Study protocol

German National Clinical registry: Treatment and medical care of patients with moderate-to-severe Atopic Dermatitis

TREATgermany

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English Version

Project management

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In kooperation with the German Dermatological Society

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Appendix

List of abbreviations

AD	Atopic Dermatitis
ADR	Adverse Drug Reaction
BSA	Body Surface Area
cDLQL	Children's Dermatology Life Quality Index
CES-D	Center for Epidemiological Studies – Depression
CSHQ	Children's Sleep Habits Questionnaire
DLQI	Dermatology Life Quality Index
EASI	Eczema Area Severity Index
EQ-5D	EuroQoL
FSS	Fatigue Severity Scale
IGA	Investigator Global Assessment
IVIG	Intravenous immune globulin
MFQ	Mood and Feelings Questionnaire
MTX	Methotrexat
NRS	Numeric Rating Scale
oSCORAD	objective SCORAD
PGA	Patient Global Assessment
POEM	Patient-oriented eczema measure
QALY	Quality adjusted life years
QoL	Quality of Life
SCORAD	Severity Scoring Of Atopic Dermatitis
SDQ	Strengths and Difficulties Questionnaire
SSR	Sleep Self Report
VAS	Visuelle Analogue Scale
WLQ	Work Limitation Questionnaire

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Survey locations:	Dermatological clinics and practices in Germany, pediatric practices specialized in allergology / atopic dermatitis
Scientific-strategic advisory board: The scientific-strategic advisory board consists of at least 8 voting members and is to contribute scientific, clinical, methodological and strategic expertise to the	Members with voting rights: Prof. Dr. med. Andreas Wollenberg, LMU Munich (ETFAD)

register. Unanimous recommendations of the Expert Advisory Board are sought, otherwise a simple majority applies. Sponsors of the Registry (e.g. pharmaceutical manufacturers, foundations, etc.) are granted the right to nominate up to 2 guests for the advisory board who have an advisory function but are not entitled to vote. The nomination of additional persons with guest status is reserved for the study directors.	Prof. Carsten Flohr (King‘s College London) Prof. Dr. Christian Apfelbacher (University Magdeburg) Two representative of the German Dermatological Society (Deutschen Dermatologische Gesellschaft (DDG)). One representative of the Professional Association of German Dermatologists (Berufsverband der Deutschen Dermatologen (BVDD)). Two representatives of the German Society for Allergology and Clinical Immunology (DGAKI)

Synopsis (english)

Title	German National Clinical registry: Treatment and medical care of patients with moderate-to-severe Atopic Dermatitis.
Acronym	TREATgermany
Study lead	Prof. Dr. Jochen Schmitt (Dresden) (coordinating study lead) Prof. Dr. Thomas Werfel (Hannover) Prof. Dr. Stephan Weidinger (Kiel)
Study design	Prospective multicenter registry for patients with moderate-to-severe atopic dermatitis
Background	- Atopic dermatitis (AD) constitutes significant burden to patients, families, and healthcare systems. [1-3] - About 60% of all patients with AD are adults. [4] However, the prevalence and incidence is significantly higher in childhood and adolescence. - Some children, adolescents and adults with moderate-to-severe AD cannot be sufficiently controlled with topical treatments alone and require intermittent or continuous treatment with systemic immunomodulating therapies or UV-therapy. [5] - Systematic reviews and meta-analyses [6-9] indicate that although several different interventions for moderate-to-severe AD have been investigated in clinical trials, therapy recommendations are currently only possible for dupilumab (from 6 years of age) [10-12], Baricitinib (from 18 years of age) [13, 14], and for the short-term use of cyclosporine A. - Methodological limitations in the majority of trials on conventional immunosuppressive therapies, such as the use of non-validated outcomes that are not relevant to patients, prevent evidence-based clinical decision making. [15-17] - Pharmaceutical treatment of patients suffering from AD is diverse and frequently not in line with the current guidelines (for example S2-guideline in Germany). [18] - Systemic antiinflammatory and immunemodulatory therapies include several conventional immunosuppressive therapies such as glucocorticosteroids, cyclosporine A (CSA), methotrexate (MTX), or azathioprine (AZA). [6-9] Further, dupilumab became the first biologic medication approved for the treatment of moderate-to-severe AD for adult patients in 2018, in 2019 the approval was expanded for adolescents (from 12 years of age), and in 2020 for children (from 6 years of age). [10-12] Since 2020, baricitinib has also been approved for the treatment of moderate-to-severe AD for adult patients. [13, 14] In 2021, tralokinumab for adults [19, 20] and upadacitinib from the age of 12 years [21, 22] were also approved for the treatment of moderat-to-severe AD. - Large head-to-head trials are missing so that long-term effectiveness of systemic interventions for moderate-to-severe AD is speculative. [6] - In this situation, clincial registries can provide valuable information for evidence-based clinical decision making.

Background (cont)	***The German AD registry*** - In 2011, the German Registry "TREATeczema" was initiated by Prof. Schmitt (Dredsen) and Prof. Werfel (Hannover) to investigate treatment and medical care of adult patients with severe AD in Germany in routine care. - TREATeczema stimulated initiatives in other European countries that currently plan to establish the prospective investigation of clinical cohorts with AD. - The experiences with the German AD-registry from the past 4 years also highlight the necessity for some important modifications to increase the acceptance, implications, and recruitement in clinical care. - These modifications include: o Expansion to patients with moderate-to-severe AD, as these patients are also potential candidates for systemic treatment. o Observation for more than 36 months. o Separation of the coordinating register center (responsible for data management, quality assurance, data storage and data analysis) from the recuiting centers. o Increase of the acceptance of the registry for patients and physicians by offering financial compensation and electronic data collection software. Extension of TREATgermany to children and adolescents is necessary as - moderate-to-severe AD is frequent in this age group, but the effectiveness of existing topical and systemic agents in the routine care setting on clinical severity, patient-reported outcomes, and the course of AD and associated atopic and non-atopic comorbidities over time is still poorly understood - it is unclear how many children and adolescents cannot be effectively controlled with the avoidance of trigger factors, patient education, and topical anti-inflammatory treatment alone (i.e. how many children would require systemic therapy given safe and effective treatment is approved) - innovative agents will become available for these age groups within the next years and reference data will be necessary to evaluate their effectiveness and indication criteria - adequate evidence regarding patient needs in children and adolescents with moderate-to-severe AD is urgently needed to provide value-based healthcare for this vulnerable patient group - Best-practice models of transition from adolescent to adult care of patients with moderate-to-severe AD do not exist yet, but constitute a prerequisite for the establishment of efficient patient care - The different European AD-registry initiatives also require the coordination in terms of data assessment to enable pooled international comparisons. Based on these grounds the European registry network (TREAT) was initiated. It is lead by Prof. Schmitt, Prof. Flohr (UK), Prof. Spuls (Netherlands), PD Dr. Apfelbacher (Magdeburg, Germany) and Prof. Irvine (Ireland). The contributing national registries remain formally independent.

