of authorized users, subjects, study event definitions, and CRFs. Support for sharing resources across studies in a secure manner.
- Management of longitudinal data for complex and recurring patient visits.
- Validation Rules. A specialized engine performs advanced validation of study data and define automated actions within the system.

OpenClinica uses differentiated user roles and privileges, password and user authentication security, electronic signatures, SSL encryption, de-identification of Protected Health Information (PHI), and comprehensive auditing to record and monitor access and data changes. Fully validated software development lifecycle (SDLC). It Is a robust and scalable technology infrastructure developed using the Java J2EE framework and powerful PostgreSQL database. Modular architecture incorporating web services for extensibility.

Whereas dermatologist and patient eCRFs at study center visits are directly entered via the internet, forms including personal data to be especially protected, pCRFs printed from the data capturing system and pCRFS returned from patients at interim visits will be entered at the coordination center CVderm. These paper forms and CRFs will be entered into the database by independent double entry of trained coders. Conflicting results of double entry will be checked by a third person especially assigned this supervising role in patient registries at CVderm (datamanager).

All data from forms, eCRFs and pCRFs will be checked for completeness and plausibility by predefined checks. Missing or implausible values will be requested and obtained as soon as possible from the study centers via openclinica, by fax, phone or e-mail.

7.9. Methods for data analysis

Data analysis will be performed using SPSS and more specialized statistical packages.

Data for analysis will be checked by predefined plausibility analyses via a stored and validity checked SPSS-routines. Other SPSS-routine will do the obligatory data transformations and score computations. The algorithms implemented are extracted from the published literature and manuals of the measurement instruments and are checked for appropriateness and validity for years of use in clinical and scientific routine of CVderm.

While details of statistical analysis and modeling will be given in separate statistical analysis plans per objective, the methods used for reporting and major rules and procedures of statistical analyses will be described shortly by type of analysis and by type of objective.

Type of analysis

Descriptive analyses at fixed time points:

Descriptive analysis generally lead to tabulations and/or graphs showing the univariate distributional characteristics of variables in the sample and/or subgroups of the sample (e.g. cohorts). Dependent on the scaling of variables frequency distributions of variable values (including count and percentages) will be computed. As this is the only option for nominal scaled variables, this might also be needed for ordinal or even interval or cardinal scaled variables. Distributional properties of ordinal scaled variables or variables deviating from normal distribution will be given by non-parametric descriptors of central tendency and dispersion like median and percentiles. For approx. normally distributed and interval scaled variables properties of distribution will be summarized by mean, standard deviation, range (minimum, maximum) and where needed additionally by median and percentiles.

Descriptive analyses over time:

To describe aggregated data over time, fixed time points and interval analysis schemes are distinguished. In the fixed time point's scheme, descriptive data are analyzed cross-sectional by visit numbers. In interval analyses, data is aggregated within defined time intervals, e.g. from baseline up to 1 year. The lower interval limit is usually the baseline (visit 1 of each patient).

Usually only one interval is specified, so that all available data within that interval will be aggregated. The description over time within more than one interval is more complex and not considered here. Methods for description are the same as given above. If justified, missing data are substituted by last observation carried forward.

To describe the registry courses of single patients over time, the data are given along the chronologic metric of dates when they were measured. A description as aggregate of the time courses of patients is more complex and not considered here.

Time-to-event analyses:

For time-to-event analysis Kaplan-Meyer survival analyses and/or Cox-regression will be applied.

Comprehensive statistical modeling:

More comprehensive analyses will consider cohorts and time as well as cluster-effects and time-dependent and/or time-varying predictors, potential confounder and effect modifier by complex statistical modeling (e.g. mixed models).

Type of objective

Registry and Cohort description

Regular description of registry growth and Registry baseline description by cohorts will involve the methods described in Descriptive analyses at fixed time points.

Effectiveness, clinical outcome and PROs

Description of cohorts on clinical and patient reported outcomes as well as quality of care during registry time will involve the methods described in descriptive analyses over time in a fixed time point's scheme. For center reporting, the data of each center will be benchmarked against data of all other centers. For each patient, the course will be plotted on outcomes against registry time.

Safety

Safety data will be reported for an actual report period and cumulatively and separately for adverse and serious adverse events by treatment. Events will be reported as preferred terms (PT) within system-organ-classes (SOC) of the MedDRA-terminology. Events within SOCs are summed for SOC-reporting. Reports will show counts of events as well as counts of patients with events and the percentage of these patients of all exposed in the respective time interval. For comparative purposes, the rates of patients with events will be standardized by exposure time (per 100 patient years) along with approp. poisson 95%-confidence intervals by sex and total. Malignancies and death will be assigned for all patients ever exposed to a treatment. Time-to-event analyses will involve the methods described above and for more complex objectives, comprehensive statistical modeling will be necessary as well as specific statistical analysis plans.

Persistence/Adherence

Analyses of treatment persistence or adherence will involve time-to-event analyses and, for more complex objectives, comprehensive statistical modeling. Specific statistical analysis plans will be necessary.

Additional rules

Absolute and relative effects

In order to facilitate interpretation of effects and results, relative effects will be accompanied by the respective absolute effects/results. To give an example, for all results, sample size will be given and wherever percentages are reported, the respective nominator and denominator will be given

Missing values

Missing values are minimized by definition as mandatory in OpenClinica in data collection and by query-mechanisms of the data management procedures. If data is still missing, this will be reflected in descriptive analyses. In statistical modeling the usual substitutions will be applied, i.e. LOCF wherever justified. More complex statistical models compensate for missings by the algorithms of estimation involved.

Adjustments for multiple testing

Adjustment for multiple testing will be applied as sensitivity analysis. Wherever justified, a familywise adjustment to guarantee a nominal type I error level for multiple testing “families” of independent for each dependent variables. The Bonferroni-method will be the standard procedure for adjustment.

Bias, confounder and effect modifier

Since the registry is an observational study, potential bias has to be expected on all analyses. Whereas most of the potential biases are minimized in the data acquisition phase by definition, standardization and data collection, statistical control of potential confounders and effect modifiers is planned throughout all analyses by stratification and/or (usual and time-dependent/time-variing) covariate modelling. Where matching is thought, control cases and exposure cases will be matched by propensity scores obtained from logistic regressions. Sensitivity analyses will be applied where judged to be needed.

