

Case Study:

Defining value and identifying benefits of integrating digital measurement of nocturnal scratch into clinical studies

NOCTURNAL SCRATCH

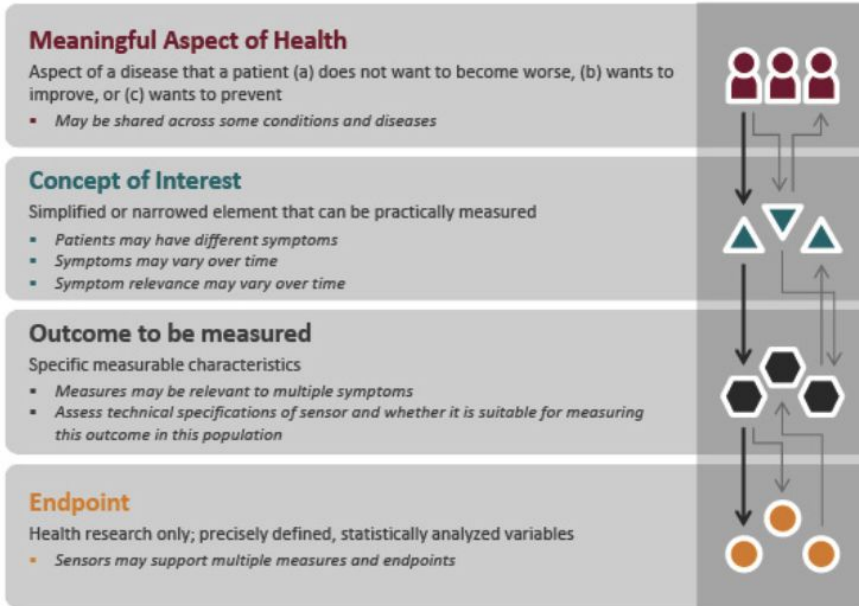


Digital Measures Development

www.dimesociety.org/tours-of-duty/digital-measures-nocturnal-scratch



Measuring what's important to patients



[*Digital Measures That Matter to Patients: A Framework to Guide the Selection and Development of Digital Measures of Health*](#)

According to the **Measures that Matter** framework, all measures should be meaningful to the patients.

Incorporating **patient input** is a dynamic process that should be conducted continuously throughout the measurement selection process.

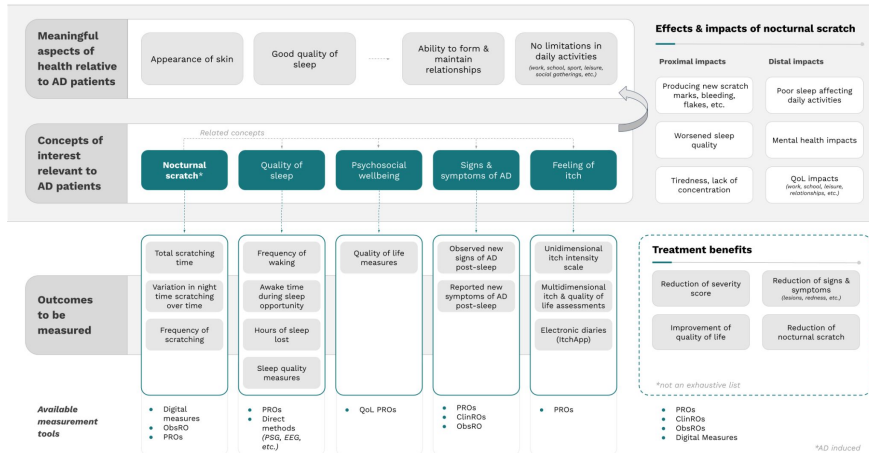
We have explored the **meaningfulness of nocturnal scratching** to patients to aid the development, deployment, and interpretation of this particular digital measure.

[Read about the results here →](#)



Measuring what's important to patients

Conceptual Model: Nocturnal Scratching in Atopic Dermatitis Patients



Open conceptual model →

Outputs of our research were represented according to the Measures that Matter framework.

Nocturnal scratching has been positioned as a concept of interest that is important to patients with AD and connected to meaningful aspects of their lives.

The extensive patient input collected on the burden and experience of this symptom supports the intention to separate it as an **outcome measure** in clinical research.

Digital Measurement of Nocturnal Scratch: Complementing Traditional AD Clinical Measures

Assessment of nocturnal scratching provides a **quantifiable measure** of a key aspect of the disease that can be **measured passively over time**.

