The HOME Core outcome set for clinical trials of atopic dermatitis

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List of abbreviations:

COS: Core outcome sets,

AD: atopic dermatitis

HOME: Harmonising Outcome Measures for Eczema

POEM: patient-oriented eczema measure

NRS 11: numerical rating scale 11 for itch intensity

EASI: Eczema Area Severity Index

DLQI: Dermatology Life Quality Index

CDLQI: Children's Dermatology Life Quality Index

IDQOL: The Infants' Dermatitis Quality of Life Index

RECAP: Recap of atopic eczema

ADCT: Atopic Dermatitis Control Test

Conflicts of interest:

The following people were involved with the development of the following instruments and present at a HOME consensus meeting at which these were considered:

- ADCT: Eckert L, Gadkari A, Simpson E
- ADQoL-J: Kataoka Y
- BODE: Drucker A
- CADIS/Skindex Teen: Chamlin S
- CADIS short form: Apfelbacher C, Chamlin S, Gabes M
- DLQI, CDLQI, DFI, FDLQI, FROM-16, EDI, IDQoL: Finlay A
- EASI: Eichenfield L, Hanifin J, Leshem YA
- Japanese versions of POEM, DLQI, CDLQI, DFI, IDQOL, POEM, QPCAD, PQCAD short form: Ohya Y
- NESS: Williams H
- POEM: Williams H
- PO-SCORAD: Barbarot S, Stalder J-F, Svensson Å, Wollenberg A
- RECAP: Apfelbacher C, Burton T, Chalmers J, Howells L, Howie L, Spuls P, Thomas K
- VAS: Weisshaar E
- Ziarco Itch Diary: Purkins L

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Y.A.L has received honoraria as a consultant from AbbVie, Sanofi, Genentech, Regeneron Pharmaceuticals, Pfizer, Janssen, and Dexcel Pharma, an independent research grant from AbbVie, and has, without personal compensation, provided investigator services for Eli Lilly, Pfizer, and AbbVie. N.K. has received honoraria as a speaker/consultant for Sanofi, Maruho, Abbvie, Ely-Lilly Japan, Taiho Pharmaceutical, Jansen Pharma, Mitsubishi Tanabe Pharma, Abbvie, Kyowa Kirin, Celgene Japan and Leo Pharma, and has received grants as an investigator from Sanofi, Maruho, Abbvie, Mitsubishi Tanabe Pharma, Ely-Lilly Japan, Kyowa Kirin, Sun Pharma, Taiho Pharmaceutical, and Leo Pharma. PS has done consultancies in the past for Sanofi 111017 and AbbVie 041217 (unpaid), receives departmental independent research grants for TREAT NL registry, for which she is Chief

Investigator (CI), from pharma companies since December 2019, is involved in performing clinical trials with many pharmaceutical industries that manufacture drugs used for the treatment of e.g. psoriasis and atopic dermatitis, for which financial compensation is paid to the department/hospital. N.K. has received honoraria as a speaker/consultant for Sanofi, Maruho, Abbvie, Ely-Lilly Japan, Taiho Pharmaceutical, Jansen Pharma, Mitsubishi Tanabe Pharma, Abbvie, Kyowa Kirin, Celgene Japan and Leo Pharma, and has received grants as an investigator from Sanofi, Maruho, Abbvie, Mitsubishi Tanabe Pharma, Ely-Lilly Japan, Kyowa Kirin, Sun Pharma, Taiho Pharmaceutical, and Leo Pharma. CA has received institutional funding from the Dr Wolff Group and Bionorica, and consultancy fees from the Dr Wolff Group, Sanofi Genzyme, Sanofi-Aventis, AstraZeneca, LeoPharma and Bionorica. MB is a consultant for Novartis. Jochen Schmitt acted as a payed consultant for Novartis, Sanofi, ALK and received institutional grants for investigator-initiated research from Sanofi, Lilly, Pfizer, ALK, and Novartis. He is the lead investigator of the German eczema registry TREATgermany. Eric Simpson reports grants and fees for participation as a consultant and principal investigator for Eli Lilly and Company, LEO Pharma, Pfizer, and Regeneron; grants for participation as a principal investigator from Galderma and Merck; and fees for consultant services from AbbVie, Boehringer-Ingelheim, Dermavant Incyte, Forte Bio, Pierre Fabre Dermo, and Sanofi-Genzyme.

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Abstract:

Core outcome sets (COS) are critically important outcomes that should be measured in clinical trials. Their absence in atopic dermatitis (AD) is a form of research waste and impedes combining evidence to inform patient care. Here, we articulate the rationale for COS in AD and review the work of the international Harmonising Outcome Measures for Eczema (HOME) group from its inception in Munich, 2010. We describe core domain determination (what should be measured), to instrument selection (how domains should be measured), culminating in the complete core outcome measurement set in Tokyo, 2019. Using a “road map”, HOME includes diverse research methods including Delphi and nominal group techniques informed by systematic reviews of properties of candidate instruments. The four domains and recommended instruments for including in all clinical trials of AD are patient symptoms, measured by Patient-Oriented Eczema Measure (POEM) and peak Numerical Rating Scale 11 (NRS-11) for itch intensity over 24 hours, clinical signs measured using the Eczema Area and Severity Index (EASI), quality of life measured by the Dermatology Life Quality Index (DLQI) series for adults, children and infants, and long term control measured by either Recap of atopic eczema (RECAP) or Atopic Dermatitis Control Tool (ADCT).

