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HOME Long-term control working group

Dr Kim Thomas on behalf of the long-term control group

Centre of Evidence Based Dermatology

University of Nottingham

Overview

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- Clarification of the scope of this domain
- Overview of progress to date
- Highlight some of the key issues for further discussion
- Interactive sessions and voting

Members of the group

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Kim Thomas (Lead)
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Amy Paller
Matt Ridd
Marie-Louise Schuttelaar
Kyle Tang
Annika Volke
Stephan Weidinger
Andreas Wollenberg

Projects conducted to date

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- Systematic review of flares definitions used (update of 2005 review)
- Validation study on "escalation of treatment" as a possible flare definition (experience from two clinical studies)
- Validation study on "well-controlled weeks" as a possible outcome for capturing long-term control

What do we mean by long-term control?

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- Seems obvious…….but what do we mean and how should we measure it?
- Is this really a separate domain, or repeated measurement of other core outcomes?
- Flares, escalation of treatment, well-controlled weeks, accessing of health resources?
- Can we learn from other chronic disease (e.g. asthma)?

Asthma composite measures of control

TABLE VI. Summary of the characteristics of asthma control score instruments

Instrument	No. of questions	Recall window	Questionnaire content						Physiologic measures
			Symptom frequency	Rescue therapy use	Sleep interference	Activity limitation	Exacerbations	Other	
ACCI	5	1 week (2 weeks for sleep)	X	X	X	X	X		
ACQ	6	1 week	X	X	X	X			FEV_1
ACSS	8	1 week	X	X	X	X			PEF or FEV_1, sputum eosinophilia
ACT	5	4 weeks	X	X	X	X		Self-rating of control	
ATAQ	4 (control dimension)	4 weeks		X	X	X		Self-rating of control	
Breathmobile	7	4 weeks (3 items); 2 years (2 items); no specific window (2 items)	X	X	X	X	X		
cACT	7	4 weeks	X		X	X		Self-rating of control	
CAN	9	4 weeks	X		X	X	X		
30-Second	5	1 week (3 items); 3 months (2 items)	X	X	X	X			

