Study Protocol

Register project for the Characterization and Treatment of moderate to severe atopic Hand and Foot eczema (ReaCT aH&FE)

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Study Lead

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Abbreviations

AD	Atopic dermatitis
ADR	Adverse drug reaction
aH&FE	Atopic hand and foot eczema
BDSG	Bundesdatenschutzgesetz
CES-D	Center for Epidemiological Studies – Depression
DLQI	Dermatology Life Quality Index
EASI	Eczema Area Severity Index
FECSI	Foot Eczema Severity Index
IGA	Investigator’s Global Assessment
HE	Hand eczema
HECSI	Hand Eczema Severity Index
HEIS	Hand Eczema Severity Index
HOME	Harmonizing Outcome Measures for Eczema
ISF	Investigator Site File
KKS	Koordinierungszentrum für Klinische Studien Dresden
QoL	Quality of Life
NRS	Numeric rating scale
PGA	Patient Global Assessment
POEM	Patient-oriented eczema measure
REDCap	Research Electronic Data Capture
UAW	Unerwünschte Arzneimittelwirkungen
WPAI	Work Productivity and Activity Impairment Questionnaire

Persons and institutions involved

Funding	Sanofi Lützowstraße 107, D-10785 Berlin, Germany
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Register coordination (management) (Site management Quality assurance Monitoring)	Dr. Sigrid Müller* Medizinische Fakultät der TU Dresden Zentrum für Evidenzbasierte Gesundheitsversorgung (ZEGV) Fetscherstraße 74, 01307 Dresden E-Mail: sigrid.mueller@ukdd.de Tel. : +49 (0)351 458-3247
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Data preparation and data analysis (biometrics)	Frederic Gehrke* Medizinische Fakultät der TU Dresden Zentrum für Evidenzbasierte Gesundheitsversorgung (ZEGV) Fetscherstraße 74, 01307 Dresden E-Mail: frederic.gehrke@ukdd.de Tel. : +49 (0)351 458-3247
Recruitment site (data collection sites)	Dermatologische Kliniken und Praxen in Deutschland mit Schwerpunkt Handekzem/ Allergologie / Neurodermitis

* Contact persons may change in the course of the registry. Current contact persons will be listed on the registry website.

Synopsis (English)

Title	Register project for the Characterization and Treatment of moderate to severe atopic Hand and Foot eczema (aH&FE)
Acronym	ReaCT aH&FE
Study lead	Univ. - Prof. Dr. Andrea Bauer, MPH (Dresden)
Study design	Prospective multicenter registry for patients with moderate-to-severe atopic hand- and foot eczema (aH&FE) (non-interventional registry study)
Background	- Hand eczema (HE) is a heterogeneous, often chronic disease on hands and wrists. [1] - It is frequently associated with eczema on the feet (30%). Incidence rates are as high as 5-8% per year. - One-year prevalence is 10%. - HE has a negative impact on quality of life and bears a high economic burden for the society. - In the last years innovative systemic therapeutics became available in Germany for the treatment of patients with moderate-to-severe aH&FE [2]: in September 2017 dupilumab (biologic) [3, 4], in October 2020, the small molecule baricitinib [5-7], a Janus Kinase1/2-inhibitor, in June 2021 tralokinumab (biologic) [8, 9], followed by the selective JAK1-inihibitors upadacitinib (from the age of 12 years) in August 2021 [10-12] and abrocitinib in December 2021 [13] as well as lebrikizumab (biologic) in November 2023[14], respectively. - The license of further systemic therapeutics is expected in the next few years. - Clinical registries provide valuable information for evidence-based clinical decision making [15] and, in addition, to investigate access to and implementation of therapeutic innovations in routine care.
Objectives:	**Primary objectives** • To establish a national, science-led clinical registry and research network • To characterize medical care and pharmaceutical therapies in adults suffering from moderate-to-severe aH&FE • To investigate the perspective of the patient (quality of life, POEM, itch, pain, sleep disturbance, ability to work, treatment satisfaction) • To investigate the real-world efficacy of biologicals vs. conventional therapies, tolerability and safety of conventional and biologic treatment modalities, sequence of treatments, drug survival and change of treatments in patients suffering from moderate to severe aH&FE • To register adverse events of systemic treatments in moderate to severe aH&FE **Secondary objectives** • To investigate patient characteristics, burden of disease and healthcare delivery patterns in patients affected by aH&FE

	• To evaluate guideline compliance of diagnostic and treatment procedures among previous and current healthcare providers • To develop of a platform for further investigations, such as pragmatic clinical trials, epidemiologic studies and outcomes research Exploratory objectives • To identify factors for disease, disease progression and therapy response in aH&FE • To identify clinical subtypes and endotypes of aH&FE Adverse events and reasons for withdrawals will be documented by recruiting sites. Patient/caregiver and physician treatment satisfaction and physicians' reasons for the choice of specific interventions will be assessed.
Study sites:	**Registry head office:** responsible for data management, quality assurance, data storage and data analysis: ZEGV Dresden **Recruitment sites:** All dermatological hospitals, outpatient dermatologists with focus on aH&FE/ allergology/ atopic dermatitis in Germany are invited to participate as recruitment sites.
Number of patients included:	At least 500 patients with aH&FE will be included.
Inclusion criteria:	- 18-100 years of age - Consultation at one of the (German) study sites - Confirmed diagnosis of aH&FE - At least moderate AD of either hands or feet - assessed with Hand Eczema Severity Index (HECSI) ≥ 17 [16] and/or Foot Eczema Severity Index (FECSI, which will be developed based on the HECSI) ≥ 17 - Indication of anti-inflammatory systemic therapy for aH&FE, or anti-inflammatory systemic therapy for aH&FE conducted within the past 24 months
Exclusion criteria	- Insufficient German skills for completion of study questionnaires - EASI ≥ 16 - Any condition which, in the opinion of the investigator, would not be in the best interest of the participant to participate (e.g. impairment of well-being, incapacitated patients) or which could prevent, limit or defeat the assessments in the protocol.
Study procedures	- No study related intervention will be performed. - Included patients will be prospectively followed. 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-visit; V1). The second and third study visits are scheduled 3 and 6 months after baseline, respectively. Thereafter, study visits are

	scheduled every 6 months. In case a new systemic therapy is initiated, follow-up visits are scheduled 3 and 6 months after therapy start visit, after that every 6 months. - The documentation of short-term therapy effects of a systemic treatment is made possible by a 4-week-visit after therapy-start. - Flares, adverse events, inpatient care or similar disease periods can be documented as interim visit. - None of these visits serves solely for documentation purposes of the register. - No therapeutic, diagnostic or monitoring procedures exceeding usual clinical practice are applied.

Data capture	- Prospective electronic documentation of disease course and severity, medical care and pharmaceutical treatment of aH&FE
	- Pseudonymized data will be collected and stored in a REDCap database of the KKS at the TU Dresden. Data analysis is conducted at the registry head office (ZEGV Dresden) and is based on pseudonymized data of the REDCap-database.
	- Completion of patient and physician report forms by *paper and pencil* will be possible upon request if electronic documentation is impossible. In this case the completed study forms will be sent to the registry head office (ZEGV Dresden) for data entry.
	- 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 aH&FE including adverse events.
	  Important known comorbidities are recorded at inclusion and in the case of change. (see p. 15, Tab. 1 for details)
	  - A patient report form to assess important subjective parameters, patient reported outcomes such as symptoms, quality of life, treatment satisfaction, patient's assessment of global disease severity, totally/partially well-controlled weeks, sickness leave due to aH&FE and visits to healthcare professionals, sociodemographic parameters in the case of inclusion and at biennial intervals. (see p. 16, Tab. 2 for details)

Duration	- For the national, academic clinical registry ReaCT an indefinite time frame is envisioned.
Endpoints	All results will be reported in aggregated form so that no conclusions can be drawn about individual patients. **Primary Endpoints** In analogy to the recommendations of the HOME initiative, we consider changes in the following primary endpoints for real-world efficacy of applied therapies: • Objective severity of clinical signs, in ReaCT measured with HECSI-50, HECSI-75, and HECSI-90 six months after treatment was first prescribed (analogue analyses concerning FE) • Patient-reported symptoms measured with POEM six months after treatment was first prescribed • Disease control over time measured with RECAP six months after treatment was first prescribed

	• Quality of life measured with HEIS six months after treatment was first prescribed Another primary endpoint is the safety of applied treatments at each visit. **Secondary Endpoints** • Impact of applied treatment on primary endpoints: biologics vs conventional treatment • Impact of potential risk factors on primary endpoints Evaluation per visit including changes over time: • Proportion of treatment response and duration of response based on IGA changes • Disease modification measured as complete remission and number of flares since latest consultation on hands and feet, respectively, HECSI, FE severity, EASI, IGA, RECAP, POEM, DLQI, PGA, WPAI, pruritus NRS, pain NRS, sleep disturbance NRS, depression CES-D
Reporting	A standard descriptive data analyses will be performed regularly by the ZEGV Dresden. Annual reports will be provided from 2025 onwards. Interim reports and the final report will be provided according to the milestones.
Ethics and legal aspects:	The study will be conducted in accordance 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.

