How to use the HOME Core Outcome Set for atopic dermatitis trials – a users' guide

Running head: The HOME "How to Guide"

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Funding sources: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest disclosures: **KST** was involved in development and testing of one of the HOME core outcome instruments (Recap of atopic eczema (RECAP)) and is employed at the research centre where the Patient Oriented Eczema Measure (POEM) was developed. The University of Nottingham owns copyright to license Patient Oriented Eczema Measure – chargeable for commercial users. **LH** received consultation fees from the University of Oxford on an educational grant funded by Pfizer, unrelated to submitted work. Involved in the development of the Recap of atopic eczema (RECAP) instrument and is employed at the research centre where the Patient Oriented Eczema Measure (POEM) was developed. The University of Nottingham owns copyright to license Patient Oriented Eczema Measure – chargeable for commercial users. **YAL** received honoraria or fees from AbbVie, Sanofi, Genentech, Regeneron, Pfizer, and Dexcel Pharma, an independent research grant from Abbvie, and has, without personal compensation, provided investigator services for Eli Lilly, Pfizer, and AbbVie, all unrelated to this study. **ELS** reports personal fees from Advances in Cosmetic Medical Derm Hawaii LLC, AbbVie, Amgen, AOBiome LLC, Arcutis Biotherapeutics, Arena Pharmaceuticals, Aslan Pharma, Boehringer Ingelheim USA, Inc., Boston Consulting Group, Bristol Myers Squibb – BMS, Collective Acumen LLC (CA), CorEvitas, Dermira, Eli Lilly, Evelo Biosciences, Evidera, ExcerptaMedica, FIDE, Forte Bio RX, Galderma, GlaxoSmithKline, Incyte, Janssen, Johnson & Johnson, Kyowa Kirin Pharmaceutical Development, Leo Pharm, Medscape LLC, Merck, MauiDerm, MLG Operating,

MJH holding, Pfizer, Physicians World LLC, PRImE, Regeneron, Revolutionizing Atopic Dermatitis Inc, Roivant, Sanofi-Genzyme, Trevi therapeutics, Valeant, Vindico Medical education, WebMD. He also reports grants (or serves as Principal investigator role) from AbbVie, Acrotech Biopharma Inc, Amgen, Arcutis, Aslan, Castle Biosciences, CorEvitas, Dermavant, Dermira, Eli Lilly, Incyte, Kymab, Kyowa Kirin, National Jewish Health, Leo, Pfizer, Regeneron, Sanofi, and Target RWE. These potential conflicts of interest have been reviewed and managed by OHSU. **CA** received institutional funding from Dr Wolff Group and Bionorica, and consultancy fees or honoraria from Dr Wolff Group, Bionorica, Sanofi, LEO and Rheacell. He was also involved in development and testing of one of the HOME core outcome instruments (Recap of atopic eczema (RECAP). **PS** received a departmental independent research grants for TREAT NL registry from Pharma 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 and, is Chief Investigator (CI) of the systemic and phototherapy atopic eczema registry (TREAT NL) for adults and children and was involved in the development of one of the HOME core outcome instruments (Recap of atopic eczema (RECAP)). **JS** reports institutional grants for investigator-initiated research from the German GBA, the BMG, BMBF, EU, Federal State of Saxony, Novartis, Sanofi, ALK, and Pfizer. He also participated in advisory board meetings as a paid consultant for Sanofi, Lilly, and ALK. **LG:** No conflicts to disclose. **MEJ:** No conflicts to disclose. **NK** received honoraria as a speaker/consultant for Sanofi, Maruho, Abbvie, Ely-Lilly Japan, Mitsubishi Tanabe Pharma, Jansen Pharma, Taiho Pharmaceutical, Torii Pharmaceutical, Kyowa Kirin, Celgene Japan and Leo Pharma, and has received grants as an investigator from Maruho, Ely-Lilly Japan, Sun Pharma, Taiho Pharmaceutical, Torii Pharmaceutical, Boehringer Ingelheim Japan, Kyowa Kirin, Jansen Pharma, Boehringer Ingelheim Japan, A2 Healthcare, Abbvie, and Leo Pharma. **HCW** chaired the HOME core outcome set initiative from 2008 to 2021 and was involved in the development of the Patient Oriented Eczema Measure (POEM) and is employed at the research centre where the Patient Oriented Eczema Measure (POEM) was developed. The University of Nottingham owns copyright to license Patient Oriented Eczema Measure – chargeable for commercial users. **BS** – No conflicts to disclose.
Data availability: No new data were generated or analysed in support of this research.
Ethics statement: Not applicable.