Measurement of nocturnal scratch has the potential to complement holistic overview of the physiology, functioning, feelings, and outcomes of the patients (measured by established clinical measures), with a passively collected digital endpoint **quantifying functionally relevant characteristics of behavior**.



Observation

Appearance of skin

Signs and symptoms



Perception

Subjective sensation

Itch



Experience

Personal experience

QOL, sleep



Behavior

Performed actions

Nocturnal scratch



A closer look at nocturnal scratching

Itch & scratch

Scratching, from the medical & physiological standpoint

Nocturnal scratching, from the perspective of effect on patient lives, feelings, & functions

Why measure scratching at night?

Itch is not scratch, nor proxy for scratch, and these two symptoms should be measured separately

- They can be **interrelated:**
 - Itch-scratch cycle
- But also **happen on their own:**
 - Itching, but not scratching (e.g. conscious behaviors not to scratch)
 - Scratching without itch (e.g. habitual movements)
- Many standard itch questionnaires often omit or do not inquire in depth about the behavioral responses to itch - only **37%** of itch questionnaires include inquiry of scratching as a response to itch⁹



A closer look at nocturnal scratching

Itch & scratch

Scratching, from the medical & physiological standpoint

Nocturnal scratching, from the perspective of effect on patient lives, feelings, & functions

Why measure scratching at night?

- **Damages the skin barrier**, leading to allergen and bacterial infiltration
- Leads to inflammatory and immune responses
- Triggers **downstream signaling** and stimulation of itch sensory neurons¹⁰
 - Science suggests that reducing scratching behavior could be measured as a direct consequence of targeting molecular pathways by novel biologics (such as JAK inhibitors¹¹)
- Is impacted by **circadian changes** in temperature, trans-epidermal water loss, and antibody levels often lead to worsening of itching and scratching in the evening and at night¹²



A closer look at nocturnal scratching

Itch & scratch

Scratching, from the medical & physiological standpoint

Nocturnal scratching, from the perspective of effect on patient lives, feelings, & functions

Why measure scratching at night?

- Impacts overall **quality of sleep** by frequent awakenings, shortened periods of deep or REM sleep, or inability to fall asleep
- Can cause unconscious **damage to skin** during sleep periods
- Impacts patients' overall mood, mental health, and/or ability to perform daily activities



A closer look at nocturnal scratching

Itch & scratch

Scratching, from the medical & physiological standpoint

Nocturnal scratching, from the perspective of effect on patient lives, feelings, & functions

Why measure scratching at night?

- Scratching at night, especially during sleep, can be **habitual or unconscious**, often without the conscious decision "not to scratch"
- **Circadian changes** in temperature, trans-epidermal water loss, and antibody levels often lead to worsening of itching and scratching in the evening and at night¹³
- **Circadian behaviors** such as environment change or alcohol intake may affect manifestation of disease and lead to worsening of the signs and symptoms at night
- Regular **daily movements subside** and scratching behavior is easier to distinguish from other movements
- A closer look at nocturnal scratching can offer indirect assessment of treatment effect on sleep quality, such as **sleep disturbances** and interferences, which were established as a proximal impact of AD signs and symptoms¹⁴

Scratching is beginning to be defined as not only patient behavior, but also as one of the **key disease components** causing skin damage and leading to infections and further worsening of the condition.

It is also connected to neural and molecular pathways that are involved in symptom signaling and are being targeted by novel treatments.⁷

Identifying which drugs or mechanisms improve scratching the most can lead to **better outcomes** for patients and **deeper understanding** of the disease pathways.

Measurement of nocturnal scratching is **objective** and **less prone to bias**, as it does not rely on the clinician's, patient's, or caregiver's perception or observation, particularly during sleep, where recall or proxy-reporting can be impaired.

Measurement of nocturnal scratching assesses a concept of interest that impacts **meaningful aspects of health** defined by AD patients, such as sleep quality, mental health, or appearance of the skin.

Can be **useful in pediatric populations** that can't self-report.

The inclusion of both PROs and DHTs can offer a **more complete picture of how patients function**.

Can offer indirect assessment of treatment effect on **sleep quality**, as the sleep disturbances and interferences are established as a proximal impact of AD signs and symptoms.⁸

Why measure nocturnal scratching ?