Synopsis (Deutsch)

Titel:	Register-Projekt für die Charakterisierung und die Behandlung von moderaten bis schweren atopischen Hand- und Fußekzemen (aH&FE)
Akronym:	(ReaCT aH&FE)
Studienleitung:	Univ. -Prof. Dr. Andrea Bauer, MPH (Dresden)
Studiendesign:	Prospektives Register für Patienten mit moderaten bis schweren atopischen Hand- und Fußekzemen (nicht-interventionelle Registerstudie)
Hintergrund	- Das Handekzem (HE) ist eine heterogene, entzündliche und oft chronische Erkrankung an Händen und Handgelenken. [1] - Es ist häufig mit Ekzemen an den Füßen verbunden (30 %). - Die Inzidenzrate liegt bei 5-8 % pro Jahr. - Die Ein-Jahres-Prävalenz beträgt 10 %. - Das HE wirkt sich negativ auf die Lebensqualität der Betroffenen aus und stellt eine große ökonomische Belastung für die Gesellschaft dar. - Viele Erwachsene mit moderatem bis schwerem atopischen Hand- und Fußekzem (aH&FE) können nicht ausreichend mit topischen antientzündlichen Therapien behandelt werden, so dass ein kontinuierlicher oder intermittierender Einsatz von UV-Therapie oder antientzündlicher Systemtherapie indiziert ist. [1, 17] - In den vergangenen Jahren wurden eine Reihe innovativer Systemtherapien zur Behandlung von Patienten mit moderatem bis schwerem aH&FE in Deutschland verfügbar [2]: seit September 2017 Dupilumab (Biologikum) [3, 4], seit Oktober 2020 Baricitinib (JAK1 und JAK2-Inhibitor) [5-7], seit Juni 2021 Tralokinumab (Biologikum) [8, 9], seit August 2021 Upadacitinib (JAK1-Inhibitor) [10-12], seit Dezember 2021 Abrocitinib (JAK1-Inhibitor) [13] und seit November 2023 Lebrikizumab (Biologikum) [14] zugelassen. - Eine Zulassung weiterer Systemtherapeutika ist für die nächsten Jahre zu erwarten. - Klinische Register bieten eine unverzichtbare Möglichkeit, Informationen für evidenzbasierte klinische Entscheidungen in der Routineversorgung zu generieren [15] und darüber hinaus den Zugang zu und die Implementierung von therapeutischen Innovationen in der Regelversorgung zu untersuchen.
Ziele	**Primäre Ziele** - Auf- und Ausbau sowie Betrieb eines nationalen, wissenschaftsgeleiteten klinischen Registers und Forschungsnetzwerks - Charakterisierung der medizinischen Versorgung und medikamentösen Therapie von Erwachsenen mit moderatem bis schwerem aH&FE - Erforschung von Patientenperspektive (Lebensqualität, POEM, Juckreiz, Schmerz, Schlafstörungen, Arbeitsfähigkeit, Behandlungszufriedenheit) - Erforschung der „real world“ Wirksamkeit von Biologika vs. konventionelle Behandlung, Verträglichkeit und Sicherheit der verfügbaren konventionellen und Biologika-Therapien, Therapiereihenfolge, Drug Survival und Therapiewechsel bei moderatem bis schweren aH&FE

	- Dokumentation von unerwünschten Ereignissen bei systemischen Behandlungen bei mittelschwerem bis schwerem aH&FE **Sekundäre Ziele** - Untersuchung der Patientencharakteristika, der Krankheitslast und die Gesundheitsversorgung bei Patienten mit aH&FE - Bewertung der Einhaltung von Leitlinien für Diagnose- und Behandlungsverfahren bei früheren und aktuellen Gesundheitsdienstleistern - Entwicklung einer Grundlage/Plattform für weitere klinische, (versorgungs-) epidemiologische Untersuchungen Explorative Ziele - Identifizierung von Faktoren für die Entwicklung von aH&FE, Krankheitsverlauf und Therapieansprechen - Identifizierung klinischer Subtypen und Endotypen des aH&FE UAW und Gründe für Ausscheiden aus dem Register werden ärztlich dokumentiert. Die Gründe für die Wahl spezifischer Therapieoptionen werden analysiert, ebenso wie die Zufriedenheit mit der Behandlung aus Sicht des Arztes und des Patienten.
Studienzentren:	**Registerzentrale** für Koordination, Datenmanagement, Qualitätssicherung, Datenhaltung und Analyse: ZEGV Dresden **Rekrutierungszentren:** Alle Hautkliniken, dermatologische Praxen und Allgemeinarztpraxen in Deutschland können sich an dem Register beteiligen.
Patientenzahl:	Mindestens 500 Patienten mit moderatem bis schwerem aH&FE
Einschlusskriterien:	- Alter: 18-100 Jahre - Vorstellung in einem deutschen REACT Studienzentrum - Bestätigte Diagnose eines aH&FE nach den „U. K. diagnostic criteria for atopic dermatitis“ [18-20] - Vorliegen eines mindestens moderaten atopischen Hand- oder Fußekzems gemessen mit dem Hand Eczema Severity Index (HECSI) ≥ 17 [16] und/oder Foot Eczema Severity Index (FECSI: analoge Anwendung des HECSI für die Füße) ≥ 17 - Aktuelle Indikation für eine anti-entzündliche Systemtherapie für das aH&FE oder anti-entzündliche Systemtherapie für das aH&FE innerhalb der letzten 24 Monate
Ausschlusskriterien	- Unzureichende Deutschkenntnisse - EASI ≥ 16 - Jeder Zustand, bei dem nach Ansicht des Prüfers eine Teilnahme nicht im besten Interesse des Teilnehmers wäre (z. B. Beeinträchtigung des Wohlbefindens, Nichteinwilligungsfähige Patienten) oder der die im Prüfplan vorgesehenen Bewertungen verhindern, einschränken oder vereiteln könnte.
Studienablauf:	- Es erfolgt keine studienbedingte Intervention. - Eingeschlossene Patienten werden prospektiv beobachtet. - Ein Ausscheiden von Patienten nach einer definierten Beobachtungszeit ist nicht vorgesehen.

	- Während des Beobachtungszeitraums finden pro Patient standardisierte Studienvisiten statt, bei denen Patientencharakteristika, klinische Daten, patientenberichtete Outcomes, ärztliche Gründe für Therapieentscheidungen und die Zufriedenheit mit der Behandlung dokumentiert werden. - Die erste Studienvisite findet bei Einschluss statt (Baseline-Visite; V1). Die zweite und dritte Visite finden jeweils im Abstand von 3 Monaten nach Baseline statt. Danach erfolgen Visiten nach jeweils 6 Monaten. Sofern eine Systemtherapie initiiert wird, finden die folgenden Visiten 3 und 6 Monate nach Initiierung der neuen Therapie, anschließend alle 6 Monate statt. - Die Dokumentation kurzfristiger Therapieeffekte ist im Rahmen einer 4-Wochen-Visite nach Einleitung einer Systemtherapie vorgesehen. - Bei Erkrankungsschüben, bei Auftreten unerwünschter Nebenwirkungen, stationären Aufenthalten oder ähnlichen Ereignissen können zusätzlich Interimsvisiten durchgeführt werden. - Keine der Visiten wird ausschließlich zu Dokumentationszwecken für das Register durchgeführt. - Es werden keine therapeutischen, diagnostischen oder Überwachungsverfahren angewendet, die über die normale klinische Praxis hinausgehen.