Asthma - exacerbations

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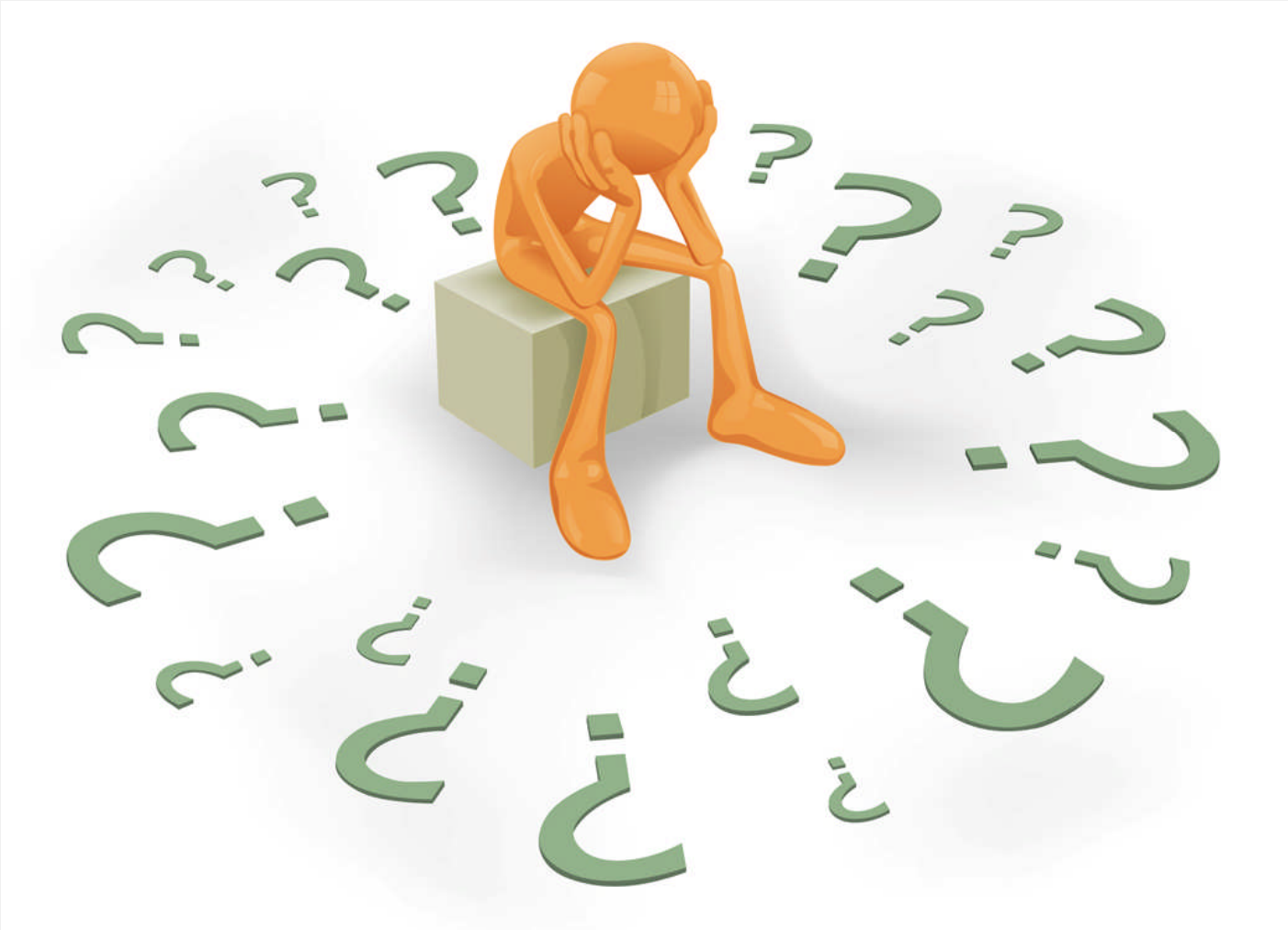
"The working group participants propose that the definition of ''asthma exacerbation'' be ''a worsening of asthma requiring the use of systemic corticosteroids to prevent a serious outcome.''

- Fuhlbrigge A Asthma outcomes: Exacerbations 2012 *J Allergy Clin Immunol* 2012;129:S34-48.

What do we mean by long-term control?



Group responses

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- Need to intervene with a treatment
- Escalation of treatment (what treatment)
- Duration of trial – needs to suit all
- Serial measurement of signs, symptoms and QoL
- Need to reflect that eczema is a chronic disease
  - Capture periodicity OR a serial measurement of the 3 domains
  - Number of bad days / clusters of bad days
  - Avoid term average

Progress to date

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A. Systematic review of flares definitions

B. Validation study - “escalation of treatment” as a flare definition

C. Validation study - “well-controlled weeks” as an outcome for capturing long-term control a picture

Systematic review of flares

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How should atopic dermatitis “flares” be defined? Implications for designing and conducting trials

Systematic review of flares (Lead: Sinéad Langan)

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- Update of 2005 review (last search date 12th Feb 2013)
- All prospective clinical studies that included “flare” as an outcome
- Search terms: flare$”; “exacerbation$”; "relaps$”; remission$; worse$ and *recurrence”
- A-priori criteria were defined for assessing flare definitions:
  - Assessed by patients
  - Feasible to collect in all settings
  - Flares assessed at the time symptoms experience

Systematic review of flares - results

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- 26 / 414 studies included flare outcomes
  - 12 from original review (additional data extracted)
  - 14 new studies
- 21 different definitions were used
- Definitions categorised:
  - Behavioural definitions (n = 6)
  - Arbitrary cut-off on a scale (n = 11)
  - Symptom-based scales (n = 1)
  - Composite scales - combination of 2 or more (n = 7)