	- **TREATgermany** emerges from the previous German AD-registry TREATeczema. It includes all the necessary modifications outlined above and is part of the European registry family TREAT.
Objectives	Establishment of a national evidence-based clinical registry and research network with the following objectives: - *Characterization* of medical care and pharmaceutical therapies adults suffering from moderate-to-severe AD. The perspective of the patient (utility, treatment goals, quality of life, and treatment satisfaction), sequence of treatments, and change of treatments will be a primary focus. - *Investigation* of comparative effectiveness, tolerability and safety of systemic therapies for moderate-to-severe AD. - *Developement of a platform* for further investigations, such as pragmatic clinical trials, epidemiologic studies, outcomes research, immunologic and molecular research (given approval of responsible ethics commission).
Study sites:	**Coordinating register center** responsible for data management, quality assurance, data storage and data analysis: ZEGV Dresden **Recruitment sites:** All dermatological hospitals, outpatient dermatologists, and general physicians with focus on AD in Germany are invited to participate as recruitment sites. We aim to involve at least 40 recruitment sites in TREATgermany for adult patients and 30 recruitment sites for children and adolescents. The enrolment of children/adolescents and adults in a centre is possible. The protagonists of TREATgermany and the German national AD patient education network AGNES “Arbeitsgemeinschaft Neurodermitisschulung” cooperate very well. AGNES includes eight academies that are responsible for the standardized education of dermatologists and pediatricians, nurses, nutritionists and psychologists. These professionals form training teams that are active in 120 education centers in Germany. In the past year, about 3,000 patients (children, adolescents and parents) were successfully trained in self-management, coping and treatment of AD according to the AGNES curriculum. The use of the well established, preexisting AGNES network for recruitment and follow up of children and adolescents with moderate-to-severe AD for inclusion in TREATgermany will ensure high feasibility, quality, and representativeness of recruitment into the registry.
Number of patients included:	Within the first 6 years we aim to include at least 800 adult patients with follow-up of at least 36 Months and up to 2025 600 children/adolescents with follow-up of 3 years in the registry.

Inclusion criteria:	- AD according to the UK working party diagnostic criteria [23, 24]
	- Moderate-to-severe AD
	  o objective SCORAD > 20 [25] *or*
	  o currently antiinflammatory systemic treatment for AD *or*
	  o Z.n. antiinflammatory systemic treatment for AD within past 24 months
	
	Patients who have been enrolled into the previous AD-registry TREATeczema may be enrolled into TREATgermany following informed consent if they meet the above inclusion criteria.

Study procedures	- No study related intervention will be performed - Included patients will be prospectively followed for at least 24 months. A maximum duration of follow-up is not intended. - During the observation period standardized study visits are performed to prospectively document patient characteristics, clinical data, patient-reported outcomes, physicians‘ reasons for treatment decisions, and satisfaction with treatment. - The first study visit is scheduled at patient inclusion (Baseline-visite; V1). The second and third study visit are scheduled 3 and 6 months after baseline, respectively. (V2 after 3 months, V3 after 6 months). Thereafter, study visits are scheduled after 3 months (if a new systemic treatment was initiated) or after 6 months (in case no new systemic treatment was prescribed). - Adolescent patients who reach the age of 18 years will be followed through transition of care into adulthood after informed consent and further followed through the adult patient part of TREATgermany.
Duration	- TREATgermany for adults: follow up until 01/2023 - TREATgermany for children/adolescents: 01/2020 to 12/2025

Data assessment	- Prospective electronic documentation of disease course and severity, medical care and pharmaceutical treatment of AD.
	- Pseudomized data will be stored at the registry center (ZEGV Dresden).
	- Completion patient and physician report form by *paper and pencil* will be possible upon request. In this case the completed study forms will be sent to the ZEGV Dresden.
	- Study assessments include:
	  - A physician report form to document patient history and clinical parameters such as the objective severity of clinical signs, affected body regions, physician's global assessment of disease severity, course of disease and medical treatment of AD including adverse events.
	  - Important comorbidities are recorded in the case of inclusion and change, sociodemographic parameters in the case of inclusion and at biennial intervals.A patient report from to assess important subjective parameters, patient reported outcomes such as symptoms, quality of life, treatment satisfaction, patient's assessment of global disease severity including %BSA, totally/partial well-controlled weeks, sickness absence due to AD and visits to healthcare professionals.
	  - A customized patient report for children/adolescents to assess important subjective parameters, patient-/caregiver-reported outcomes such as AD symptoms, quality of life, sleeping disorders, treatment satisfaction, patient's assessment of global disease severity, totally/partial well-controlled weeks, drug adherence, days absent at school, mental health problems (Strengths and Difficulties Questionnaire), AD family impact, parental work limitations and absenteeism due to child's AD, visits to healthcare professionals.
	
	- Data from patients who have been previously enrolled in TREATeczema (about 80 patients) may be transferred into TREATgermany following informed consent.
	
	  - Participation in the optional Biospecimen Database, Biorepository and Molecular Analysis requires separate informed consent.

Outcomes:	Target parameters to evaluate the effectiveness of AD treatment include according to the recommendations of the HOME initiative [17, 26, 27]: - objective clinical severity (EASI, oSCORAD) [25, 28] - disease symptoms (POEM, POEM for children) [29], severity of pruritus and sleeping problems (VAS) [30] - flares and level of disease control over time [31] - health-related quality of life (DLQI, cDLQI) [32] Adverse events and reasons for withdrawals will be documented for both adults and children and adolescents by recruiting sites. Patient/caregiver and physician treatment satisfaction and physicians' reasons for the choice of specific interventions will be assessed.
Data analysis	Descriptive and exploratory data analyses will be performed at least once per year by the ZEGV Dresden. Recruiting sites will receive aggregated annual results from all patients included in the registry and all patients recruited at their recruitment site.
Ethics and legal aspects:	The study will be conducted in consistency with the declaration of Helsinki, data protection laws, and professional regulations. Prerequirement for study initiation is approval by the ethics commission of the Medical Faculty Carl Gustav Carus Dresden and the ethics commissions of the participating recruitment sites. Inclusion of patients is only possible following informed consent.