What is already known about this topic?

- The Harmonising Outcome Measures for Eczema (HOME) initiative have recommended core domains and outcome instruments that should be included and reported in all intervention trials of atopic dermatitis treatments.
- Use of the core outcome set in trials and systematic reviews is currently low.
- Guidance is needed on how to access the HOME core instruments, how to use them, and how to report trial findings.

What does this study add?

- This paper provides a "how to" guide to promote use of the HOME core outcome set.
- It addresses common questions that people ask when trying to use the core instruments and provides data to support sample size calculations and interpretation of results.

What are the clinical implications of this work?'

- By increasing uptake of the HOME core outcome set, clinical practice will be improved as data from published trials will be more easily combined in meta-analyses, thus improving clinical decision-making.
- Improving the reporting of trial data in a consistent way for defined sub-groups (e.g child/adult) can boost the power of sub-group analyses in systematic reviews and help make informed personalised-medicine decisions.

Abstract

The Harmonizing Outcome Measures for Eczema (HOME) initiative has agreed upon the core outcome set for use in atopic dermatitis (AD) clinical trials, but additional guidance is needed to maximise uptake of the core set.

This article provides answers to some of the commonly asked questions about using the HOME core outcome set. It also provides data to aid interpretation of trial results and to support sample size calculations for future trials.

By encouraging adoption of the core outcome set and facilitating consistent reporting of outcome data, we hope that results of eczema trials will be more comprehensive and readily combined in meta-analyses and patient care will be improved.

Background

The Harmonising Outcome Measures for Eczema (HOME) initiative has published an agreed core outcome set for use in atopic dermatitis (AD) (syn, atopic eczema, eczema) trials.(1)

Whilst it is hoped that the core outcome set will be widely adopted, this will not happen without broad awareness, ownership and acceptance of the core outcome set throughout the eczema research community. Uptake of core outcome sets across medicine is known to be variable(1, 2) and guidance on how best to support uptake of core outcome sets suggests a need for recommendations on how to measure outcomes(3, 4). Tracking of use of the HOME core outcome set shows that uptake of the core domains and outcome instruments is increasing over time but there is still much room for improvement.(5, 6)

This paper aims to provide practical guidance on the use of the HOME core outcome set for investigators planning clinical trials in patients with AD. It answers some of the common questions about using the HOME core outcome set, how to access the outcome measurement instruments, what training/resources are needed to use them appropriately and clarifies when the Core Outcome Set is applicable. We also provide exemplar data to inform sample size calculations for eczema trials and encourage standardised data collection and reporting of the core outcomes set.

Which trials does the Core Outcome Set apply to?

The HOME core outcome set is recommended for use in all trials testing AD interventions, if they are asking a question for which clinical outcomes are relevant. This includes drug trials and non-drug trials.

The HOME core outcome set is NOT relevant for early phase dose finding studies or mechanistic studies (e.g. capturing biomarkers); primary prevention trials (when incidence of eczema may be a more appropriate outcome); or trials of other types of eczema (e.g. for hand eczema there is a separate core outcome set initiative https://www.c3outcomes.org/heCore Outcome Set).

The domain of long-term control is only required if a trial is 3-months' duration or longer.

If a trial includes people with a range of skin conditions (e.g. people with both AD and psoriasis), we would recommend that the HOME core outcome instruments be considered for the trial where possible, but adherence to the core set would not be mandated as this might result in undue data collection burden. If data are collected of relevance to the HOME core outcome set (e.g. quality of life using the DLQI family of instruments), then ideally data should be presented separately for participants with AD. This could be provided as supplementary materials.

Is the Core Outcome Set suitable for all people?

The core outcome set has been chosen to be relevant for all severities of AD, all ages and all ethnic groups, although some of the recommended instruments are age specific (see Figure 1). Training for assessors may be needed to ensure applicability across all skin tones (particularly for the assessment of clinical signs in people with dark skin tones)(7, 8). There is a need for ongoing validation work to test the suitability of all instruments in different cultures, ethnicities and ages but current evidence supports their wide use and applicability.