Results

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- Data collection methods used:
  - Unscheduled (emergency visits)
  - Daily diaries
  - Scheduled trial visits

- A-priori criteria for flares:
  - Assessed by patients (4 / 21)
  - Feasible to collect in all settings (0 / 21)
  - Flares assessed at the time symptoms experienced (15 / 21)

- **None fulfilled all THREE criteria**

Conclusion

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- None of the currently used definitions seem fit for purpose
- Collection of flares is resource intensive
- Possible most useful for short-term studies, or studies looking at “prevention” of flares

- Flares (as currently defined) = NOT a good contender as a “core outcome” for HOME long-term control

Validation of flares

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Validation study of “escalation of treatment” as an indicator of atopic dermatitis flares

Validation of flares (Lead: Kim Thomas)

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- Data available from two datasets
  - **Study A:**
    RCT of water softeners for eczema (4 months, n = 336))
  - **Study B:**
    Cohort study of environmental triggers for flares
    (6 months, n = 60)

- Definition of flare proposed in 2005 systematic review:
  - Escalation of therapy due to worsening of disease
  - Escalation therapy defined at baseline on individual basis
  - Required daily diaries (paper and electronic)

AIM – to apply the OMERACT filter

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- FEASIBILITY:
  - How acceptable and easy to use was the concept of “escalation of treatment”?
  - How much missing data?
- TRUTH:
  - What proportion of days did participants experience a “flare”?
  - How well does days in flare correlate with “global bother” scores and use of topical medication?
- VALIDITY:
  - How well does days in flare correlate with other scales?
  - Is it responsive to change?

Feasibility

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- Well accepted by patients and investigators
- Patients generally liked being able to “track” the eczema on a daily basis (gave feeling of control)
- Missing data surprisingly low
  - STUDY A: 94% of data points complete
  - STUDY B: 60% of data points complete (longer study and electronic diaries prevented data entry after midnight each day)
- **Problems included**: data burden (patients and data management team), potential confusion if “escalation treatment” changed during the study, confusion over dates

Truth – what is it measuring?

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Bother score (0 to 10) 0 = no bother 10 = most bother	Study A Odds ratio (95% CI)	Study B Odds ratio (95% CI)
0	0.007 (0.004, 0.01)	0.08 (0.06, 0.11)
1	0.04 (0.03, 0.05)	0.15 (0.11, 0.21)
2	0.19 (0.16, 0.23)	0.27 (0.21, 0.35)
3	0.42 (0.37, 0.49)	0.63 (0.50, 0.80)
4	1.00	1.00
5	2.16 (1.90, 2.45)	1.43 (1.11, 1.84)
6	4.06 (3.55, 4.65)	2.73 (2.05, 3.65)
7	7.78 (6.70, 9.03)	4.21 (3.08, 5.76)
8	13.24 (11.21, 15.64)	6.43 (4.43, 9.35)
9	19.36 (15.67, 23.92)	6.91 (4.41, 10.81)
10	34.18 (25.54, 45.73)	7.34 (4.69, 11.49)