Background: The critical importance of core outcome sets

One clinical trial is rarely enough to change practice, especially as early high profile studies[1] are frequently contradicted by subsequent trials. Trials have a “second life” within systematic reviews that assemble all trial evidence systematically to create an unbiased assessment for guiding clinical practice. Results of clinical trials summarising interventions such as emollients in atopic dermatitis (AD) should be combined in a systematic review in order to make sense of the totality of evidence and to determine whether some factors such as participant characteristics, differences in the intervention, source of funding and study quality influence the pooled estimate of effect. Sadly, the ability to combine clinical outcomes in dermatology is poor. Schmitt *et al.* systematically assessed[2] the concordance between efficacy outcomes in 220 clinical trials from 10 Cochrane Skin systematic reviews and found that of the 60 main outcomes pre-specified in the 10 systematic reviews, 28% (17) were not reported in any trial. Of the 1,086 reported trial outcomes, 68% (742) were not used at all in those reviews. Meta-analysis was impossible for 11 out of 23 primary outcomes in those reviews because trial outcomes were absent or poorly reported. In the field of AD, systematic reviews of important therapeutic interventions are rarely able to combine trial results, mainly due to lack of use of shared important outcomes. In a Cochrane review of emollients for AD, only 12 out of 77 studies could be combined to summarise investigator disease severity score, and no studies could be combined for participant-assessed disease severity. In another important review assessing the effects of interventions to reduce *Staph. aureus* for treating AD[3], efficacy results of only 5 out of 41 studies could be combined in some form of meta-analysis.

Inability to combine and compare clinically important outcomes is one of the greatest barriers for understanding the evidence base for AD treatments. It is a form of research waste[4] that affects healthcare professionals and patients who are unable to benefit from clear unbiased assessments of all relevant evidence. Such is the rationale for core outcome sets. The Core Outcome Measures for Effectiveness Trials (COMET) Group[5] define a core outcome set (COS) as “an agreed standardised set of outcomes that should be measured and reported, as a minimum, in all clinical trials in specific areas of health or health care." Such a definition makes it clear that core outcomes do not have to be the only outcomes. Researchers can measure whatever they choose provided they include core outcomes somewhere so that their study can be combined with other similar studies in future. Similarly, core outcomes do not have to be the *primary* outcomes of a clinical trial of AD treatment.

The Harmonising Outcome Measures for Eczema (HOME) initiative

HOME was founded in 2010 to establish a complete COS for AD clinical trials that includes recommended instruments and how they should be used and reported. A secondary aim is to suggest a choice of instruments for clinical practice. For the sake of clarity, we use the widely used term “atopic dermatitis” throughout (rather than atopic eczema or just eczema[7, 8]), apart from where the term eczema is used within and acronym such as HOME. A chronological depiction of international HOME consensus meetings over a 10 year period is shown in Table 1. Notable points include the spread of key meetings over the globe to ensure international engagement, consistent and accurate use of terminology, use of a specially developed roadmap, and progressing at the right pace to ensure the growing international community was kept on board. Meetings required extensive planning between the team at the University of Nottingham, the HOME Executive Committee,

and the local organising team for each meeting in order to ensure consistency of methods, ample break-out rooms and anonymous voting. Specially convened refresher and introductory sessions were set up for new members and for patients and carers. Each meeting is described in follow-up meeting report[9] along with academic publication relating to any novel findings.[10]

TABLE 1: HOME consensus meetings at which domains and instruments were recommended for the Core Outcome Set (COS) for atopic dermatitis clinical trials. HOME VI (2018) and HOME VIII (virtual meeting 2020) are not listed here as they were focussed on the Clinical Practice Set rather than clinical trials COS.

Meeting	Main objective(s)	Research undertaken prior to the meeting to inform decisions	Main outcomes of the meeting
HOME I 2010 Munich, Germany (held during the 6th Georg Rajka Symposium/ISAD meeting) 40 participants	To determine whether there was **sufficient interest** in developing a COS for atopic dermatitis.	**Domains**	
		International e-Delphi consensus study involving 46 participants to establish a preliminary core set of domains for inclusion in clinical trials AND clinical practice.[11] Systematic review of outcome instruments used in atopic dermatitis trials[12]	Clear enthusiasm from the atopic dermatitis community to establish an initiative to develop a core outcome set for atopic dermatitis.[13] The COS initiative needs to be global. Patient involvement needed to be meaningful and representative. Preliminary COS domains from the e-Delphi were clinical signs, symptoms and long-term control of flares. No consensus on the inclusion of health-related quality of life.
HOME II 2011 Amsterdam, The Netherlands 43 participants From 5 continents	To agree which **domains** should be included in the core outcome set.	**Domains**	
		Building on previous international e-Delphi consensus study of 46 participants to establish a preliminary core set of domains for inclusion in clinical trials AND clinical practice.[11]	Consensus reached to recommend the domains for the core outcome set as clinician-reported **signs**, patient-reported **symptoms**, **quality of life** and **long-term control**.[14] HOME group would focus initially on the clinical trials COS, with clinical practice following later.
HOME III 2013 San Diego, USA 56 participants From 4 continents	To reach consensus on recommended outcome measurement instrument(s)) for **Clinician-reported signs**	**Clinician-reported signs**	
		Systematic review of the measurement properties of clinician-reported signs instruments**.[15]**	Essential clinical signs are erythema, excoriation, oedema/papulation and lichenification. Both intensity and extent should be measured. Consensus reached to recommend the Eczema Area Severity Index (**EASI**) as the core outcome instrument for measuring **clinician-reported signs** in atopic dermatitis clinical trials.[16]
HOME IV 2015 Malmö, Sweden 70 participants From 5 continents	To reach consensus on the recommended instrument(s) for measuring: **Patient-reported symptoms** **Quality of life (in adults)**	**Patient-reported symptoms**	
		Systematic review identifying **patient-reported** symptoms instruments used in atopic dermatitis clinical trials.[17] Systematic review of **the measurement properties of patient-reported** symptoms instruments.[17] International survey of which symptoms are important to patients.[18]	Consensus reached to recommend the Patient-oriented Eczema Measure (**POEM)** as the core outcome instrument for measuring **patient-reported symptoms** in atopic dermatitis clinical trials. [10]
		Quality of life in adults	
		Systematic review identifying skin-specific quality of life instruments used in atopic dermatitis clinical trials.[19]	Instruments for measuring quality of life (QoL) in adults were assessed but **no consensus reached** on recommending a core outcome instrument for atopic dermatitis clinical trials.[21]