Visit plan

Visit	**V_1** **Baseline**	**V_2** **3 months after baseline**	**V_3** **6 months after baseline**	**V_{4-n}** **At intervals of 3 or 6 months***
Time frame		±2 weeks	±2 weeks	±2 weeks
Clarification / Declaration of consent	X			
Inclusion / exclusion criteria	X			
Physician questionnaire				
Demographic information	X			
Anamnesis/ medical history	X	X	X	X
Physical examination	X	X	X	X
Therapy (prescribed / actual)	X	X	X	X
Clinical signs (obj. SCORAD and EASI)	X	X	X	X
Affected parts of the body	X	X	X	X
Investigator's Global Assessment (IGA)	X	X	X	X
Reasons for therapy choice	X	X	X	X
Physician satisfaction with treatment (VAS)	X	X	X	X
Adverse drug reactions (AE/SAE)	X	X	X	X
Optional add-on module Bioanalytics (after prior separate consent)	X	(X)$^{\$}$	(X)$^{\$}$	(X)$^{\$}$
Patient questionnaire				
Compliance with atopic dermatits treatment				
Patient's Global Assessment (PGA)	X	X	X	X
Dermatology Life Quality Index (DLQI, cDLQI)	X	X	X	X
Symptoms of atopic dermatitis (POEM, POEM for children, NRS pruritus, pain and sleep disturbance)	X	X	X	X
Center for Epidemiological Studies – Depression Scale (CES-D)	X	X	X	X
Strengths and Difficulties Questionnaire for Children (SDQ2-4, SDQ4-17, SDQ11-17 (self-report))	X	X	X	X
Children's Sleep Habits Questionnaire (CSHQ-DE)	X	X	X	X
Fatigue (FSS)	X	X	X	X

Work Limitations Questionnaire (WLQ) / School Life Quality (as part of the KINDL)	X	X	X	X
Sick leave due to atopic dermatitis/ receiving medical treatment	X	X	X	X
School sick leave / parents' sick leave due to atopic dermatitis/receicing medial treatment	X	X	X	X
Benefit / Aim (PBI)	X	X	X	X
Generic quality of life EuroQoL (EQ-5D) / KINDL for children and adolescents	X	X	X	X
Patient satisfaction (NRS)	X	X	X	X
Mood and Feelings Questionnaire (MFQ) self-reported for adolescents / parents' report	X	X	X	X
Sleep Self Report (SSR-DE)	X	X	X	X
Recap of atopic eczema (RECAP)	X	X	X	X

* 3 months between visits if a new systemic therapy has been initiated, otherwise 6 months
$ for the change of the anti-inflammatory system therapy of atopic dermatitis

1. INTRODUCTION

1.1 Atopic dermatitis

Atopic dermatitis (synonyms: atopic eczema) is a chronic or chronic-relapsing, non-contagious inflammatory skin disease. [3] The UK Working Party definition of atopic dermatitis (*see Appendix 1)* is itchy skin plus three or more of the following features: (i) onset under the age of 2 y; (ii) a history of flexural involvement; (iii) a history of asthma or hayfever (or a history of atopic disease in siblings and parents if the child is under 4 y); (iv) a history of generally dry skin in the last year; and (v) visible flexural dermatitis. [33] The prevalence of atopic dermatitis in western industrialized nations is up to 10-20% in infancy and 5-10% in adulthood. [34-37]

Despite the greater prevalence in infancy, approximately 60% of all patients with atopic dermatitis are adults. [4] Among adults under dermatological care atopic dermatitis is the fourth most common diagnosis. [4] About 60% of the adults with atopic dermatitis are in outpatient dermatological care. About 40% of the patients are treated by general practitioners, and the implementation of a consultation fee has led to a further drop of the percentage of patients in dermatological care. [38] Despite the high prevalence and the socio-medical significance, medical care patterns for atopic dermatitis in adulthood are insufficiently known.

In a large number of patients signs and symptoms of the disease cause a profound and multifaceted impact on the quality of life and professional performance. [39-41] Physicians often misjudge the treatment goals of their patients with atopic dermatitis. [42] Due to allergic [43], mental [44, 45], and somatic comorbidities [46], the intractable itch, and the associated sleep impairment [47], the quality of life and performance in professional life of patients with atopic dermatitis and their relatives is significantly impaired. [1, 48] Both affected patients and the general population perceive uncontrolled atopic dermatitis as having a comparably large impact on health as e.g. angina pectoris, chronic anxiety disorder or rheumatoid arthritis. [49] Due to the high direct and indirect medical costs and the association with multiple comorbidities [44, 50-54], atopic dermatitis has a tremendous economic and socio-medical relevance. [1, 39, 55]

In children and adolescents, only little is known about the effectiveness of existing topical and systemic therapeutics in routine care in terms of clinical severity, patient-reported outcomes and AD progression as well as associated atopical and non-atopical comorbidities over time. In addition, it is unclear how many children and adolescents cannot be effectively controlled by avoiding trigger factors, patient education and topical anti-inflammatory treatment alone (i.e. how many children would need systemic therapy if safe and effective treatment is given).

Innovative therapeutics will also be available for these age groups within the next few years, so reference data are required to evaluate their effectiveness and indication criteria.
Best-practice models for the transition from adolescent to adult care of patients with moderate-to-severe AD do not yet exist, but they are a prerequisite for establishing efficient patient care.

1.2 Treatment of atopic dermatitis

Despite numerous new insights on the pathogenesis of atopic dermatitis, no causal treatment is currently available. [3] AD management aims to improve symptoms and establish long-term disease control by avoidance of individual trigger factors, skin barrier restoration through moisturizer use, and a step-up/step-down approach aimed at reducing inflammation. [35] The choice of anti-inflammatory therapy is largely based on AD severity/activity; mild AD can usually be controlled with topical treatments; more severe disease may require phototherapy and/or systemic immunomodulatory therapy. [5]

An analysis of routine medical care health insurance suggested that 10 to 15% of all patients with atopic dermatitis were treated systemically within a 2-year observation period from 2003 to 2004. [4] Despite insufficient trial evidence [7, 56], systemic steroids were the most frequently used systemic therapeutics. In contrast, ciclosporin and other systemic therapies such as azathioprine, MTX and mycophenolate mofetil were rarely used in clinical practice [4], despite available evidence for their efficacy from clinical studies. [6, 8, 57] Many important questions about healthcare delivery and medical care for patients with moderate-to-severe atopic dermatitis are still unknown. This includes reasons for or against using (a specific) systemic therapy, their clinical benefit, and physician and patient satisfaction.
Further important gaps in research concerning the medicinal treatment in patients with moderate-to-severe atopic dermatitis are, among other things, the following:

- Studies on the effectiveness and patient safety of treatments under real-life conditions
- Long-term observations
- Physicians' reasons to prescribe or not prescribe systemic therapies to children / adolescents / adults with severe AD
- the transition in the care of children / adolescents during the transition into adulthood
- Health economic evaluations
- Patients' preference and decision studies.