Representativeness/Generalizability

The profiles of the patients included in the registry will be compared with available data from treatment studies and epidemiological studies to verify representativeness. Although possible differences cannot be corrected, they will be discussed.

7.10. Description of quality assurance and quality control procedures for all phases of the study

7.10.1. Guidelines and quality standards

The following guidance and standards are considered in the setup of HSBest:

AHRQ: Gliklich R, Dreyer N, Leavy M, eds. Registries for Evaluating Patient Outcomes: A User's Guide. Third edition. Two volumes. (Prepared by the Outcome DEcIDE Center [Outcome Sciences, Inc., a Quintiles company] under Contract No. 290 2005 00351 TO7.) AHRQ Publication No. 13(14)-EHC111. Rockville, MD: Agency for Healthcare Research and Quality. April 2014. http://www.effectivehealthcare.ahrq.gov/registries-guide-3.cfm.
DNVF: Müller D., Augustin M., Banik N., Baumann W., Bestehorn K., Kieschke J., Lefering R., Maler B., Mathis S., Rustenbach S., Sauerland S., Semler S.C., Stausberg J., Sturm H., Unter C., Wiesel A., Neugebauer E.A.M.: Memorandum Register für die Versorgungsforschung. Gesundh.wes., 2010, 72: 824-839.
AWMF: S1-Leitlinie zur Hidradenitis suppurativa / Akne inversa der Deutschen Dermatologischen Gesellschaft (DDG). In: AWMF online (Stand 2011).

ENCePP: Guide on Methodological Standards in Pharmacoepidemiology (Revision 3). EMA/ 95098/2010 Rev. 3.

BfArM: Gemeinsame Empfehlungen des Bundesinstituts für Arzneimittel und Medizinprodukte und des Paul-Ehrlich-Instituts zur Planung, Durchführung und Auswertung von Anwendungsbeobachtungen (Entwurfsfassung vom 09. Mai 2007)

Bundesanzeiger: Gesetz über den Verkehr mit Arzneimitteln (Arzneimittelgesetz - AMG). "Arzneimittelgesetz in der Fassung der Bekanntmachung vom 12. Dezember 2005 (BGBl. I S. 3394;), zuletzt geändert durch Artikel 2 des Gesetzes vom 14. Juni 2007 (BGBl. I S. 1066)"

EMA: Note for guidance on clinical safety data management. Version 2006

EMA: Note for guidance on good clinical practice (CPMP/ICH/135/95), 2006

EMA: Guideline on good pharmacovigilance practice (GVP)-Module VIII, EMA/813938/2011 Rev 1

FDA: Guidance for Industry - Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. U.S. Department of Health and Human Services. Food and Drug Administration, February 2006

GMDS and BfArM: Victor N, Windeler J, Hasford J, Köpcke W, Linden M, Michaelis J, Röhmel J, Schäfer H (1997). Empfehlungen zur Durchführung von Anwendungsbeobachtungen. Informatik, Biometrie und Epidemiologie in Medizin und Biologie 28, 247-252

IEA European Epidemiology Federation (2004). Good epidemiological practice: proper conduct in epidemiologic research. http://www.dundee.ac.uk/iea/GoodPract.htm.

CIOMS: International guidelines for ethical review of epidemiological studies. http://www.cioms.ch/frame_1991_texts_of_guidelines.htm

CIOMS : International Ethical Guidelines for Biomedical Research Involving Human Subjects, Genf 2002

ISPE Guidelines for Good Pharmacoepidemiology Practices (GPP); in: http://www.pharmacoepi.org/resources/policies.cfm

MedDRA: ICH-Endorsed Guide for MedDRA Users: Application to Adverse Drug Reactions / Adverse Events & Medical and Social History & Indications, MedRA 2003

VFA-Empfehlungen zur Verbesserung der Qualität und Transparenz von nicht-interventionellen Studien (Stand 31. Januar 2007)

World Medical Association (2013). Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. www.wma.net/e/policy/b3.htm. The study protocol is in compliance with these standards.

7.10.2. German task force of HSBest

The planning, conductance and reporting of HSBest will be supervised by a scientific Advisory Board. The task of the scientific Board is to advise CVderm, monitor the quality of procedures and the achievement of the registry objectives. The task force will work on selected issues of HSBest.

The German task force for hidradenitis suppurativa also inspects the annual reports of HSBest and communicates transparency of contacts and scientific independency of HSBest to the sponsors.

The German task force for hidradenitis suppurativa appoints personal meetings as needed and communicates otherwise by Email and by Telephone conferences.

The members of the German task force for hidradenitis suppurativa are appointed by the executive boards of the DDG/BVDD. The size of the panel is variable but should be limited for reasons of practicability. The current members are listed on page 4 of this protocol.

7.10.3. Quality standards at the study centers

The objective is sufficient qualification of all participating centers in performing patient recruitment, determination of all outcome parameters, completing and correcting of CRFs and reliable organizational handling of the registry.

Maintaining a high quality of performance at the participating centers is the goal of HSBest. This qualification is oriented to the regulations of GCP/ICH and GEP. In particular, the following quality characteristics are to be fulfilled:

1. Reports are made exclusively by trained dermatologists.
2. The centers should have adequate experience in the therapy of HS.
3. The doctors at the centers are familiar with the use of customary outcomes parameters (DLQI). To guarantee a well-founded clinical severity estimation, the following additional measures will be implemented:

a. An Internet platform will be set up for all centers, in which the use of the instruments is described and can be practiced.

b. All case report forms received will be subjected to a plausibility check at the coordination center. The plausibility criteria will be defined in advance and stored in the software.

A website will also be set up to provide all study centers with current information. The access is limited to participating doctors and patients. The website will contain both specific information for patients and information for the doctors. Important information and listings of links will be given in advance by mail (or fax).

The reporting of AE and SAE is regulated by German Ethics. All centers are informed and will comply with these regulations.

If data turn out to be of questionable quality, discussions will be held on site and measures to improve personnel performance will be implemented.

7.10.4. Quality standards of data acquisition

All forms and CRFs (eCRFs and pCRFs) to collect the data are standardized and were developed within the framework of patient registries at CVderm. Internationally accepted and recommended questionnaires and scales are incorporated.