Datenerfassung:	- Prospektive elektronische Dokumentation des klinischen Verlaufs, der medizinischen Versorgung und medikamentösen Therapie des aH&FE.
	- Die Daten werden in pseudonymisierter Form in einer REDCap Datenbank am KKS an der TU Dresden gespeichert. Die Analyse der pseudonymisierten Daten erfolgt an der Registerzentrale (ZEGV Dresden).
	- Der Arzt- und Patientenfragebögen ist alternativ auch per *paper and pencil* möglich, sofern eine elektronische Erfassung nicht möglich ist. Die Fragebögen können zur Datenerfassung in der Datenbank an die Registerzentrale am ZEGV Dresden geschickt werden.
	- Die Datenerfassung beinhaltet:
	  - Einen Arztfragebogen zur Dokumentation anamnestischer und klinischer Faktoren wie der ärztlich-erfassten Erkrankungsschwere (klinische Zeichen und betroffene Körperregionen), der globalen Erkrankungsschwere aus Sicht des Arztes, des Erkrankungsverlaufs und der Therapie des aH&FE inkl. unerwünschter Arzneimittelwirkungen (UAW). Wichtige bekannte Komorbiditäten werden bei Einschluss und bei Veränderung erfasst, soziodemografische Parameter bei Einschluss und in zweijährigem Abstand. (Details auf S. 15, Tab. 1)
	  - Ein Patientenfragebogen zur Erfassung wichtiger subjektiver Parameter und Patienten-berichteter Outcomes wie Erkrankungssymptome, Lebensqualität, Zufriedenheit mit der Behandlung, globale Erkrankungsschwere aus Sicht des Patienten und Grad der Erkrankungskontrolle seit der letzten Visite (bzw. innerhalb der vergangenen 12 Wochen bei V1) sowie Arbeitsunfähigkeit infolge des aH&FE und Inanspruchnahme

	medizinischer Leistungen/Arztbesuche. (Details auf S. 16, Tab. 2)
Laufzeit	ReaCT ist als akademisch geleitetes, klinisches bundesweites Register nicht zeitlich befristet.
Endpunkte	Alle Ergebnisse werden jeweils in aggregierter Form dargestellt, so dass keine Rückschlüsse auf individuelle Patienten möglich sind. **Primäre Endpunkte** In Anlehnung an die Empfehlungen der HOME-Initiative betrachten wir Änderungen in den folgenden primären Endpunkten für die Wirksamkeit unter Alltagsbedingungen der angewandten Therapien: - Objektiver Schweregrad der klinischen Symptome, gemessen mit HECSI-50, HECSI-75 und HECSI-90 sechs Monate nach der Erstverschreibung der Behandlung (analoge Analysen beim FECSI) - Von den Patienten angegebene Symptome, gemessen mit POEM sechs Monate nach der Erstverschreibung der Behandlung - Krankheitskontrolle im Zeitverlauf, gemessen mit RECAP sechs Monate nach der Erstverschreibung der Behandlung - Lebensqualität, gemessen mit HEIS sechs Monate nach der Erstverschreibung der Behandlung Ein weiterer primärer Endpunkt ist die Sicherheit der angewandten Behandlungen bei jedem Besuch. **Sekundäre Endpunkte** - Einfluss der angewandten Behandlung auf primäre Endpunkte: Biologika vs. konventionelle Behandlung - Auswirkungen potenzieller Risikofaktoren auf die primären Endpunkte Auswertung pro Besuch, einschließlich Veränderungen im Laufe der Zeit: - Anteil des Ansprechens auf die Behandlung und Dauer des Ansprechens auf der Grundlage von IGA-Veränderungen - Krankheitsveränderung, gemessen als komplette Remission und Anzahl der Schübe seit der letzten Konsultation an Händen und Füßen - HECSI, FECSI, EASI, IGA, RECAP, POEM, DLQI, PGA, WPAI, Pruritus NRS, Schmerz NRS, Schlafstörung NRS, Depression CES-D
Berichte:	Eine standardisierte deskriptive Auswertung erfolgt regelmäßig durch das ZEGV Dresden. Jährliche Berichte werden ab 2025 erstellt. Zwischenberichte und der Schlussbericht werden gemäß Meilensteinplan erstellt.
Ethische und rechtliche Aspekte:	Die Studie wird in Einklang mit der Deklaration von Helsinki, den Vorgaben des Datenschutzes und den geltenden berufsrechtlichen Bestimmungen durchgeführt. Voraussetzung zur Studiendurchführung ist die Vorlage bei der Ethikkommission an der TU Dresden und der für die Rekrutierungszentren zuständigen Ethikkommissionen. Patienten können nur nach schriftlicher und mündlicher Aufklärung und schriftlicher Einwilligung in das Register eingeschlossen werden.

Visit schedule

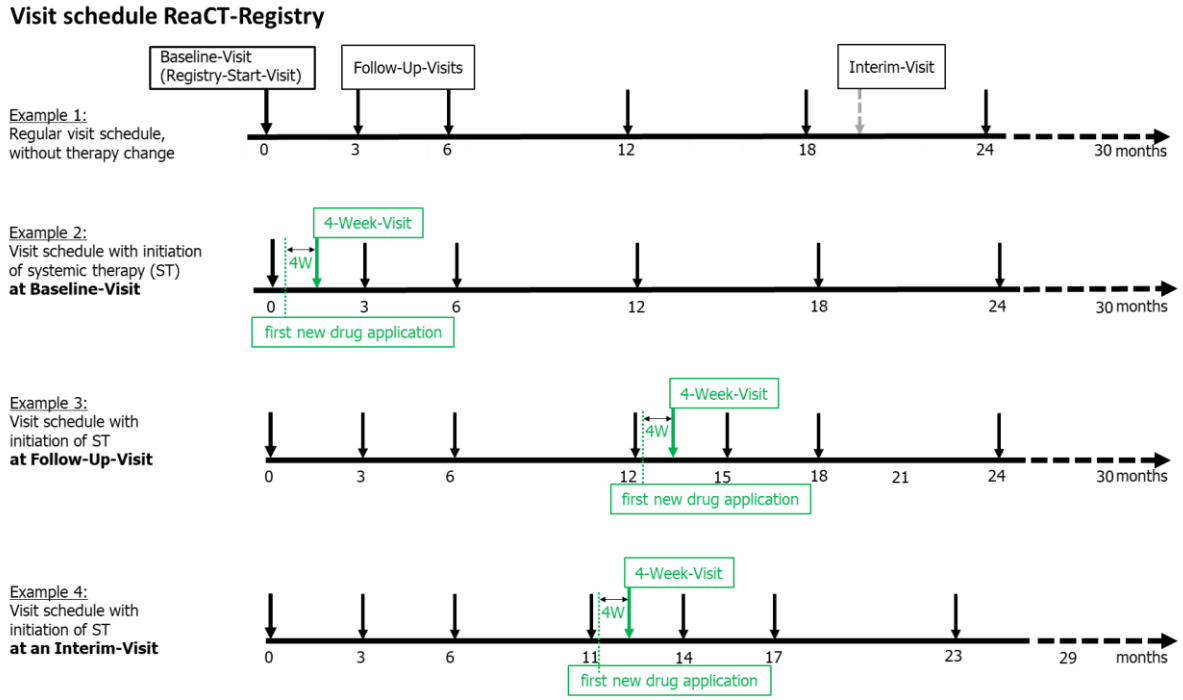

Figure 1: Visite schedule ReaCT with Baseline-Visit, Follow-Up-Visit, Interim-Visit and 4-Week-Visit; examples illustrate visit schedule with respect to different points in time of initiation of a new systemic therapy (ST)

The visit schedule is described in detail in chapter 5.