1.3 The TREAZeczema registry

Against this background the registry TREATeczema for adults with severe atopic dermatitis was planned and established in Germany by Prof. Schmitt, Prof. Werfel and Prof. Weidinger

in 2011. Until October 2014 in total 78 patients (average age 39 years, 61% male) were included at five study centres. A high demand of outpatient and inpatient services by the patients included in the registry was noted. The most frequently administered systemic treatment was cyclosporine, which also showed the greatest clinical effectivity (EASI-50 response rate 51%; EASI-75 response rate 34% after a 12-week treatment period). Azathioprine, MTX, oral prednisolone, mycophenolate mofetil, alitretinoin and leflunomide had been prescribed to single patients only.

Based on the experiences from TREATeczema, it became apparent that important modifications are necessary in order to increase patients' and physicians' willingness to participate and to improve the registry's validity.

These modifications/amendments included:

- Expansion to "moderate-to-severe AD" in order to include all patients eligible for systemic therapy
- Extension of the observation period, preferably without a time limit, to examine long-term outcomes
- Separation of coordination, data management, quality assurance, data repository and analysis from recruitment centres (according to DNVF-Methoden-Memorandum registry) [58]
- Reimbursement of study centers and provision of electronic data capturing toold to increase motivation of investigators

1.4 The European registry network TREAT

The German registry of atopic dermatitis TREATeczema was the first atopic dermatitis registry worldwide and served as a role model for similar initiatives in other European countries. In order to ensure collaboration and coordination of different national registries being planned and established, the International TREAT Registry Taskforce (treat-registry-taskforce.org) as an umbrella was established. The task force is coordinated by Prof. Schmitt (GER), Prof. Flohr (UK), Prof. Spuls (NL), Prof. Apfelbacher (GER) and Prof. Irvine (Ireland). The individual national registries remain independent, but are closely aligned in terms of outcome assessments.

2 STUDY OBJECTIVES

TREATgermany is based on the registry TREATeczema and part of the European registry family TREAT. The main aim of TREATgermany is the development and expansion of a nationwide clinical academic registry for patients with moderate-to-severe atopic dermatitis and to characterize healthcare delivery patterns, to investigate the comparative effectiveness, tolerability and safety of available systemic therapies, and to gain insights into physicians' and patients' treatment goals and satisfaction.

TREATgermany has 3 main aims:

1. Healthcare research

To characterize patients with moderate-to-severe atopic dermatitis and their medical care. Special consideration is given to the patients' perspective (e.g., disease burden, treatment goals, quality of life), reasons for the use of specific systemic therapies, changes and sequence of therapies, use of medical services, use of alternative treatment methods, satisfaction with applied treatments from the perspective of both the physician and the patient, impact of comorbidities, influence of atopic dermatitis on productivity/ performance at school and cost of illness.

2. Effectiveness research, evidence-based medicine

To investigate the comparative effectiveness, tolerability and safety of available systemic of treatment options for moderate-to-severe atopic dermatitis.

3. Creation of a platform for basic and clinical research

To provide a platform for clinical, epidemiological, and molecular research.

3 STUDY DESCRIPTION

3.1 Study design

TREATgermany is a non-interventional study (observational study), which is performed as prospective cohort study in form of a clinical registry.

Data are collected during routine care for patients with moderate-to-severe atopic dermatitis without any further intervention or direct comparison of different therapies (e.g. cross-over). It is non-clinical study according to § 40-42 AMG.

3.2 Institutions involved

Coordinating registry centers are the Zentrum für Evidenzbasierte Gesundheitsversorgung (ZEGV) of the Medizinischen Fakultät Carl Gustav Carus der TU Dresden, the Department of Dermatology and Allergy of the University Hospital Schleswig-Holstein, Campus Kiel as well as the Department of Dermatology and Allergy at the University Medical School Hannover. The ZEGV is responsible for clinical data management, storage, analysis and reporting.

Recruitment centers: Every dermatology clinic, dermatology office and primary care provider with a specific focus on allergology / AD (pediatricians and GP office) in Germany can participate in the registry. The goal is to have at least 40 recruitment centers for adult patients and 30 recruitment centers for children and adolescents. The recruitment of children / adolescents and adults in the same center is possible. In order to ensure that observations are representative for the German healthcare system, a mix of tertiary care/specialised centers (e.g. university and hospital-based dermatology and allergy departments) and office-based dermatology centers should be achieved. Participating centers will be asked to include as many (consecutive) patients as possible. Participating centers will also be offered opportunities for scientific cooperation. For every patient included and observed for at least 3 years an incentive of 250 Euros will be provided.

3.3 Scientific-strategic advisory board

The scientific-strategic advisory board supports the principal investigators in all scientific and strategic concerns, helps with the recruitment of new centers, can propose and comment on analyses, and propose modifications of data acquisition.

The scientific-strategic advisory board must be composed of 6 full members with a voting right and guests members without the right to vote.

Full members are: Prof. Carsten Flohr (King‘s College London) will act as international expert. Prof. Flohr is building up a registry for atopic dermatitis in UK and is one of the coordinators of the European registry-network TREAT. Prof. Christian Apfelbacher (University of Magdeburg)

is an expert in health care and epidemiological research, and has built up the CARPE registry on hand eczema. Prof. Zink is head of the German Rheumatism Research Center Berlin and the RABBIT-Registry for arthritis. The German Dermatological Society (DDG) will nominate two experts and the Professional Association of German Dermatologists (BVDD) is invited to nominate one expert for the advisory board. 3 members to be appointed shall act as representatives of office-based dermatology. Unanimous recommendations of the expert advisory board are aimed at, otherwise the simple majority applies.

In addition to the 6 full members, every sponsor of the registry (e.g. pharma companies, foundations, etc.) are granted the right to nominate up to 2 guest members. The nomination of further persons with guest status is reserved for the coordinators of the registry.

The composition of the scientific-strategic advisory board shall comprise excellent clinical, methodological and strategic expertise.

4 PATIENT POPULATION

4.1 Number of patients

The goal is to include at least 800 patients in the registry within 6 years after initiation (realized in April 2016).

4.2 Inclusion and exclusion criteria

The following inclusion criteria must be met for a patient to be included in the registry:

- Confirmed diagnosis of atopic dermatitis [23, 24]
- Moderate-to-severe atopic dermatitis
    - Objective SCORAD > 20 [25] and/or
    - Current systemic therapy of atopic dermatitis and/or
    - Systemic therapy for atopic dermatitis within the past 24 months

Patients who were already included in the previous registry (TREATeczema) can be included in the TREATgermany registry after they have been informed and given their consent, if they meet the inclusion criteria.