		Systematic review of the measurement properties of adult quality-of-life measurement instruments for atopic dermatitis.[20]	Consensus reached that psychological, social and physical functioning are the only essential subdomains for QoL.
HOME V 2017 Nantes, France 81 participants From 5 continents	To reach consensus on: How the domain of **long-term control** should be **defined** and **measured.** Priority areas of future research for measuring **quality of life (in children)**	**Long-term atopic dermatitis control**	
		Systematic review identifying how long-term control has been measured previously in atopic dermatitis clinical trials. [22] International survey of clinicians/methodologists and international focus groups with patients/carers regarding what constitutes long-term control of atopic dermatitis.[23, 24]	Consensus reached that long-term atopic dermatitis control should include repeated measures of the signs, symptoms, QoL and a patient-reported global assessment. [25] Agreed that further work was required to refine this definition and to identify and/or develop an appropriate patient global instrument.
		Quality of life in children (children)	
		Systematic review identifying skin-specific quality of life instruments used in atopic dermatitis clinical trials.[19] Systematic review of the measurement properties of infant, children and adolescent quality-of-life measurement instruments for atopic dermatitis.	Instruments for measuring quality of life (QoL) in children were assessed for face validity and feasibility but **no consensus reached** on recommending a core outcome instrument for atopic dermatitis clinical trials due to a lack of instruments identified as having sufficient validity.[25]
HOME VII 2019 Tokyo, Japan 75 participants From 5 continents	To reach consensus on the recommended instrument(s) for measuring: **Quality of life (in adults and children)** **Atopic dermatitis control** **Itch intensity (Patient-reported symptoms)**	**Quality of life**	
		Updated systematic review of validation studies of instruments to assess quality of life in adults and children.[26]	Consensus reached to recommend the Dermatology Life Quality Index (**DLQI)** for adults, Children's Dermatology Life Quality Index **CDLQI** for children and Infants' Dermatitis Quality of Life Index **(IDQoL)** for infants as the core outcome instrument for measuring **skin-related quality of life** in atopic dermatitis clinical trials.[27]
		Atopic dermatitis control	
		Conceptual model to describe the construct of long-term control domain.[28] Systematic review of the measurement properties of atopic dermatitis control instruments.[29]	Further refined the domain definition agreed at HOME V to state that long-term control is atopic dermatitis control over time. Consensus reached to recommend Recap of atopic eczema (**RECAP)** and the Atopic Dermatitis Control Tool (**ADCT)** as the core outcome instruments for measuring **atopic dermatitis control** in clinical trials. Both were similar in content and validity.[27] Only **one of** RECAP and ADCT needs to be included in a clinical trial. Agreed that a single-item patient-reported global atopic dermatitis control instrument should be developed and validated, and considered for the COS.
		Itch intensity (symptoms)	
		Systematic review of the measurement properties of patient-reported outcome measures of itch intensity (updated for this meeting).[30]	Consensus reached to recommend the 11-point numerical rating scale (NRS) capturing the peak itch over the past 24 hours (**NRS-11 peak itch**

			24) for measuring **the itch intensity** in adults and older children in atopic dermatitis clinical trials.[27]

General methods

COS development is a relatively new research methodology[31] that employs international consensus exercises, supplemented by rigorous systematic reviews to identify candidate instruments with the best psychometric properties. The range of methods used at various stages of the HOME initiative along with an explanation of their rationale is given in Table 2.

TABLE 2: Research methods used in the development of the HOME core outcome set for atopic dermatitis clinical trials based on the HOME roadmap[6]

Stage	Purpose/ output	Method(s) used	Further description of method
Agree core outcome domains	Identify potential outcome domains	• Systematic review of all domains reported in clinical trials and qualitative studies	This allows identification of all potential domains i.e. “what is to be measured”. Qualitative studies will add patient views on what is important to them about their atopic dermatitis.
	Rank / prioritise domains	• eDelphi exercise involving all stakeholders	All stakeholders rate each domain on importance in a multi-round Delphi exercise. At each round participants are provided with a summary of what their and other stakeholder groups rated in the previous round.
	Agree recommended core domains to be measured in all clinical trials	• Consensus meeting involving all stakeholders.	These are typically face to face meetings, with an independent facilitator knowledgeable in COS methodology, held in different locations around the world to encourage global participation. Consensus meetings are increasingly being held online. Care is taken to ensure representation from all stakeholders especially patients. Small and large group work (a modified nominal group technique) is employed to facilitate all stakeholder input. Anonymous voting with real time feedback of results to the group is used to achieve consensus, based on a pre-defined rule of fewer than 30% disagreement.