Tabelle 1: Physician case report form

Physician case report form	Visit 1 Baseline visit (register inclusion)	Visit n Follow-up visits 4-week visits, iterim visits
Visit date, type of visit*	O	O
Inclusion and exclusion criteria*	O	
Registration (incl. confirmation of the declaration of consent)*	O	
Anamnesis*	O	
Course of AD therapy prior to V1*	O	
Comorbidity*	O	O
Current skin findings - IGA**,†, HECSI***,†, FECSI****,†	O	O
Current severity of atopic dermatitis - EASI***,†	O	O
Current topical and physical treatment of moderate to severe aH&FE*	O	O
Current anti-inflammatory systemic therapy*	O	O

* Questionnaire developed by ReaCT team based on questionnaires applied in the TREATgermany registry (EK TUD 118032016)
** IGA: Non-validated outcome measurement instrument developed by Simpson et al. [21]
*** Validated outcome measurement instrument
**** FECSI: Outcome measurement instrument developed by ReaCT team based on HECSI, not yet validated
† See p. 26ff for details

Tabelle 2: Patient case report form

Patient case report form	Visit 1 Baseline visit (register inclusion)	Visit n Follow-up visits 4-week visits, iterim visits	Every 2 years At a follow-up, 4-week, or interim visit
Year of birth, sex*	O		
Personal details*	O		O
Medical history prior to V1*	O		
Relapses since previous visit*		O	O
Utilization of medical services (retrospective before V1 or since previous visit)*	O	O	O
Satisfaction with treatment in the past 3 months*	O	O	O
Disease severity in the past 3 days or 24 h - NRS for itching, pain, sleep disturbances*,†	O	O	O
Patient involvement in treatment decisions*	O	O	O
Assessment of severity of the moderate to severe aH&FE - current (PGA), NRS on disease control in the past 12 weeks*	O	O	O
Disease severity in the past week - RECAP**,† (separately for hand and foot eczema)	O	O	O
Dermatological quality of life - DLQI**,†	O	O	O
Hand eczema-related quality of life - HEIS**,†	O	O	O
Patient Oriented Eczema Measure - POEM**,† (separately for hand and foot eczema)	O	O	O
Depression CES-D**,†	O	O	O
Work Productivity and Activity Impairment Questionnaire - WPAI**,† (separately for hand and foot eczema)	O	O	O

* Questionnaire developed by ReaCT team based on questionnaires applied in the TREATgermany registry (EK TUD 118032016)
** Validated outcome measurement instrument
† See p. 26ff for details

1 INTRODUCTION

1.1 Atopic hand- and foot eczema (aH&FE)

Hand eczema (HE) is a heterogeneous, often chronic disease on hands and wrists. It is frequently associated with eczema on the feet (30%). Incidence rates are as high as 5-8% per year. One-year prevalence is 10%. HE has a negative impact on quality of life and bears a high economic burden for the society. Etiology of HE is diverse, and eczema may present with a variety of clinical symptoms. Besides hyperkeratotic and recurrent vesicular HE, atopic hand and foot eczema (aH&FE) is common. Atopic HE has its onset at an early age, and the mean age for patients with atopic HE is significantly lower than for other etiologies. Previous or current atopic dermatitis is known as a major risk factor for the development of HE, especially in skin risk occupations, because of the impaired barrier function. Despite numerous new findings on the pathogenesis of atopic dermatitis, no causal treatment is currently available. [22]

1.2 Treatment of atopic hand- and foot eczema

Management can be challenging, as delay in adequate treatment and trigger avoidance increase the risk of chronic disease. Symptomatic local therapy includes a stage-adapted application of moisturisers and topical medicaments, and if necessary, antiseptic and anti-inflammatory topical preparations, supplemented by phototherapy and systemic therapy in moderate to severe cases. [23, 24] Systemic therapy is often required for the treatment of moderate to severe chronic HE as indicated by the 5-year follow-up data of the CARPE hand eczema registry (including 35. 8% atopic HE), where up to 39% of all patients with chronic HE were treated systemically. [25] However, evidence from randomized controlled trials on aH&FE is still limited as a recent Cochrane review showed. [26] Despite its high impact, aH&FE is not sufficiently characterized in epidemiological and health care research terms. Particularly, data on real-world efficacy and safety of conventional and biologic treatment modalities, drug survival, burden of disease, care provision and clinically relevant (risk) factors for therapy response, chronicity, disease progression, and prognosis are lacking.

Other relevant research gaps with regard to drug therapy for patients with moderate to severe aH&FE include

- Effectiveness and patient safety studies in everyday care,
- Long-term observations,
- Medical reasons for or against the prescription of systemic therapeutics in patients with moderate to severe aH&FE,
- Treatment sequence and drug survival in everyday care
- Health economic evaluations, and
- Data on patient preferences.

Clinical registries offer an indispensable opportunity to generate information for evidence-based clinical decisions in routine care. [15]

2 STUDY AIMS

2. 1. Primary Objectives

Primary objectives of ReaCT are:

- To establish a science-led clinical registry and research network to investigate the real-world efficacy and safety of conventional and biologic treatment modalities and drug survival in patients suffering from aH&FE
- To register adverse events of systemic treatments in aH&FE

Secondary objectives of ReaCT are:

- To investigate patient characteristics, burden of disease and healthcare delivery patterns in patients affected by aH&FE
- To evaluate guideline compliance of diagnostic and treatment procedures among previous and current healthcare providers

Exploratory objectives:

- To identify risk factors for disease, disease progression and therapy response in aH&FE
- To identify clinical subtypes and endotypes of aH&FE

3 STUDY DESCRIPTION

3.1 Study design

This is a non-interventional (observatory), prospective clinical register. It gathers data that are routinely collected in the course of clinical diagnostics and therapy of patients with moderate to severe aH&FE, supplemented by questionnaires collected at the visits, without diagnostic, monitoring or therapeutic procedures exceeding usual clinical practice, without additional interventions, and without comparative treatments such as cross-over interventions.

3.2 Study sites

Study lead: Study lead is the Department of Dermatology, University Hospital Carl Gustav Carus, Faculty of Medicine at the TU Dresden.

Registry head office: The registry head office of the ReaCT registry is the Centre for Evidence-based Healthcare (ZEGV), University Hospital and Faculty of Medicine Carl Gustav Carus, TU Dresden. It is responsible for the coordination of cross-site registry activities, the coordination of the recruitment sites, data management, quality assurance, data storage, data analysis and reporting.

Recruitment sites: All dermatological hospitals, outpatient dermatologists with focus on aH&FE/ allergology/ atopic dermatitis in Germany are invited to participate as recruitment sites. The aim is to involve at least 30 recruitment sites. In order to achieve a high representativeness of the results, a mix of specialized sites (e. g. university hospitals and allergy centres) and practices should be achieved. Furthermore, participating sites are encouraged to include as many (consecutive) patients as possible who meet the inclusion criteria. Participating sites are given the opportunity for scientific cooperation. Participation is for scientific reasons. An expense allowance is paid for the documentation of the visits to the recruitment sites.

4 PATIENT POPULATION

4.1 Patients

Adults who refer to dermatology clinics or dermatology practices in Germany with indication for or under systemic therapy due to moderate to severe aH&FE. The registry will include at least 500 patients. The observation period is not limited in time.

4.2 In- and exclusion criteria

Inclusion Criteria

- 18-100 years of age
- Confirmed diagnosis of AD by U. K. diagnostic criteria for atopic dermatitis (see Appendix 1) [18-20]
- At least moderate AD of either hands or feet - assessed with HECSI ≥ 17 [16] and/or FECSI severity score (based on the HECSI) ≥ 17
- Indication of anti-inflammatory systemic therapy for aH&FE, or antiinflammatory systemic therapy for aH&FE conducted within the past 24 months [1]

Exclusion Criteria

- Insufficient German skills for completion of study questionnaires
- EASI ≥ 16
- Any condition which, in the opinion of the investigator, would not be in the best interest of the participant to participate (e.g. impairment of well-being, incapacitated patients) or which could prevent, limit or defeat the assessments in the protocol.

4.3 Endpoints

Primary Endpoints

In analogy to the recommendations of the HOME initiative, we consider changes in the following primary endpoints for real-world efficacy of applied therapies:

- Objective severity of clinical signs, in ReaCT measured with HECSI-50, HECSI-75, and HECSI-90 six months after treatment was first prescribed (analogue analyses concerning FECSI)
- Patient-reported symptoms measured with POEM six months after treatment was first prescribed
- Disease control over time measured with RECAP six months after treatment was first prescribed
- Quality of life measured with HEIS six months after treatment was first prescribed

- Another primary endpoint is the safety of applied treatments at each visit.