5 STUDY DESIGN

There is no study-related intervention. Enrolled patients are observed for a period of at least 24 months without a predetermined maximum observation period. During the observation period, study visits take place at intervals of 3 or 6 months (see visit plan).

5.1 Selection of patients, round 1 (baseline)

Prior to enrollment, patients will receive appropriate information about the purpose of the study, its design and procedures, and possible risks and benefits of participation. The information about the study is provided personally by the treating physician and in a written form by the patient information/parent information. Only after all questions of the patient/parents have been clarified, the patient/parents will be asked to sign **two** copies of the consent form, one of which will be provided to the patient/parents. Patients who meet the inclusion criteria will be enrolled into the study after having provided written consent. The consent of the underage participants is renewed when the age limit of 7 or 12 years is exceeded, the consent is obtained when they reach the age of majority.

Physician questionnaire: During the baseline visit, a detailed medical history, a physical examination (using established tools such as the SCORAD, EASI, investigator's global assessment (IGA), etc.), a photo documentation (typical lesion and distribution patterns of the skin changes in the extremities and trunk) as well as the documentation of the prescribed therapies and the reasons/motivation for therapy decisions are performed. Potential adverse drug reactions of atopic dermatitis therapies are recorded.

Patient questionnaire for adults: Patients are asked to fill in the patient questionnaire, which captures socio-demographic information, history of the disease, current treatment (and compliance), quality of life impairment (DLQI, EuroQoL), and symptoms (POEM, NRS itching and sleep disorders), the course of atopic dermatitis, occupational limitations due to atopic dermatitis (WLQ), depressive symptoms (CES-D), fatigue (FSS), therapy goals/benefits (PBI) and treatment satisfaction are assessed.

Patient questionnaire for children/adolescents: Parents or children/adolescents (from the appropriate age) are asked to fill out the patient questionnaire completely, including information on socio-demographic characteristics, disease history, actual therapy (compliance), quality of life (cDLQI, KINDL^{R}), symptoms (POEM for children, NRS pruritus and sleep disturbances), course of AD (including degree of disease control), school restrictions due to AD (partial scale of the KINDL^{R}), strengths and weaknesses (SDQ2-4, SDQ4-17, SDQ11-17 (self-reported) for

children and adolescents), sleep quality (CSHQ for children and adolescents), therapy goals/ benefits and satisfaction with treatment. In addition, there is the recording of absence from school due to AD and the inability of the parents to work due to their childrens' AD as well as due to receiving medical treatments/number of doctor visits.

5.2 Follow-up visits

The second and third visitis take place every 3 months according to the baseline (V2: after 3 months, V3: after 6 months).
Thereafter, the intervals between visits depend on newly initiated systemic therapies. If a new system therapy has been initiated during a visit, the next visit will take place after 3 months. If no new system therapy was prescribed, the next visit is after 6 months.

At each follow-up visit, the physician documents the clinical examination findings (objective SCORAD, EASI, global severity of disease, affected body parts), the prescribed therapy including the rationale for the prescription, as well as reasons for a change or continuation of therapy and possible adverse drug reactions (ADR).
The patient questionnaire for follow-up visits is similar to the questionnaire for the baseline visit (see visit schedule).

5.3 Interim visits

Interim visits can be made between the regular study visits if the attending physician considers this necessary. Reasons for interim visits can be e.g. relapses of disease, the occurrence of adverse events due to atopic dermatitis treatment, inpatient stays due to atopic dermatitis or the change of the anti-inflammatory systemic therapy. Doctor and patient questionnaires of the interim visits correspond to those of the follow-up visits (see 5.2).

5.4 Withdrawal of patients and drop-outs

Patients can withdraw from the study at any time at their own request, without giving any reason and without consequences for their future treatment.

5.5 Optional module „Biobanking and Bioanalytics“

Atopic dermatitis is a disease that typically occurs in infancy, but can sometimes only manifest itself later. In some of the affected children, for unclear reasons, the typical symptoms spontaneously subside in the course of childhood, although they may recur later, while others suffer from chronic, persistent courses. Some children with AD also develop atopical and affective comorbidities. Although the disease can take a variety of long-term courses, its determinants are largely not understood and cannot currently be predicted either clinically or by laboratory methods. [59] To date, no markers exist that predict the course of the disease or

the development of comorbidities and thus could be used to control treatment or preventive measures.
The influence of certain treatments on molecular mechanisms in terms of disease modification is also insufficient and has been studied especially in adults, although children and adolescents represent the largest group of patients. Furthermore, the few available molecular studies on children with AD indicate that other mechanisms than in adulthood may determine the disease activity and the perpetuation of the inflammation and that therefore other sensible target structures for drug therapies [60] might exist. For these reasons, molecular studies on children and adults are of outstanding importance.

In order to answer further scientific questions, from all registry patients who give their informed consent, biological samples are systematically collected at baseline and at final visit (blood and stool), and at initiation of a new systemic therapy (blood – no more than 5 ml from children up to 11 years old / no more than 19 ml from adolescents from 12-17 years / no more than 20 ml from adults older than 18 years- and skin swabs -only adults-).
The blood (no more than 20 ml) and skin samples are used to isolate genetic material (DNA and RNA). The genetic material is used to identify genetic factors involved in the development, course and response to therapy of AD.Whole-genome sequencing is currently not planned, but should not be ruled out in the future. Additionally, the transcriptome and proteome are to be analysed. Furthermore, non-invasive skin swabs are sampled for microbiome analysis and skin flakes for are sampled for skin physiology analysis. This minimally invasive collection of biosamples, which can be carried out with minimal stress as part of routine blood sampling, and whose processing, as shown in the patient information, does not result in any individual benefit.
All biosamples are stored pseudonymized and until further notice at the biobank of the Laboratory for Molecular Dermatology in Kiel (Prof. Dr. Stephan Weidinger) separately from the phenotypic data (held at the ZEGV Dresden). In compliance with data protection regulations, pseudonymised data from biomaterial and from medical examinations or surveys collected within the context of this registry are matched for research purposes. Accompanying molecular analyzes could lead to an enormous gain in knowledge and help to make better disease prediction and targeted prevention recommendations. This data is then anonymised. Individual backtracking of results from molecular analysis is not possible and not planned. Participation in the additional module is voluntary and requires a separate explanation of its purpose, procedure, possible risks and advantages personally by the treating doctor and in writing by means of a separate patient information. Non-participation in the additional module "Bioanalytics" in no way affects the main study.

