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# A prospective, observational, longitudinal study in paediatric patients with moderate-to-severe atopic dermatitis (PEDISTAD): study objectives, design and methodology



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# A prospective, observational, longitudinal study in paediatric patients with moderate-to-severe atopic dermatitis (PEDISTAD): study objectives, design and methodology

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**Tables:** 3

## ABSTRACT

**Introduction:** Atopic dermatitis (AD) is a chronic inflammatory skin disease often associated with atopic comorbidities and has significant impact on children and their families. There is a lack of robust and longitudinal long-term data on disease characteristics and typical clinical practice with currently available treatments in children with moderate-to-severe AD. Hence, an observational study is needed to evaluate AD characteristics and progression in paediatric patients with moderate-to-severe AD.

**Methods and analysis:** Pediatric Study in Atopic Dermatitis (PEDISTAD) is a prospective, observational, longitudinal study in paediatric patients with moderate-to-severe AD who are currently receiving systemic or topical treatment and whose disease is not adequately controlled by topical prescription therapies or for whom those therapies are not medically advisable. 1300 children at 100-150 sites in approximately 20 countries worldwide will be enrolled and followed for 5 years. AD therapy is at the discretion of the investigator. Data collected will include: AD disease characteristics and comorbidities; current therapy for AD and initiation of new treatments/changes in current treatment; patient-/caregiver-reported outcomes; days missed from school/work for the patient/caregiver; healthcare professional visits; safety; and biomarkers.

**Ethics and dissemination:** This study is conducted in accordance with the principles established by the 18th World Medical Assembly and all subsequent amendments and the guidelines for Good Epidemiology Practice. Each individual country assures that ethics approval has been received and local regulatory requirements are met. Study data will be disseminated in manuscripts submitted to peer-reviewed medical journals as well as in abstracts submitted to congresses, and in the resulting posters and presentations.

ClinicalTrials.gov Identifier: NCT03687359.

**Key words:** atopic dermatitis, observational, paediatric, systemic treatment

## Strengths and limitations of this study

- PEDISTAD is a multinational, observational, longitudinal study in a large cohort of paediatric patients with moderate-to-severe atopic dermatitis (AD) that will collect long-term data on patient and disease characteristics, progression of disease, selected atopic comorbidities, real-world treatment patterns, efficacy and safety.
- Previous observational studies in patients with AD have not focused on moderate-to-severe disease leading to a gap in knowledge that will be addressed by this study.
- The observational nature of the study limits the robustness of the collected data compared to that obtained from blinded studies with control groups.
- Challenges of the study include patient recruitment in multiple countries and retention of patients through the observation period of 5 years, both of which can be difficult in young children.

## INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin disease often associated with atopic comorbidities.[1,2] Due to lack of standardised diagnostic criteria and outcome measures of disease severity, there is variability in the reported prevalence rates of AD in children.

AD profoundly affects the quality of life of children and family members.[3] Itching can affect mood and sleep quality, and the chronic relapsing nature of AD has a detrimental impact on the quality of life of the family.[3] Children with AD may also have symptoms of anxiety and depression.[4]

Limited treatment options are available for children with moderate-to-severe AD and primarily include topical corticosteroids, topical calcineurin inhibitors, topical crisaborole and systemic immunosuppressants.[5-8] Most systemic agents are broadly immunosuppressive, used off-label and are not currently approved for use in children. In general, they do not provide a favourable long-term benefit–risk profile for paediatric patients with AD inadequately controlled by topical therapies. Furthermore, disease can often rebound after cessation of systemic therapy, especially after administration of systemic cyclosporine.[9]

There is a lack of robust and longitudinal long-term data related to disease characteristics and typical clinical practice with currently available treatments in children. Hence, an observational study is necessary to evaluate the characteristics of paediatric patients with moderate-to-severe AD whose disease is not adequately controlled with topical therapies or when those therapies are not medically advisable.

The Pediatric Study in Atopic Dermatitis (PEDISTAD) aims to address the substantial need for a better understanding of AD characteristics and progression, including patient and caregiver burden, in paediatric patients with moderate-to-severe AD who initiate, or are candidates for, systemic therapy. The study will document patient characteristics, patient- and caregiver-reported outcomes, AD progression, and atopic comorbidities and assess the effectiveness and safety of therapies (systemic and

topical) while describing real-world treatment patterns over a 5-year period. Here we describe the objectives, design and endpoints of PEDISTAD.

## METHODS AND ANALYSIS

PEDISTAD is an international, multicentre, longitudinal, prospective, non-interventional study designed to describe the disease life course and comorbidities of paediatric patients with moderate-to-severe AD whose disease is not adequately controlled with topical therapies or for whom those therapies are not medically advisable (NCT03687359, study OBS15333, protocol version 1, 01 May 2018 and sub-study LPS15496, protocol version 1, 10 April 2018). Current participating sites are listed in the Clinicaltrials.Gov record.

### Patients

This study will enrol a balanced number of patients aged <2 years, ≥2 to <6 years and ≥6 to <12 years at baseline. Enrolment quotas with respect to treatment types (systemic vs topical) may be imposed to ensure target numbers of patients in each treatment category. To minimise patient selection bias, all eligible patients at each selected site should be invited to participate in this registry, until the global enrolment goal or the site enrolment limit is met.

AD therapy prescribed to patients who are enrolled in the study is not dictated per study protocol, and the therapeutic drug prescription is decided by the medical judgement of the study investigator. Patients may begin treatment with therapies that become commercially available during the course of the study.

Inclusion and exclusion criteria are reported in table 1. Briefly, patients are eligible for the study if they are <12 years of age at baseline, have investigator-assessed moderate-to-severe disease and are either receiving systemic treatment for AD (including UV therapy) or are currently on topical treatment

but would otherwise be candidates for systemic therapy (systemic therapies do not include systemic antihistamines).

**Table 1** Inclusion and exclusion criteria

| | |
|---|---|
| **Inclusion criteria** | • Male or female <12 years of age at baseline<br>• Patients with moderate-to-severe AD according to the investigator's assessment<br>• Treatment<br>  – Currently receiving systemic treatment (including UV therapy) for AD or<br>  – Currently on topical treatment, but otherwise candidates for systemic treatment due to<br>  ▪ Lack of adequate control and/or<br>  ▪ Safety concern with long-term topical treatment<br>• Signed informed consent by the parent/legally acceptable representative and assent by the patient appropriate to the patient's age, including willingness to participate in long-term follow-up |
| **Exclusion criteria** | • Concurrent participation in an interventional clinical trial that modifies patient care |

AD, atopic dermatitis.



**Ethics**

This study is being conducted in accordance with the principles established by the 18th World Medical Assembly and all subsequent amendments and in accordance with the guidelines for Good Epidemiology Practice. Each participating country should locally ensure all necessary regulatory submissions (for example, Institutional Review Board/Institutional Ethics Committee) are performed in accordance with local regulations, including local data protection regulations.

**Patient and public involvement**

Patients and the public were not involved in the design of this study.

**Study locations and timings**

Approximately 100-150 sites in approximately 20 countries are expected to enrol 1300 patients (figure 1). Patient enrolment is expected to take 2 years, and the study duration for each patient is 5 years. A total of 12 visits are planned for each enrolled patient. The study began on 28 September 2018 and is expected to be completed in September 2025.

**Study endpoints and data collection**

Data collected will include: demographics; AD disease characteristics at baseline; the presence of selected comorbidities at baseline; time course of conditions including AD; current therapy for AD and initiation of new treatments/changes in current treatment over time; severity of disease at baseline and over the follow-up period; patient-/caregiver-reported outcomes at baseline and over the follow-up period; days missed from school for the patient and days missed from work for the primary caregiver due to AD; visits to healthcare professionals; disease state and evolution of selected atopic comorbid conditions; and photography of a representative area affected by AD at select centres and safety. The association between biomarkers and disease state and time course of AD will be examined by a biomarker sub-study collecting blood samples for analysis of protein and RNA biomarkers and cheek swabs for DNA genomic biomarkers. The data being collected in PEDISTAD are summarised in table 2, and the timings for data collection are shown in figure 2.

**Table 2** Data being collected in PEDISTAD

| Type | Collected data |
|---|---|
| **Patient and disease characteristics** | • Patient demographics and medical history<br>• Personal and family history of AD and selected atopic comorbidities<br>• Prior and concomitant medications for AD and comorbidities—all prior systemic therapy ever used, all topical and UV therapy in the previous 3 months as well as treatment(s) for other diseases including name, dose, route, frequency and start/stop date<br>• Selected comorbidity presence throughout the study (as diagnosed by an HCP) |
| **Patient-/caregiver-reported outcomes** | • POEM<br>• CDLQI/IDQOL<br>• DFI<br>• Peak Pruritus NRS/Worst scratching NRS<br>• CGAD<br>• Days missed from school for the patient and days missed from work for the primary caregiver due to AD since last visit<br>• TNSS |
| **Physician assessments of AD disease activity** | • EASI<br>• BSA (%) affected by AD |
| **Safety data** | • All adverse events regardless of seriousness |
| **Other data** | • Visits to HCPs—type of HCP and reason for the visit<br>• Investigator specialty and setting<br>• Photography of a representative area affected by AD—optional (at select centres)<br>• Reason for end of study |
| **Biomarker data** | • Serial blood samples for protein and RNA expression<br>• Cheek swabs for DNA genomic biomarkers |

AD, atopic dermatitis; BSA, body surface area; CGAD, Caregiver Global Assessment of Disease; CDLQI, Children's Dermatology Life Quality Index; DFI, Dermatitis Family Impact; EASI, Eczema Area and Severity Index; HCP, healthcare professional; IDQOL, Infant's Dermatitis Quality of Life; NRS, Numerical Rating Scale; POEM, Patient-Oriented Eczema Measure; TNSS, Total Nasal Symptom Score.

**Dissemination plan**

The study team and the study steering and scientific committees are responsible for study reporting and interpretation, including interim data analyses and sub-group analyses. The data from the PEDISTAD study will be disseminated in manuscripts for submission to peer-reviewed medical journals as well as in abstracts for submission to congresses and in the resulting posters and presentations. The final decision to publish will be made by the study scientific steering committee after prior notice to the sponsor to allow for its internal review and comments.

**Statistical analysis**

Sample size

To ensure that approximately 930 patients complete the 5-year follow-up, approximately 1300 patients will be enrolled (about 435 in each age group). A sample of approximately 310 participants per age group will ensure a maximum width for the confidence interval of 11% for the estimates based on binary endpoints (table 3). This sample size needed requires that a total of 930 patients complete the study. The biomarker sub-study will be conducted in approximately 300 participants (100 participants within each age cohort), whose sample size is based empirically on the results of a previous biomarker study with similar objectives.[10]

**Table 3** Precision estimates for the overall population

| **Width of the 95% CI** | **Overall population N=930** | **33% of overall population N=310** |
|---|---|---|
| Binary data–widest width | 6.4% | 11.1% |
| Normal data | 0.13 SD | 0.22 SD |

CI, confidence interval; SD, standard deviation.

Analysis

All statistical analyses will be performed descriptively with no hypothesis testing. Patient- and care-giver reported outcomes will be summarised within each age cohort, as many are age-based assessments. Continuous data will be described using summary statistics, including arithmetic mean, standard deviation, median and range, while categorical data will be summarised using counts and percentages.

## DISCUSSION

The PEDISTAD study aims to address the lack of robust and longitudinal long-term data related to AD characteristics, disease progression, development of comorbidities and the typical clinical practice with currently available treatments in children with AD. By collecting information about clinical characteristics, including patient- and care-giver reported outcomes, physician-assessed clinical severity, safety of currently used medicines and photographs of a representative area affected by AD (at select centres), over time, the PEDISTAD study aims to bridge this knowledge gap. A biomarker sub-study of PEDISTAD will analyze the association between biomarkers and disease state and time course of AD in a sub-set of PEDISTAD study participants.

There are various disease trajectories in paediatric patients with AD, and clinical presentation varies with different ages of onset and development of comorbid atopic conditions.[11,12] Patients in this

study will, hence, be recruited into 3 age cohorts (<2 years, ≥2 to <6 years and ≥6 to <12) and followed for 5 years.

A significant proportion of children have persistent disease;[12,13] thus, treatment approaches that are effective and tolerated over large timespans are desired. The observational and long-term nature of the PEDISTAD study serves to better understand the long-term evolution of disease burden in patients and caregivers as well as to identify any unmet therapeutic need for moderate-to-severe AD.

Although there are no universal definitions of recalcitrance in AD patients, expert recommendations mention that failure to respond to adequate topical therapy, a need for prolonged use of high-potency topical steroids or repeated flares are suggestive of recalcitrance and make a patient eligible for systemic therapy.[14] This observational study will provide insight into the characteristics of paediatric patients initiated on or who become candidates for systemic therapy to better define when systemic therapy is warranted.