Secondary Endpoints

Secondary Endpoints are:

- Impact of applied treatment on primary endpoints: biologics vs conventional treatment
- Impact of potential risk factors on primary endpoints

Evaluation per visit including changes over time:

- Proportion of treatment response and duration of response based on IGA changes
- Disease modification measured as complete remission and number of flares since previous consultation on hands and feet, respectively, HECSI, FECSI, EASI, IGA, RECAP, POEM, DLQI, PGA, WPAI, pruritus NRS, pain NRS, sleep disturbance NRS, Depression CES-D

5 STUDY COURSE

There will be no study-specific intervention. Included patients will be observed without a patient-related maximum observation time. A baseline visit takes place upon patient inclusion in the registry. Follow-up visits are intended as part of the outpatient visits at the participating centres at 3 months and 6 months after baseline, and then every 6 months to document the course of the therapy. When a new systemic treatment was started (at baseline or later) the following visits take place 4 weeks after first new drug application, then 3 months and 6 months after therapy start, and then every 6 months.

These dates may vary by ±2 weeks. Fig. 1 shows an exemplary visit plan.

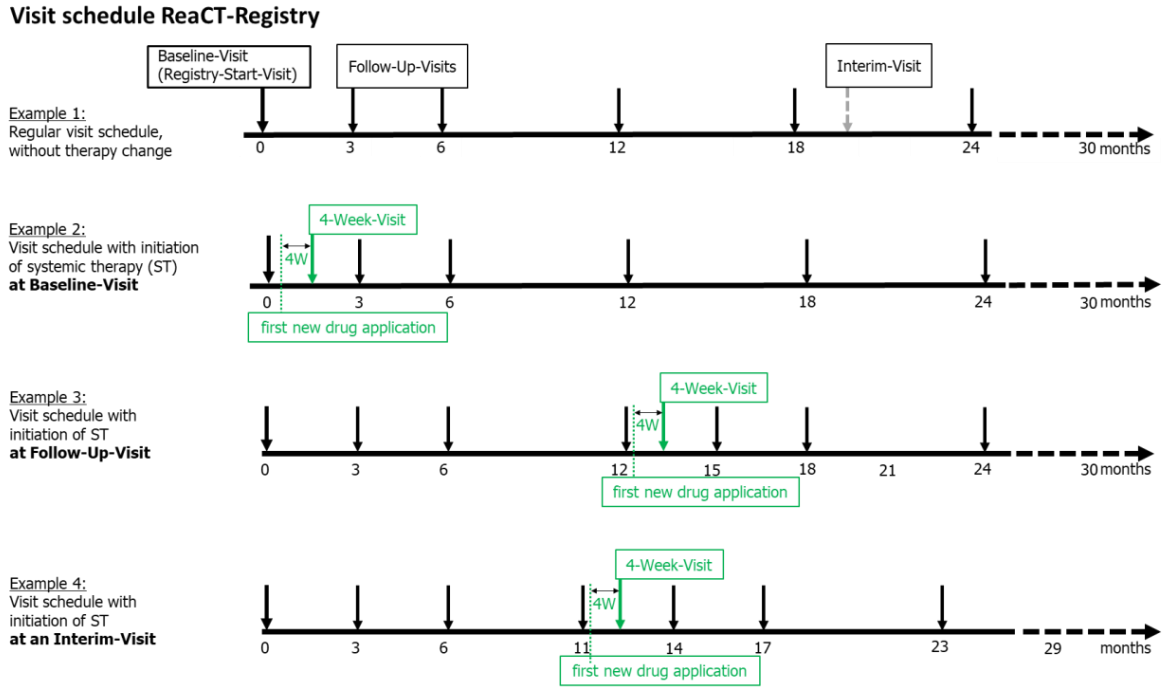

Figure 1: Visite schedule ReaCT with Baseline-Visit, Follow-Up-Visit, Interim-Visit and 4-Week-Visit; examples illustrate visit schedule with respect to different points in time of initiation of a new systemic therapy (ST)

5.1 Patient recruitment, Visit 1 (baseline/inclusion in the register)

A prerequisite for the inclusion of patients in the registry is appropriate information about the purpose of the study, the procedure, possible risks and benefits of participation in the study. Information about the study is provided in person by the attending physician and in writing in the patient information leaflet. Only after all the patient's questions have been clarified will the patient be asked to sign **two** copies of the consent form. The patient is then given a copy of the patient information/informed consent form. Patients who fulfil the inclusion criteria can be included in the study after providing written informed consent.

Physician questionnaire (Table 1): During the baseline visit, the general and specific medical history, the physical examination with documentation of the skin findings (HECSI, FECSI, EASI, global disease severity (IGA for hand and feet, respectively), the documentation of typical lesions and the documentation of the previous therapy as well as the therapy prescribed from this visit onwards and the reasons for this therapy decision are documented first. Adverse events and possible adverse drug reactions (ADR) of the aH&FE therapy are also recorded using the physician questionnaire.

Patient questionnaire (Table 2): Patients are asked to complete the patient questionnaire, which records information on sociodemographic characteristics, disease history, quality of life (DLQI, HEIS), symptoms (POEM, NRS itching, pain and sleep disturbances, peak itch), current

skin findings (PGA for hand and feet, respectively; RECAP disease control), occupational restrictions due to atopic dermatitis (WPAI), depressive symptoms (CES-D) and treatment satisfaction.

The questionnaires are provided by the REDCap database.

5.2 Follow up visits

At each follow-up visit (see Figure 1 for the visit schedule), the physician documents the clinical examination findings (HECSI, FECSI, EASI, global disease severity (IGA)), the prescribed therapy including the rationale for the prescription, as well as reasons for changing or continuing therapy and possible adverse drug reactions (ADRs).
The patient questionnaire for follow-up visits is analogous to the questionnaire for baseline visits (see Table 2).

5.3 Interim visits

Interim visits may take place between the regular study visits if the treating physician deems this necessary. Reasons for interim visits can be, for example, flares of the disease, the occurrence of ADRs due to the treatment of aH&FE, hospitalization due to aH&FE or a change in the anti-inflammatory systemic therapy.
The physicians' and patients' questionnaires for the interim visits correspond to those for the follow-up visits (see 5. 2, Table 2).

5.4 Drop-out

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

6 STUDY DOCUMENTATION / DATA MANAGEMENT

6.1 Site signature log of recruitment sites

It is the responsibility of the investigator of the recruitment sites to ensure that the registry project is conducted in accordance with all legal requirements and the registry protocol and that data is documented correctly.

It must be ensured that all data collected as part of this registry study (including medical history, concomitant diseases, examination data, results of examinations and adverse events) is only collected by appropriately authorized persons. The authorization of these persons and their scope of authorization is carried out by the investigator of the recruitment site via an authorization list (Delegation Log/Site Signature Log), which is filed as an original in the registry study folder. Furthermore, it must be ensured that the signatures and abbreviations can be clearly assigned to the authorized persons.

6.2 Patient identification log

Data collection is pseudonymized. The recruitment site notes the persons enrolled into the registry on a special patient identification list (Patient Identification Log). This must ensure a clear assignment of the participating person to the patient ID number in the registry.
The patient identification list must be treated confidentially and remains at the recruitment site. In addition, the participation of the person concerned in the registry must be noted in the patient file. In the physician and patient questionnaires, the data are entered in pseudonymous form. The registry head office receives pseudonymized data only.

6.3 Recruitment site registry study file

For the registry study an Investigator Site File (ISF) is provided to the recruitment site by the registry head office. All documents required for the registry study are stored in this file. It contains the essential documents, such as the registry protocol, a sample of the patient information/consent form, the favourable assessment of the lead ethics committee, etc. Forms provided by the registry head office must be used.
The recruitment site is responsible for ensuring that the ISF is up-to-date and complete. This is checked as part of the monitoring process in accordance with the regulations.
After completion or cancellation of the study, the documents must be kept for 10 years.

6.4 Data capture, data protection and data security

All clinical and patient-reported data are entered into an electronic data entry system specially developed for the ReaCT registry. A REDCap (Research Electronic Data Capture) database is used for this purpose. [27, 28]

REDCap is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources.

The physician enters clinical data browser-based on a PC or other terminal device. The corresponding questionnaire for the patient is opened on an iPad/mobile device using a QR-Code that is created from the physician's data-recording system. The patient enters their data web-based into the REDCap database using the iPad/mobile device. This ensures that the patient cannot view any data other than the questionnaire they are working on (neither their own previously entered data nor the physician's treatment data or data from other patients).

Data is primarily entered directly into this database. Alternatively, data can also be collected with a paper version of the questionnaires and later documented in the REDCap database if electronic data entry is not possible at the site.