OpenClinica was chosen as the web-based software for capturing and managing registry data, since it was developed to achieve high quality data and maximize quality control in each phase of study conductance.

7.10.5. Quality standards at the coordination center CVderm

CVderm is a high specialized scientific institute in health services research. CVderm is certified by DIN ISO 9001:2008 and within the quality management system by specific SOPs for patient registry conductance are used.

CVderm bears the responsibility for all phases of planning and execution of HSBest including performance during the study course, supervision of study centers, spotted monitoring, data administration and analysis, as well as coordination and communication with the sponsors and professional societies.

CVderm employees represent a multidisciplinary team of academics from a variety of disciplines in empirical health sciences. This includes disciplines of medicine, psychology, epidemiology, biomathematics, public health, health economy, sociology, geography, medical documentation, media science. The academic team is (more than) supported by an administration team for documentation and data management at all stages of registry conductance. All employees are highly skilled in their profession and familiar with health care services research and patient registry research by profession and routine.

CVderm employees have their professional skills and essential tasks in the following domains of registry conductance:

a. CRF development
b. Questionnaire and Scale development and validation
c. Project management
d. Coordination and communication with participating centers
e. Monitoring (for a detailed description of monitoring see section “Quality Assurance monitoring” below)
f. Quality control and assurance
g. OpenClinica Mangement
h. Data management
i. Data analysis
j. biometric reporting and publication
k. Pharmacovigilance, reporting of AEs and SAEs
l. Coding with MedDRA
m. Data protection
n. General finances and organization

Quality Assurance measures will be taken at the performance levels of the central study management office CVderm. All tasks are supervised and trained regularly in routine. SOPs for all domains are regularly updated and adopted to changing requirements and demands.

7.10.6. Reporting System

CVderm reports to the principal investigator and to the members of the German task force regularly at 12-month intervals. The reports will include data on recruitment status, clinical baseline, and safety.

7.10.7. *Quality Assurance Monitoring (direct Source Data Verification)*

Monitoring will be implemented in HSBest in the year 2020. A monitoring plan will be developed in advance.

In sum, a monitoring visit is planned at each site having documented >10 subjects in HSBest. The site will be visited at least once every 30 months as long as subjects are participating in the study. The monitor will perform simple center facility tasks and source data verification between the data documented in the CRF and the patient file for target data defined in the monitoring plan. The monitor will be instructed by CVderm data management beforehand of a visit on data problems relevant to monitoring, e.g. unsolved queries.

7.10.8. Measures for quality management on the part of the patients

The validity of the information obtained by the registry depends nearly completely (apart from dermatologist information) on the quality of data reported by the patients.

Measures to improve patient performance are:

1. Patients are thoroughly informed, in an easy-to-understand way, using the Information Sheet and the Informed Consent Statement.
2. Patients are contacted at home on a regular basis (6 months after physician visits) and in case of not presenting to the regular office visits.
3. Patients are reminded for three times to send the CRFs if these are overdue for a week.
4. Patients are informed on the status and course of HSBest at the website: https://www.dermregister.com/de/hs-best.html

7.11. Limitations of the study design, data sources and analytic methods

Bias

The intended population will differ from the not-intended population in various known and unknown characteristics. Since there's a part of the target population that doesn't seek treatment, no qualified data on disease and no data on treatment and care can be obtained from these persons.

One threat to representativeness will be the selection of study centers at the first stage of cluster-sampling, since participation is voluntary and might result in an unrepresentative sample of centers treating hidradenitis suppurativa in Germany. Participation might be more relevant to dermatologists with excellence in treatment of HS. Secondly, very active and innovative dermatologists may be predominant. This may lead to a more sophisticated treatment behavior than expected. However, these dermatologists are likely to provide a more accurate study performance.

On the other side, study centers that declared participation beforehand, are geographically distributed across Germany, so that geographical representativeness might be a minor threat.

To minimize selection bias at the second stage of cluster-sampling, consecutive enrolment of all patients seeking treatment is planned and only a minimum set of inclusion criteria were defined. At this stage, the major threat might arise by patients refusing to participate. Therefore, the patient information was written thoroughly to maximize comprehensibility, underlining the value of participation for future treatments, patients and care.

To judge the extent of representativeness and selection bias, profiles of the registry patients will be compared to data from treatment studies and epidemiological studies.

Misdiagnosis

- Since all participants are experienced dermatologists and the diagnosis of hidradenitis suppurativa is relatively easy, the risk of disease misclassification is low.
- Exposure: Treatment is easily and definitely classifiable. Exposure misclassification may arise from non-compliance. In order to control non-compliance, which may not be reported to the physician, a CRF-question on the direct contact with the patient every 6 months is given.

Confounding

In contrast to bias, the minimization of confounding was considered throughout the methodological planning of the registry. Confounding will be controlled at all phases of the study and in statistical modeling. Potential confounders such as patient, disease, and registry as well as treatment course characteristics will be obtained in the registry for statistical control. Inclusion criteria represent a form of specificity thus reducing confounding.

8. Description of plans for protecting human subjects

The HSBest registry was planned and will be performed under strict rules of patient protection as suggested by the German and European laws, the Declaration of Helsinki and the GCP/ICH guidelines. Before start of the study, consent from the ethics committee of the physicians in Germany will be obtained.

The conductance of patient registries at CVderm follows a special data protection plan to secure and protect the patient's personal information and health data at the high level demanded by European, German and German data protection law.

Since the registry is non-interventional by definition, patients and treatment are observed as it is decided by the dermatologists in routine care, and not mandated or even influenced by study protocol. Accordingly, there is no increased risk of study participation compared to non-participation since treatment will be identical.

9. Management and reporting of adverse events/adverse reactions

This section includes the procedures for the collection, management, and reporting of individual cases of adverse events or adverse reactions, as appropriate.

9.1. Definitions:

9.1.1. Adverse events (AE)

An adverse event is any untoward medical occurrence in a patient administered a pharmaceutical product. An AE does not necessarily have a causal relationship with the treatment/ pharmaceutical product.