Observational studies in patients with AD to date have been limited by a variety of factors, including number of participants, participating countries and the extent and duration of data collection. The PEDISTAD study aims to address all these issues. Furthermore, the PEDISTAD study will be the largest study to date in a paediatric population with moderate-to-severe AD; by not focusing on moderate-to-severe disease, other observational studies may have underestimated the risk of comorbidities and disease persistence in this patient population.

Limitations of the PEDISTAD study include the open-label observational nature; thus, the collected data may not be as robust as blinded studies with control groups. However, the challenges of running long-term controlled studies, especially in this age group, are well known, and a control group may not be crucial to fulfil the objectives of this study. Therefore, the data from this study are anticipated to be highly valuable. Challenges include patient recruitment in multiple countries and sites and retention of patients in this age group for up to 5 years, which is particularly difficult in very young children. Parental

education will be key to keeping patients enrolled in the study and to provide robust and reliable patient-, caregiver- and physician-reported outcomes at reasonable intervals.

In summary, PEDISTAD will improve our understanding of the long-term evolution of AD, disease burden in patients and caregivers and the impact of therapy on paediatric patients with moderate-to-severe AD and their families.

**Competing interests**

**ASP:** AbbVie, AnaptysBio, Eli Lilly, Galderma, Incyte, Janssen, LEO Pharma, Novartis, Regeneron Pharmaceuticals, Inc., Sanofi – investigator; AbbVie, Amgen, Asana, Dermavant, Dermira, Galderma, Eli Lilly, Forte, LEO Pharma, Matrisys Bioscience, Menlo Therapeutics, Morphosys/Galapagos, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc., Sanofi – consultant.

**EG-Y:** AbbVie, Celgene, Eli Lilly, Galderma, GlaxoSmithKline, Glenmark, LEO Pharma, Pfizer, Regeneron Pharmaceuticals, Inc., Sanofi – investigator; AbbVie, Anacor, Asana Biosciences, Daiichi Sankyo, DBV, Dermira, Eli Lilly, Galderma, GlaxoSmithKline, Glenmark, Kiniksa Pharmaceuticals, Kyowa, LEO Pharma, Menlo Therapeutics, Novartis, Pfizer, Realm, Regeneron Pharmaceuticals, Inc., Sanofi – consultant; AbbVie, Celgene, Dermira, Galderma, Innovaderm, Janssen, LEO Pharma, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc., Sanofi – research grants.

**ADI:** AbbVie, Chugai Pharma, Genentech, Janssen, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc., Sanofi Genzyme – consultant.

**EB:** Almirall – speaker; AbbVie, Eli Lilly, Pfizer – investigator; Pierre Fabre Dermatology – investigator, consultant; Regeneron Pharmaceuticals, Inc., Sanofi Genzyme – consultant; Venthera – co-founder, consultant.

**MdeB-W:** Regeneron Pharmaceuticals, Inc., Sanofi Genzyme – investigator, advisory board member, speaker, consultant; AbbVie, Pfizer – investigator, advisory board member; Eli Lilly, UCB – advisory board member

**SJ, AZ, ER, ZEO:** Sanofi – employees, may hold stock and/or stock options in the company.

**PM-O:** Regeneron Pharmaceuticals, Inc. – employee and shareholder.

**Funding** This work was supported by Sanofi and Regeneron Pharmaceuticals, Inc. Medical writing and editorial assistance was provided by Carolyn Ellenberger, PhD, of Excerpta Medica, funded by Sanofi Genzyme and Regeneron Pharmaceuticals, Inc. Investigators will collect consent forms and data. Analysis of the data will be performed by the sponsor. The scientific committee of the study will have full access to the final data allowing for appropriate analysis and reporting of the study results.

**Contributors to the protocol**

ASP, EG-Y, ADI, EB, MdeB-W were involved in design of the study and are active steering committee members for the study.

SW contributed to the design and development of the protocol and is the statistical lead.

PM-O, AZ, ER, ZEO contributed to the design and development of the protocol and are medical leads.

## REFERENCES


1. Shrestha S, Miao R, Wang L, *et al*. Burden of atopic dermatitis in the United States: Analysis of healthcare claims data in the Commercial, Medicare, and Medi-Cal databases. *Adv Ther* 2017;34:1989–2006.
2. Weidinger S, Beck LA, Beiber T, *et al*. Atopic dermatitis. *Nat Rev Dis Primers* 2018;4:1.
3. Ricci G, Bellini F, Dondi A, *et al*. Atopic dermatitis in adolescence. *Dermatol Reports* 2011;4:e1
4. Rønnstad ATM, Halling-Overgaard AS, Hamann CR, et al. Association of atopic dermatitis with depression, anxiety, and suicidal ideation in children and adults: A systematic review and meta-analysis. *J Am Acad Dermatol* 2018;79:448–56.
5. Wollenberg A, Oranje A, Deleuran M, *et al*. ETFAD/EADV Eczema task force 2015 position paper on diagnosis and treatment of atopic dermatitis in adult and paediatric patients. *J Eur Acad Dermatol Venereol* 2016;30:729–47.
6. Sidbury R, Tom WL, Bergman JN, *et al*. Guidelines of care for the management of atopic dermatitis: Section 4. Prevention of disease flares and use of adjunctive therapies and approaches. *J Am Acad Dermatol* 2014;71:1218–33.
7. Ring J, Alomar A, Bieber T, *et al*. Guidelines for treatment of atopic eczema (atopic dermatitis) Part II. *J Eur Acad Dermatol Venereol* 2012;26:1176–93.
8. EUCRISA. Highlights of Prescribing Information, FDA 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/207695s002lbl.pdf. (accessed 4 January 2019).
9. Sibbald C, Pope E, Ho N, *et al*. Retrospective review of relapse after systemic cyclosporine in children with atopic dermatitis. *Pediatr Dermatol* 2015;32:36–40.

10. Thijs JL, Strickland I, Bruijnzeel-Koomen CAFM, *et al.* Moving toward endotypes in atopic dermatitis: Identification of patient clusters based on serum biomarker analysis. *J Allergy Clin Immunol* 2017;140:730–7.

11. Irvine AD, Mina-Osorio P. Disease trajectories in childhood atopic dermatitis: an update and practitioner's guide. *Br J Dermatol* doi: 10.1111/bjd.17766. [published Online First 13 February 2019].

12. Paller AS, Spergel JM, Mina-Osorio P, *et al*. The atopic march and atopic multimorbidity: Many trajectories, many pathways. *J Allergy Clin Immunol* 2019; 143:46–55.

13. Kim JP, Chao LX, Simpson EL, *et al*. Persistence of atopic dermatitis (AD): a systematic review and meta-analysis. *J Am Acad Dermatol* 2016;75:681–7.

14. Simpson EL, Bruin-Weller M, Flohr C, *et al*. When does atopic dermatitis warrant systemic therapy? Recommendations from an expert panel of the International Eczema Council. *J Am Acad Dermatol* 2017;77:623–33.

**Figure legends**

**Figure 1** Patients and study locations

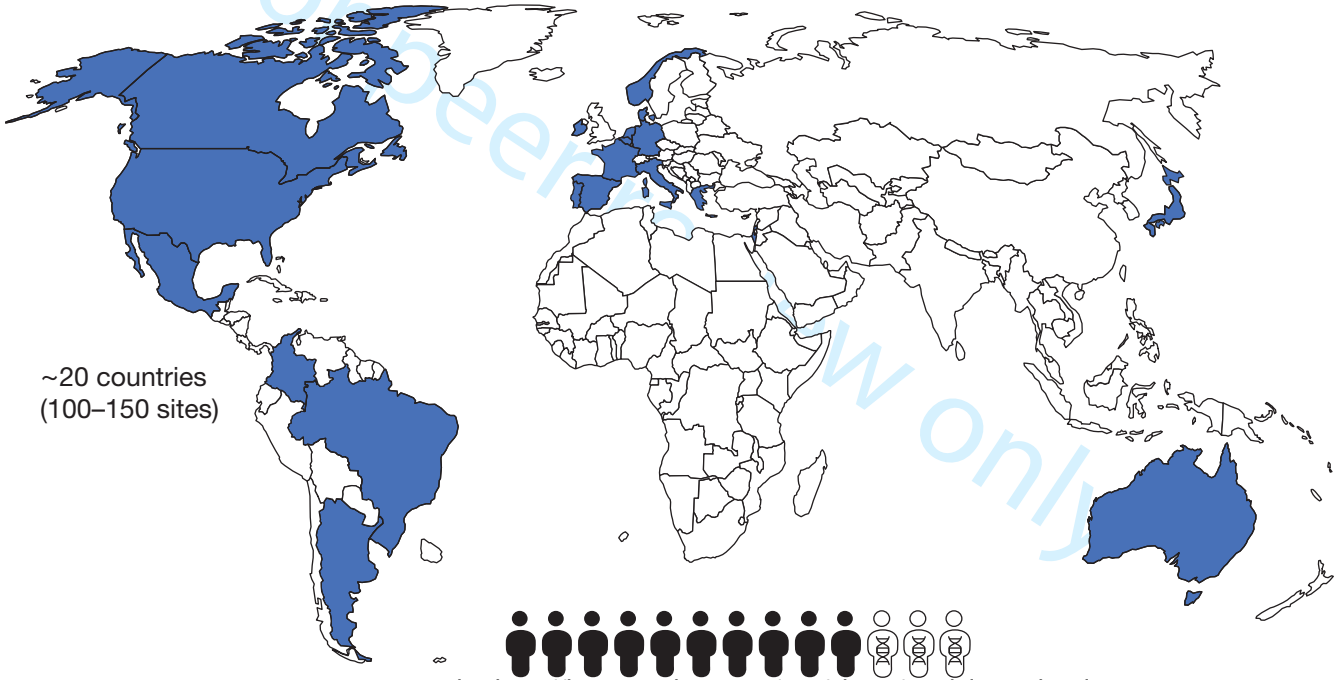
**Figure 2** Data collection schedule

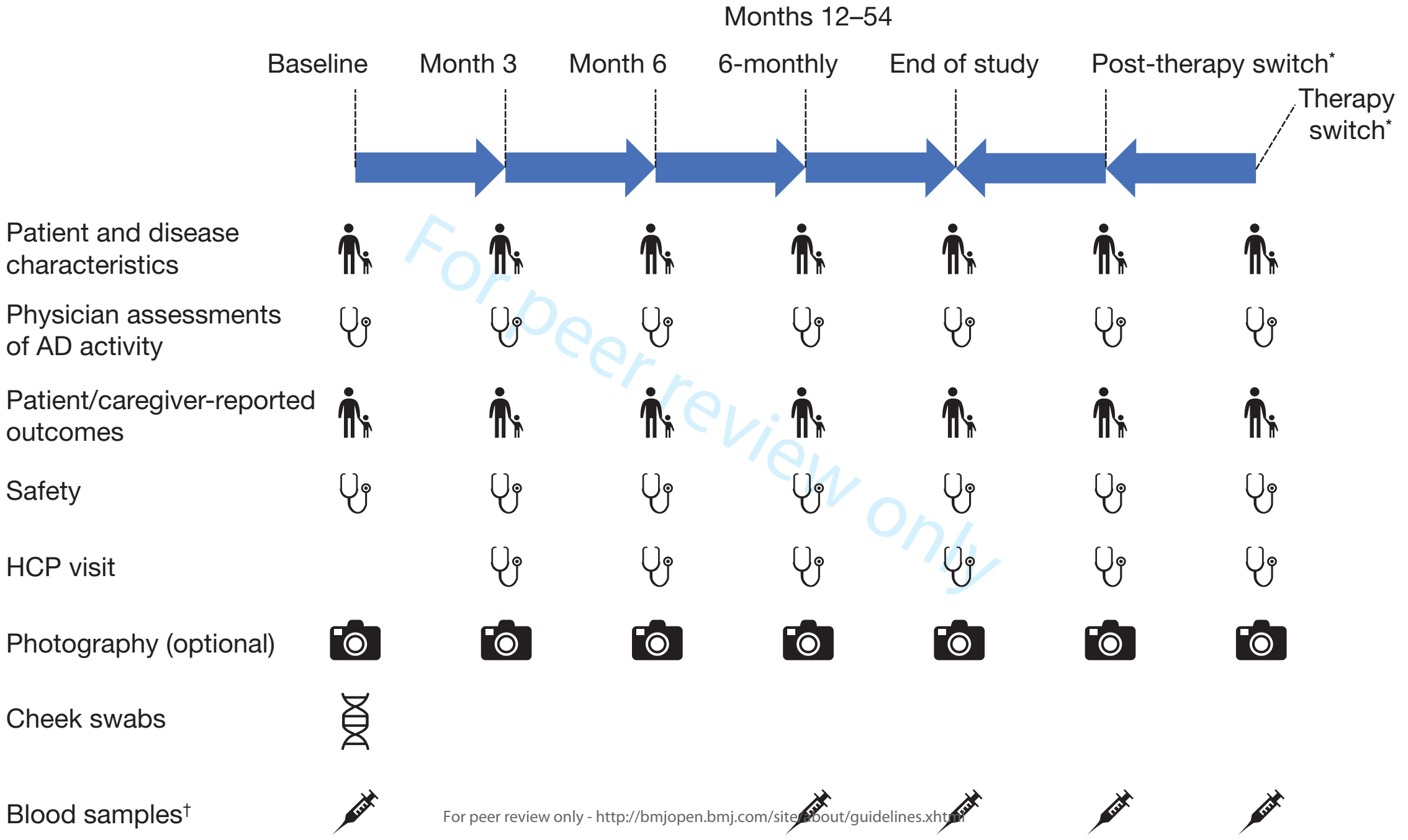
AD, atopic dermatitis; HCP, healthcare professional.