	Further define the domain and identification of essential subdomains	• International qualitative studies. • Stakeholder input at consensus meeting	Qualitative studies can include focus groups and surveys of patients and clinicians). For a global COS, international input is important. A conceptual model of the domain can be developed based on these qualitative studies which can be used to further define the domain and to identify all essential subdomains
Agree core outcome instruments	Identify instruments that measure the domain and produce a long list of candidate instruments	• Systematic review of all instruments used previously in clinical trials	This allows identification of all potential outcome measurement instruments for each domain i.e. “how to measure the domain”. The long list can be supplemented by input from experts in the field to add any unpublished instruments.
	Determine the measurement properties of identified instruments in atopic dermatitis patients. Establish a short list of potential candidate instruments.	• Systematic review to identify all validation studies conducted on long-listed instruments • Apply the COSMIN checklist to the validation studies [32, 33]	The COSMIN checklist is applied to the validation studies in order to assess the outcome and quality of the validation studies. Each instrument is rated as either: A. Good quality evidence showing instrument performs well B. Good quality evidence but only for limited number of measurement properties. Further validation studies needed C. Evidence that at least one important measurement property is low

			quality and so shouldn't be considered for the core outcome set D. Minimal validation work identified so the performance of the instrument is unclear. Further validation studies needed before it can be considered
	Select a recommended instrument(s) for the COS	• Consensus meeting • Vote on preferred instrument(s) for the core set	At the consensus meeting, the evidence on the measurement properties of each instrument is presented to enable evidence-based decision making. The evidence is used to determine which instruments should be given further consideration for the core set. Each instrument is assessed to determine the degree to which it meets the OMERACT filter of truth, discrimination and feasibility.[34] If consensus is not achieved then what research is needed (instrument development or validation) is agreed to enable consensus at a future meeting. If consensus achieved any validation gaps are identified and agreement made on research to be conducted to fill those gaps.

The HOME group developed its own roadmap for developing the AD COS (Figure 1)[6]. At a time when COMET had just started in 2010, such a roadmap was quite innovative in suggesting a clear pathway for COS development including a preference for one instrument per domain (what should be measured) and a clear eye towards implementation - a current hot topic in COS research.[35] The roadmap describes four steps, starting with identifying the scope and setting with a panel representing all relevant stakeholders and a team experienced in outcomes research. The second step is for the group to consider what core aspects of that disease (domains) must be measured in a clinical trial. Domains may include aspects such as symptoms (what patients experience such as itch or sleep loss), signs (what clinicians see such as erythema or lichenification) or other aspects such as impact on quality of life. Adverse effects of treatments should also be recorded, but these are not typically included in COS of efficacy/effectiveness measures. Once domains are agreed, the next step is to agree *how* to measure such domains using the best possible instruments. As suggested by pioneering work from the Outcome Measures in Rheumatology (OMERACT) Initiative and its 'filter',[36] good instruments need to be relevant (applicable to the condition), valid (measure what they are meant to measure), reliable (be reproducible and able to discriminate between groups) and feasible (easy enough to use). Candidate instruments are identified by rigorous searches within a systematic review. Their psychometric properties (such as validity or responsiveness to change) are then compared. Further validation work on candidate instruments that are identified as "good enough" may be needed at this stage. We used the COSMIN (COnsensus-based Standards for the selection of health Measurement Instruments) checklist for evaluating the methodological quality

of studies that evaluate measurement properties of outcome measures[32]. All evidence is then summarised and presented at dedicated international meetings[25] that employ formal consensus techniques using nominal groups and anonymous voting to propose preferred core instruments (Figure 2). Additional material is provided for patients and carers at meetings to promote genuine involvement. Once preferred instruments for recommended domains have been identified and agreed, it is then necessary to identify *how* those preferred instruments need to be reported e.g., mean plus 95% confidence intervals and standard deviation or median plus interquartile ranges[37]. The final step of COS development is dissemination and implementation to a wide range of stakeholders so that their benefits can become manifest - as exemplified by this review.