9.1.2. Serious adverse event (SAE)

An AE that, at any dose, meets any of the following conditions disregarding causal relationship:

- ✓ results in death
- ✓ is life-threatening
- ✓ requires inpatient hospitalisation or prolongation of existing hospitalisation
- ✓ results in persistent or significant disability/incapacity
- ✓ results in a congenital anomaly/birth defect
- ✓ is an important medical events

Life-threatenting means that the patient was concretely at risk of dying at any timepoint of the study. It is not an event that hypothetically may have resulted in death if the event has been more pronounced.

Important medical events:

Events which may not be immediately life-threatening but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above. Important medical events should be reported as SAE.

9.1.3. Pregnancy

Pregnancy of a female patient or of a female partner of a male patient are to be reported to CVderm as a serious adverse event, irrespective of any occurrences of other (adverse) events.

9.1.4. Product Quality Complaints (PQC) with/without AE/SAE

PQC which correspond to product quality, physical appearance, packaging, or labelling (like package leaflet and product information) or which may be associated with the intended storing. PQC may be associated with an AE/SAE or the suspicion of a PQC may have caused an AE/SAE respectively like lack of efficacy.

9.1.5. Causal relationship assessment by the treating physician

For every AE, the physician needs to evaluate the causal relationship between the occurring serious adverse event and the administered (observed) drug according to the following definition:

Very likely

An AE which is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, e.g. concomitant drug(s), concomitant disease(s). The relationship in time (with the use of the drug) is very suggestive (e.g. it is confirmed by de-challenge and re-challenge).

Probable

An AE which might be due to the use of the drug. The relationship in time is suggestive (e.g. confirmed by de-challenge). An alternative explanation is less likely, e.g. concomitant drug(s), concomitant disease(s).

Possible

An AE which might be due to the use of the drug. An alternative explanation, e.g. concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Doubtful

An AE for which an alternative explanation is more likely, e.g. concomitant drug(s), concomitant disease(s) and/or the relationship in time suggests that a causal relationship is unlikely.

Not related

An AE which is not related to the use of the observed drug (as evaluated by the treating physician).

For regulatory reporting purposes, as detailed in the ICH - E2D guideline, if an event is spontaneously reported, even if relationship is unknown or unstated, it meets the definition of an adverse reaction. **Therefore all spontaneous reports notified by healthcare professionals, patients or consumers are considered suspected adverse reactions**, since they convey the suspicions of the primary sources , unless the reporter s specifically state that they believe the events to be unrelated or that a causal relationship can be excluded.

9.2. Assignment of events to treatments

Reporting of AE and SAE is optionally based on the EU pharmacovigilance legislation 2012 and the corresponding EMA Guidelines on good pharmacovigilance practices (GVP). A specific reporting plan was developed.

The following rationale will be implemented:

An event is assigned to a treatment if the date of the event is at the day of treatment start, within 30 days after the end of treatment or in the period between start and stop of the treatment, regardless of co-medication.

Events observed for combined or overlapping (as defined in the '30-day rule' risk window) treatments will be reported for each treatment.

For any treatment the risk window for malignancies and deaths includes all prospective person-time documented in the registry for a specific therapy and extends until the date of the event, the date of the last observation, whichever comes first.

9.3. AE/SAE Forms:

All adverse events (non-serious and serious) will be documented on the respective forms (Meldung einer vermuteten unerwünschten Arzneimittelwirkung (UAW)) as soon as the dermatologist gets aware of them and the following minimum criteria are given:

- One or more identifiable reporter
- One single identifiable patient
- One or more suspected treatment of chronic pruritus/prurigo
- One or more suspected adverse reaction

The events are submitted to the „Gemeinsame Datenbank von BfArM und PEI zur Meldung von Nebenwirkungen, auch bekannt unter der Bezeichnung „unerwünschte Arzneimittelwirkungen" (UAW)". There will be no routine submissions to the central CVderm registry database except for treatment-emergent adverse events (TEAE) of particular interest. These events will be submitted to CVderm using a standard form.

9.4. Responsibility for sending TEAE and AE/SAE forms:

Each (serious) adverse event of special interest has to be reported to CVderm (Fax-No. +49-40 – 74105-7227). In case of SAE, these needs to be done within a timeframe of 24 hours after noticing.

All other (serious) adverse event (standardized form) have to be reported to BfARM. In case of SAE within a timeframe of 24 hours after noticing. The form should contain all available medical information. Medical information like laboratory results, hospital discharge letters etc. should be sent along with the form.

Information on TEAE amending an initial report (follow-up reports) have to be reported to CVderm within 24 hours after noticing. A follow-up report should be marked as such.

9.5. Responsibility of study center for sending form:

CVderm is not responsible for forwarding to the BfArM. The reporting dermatologist is responsible to send the form to the regional pharmacovigilance centre in Germany. Under the Law on Therapeutic Products (Heilmittelgesetz) all professionals who are entitled to distribute, administer or prescribe medicines are subject to the obligation of reporting suspected adverse reactions to drugs .

9.6. Responsibility of DDG/BVDD/HSBest to provide contact data of license holders:

DDG/BVDD/HSBest is responsible to provide contact data of licence holders of treatments for hidradenitis suppurativa to CVderm during the whole registry conductance.

9.7. Responsibility for forwarding to license holders of CVderm:

CVderm is responsible for forwarding incoming AE/SAE forms (initial and follow-up) after a plausibility check and a positive minimum criteria check to the licence holder of suspected treatments of hidradenitis

suppurativa within a timeframe of 24 hours after plausibility and minimum criteria have been positively checked.

9.8. Responsibility to collect follow-up information of CVderm:

CVderm contacts the treating physician to collect follow-up information.

10. Description of plans for disseminating and communicating study results

There is an ethical obligation to disseminate findings of potential scientific or public health importance (e.g. results pertaining to the safety of a marketed medicinal product).

Descriptive clinical and safety data are reported at annual intervals starting in 1/2023 for clinical data and 07/2023 for safety data to DDG/BVDD.

Clinical data reporting include the recruitment status and selected baseline data. These data will be reported for the whole registry and for each center.