**Total duration:** 5 years

**Enrolment:** 2 years

**Visits:** 12 planned (according to standard of care)





SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | ItemNo | Description | Page |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | 2, 3, 6 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | |
| Protocol version | 3 | Date and version identifier | 6 |
| Funding | 4 | Sources and types of financial, material, and other support | 14–15 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 1, 15 |
| | 5b | Name and contact information for the trial sponsor | 1, 14 |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | 14–15 |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | 10, 15 |
| **Introduction** | | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 5–6 |
| | 6b | Explanation for choice of comparators | N/A |

| | | | |
|---|---|---|---|
| Objectives | 7 | Specific objectives or hypotheses | 5–6 |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | 6 |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 6, figure 1 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 6–7, table 1 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | N/A, observational |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | 6 |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | N/A, observational |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | N/A, observational |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | Page 8-9, table 2 |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | 8, figure 2 |

| | | | |
|---|---|---|---|
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 10–11, table 3 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | N/A |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | N/A, observational |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | N/A, observational |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | N/A, observational |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | N/A, observational |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | N/A, observational |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 8, 10 |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | N/A |

| | | | |
|---|---|---|---|
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | N/A |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 10 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | N/A |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | N/A, observational |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | N/A |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | N/A, observational |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | N/A, observational |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | N/A |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 7 |

| | | | |
|---|---|---|---|
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | N/A |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | N/A |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | N/A |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | N/A |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 14–15 |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | N/A |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | N/A, observational |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 10 |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | N/A |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | N/A |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | N/A |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

# A prospective, observational, longitudinal study in paediatric patients with moderate-to-severe atopic dermatitis (PEDISTAD): study objectives, design and methodology

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# A prospective, observational, longitudinal study in paediatric patients with moderate-to-severe atopic dermatitis (PEDISTAD): study objectives, design and methodology

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## ABSTRACT

**Introduction:** Atopic dermatitis (AD) is a chronic inflammatory skin disease often associated with atopic comorbidities and has significant impact on children and their families. There is a lack of robust and longitudinal long-term data on disease characteristics and typical clinical practice with currently available treatments in children with moderate-to-severe AD. Hence, an observational study is needed to evaluate AD characteristics and progression in paediatric patients with moderate-to-severe AD.

**Methods and analysis:** Pediatric Study in Atopic Dermatitis (PEDISTAD) is a prospective, observational, longitudinal study in paediatric patients with moderate-to-severe AD who are currently receiving systemic or topical treatment and whose disease is not adequately controlled by topical prescription therapies or for whom those therapies are not medically advisable. 1300 children at 100-150 sites in approximately 20 countries worldwide will be enrolled and followed for 5 years. AD therapy is at the discretion of the investigator. Data collected will include: AD disease characteristics and comorbidities; current therapy for AD and initiation of new treatments/changes in current treatment; patient-/caregiver-reported outcomes; days missed from school/work for the patient/caregiver; healthcare professional visits; safety; and biomarkers.

**Ethics and dissemination:** This study is conducted in accordance with the principles established by the 18th World Medical Assembly and all subsequent amendments and the guidelines for Good Epidemiology Practice. Each individual country assures that ethics approval has been received and local regulatory requirements are met. Study data will be disseminated in manuscripts submitted to peer-reviewed medical journals as well as in abstracts submitted to congresses, and in the resulting posters and presentations.

ClinicalTrials.gov Identifier: NCT03687359.


**Key words:** atopic dermatitis, observational, paediatric, systemic treatment

## Strengths and limitations of this study

- PEDISTAD is a multinational, observational, longitudinal study in a large cohort of paediatric patients with moderate-to-severe atopic dermatitis (AD) that will collect long-term data on patient and disease characteristics, progression of disease, selected atopic comorbidities, real-world treatment patterns, efficacy and safety.
- Previous observational studies in patients with AD have not focused on moderate-to-severe disease leading to a gap in knowledge that will be addressed by this study.
- The observational nature of the study limits the robustness of the collected data compared to that obtained from blinded studies with control groups.
- Challenges of the study include patient recruitment in multiple countries and retention of patients through the observation period of 5 years, both of which can be difficult in young children.

## INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin disease often associated with atopic comorbidities.[1,2] Due to lack of standardised diagnostic criteria and outcome measures of disease severity, there is variability in the reported prevalence rates of AD in children.

AD profoundly affects the quality of life of children and family members.[3] Itching can affect mood and sleep quality, and the chronic relapsing nature of AD has a detrimental impact on the quality of life of the family.[3] Children with AD may also have symptoms of anxiety and depression.[4]

Limited treatment options are available for children with moderate-to-severe AD and primarily include topical corticosteroids, topical calcineurin inhibitors, topical crisaborole and systemic immunosuppressants.[5-8] Most systemic agents are broadly immunosuppressive, used off-label and are not currently approved for use in children. In general, they do not provide a favourable long-term benefit–risk profile for paediatric patients with AD inadequately controlled by topical therapies. Furthermore, disease can often rebound after cessation of systemic therapy, especially after administration of systemic cyclosporine.[9]

There is a lack of robust and longitudinal long-term data related to disease characteristics and typical clinical practice with currently available treatments in children. Hence, an observational study is necessary to evaluate the characteristics of paediatric patients with moderate-to-severe AD whose disease is not adequately controlled with topical therapies or when those therapies are not medically advisable.

The Pediatric Study in Atopic Dermatitis (PEDISTAD) aims to address the substantial need for a better understanding of AD characteristics and progression, including patient and caregiver burden, in paediatric patients with moderate-to-severe AD who initiate, or are candidates for, systemic therapy. The study will document patient characteristics, patient- and caregiver-reported outcomes, AD progression, and atopic comorbidities and assess the effectiveness and safety of therapies (systemic and

topical) while describing real-world treatment patterns over a 5-year period. A biomarker sub-study will analyze the association between biomarkers and disease state and time course of AD in a subset of PEDISTAD study participants. Here we describe the objectives, design and endpoints of the PEDISTAD.

## METHODS AND ANALYSIS

PEDISTAD is an international, multicentre, longitudinal, prospective, non-interventional study designed to describe the disease life course and comorbidities of paediatric patients with moderate-to-severe AD whose disease is not adequately controlled with topical therapies or for whom those therapies are not medically advisable (NCT03687359, study OBS15333, protocol version 1, 01 May 2018 and sub-study LPS15496, protocol version 1, 10 April 2018). Current participating sites are listed in the Clinicaltrials.Gov record.

### Patients

This study will enrol a balanced number of patients aged <2 years, ≥2 to <6 years and ≥6 to <12 years at baseline. Enrolment quotas with respect to treatment types (systemic vs topical) may be imposed to ensure target numbers of patients in each treatment category. To minimise patient selection bias, all eligible patients at each selected site should be invited to participate in this registry, until the global enrolment goal or the site enrolment limit is met.

AD therapy prescribed to patients who are enrolled in the study is not dictated per study protocol, and the therapeutic drug prescription is decided by the medical judgement of the study investigator. Patients may begin treatment with therapies that become commercially available during the course of the study.

Inclusion and exclusion criteria are reported in table 1. Briefly, patients are eligible for the study if they are <12 years of age at baseline, have investigator-assessed moderate-to-severe disease and are

either receiving systemic treatment for AD (including biologics (currently used off-label), UV therapy, and immunomodulators such as cyclosporine, azathioprine, methotrexate, mycophenolate mofetil, and corticosteroids) or are currently on topical treatment but would otherwise be candidates for systemic therapy (systemic therapies do not include systemic antihistamines).

**Table 1** Inclusion and exclusion criteria

| | |
|---|---|
| **Inclusion criteria** | • Male or female <12 years of age at baseline<br>• Patients with moderate-to-severe AD according to the investigator's assessment<br>• Treatment<br>  – Currently receiving systemic treatment (including biologics (currently used off-label), UV therapy, cyclosporine, azathioprine, methotrexate, mycophenolate mofetil, and corticosteroids) for AD or<br>  – Currently on topical treatment, but otherwise candidates for systemic treatment due to<br>  ▪ Lack of adequate control and/or<br>  ▪ Safety concern with long-term topical treatment<br>• Signed informed consent by the parent/legally acceptable representative and assent by the patient appropriate to the patient's age, including willingness to participate in long-term follow-up |
| **Exclusion criteria** | • Concurrent participation in an interventional clinical trial that modifies patient care |

AD, atopic dermatitis.

**Ethics and Dissemination**

This study is being conducted in accordance with the principles established by the 18th World Medical Assembly and all subsequent amendments and in accordance with the guidelines for Good Epidemiology

Practice. Each participating country should locally ensure all necessary regulatory submissions (for example, Institutional Review Board/Institutional Ethics Committee) are performed in accordance with local regulations, including local data protection regulations.

The study team and the study steering and scientific committees are responsible for study reporting and interpretation, including interim data analyses and sub-group analyses. The data from the PEDISTAD study will be disseminated in manuscripts for submission to peer-reviewed medical journals as well as in abstracts for submission to congresses and in the resulting posters and presentations. The final decision to publish will be made by the study scientific steering committee after prior notice to the sponsor to allow for its internal review and comments.

**Patient and public involvement**

Patients and the public were not involved in the design of this study.

**Study locations and timings**

Approximately 100-150 sites in approximately 20 countries are expected to enrol 1300 patients (figure 1). Patient enrolment is expected to take 2 years, and the study duration for each patient is 5 years. A total of 12 visits are planned for each enrolled patient. The study began on 28 September 2018 and is expected to be completed in September 2025.

**Study endpoints and data collection**

The primary and secondary objectives of the PEDISTAD are reported in table 2.

**Table 2** Primary and secondary objectives

| | |
|---|---|
| **Primary objectives** | • To describe the characteristics of pediatric patients with moderate to severe AD whose disease is not adequately controlled with topical therapies or when those therapies are not medically advisable<br>• To evaluate the time course of AD and selected atopic comorbidities |
| **Secondary objectives** | • To characterize disease burden and unmet need<br>• To describe real-world treatment patterns (e.g., dosing regimens, treatment duration, and reasons for discontinuation and/or switching)<br>• To document the real-world effectiveness and safety of treatments |

AD, atopic dermatitis.

Data collected will include: demographics; AD disease characteristics at baseline; the presence of selected comorbidities at baseline; time course of conditions including AD; current therapy for AD and initiation of new treatments/changes in current treatment over time; severity of disease at baseline and over the follow-up period (as assessed by Eczema Area and Severity Index (EASI) and Body Surface Area (BSA) percentage affected by atopic dermatitis, which the study investigators can use to assess disease severity at baseline); patient-/caregiver-reported outcomes at baseline and over the follow-up period; days missed from school for the patient and days missed from work for the primary caregiver due to AD; visits to healthcare professionals; disease state and evolution of selected atopic comorbid conditions; and photography of a representative area affected by AD at select centres and safety. The association between biomarkers and disease state and time course of AD will be examined by a biomarker sub-study collecting blood samples for analysis of protein and RNA biomarkers and cheek swabs for DNA genomic biomarkers. The data being collected in PEDISTAD are summarised in table 3, and the timings for data collection are shown in figure 2.