Correlation of mean bother with % of days in flare

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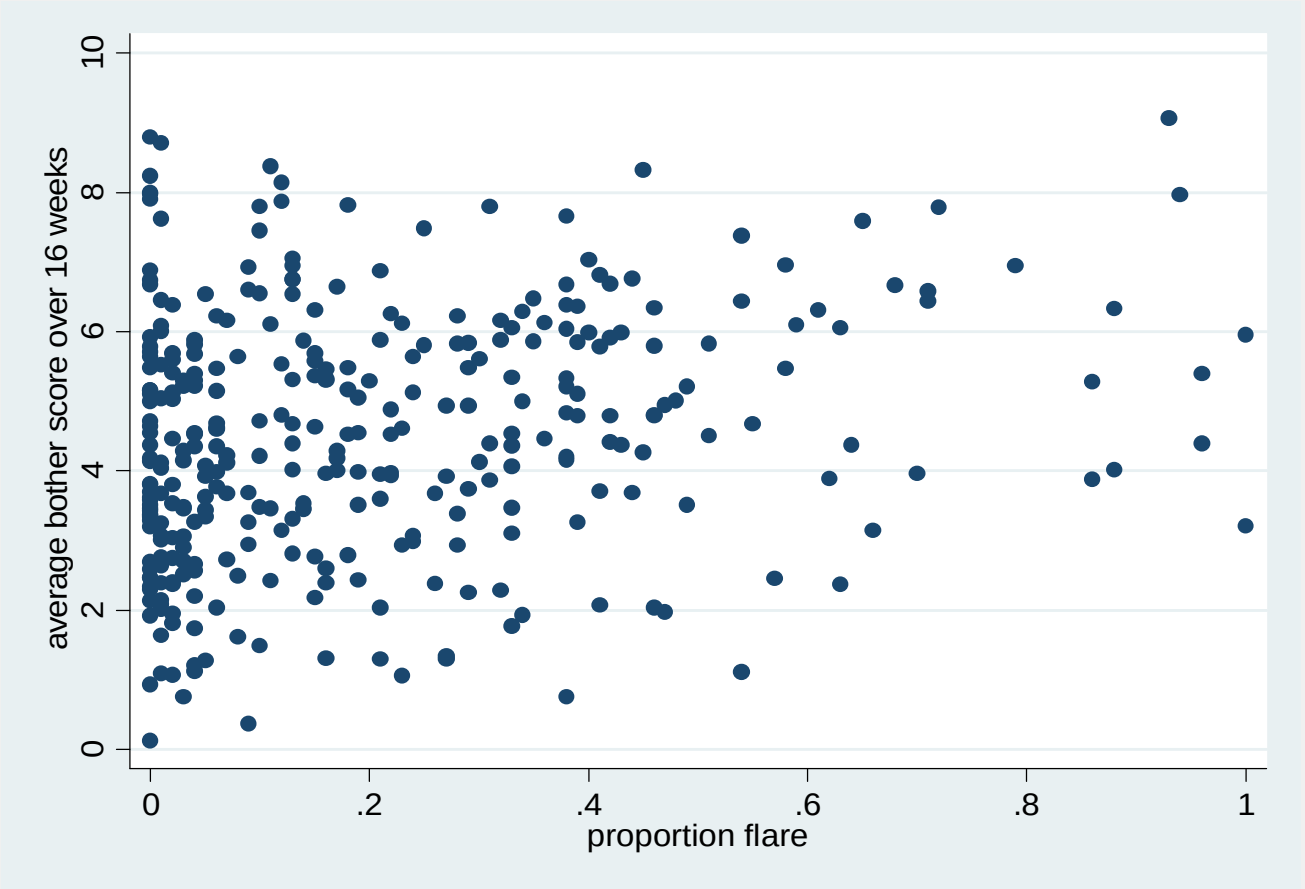
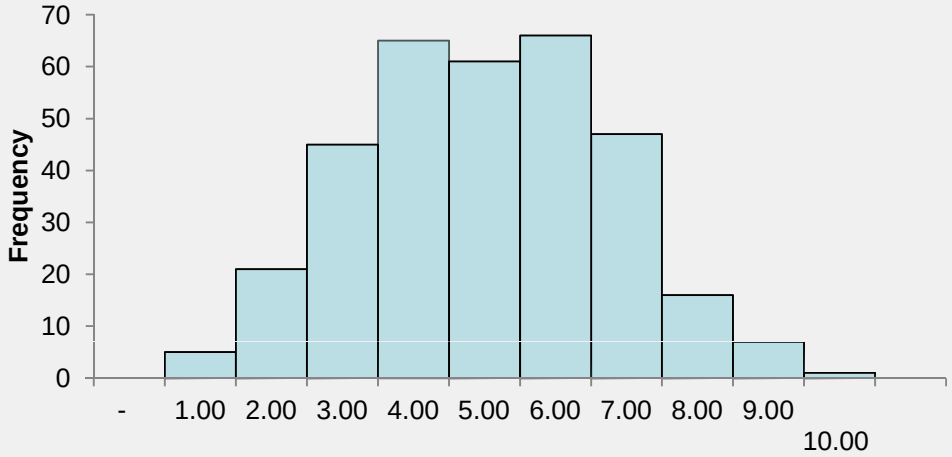
r = 0.23