Domain selection - what should be measured

Guided by the work on core outcomes by our rheumatology colleagues from OMERACT[38], two HOME founding members (JS and HW) in 2005 initiated a systematic review that informed a multi-stakeholder Delphi study on core domains for atopic dermatitis trials in 2007.[11, 12] The consensus panel included six consumers (patients or carers with lived experience), 32 clinical experts (selected from the scientific committees of the International Society for Atopic Dermatitis and other groups), seven editors from leading international dermatological journals, and one regulatory agency representative. Individuals from 13 countries contributed as panel members, making the study truly international. In a three-round Delphi study, outcome domains identified in a systematic review[12] and additional domains suggested by the panel were rated with individual feedback on participants own

previous rating alongside stakeholder group's previous rating. In this study, it was explicitly defined that a core outcome "*should be assessed routinely in <u>every</u> clinical trial, but not necessarily as a primary outcome."* Consensus was defined as agreement to include an outcome domain into the core set by at least 60% of all members of at least three stakeholder groups including consumers. Consumers had a veto as it was decided that outcome domains that are not considered as having key relevance by patients should not to be included into the core set. After the three rounds of the Delphi exercise, there was 100% consensus of all stakeholders, that "clinical signs assessed by a physician using a score" should be included into the core outcome domain set. The consensus criterion was also met by the domains "symptoms" and "long-term control of flares". Interestingly, the domain "quality of life (dermatology specific) was recommended for the core domains set by clinical experts, journal editors, and the regulatory agency representative, but only 2/6 (33%) of the consumers indicated that quality of life should be assessed in every AD trial. The role of quality of life as a domain for the core set became the focus of the HOME II meeting in Amsterdam in July 2011[14]where consensus rules were refined following OMERACT recommendations. Stakeholder groups now included clinicians, consumers, industry representatives, and methodologists. We defined that consensus is reached if "less than 30% of voters disagree". Small group discussions at HOME II indicated that the construct "quality of life" was unclear to some consumers during the previous Delphi exercise which is why they did not recommend it as a core domain. This was a critically important result of HOME 2 as it indicated the importance of clarifying domains, procedures and definitions for patients participating in HOME meetings and when voting. Eventually, there was broad consensus among the 43 individuals from 10 countries attending HOME II,

that quality of life *should* be included into the core domain set for AD trials, along with clinical signs, symptoms, and long-term control of flares.[14]

Instrument selection – how to measure the selected domains

SYMPTOMS:

Identify instruments (stage 1): A systematic review to identify instruments to measure symptoms in AD trials was performed[14]. Symptoms were reported in 78% of trials published since 2000, with itch and sleep loss most frequently measured. Symptoms were assessed in 37% of trials using a stand-alone measurement (visual analogue scale (VAS) or numeric rating scale (NRS)), and in 63% as part of a composite measure (e.g., measuring clinical signs as well as patient-reported symptoms). A total of 30 composite instruments with symptoms were identified, of which SCORing Atopic Dermatitis index (SCORAD) was the most commonly used. However, only 23% of trials reported the SCORAD symptom score separately.

Evaluate the measurement properties and quality of validation studies for the identified instruments (stage 2): A systematic review of validation studies of instruments to measure symptoms, identified 18 different instruments[17]. Only 5 instruments had sufficient validation data to consider them for recommendation for the COS: paediatric Itch Severity Scale (ISS), POEM, Patient-Oriented (PO-) SCORAD, Self-Administered (SA-) EASI and adapted SA-EASI. The most extensively validated instrument was the POEM with adequate internal consistency, construct validity, responsiveness[39-41] and content validity.

Determine which instruments are preferred for COS (stages 3-5): The systematic reviews were presented at the HOME IV consensus meeting in Malmö, Sweden, 2015[21]. Review results were considered alongside a short-list of essential

symptoms to determine both sufficient quality and relevance of instruments. The POEM, PO-SCORAD and SA-EASI were considered for their suitability. Consensus was achieved that POEM is the most suitable instrument to measure the many symptoms of importance and was therefore included in the COS[10]. The POEM[42] is free to use and typically takes less than two minutes to complete. The POEM generally meets the OMERACT filter of truth, discrimination and feasibility, but some validation gaps remain including cross-cultural validity which need future research. Structural validity was not appropriate for POEM as it was developed as a formative model.[43]

At the HOME IV and V meeting it was agreed that itch intensity should be measured in addition to frequency of itch that is covered in POEM[25]. Pain was also suggested as a potential additional symptom, but more research is needed before it will be considered further. During the HOME VII two updated systematic reviews on identified instruments were presented[17, 30, 44, 45]. Consensus was reached to use the peak NRS-11 past 24 hours[45, 46] as instrument for measuring itch intensity in adults. The peak itch NRS-11 past 24 hours has been validated for several measurement properties (i.e., content validity, test-retest reliability, discriminating/known-groups validity, construct validity, sensitivity to change). Further validation data on this instrument will be investigated in the future.

SIGNS:

Identify instruments (stage 1): A systematic review in 2007 identifying instruments to measure AD severity revealed 20 different instruments used in AD trials[12]. Another review found the EASI and SCORAD were the most commonly used instruments in AD trials.[47]

Evaluate the measurement properties and quality of validation studies for the identified instruments (stage 2): Schmitt, et al. identified and evaluated 45 articles describing 16 different instruments measuring the signs of AD.[15] Across instruments, erythema, papulation, lichenification, oozing/crusting, and excoriation were the most commonly included signs. The majority of instruments included assessments of both the intensity of lesions and the extent of body involvement. The SCORAD and EASI were the two most extensively studied instruments with over 2000 patients included in validation studies. Both EASI and SCORAD included content previously shown to be relevant to patients and providers for assessing disease severity including disease extent[48] and the intensity of the most relevant signs- erythema, papulation, lichenification and excoriation.[12] Based on critical appraisal of the validation studies and measurement properties utilizing COSMIN criteria, the authors concluded that the EASI and SCORAD represent the two best validated instruments to measure AD signs despite some minor validation gaps that have since been filled[49]. In summary, the EASI displayed adequate content validity, responsiveness, internal consistency, intraobserver reliability, and intermediate interobserver reliability. The objective SCORAD index displayed adequate content validity, responsiveness, and interobserver reliability but unclear intraobserver reliability.