**Table 3** Data being collected in PEDISTAD

| Type | Collected data |
|---|---|
| **Patient and disease characteristics** | • Patient demographics and medical history<br>• Personal and family history of AD and selected atopic comorbidities<br>• Prior and concomitant medications for AD and comorbidities—all prior systemic therapy ever used, all topical and UV therapy in the previous 3 months as well as treatment(s) for other diseases including name, dose, route, frequency and start/stop date<br>• Selected comorbidity presence throughout the study (as diagnosed by an HCP) |
| **Patient-/caregiver-reported outcomes** | • POEM<br>• CDLQI/IDQOL<br>• DFI<br>• Peak Pruritus NRS/Worst scratching NRS<br>• CGAD<br>• Days missed from school for the patient and days missed from work for the primary caregiver due to AD since last visit<br>• TNSS |
| **Physician assessments of AD disease activity** | • EASI<br>• BSA (%) affected by AD |
| **Safety data** | • All adverse events regardless of seriousness |
| **Other data** | • Visits to HCPs—type of HCP and reason for the visit<br>• Investigator specialty and setting<br>• Photography of a representative area affected by AD—optional (at select centres)<br>• Reason for end of study |
| **Biomarker data** | • Serial blood samples for protein and RNA expression<br>• Cheek swabs for DNA genomic biomarkers |

AD, atopic dermatitis; BSA, body surface area; CGAD, Caregiver Global Assessment of Disease; CDLQI, Children's Dermatology Life Quality Index; DFI, Dermatitis Family Impact; EASI, Eczema Area and Severity Index; HCP, healthcare professional; IDQOL, Infant's Dermatitis Quality of Life; NRS, Numerical Rating Scale; POEM, Patient-Oriented Eczema Measure; TNSS, Total Nasal Symptom Score.

**Statistical analysis**

Sample size

To ensure that approximately 930 patients complete the 5-year follow-up, approximately 1300 patients will be enrolled (about 435 in each age group). A sample of approximately 310 participants per age group will ensure a maximum width for the confidence interval of 11% for the estimates based on binary endpoints (table 4). This sample size needed requires that a total of 930 patients complete the study. The biomarker sub-study will be conducted in approximately 300 participants (100 participants within each age cohort), whose sample size is based empirically on the results of a previous biomarker study with similar objectives.[10]

**Table 4** Precision estimates for the overall population

| **Width of the 95% CI** | **Overall population N=930** | **33% of overall population N=310** |
|---|---|---|
| Binary data–widest width | 6.4% | 11.1% |
| Normal data | 0.13 SD | 0.22 SD |

CI, confidence interval; SD, standard deviation.

Analysis

All statistical analyses will be performed descriptively with no hypothesis testing. Patient- and care-giver reported outcomes will be summarised within each age cohort, as many are age-based assessments.

Continuous data will be described using summary statistics, including arithmetic mean, standard deviation, median and range, while categorical data will be summarised using counts and percentages.

## DISCUSSION

The PEDISTAD study aims to address the lack of robust and longitudinal long-term data related to AD characteristics, disease progression, development of comorbidities and the typical clinical practice with currently available treatments in children with AD. By collecting information about clinical characteristics, including patient- and care-giver reported outcomes, physician-assessed clinical severity, safety of currently used medicines and photographs of a representative area affected by AD (at select centres), over time, the PEDISTAD study aims to bridge this knowledge gap. A biomarker sub-study of PEDISTAD will analyze the association between biomarkers and disease state and time course of AD in a sub-set of PEDISTAD study participants.

There are various disease trajectories in paediatric patients with AD, and clinical presentation varies with different ages of onset and development of comorbid atopic conditions.[11,12] Patients in this study will, hence, be recruited into 3 age cohorts (<2 years, ≥2 to <6 years and ≥6 to <12) and followed for 5 years.

The PEDISTAD is a real-world study and, therefore, strict entry criteria are not set. Enrolling physicians are enabled to use their best judgement as to whether a patient meets the inclusion criteria of moderate-to-severe AD using the assessment(s) of their choice. Physician assessment of disease severity will be collected by Eczema Area and Severity Index (EASI) and Body Surface Area (BSA) percentage affected by atopic dermatitis, which the study investigators can use to assess disease severity at baseline. These assessments can also later be used to assess disease severity in patients over time. Other objective measures of severity may be unfamiliar to clinicians who do not regularly

participate in clinical trials in atopic dermatitis, and a lack of familiarity may potentially diminish the reliability of their results.

A significant proportion of children have persistent disease;[12,13] thus, treatment approaches that are effective and tolerated over large timespans are desired. The observational and long-term nature of the PEDISTAD study serves to better understand the long-term evolution of disease burden in patients and caregivers as well as to identify any unmet therapeutic need for moderate-to-severe AD.

Although there are no universal definitions of recalcitrance in AD patients, expert recommendations mention that failure to respond to adequate topical therapy, a need for prolonged use of high-potency topical steroids or repeated flares are suggestive of recalcitrance and make a patient eligible for systemic therapy.[14] This observational study will provide insight into the characteristics of paediatric patients initiated on or who become candidates for systemic therapy to better define when systemic therapy is warranted.

Paediatric AD presents clinically with a high degree of heterogeneity. In addition to the clinical phenotype, biomarkers and endophenotypes are now considered fundamental to stratify complex diseases into subgroups for which more tailored prevention and therapeutic strategies can be developed. Due to the waxing and waning nature of AD and the fact that it can present throughout a lifetime with long periods of remission in some individuals, the ability to predict disease exacerbations or the appearance of associated atopic conditions using biomarkers could have a great impact in the ability to manage the disease for long-term control. For this reason, a biomarker substudy in parallel with the PEDISTAD study will collect blood samples with the objectives of exploring associations between biomarkers of AD and disease state and time course of AD; disease state and evolution of selected atopic comorbid conditions; and effectiveness of specific AD treatments.

Observational studies in patients with AD to date have been limited by a variety of factors, including number of participants, participating countries and the extent and duration of data collection. The

PEDISTAD study aims to address all these issues. Furthermore, the PEDISTAD study will be the largest study to date in a paediatric population with moderate-to-severe AD; by not focusing on moderate-to-severe disease, other observational studies may have underestimated the risk of comorbidities and disease persistence in this patient population.

Limitations of the PEDISTAD study include the open-label observational nature; thus, the collected data may not be as robust as blinded studies with control groups. However, the challenges of running long-term controlled studies, especially in this age group, are well known, and a control group may not be crucial to fulfil the objectives of this study. Therefore, the data from this study are anticipated to be highly valuable. Challenges include patient recruitment in multiple countries and sites and retention of patients in this age group for up to 5 years, which is particularly difficult in very young children. Parental education will be key to keeping patients enrolled in the study and to provide robust and reliable patient-, caregiver- and physician-reported outcomes at reasonable intervals.

In summary, PEDISTAD will improve our understanding of the long-term evolution of AD, disease burden in patients and caregivers and the impact of therapy on paediatric patients with moderate-to-severe AD and their families.

**Competing interests**

**ASP:** AbbVie, AnaptysBio, Eli Lilly, Galderma, Incyte, Janssen, LEO Pharma, Novartis, Regeneron Pharmaceuticals, Inc., Sanofi – investigator; AbbVie, Amgen, Asana, Dermavant, Dermira, Galderma, Eli Lilly, Forte, LEO Pharma, Matrisys Bioscience, Menlo Therapeutics, Morphosys/Galapagos, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc., Sanofi – consultant.

**EG-Y:** AbbVie, Celgene, Eli Lilly, Galderma, GlaxoSmithKline, Glenmark, LEO Pharma, Pfizer, Regeneron Pharmaceuticals, Inc., Sanofi – investigator; AbbVie, Anacor, Asana Biosciences, Daiichi Sankyo, DBV, Dermira, Eli Lilly, Galderma, GlaxoSmithKline, Glenmark, Kiniksa Pharmaceuticals, Kyowa, LEO Pharma, Menlo Therapeutics, Novartis, Pfizer, Realm, Regeneron Pharmaceuticals, Inc., Sanofi – consultant; AbbVie, Celgene, Dermira, Galderma, Innovaderm, Janssen, LEO Pharma, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc., Sanofi – research grants.

**ADI:** AbbVie, Chugai Pharma, Genentech, Janssen, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc., Sanofi Genzyme – consultant.

**EB:** Almirall – speaker; AbbVie, Eli Lilly, Pfizer – investigator; Pierre Fabre Dermatology – investigator, consultant; Regeneron Pharmaceuticals, Inc., Sanofi Genzyme – consultant; Venthera – co-founder, consultant.

**MdeB-W:** Regeneron Pharmaceuticals, Inc., Sanofi Genzyme – investigator, advisory board member, speaker, consultant; AbbVie, Pfizer – investigator, advisory board member; Eli Lilly, UCB – advisory board member

**SJ, AZ, ER, ZEO:** Sanofi – employees, may hold stock and/or stock options in the company.

**PM-O:** Regeneron Pharmaceuticals, Inc. – employee and shareholder.

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**Contributors to the protocol**

ASP, EG-Y, ADI, EB, MdeB-W were involved in design of the study and are active steering committee members for the study.

SJ contributed to the design and development of the protocol and is the statistical lead.

AZ, PM-O, ER, ZEO contributed to the design and development of the protocol and are medical leads.

All authors critically revised the manuscript, gave final approval of the manuscript, and are accountable for the accuracy and integrity of the manuscript.

## REFERENCES

1. Shrestha S, Miao R, Wang L, *et al*. Burden of atopic dermatitis in the United States: Analysis of healthcare claims data in the Commercial, Medicare, and Medi-Cal databases. *Adv Ther* 2017;34:1989–2006.
2. Weidinger S, Beck LA, Beiber T, *et al*. Atopic dermatitis. *Nat Rev Dis Primers* 2018;4:1.
3. Ricci G, Bellini F, Dondi A, *et al*. Atopic dermatitis in adolescence. *Dermatol Reports* 2011;4:e1
4. Rønnstad ATM, Halling-Overgaard AS, Hamann CR, et al. Association of atopic dermatitis with depression, anxiety, and suicidal ideation in children and adults: A systematic review and meta-analysis. *J Am Acad Dermatol* 2018;79:448–56.
5. Wollenberg A, Oranje A, Deleuran M, *et al*. ETFAD/EADV Eczema task force 2015 position paper on diagnosis and treatment of atopic dermatitis in adult and paediatric patients. *J Eur Acad Dermatol Venereol* 2016;30:729–47.
6. Sidbury R, Tom WL, Bergman JN, *et al*. Guidelines of care for the management of atopic dermatitis: Section 4. Prevention of disease flares and use of adjunctive therapies and approaches. *J Am Acad Dermatol* 2014;71:1218–33.
7. Ring J, Alomar A, Bieber T, *et al*. Guidelines for treatment of atopic eczema (atopic dermatitis) Part II. *J Eur Acad Dermatol Venereol* 2012;26:1176–93.
8. EUCRISA. Highlights of Prescribing Information, FDA 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/207695s002lbl.pdf. (accessed 4 January 2019).
9. Sibbald C, Pope E, Ho N, *et al*. Retrospective review of relapse after systemic cyclosporine in children with atopic dermatitis. *Pediatr Dermatol* 2015;32:36–40.

10. Thijs JL, Strickland I, Bruijnzeel-Koomen CAFM, *et al.* Moving toward endotypes in atopic dermatitis: Identification of patient clusters based on serum biomarker analysis. *J Allergy Clin Immunol* 2017;140:730–7.
11. Irvine AD, Mina-Osorio P. Disease trajectories in childhood atopic dermatitis: an update and practitioner's guide. *Br J Dermatol* doi: 10.1111/bjd.17766. [published Online First 13 February 2019].
12. Paller AS, Spergel JM, Mina-Osorio P, *et al*. The atopic march and atopic multimorbidity: Many trajectories, many pathways. *J Allergy Clin Immunol* 2019; 143:46–55.
13. Kim JP, Chao LX, Simpson EL, *et al*. Persistence of atopic dermatitis (AD): a systematic review and meta-analysis. *J Am Acad Dermatol* 2016;75:681–7.
14. Simpson EL, Bruin-Weller M, Flohr C, *et al*. When does atopic dermatitis warrant systemic therapy? Recommendations from an expert panel of the International Eczema Council. *J Am Acad Dermatol* 2017;77:623–33.