Current state of clinical outcome assessments (COAs) used in atopic dermatitis (AD) drug development

COA definition

A clinical outcome assessment is a measure that describes or reflects how a patient feels, functions, or survives

Commonly used **primary** outcomes in AD drug trials

ClinROs: IGA score, Eczema Area and Severity Index (EASI)

Commonly used **secondary** outcomes in AD drug trials

ClinROs: Eczema Area and Severity Index (EASI), SCORAD

PROs: Dermatology Life Quality Index (DLQI), Pruritus NRS, Sleep Loss Due to Pruritus, and others



Shortcomings & challenges of the traditionally used COAs for atopic dermatitis

Primary outcomes lacking inquiry into subjective symptoms

IGA and EASI ClinROs include a lack of subjective symptoms. Unlike the SCORAD, these two scales don't assess symptoms such as pruritus and sleep loss. Some investigators state that subjective symptoms may be the most important marker for assessing patient morbidity and may also be a good indicator of disease severity.¹

Difficulty of use & administration

Although SCORAD and EASI are by far the most widely used and validated instruments, they are time consuming and difficult to understand. In contrast, IGAs are simple and easy to administer but come with the trade-off of a lack of validity, comprehensiveness, and standardization.²

Scratch is often not assessed

ClinROs and PROs are based on observations or reports by clinicians or patients themselves.

Many standard itch questionnaires often omit or do not inquire in depth about the behavioral responses to itch - only 37% of itch questionnaires include inquiry of scratching as a response to itch.³ There is currently no measure directly assessing behavioral responses to AD signs and symptoms.

Indirect connection between symptoms and HRQoL

While disease severity is central for clinical evaluation and monitoring treatment response, QoL measures are as important for determining the effect of a disease or intervention on a patient's general welfare.⁴ The impairment can be significant in generalized AD, exceeding the impact on quality of life of other diseases such as asthma, epilepsy, and diabetes, and comparable with that of renal disease and cystic fibrosis.⁵

Not suitable for frequent assessments

There are limitations when it comes to the use of ClinROs and PROs outside of the clinic and in assessment of symptom fluctuation in real time.

Prone to bias

Because of the subjective nature of the outcomes assessed, there are many factors that may influence clinicians' evaluations and patients' responses and thus challenge the overall quality of the data, such as patient background, accuracy of recollection, recall bias, bias related to data collection mode, and proxy-caregiver bias (relevant in pediatric AD population).⁶



Digital measurement of nocturnal scratch is a meaningful clinical outcome measure for clinical trials that supports patient centricity

- ✓ Measurement of nocturnal scratching assesses a concept of interest that is **rooted in meaningful aspects of health** defined by AD patients, such as sleep quality, mental health, or appearance of the skin
- ✓ Measurement of nocturnal scratching more fully addresses **holistic effects of the disease** on patients
- ✓ Can be an especially valuable addition to traditional COAs for **vulnerable populations**, such as children or patients who can't report for themselves
- ✓ Passive and remote assessment in the **comfort and familiar surroundings** at home (as compared to sleep labs) may be more important to the patients than travel costs
- ✓ Offers opportunity for **continuous passive monitoring** in between study visits
- ✓ DHTs passively measuring the symptoms offer opportunity to **reduce patient study participation burden** as compared to PROs (such as diaries or questionnaires)

For additional information about specifics of atopic dermatitis patient population, refer to toolkit document: [Study population considerations for clinical trial design utilizing digital measurement of nocturnal scratch](#)



Digital measurement of nocturnal scratch may offer better disease phenotyping

- ✓ Measurement of nocturnal scratching can more fully **characterize the disease presentation** for the development of better treatments, as we are missing the key component of the disease in our current paradigm of labeling and treating
- ✓ Offers **multi-dimensional, more holistic picture** of the disease and variability across individuals or severities, **interlinked** with other outcomes
- ✓ Better understanding of how the action of scratching relates to how the patient **functions** (sleep) or **feels** (stress, severity of pruritus)
- ✓ Provides value in assessment of scratch in **infants or young children** - not depending on caregiver report
- ✓ Can uncover new disease phenotypes
- ✓ Can help better understand flares and effect of therapies on flares



Digital measurement of nocturnal scratch may optimize efficacy evidence generation in drug development program