Determine which instruments are preferred for COS (stages 3-5): At the HOME III meeting (San Diego, California; April 6-7, 2013), 56 participants attended from 10 countries spanning the regions of Asia, Europe, South and North America and included patients, dermatologists, nurses, methodologists, and the pharmaceutical industry.[9] After a review of the literature was presented, participants agreed upon the most important minimum set of signs an instrument should include- erythema, papulation, lichenification, and excoriation. Only the SCORAD and the EASI

measured at least these four signs and had adequate validation to be recommended to be included in the COS. After small group discussions and whole-group voting, the EASI was voted as the recommended instrument for inclusion in the COS (90% for EASI, 7% for SCORAD, 2% unsure). Participants appreciated the inclusion of only the most relevant signs in the EASI and the increased importance of extent in EASI compared with SCORAD. Participants also preferred the regional assessment of signs intensity utilized by the EASI as opposed to the "representative lesion" approach utilized by the SCORAD, and also the fact that EASI is only concerned with measuring signs whereas SCORAD is a composite score including symptoms. Of note, although EASI is the only signs score included in the HOME COS, SCORAD use remains common in AD trials alongside the EASI and the pros and cons of each instrument have been compared in a clinical practice setting.[50]

QUALITY OF LIFE:

Identify instruments (stage 1): A systematic review on quality of life (QoL) instruments used in clinical trials found that of 303 trial reports, 21% measured quality of life using 18 named and 4 unnamed instruments.[19] The Dermatology Life Quality Index (DLQI), the Children's Dermatology Life Quality Index (CDLQI), the Infant's Dermatitis Quality of Life Index (IDQOL), and the Dermatitis Family Impact (DFI) were the most commonly used instruments in adults, children, infants, and caregivers, respectively.

Evaluate the measurement properties and quality of validation studies for the identified instruments (stage 2): The quality of existing quality of life instruments was investigated in one systematic review for adults[20] and one for infants, children

and adolescents with AD[51]. Both reviews were updated using the COSMIN risk of bias checklist and published in a single systematic review in which 133 measurement properties of nine different quality of life instruments were evaluated.[26]

Determine which instruments are preferred for COS (stages 3-5): At the HOME IV meeting, the group voted that psychological functioning, social functioning and physical functioning are essential subdomains for the construct of QoL, and that there are no other essential subdomains.[21] Discussions at HOME IV focused on QoL instruments for adults with AD.[20] The DLQI, the Quality of Life Index for Atopic Dermatitis (QoLIAD) and the Skindex-29 were discussed as candidate instruments but consensus was not achieved to include any in the core set. The HOME V meeting focused on QoL instruments for children[25]. Candidate instruments were assessed in terms of face validity and feasibility and ranked. Agreement was achieved that future validation research on both proxy and self-report instruments should be prioritized according to this ranking. The meeting ended with no recommendation for a QoL instrument for children with AD to be included in the core set. Discussions at HOME VII were based on the updated systematic review, presentation of validity evidence for a new short form of the Childhood Atopic Dermatitis Impact Scale (CADIS)[52] and six group discussions (composed of 8–12 mixed stakeholders including patients or parents) in which the content validity of candidate instruments was assessed using COSMIN criteria on relevance, comprehensiveness and comprehensibility.[53] Content validity of the IDQOL, CDLQI, CADIS long form were rated as sufficient (+) and DLQI, Skindex-16, CADIS short form were rated as inconsistent (+/-). DISABKIDS, Infants and Toddlers Dermatology Quality of Life and Atopic Dermatitis Burden Scale for Adults (ABS-A) received an insufficient content validity rating. Finally, the IDQOL, CDLQI and DLQI were agreed

on as the preferred instruments for the core outcome set by consensus voting[27]. These are the most frequently used instruments for AD in the literature and can be considered a family or series of instruments that cover all ages.

LONG-TERM CONTROL:

Identify instruments (stage 1): systematic reviews that informed this domain include a review of long-term control measures used in randomised controlled trials[22] and a review of AD flare definitions[54]. These reviews identified varied approaches to capturing long-term control, and discussion at HOME III and IV meetings revealed varying views over how to conceptualise this domain[9, 21].

Additional qualitative studies were required to allow definition of the construct of interest. A survey of the HOME membership and international qualitative studies involving people with AD[23, 24] were used to inform preliminary consensus decisions over preferred aspects to be measured in the Long-term control domain[25]. They also helped to refine the domain from “Long-term Control of Flares” to “Long-term Control” and allowed development of a conceptual model for AD control that was used to assess face validity of the chosen instruments[23, 27].

Evaluate the measurement properties and quality of validation studies for the identified instruments (stage 2): Consensus discussions at HOME V confirmed that repeated measurement of the other three core domains (clinical signs, symptoms and quality of life) was insufficient to capture long-term control and that long-term control should remain as a separate distinct domain, to be captured using a global measure of AD control recorded repeatedly over time[21]. Subsequent evaluation of candidate instruments for AD control therefore focussed on global

measures of AD control (either single-item or multi-item instruments). A systematic review revealed one single-item instrument, and four multi-item candidate instruments[29], two of which: RECAP of eczema control[28] and the Atopic Dermatitis Control Tool[55, 56], had been specifically developed to assess AD control.