6 DOCUMENTATION / DATA MANAGEMENT

It is the physician's responsibility to ensure that the study is conducted in compliance with all legal requirements and that the data are correctly recorded in the corresponding data entry forms.

All data generated in the course of this study (including anamnesis, concomitant diseases, experimental data, results of examinations and adverse events) must be recorded in the data entry forms by appropriately authorized persons. This also applies to data from patients who were excluded from the study. It must be ensured that all persons involved in the trial can be identified.

The data collection is pseudonymised. The physician documents the participation of patients on a special identification list in order to ensure that a patient can be identified after the study has been completed. In addition, the participation of the patient in this study should be noted in the patient record. An assignment list of patient name and pseudonym remains in the recruiting office. In the physician and patient questionnaires, the data are entered in pseudonym form. Only pseudonymised data is sent to the registry office.

6.1 Data entry forms

All patient data and examination results are entered into the data entry forms (physicians and patient questionnaires) specially created for these studies. The data is primarily collected electronically.

Technical implementation

With REDcap (database including mobile survey module) the patient enters his data directly using an iPad. The physician works browser-based on a desktop PC. The corresponding questionnaire for the patient is generated on the iPad using a QR code from the attending physician’s entry system. This ensures that the patient does not see any further data apart from the questionnaire to be processed by him (neither his own previously entered data, nor treatment data of the physician or data of other patients).

This recording system was developed in direct cooperation with the KKS Dresden. The KKS has a REDCap license that TREATgermany can use on a contractual basis. The entries in the data entry system are immediately checked for completeness and plausibility and, if necessary, corrected with the help of automatic feedback or help instructions. The medical study staff has an up-to-date view of all entries at all times and can check them for completeness and quality. The management of the digital questionnaires as well as the

administration of access authorizations, study centers and involved personnel is carried out by the administrative area at the KKS Dresden (responsible administrator: Ms. Katja Wendrich). The REDCap database for TREATgermany is also hosted at KKS. A corresponding contract was concluded between the registry center and the KKS for this purpose. No data is stored on the mobile devices. The pseudonymized data is transmitted directly to the REDCap database via WLAN. At the end of the study, the database will be closed after all entries have been entered and queries have been clarified. This process is documented.

Data protection and security

The entries in the data acquisition system are immediately checked for completeness and plausibility and, if necessary, corrected with the help of automatic feedback or help instructions. The medical study staff has an up-to-date view of all entries at all times and can check them for completeness and quality. The management of the digital questionnaires as well as the administration of access authorizations, study centers and involved personnel is carried out by the administrative area at the KKS Dresden (responsible administrator: Ms. Katja Wendrich).

The KKS also hosts the REDCap database for TREATgermany (and manages the corresponding server). A corresponding contract was concluded between the registry office and the KKS for this purpose. The mobile devices are the property of the medical faculty of the TU Dresden, whose IT division is responsible for the mobile device management. No data is stored on these devices. The pseudonymized data is transmitted directly to the REDCap database via WLAN. The WLAN is end-user specific.

Alternatively, it is possible to fill out the physician and patient questionnaires using a paper and pencil version of the physician and patient questionnaires. In this case the completed original pages (without names or initials) are sent to the data center at ZEGV Dresden, a copy remains at the study centre and is stored there according to the legal requirements.

The physician ensures that all patient data are entered into the study documents immediately, legibly, completely, correctly and in accordance with the patient files. In case of incomplete or implausible data, the registry office at ZEGV Dresden will contact the respective recruitment centre.

At the end of the study, the database is closed after all entries have been made and the queries have been clarified. This process is documented.

6.2 Assessment tools

SCORAD (see Appendix 2)

The SCORAD was introduced in 1993 by the European Task Force on Atopic Dermatitis and is today a common and sufficiently validated assessment tool for the severity classification of atopic dermatitis. [15, 30, 61]

The SCORAD is calculated according to a formula that takes into account objective criteria (body surface area manifestation (BSA) and intensity of typical skin conditions) and subjective complaints of the patient (itching and insomnia, on a VAS scale). The minimum SCORAD is 0, the maximum SCORAD 103 points. [62-64]

In 1997, the European Task Force on Atopic Dermatitis also introduced the so-called **objective SCORAD (oSCORAD),** which does not take into account itching and insomnia, as these subjective symptoms are subject to the greatest variability.

The maximum oSCORAD is 83, the minimum 0 points. The task force proposes to use the oSCORAD as inclusion criterion for studies and defines: mild AD as oSCORAD < 15, moderate AD as oSCORAD 15-40 and severe AD with an oSCORAD > 40 points. [25]

Dermatology Life Quality Index (DLQI) (see Appendix 3)

The Dermatological Quality of Life Index (DLQI), developed by Finlay and Kahn in 1994, is a widely used, well validated and practicable instrument in clinical routine, which has proven its worth in measuring the quality of life (QoL) in dermatology [32, 41, 65] The questionnaire records the QoL of the last 7 days and consists of 10 questions each, which can be evaluated as an overall score or assigned to the following 6 dimensions: symptoms, daily life, leisure/sport, work/school, social life/relationship and treatment. For each question, 0 to 3 points are given, whereby 3 points indicate the greatest possible impairment of the QoL in the queried area. A validated German translation is available. The DLQI is a validated instrument which is very often used to assess the dermatological QoL in patients with AD. [41, 65-67]

Assessment of global disease severity by physician (IGA) and patient (PGA) (see Appendix 4)

Charman et al. recommend that in studies, in addition to a complex, symptom-related score system such as SCORAD and the recording of QoL, a global, basic assessment of the severity of the disease or its modification by both the patient and the physician should always be performed. As a static, six-degree assessment instrument, the Investigator's Global Assessment (IGA) is a frequent target criterion of clinical studies. Severity levels 0 (healed) to 5 (very severe) are defined exclusively by the intensity of an average skin change, the intensity

of which is not taken into account. The Patient's Global Assessment (PGA) is a target criterion corresponding to the IGA, in which the patient himself makes the assessment. [68]

Work Limitations Questionnaire (WLQ) (see Appendix 5)
The WLQ measures valid and reliable the productivity at the workplace within the past 2 weeks. Altogether 4 dimensions of productivity at the workplace (presenteeism) are recorded: Time management, physical resilience, mental resilience, performance at work. The WLQ is validated against actual productivity, so that a monetary amount can be assigned to loss of productivity. This makes the WLQ ideally suited for pharmacoeconomic analyses from a social perspective. A German translation is available. [69-73]

EuroQoL (EQ-5D) (see Appendix 6)
The EuroQoL is a well validated instrument for measuring the general health-related quality of life impairment. The results of the EuroQoL have been validated against utility values determined by the time-tradeoff method. On the basis of multiple time-delayed measurements of morbidity using EuroQoL, lost quality of adjusted life years (QALY) can be calculated. Thus, EuroQoL is ideally suited for the measurement of morbidity in cost-effectiveness analyses. [74, 75]

Patient-oriented eczema measure (POEM) for adults and children (see Appendix 7 and Appendix 13)
POEM is a well validated instrument to measure the typical symptoms of patients with AD. [15, 29] The patient himself evaluates the frequency of occurrence and severity of 7 symptoms (such as itching and burning of the skin) within the last week, each according to a 5-point Likert scale. The maximum POEM score is 28 points. The POEM measures the symptoms relevant to the patient and correlates well with the DLQI and PGA.