How can the HOME Core Outcome Set instruments be accessed?

Details of how to access the recommended core outcome instruments are available through the HOME website (www.homeforeczema.org). All instruments are freely available for use in non-commercial studies and for academic purposes, but copyright is usually retained by the developer and so permission for use should be obtained (see individual instruments' websites for details of how this can be obtained). Some instruments may charge for commercial use.

Many of the preferred outcome instruments have been translated (and checked for quality of translation) and these translations are made available via the instrument's individual websites where possible. The HOME initiative encourages sharing of validated versions of the translated instruments to reduce research waste and ensure consistency.

If a specific language version of the outcome instruments has not yet been made available, best practice guidance on how to translate the instrument and ensure that the translated version is fit for purpose is available on the HOME website. Alternatively, various commercial companies offer suitable translation services and accreditation certificates.

The patient reported outcomes included in the HOME core outcome set are simple to use and all take less than 2 minutes to complete. Specific instructions for completion are included within the instruments. For the assessment of clinical signs with the Eczema Area and Severity Index (EASI), a practical guide on how to complete the instrument is available(9) and training materials for clinicians or researchers making the assessments are available on the HOME website.

How should the CORE OUTCOME SET outcomes be collected?

There is currently no agreed consensus from HOME as to the preferred timing of outcome data collection, although the TREAT Taskforce has published a consensus statement for use in clinical registries suggesting that outcomes should be collected at "a minimum follow-up frequency of initially 4 weeks after commencing treatment, then every 3 months while on treatment and every 6 months while off treatment." (10)

It has been reported that collecting outcomes for at least 4-5 timepoints during a trial is most efficient(11), but the exact timing of these assessments still lacks consensus agreement. Collecting outcomes very frequently throughout a trial (e.g. weekly) may lead to non-specific trial effects for both groups that could mask small treatment effects(12).

How should the CORE OUTCOME SET outcomes be reported?

Encouraging all trials to report outcomes at consistent timepoints can facilitate meta-analysis in systematic reviews(10). In the absence of consensus from the HOME initiative over timing of outcome assessments, we would propose a pragmatic solution of trialists reporting outcome data at 4 weeks after starting treatment (to demonstrate short-term effect) and between 12 and 16 weeks (to capture medium term effects). In so doing, these recommendations reflect the consensus recommendation by the TREAT Taskforce[7] and systematic review teams would be able to combine data at these two timepoints with relative confidence. Data for these timepoints could be made available as supplementary data files if necessary.

Trial reports should include the mean and standard deviation for each timepoint (or median and interquartile range, depending on the distribution of the data) to facilitate inclusion in meta-analyses. (13) Presenting data as a categorised outcome e.g. the proportion achieving clinically significant improvement can aid interpretation of the trial findings, but is not sufficient for reporting of the core outcome set without also including summary data for the continuous data.

To facilitate meta-analyses, we would advise the sharing of trial datasets so that important sub-group effects can be explored with combined data sets. If full data sharing is not possible, then it can be helpful to provide summary data for key characteristics separately from the main trial effects (e.g. age, gender, ethnicity, eczema severity). Such comparisons are generally underpowered in most trials, but by reporting these data separately, subsequent meta-analyses may be able to explore important sub-group effects and better inform clinical practice.

A template data table for use when reporting the HOME core outcome set is provided (supplementary materials) and is available on the HOME website. If trialists routinely use this and provide it as supplementary information alongside trial reports, this could significantly enhance the speed and reliability of conducting meta-analyses in systematic reviews and inform sub-group analyses for specific patient groups.

How should data from the core outcome instruments be interpreted?
When reporting changes in scores for the HOME core outcome instruments, it is useful to understand the clinical relevance of any observed changes.

Many of the HOME core outcome instruments have been mapped to severity bandings to aid interpretation (Table 1) and this can be helpful when characterising a study population.

The minimum important change (MIC) is often described as the smallest within-person change that is important to patients.(14) This can be an important concept to aid interpretation of trial results. For example, it can be used to report the proportion of people responding to treatment (i.e. achieving the MIC) for each of the compared treatments(15).