The electronic data capture tool REDCap is hosted at the Koordinierungszentrum für klinische Studien Dresden (KKS). The KKS holds a REDCap-licence that can be used for the ReaCT registry on a contractual basis. The KKS is responsible for the management of the digital questionnaires as well as the administration of access authorizations for the involved study personnel of the recruitment sites. Moreover, the KKS also manages the corresponding server for data base storage, which is based in Dresden, Germany. The cooperation is based on a contract between the registry head office and the KKS. Mobile devices will be provided to all recruitment sites for the entry of patient questionnaires. The 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 to the REDCap database online via a browser-based web-application. Data transfer is encrypted. All data entry is tracked in the REDCap audit trail.

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

The entries in the data collection system are immediately checked in REDCap for completeness and plausibility and, if necessary, corrected using automatic feedback or help instructions. The medical study personnel have an up-to-date view of all entries at all times and can

check them for completeness and quality. A final plausibility check is carried out after the database has been extracted to create a plausibility-checked data set. This is necessary to clarify discrepancies in the documentation of the course of therapy in addition to data completeness to obtain an analyzable data set. Any discrepancies are requested from the recruiting sites for clarification and correction.

In case of a termination of the registry study, the database is closed after all entries have been entered and any queries have been clarified. This process is documented.

Data protection and data security

In the database only pseudonymized data is collected. Clinical and patient-reported data is linked via a patient ID to an individual person. This is documented in the Patient Identification Log that is kept in the recruitment sites. Neither in the electronic database nor the paper and pencil version of the questionnaires patient-identifying data such as name, address or date of birth appear. It is therefore ensured that only pseudonymized data is collected.

If the electronic data entry system cannot be fully applied at a study site, it is possible to complete the physician and patient questionnaires using a paper-based version of the physician and patient questionnaires (paper and pencil). Data entry into the database is done by the study personnel later on. In case the recruitment site is not able to enter paper-based questionnaires by itself, the completed original pages (without names or initials) are sent to the registry head office at ZEGV Dresden, a copy remains at the recruitment site. After data entry and electronic storage of the paper questionnaires, the original questionnaire is returned to the recruitment site for storage in accordance with legal requirements.

6.5 Description of measurement instruments

As detailed below, we follow the recommendation of the HOME initiative the use the core outcome instruments EASI, POEM, NRS 11 for intensity of itch, RECAP, and DLQI in all atopic dermatitis studies. [29] Whenever available, validated outcome measurement instruments are applied.

HECSI and FECSI Scores (see CRF physician, German)

The Hand Eczema Severity Index (HECSI) is used to measure the severity of hand eczema. The HECSI gives a total score from 0 to 360 points, based on assessments of the severity of six different morphological signs (erythema, infiltration/papulation, vesicles, fissures, scaling and edema) using a 4-point severity scale (0, no skin changes, to 3, severe disease), and the extent of eczema in five areas of the hands (fingertips, fingers (except fingertips), palms of hands, back of hands, wrists) by assessing the percentage of the regions these lesions occupy and converting it to a score based on a 5-point scale (the area score). For each of the hand regions, the region score will be calculated by adding up the severity scores for the 6 clinical signs of hand eczema and multiplying with the area score. The HECSI score equals the sum of the region scores. It is one of the most widely used measurement instruments for hand eczema severity and its reliability and validity has been studied in detail. HECSI was shown to pick up changes in hand eczema severity. HECSI severity grades are: clear = 0; almost clear = 1-16; moderate = 17-37; severe = 38-116; very severe ≥117. [16, 30, 31] The severity of foot eczema will be measured with the Foot Eczema Severity Index (FECSI), which has been created based on the HECSI for ReaCT.

Dermatology Life Quality Index (DLQI) (see CRF patients, German)

The DLQI is a validated questionnaire with content specific to those with dermatologic conditions. It consists of 10 items addressing the subject's perception of the impact of their skin disease on different aspects of their quality of life over the past week such as dermatology-related symptoms and feelings, daily activities, leisure, work or school, personal relationships, and the treatment. [32-34] The questionnaire records the QoL of the past 7 days. Each item is scored on a 4-point scale (0 = 'not at all/not relevant'; 1 = 'a little'; 2 = 'a lot'; 3 = 'very much'). The total score is the sum of the 10 items (score range from 0 to 30); with 0–1 = no effect at all on patient's life, 2–5 = small effect on patient's life, 6–10 = moderate effect on patient's life, 11–20 = very large effect on patient's life, and 21–30 = extremely large effect on patient's life. [35] A decrease in DLQI represents an improvement. The minimum clinically important difference for the DLQI is 4; a high score is indicative of a poor quality of life. [36] A validated German version is available. [33, 34, 37, 38]. The DLQI allows comparisons across studies of different dermatological diseases.

Hand Eczema Impact Scale (HEIS) (see CRF patients, German)

Health-related quality of life is widely used as a patient-reported outcome to evaluate clinical trials. The Hand Eczema Impact Scale (HEIS) (n=9 questions) is a validated disease-specific instrument used to assess health-related quality of life in patients with hand eczema according to the domains of (a) proximal daily activity limitations (PDAL), (b) embarrassment with appearance of the hands (Emb), (c) frustration with chronic hand eczema, (d) sleep, and (e) work. Improvements of ≥ 1.3 points in HEIS score and HEIS PDAL score represent clinically meaningful, important changes. Improvements of ≥ 1.5 points in HEIS Emb score represent clinically meaningful, important changes. A validated German version is available. [39]

Assessment of global disease severity at hands and feet, respectively, by physician (IGA) and patient (PGA) (see CRF physicians/patients, German)

In addition to a complex, symptom-based score system such as the HECSI and QoL assessments, Held et al. recommend that a global, basic assessment of the severity of the disease or its change should always be made in studies. [40] An IGA (Investigator's Global Assessment) is a frequent target criterion in clinical studies. This register applies the HF (hand and foot) IGA, an assessment tool that distinguishes between five degrees of severity. [21] The severity grades from 0 (clear) to 4 (severe) are defined by the presence and intensity of certain skin changes. Severity is stepped down if the extent of lesions is limited and stepped up according to the severity of vesicles or fissures.

The PGA (Patient's Global Assessment) is a target criterion similar to the IGA, in which the patient himself makes the assessment. It distinguishes six degrees: clear, almost clear, mild, moderate, severe, and very severe. These categories are not defined by signs or symptoms and therefore provide an easy, subjective assessment from the patient’s perspective.

Work Productivity and Activity Impairment Questionnaire (WPAI) (see CRF patients, German)

The impact of aH&FE on the subject’s ability to work and perform regular activities will be assessed by WPAI, which is an instrument to measure impairments in both paid work and activity impairment in leisure time. The WPAI consists of six items, and scores can be calculated for four domains, each reflecting the percentage impairment due to aH&FE during the past seven days, with higher numbers indicating greater impairment and less productivity.

The questions cover the characteristic areas of absenteeism and restricted productivity due to attendance at work with health problems (presenteeism). With regard to the areas of application, the WPAI can be used across all occupations and a variety of illnesses. A WPAI version

for chronic hand dermatitis in English has been validated (WPAI-ChHD); the discriminative and evaluative validity were established with the exception of work time missed (due to a low rate of absenteeism). [41] A German translation of the WPAI is available, and will be adapted to refer specifically to hand eczema and foot eczema, respectively, in accordance with the developers' recommendations. [42]

Patient-oriented eczema measure (POEM) (see CRF patients, German)
The Patient Oriented Eczema Measure (POEM) is a 7-item validated questionnaire used to assess disease symptoms in children and adults. [43] Patients evaluate frequency and severity signs and symptoms of AD during the past week: individual items of bleeding, oozing, cracked, flaking and dry/rough skin, and their impact on sleep on a 5-point scale. [43, 44] The maximum value of the POEM is 28 points. The POEM captures the symptoms relevant to patients and correlates well with the DLQI and PGA.
The original POEM questionnaire is adapted for ReaCT to refer to either hand eczema or foot eczema.