Center for Epidemiological Studies Depression Scale (CES-D) (see Appendix 8)
The CES-D scale is a scale for measuring depressive symptomatology in the general population and is considered a useful tool for epidemiological studies on depression. The items on the scale are the symptoms that are associated with depression and that have already proven to be validated. [76, 77]

Patient Benefit Index (PBI) (see Appendix 9)
The PBI is a validated instrument introduced in the dermatology department of M. Augustin for the determination of specific, individual patient goals in the current treatment of the skin disease. [78, 79] A total of 23 possible treatment goals are evaluated on an importance scale

from 0 ("not at all") to 5 ("very"). In the respective follow-up visit, the degree to which the goals have been achieved is also assessed on a scale from 0 ("not at all") to 5 ("very") based on the 23 previously prioritized treatment goals. In a retrospective cohort study, the PBI was used in about 1600 patients with AD. [78, 79]

Fatigue Severity Scale (see Appendix 10)
The FSS is a widely used, well validated tool for recording fatigue symptoms over the past week using 9 items. A validated German translation is available. [80, 81] Fatigue in patients with AD has not yet been sufficiently investigated. However, it is known from other chronic inflammatory diseases (psoriasis, MS) that fatigue is frequent, can cause relevant limitations in patients and can be treated by effective therapy of the underlying disease. [82]

Eczema Area Severity Index (EASI) (see Appendix 11)
The Eczema Area Severity Index (EASI) [28, 83] is a very well validated [61] and widely used instrument in clinical studies to measure the objective severity of AD based on the intensity and extent of typical skin lesions on a scale of 0 to 72. The HOME Initiative recommends the use of the EASI as a core outcome instrument in all AD studies. [27] The particular use of the tool is to highlight changes in the severity of the disease over the course of treatment. [28]

Children's Dermatology Life Quality Index (cDLQI) (see Appendix 12)
This is the analogue of the Dermatology Life Quality Index (DLQI) for adults. Skin diseases can lead to severe impairment of quality of life and handicaps in children. The measurement of the impact of skin diseases on quality of life is necessary to facilitate clinical decision-making, for clinical research, for the examination of pediatric care and for political reasons, in order to deliver arguments for more resources for the care of children with skin diseases. Measures for adults are unsuitable because the life of children is very different from that of adults. [84]

Strengths and Difficulties Questionnaire (SDQ-Deu) (see Appendix 14)
The Strengths and Difficulties Questionnaire (SDQ) is a practicable and economical diagnostic tool for the quantification of behavioral aspects in children and in the developmental framework. Particular attention is paid to the balanced proportion of positively formulated behavioral aspects in the self-assessment and external assessment of children and adolescents. The following questionnaire versions are available: Questionnaires for parents of 3 and 4 or 4-16 year olds and for self-assessment for 11-17 year olds. The following five scales are addressed: emotional problems, behavior problems, hyperactivity, behavior problems with peers, prosocial behaviour. [85]

Questionnaire on the quality of life of children and adolescents (KINDL) (see Appendix 15)

The KINDL^R is a generic instrument for recording health-related quality of life in children and adolescents from 3 years of age. The KINDL^R has been translated into numerous languages and used in numerous national and international studies. The representative study KiGGS on the health of children and adolescents in Germany - initiated by the Robert Koch Institute (RKI) - provides standard values. With 24 questions, the KINDL^R is a short, methodically tested and flexible instrument. There are three versions of the KINDL^R for different ages and levels of development. In addition, a self-survey and a third-party survey are offered for each age version of the KINDL^R.

In principle, the KINDL^R follows a cross-disease (generic) approach and can therefore be used to record the quality of life in both healthy and sick children. In addition, the KINDL^R offers various modules that can be used in addition to the main instrument. One of these modules aims to record the quality of life in connection with chronic illnesses or longer hospital stays. Further modules record the disease or complaint-specific quality of life in selected complaints (adiposity, bronchial asthma, diabetes, epilepsy, cancer, AD and spina bifida). [86]

Children's Sleep Habits Questionnaire (CSHQ-DE) (see Appendix 16)

The CSHQ is a retrospective screening questionnaire for parents of children of preschool and elementary school age, which has already been used in a number of studies to determine children's sleep behavior. It can also be used for orientation in younger children. [87]

Sleep Self Report – DE (SSR) (see Appendix 17)

The German version of the Sleep Self Report (SSR) is a screening tool for physically and mentally healthy children to record sleep behavior in self-assessment for children between 7 and 12 years of age. It records the sleep behavior from the child's point of view and thus enables a direct comparison between self-judgment and that of others. In addition, his items meet the ICSD criteria for sleep disorders. [88]

Mood and Feelings Questionnaire (MFQ) (see Appendix 18)

A questionnaire for recording depressive symptoms in children and adolescents, which enables a comparison between self-reported information and information provided by parents or other attachment figures. [89]

6.3 Adverse drug reactions (ADR) and regulations applying to pharmacovigilance

Definition: Adverse drug reactions (ADR) are any harmful and unindented response to a medicinal product which is intended to be applied to humans. More precisely an ADR are deemed to occur if the causal link between medicinal product and the incident can not be excluded with complete certainty. ADR are regardless of the medical products´s intentional purpose. Thus, by definition, results from e.g. overdosage, abuse, improper use, application errors or application in pregnancy and lactation period are excluded.

ADR or the clinical suspicion of ADR by patients or medical professionals in the treatment of atopic dermatitis are supposed to be identified and reported according to the current legal regulations.

The type of ADR (signs, symptoms or disease, preferably diagnosis), its onset and recovery, its intensity (mild = tolerable, moderate = influence on daily activities, severe = daily activities/ work not possible), the suspected link to the systemic treatmend of AD, the measures or acts to restore, correct or modify the subjects health or well-being and the events outcome should be recorded.