The MIC is a difficult concept to characterise and is rarely a fixed value. Rather it depends on the type of participants included in a trial, the setting and the nature of the interventions being compared.(16) The values may also vary depending on whether you are interested in improvement or deterioration.(17)

A summary of published data relating to severity bandings and minimum important change for each of the HOME core outcome instruments is outlined (Table 1).

How can sample size estimates be made?
It has been advocated that sample sizes for trials should be based on the reasonable estimates of the true benefit of a given intervention (e.g. based on effect size anticipated, estimates from previous studies or values that are considered to be a realistic benefit), rather than the size of benefit judged to be important (MID) (ref Wong).

For example, a trial testing a simple, low-cost intervention with minimal side-effects may seek to detect a relatively small treatment effect that has broad applicability and benefit for many people, whereas a trial testing a new systemic drug for people with severe disease and with potential side-effects is likely to require a larger treatment effect to justify going ahead with the trial.

It may also be important to consider whether effect sizes vary according to baseline characteristics of the included population (e.g. eczema severity, age, gender). A study by Howells *et. al.(18)* explored the impact of different demographic characteristics of participants included in five randomised controlled trials that used the POEM instrument in children with AD. This study provided some reassurance that effect sizes were relatively stable across key demographic characteristics, including ages, gender, ethnicity and disease severity.

One of the key challenges for designing eczema trials is to source relevant data to inform sample size estimations. To facilitate researchers in designing trials of AD treatments we have collated summary statistics for each of the HOME core outcome instruments according to setting, age of participants and disease severity. Where possible, details of the correlation between timepoints are also provided to inform analyses using repeated measures techniques (Tables 2A to 2E). Data for quality-of-life instruments have not been provided as this requires a different instrument for different ages.

Areas of ongoing methodological debate

As with all core outcome sets, the HOME core set is provisional and may be adapted in time as new information comes to light. Several areas of debate remain, for which consensus discussions and agreement are still required.

Work is ongoing to establish the most efficient way of collecting the HOME core outcome set and to reduce repetition of items across different domains. In the current core set, itch is captured in different ways in all three of the patient-reported domains, which is potentially frustrating and burdensome for people taking part in eczema trials. Future HOME meetings will consider whether all items are necessary and whether a more streamlined approach could be adopted. It is also unclear whether the HOME patient-reported outcomes should be administered in a consistent order or not.

Some of the instruments (POEM and DLQI family of instruments) were originally designed and validated using paper questionnaires rather than online versions, but preliminary evidence suggests that use in either format is appropriate(19). With increasing use of online data capture forms, it is tempting to make answering all items on the outcome instruments mandatory. We do not generally advise making electronic data items mandatory as this does not reflect how the instruments were developed or validated. An alternative approach that may help to minimise missing data during electronic data capture, could be to make individual response items "non-mandatory" but to add a warning to remind participants that not all of the questions have been completed as they attempt to navigate away from the form. If outcomes are collected using mandatory fields, it would be helpful to report this transparently in trial report so that further exploration of the validity of both approaches could be explored.

In relation to capturing the domain of long-term control, whilst agreement over the possible instruments to measure 'eczema control' has been reached, it is not yet clear how often these instruments should be used to capture control over time. Further work is also needed to establish if a single-item global measure of control would be sufficient.

For trials requiring health utility data to inform health economic analyses, it may be possible to map scores from the DLQI quality of life instruments to EQ-5D utility scores (20), thus reducing the data collection burden of using multiple quality of life questionnaires.

How best to combine and analyses quality of life data across different age groups can be challenging and potentially limit the power of studies to look at quality of life outcomes. For

example, methodological guidance is needed to establish whether scores across the three age-specific quality of life instruments can be combined for analysis.
Similarly, it is unclear whether scores derived by proxy reporting can be combined with self-reported outcomes when including children and adults in the same trial.

Conclusion

We hope that this "How to Guide" will support the uptake and reporting of the HOME Core Outcome Set, and by doing so, will improve the evidence-base for clinical decision-making and improve patient care.

Acknowledgements

Thank you to all members of the HOME initiative who have contributed to consensus discussions over the core outcome set.
Thanks also to Natasha Rogers for her help in preparing this manuscript for submission and for creating Figure 1.