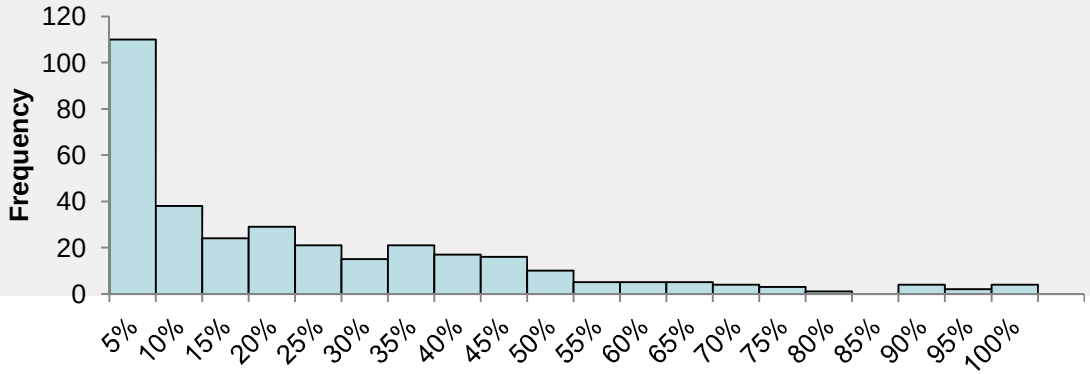


Interpretability, floor & ceiling effects

Average bother score over 16 weeks (Study A)



Proportion of the 16 week period spent in flare (Study A)



Validity – construct validity

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	Study A * Flares (95% CI) n=331	Correlation	Study B * Flares(95% CI) n=59	Correlation
POEM	0.51 (0.33, 0.69); p<0.001	0.527	0.63 (0.10, 1.16); p=0.021	0.609
TIS	0.04 (-0.01,0.09); p=0.138	0.551	0.08 (-0.07, 0.22); p=0.321	0.61
SASSAD	0.43 (0.14, 0.71); p=0.004	0.762	N/A	N/A

* Increase in outcome measure for one unit increase in number of days in the previous week that treatment was stepped up. Uses data from weeks 4, 12 and 16.

Conclusion

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- This flare definition appears to have face validity and is acceptable to patients, despite relatively high burden in longer term studies
- Flare outcomes correlate moderately well with eczema severity scales POEM, TIS and SASSAD
- Large floor effect seen - even in a population with moderate to severe eczema
- Could be useful in some circumstances, but probably NOT a good option for HOME core outcome

Validation of well-controlled weeks

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Validation study of “well controlled weeks” as a measure of long-term disease control in atopic dermatitis

Validation of well-controlled weeks

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- Well-controlled weeks – a concept “borrowed” from asthma research