Determine which instruments are preferred for COS (stages 3-5): Systematic review results were presented at HOME VII in Tokyo, 2019. Candidate instruments were assessed using COSMIN methodology[57], evaluated through small group and whole group discussions and voted using anonymous voting. Unusually, two multi-item control instruments were provisionally chosen for inclusion in the COS as both RECAP and ADCT were high quality and similar in content, making it difficult to choose one over the other. Both RECAP and ADCT have good content validity, responsiveness and show promising results on all psychometric properties that have been tested to date. Ongoing validation is required to test performance in a variety of settings and languages, and further work to develop a single-item global control instrument is recommended[27].

How to use the selected instruments. Nominating a preferred instrument for a core domain is necessary, but not sufficient for achieving harmonisation of outcomes. If for example EASI scores in one study are reported as means at 4 weeks and in another as medians at 6 weeks, meta-analysis of results is problematic. Similarly, dichotomising scores into an array of different cut-offs is unhelpful unless all include the same one to enable meaningful comparisons to be made. There is also little point in only reporting means without standard deviations as the latter is needed to undertake formal meta-analysis. Table 3 summarises

HOME guidance on how the various selected instruments should be reported as a minimum in future publications.[27] The issue of which time points and recommended frequency of measurement of each instrument has been debated at various HOME meetings without consensus being achieved as these are likely to be highly dependent on the research question. Given that AD is a chronic and usually fluctuating inflammatory condition, clinical trials should be of long enough duration to capture the fluctuating nature of disease e.g. a minimum duration of 4 months.[58]

Purpose	To **standardize reporting of endpoints** in line with general trial reporting recommendations which will: • Increase the ability to pool data in meta-analyses and compare results of trials. • Minimize bias • Improving interpretation of trial results
Recommended reporting guidance[37]	• Always report the **mean and standard deviation** (SD) for **each randomized group** (or median and quartile range for skewed data) plus the number of participants analysed. • Preferably, these should be reported for each time point but as a **minimum** at **baseline and at the primary endpoint** and end of treatment if later than the primary endpoint.

	• There is no requirement for these recommendations to be the primary analysis but they should be available in the results paper or in an online results repository. • Where the data using instruments such as EASI are dichotomised e.g. number achieving 75% improvement, the minimum reporting guidance should also be included.

TABLE 3: Recommendations on minimum reporting standards for HOME core outcome instruments in atopic dermatitis clinical trials based on the Consolidated Standards of Reporting Trials (CONSORT) 2010 statement.

The HOME Core Outcome Set

Figure 3 summarises the HOME core outcome set that should be reported in all future clinical trials of AD. We hesitate to use the term “final core outcome set” as decisions based on current evidence may be overturned by new evidence on existing instruments or better instruments. However, changing a COS each year with minor modifications would defeat the higher purpose of harmonising outcomes so that they can be combined in meta-analyses. Therefore, in the absence of any *major* developments, we recommend a period of stability for the COS to “settle down” in order to achieve its purpose of harmonising trial outcomes. This does not mean that work stops on the existing COS. Many knowledge gaps have been highlighted for specific instruments and other gaps such as the need to identify a single global

question have also been highlighted and will become the topics of future HOME meetings. It is also worth mentioning at this stage that HOME has also been engaged in recommending valid instruments for routine clinical practice of AD.[59] The choice of instruments to be used in routine care is more of a “pick and choose” rather than a mandated list, but their overlap with those that are used in clinical trials can only help with interpretation to everyday patient care as users of the instruments become familiar with their clinical interpretation.

Key lessons learnt and future challenges

Lessons learnt: The formation of domain specific groups with leads and co-leads was instrumental to the success of HOME. Meeting preparation, producing manuals, workbooks and walking through possible scenarios is also key, and is resource intensive. Meeting structure and conduct is important– for example by working in small groups and ensuring that all contributors feel heard and valued – by listening, acknowledging and recording dissenting views and accepting when consensus is not possible. Ann executive committee to facilitate decisions and to steer meetings in real-time as new problems and solutions emerge is also useful. Managing conflicts can be challenging, and efforts were made into preventing the development of partisan factions within the HOME community by including strict conflict of interest policies (e.g., instrument developers not being allowed to vote), anonymous voting and transparent reporting of processes and findings. Having independent moderators (MB and JS) with extensive experience of COS outside of dermatology was very helpful in ensuring fair process and progress. As we found with long term

control, it is important to clearly define domains prior to consensus voting. Engagement of patients and carers needs special attention in the form of dedicated pre-meeting materials, explanatory pre-meetings and de-briefing meetings, and making sure their health needs were met during the meeting. Other facilitatory patient/carer approaches included smaller breakout groups that are less intimidating than a full meeting, chairs empowering patients/carers by asking for their views first during discussions and by encouraging speakers to present material in an understandable way.