Center for Epidemiological Studies Depression Scale (CES-D) (see CRF patients, German)
The CES-D scale is a scale to measure depressive symptomatology in the general population and is considered a useful tool for epidemiological studies on depression. The items of the scale are the symptoms associated with depression and have already been validated. [45]

Eczema Area Severity Index (EASI) (see CRF patients, German)
The EASI is a validated measure used in clinical practice and clinical trials to assess the severity and extent of AD. [46] The EASI is a composite index with scores ranging from 0 to 72. Four AD disease characteristics (erythema, thickness [induration, papulation, edema], scratching [excoriation], and lichenification) will each be assessed for severity on a scale of 0 (absent) through 3 (severe). In addition, the area of AD involvement will be assessed as a percentage by body area of head, trunk, upper limbs, and lower limbs, and converted to a score of 0 to 6. In each body region, the area is expressed as 0, 1 (1% to 9%), 2 (10% to 29%), 3 (30% to 49%), 4 (50% to 69%), 5 (70% to 89%), or 6 (90% to 100%). Higher values indicating more severe disease. [46-48] The particular benefit of the instrument lies in highlighting changes in the severity of the disease during the course of treatment. [27]

RECap of AtoPic eczema (RECAP) (see CRF patients, German)
Recap of atopic eczema (RECAP) is a patient-reported outcome measure assessing eczema control. The severity of atopic dermatitis in the past 7 days is recorded in seven dimensions

on a 5-point scale. [86-89] This instrument has been developed and validated in the UK. There are self-reported and proxy-reported versions in English, Dutch and German. [49] The HOME Initiative recommends the use of the RECAP as a core outcome instrument in all atopic dermatitis studies. [50]
The original RECAP questionnaire is adapted for ReaCT to refer to either hand eczema or foot eczema.

Numeric rating scales NRS itch and worst itch (see CRF patients, German)
The NRS itch is comprised of two items and represents the numbers 0 (no itch) to 10 (worst imaginable itch). Subjects are asked to rate the average intensity during the past 3 days and the worst intensity of their itch within the past 24h using this scale.
The itch caused by hand eczema and foot eczema is rated separately.

Sleep Disturbance Numerical Rating Scale (SD NRS) (see CRF patients, German)
The SD NRS is measuring sleep loss during the past 3 days and comprises of one item. It represents the numbers 0 (no sleep impairment) to 10 (unbearable sleep impairment). SDs caused by hand eczema and foot eczema are rated separately.

6.6 Adverse drug reactions (ADR) and pharmacovigilance regulations

The registry also records adverse drug reactions that occur during the use of new system therapies. The aim is to gather information on the safety of authorized therapies in routine care.

Definition: Adverse drug reactions (ADRs) are harmful and unintended reactions to medicinal products intended for use in humans. Adverse drug reactions therefore mean that a causal relationship between the medicinal product and the event that has occurred cannot at least be ruled out. Adverse drug reactions are generally independent of the intended use of the medicinal product. The definition of the term therefore includes the consequences of e. g. overdose, misuse, abuse, misapplication, improper use or application errors, as well as use during pregnancy and breastfeeding.

Adverse drug reactions (ADRs) from the treatment of aH&FE are recorded and documented in a standardized manner in accordance with the applicable legal requirements if suspected by the physician and/or patient.

The type of ADR (sign, symptom or disease, preferably diagnoses), start and end of occurrence, intensity (mild = easily tolerated, moderate = affects daily activities, severe = daily activities/work not possible), suspected connection with current system therapy of the aH&FE,

measures or actions to restore or improve the well-being of the person concerned and outcome of the event are recorded.

The reporting process is illustrated in Figure 2. Physicians participating in the registry report ADRs occurring in routine care that are suspected to be related to a product of a pharmaceutical company that supports the registry to the principal investigator without personal reference (pseudonymized).
The study director forwards this report to the pharmacovigilance contact of the pharmaceutical company concerned, provided this has been contractually agreed. The participating physicians agree to make the results of additional examinations that serve to confirm the diagnosis of ADRs (e. g. autopsy findings, hospital reports, consultation reports, etc.) accessible in a suitable manner without personal reference (pseudonymized). The study director will establish the relevant contact between the pharmacovigilance department of the pharmaceutical company concerned and the reporting physician. A list of products relevant for ADR reporting will be made available to the participating physicians by the study management.

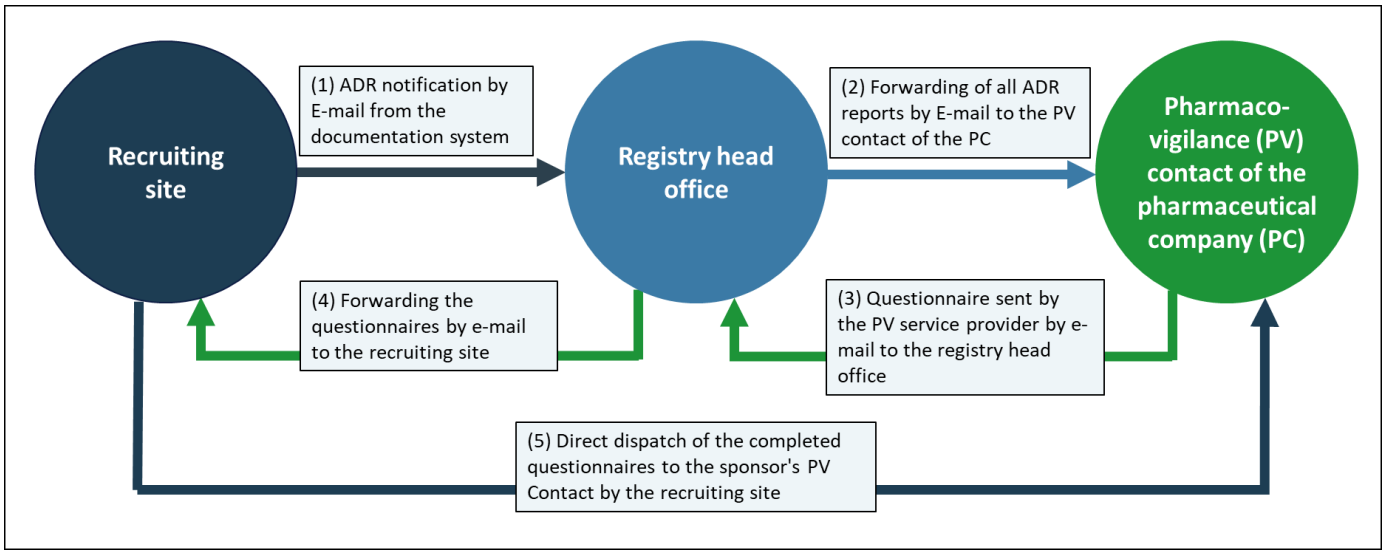

Figure 1: Pharmacovigilance Process

7 STATISTICS

Data will be checked for plausibility. Descriptive/explorative data analyses will be performed. Mean differences will be analyzed with the *t*-test or Mann-Whitney *U* test, where applicable; differences in frequencies will be analyzed with the Chi square test or with Fisher's exact test, where applicable. For more complex research questions such as changes in the course of time as well as associations to several risk factors, we apply multivariate regression analyses and analyses of variance. The ZEGV Dresden will routinely perform evaluations once yearly.

Since the study is non-interventional (observatory), no confirmatory analyses are planned.

In analogy to the recommendations of the HOME initiative, we consider changes in the following primary endpoints for real-world efficacy of applied therapies: [29, 51, 52]

- Objective severity of clinical signs, in ReaCT measured with HECSI-50, HECSI-75, and HECSI-90 six months after treatment was first prescribed (analogue analyses concerning FE)
- Patient-reported symptoms measured with POEM six months after treatment was first prescribed
- Disease control over time measured with RECAP six months after treatment was first prescribed
- Quality of life measured with HEIS six months after treatment was first prescribed

- Another primary endpoint is the safety of applied treatments at each visit.

To assess the needed number of patients to evaluate the comparative effectiveness of systemic treatments a calculation by "detectable alternative" for various scenarios was made. Based on the assumption of HECSI-50 response rate of 50% (i. e. 50% of treated patients show an improvement in HECSI of at least 50%) under one treatment option, a difference in HECSI-50 response rate of 27%, 19% and 14% can be shown for n=50, n=100 and n=200 patients per treatment group, respectively, at a power of 80% and 5% significance level (PS Power and Sample Size Calculations Version 2.1.30).

8 REPORTING AND PUBLICATION

All data collected will be used exclusively for scientific purposes. Annual reports will be provided from 2025 onwards.

Based on the data collected as part of the research project, it is planned to present several publications in scientific journals with a broad readership and also to present the results in a publication and/or lecture that is comprehensible to the general public.

For all publications, data protection will be maintained for all patient data as well as for the data of the participating physicians. All results will be reported in aggregated form so that no conclusions can be drawn about individual patients.