- Same datasets as previous study
- Requires daily dairy data

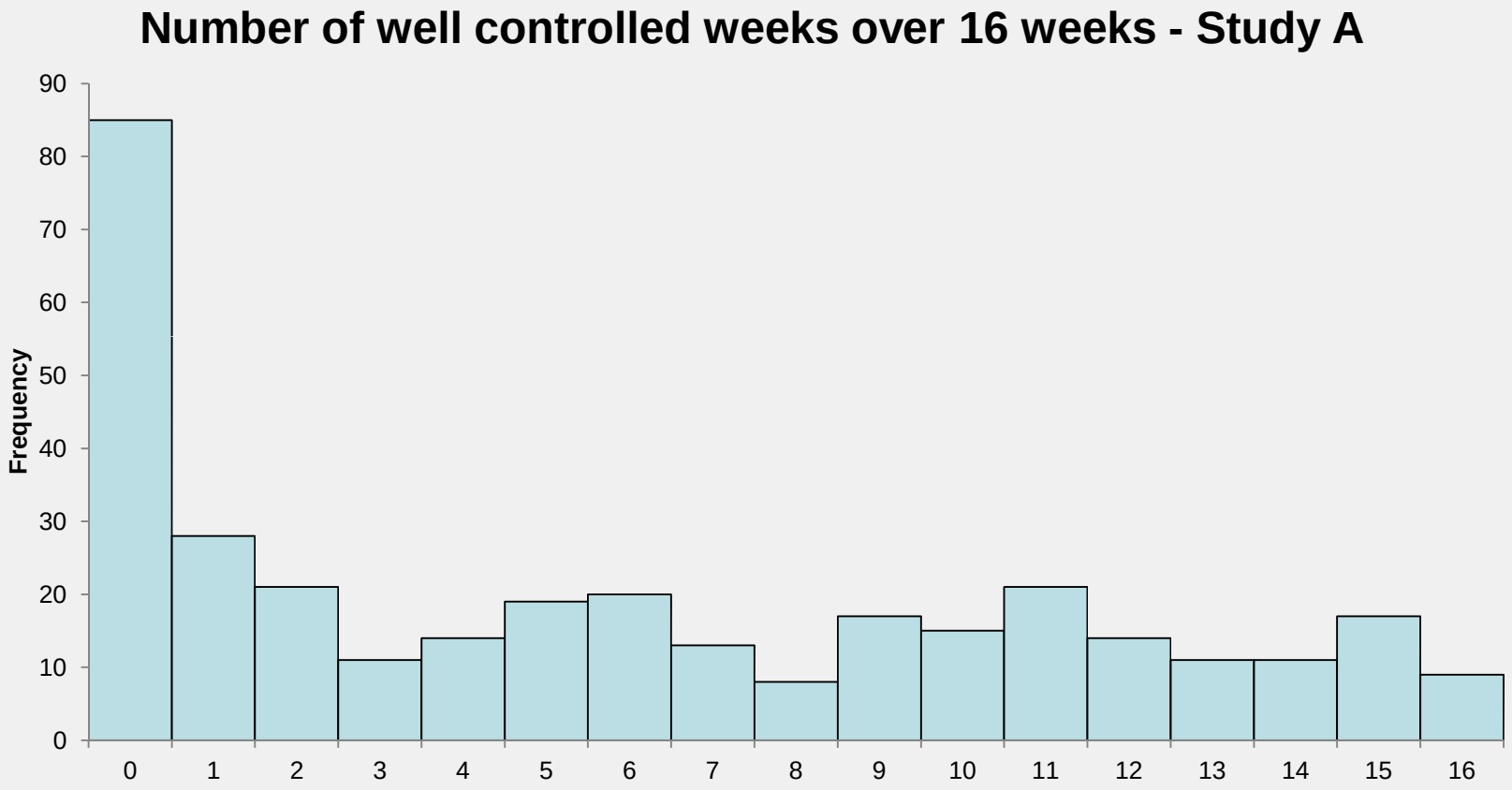
- Well-controlled week defined as:

Treatment “escalated" for ≤ 2 days

plus

≤ 2 days with bother score>4

Interpretability – floor effects



Severity scores by well controlled weeks

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	STUDY A score for those with a well controlled week compared to not well controlled (95% CI)	STUDY B score for those with a well controlled week compared to not well controlled (95% CI)
POEM	-4.28 (-5.08, -3.48)	-5.26 (-7.24, -3.28)
TIS	-0.49 (-0.72, -0.27)	-0.98 (-1.53, -0.43)
SASSAD	-4.34 (-5.61, -3.07)	N/A

Construct validity

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POEM scores	STUDY A (95% CI)	STUDY B (95% CI)
Mild (POEM 0 - 7)	5.78 (3.46, 9.67)	7.46 (2.06, 26.93)
Moderate (POEM 8 - 16)	1.00	1.00
Severe (POEM 17 - 28)	0.30 (0.17, 0.52)	0.44 (0.07, 2.79)

Conclusion

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- Concept intuitively understood (number of weeks when eczema controlled)
- Significant relationship with validated severity scales, but “floor effect”
- Reliant on complex data collection and data manipulation (combination of symptoms & escalation of treatment)
- Not suitable for all trials, so NOT likely to be a good option for HOME core outcome

Take home messages

- Capturing disease control in “real time” is challenging
- Intensive data collection may be suitable for some trials (particularly if short-term)
- “Well-controlled weeks” and “flares” seem to be intuitively useful concepts, but how to measure them is unclear

Future Direction

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- Follow HOME roadmap
  - Systematic review of "long-term control" not just flares
  - Systematic review of validation studies (if there are any)
- Consensus over whether this is a "new domain" or serial measurement of other core outcomes

Group discussions

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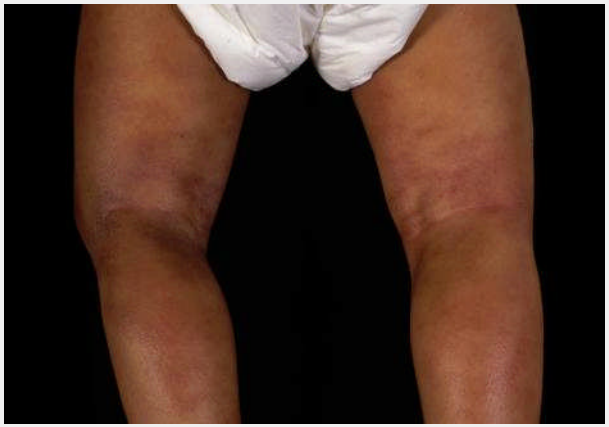
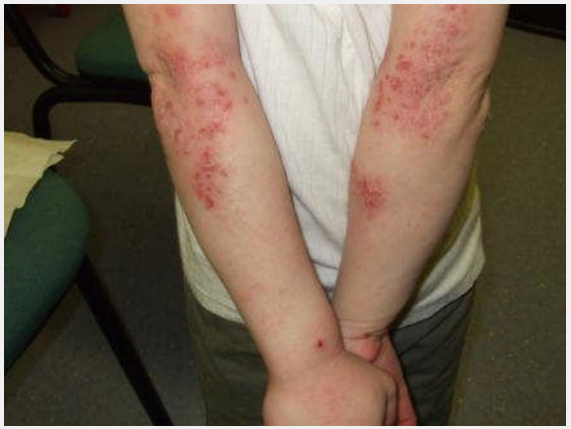
- What needs to be done to progress this work stream?
- Can we reach consensus over what we are trying to capture?
- Start to plan methods for necessary systematic review (identify lead and co-authors)





Disclaimer

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Truth – what is it measuring?

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Change in Bother score	Study A Odds ratio (95% CI)	Study B Odds ratio (95% CI)
No change or improved	1.00	1.00
1	2.01 (1.85, 2.18)	1.87(1.45, 2.41)
2 or more	3.92 (3.47, 4.43)	3.17 (2.50, 4.03)

Bother assessed on a scale from 0 (no bother) to 10 (most bother you can imagine)