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Figure legend

Figure 1: The HOME Core Outcome Set. *Copyright: University of Nottingham 2023*

1 Table 1: Interpretability of the HOME core outcome instruments

2

Core instruments (key publications)	Severity bandings	Minimum important within person change (MIC)
EASI (Hanifin 2022)(9)	(Lesham 2015)(21, 22) Clear or no eczema = 0 Almost clear = 0.1-1.0 Mild disease = 1.1-7.0 Moderate disease = 7.1-21 Severe disease = 21.1-50 Very severe disease = 50.1+ (Chopra 2017)(22) Clear = 0 Mild = 0·1-5·9 Moderate = 6·0-22·9 Severe = 23·0-72	(Schram 2012)(23) 6.6 points Less than 3 points (likely to be measurement error)
POEM (Charman 2004)(24)	(Charman 2013) (25) Very mild = 0 to 2 Mild = 3 to 7 Moderate = 8 to 16 Severe = 17 to 24 Very severe = 25 to 28	(Howells 2018)(26) ≤ 2 points (likely to be measurement error) 2.1 to 2.9 points (small change, but may not be clinically important, depending on context) 3 to 3.9 (small, but potentially important difference) ≥ 4 points (very likely to be clinically important difference)
NRS peak itch	Not applicable	(Yosipovitch 2019) (27)

Yosipovitch 2019 (27)		≥2 to 4 points
Recap (Howells 2019) (28)	(Zhang 2023)(29) ≥ 6 points = AD not controlled Also see: Bhanot (2021)(30)	(Zhang 2023)(29) 4 points
ADCT (Pariser 2019)(31)	(Pariser 2019)(31) ≥ 7 points = AD not controlled	(Simpson et al 2019)(32) 5 points
DLQI Finlay (1994)(33)	(Hongbo 2005)(34) No effect on patient's life = 0-1 Small effect on quality of life = 2-5 Moderate effect of quality of life = 6–10 Very large effect of quality of life = 11-20 Extremely large effect on quality of life = 21-30	(Basra 2015)(35) 4-point change (for inflammatory skin disease, people with AD made up 12.5% of sample)
CDLQI Lewis-Jones MS (1995) (36)	Waters A (2010)(37) 0-1 = no effect on child's life 2-6 = small effect 7-12 = moderate effect 13-18 = very large effect 19-30 = extremely large effect	(Simpson 2019)(38) 6 – 8 points (based on adolescents with moderate to severe disease)

IDQLI Lewis-Jones MS (2001)(39)	Not yet available	Not yet available

Table 2 Data to inform sample size calculations

Table 2A: Clinical Signs – EASI

Trial (setting)	Eligibility for trial	Age	Baseline Mean (SD)	12 weeks Mean (SD)	16 weeks Mean (SD)	Correlations between timepoints (if repeated measures)
BEE Trial (primary care, UK)(40) N= 550	Mild/ Moderate AD	Child	Intervention (cream): 3.2 (IQR 2.0; 6.3) Control (lotion): 3.3 (IQR 2.0; 7.2)	Not available	Intervention (cream): 2.3 (IQR 0.9; 5.2) Control (lotion): 2.2 (IQR 0.6; 3.6)	
*CLOTHES Trial (41)(primary & secondary care, UK) N=300	Moderate/ severe AD	Child	Intervention: Geometric mean 9.6 (7.8) Control: Geometric mean 11.4 (10.6)	NA	Intervention: Geometric mean 7.7 (10.1) Control: Geometric mean 7.7 (8.7)	Correlation between baseline and 16 weeks: 0.65
Dupilumab	Moderat	Adolescen	Interventio		Interventio	

Trial (42)(secondary care, US and Canada) N=251	e/ severe AD	ts (12 to 18 years)	n: 35.8 (14.8) Control: 35.5 (14.0)		n: 12.3 (11.1) Control: 24.1 (15.5)	

*Data in the CLOTHES trial were skewed and so geometric mean was used for analysis.