- ✓ Generating more complete and patient centric substantial **evidence of effectiveness** of the new therapy can increase likelihood of regulatory approval
- ✓ Measurement of nocturnal scratching can more fully **characterize the disease presentation** for the development of better treatments, as we are missing the key component of the disease in our current paradigm of labeling and treating
- ✓ This new, objectively assessed endpoint rooted in a meaningful concept of interest can provide a more holistic view of the treatment efficacy and thus support **broader label claims**
- ✓ Generate publications of new research, contributing to promotion/revenue and eventually pricing opportunities
- ✓ With more complete and patient centric information, this endpoint can increase the likelihood of positive reception and higher adoption levels by clinicians and patients
- ✓ Passive and remote assessment can **drive engagement** in clinical trials¹⁵
- ✓ Can provide better on-hand information for clinical trialists for **trial optimization** - richer data from patients can lead to shorter trial duration
- ✓ Data from DHTs can complement answers to clinical validation questions - for example, measuring the **clinically meaningful difference** in scratching for various disease severities
- ✓ Earlier go/no-go decisions in vulnerable populations (e.g. children)



Digital measurement of nocturnal scratch may bring new opportunities for care & management of atopic dermatitis beyond clinical trials

- ✓ **Patients:** digital measurement of nocturnal scratch may become a new avenue to disease self-management and communication with providers
 - In real world settings, having "proof in hand" validates patient experience, empowers their disease management decisions, and aids conversations with providers
 - Validating effects on everyday life of patients in all severities, even for patients with mild eczema
- ✓ **Providers:** Ability to obtain metrics about the patient disease course and treatment effects over time and aiding to personalized approaches to treatment
- ✓ **Payers:** Ability to better illustrate treatment benefits for value and reimbursement decision through objective measure reflecting quality of life

Program & system level

- 1 Characterize the natural history of disease progression (naive or standard of care)

Revenue

- 5 Increase likelihood of regulatory approval
- 6 Broader label claims; higher likelihood of reimbursement for new therapy
- 7 Improve understanding of QoL comparative benefits of new therapy
- 8 With more complete and patient centric information, this endpoint can bring higher likelihood of being well received and adopted by clinicians and patients
- 9 Identify new disease phenotypes & nascent conditions

Risk reduction

- 13 Reduced dependence on clinic visits

Cost reduction

- 20 Better information for trial optimization - richer data from patients can lead to shorter trial duration
- 21 Remote monitoring with fewer clinic visits per patient
- 22 More efficient post-market surveillance

References

1. Rehal, B., & Armstrong, A. W. (2011). Health outcome measures in atopic dermatitis: a systematic review of trends in disease severity and quality-of-life instruments 1985-2010. *PLoS one*, 6(4), e17520. <https://doi.org/10.1371/journal.pone.0017520>
2. Yang, Y. B., Lynde, C. W., & Fleming, P. (2020). Common Atopic Dermatitis Rating Scales: A Practical Approach and Brief Review. *Journal of Cutaneous Medicine and Surgery*, 120347542092364. doi:10.1177/1203475420923644
3. <https://www.sciencedirect.com/science/article/pii/S0896627321005419#bib12>
4. Rehal, B., & Armstrong, A. W. (2011). Health outcome measures in atopic dermatitis: a systematic review of trends in disease severity and quality-of-life instruments 1985-2010. *PLoS one*, 6(4), e17520. <https://doi.org/10.1371/journal.pone.0017520>
5. Beattie, P. E., & Lewis-Jones, M. S. (2006). A comparative study of impairment of quality of life in children with skin disease and children with other chronic childhood diseases. *The British journal of dermatology*, 155(1), 145–151. <https://doi.org/10.1111/j.1365-2133.2006.07185.x>
6. Chang, E. M., Gillespie, E. F., & Shaverdian, N. (2019). Truthfulness in patient-reported outcomes: factors affecting patients' responses and impact on data quality. *Patient related outcome measures*, 10, 171–186. <https://doi.org/10.2147/PROM.S178344>
7. Howell, M. D., Kuo, F. I., & Smith, P. A. (2019). Targeting the Janus Kinase Family in Autoimmune Skin Diseases. *Frontiers in immunology*, 10, 2342. <https://doi.org/10.3389/fimmu.2019.02342>
8. Grant, L., Seiding Larsen, L., Trennery, C., Silverberg, J. I., Abramovits, W., Simpson, E. L., Stalder, J. F., Paty, J., Hahn-Pedersen, J., Kragh, N., Bang, B., & Arbuckle, R. (2019). Conceptual model to illustrate the symptom experience and humanistic burden associated with atopic dermatitis in adults and adolescents. *Dermatitis: contact, atopic, occupational, drug*, 30(4), 247–254. <https://doi.org/10.1097/DER.0000000000000486>
9. Wimalasena, N. K., Milner, G., Silva, R., Vuong, C., Zhang, Z., Bautista, D. M., & Woolf, C. J. (2021). Dissecting the precise nature of itch-evoked scratching. *Neuron*, 109(19), 3075–3087.e2. <https://doi.org/10.1016/j.neuron.2021.07.020>
10. Howell, M. D., Kuo, F. I., & Smith, P. A. (2019). Targeting the Janus Kinase Family in Autoimmune Skin Diseases. *Frontiers in immunology*, 10, 2342. <https://doi.org/10.3389/fimmu.2019.02342>
11. Cartron, A. M., Nguyen, T. H., Roh, Y. S., Kwatra, M. M., & Kwatra, S. G. (2021). Janus kinase inhibitors for atopic dermatitis: a promising treatment modality. *Clinical and experimental dermatology*, 46(5), 820–824. <https://doi.org/10.1111/ced.14567>
12. Lavery, M. J., Stull, C., Kinney, M. O., & Yosipovitch, G. (2016). Nocturnal Pruritus: The Battle for a Peaceful Night's Sleep. *International journal of molecular sciences*, 17(3), 425. <https://doi.org/10.3390/ijms17030425>
13. Lavery, M. J., Stull, C., Kinney, M. O., & Yosipovitch, G. (2016). Nocturnal Pruritus: The Battle for a Peaceful Night's Sleep. *International journal of molecular sciences*, 17(3), 425. <https://doi.org/10.3390/ijms17030425>
14. Grant, L., Seiding Larsen, L., Trennery, C., Silverberg, J. I., Abramovits, W., Simpson, E. L., Stalder, J. F., Paty, J., Hahn-Pedersen, J., Kragh, N., Bang, B., & Arbuckle, R. (2019). Conceptual Model to Illustrate the Symptom Experience and Humanistic Burden Associated With Atopic Dermatitis in Adults and Adolescents. *Dermatitis: contact, atopic, occupational, drug*, 30(4), 247–254. <https://doi.org/10.1097/DER.0000000000000486>
15. Tan, R.K.J., Wu, D., Day, S. et al. Digital approaches to enhancing community engagement in clinical trials. *npj Digit. Med.* 5, 37 (2022). <https://doi.org/10.1038/s41746-022-00581-1>

