Insights from FDA

Learnings from the Critical Path Innovation Meeting (CPIM) with FDA on digital measurement of **nocturnal scratch**

NOCTURNAL SCRATCH

Digital Measures Development

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A project by the DIGITAL MEDICINE SOCIETY

Critical Path Innovation Meeting: Advancing Nocturnal Scratch as a Digital Endpoint for Atopic Dermatitis

- On July 22 2022, DiMe and Nocturnal Scratch Project consortium attended a Critical Path Innovation Meeting (CPIM) with the U.S. Food and Drug Administration (FDA) about **advancing nocturnal scratch as a digital endpoint for atopic dermatitis.**

- Discussions at Critical Path Innovation Meetings are informal. All opinions, recommendations, and proposals are unofficial and nonbinding by FDA and all other participants.

Critical Path Innovation Meeting: Advancing Nocturnal Scratch as a Digital Endpoint for Atopic Dermatitis

- The new measure shall be **rooted in patients' needs** and most important aspects of their lives
- The research and discussion about **connection between itch and scratch** is encouraged towards separation of these two phenomena, exploring their relationship and defining their specific unique roles in atopic dermatitis
- It is important to **conceptualize** the measurement of nocturnal scratch within the context of a specific research trial and validation
- The research field must adopt **unified terminology** and measurement definitions to advance use of nocturnal scratch as a digital endpoint
- Clinical validation in **target populations**, including pediatrics, is crucial
- It is important to demonstrate that a **reduction in nocturnal scratching** correlates with treatment effects
- **Collaboration** between stakeholders, as well as publishing and sharing the data, is encouraged to advance adoption of nocturnal scratch as a digital endpoint for atopic dermatitis

Representatives from the DiMe Nocturnal Scratch Consortium

- **Mike Benecky**, Senior Director, Regulatory Affairs/UCB
- **Lucy Cesnakova**, Program Lead/Digital Medicine Society
- **Aude Clement**, Director, Regulatory Affairs Innovation/Novartis
- **Andrew Elias**, Associate Director, Global Regulatory Affairs/Janssen
- **Jennifer Goldsack**, CEO, Digital Medicine Society
- **Sandra Goss**, Director of Digital Health Strategy/Abbvie
- **Carrie Northcott**, Senior Director, Digital Medicine/Pfizer
- **Jonathan Silverberg**, Physician, Professor of Dermatology/George Washington University
- **Wendy Smith Begolka**, Senior VP, Scientific and Clinical Affairs/National Eczema Association
- **Kevin Thomas**, Principal Investigator/Boston University School of Medicine
- **Steven Xu**, Physician, Clinical Technologist, CEO/ Northwestern University

Representatives from the FDA

- Center for Devices and Radiological Health (CDRH)
- CDRH/Office of Science and Engineering Laboratories (OSEL)/Division of Imaging, Diagnostics and Software Reliability (DIDSR)
- CDRH/Office of Product Evaluation and Quality (OPEQ)/Office of Clinical Evidence and Analysis II (OCEAII)
- CDRH/Office of Strategic Partnerships and Technology Innovation (OSPTI)
- CDRH)/OSPTI/Division of All Hazards Response, Science and Strategic Partnerships (DAHRSSP)
- CDRH/OSPTI/DAHRSSP/Patience Science Engagement (PSE)
- Center for Drug Evaluation and Research (CDER)
- CDER/Office of New Drugs (OND)/Office of Drug Evaluation Sciences (ODES)/Division of Clinical Outcome Assessment (DCOA)
- CDER/OND/Office of Immunology and Inflammation (OII)/Division of Dermatology and Dentistry (DDD)
- CDER/Office of Translational Science (OTS)
- CDER/OTS/Office of Biostatics (OB)/Division of Biometrics I (DBI)
- CDER/OTS/OB/Division of Biometrics III (DBIII)
- CDER/Office of Medical Policy (OMP)
- CDER/Office of Center Director (OCD)

Meeting Goal & Objectives

GOAL: Obtain FDA's feedback on digital measurement of nocturnal scratch for atopic dermatitis

1

What is it?

Concept of the measure & importance to patients

2

How to measure it?

Ontology & terminology

3

How to use it?

Context of use

1. Concept of the measure & importance to patients

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

It has the potential to **complement** a 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 behavior.