A **suspected case of a serious unexpected adverse reaction** is according to the Directive 2001/20/EG supposed to be labeld as a **Suspected Unexpected Serious Adverse Reaction (SUSAR).** If the serious ADR does not appear on the appropriate professional information it is defined as unexpected. The physician in charge is supposed to report the Suspected Unexpected Serious Adverse Reaction immediately, but at the latest within 15 days, to the responsible regulatory authorities, the physicians behind the clinical registry and the registry´s head office. The physician in charge is supposed to report every Suspected Unexpected Serious Adverse Reaction leading to **death** or **has been life-threatening**, immediate, but at the latest within 7 days, the responsible regulatory authorities (BfArM), the participating physicians, die director of studies and the coordination registry center (ZEGV). The director of the registry is suposed to inform all participating physicians about the event.

The participating physicians report on ADR which are suspected to be associated with a medical product of a pharmaceutical company founding the registry pseudonymised to the study director.

The registry is financed through Sanofi-Aventis Deutschland GmbH. The study director has to forward the report to the corresponding department of Sanofi-Aventis Deutschland GmbH or

rather the sponsoring company. The participating doctor agrees to give access to the findings of additional examinations concerning ADR (e.g. results of autopsy, hospital report, consultant report). The study director is responsible for esthablishing the contact between the corresponding department of Sanofi-Aventis Deutschland GmbH (or rather the sponsoring company) and the reporting physician. A detailed list of the relevant products of Sanofi-Aventis (or rather the sponsoring company) is provided for the participating physicians.

7 STATISTICS

The data is checked for plausibility. Data analysis is performed descriptively and exploratively. Measured values are calculated by t-Test and/or Mann-Whitney-U-Test and frequencies by Chi-Quadrat-Test and/or by exact Fisher-Test. In order to answer complex questions multivariate regression- und variance-analytical methods are additionally used. The analysis are performed by the ZEGV Dresden at least annualy. Recruitment centres obtain the annual analysis on all patients of the registry and on the particular centre.

No confirmatory analysis are planned due to the non-interventional character of the study (observational study). The inclusion of at least 600 patients is planned to picture the medical supply of adults with moderate-to-severe AD adequately.
Consistent with the recommendations of the HOME Initiative [17, 26, 27] the key target figures in the analysis of the efficacy of the AD treatment include the following scores:

- Objective severity of clinical signs of AD (EASI, objective SCORAD) [25, 28]
- Symptoms (POEM, POEM for children) [29], severity of itch and sleep disturbances (VAS) [30]
- Flare-ups and the course of disease [31]
- Quality of life (DLQI, cDLQI) [32]

To assess the needed number of patients to evaluate the comparative effectiveness of systemic treatments in adults with moderate-to-severe AD a calculation by „detectable alternative“ for various scenarios was made. Based on the assumption of an oSCORAD-50 Response Rate of 50% (viz. 50% of the treated patients show an improvement of at least 50% in oSCORAD) during therapy (e.g. CSA) a difference in the oSCORAD-50 Response Rate of 27%, 19% or rather 14% can be demonstrated with a power of 80% and 5% significance level n=50, n=100 more specifically n=200 patients per treatment group. (PS Power and Sample Size Calculations Version 2.1.30)

8 REPORTING

The collected data serve exclusively academic purposes. The intention is to publish the collected data in scientific journals with broad readership and additionally present the results understandable for laymen in publications and/or public lectures. Data protection concerning the patient´s and the participating physician´s data applies to all publications.

9 ETHICAL, LEGAL AND ADMINISTRATIVE ASPECTS

The investigation is conducted in accordance to the Declaration of Helsinki and the professional code of the responsible federal states Medical Associations in the version curent of any time.

Patient´s participation in the investiagtion is voluntary. The consent for participation can be withdrawn at any time without justification or disadvantages concerning the further necessary medical care. Prior to study participation patients will be informed in written and spoken form on the nature and scope of the investigation, in particular on the health benefits and potential risks. The patients´agreement is documented by the signed consent. In the case of withdrawal from the investigation the data already acquired will not be deleted. The patient has to be informed concerning this matter prior to study inclusion.
To verify the diagnosis AD clinical fotographs are used on top of the epidemiological criteria of the UK Working Party (see Appendix 1). [24] By means of the photographs the members of the steering committee/ scientific board check the correctness of the diagnosis. Given the fact, that in adulthood e.g. a cutaneaos T cell lymphoma can be misjudged as an AD the photo documentation is essential. The documentation of the clinical finding is done at baseline and incudes photographs of characteristic lesions and the distribution patterns on extremities and trunk. Patients will be informed about the purpose of the photo documentation. In the event of rejection, participation in the investigation will still be possible.

Prior to study initiation the study plan is submitted for appraisal to the ethics committee of the Medical faculty Dresden. Without the approval in written form the recruitment process of patients/subjects will not be started. Necessary requirement to conduct the study at the recruitment sites is an approval of the responsible ethics committee.

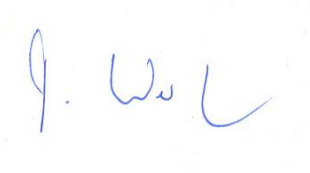
The patients´name and any other confidential information will be handled in strict adherence to medical secrecy, the European Data Protection Regulation and the Federal Data Protection Act (Bundesdatenschutzgesetz, BDSG).

In general, it is thus the intension that within the registry TREATgermany and within the additional registry „Bioanalytics“ the collected data are exchanged in encrypted form between the headquarter of the registry, the operator of the biobank and the coordination centres (Clinic for Dermatology, Venerology and Allergology at the Universitätsklinikum Schleswig-Holstein, Campus Kiel and Clinic for Dermatology, Venerology and Allergology at the Medizinischen Hochschule Hannover) to investigate scientific questions concerning AD and are transmitted to uncommercial collaboration partners. For this purpose the patient´s approval will be obtained. The disclosure of the research data to uncommercial collaboration partners is based on contractual arrangements and is characterised by the SOP „Publikationsvereinbarung und Datenanforderung“ (Appendix 19).

10 SIGNATURES

PD Dr. med. J. Schmitt

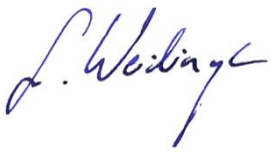
Dresden, 15.09.2021



Prof. Dr. med. T. Werfel

Hannover, 17.09.2021

Prof. Dr. med. S. Weidigner



Kiel, 21.09.2021

Physician

I hereby confirm that I have read and understood the present study protocol and accept it in all parts. I undertake to ensure that the patients brought into the study by my centre are treated, observed and documented according to the provisions of this protocol.

Name	Ort, Datum
	Unterschrift

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