**Figure legends**

**Figure 1** Patients and study locations

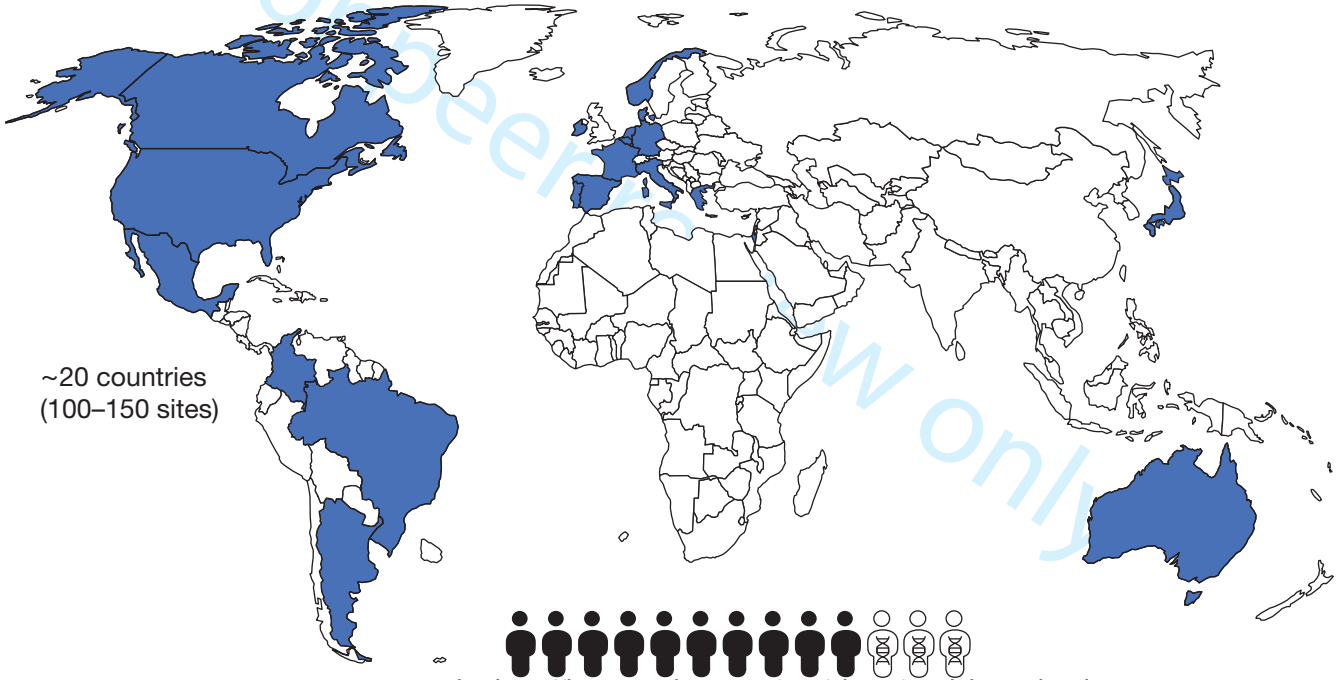
**Figure 2** Data collection schedule

AD, atopic dermatitis; HCP, healthcare professional.

**Total duration:** 5 years

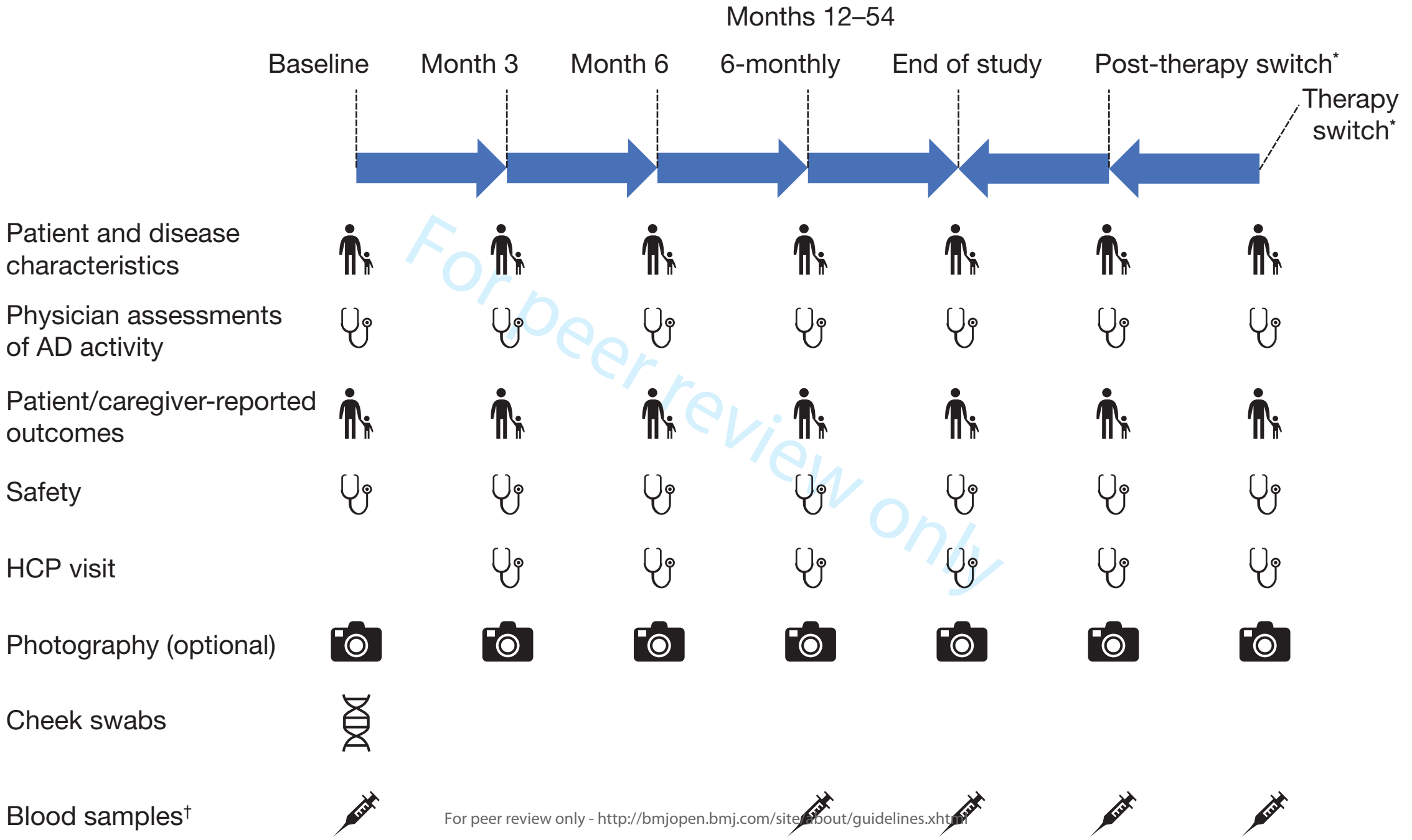
**Enrolment:** 2 years

**Visits:** 12 planned (according to standard of care)






1,300 patients (300 for biomarker study)




SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | ItemNo | Description | Page |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | 2, 3, 6 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | |
| Protocol version | 3 | Date and version identifier | 6 |
| Funding | 4 | Sources and types of financial, material, and other support | 14–15 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 1, 15 |
| | 5b | Name and contact information for the trial sponsor | 1, 14 |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | 14–15 |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | 10, 15 |
| **Introduction** | | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 5–6 |
| | 6b | Explanation for choice of comparators | N/A |

| | | | |
|---|---|---|---|
| Objectives | 7 | Specific objectives or hypotheses | 5–6 |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | 6 |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 6, figure 1 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 6–7, table 1 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | N/A, observational |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | 6 |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | N/A, observational |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | N/A, observational |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | Page 8-9, table 2 |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | 8, figure 2 |

| | | | |
|---|---|---|---|
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 10–11, table 3 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | N/A |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | N/A, observational |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | N/A, observational |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | N/A, observational |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | N/A, observational |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | N/A, observational |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 8, 10 |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | N/A |

| | | | |
|---|---|---|---|
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | N/A |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 10 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | N/A |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | N/A, observational |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | N/A |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | N/A, observational |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | N/A, observational |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | N/A |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 7 |

| | | | |
|---|---|---|---|
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | N/A |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | N/A |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | N/A |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | N/A |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 14–15 |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | N/A |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | N/A, observational |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 10 |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | N/A |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | N/A |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | N/A |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

# A prospective, observational, longitudinal study in paediatric patients with moderate-to-severe atopic dermatitis (PEDISTAD): study objectives, design and methodology: a study protocol



| | |
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# A prospective, observational, longitudinal study in paediatric patients with moderate-to-severe atopic dermatitis (PEDISTAD): study objectives, design and methodology: a study protocol

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**Figures:** 2

**Tables:** 4

## ABSTRACT

**Introduction:** Atopic dermatitis (AD) is a chronic inflammatory skin disease often associated with atopic comorbidities and has significant impact on children and their families. There is a lack of robust and longitudinal long-term data on disease characteristics and typical clinical practice with currently available treatments in children with moderate-to-severe AD. Hence, an observational study is needed to evaluate AD characteristics and progression in paediatric patients with moderate-to-severe AD.

**Methods and analysis:** Pediatric Study in Atopic Dermatitis (PEDISTAD) is a prospective, observational, longitudinal study in paediatric patients with moderate-to-severe AD who are currently receiving systemic or topical treatment and whose disease is not adequately controlled by topical prescription therapies or for whom those therapies are not medically advisable. 1300 children at 100–150 sites in approximately 20 countries worldwide will be enrolled and followed for 5 years. AD therapy is at the discretion of the investigator. Data collected will include: AD disease characteristics and comorbidities; current therapy for AD and initiation of new treatments/changes in current treatment; patient-/caregiver-reported outcomes; days missed from school/work for the patient/caregiver; healthcare professional visits; safety; and biomarkers.

**Ethics and dissemination:** This study is conducted in accordance with the principles established by the 18th World Medical Assembly and all subsequent amendments and the guidelines for Good Epidemiology Practice. Each individual country assures that ethics approval has been received and local regulatory requirements are met. Ethics approval has been obtained in all countries currently participating in PEDISTAD. Study data will be disseminated in manuscripts submitted to peer-reviewed medical journals as well as in abstracts submitted to congresses, and in the resulting posters and presentations.

ClinicalTrials.gov Identifier: NCT03687359.

**Key words:** atopic dermatitis, observational, paediatric, systemic treatment

## Strengths and limitations of this study

- PEDISTAD is a multinational, observational, longitudinal study in a large cohort of paediatric patients with moderate-to-severe atopic dermatitis (AD) that will collect long-term data on patient and disease characteristics, progression of disease, selected atopic comorbidities, real-world treatment patterns, efficacy and safety.
- Previous observational studies in patients with AD have not focused on moderate-to-severe disease leading to a gap in knowledge that will be addressed by this study.
- The observational nature of the study limits the robustness of the collected data compared to that obtained from blinded studies with control groups.
- Challenges of the study include patient recruitment in multiple countries and retention of patients through the observation period of 5 years, both of which can be difficult in young children.

## INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin disease often associated with atopic comorbidities.[1,2] Due to lack of standardised diagnostic criteria and outcome measures of disease severity, there is variability in the reported prevalence rates of AD in children.

AD profoundly affects the quality of life of children and family members.[3] Itching can affect mood and sleep quality, and the chronic relapsing nature of AD has a detrimental impact on the quality of life of the family.[3] Children with AD may also have symptoms of anxiety and depression.[4]

Limited treatment options are available for children with moderate-to-severe AD and primarily include topical corticosteroids, topical calcineurin inhibitors, topical crisaborole and systemic immunosuppressants.[5-8] Most systemic agents are broadly immunosuppressive, used off-label and are not currently approved for use in children. In general, they do not provide a favourable long-term benefit–risk profile for paediatric patients with AD inadequately controlled by topical therapies. Furthermore, disease can often rebound after cessation of systemic therapy, especially after administration of systemic cyclosporine.[9]

There is a lack of robust and longitudinal long-term data related to disease characteristics and typical clinical practice with currently available treatments in children. Hence, an observational study is necessary to evaluate the characteristics of paediatric patients with moderate-to-severe AD whose disease is not adequately controlled with topical therapies or when those therapies are not medically advisable.

The Pediatric Study in Atopic Dermatitis (PEDISTAD) aims to address the substantial need for a better understanding of AD characteristics and progression, including patient and caregiver burden, in paediatric patients with moderate-to-severe AD who initiate, or are candidates for, systemic therapy. The study will document patient characteristics, patient- and caregiver-reported outcomes, AD progression, and atopic comorbidities and assess the effectiveness and safety of therapies (systemic and

topical) while describing real-world treatment patterns over a 5-year period. A biomarker sub-study will analyze the association between biomarkers and disease state and time course of AD in a subset of PEDISTAD study participants. Here we describe the objectives, design and endpoints of the PEDISTAD.

## METHODS AND ANALYSIS

PEDISTAD is an international, multicentre, longitudinal, prospective, non-interventional study designed to describe the disease life course and comorbidities of paediatric patients with moderate-to-severe AD whose disease is not adequately controlled with topical therapies or for whom those therapies are not medically advisable (NCT03687359, study OBS15333, protocol version 1, 01 May 2018 and sub-study LPS15496, protocol version 1, 10 April 2018). Current participating sites are listed in the Clinicaltrials.Gov record.