Observation

Appearance of skin

Signs and symptoms

Perception

Subjective sensation

Itch

Experience

Personal experience

QOL, sleep

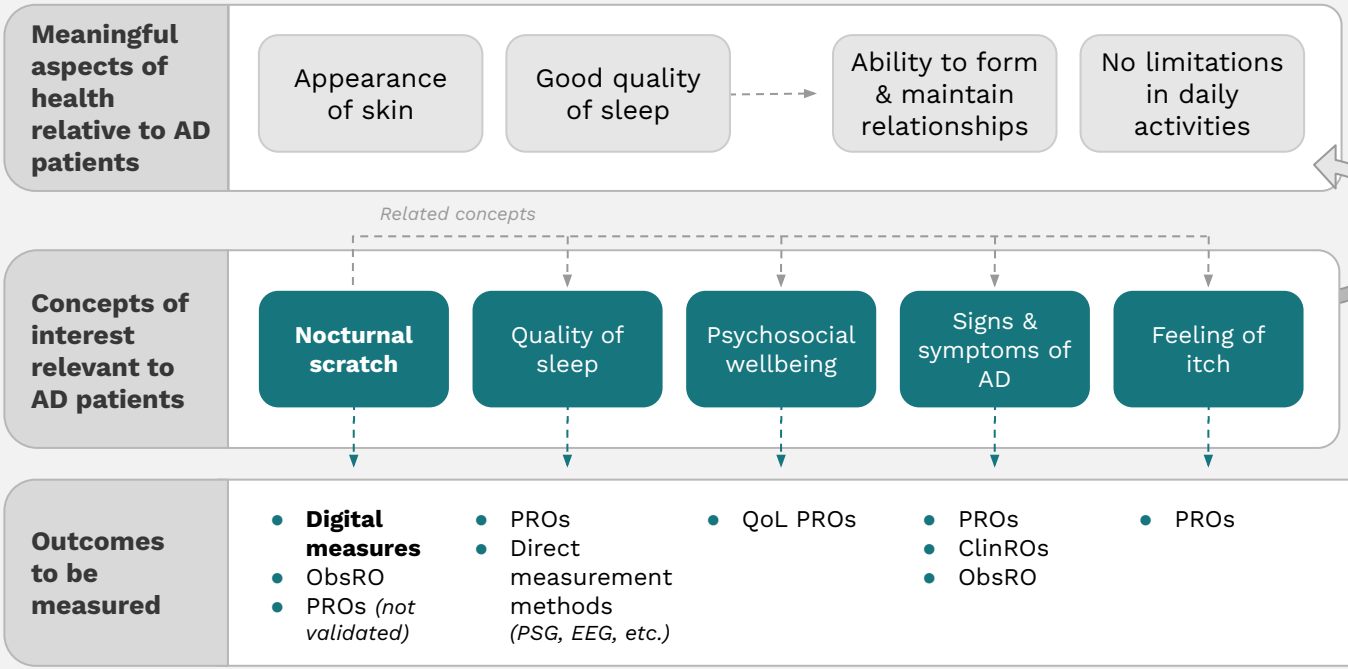
Behavior

Performed actions

Nocturnal scratch

1. Concept of the measure & importance to patients

A concept of interest connected to the meaningful aspects of patients' lives (simplified)



Effects & impacts of nocturnal scratch

- Producing new scratch marks, bleeding, flakes, etc.
- Worsened sleep quality
- Tiredness, lack of concentration
- Poor sleep affecting daily activities
- Mental health impacts
- QoL impacts (Work, school, leisure, relationships, etc.)

Treatment benefits

- PROs
- ClinROs
- ObsROs
- Digital Measures

Full framework: https://www.dimesociety.org/tours-of-duty/digital-measures-nocturnal-scratch/#research

Agency feedback

- Agency recommends that clinical outcome assessments (COAs) and digital health technologies measure the **most important and relevant concepts to the target population**, which can be found using qualitative or quantitative research. Selecting the most meaningful measure of scratch should be guided by patient and/or caregiver input.
- Regarding the consortium research with the patients, DiMe seems to be moving in the right direction based on the description of the completed and planned developmental work, and they will be awaiting published final data (*note: at the time of the meeting, the results of the research with the patients had not yet been published, nor were available to FDA. More info here).*
- There was significant discussion about the **concept of nocturnal scratch as an endpoint**. This discussion included the importance of scratching in AD and the relationship between itch and scratch. Assessments of the impact of a drug on the behavior of nocturnal scratch are expected to be at least somewhat correlated with impact of a drug on other measures of pruritus, as well as other direct manifestations of the disease or its other aspects.
- DiMe has invited **clinician representatives** to the discussion to bring their perspectives. For them, nocturnal scratch is a proxy measure of itch and excoriation, which are manifestations of AD. For the clinicians, the tool may provide an objective and quantifiable measure of excoriation, for which no well-accepted measures currently exist. It can also be a useful measurement apart from reported itch, especially in those patients who scratch but report little itch, or in pediatric patients.

Actions & next steps following the CPIM Meeting

- **Publishing the study results** together with extensive supplementary materials, such as qualitative discussion guides for patients and caregivers in the research, quotes from the interviews with patients and caregivers, and data from the quantitative survey.
- Bring attention to the **connection between itch and scratch**. This is a difficult comparison because while they are interrelated concepts, they do not always correlate (one can be itchy and not scratch and vice versa). However, there is inherent validity in saying that scratching behavior is attributed to itch, even though many factors influence it.
- Establishing that **scratching is part of the perpetuation of AD,** which causes allergic reactions and bacterial inflammation and stimulates signaling cascades that are part of AD. Reduction of the scratching action could reduce some of the inflammatory response that is part of the disease itself.
- Advocating for nocturnal scratch as a measurement with significant **additive independent value** when connected with other measures. In addition to an itch-specific PRO, ClinRO and ObsRO measures can bring an additional body of evidence to support the efficacy of a treatment.