Whenever convenient from a medical and scientific point of view, the HSBest task force decides, to present results from the registry at scientific convents/congresses and to submit publications to medical journals. In addition to publication in medical journals, important results will be published on the internet (HSBest - Home (dermregister.com)

11. Resources required to conduct the study

The Coordination Center CVderm will be financed by third-party support of DDG/BVDD. Since no financing with public funds is to be expected in the foreseeable future, the required funds have to be obtained primarily from the participating companies holding the licenses of hidradenitis suppurativa treatments. Financing and services will be regulated by bilateral contracts between DDG/BVDD/HSBest and the participating companies.

Figure 1: Flowchart

Physician visit no.	**V0**		**V1**			**V2**			**V3**		*
Patient visit no.		P0		P1	P1a		P2	P2a		P3	
	Phy	Pat	**Phy**	Pat	Pat	**Phy**	Pat	Pat	**Phy**	Pat	
Parameter Months	**0**	0	**6**	6	12	**18**	18	24	**30**	30	
Pat. ID	**x**	x	**x**	x	x	**x**	x	x	**x**	x	
Patient consent	**x**	x									
Demographics (age, gender)		x									
HS risk factors (obesity, smoking, etc.)		x		x			x			x	
Family history for HS		x									
Previous history / duration of disease		x									
Previous diagnostics		x									
Previous / intermediate tx types		x		x	x		x	x		x	
Previous / intermediate tx duration		x		x	x		x	x		x	
Skin type (Fitzpatrick)	**x**										
HS classification	**x**		**x**			**X**			**x**		
HS lesion count	**x**		**x**			**x**			**x**		
Therapy decision	**x**		**x**			**x**			**x**		
AE/SAE			**x**			**x**			**x**		
Treatment convenience/burden		x		x	x		x	x		x	
DLQI		x		x	x		x	x		x	
Electronic data entry (eCRF)	x	x	x	x	x	**x**	x	x	x	x	
Emergency Paper CRF	x	x	x	x	x	**x**	x	x	x	x	
Hardcopy questionnaires for patients					x			x			
Photo documentation (optional)	**x**		**x**			**x**			**x**		

*Further visits are to be added.

SIGNATURE PAGE

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HSBest-Registry for hidradenitis suppurativa treatment

Objective

Long-Term Benefits and Safety of hidradenitis suppurativa therapy:

German Registry on the Treatment of hidradenitis suppurativa in operational cooperation with CVderm in Hamburg.

Prof. Dr. Matthias Augustin

Principal Investigator

Hamburg, ----------

12. Attachment 1: Checklist of Registry Quality to be applied

The following criteria derived from the German National Consensus on patient registries (Müller 2010) will be applied:

Domäne	Item	Obligat
Systematik und Angemessenheit	Vorliegen eines Registerprotokolls	+
	Ableitung und Begründung der Fragestellungen sowie des erwarteter Nutzens	+
	Darstellung der Registerorganisation (Personal, Hard- und Software)	
	Wahrung der Patientenrechte und des Datenschutzes	+
	Darlegung des Registerdesigns	+
	Detaillierte Beschreibung des Vorgehens bei der Gewinnung der Untersuchungseinheiten, Datenerhebung, Datenverarbeitung, statistische Analyse (Analyseplan) und Berichterstattung	+
	Einrichtung Advisory Board / Steering Comitees	
Standardisierung	Festlegung von Standards („Standard Operating Procedures„)	+
	Definition und Operationalisierung Expositionen, Kohorten, Ereignisse, Outcome und potentiell konfundierender und Effekt modifizierender Variablen	+
	Schulung/ Überprüfung der Datenerhebung/ -erfassung	+
Stichproben / Quellpopulation / Zielpopulation	Definierte Ein- / Ausschlusskriterien (Selektionsparameter)	+
	Abschätzung der Vollzähligkeit bzw. Repräsentativität	+
	Abschätzung des Stichprobenumfangs/ Effekts	
	Festlegung der Strategien zur Minimierung von Verzerrungen	+
Validität der Datenerhebung	Darstellung der Vollständigkeit der Daten	+
	Darstellung der Vollständigkeit der Dokumentationszeitpunkte (Drop-out)	+
	Nachverfolgung	bei unvollständigen Meldungen
	Eindeutige Identifikatoren (Zuordnung der Daten zu den Merkmalsträgern / Ausschluss vom Mehrfachregistrierungen)	+
	Mehrfacheingabe der Daten	Bei Nacherfassung (übertragender Dokumentation)
	Darlegung der Verteilungseigenschaften, Konkordanz, Plausibilität (Widerspruchsfreiheit)	+
	Monitoring / Externe Audits	
Validität der statistischen Analysen und Berichte	Darstellung des Patientenflusses	+
	Darstellung des Verfahrens mit fehlenden Werten / Drop-out	+
	Darstellung der soziodemographischen und klinischen Merkmale sowie der relevanten Zielgrößen	+
	Darstellung von Präzisionsmaßen	+
	Prüfung der Strukturgleichheit (obligat bei Kohorten)	+

	Adjustierung (Berücksichtigung potentiell konfundierender und den Effekt modifizierender Variablen)	+
	Adjustierung multipler inferenzstatistischer Testung	
	Darstellung relativer und absoluter Effekte, adjustierter und unadjustierter Ergebnisse	+
	Multivariate Modellbildung bei komplexen Fragestellungen	+
	Berücksichtigung der Zeitachsen bei Längsschnittregistern	+
	Kontrolle potentieller Meldeeinrichtungseffekte (falls unterschiedlich Meldeeinrichtungen möglich sind)	+
Übergreifende Qualitätsanforderungen	Umgang mit limitierenden Rahmenbedingungen	
	CPzeptanz bei Meldern und PatientInnen, Effizienz	
	Transparenz und wissenschaftliche Unabhängigkeit	+
	Flexibilität und Anpassungsfähigkeit	
	CPtualität	

13.Attachment 2: Checklist of Registry development and conductance

The following development steps will be taken and are specified in the consecutive table:

1. Registry planning

- Initial concept
- Writing a proposal
- Biometrics and statistics
- Cost calculation
- Funding
- Contracts
- Study protocol
- Staff
- Room/work equipment calculation
- Time calculation
- IT basis
- Ad Board
- Quality control
- Ethics
- Data protection
- Study documents
- Centres
- Dispatches
- Trainings
- Motivation and retention
- Dissemination