Table 2B: Patient-reported symptoms – POEM

Trial (setting)	Eligibility for trial	Age	Baseline Mean (SD)	12 weeks Mean (SD)	16 weeks Mean (SD)	Correlations between timepoints (if repeated measures)
BATHE Trial (primary care, UK)(43) N=482	Mild/ Moderate AD	Child	Intervention :9.5 (5.7) Control: 10.1 (5.8)	Intervention: 7.7 (6.2) Control: 7.9 (5.9)	Intervention: 7.1 (6.1) Control: 8.2 (6.3)	Correlation between baseline and 12 weeks: 0.52 Correlation between baseline and 16 weeks: 0.48
ECO Trial (44)(primary care, UK) N=337	All severities	Young people (13 to 25 years)	Intervention : 15.1 (5.3) Control: 15.3 (5.5)	Intervention: 11.1 (5.9) Control: 14.0 (6.0)	Intervention: 11.2 (5.9) Control: 14.4 (6.3)	Correlation between baseline and 12 weeks: 0.57

						Correlation between baseline at 16 weeks: 0.56
ECO Trial (44)(primary care, UK) N=340	All severities	Child	Intervention: 12.9 (5.2) Control: 12.8 (5.4)	Intervention: 9.6 (6.1) Control: 10.0 (6.1)	Intervention: 9.7 (6.1) Control: 10.0 (6.0)	Correlation between baseline and 12 weeks: 0.61 Correlation between baseline at 16 weeks: 0.61
CLOTHES Trial (41)(primary & secondary care, UK) N = 330	Moderate/ severe AD	Child	Intervention: 15 (6.0) Control: 15.8 (5.6)	Intervention: 11.5 (7) Control: 13.4 (6.7)	Intervention: 10.9 (6.6) Control: 13.3 (7.2)	Correlation between baseline and 16 weeks: 0.64
Dupilumab Trial (42)(secondary care, US and Canada) N=251	Moderate/ severe	Adolescents (12 to 18 years)	Intervention: 21.1 (5.5) Control: 21.1 (5.4)		Intervention: 11.2 (7.4) Control: 16.2 (8.3)	
EMO Trials (online, UK)(12)	Mild to severe	Mostly adults (93%)	Intervention:	(8 weeks) Intervention:		

N = 296			15.42 (6.02) Control: 14.28 (6.06)	12.00 (6.08) Control: 12.94 (6.47)		

Table 2C: Itch intensity – NRS-11 peak itch

Trial (setting)	Eligibility for trial	Age	Baseline Mean (SD)	12 weeks Mean (SD)	16 weeks Mean (SD)	Correlations between timepoints (if repeated measures)
ECO Trial (44)(primary care, UK) N=337	Mild/ Moderate	Young people	Intervention :5.7 (2.2) Control: 5.6 (2.4)	Intervention :5.0 (2.6) Control: 5.0 (2.5)	Intervention: 4.5 (2.6) Control: 4.7 (2.7)	Not available
Dupilumab Trial (42)(secondary care, US and Canada) N=251	Moderate/ severe	Adolescents (12 to 18 years)	Weekly average Intervention : 7.5 (1.8) Control: 7.7 (1.6)		Weekly average Intervention: 4.0 (2.7) Control: 6.0 (2.3)	Not available

Table 2D: Eczema Control – RECAP

Trial (setting)	Eligibility for trial	Age	Baseline Mean (SD)	12 weeks Mean (SD)	16 weeks Mean (SD)	Correlations between timepoint

						s (if repeated measures)
ECO Trial (44)(primary care, UK) N=340	Mild/ Moderate AD	Child	Intervention: 12.8 (5.4) Control: 12.3 (5.5)	Intervention: 9.0 (6.1) Control: 9.7 (6.3)	Intervention: 8.6 (6.0) Control: 9.4 (6.9)	Not available
ECO Trial (44)(primary care, UK) N=337	Mild/ Moderate	Young people	Intervention: 13.0 (5.1) Control: 13.1 (5.6)	Intervention: 10.3 (6.0) Control: 11.5 (6.3)	Intervention: 9.2 (6.0) Control: 10.7 (6.6)	Not available
EMO Trial (12)(community, UK) N= 232	All severities	Mostly adults	Intervention: 12.29 (6.14) Control: 11.79 (6.30)	(8 weeks) Intervention: 10.67 (5.66) Control: 11.18 (5.86)		Not available