Clinical outcome assessments (COAs) used in atopic dermatitis (AD)

- Hanifin, J. M., Thurston, M., Omoto, M., Cherill, R., Tofte, S. J., & Graeber, M. (2001). The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. *EASI Evaluator Group. Experimental dermatology*, 10(1), 11–18. <https://doi.org/10.1034/j.1600-0625.2001.100102.x>
- Severity scoring of atopic dermatitis: the SCORAD index. Consensus Report of the European Task Force on Atopic Dermatitis. *Dermatology*. 1993;186(1):23-31. doi:10.1159/000247298
- Validated Investigator Global Assessment scale for Atopic Dermatitis - vIGA-AD: https://www.eczemacouncil.org/assets/docs/Validated-Investigator-Global-Assessment-Scale_vIGA-AD_2017.pdf
- Finlay, A. Y., & Khan, G. K. (1994). *Dermatology Life Quality Index (DLQI)*--a simple practical measure for routine clinical use. *Clinical and experimental dermatology*, 19(3), 210–216. <https://doi.org/10.1111/j.1365-2230.1994.tb01167.x>



Additional Relevant Resources:

- The Playbook: [Benefits matrix](#)
- The Playbook: [How will this endpoint benefit our trial?](#)

Acknowledgements

DiMe and the project team would like to express their gratitude and appreciation to the patient advocacy groups, ambassadors, and experts that took a crucial part in development of these resources:

- Ashley Blua, patient ambassador, National Eczema Association
- Christine Pham-Cutaran, patient ambassador, Global Parents for Eczema Research
- Wendy Smith Begolka, Senior Vice President, Scientific and Clinical Affairs, National Eczema Association
- Nina Shaafi Kabiri, Research Scientist, Boston University School of Medicine



National
Eczema
Association



GLOBAL PARENTS
FOR ECZEMA RESEARCH
RESEARCH • SUPPORT • CHANGE



Boston University
School of Medicine

NOCTURNAL SCRATCH



Digital Measures Development

www.dimesociety.org/tours-of-duty/digital-measures-nocturnal-scratch

**Let us know how you've used this
resource in action!**

*Check out our [Resource in Action Hub](#) to learn
about how others are using DiMe resources*