2. Registry conductance

- Data acquisition
- Data protection and pseudonymisation
- Database management
- Tabulation of recruitment
- Actual-target monitoring of recruitment
- Actual-target monitoring of the course of the visit
- Tabulation of the exposures
- Completeness/completeness
- Monitoring
- Website
- SUE management
- MedDra/ICD, ATC coding
- Database: Hardware and software
- Data management (using the example of safety reporting)
- Data analysis
- Organisation
- Communication
- External reporting (data)
- Internal reporting (operation)
- Fees
- Topicality
- Finance
- QM

Organisation von PruriBest

1. Registerplanung

Bereich	Beschreibung	Tätigkeiten	Zuständig	Vertreter	Zeitaufwand
Erstkonzept	Mündliche Überlegungen und Literaturrecherche	O Datenbank-basierte Recherche nach Vorarbeiten und laufenden Registern O Ziele, Bedarf und Nutzen definieren			
Proposal schreiben	Proposal wird gemäß der IVDP- Standardgliederung 1-3seitig verfaßt	O Erster Entwurf Proposal O In Umlauf bringen O Abschlußkorrektur			
Biometrie und Statistik	Erstellung eines vorläufigen biometrischen Planes incl. Fallzahlschätzung	O Biometrischen Plan erstellen O Check auf Plausibilität			
Kostenkalkulation	Erstellung einer Kostenabschätzung	O Rohkostenplanung aufgrund Proposaldaten und Biometrie O Check auf Plausibilität			
Finanzierung	Potentielle Förderer werden direkt angesprochen	O Proposal nach Rücksprache mit Förderer versenden oder O Studienantrag erstellen			
Vertragswesen	Studienverträge mit Sponsoren und Zentren abschließen	O Vertragsvorlagen durch Medigate erstellen O Firmenverträge O Zentrumsverträge: initial pro Zentrum abschließen; laufend prüfen O ggf. Zulieferverträge			
Studienprotokoll	Bei geklärter Finanzierung wird ein Studienprotokoll gemäß EMA-Vorgabe erstellt Vorlage: Muster-Studienprotokoll	O Vorlage gemäß Proposal an Studienzweck anpassen O Sprache: Englisch O Protokoll gegenlesen			
Personal	Planung und laufende Prüfung	O Aufgabenbereiche definieren (mind. Projektmanagement, Datenschutz, Dokumentation, Assistenz, Daten-/Webmanagement, Statistik, Klinik) O Qualifikationsanalyse (Schulungsbedarf ermitteln) O Stellenschlüssel ableiten O Aufgabenverteilung nach Qualifikation O ggf. Ausschreibungen nach Qualifikation O Soll-Ist-Vergleich des Personaleinsatzes im Registerverlauf			
Raum-/Arbeitsmittelkalkulation	Sicherung der Betriebsräume und -mittel	O Bedarfsermittlung Räume 0 Bedarfsermittlung Arbeitsmittel (Möbel, Kommunikation, Hard- und Software, Büromaterial etc.) O Ressourcenbereitstellung			

Zeitkalkulation	Planung	O Meilensteine zu Umsetzung und Betrieb definieren			
IT-Basis	Digitale Datenaufnahme planen	O Vorlage gemäß Proposal an Studienzweck anpassen O Provider für IT-Lösung suchen O Leistungsverzeichnis erstellen (Hard- und Software) O Zeiplan definieren			
Ad Board	Einsetzen eines wiss. Beirates – frühe und späte Besetzungen möglich	O Vorlage gemäß Proposal an Studienzweck anpassen O Protokoll gegenlesen			
Qualitätskontrolle	Prüfung der Studienmethodik und –unterlagen auf Kompatibilität	Prüfen auf … O DNVF-Kriterien O EMA / ENCePP O FDA O ggf. indikationsspezif. Kriterien O GCP/ICH O International Ethical Guidelines for Epidemiological Studies O Strobe, GEP, GPP, etc.			
Ethik	Ethikantrag unter Verwendung von Ethik-Vorlagen erstellen: 1. Antragsformular 2. Pat.Info 3. Pat.einwilligung 4. Studienprotokoll 5. Anschreiben	O Ethik-Antrag anpassen (Verwendung des Proposals) O Pat.Info und Einwilligung von Vorlage anpassen O Anschreiben von Vorlage anpassen O Unterlagen versenden O Monitoring des Antrags			
Datenschutz	Datenschutzkonzept erstellen	O Gesetzliche Regelungen beachten O Europäisches Recht berücksichtigen O Dateneigentum und Datenverwendung regeln			
Studienunterlagen	Zusammenstellung aller für die Studie benötigten Unterlagen	O CRFs erstellen (→ ggf. IT) O Pat.info und –einwilligung (→ siehe Ethik-Antrag) O Anschreiben an Ärzte O Kurzinfo an Ärzte O Arztordner O Einschlusslisten O Unterlagen konfektionieren			
Zentren	Rekrutierung der teilnehmenden Zentren; erstmalig und laufend	O Zentrumsliste erstellen O Brief an Zentren verfassen O Serienbrief erstellen O Ggf. direkte Ansprache von Zentrumsleitern			
Versendungen	Aussendung aller Studienunterlagen	O Versendungsmuster erstellen			

		O Check des Musters O Unterlagen einpacken O Abstimmung mit Poststelle O Zur Versendung ausliefern (→ vgl. SOP Postversendung)			
Schulungen	Mindeststandard für Personal und Zentren (Struktur, Prozess und Inhalt)	O Interne Personalschulungen O Qualifizierende Personalfortbildungen O Schulungsmaterial Teilnahme zusammenstellen, zur Verfügung stellen, Dokumentation der Kenntnisnahme O Schulungsmaterial Inhalt/CRF zusammenstellen O Schulungsform organisieren (vor Ort, Web, externe Trainer)			
Motivation und Retention	Zentren und Patienten	O Verstärker für Zentren definieren O Verstärker für Patienten definieren			
Dissemination		O Public Relation Management O Kongressplanungen O Publikationsstrategie festlegen			