Future challenges: Although many AD outcome measures have been published, few have met the quality standards required for core outcome selection, so the first challenge is “less but better”. Implementation of the COS according to our roadmap[6, 35] is our next major challenge and has been the topic of our virtual HOME IX meeting (September 2021). If no trialists, regulators, funders, systematic reviewers, clinical guideline developers or journals use the COS, then the current status quo of not being able to combine and compare trials will prevail. Some major funders such as the UK Health Technology Assessment Programme[60] or the German clinical trial funding program of the DFG/BMBF already encourage the use of core outcome sets in their publicly-funded trials and others such as the international Cochrane Skin Group[61] strongly encourage those undertaking reviews to use core outcome sets[62]. Engagement with targeted material for different clinical communities and audiences (allergologists, paediatricians, dermatologists, generalists) is important as is engagement with self-help social media groups that are run by patients/carers. Additional implementation facilitators recognized at the HOME IX meeting include improving the universal applicability of the COS for diverse groups, and finding ways to decrease the administrative burden of using COS while increasing their benefit.

Although early indications demonstrate good uptake of individual HOME recommended instruments [63], more focused implementation work is needed.

Further specification of instrument is needed concerning *when* the measurement should be done and *how* scales might be dichotomised and which groups should be compared[64]. If for example all trials use the EASI to measure clinical signs of AD, but trial A reports EASI 75 at week 12, trial B reports mean EASI change at 8 weeks, trial C reports proportion of patients <EASI 50 at week 4, then the results of these 3 trials cannot be compared although they adhere to the HOME COS[65].

The lack of permanency of any COS needs to be acknowledged. New generic domain-specific single items measuring domains such as anxiety, sleep loss or itch such as those developed by the NIH Patient-reported Outcome Measures Information System (PROMIS) system[66] is an area that needs revisiting at future HOME meetings.

There is always a danger of “rival” COS developed by other international groups, but a profusion of COS will be as damaging to patient needs as the absence of a COS. During the COVID-19 pandemic for example, four core outcome sets were being developed independently and had to be combined into a meta-COS[67] – a clunky process that would have been better done in one collaborative group from the start.. We encourage all researchers interested in AD outcomes to work with HOME where diverse views will be welcome.

It is also worth re-emphasising that the core outcomes do not need to be primary outcomes or the sole outcomes. Researchers are free to continue to use other outcome measures such as SCORAD or biological markers providing they also include the HOME COS.

Clinical interpretability of what a given score means is also a challenge that can be mitigated by descriptive anchors for cut-off points, and the more widespread use of such scales in everyday practice. To this end, the decision of the HOME group to work on outcomes for clinical practice[59] has helped e.g. the POEM and NRS-11 for itch are common to the clinical trial and clinical practice datasets allowing clinicians to calibrate scales to their own rules of thumb when assessing AD severity. Cross-compatibility with trial registry outcomes as exemplified by the international TREatment of ATopic eczema (TREAT) Registry Taskforce[68] basing many of its recommendations on the HOME initiative. Table 4 summarises key remaining research gaps.

• For the patient-reported symptoms domain, it is not known whether the NRS-11 peak itch past 24h is suitable for young children as it is currently only validated in adults.
• For atopic dermatitis control, further validation studies are required to determine whether either of the two recommended multi-item instruments (ADCT and RECAP) have any advantage over the other. Additionally, it is unknown how they compare to a single item patient global instrument, and whether a single item instrument could be sufficient.
• The potential use of non-disease-specific patient-centred measures such as the PROMIS dataset[69] for the COS needs to be assessed, particularly for the quality of life domain.
• It is not clear how often the COS need to be measured and what the optimal time points for measurement are. Consultation is required to determine to what degree a COS should dictate timing of assessments.

TABLE 4: What is not known in relation to the four core outcome domains and their measurement

Finally, in the interests of efficiency and methodological rigour, it is important to share learning from HOME across other dermatology groups wishing to develop core outcome sets. The recent fusion of the Cochrane Skin Core Outcomes Set Initiative with the Consortium for Harmonizing Outcomes Research in Dermatology into one

CHORD COUSIN Collaboration (C3) that now includes over 25 dermatology COS groups is helping to reduce duplication of effort[61]. Complete reporting of COS should follow recommended reporting guidance[31]. It is possible that some core outcomes will be common across several if not all skin disease in time. Others have developed a hierarchical and dermatology-specific taxonomy for outcome classification that provides an opportunity to enhance comparison of evidence.[64]

Conclusions

This article has described the story of the HOME core outcome set for clinical trials of interventions for AD from its inception on domain selection through to instrument selection and standardised reporting, guided by the HOME roadmap using up to date rigorous methodology (Figure 1). Although the work of HOME has spanned over 10 years and has been largely unfunded, it has nevertheless achieved its original aim of establishing a COS for AD trials. The value of this work is nil if the core outcomes are not used in current and new AD trials, whether these be pharmacological or behavioural interventions. All of the HOME publications and recommended instruments along with translations and instructions on how to use them are available on the HOME website[70]. We urge researchers, funders, regulators, commissioners of health care, patients and carers and all health care professionals dealing with AD to demand the use of the HOME COS so that all new evidence can be combined in a meaningful way for patient benefit.

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690 **Figure legends**

691 **Figure 1:** The Harmonizing Outcome Measures for Eczema (HOME) roadmap to
692 develop core sets of outcome measurement instruments for atopic dermatitis.
693 Reprinted from [6]

694 **Figure 2:** Overview of consensus meeting structure

695 **Figure 3:** The HOME core outcome set domains and instruments that should be
696 reported in all future AD clinical trials. Instruments should report mean and standard
697 deviation for each randomised group at baseline and at primary outcome and end of
698 study measurement points.

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