9 ETHICAL, LEGAL AND ADMINISTRATIVE ASPECTS

The investigation is conducted in accordance with the Declaration of Helsinki, the Declaration of Taipei and the current version of the professional code of conduct of the relevant federal state medical associations.

The patient´s participation in the investigation is voluntary. The consent for participation can be withdrawn at any time without giving reasons and without disadvantages concerning the further medical care. Prior to study participation, patients will be informed verbally and in writing about the nature and scope of the planned study, in particular about the potential benefits for their health and any possible risks. Their consent is documented by signing the informed consent form. In the event of withdrawal from the study, data material already obtained will not be destroyed. Patients are informed of this fact before inclusion in the study.

The study plan will be submitted to the Ethics Committee of the Dresden Medical Faculty for review prior to the start of the study. The inclusion of patients / subjects will not begin before the written, favourable vote of the ethics committee has been received. The prerequisite for conducting the study and the inclusion of patients at recruitment sites is an approving vote by the Ethics Committee of the Faculty of Medicine Dresden and the respective responsible Ethics Committee of the recruitment sites.

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

In principle, the data collected as part of the ReaCT registry will be exchanged in encrypted form between the recruiting site and the registry coordination site (ZEGV, Medical Faculty Carl Gustav Carus, Technische Universität Dresden) and the registry lead (Department of Dermatology, University Hospital Carl Gustav Carus, Technische Universität Dresden), and passed on to non-commercial cooperation partners. The patient's consent is obtained for this. The transfer of this research data to non-commercial scientific co-operation partners is carried out on the basis of contractual regulations in compliance with all data protection regulations and is regulated by the SOP "Publication agreement and data access requirements".

Governance arrangements (following Declaration of Taipei)

1 Purpose of the register

Primary objectives of ReaCT are:

- To establish a science-led clinical registry and research network to investigate the real-world efficacy and safety of conventional and biologic treatment modalities and drug survival in patients suffering from aH&FE
- To register adverse events of systemic treatments in aH&FE

Secondary objectives of ReaCT are:

- To investigate patient characteristics, burden of disease and healthcare delivery patterns in patients affected by aH&FE
- To evaluate guideline compliance of diagnostic and treatment procedures among previous and current healthcare providers

Exploratory objectives:

- To identify risk factors for disease, disease progression and therapy response in aH&FE
- To identify clinical subtypes and endotypes of aH&FE

2 Nature of health data that will be contained in the register

- This is a non-interventional (observatory), prospective clinical register. It gathers data that are routinely collected in the course of clinical diagnostics and therapy of patients with moderate to severe aH&FE, supplemented by questionnaires collected at the visits, without diagnostic, monitoring or therapeutic procedures exceeding usual clinical practice, without additional interventions, and without comparative treatments such as cross-over interventions.

3 Arrangements for the length of time for which the data will be stored

- The register is open-ended. If a recruiting site ends its participation, the identification list will be stored there for 10 years. The registry database contains only pseudonymized data. If the registry is terminated, all data will be anonymised no later than 20 years after the database is closed.

- The research data may be used for scientific publications and/or made available to other researchers in scientific databases for an unlimited period of time. The data will be used in a form that does not allow any conclusions to be drawn about individual study participants (anonymised).

4 Arrangements for regulations of the disposal and destruction of data

- If a recruiting site ends its participation, the identification list will be stored there for 10 years. The registry database contains only pseudonymized data. If the registry is terminated, all data will be anonymised no later than 20 years after the database is closed.

5 Arrangement for how the data will be documented and traceable in accordance with the consent of the concerned persons

- Data documentation procedures are provided above (6.4).
- The patient information and consent document outlines these procedures in simplified terms. Patients are informed orally and in writing about their legal rights concerning their personal data.

6 Arrangement for how the data will be dealt with in the event of change of ownership or closure

- A change of ownership of the data is not intended. If a recruiting site ends its participation, the identification list will be stored there for 10 years. The registry database contains only pseudonymized data. If the registry is terminated, all data will be anonymised no later than 20 years after the database is closed.

7 Arrangement for obtaining appropriate consent or other legal basis for data collection

- The legal basis for data collection is the patient's informed consent, obtained in the recruitment sites. The patient information and consent documents are attached to this protocol and are part of the governance arrangements.

8 Arrangements for protecting dignity, autonomy, privacy and preventing discrimination

- This register applies broad inclusion criteria for participation. Patients who are invited to participate are informed about the register and about their right

to withdraw without providing any reasons, and without any negative consequences for themselves. They are also informed that there are no disadvantages for them if they decline to participate.

9 Criteria and procedures concerning the access to and the sharing of the health data

- Researchers may request access to the health data for their own studies with or without financial interests. A study protocol must be provided. The register lead decides about these requests after considering the protocol, the academic capacities of the enquirer to conduct such studies, and potential overlap with analyses that have already been conducted or which are planned in another study protocol. If the request is granted, the parties will sign an agreement about the data sharing based on relevant legal and institutional regulations that apply at the time. Data will only be shared for study that are approved by the relevant ethical committee. Personal data will be anonymized before sharing.

10 Person responsible for the governance

- The register lead, Univ. - Prof. Dr. med. Andrea Bauer, MPH, is responsible for these governance arrangements.

11 Security measures to prevent unauthorized access or inappropriate sharing

- In the database only pseudonymized data is collected. Clinical and patient-reported data is linked via a patient ID to an individual person. This is documented in the Patient Identification Log that is kept in the recruitment sites. Neither in the electronic database nor the paper and pencil version of the questionnaires patient-identifying data such as name, address or date of birth appear. It is therefore ensured that only pseudonymized data is collected.
- If the electronic data entry system cannot be fully applied at a study site, it is possible to complete the physician and patient questionnaires using a paper-based version of the physician and patient questionnaires (paper and pencil). Data entry into the database is done by the study personnel later on. In case the recruitment site is not able to enter paper-based questionnaires by itself, the completed original pages (without names or initials) are sent to the registry head office at ZEGV Dresden, a copy remains at the

recruitment site. After data entry and electronic storage of the paper questionnaires, the original questionnaire is returned to the recruitment site for storage in accordance with legal requirements.

12 Procedures for re-contacting participants where relevant

- When necessary, in particular when important data are missing from the patient questionnaire, only the recruitment site where the patient is treated can contact them.

13 Procedures for receiving and addressing enquiries and complaints

- Enquiries and complaints can be addressed to the recruitment site where the patient is treated or the register lead. In addition, data protection officers of the recruitment site, the register lead, or the federal state can be contacted. The patient information document states these options and provides contact information.

Risk-benefit assessments

Participation in the registry project does not involve any risks. It consists of a dermatological examinations and consultations within usual clinical care as well as the completion of the above described questionnaires.

The registry study is a scientific data collection project that involves purely observing the progression of patients with moderate to severe atopic hand and foot eczema. This means that patients will receive the diagnostic and therapeutic measures that are medically indicated and planned for the treatment of their condition. Patient health data will be recorded in a structured manner in a database as part of the study and later evaluated scientifically.

Register studies such as this are essential for improving medical care and therapy and therefore benefit all patients. Participation in the study can help to ensure that patients with neurodermatitis receive better care in the future.

Pregnant or lactating women can be included in this register because their participation poses no health risks. The registry is a non-interventional observational study in routine care.

10 SIGNATURES

Dresden, 08.07.2025

Univ. - Prof. Dr. med. Andrea Bauer, MPH

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 site are treated, observed and documented according to the provisions of this protocol.

Name	Place, date	Signature

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12 APPENDIX

Appendix 1: U. K. Working Party's Diagnostic Criteria (1994) [18-20]

[German:]

Die Diagnose des atopischen Ekzems gilt als klinisch sicher, wenn

Hauptkriterium:

- juckende Dermatose

und mind. drei der folgenden Nebenkriterien zutreffen:

1. Beugenekzeme
2. Eigen- und/oder Familienanamnese Asthma/Heuschnupfen
3. generalisierte trockene Haut
4. Erkrankungsbeginn vor dem 2. Lebensjahr
5. sichtbare Hautentzündungen der Beugeseiten

[English:]

The diagnosis of atopic eczema is considered clinically certain if

main criterion:

- itchy dermatosis

and at least three of the following secondary criteria apply:

1. flexural eczema
2. personal and/or family history of asthma/hay fever
3. generalized dry skin
4. onset of the disease before the age of 2
5. visible skin inflammation on the flexor sides