2. Registerbetrieb

Bereich	Beschreibung	Tätigkeiten	Zuständig	Vertreter	Zeitaufwand
Datenaufnahme	Laufende Erfassung der Patientendaten in CRFs	O Tätigkeit in den Zentren O Übermittlung an die Studienzentrale O Beantworten von Nachfragen zu fehlenden und/oder nicht plausiblen Daten O Personalorganisation (HIWis) O Schulung (HIWis) O Arbeitsmittelorganisation (HIWis) O Strukturierung der Arbeitsverteilung (HIWis)			
Datenschutz und Pseudonymisierung	Vorgang der Pseudonym- und Echtdaten-Führung	Im Zentrum → O Führen einer Einschlußliste O Übermittlung an die Studienzentrale in der Studienzentrale → O Datenschutzbeauftragter: Verwaltung eingehender Patientendaten o Sicherung der Daten (Hard- und Softcopy, Verschlüsselung)			
Datenbankmanagement	Erfassung, Prüfung und Ablage klinischer Daten	Vorher → O Vorlagen für „Standardqueries“ generieren O Festlegen der innerhalb einer Visite vorkommenden oder (visitenübergreifender) Plausibilitäten und der Pflicht- felder Laufend → O Dokumentation eingehender klinischer Daten O Prüfung eingehender klinischer Daten auf Plausibilität und Vollständigkeit O Querymanagement klinischer Daten (CRFs & schwerwiegende, unerwünschte Ereignisse (SUE)) O Bearbeitung und Dok. Von ggf. angeforderten Nachverfolgungen zu SUEs O ständige Kommunikation mit teilnehmenden Zentren O MedDRA- Kodierung O Visitenblick O Import O Screening O Konfliktmanagement			
	Erfassung, Prüfung und Ablage personenbezogener Daten	Vorher → O Vorlagen für „Standardqueries“ generieren Laufend →			

		O Dokumentation und Verwaltung eingehender Patienteneinwilligungen (PE) und Einschlusslisten (EL) O Patientendaten ein/- pflegen O Prüfung auf SUE O Prüfung auf Vollständigkeit und Plausibilität eingehender personenbezogener Daten O Querymanagement bei fehlenden Daten O Kommunikation mit Prüfzentren und Patienten ggf. Kommunikation mit Patienten O Drop-Out- Verwaltung, "loss-to-follow-up" – Nachverfolgung Zentren, Patienten, Ämter O Organisation von Arztwechseln O Datenschutzrichtlinien updates, Oualitätsmanagement			
Tabellierung der Rekrutierung		O Führen der Inklusionstabelle O Führen der Kliniktabelle			
Ist-Soll Monitoring der Rekrutierung		O Führung der kumulativen Einschlusstabelle und Analyse			
Ist-Soll Monitoring des Visitenverlaufs		O Führung des Visitenblicks			
Tabellierung der Expositionen		O Bestimmung der Expositionen (s. Datenmanagement bis Punkt: Dynamische Kohortendefinition auf Patientenebene) O Aktualisierung der Expositionstabelle			
Vollzähligkeit/Vollständigkeit		O Capture-Recapture O Fragebogenversendung: Mögliche Inklusionen O Auswertung IST/Möglicher Inklusionen O Auswertung Queries O Auswertung Erinnerungen O Auswertung fehlender Formulare, Werte			
Monitoring		O Monitoring Plan erstellen O Organisation des Monitorings O Datenbereitstellung für Monitoring (z.B. kumulative Randomisierungslisten) O Durchführung des Monitorings (extern) O Kommunikation mit Monitoren O Monitoring Berichte auswerten O Monitoring Berichte freigeben, weiterleiten			
Webauftritt		O Pflege der Struktur O Pflege der Inhalte O Pflege der Downloads O Bereitstellung aktueller Infos O Aktualisierung			

		Rekrutierungsstatistiken O Aktualisierung Expositionsstatistiken O Pflege Verlinkungen O Twitter			
SUE-Management		O Klinische Prüfung der Meldungen O Prüfung gegen Verlaufsdaten aus Visiten O Prüfung des Risikofensters O Prüfung Komedikation O Prüfung aut idem O Prüfung der Adressaten und Zustellung O Prüfung der Eingangsbestätigung O Nachverfolgung inkl. Erinnerungsmanagement und Abrechnung			
MedDra/ICD, ATC-Kodierung		O UE und SUE Kodierung O Kodierung Komedikation O Kodierung Diagnosen O Monitoring MedDra-Versionierung/ PTC etc.			
Datenbank: Hard- und Software		O Performanz-, Reliabilitäts-, Validitäts-, Integritätsprüfungen O Kommunikation mit Providern O Treffen mit Providern O Monitoring des Fehlermanagements			
Datenmanagement (am Beispiel safety reporting)		O Erweiterung aller Routinen mit Registerfortschritt, Protokolländerungen O Datenexport und-import O Prüfung der Integrität der ID-,Visiten-, Versionschronologie O Auslesen der Freitexte O Kategorisierung der Freitexte O Umsetzung der Kategorisierungen O Prüfung: Zeitraum, Inklusionskriterien, Vorexpositionen und Vorerkrankungen O Dynamische Bestimmung der Diagnosekohorten O Prüfung der soziodemographischen und klinischen Deskriptoren O Skalierung der soziodemographischen und klinischen Deskriptoren O Festlegung Beginn, Ende, Dauer und Risikofenster der Expositionen innerhalb der Visiten O Festlegung der Expositionskohorten innerhalb der Visiten O Prüfung und Korrektur der Expositionskohorten innerhalb der Visiten O Matching der UE-, SUE-Kodierungen, Prüfung der Chronologien			

		O Umstrukturierung der Daten: Wechsel der Untersuchungseinheit O Dynamische Kohortendefinition auf Patientenebene O Dynamische Bestimmung Beginn, Ende, Dauer und Risikofenster der Expositionen auf Patientenebene O Berechnung der Patientenjahre /pro-, retrospektiv) für die Kohorten O Zuordnung der SUE, UEs zu den Kohortenexpositionszeiträumen, Berichtsperioden und Diagnosekohorten O Benennung der Kodierungen O Tabellierungen UE, SUE zur Berechnung der Konfidenzintervalle Rate/PY O Berechnung der Cis in Excel O Datenmanagement: Extraktion der UE-Lines O Transformationen, Berechnungen, Stringverkettungen UE-Lines O Datenmanagement: Extraktion der SUE-Lines O Transformationen, Berechnungen, Stringverkettungen SUE-Lines			
Datenanalyse		O Erstellung statistischer Analyseplan O Operationalisierung der Hypothesen, inkl. potentieller Biasfaktoren etc. O Auswahl der statistischen Modellierung O Herstellung der Datenstruktur (Exposition, Outcome, Biasminimierung) O Modellierung und Interpretation O Festlegung sensitivitätsanalytischer, Schritte O Ergebnisbericht O Monitoring statistischer Modellentwicklungen, Statistik-Software für Register			
Organisation		laufend → O Organisation & Versand von Nachbestellungen zu Studienunterlagen an Prüfzentren O Versand Newsletter O Führen des Projektlogbuchs			
Kommunikation		O Vorbereitung und Durchführung von Projekttreffen (z.B. Firmen, Beirat…) O teilnehmende Zentren O Patienten O Auftraggeber O externe Firmen			