### Patients

This study will enrol a balanced number of patients aged <2 years, ≥2 to <6 years and ≥6 to <12 years at baseline. Enrolment quotas with respect to treatment types (systemic vs topical) may be imposed to ensure target numbers of patients in each treatment category. To minimise patient selection bias, all eligible patients at each selected site should be invited to participate in this registry, until the global enrolment goal or the site enrolment limit is met.

AD therapy prescribed to patients who are enrolled in the study is not dictated per study protocol, and the therapeutic drug prescription is decided by the medical judgement of the study investigator. Patients may begin treatment with therapies that become commercially available during the course of the study.

Inclusion and exclusion criteria are reported in table 1. Briefly, patients are eligible for the study if they are <12 years of age at baseline, have investigator-assessed moderate-to-severe disease and are

either receiving systemic treatment for AD (including biologics (currently used off-label), UV therapy, and immunomodulators such as cyclosporine, azathioprine, methotrexate, mycophenolate mofetil, and corticosteroids) or are currently on topical treatment but would otherwise be candidates for systemic therapy (systemic therapies do not include systemic antihistamines).

**Table 1** Inclusion and exclusion criteria

| | |
|---|---|
| **Inclusion criteria** | • Male or female <12 years of age at baseline<br>• Patients with moderate-to-severe AD according to the investigator's assessment<br>• Treatment<br>— Currently receiving systemic treatment (including biologics (currently used off-label), UV therapy, cyclosporine, azathioprine, methotrexate, mycophenolate mofetil, and corticosteroids) for AD or<br>— Currently on topical treatment, but otherwise candidates for systemic treatment due to<br>▪ Lack of adequate control and/or<br>▪ Safety concern with long-term topical treatment<br>• Signed informed consent by the parent/legally acceptable representative and assent by the patient appropriate to the patient's age, including willingness to participate in long-term follow-up |
| **Exclusion criteria** | • Concurrent participation in an interventional clinical trial that modifies patient care |

AD, atopic dermatitis.

**Patient and public involvement**

Patients and the public were not involved in the design of this study.

**Study locations and timings**

Approximately 100–150 sites in approximately 20 countries are expected to enrol 1300 patients (figure 1). Patient enrolment is expected to take 2 years, and the study duration for each patient is 5 years. A total of 12 visits are planned for each enrolled patient. The study began on 28 September 2018 and is expected to be completed in September 2025.

**Study endpoints and data collection**

The primary and secondary objectives of the PEDISTAD are reported in table 2.

**Table 2** Primary and secondary objectives

| | |
|---|---|
| **Primary objectives** | • To describe the characteristics of pediatric patients with moderate to severe AD whose disease is not adequately controlled with topical therapies or when those therapies are not medically advisable<br>• To evaluate the time course of AD and selected atopic comorbidities |
| **Secondary objectives** | • To characterize disease burden and unmet need<br>• To describe real-world treatment patterns (e.g., dosing regimens, treatment duration, and reasons for discontinuation and/or switching)<br>• To document the real-world effectiveness and safety of treatments |

AD, atopic dermatitis.

Data collected will include: demographics; AD disease characteristics at baseline; the presence of selected comorbidities at baseline; time course of conditions including AD; current therapy for AD and initiation of new treatments/changes in current treatment over time; severity of disease at baseline and

over the follow-up period (as assessed by Eczema Area and Severity Index (EASI) and Body Surface Area (BSA) percentage affected by atopic dermatitis, which the study investigators can use to assess disease severity at baseline); patient-/caregiver-reported outcomes at baseline and over the follow-up period; days missed from school for the patient and days missed from work for the primary caregiver due to AD; visits to healthcare professionals; disease state and evolution of selected atopic comorbid conditions; and photography of a representative area affected by AD at select centres and safety. The association between biomarkers and disease state and time course of AD will be examined by a biomarker sub-study collecting blood samples for analysis of protein and RNA biomarkers and cheek swabs for DNA genomic biomarkers. The data being collected in PEDISTAD are summarised in table 3, and the timings for data collection are shown in figure 2.

**Table 3** Data being collected in PEDISTAD

| **Type** | **Collected data** |
|---|---|
| **Patient and disease characteristics** | • Patient demographics and medical history<br>• Personal and family history of AD and selected atopic comorbidities<br>• Prior and concomitant medications for AD and comorbidities—all prior systemic therapy ever used, all topical and UV therapy in the previous 3 months as well as treatment(s) for other diseases including name, dose, route, frequency and start/stop date<br>• Selected comorbidity presence throughout the study (as diagnosed by an HCP) |
| **Patient-/caregiver-reported outcomes** | • POEM<br>• CDLQI/IDQOL<br>• DFI<br>• Peak Pruritus NRS/Worst scratching NRS |

| | |
|---|---|
| | • CGAD<br>• Days missed from school for the patient and days missed from work for the primary caregiver due to AD since last visit<br>• TNSS |
| **Physician assessments of AD disease activity** | • EASI<br>• BSA (%) affected by AD |
| **Safety data** | • All adverse events regardless of seriousness |
| **Other data** | • Visits to HCPs—type of HCP and reason for the visit<br>• Investigator specialty and setting<br>• Photography of a representative area affected by AD—optional (at select centres)<br>• Reason for end of study |
| **Biomarker data** | • Serial blood samples for protein and RNA expression<br>• Cheek swabs for DNA genomic biomarkers |

AD, atopic dermatitis; BSA, body surface area; CGAD, Caregiver Global Assessment of Disease; CDLQI, Children's Dermatology Life Quality Index; DFI, Dermatitis Family Impact; EASI, Eczema Area and Severity Index; HCP, healthcare professional; IDQOL, Infant's Dermatitis Quality of Life; NRS, Numerical Rating Scale; POEM, Patient-Oriented Eczema Measure; TNSS, Total Nasal Symptom Score.

**Statistical analysis**

Sample size

To ensure that approximately 930 patients complete the 5-year follow-up, approximately 1300 patients will be enrolled (about 435 in each age group). A sample of approximately 310 participants per age group will ensure a maximum width for the confidence interval of 11% for the estimates based on binary endpoints (table 4). This sample size needed requires that a total of 930 patients complete the study. The biomarker sub-study will be conducted in approximately 300 participants (100 participants within

each age cohort), whose sample size is based empirically on the results of a previous biomarker study with similar objectives.[10]

**Table 4** Precision estimates for the overall population

| **Width of the 95% CI** | **Overall population N=930** | **33% of overall population N=310** |
|---|---|---|
| Binary data–widest width | 6.4% | 11.1% |
| Normal data | 0.13 SD | 0.22 SD |

CI, confidence interval; SD, standard deviation.

Analysis

All statistical analyses will be performed descriptively with no hypothesis testing. Patient- and care-giver reported outcomes will be summarised within each age cohort, as many are age-based assessments. Continuous data will be described using summary statistics, including arithmetic mean, standard deviation, median and range, while categorical data will be summarised using counts and percentages.

## ETHICS AND DISSEMINATION

This study is being conducted in accordance with the principles established by the 18th World Medical Assembly and all subsequent amendments and in accordance with the guidelines for Good Epidemiology Practice. Each participating country should locally ensure all necessary regulatory submissions (for example, Institutional Review Board/Institutional Ethics Committee) are performed in accordance with local regulations, including local data protection regulations. Ethics approval has been obtained in all countries currently participating in PEDISTAD. A list of all ethics approvals received as of 20 December 2019 is provided as supplementary file.

The study team and the study steering and scientific committees are responsible for study reporting and interpretation, including interim data analyses and sub-group analyses. The data from the PEDISTAD study will be disseminated in manuscripts for submission to peer-reviewed medical journals as well as in abstracts for submission to congresses and in the resulting posters and presentations. The final decision to publish will be made by the study scientific steering committee after prior notice to the sponsor to allow for its internal review and comments.

## DISCUSSION

The PEDISTAD study aims to address the lack of robust and longitudinal long-term data related to AD characteristics, disease progression, development of comorbidities and the typical clinical practice with currently available treatments in children with AD. By collecting information about clinical characteristics, including patient- and care-giver reported outcomes, physician-assessed clinical severity, safety of currently used medicines and photographs of a representative area affected by AD (at select centres), over time, the PEDISTAD study aims to bridge this knowledge gap. A biomarker sub-study of PEDISTAD will analyze the association between biomarkers and disease state and time course of AD in a sub-set of PEDISTAD study participants.

There are various disease trajectories in paediatric patients with AD, and clinical presentation varies with different ages of onset and development of comorbid atopic conditions.[11,12] Patients in this study will, hence, be recruited into 3 age cohorts (<2 years, ≥2 to <6 years and ≥6 to <12) and followed for 5 years.

The PEDISTAD is a real-world study and, therefore, strict entry criteria are not set. Enrolling physicians are enabled to use their best judgement as to whether a patient meets the inclusion criteria of moderate-to-severe AD using the assessment(s) of their choice. Physician assessment of disease severity will be collected by Eczema Area and Severity Index (EASI) and Body Surface Area (BSA)

percentage affected by atopic dermatitis, which the study investigators can use to assess disease severity at baseline. These assessments can also later be used to assess disease severity in patients over time. Other objective measures of severity may be unfamiliar to clinicians who do not regularly participate in clinical trials in atopic dermatitis, and a lack of familiarity may potentially diminish the reliability of their results.

A significant proportion of children have persistent disease;[12,13] thus, treatment approaches that are effective and tolerated over large timespans are desired. The observational and long-term nature of the PEDISTAD study serves to better understand the long-term evolution of disease burden in patients and caregivers as well as to identify any unmet therapeutic need for moderate-to-severe AD.

Although there are no universal definitions of recalcitrance in AD patients, expert recommendations mention that failure to respond to adequate topical therapy, a need for prolonged use of high-potency topical steroids or repeated flares are suggestive of recalcitrance and make a patient eligible for systemic therapy.[14] This observational study will provide insight into the characteristics of paediatric patients initiated on or who become candidates for systemic therapy to better define when systemic therapy is warranted.

Paediatric AD presents clinically with a high degree of heterogeneity. In addition to the clinical phenotype, biomarkers and endophenotypes are now considered fundamental to stratify complex diseases into subgroups for which more tailored prevention and therapeutic strategies can be developed. Due to the waxing and waning nature of AD and the fact that it can present throughout a lifetime with long periods of remission in some individuals, the ability to predict disease exacerbations or the appearance of associated atopic conditions using biomarkers could have a great impact in the ability to manage the disease for long-term control. For this reason, a biomarker substudy in parallel with the PEDISTAD study will collect blood samples with the objectives of exploring associations

between biomarkers of AD and disease state and time course of AD; disease state and evolution of selected atopic comorbid conditions; and effectiveness of specific AD treatments.

Observational studies in patients with AD to date have been limited by a variety of factors, including number of participants, participating countries and the extent and duration of data collection. The PEDISTAD study aims to address all these issues. Furthermore, the PEDISTAD study will be the largest study to date in a paediatric population with moderate-to-severe AD; by not focusing on moderate-to-severe disease, other observational studies may have underestimated the risk of comorbidities and disease persistence in this patient population.

Limitations of the PEDISTAD study include the open-label observational nature; thus, the collected data may not be as robust as blinded studies with control groups. However, the challenges of running long-term controlled studies, especially in this age group, are well known, and a control group may not be crucial to fulfil the objectives of this study. Therefore, the data from this study are anticipated to be highly valuable. Challenges include patient recruitment in multiple countries and sites and retention of patients in this age group for up to 5 years, which is particularly difficult in very young children. Parental education will be key to keeping patients enrolled in the study and to provide robust and reliable patient-, caregiver- and physician-reported outcomes at reasonable intervals.

In summary, PEDISTAD will improve our understanding of the long-term evolution of AD, disease burden in patients and caregivers and the impact of therapy on paediatric patients with moderate-to-severe AD and their families.

**Competing interests**

**ASP:** AbbVie, AnaptysBio, Eli Lilly, Galderma, Incyte, Janssen, LEO Pharma, Novartis, Regeneron Pharmaceuticals, Inc., Sanofi – investigator; AbbVie, Amgen, Asana, Dermavant, Dermira, Galderma, Eli Lilly, Forte, LEO Pharma, Matrisys Bioscience, Menlo Therapeutics, Morphosys/Galapagos, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc., Sanofi – consultant.

**EG-Y:** AbbVie, Celgene, Eli Lilly, Galderma, GlaxoSmithKline, Glenmark, LEO Pharma, Pfizer, Regeneron Pharmaceuticals, Inc., Sanofi – investigator; AbbVie, Anacor, Asana Biosciences, Daiichi Sankyo, DBV, Dermira, Eli Lilly, Galderma, GlaxoSmithKline, Glenmark, Kiniksa Pharmaceuticals, Kyowa, LEO Pharma, Menlo Therapeutics, Novartis, Pfizer, Realm, Regeneron Pharmaceuticals, Inc., Sanofi – consultant; AbbVie, Celgene, Dermira, Galderma, Innovaderm, Janssen, LEO Pharma, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc., Sanofi – research grants.