Table 2E: Eczema Control – ADCT

Trial (setting)	Eligibility for trial	Age	Baseline Mean (SD)	12 weeks Mean (SD)[PMM range]	16 weeks Mean (SD)[PMM range]	Correlations between timepoints (if repeated measures)
RELIEVE AD Registry real-world clinical practice (45) (Strober, et al.) N=699	Initiating dupilumab	≥18	15.8 (5.4)	5.6 (5.0) [5.1-6.9]	(6 months) 5.0 (4.9) [4.2-7.2]	
BioDay Registry N=104 (46) (Oosterhaven,	On dupilumab for >16 weeks	≥18	N/A	N/A	5.1 (3.7)	Not available

et al)	and <52 weeks					
CorEvita registry (data on file) N=1738	Systemic eligible EASI≥12 v-IGA mod-severe	≥18	13.2 (6.3)			Not available

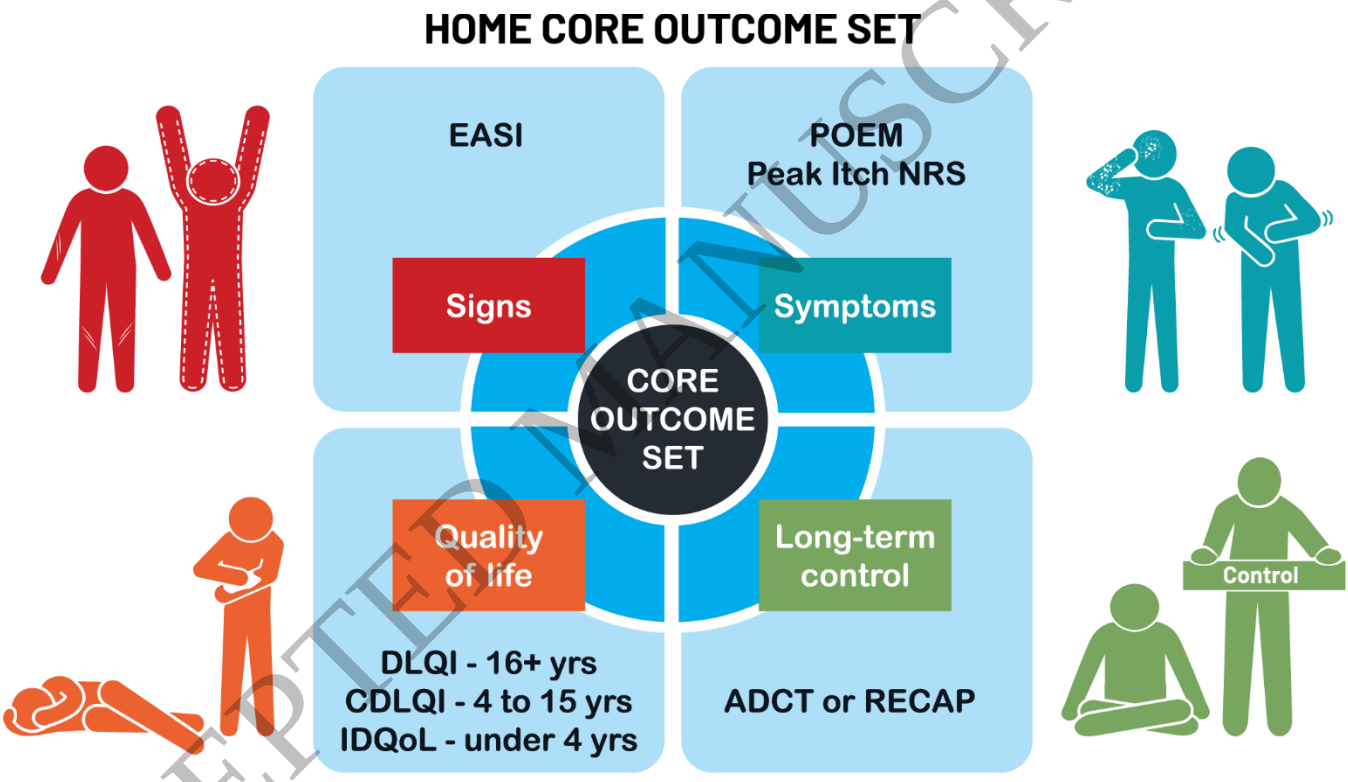

Figure 1
178x100 mm (DPI)