		O Hotline O Ad Board, Steerings, Review Boards O Fachgesellschaften, Berufsverbände O Behörden O Kongresse O Publikationen			
Externes Berichtswesen (Daten)	O Berichte zur Arzneimittelsicherheit (halbjährlich)	Tabellierungen Rekrutierung O Tabellierungen Soziodemographie O Tabellierungen Klinik O Tabellierungen Kohorten, Expositionen O Tabellierungen UE O Tabellierungen SUE O Export aller Tabellen nach Excel O Aufbereitung aller Tabellen in Excel O Export aller Tabellen nach Word O Layout aller Tabellen, Ergänzung leerer TabellenO O Tabellierung UE-Lines Tabellierung SUE-Lines O Einfügen der Lines in Berichte O Prüfung der Kumulativität der Berichte O Prüfung der klinischen Plausibilität der Berichte O Prüfung der statistischen Plausibilität der Berichte			
	O Berichte zur Wirksamkeit (jährlich)	O (s. Datenmanagement bis Punkt: Dynamische Kohortendefinition auf Patientenebene) O Festlegung der Startvisiten O Kohortenbildung nach Startvisiten			
	O Zentrums- und Patientenberichte	O (s. Datenmanagement bis Punkt: Dynamische Kohortendefinition auf Patientenebene) O Aufbereitung in SPSS O Visual-Basic Routinen nutzen O Plausibilitätskontrolle O Drucken und Patienten den Zentren zuordnen O Anschreiben O Versenden			
	O Expositionstabellierung (quartalsweise)	O Auf Anforderung Berichte an EMA, ENCePP, Behörden O Teilnahme an Psonet-Auswertungen			
	O Berichte an Behörden und andere externe Entitäten	O (s. Datenmanagement bis Punkt: Dynamische Kohortendefinition auf Patientenebene) O in Excel fürs Web aufbereiten			

Internes Berichtswesen (Betrieb)	O Berichte zum Registerbetrieb	O Intervalle und Formate der Berichterstattung festlegen O Jahresbericht O Finanzbericht an Sponsoren O Newsletter O Berichterstattung an Beirat			
Honorare	Begleichung von Honoraren an die Prüfzentren	Vorher → O Abrechnungskriterien festlegen (inkl. Vertrag) Laufend → O Abrechnungen generieren, aussenden, Eingänge verwalten & dokumentieren O Überweisungen vornehmen			
Aktualität	Anpassung des Registers an Stand der Wissenschaft, Klinik, Präparate, Outcomes, Recht, Methodologie	O regelmäßiges Screening O Amendements verfassen O Umstellung beauftragen, überwachen und implementieren			
Finanzen	Management der laufenden Register-Finanzierung	O Controlling O Rechenschaftsberichte			
QM	Aufbau und Betrieb eines QM-Systems in Abgleich mit dem CVderm-QM-System	O QM-Beauftragten für Register benennen O Indikatoren („Marker“) für die Qualität des Registerbetriebes definieren und prüfen O Regelmäßige QM-Arbeit O QM-Berichte nach Plan O Maßnahmen bei Qualitätsabweichungen (intern, extern) definieren			

Register FlowChart → laufende Tätigkeiten (CVderm)

Dateneingang

Datenschutzbeauftragter / „Trust center“

- Trennung eingehender Dokumente in klinische und personenbezogene Daten

Datenmanagement personenbezogene Daten

- Dokumente: Patienteneinwilligung
  Patienteneinschlusslisten
  Meldebogen „Drop-Out“
- Aufgaben: Dokumente prüfen, Plausibilität & Vollständigkeit
  Eingang dokumentieren
  Querymanagement
  Dateneingabe
  Verwaltung

Datenmanagement klinische Daten

- Dokumente: Case Report Forms
  Meldebogen „schwerwiegende, unerwünschte Ereignisse“ (SUE)
- Aufgaben: Dokumente prüfen: Plausibilität & Vollständigkeit
  Eingang dokumentieren
  Querymanagement
  → nur Paper-basierte CRFs: Erfassung
  Verwaltung

Abrechnung

- mehrere Male innerhalb eines Registers (nach festgesetzten Zeiträumen) oder nach Beendigung der Beobachtungszeit
- Abrechnungskriterien: CRFs vollständig
  keine offenen Queries
- Aufgaben: Abrechnungen generieren, aussenden, Eingänge verwalten & dokumentieren

Monitoring und Qualitätssicherung

- Aufbau eines Monitoringwesens
- Regelmäßige Zentrums-Monitorings
- Online-Monitorings
- Internes QM
  - Regelmäßige QM-Arbeit
  - QM-Bericht

Datenanalyse

- Berichte zur Arzneimittelsicherheit
- Zentrumsberichte
- Outcomes-Berichte gem. Studienprotokoll
- Ggf. Berichte an Behörden, EMA, ENCePP,

Registerorganisation

- Verwaltung von Neuanmeldungen
- Bestandspflege der Zentrumsdaten
- Management des Reportings
  - Versand Newsletter nach Plan
  - Berichterstattung an Beirat
  - Berichterstattung an Sponsoren
  - Jahresbericht mit Finanzreport
- PR und Kommunikation
  - Pflege Website
- Planung und Organisation der Meetings
  - Sponsoren / Prüfärzte, Beirat
- Personalplanung und -einsatz
- Finanzen
- Rechts- und Vertragsfragen

14. Attachment 3: References

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