**ADI:** AbbVie, Chugai Pharma, Genentech, Janssen, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc., Sanofi Genzyme – consultant.

**EB:** Almirall – speaker; AbbVie, Eli Lilly, Pfizer – investigator; Pierre Fabre Dermatology – investigator, consultant; Regeneron Pharmaceuticals, Inc., Sanofi Genzyme – consultant; Venthera – co-founder, consultant.

**MdeB-W:** Regeneron Pharmaceuticals, Inc., Sanofi Genzyme – investigator, advisory board member, speaker, consultant; AbbVie, Pfizer – investigator, advisory board member; Eli Lilly, UCB – advisory board member

**SJ, AZ, ER, ZEO:** Sanofi – employees, may hold stock and/or stock options in the company.

**PM-O:** Regeneron Pharmaceuticals, Inc. – employee and shareholder.

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**Contributors to the protocol**

ASP, EG-Y, ADI, EB, MdeB-W were involved in design of the study and are active steering committee members for the study.

SJ contributed to the design and development of the protocol and is the statistical lead.

AZ, PM-O, ER, ZEO contributed to the design and development of the protocol and are medical leads.

All authors critically revised the manuscript, gave final approval of the manuscript, and are accountable for the accuracy and integrity of the manuscript.

## REFERENCES

1. Shrestha S, Miao R, Wang L, *et al*. Burden of atopic dermatitis in the United States: Analysis of healthcare claims data in the Commercial, Medicare, and Medi-Cal databases. *Adv Ther* 2017;34:1989–2006.
2. Weidinger S, Beck LA, Beiber T, *et al*. Atopic dermatitis. *Nat Rev Dis Primers* 2018;4:1.
3. Ricci G, Bellini F, Dondi A, *et al*. Atopic dermatitis in adolescence. *Dermatol Reports* 2011;4:e1
4. Rønnstad ATM, Halling-Overgaard AS, Hamann CR, et al. Association of atopic dermatitis with depression, anxiety, and suicidal ideation in children and adults: A systematic review and meta-analysis. *J Am Acad Dermatol* 2018;79:448–56.
5. Wollenberg A, Oranje A, Deleuran M, *et al*. ETFAD/EADV Eczema task force 2015 position paper on diagnosis and treatment of atopic dermatitis in adult and paediatric patients. *J Eur Acad Dermatol Venereol* 2016;30:729–47.
6. Sidbury R, Tom WL, Bergman JN, *et al*. Guidelines of care for the management of atopic dermatitis: Section 4. Prevention of disease flares and use of adjunctive therapies and approaches. *J Am Acad Dermatol* 2014;71:1218–33.
7. Ring J, Alomar A, Bieber T, *et al*. Guidelines for treatment of atopic eczema (atopic dermatitis) Part II. *J Eur Acad Dermatol Venereol* 2012;26:1176–93.
8. EUCRISA. Highlights of Prescribing Information, FDA 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/207695s002lbl.pdf. (accessed 4 January 2019).
9. Sibbald C, Pope E, Ho N, *et al*. Retrospective review of relapse after systemic cyclosporine in children with atopic dermatitis. *Pediatr Dermatol* 2015;32:36–40.

10. Thijs JL, Strickland I, Bruijnzeel-Koomen CAFM, *et al.* Moving toward endotypes in atopic dermatitis: Identification of patient clusters based on serum biomarker analysis. *J Allergy Clin Immunol* 2017;140:730–7.
11. Irvine AD, Mina-Osorio P. Disease trajectories in childhood atopic dermatitis: an update and practitioner's guide. *Br J Dermatol* doi: 10.1111/bjd.17766. [published Online First 13 February 2019].
12. Paller AS, Spergel JM, Mina-Osorio P, *et al*. The atopic march and atopic multimorbidity: Many trajectories, many pathways. *J Allergy Clin Immunol* 2019; 143:46–55.
13. Kim JP, Chao LX, Simpson EL, *et al*. Persistence of atopic dermatitis (AD): a systematic review and meta-analysis. *J Am Acad Dermatol* 2016;75:681–7.
14. Simpson EL, Bruin-Weller M, Flohr C, *et al*. When does atopic dermatitis warrant systemic therapy? Recommendations from an expert panel of the International Eczema Council. *J Am Acad Dermatol* 2017;77:623–33.

**Figure legends**

**Figure 1** Patients and study locations

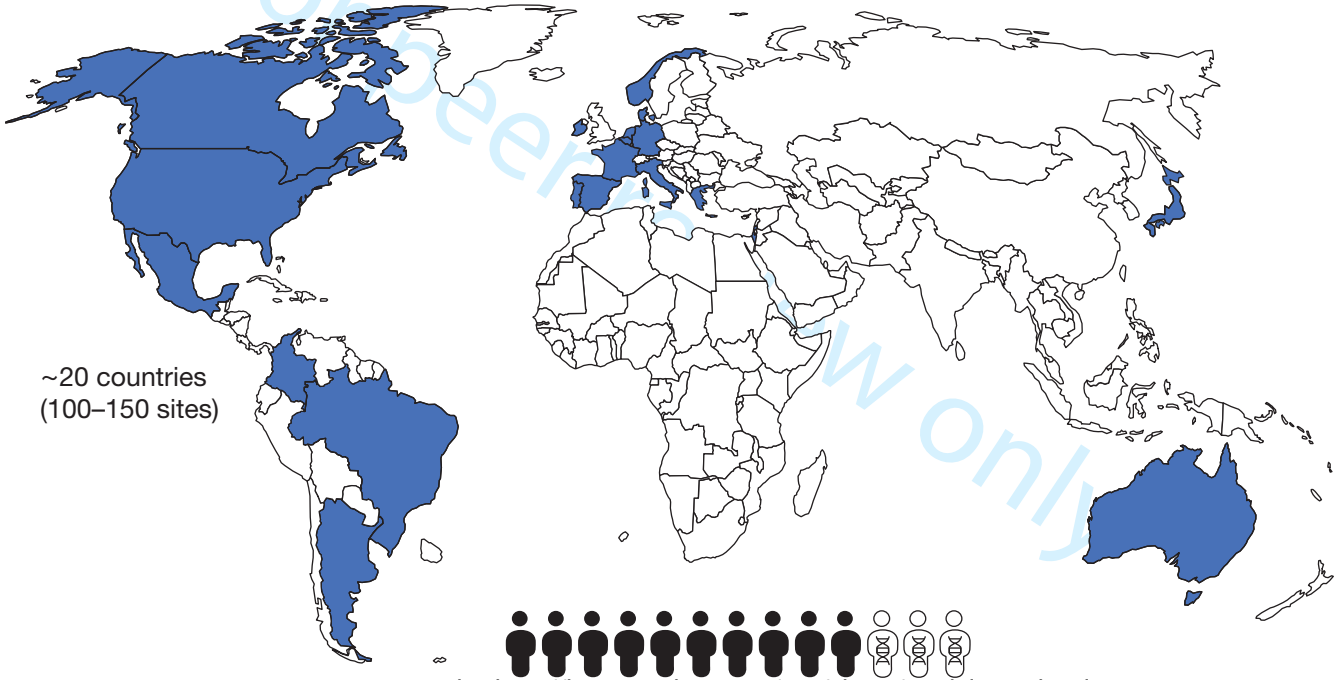
**Figure 2** Data collection schedule

AD, atopic dermatitis; HCP, healthcare professional.

**Total duration:** 5 years

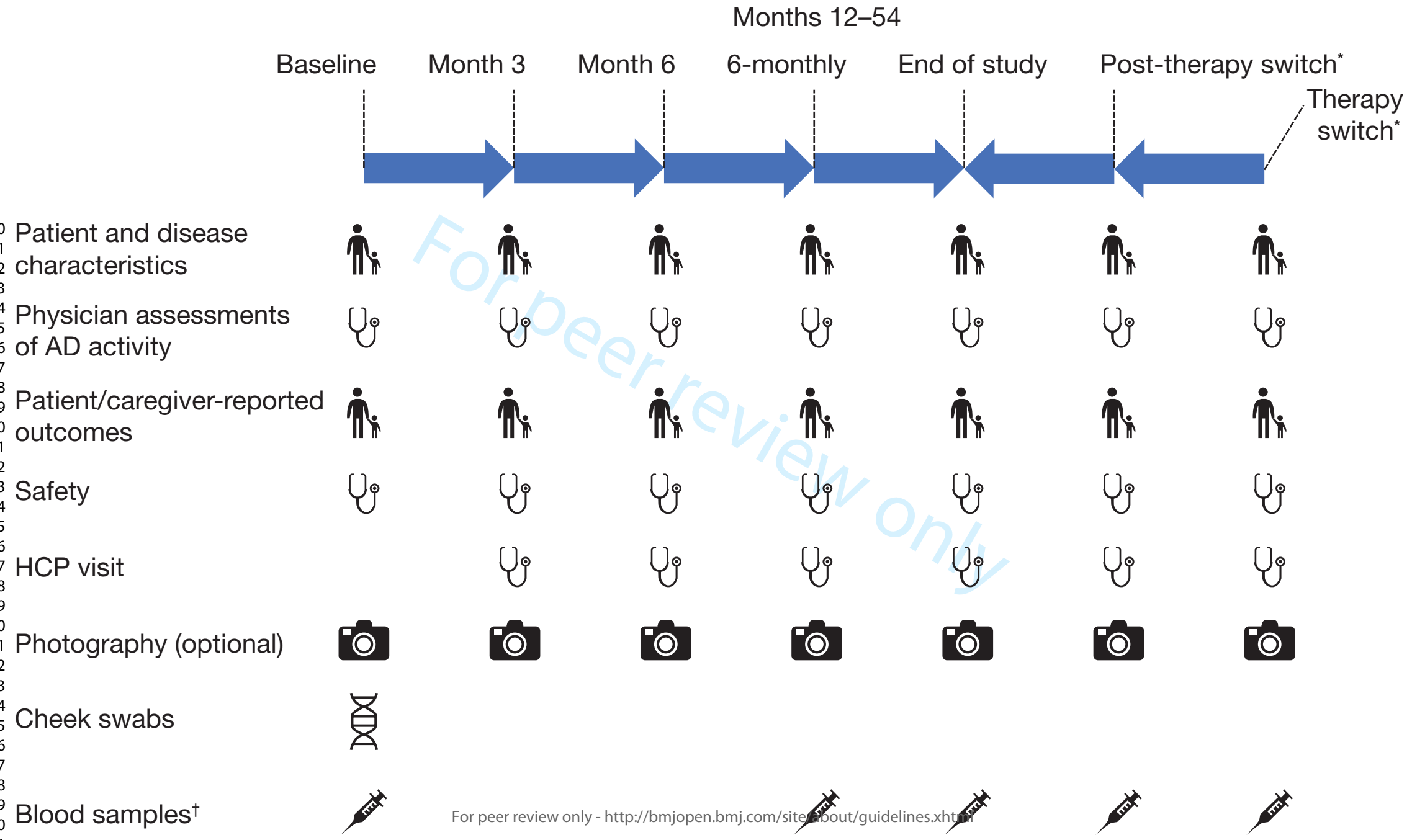
**Enrolment:** 2 years

**Visits:** 12 planned (according to standard of care)






1,300 patients (300 for biomarker study)



| Site Country | Site # | Name of applicable CEC/LEC/CIRB/LIRB |
|---|---|---|
| Argentina | 0320001 | Comité de Ética en Farmacología Clínica de la Fundación CIDEA |
| Argentina | 0320002 | Comité de Ética de Protocolos de Investigación (CEPI) |
| Argentina | 0320003 | Comite de Etica Dr Carlos Barclay |
| Argentina | 0320004 | Comité de Ética "Dr. Claude Bernard" |
| Argentina | 0320005 | Comité de Ética en Investigación del Hospital de Niños Pedro de Elizalde |
| Argentina | 0320006 | Comite de Etica en Investigacion |
| Australia | 0360003 | The Royal Children's Hospital Research Ethics and Governance |
| Australia | 0360004 | Bellberry Human Research Ethics Committee |
| Australia | 0360006 | Bellberry Human Research Ethics Committee |
| Australia | 0360007 | Epworth Research Development and Governance Unit (RDGU) |
| Australia | 0360008 | Bellberry Human Research Ethics Committee |
| Australia | 0360009 | South Western Sydney Local Health District Human Research Ethics Committee |
| Australia | 0360010 | The Eastern Health Office of Research and Ethics |
| Belgium | 0560001 | Comité d`Éthique Hospitalo-Facultaire Saint-Luc UCL |
| Belgium | 0560002 | Comité d`Éthique Hospitalo-Facultaire Saint-Luc UCL |
| Belgium | 0560003 | Comité d`Éthique Hospitalo-Facultaire Saint-Luc UCL |
| Belgium | 0560004 | Comité d`Éthique Hospitalo-Facultaire Saint-Luc UCL |
| Brazil | 0760001 | COMITÊ DE ÉTICA EM PESQUISA INVESTIGA - INSTITUTOS DE PESQUISAS |
| Brazil | 0760002 | COMITÊ DE ÉTICA EM PESQUISA DO HOSPITAL DA CRIANÇA SANTO ANTÔNIO |
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| Brazil | 0760004 | COMITÊ DE ÉTICA EM PESQUISA EM SERES HUMANOS DO COMPLEXO HOSPITAL DE CLÍNICAS DA UFPR |
| Brazil | 0760005 | COMITÊ DE ÉTICA EM PESQUISA EM SERES HUMANOS DO COMPLEXO HOSPITAL DE CLÍNICAS DA UFPR |
| Brazil | 0760006 | COMITÊ DE ÉTICA EM PESQUISA DA UNIFESP |
| Canada | 1240001 | Western Institutional Review Board (WIRB) |
| Canada | 1240002 | Western Institutional Review Board (WIRB) |
| Canada | 1240003 | Health Research Ethics Board of Alberta - Community Health Committee (HREBA CHC) |
| Canada | 1240004 | Health Research Ethics Board of Alberta - Community Health Committee (HREBA CHC) |
| Canada | 1240005 | Western Institutional Review Board (WIRB) |
| Canada | 1240006 | CHU Sainte-Justine |
| Canada | 1240007 | Conjoint Health Research Ethics Board |
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| Colombia | 1700004 | Comité Institucional de Ética en Investigación C.I.E.I CAFAM |
| Colombia | 1700006 | Comite de Etica en Investigacion del area de la Salud de la Universidad del Norte |
| Colombia | 1700007 | Comite de Etica de la Investigacion Riesgo de Fractura S.A. |
| France | 2500001 | COMITE DE PROTECTION DES PERSONNES Ile de France 1 |
| France | 2500002 | COMITE DE PROTECTION DES PERSONNES Ile de France 1 |
| France | 2500003 | COMITE DE PROTECTION DES PERSONNES Ile de France 1 |
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| Greece | 3000001 | Scientific Council of Hospital of Venereal & Skin Diseases of Athens "Andreas Syggros" |
| Greece | 3000002 | Scientific Council of General Hospital of Thessaloniki "Papageorgiou" |
| Greece | 3000003 | Scientific Council of General Hospital of Thessaloniki "Ippokratio" |
| Greece | 3000004 | Scientific Council of University General Hospital of Larissa |

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| Israel | 3760001 | Institutional Helsinki Committee of Sheba Medical Center |
| Israel | 3760002 | Institutional Helsinki Committee of Kaplan Medical Center |
| Israel | 3760003 | Institutional Helsinki Committee of Soroka Medical Center |
| Israel | 3760004 | Institutional Helsinki Committee of Bnei Zion Medical Center |
| Israel | 3760005 | Institutional Helsinki Committee of Meir Medical Center |
| Italy | 3800001 | Comitato Etico Milano Area 2 |
| Italy | 3800003 | Comitato Etico di Area Vasta Emilia Centro della Regione Emilia-Romagna (CE-AVEC) |
| Italy | 3800004 | Comitato Etico "Lazio 2" |
| Italy | 3800005 | Comitato Etico Università degli Studi della Campania "Luigi Vanvitelli" - Azienda Ospedaliera Universitaria "Luigi Vanvitelli - AORN "Ospedali dei Colli" |
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| Italy | 3800009 | CER UMBRIA |
| Italy | 3800010 | Comitato Etico Catania 1 |
| Italy | 3800012 | Comitato Etico Interregionale |
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| Japan | 3920002 | Ethical Committee of Hiroshima University Hospital |
| Japan | 3920003 | Ethical Committee of Osaka Habikino Medical Center |
| Japan | 3920004 | Ethical Committee of University Hospital Kyoto Prefectural University of Medicine |
| Japan | 3920005 | Ethical Committee of Kinki University Hospital |
| Japan | 3920008 | Ethical Committee of Aichi Children's Health and Medical Center |
| Japan | 3920009 | IRB of Sagamihara Hospital (受託研究委員会) |
| Japan | 3920011 | Ethical Committee of Tokyo Metropolitan Children's Medical Center |
| Japan | 3920014 | IRB of Tohoku Medical and Pharmaceutical University Hospital （治験審査委員会） |
| Mexico | 4840001 | Comite de Investigacion del Instututo Nacional de Pediatria<br>Comite de Etica en Investigacion del Instituto Nacional de Pediatria |
| Mexico | 4840003 | Comité de Investigación del Hospital Universitario José Eleuterio González<br>Comité de Ética en Investigación del Hospital Universitario José Eleuterio González |
| Mexico | 4840004 | Comite de Etica en Investigacion del Hospital Hispano, S.A. de C.V.<br>Comité de Investigación del Hospital Hispano, S.A. de C.V. |
| Mexico | 4840005 | Comité de Investigación de Clinical Research Institute S.C.<br>Comité de Ética en Investigación de Chirurgie & Medical |
| Mexico | 4840006 | Comité de Investigacion del Hospital Infantil de Mexico Federico Gomez<br>Comité de Ética en Investigacion del Hospital Infantil de Mexico Federico Gomez |
| Mexico | 4840007 | Comité de Investigación del Hospital Hispano, S.A. de C.V.<br>Comite de Etica en Investigacion del Hospital Hispano, S.A. de C.V. |
| Netherlands | 5280001 | Regionale Toetsingscommissie Patientgebonden Onderzoek |
| Netherlands | 5280002 | Regionale Toetsingscommissie Patientgebonden Onderzoek |
| Netherlands | 5280003 | Regionale Toetsingscommissie Patientgebonden Onderzoek |
| Netherlands | 5280005 | Regionale Toetsingscommissie Patientgebonden Onderzoek |
| Netherlands | 5280006 | Regionale Toetsingscommissie Patientgebonden Onderzoek |
| Norway | 5780001 | Regionale komiteer for medisinsk og helsefaglig forskningsetikk Sør-Øst |
| Norway | 5780002 | Regionale komiteer for medisinsk og helsefaglig forskningsetikk Sør-Øst |
| Portugal | 6200001 | Comissão de Ética do Centro Académico de Medicina de Lisboa |
| Portugal | 6200004 | Comissão de Ética do Hospital Pedro Hispano |
| Portugal | 6200005 | Comissão de Ética do Centro Hospitalar Universitário Lisboa Central |
| Spain | 7240001 | CEIm Departamento de Salud de Alicante - Hospital General ISABIAL - FISABIO |
| Spain | 7240002 | Comité de Ética de la Investigación con Medicamentos del Hospital de la Santa Creu i Sant Pau |
| Spain | 7240003 | Comité Ético de Investigación con Medicamentos del Hospital General Universitario Gregorio Marañón |
| Spain | 7240004 | Comité Ético del Instituto de Investigación del Hospital Universitario La Paz |
| Spain | 7240005 | Comité de Ética de la Investigación con Medicamentos de LA Fundación Sant Joan de Dèu |
| Spain | 7240007 | Consejería de Sanidad y Familias - Secretaría General de Investigación, Desarrollo e Innovación en Salud de la Junta de Andalucía |
| Spain | 7240008 | Comité de Ética de la Fundación de Investigación del Hospital General Universitario de Valencia |
| Spain | 7240009 | Consejería de Sanidad - Gobierno del Principado de Asturias (CEIm regional) |

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| United States | 8400001 | The Ann & Robert H. Lurie Children's Hospital of Chicago Institutional Review Board (Lurie Children's IRB) |
| United States | 8400003 | Western Institutional Review Board (WIRB) |
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| United States | 8400008 | Children's Hospital of Wisconsin IRB |
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| United States | 8400042 | Western Institutional Review Board (WIRB) |

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| 28-Dec-18 | NA |
| 22-Nov-18 | NA |
| 12-Oct-18 | NA |
| 26-Nov-18 | NA |
| 30-Apr-19 | NA |
| 31-Oct-18 | NA |
| 26-Jun-19 | 38258 |
| 28-Oct-19 | 2018-11-1009-AA (Application number on approval letter) |
| 04-Dec-19 | 2018-11-1009-AB (Application number on approval letter) |
| 19-Nov-19 | EH2019-469 (Application number on approval letter) |
| 10-Oct-19 | 2018-11-1009-A-1 (Application number on approval letter) |
| 26 Sep 2019 ( RGO approval ) | 2019/STE16409 (Site Specific Asssesment Reference) |
| 30-Oct-19 | S19/073/47302 (Application number on approval letter) |
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| 23-Sep-18 | CIRB Work Order # 3-1113472-1 |
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| 14-Nov-18 | Ethic ID: HREBA.CHC-18-0027 |
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| 22-Nov-18 | NA |
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| 06-Dec-18 | NA |
| 16-Apr-19 | NA |
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| 12-Dec-18 | NTS 18.10.01.67707 / RCB 2018-A02560-50 |
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| 26-Feb-19 | NTS 18.10.01.67707 / RCB 2018-A02560-55 |
| 13-Dec-18 | 3160 / 13-12-2018 |
| 22-Feb-19 | 197 / 27-02-2019 |
| 10-Apr-19 | Ε.Σ. 125/12.04.2019 |
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| 06-Feb-19 | 568/2018/Oss/AOUBo |
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| 13-Mar-19 | N Prot. 148 del 20/03/2019 |
| 25-Jun-19 | NA |
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| 27-Feb-19 | Acta 04/2019, de 18 de febrero |
| 20-Dec-18 | PI-3485 |
| 12-Nov-18 | EPA-17-18 |
| 20-May-19 | MV/JMR/mm/59/19 |
| 05-Feb-19 | NA |
| 19-Feb-19 | Nº Registro: SAL2019065050 |

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| 07-Aug-18 | CIRB Work Order # 9-1102660-1 |
| 10-Oct-18 | CIRB Work Order # 1-1120280-1 |
| 17-Sep-18 | CIRB Work Order # 9-1113500-1 |
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| 07-Aug-18 | CIRB Work Order # 9-1101413-1 |
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| 22-Apr-19 | N/A |
| 02-Nov-18 | CIRB Work Order # 1-1127356-1 |
| 20-Jan-19 | Study ID # 2018-8063 |
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| 25-Sep-18 | CIRB Work Order # 9-1112966-1 |
| 03-Dec-18 | CIRB Work Order # 1-1134628-1 |
| 06-Nov-18 | CIRB Work Order # 1-1128664-1 |
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| 06-Nov-18 | CIRB Work Order # 1-1128191-1 |
| 16-Jan-19 | CIRB Work Order # 1-1132624-1 |
| 12-Nov-18 | CIRB Work Order # 11-1129449-1 |
| 26-Dec-18 | CIRB Work Order # 1-1140132-1 |
| 30-Nov-18 | CIRB Work Order # 1-1134653-1 |
| 05-Jun-19 | WIRB Work Order Number: 1-1189465-1 |
| 07-Jun-19 | WIRB Work Order Number: 1-1189469-1 |
| 10-May-19 | WIRB Work Order Number: 1-1182517-1 |
| 19-Jun-19 | WIRB Work Order Number: 1-1194679-1 |
| 11-Jul-19 | WIRB Work Order Number: 1-1200720-1 |
| 31-Aug-19 | WIRB Work Order Number: 1-1215428-1 |


SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | ItemNo | Description | Page |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | 2, 3, 6 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | |
| Protocol version | 3 | Date and version identifier | 6 |
| Funding | 4 | Sources and types of financial, material, and other support | 14–15 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 1, 15 |
| | 5b | Name and contact information for the trial sponsor | 1, 14 |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | 14–15 |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | 10, 15 |
| **Introduction** | | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 5–6 |
| | 6b | Explanation for choice of comparators | N/A |

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| Objectives | 7 | Specific objectives or hypotheses | 5–6 |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | 6 |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 6, figure 1 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 6–7, table 1 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | N/A, observational |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | 6 |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | N/A, observational |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | N/A, observational |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | Page 8-9, table 2 |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | 8, figure 2 |

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| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 10–11, table 3 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | N/A |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | N/A, observational |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | N/A, observational |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | N/A, observational |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | N/A, observational |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | N/A, observational |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 8, 10 |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | N/A |

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| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | N/A |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 10 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | N/A |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | N/A, observational |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | N/A |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | N/A, observational |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | N/A, observational |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | N/A |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 7 |

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| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | N/A |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | N/A |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | N/A |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | N/A |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 14–15 |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | N/A |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | N/A, observational |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 10 |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | N/A |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | N/A |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | N/A |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.