2. Ontology & terminology of nocturnal scratch

"NOCTURNAL"

Measures

- Utilizing sleep measure of intended sleep - **total sleep opportunity (TSO)** - as the main outcome measure for "nocturnal" period*
- Delimited by bedtime (start) to getting up from bed (end)

Proposed definition*

- Defined as "during sleep" rather than "at night"
- A delimited duration of time (time period) of intended sleep;
- Not restricted to any specific time of the day or night

in the context of nocturnal scratch measure

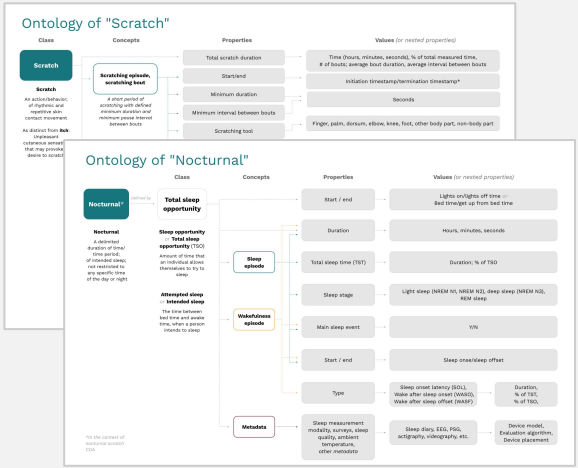
"SCRATCH"

Measures

- Main unit of measurement - **scratching bout** - is a short period of scratching with defined minimum measurable duration and minimum pause interval between bouts
- Main outcome measure - **total scratch duration** - is the sum of all scratching bouts

Proposed definition

- An action or behavior of rhythmic and repetitive skin contact movement
- **Scratch is distinct from itch,** an unpleasant cutaneous sensation that may provoke a desire to scratch



Open ontologies →

Agency feedback

- In this context, clinical validity of the tool is **dependent on the integrity of the sleep assessment**. Technologies that measure resting in bed instead of sleep may be insufficient for precise measurement. If nocturnal scratch is viewed as a physiological state that is different from behaviors during the day, integrity around the sleep assessment is crucial *(read more about ontologies for nocturnal scratch)*
- **Nocturnal scratch, as defined, is differentiated from just scratch itself**. There needs to be awareness of a hypothetical example of a product that changes sleep architecture, and therefore nocturnal scratch, without changing the pathophysiology of AD and itch during the day, as reported by the patient.
- When working with digital technologies, it is important that sponsors consider **data security** and the data privacy laws that could impact multinational trials during the technology development and potential use.

Actions & next steps following the CPIM Meeting

- Adopting **shared definition of nocturnal scratch.** This will facilitate collaboration by allowing combination of different datasets, regardless of the tool used to measure it. FDA concurred that the technology that is used does not matter and the measure can be administered using various technologies.
- Focusing on evidence: Based on our research with patients, **spending less time scratching** is the issue that patients would most like to change most about their nocturnal scratching. This supports the suggested main outcome measure for nocturnal scratch. Focusing solely on observable outcomes of nocturnal scratch (such as new excoriations or marks on skin) without the context of sleep does not provide this level of granularity.
- **Add measurements of sleep:** Additional measurements of sleep can provide useful information about changes in a patient's sleep characteristics, wakings and/or time spent in different sleep stages. Measuring patients' sleep characteristics (including baselines) would provide important data in hypothetical situations when the drug would affect sleep architecture and, thus, nocturnal scratching.

3. Context of use

- Measurement of nocturnal scratch holds an interesting **dual potential** for context of use as a drug development tool (DDT)* - as a clinical outcome assessment (COA) as well as a digital biomarker
- For both measurement contexts in this discussion, the target population are adult (18y+) and pediatric (6-17y) patients with clinician-diagnosed **atopic dermatitis (AD)** within all disease severities (mild, moderate, severe)

Clinical Outcome Assessment

Measurements of how the patients feel & function (scratch, sleep)

In DDT context:

- A digital health technology (DHT) **clinical outcome assessment** (COA)
- Used as an efficacy endpoint in drug development clinical trials of new medical products, supporting label claims of new treatments

Digital Biomarker

Characteristic or set of characteristics, collected from DHTs, measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions (scratch as part of AD)

In DDT context:

- A **digital biomarker** measuring the change in selected disease component - scratching - as a response to therapeutic intervention
- Used as pharmacodynamics endpoint, baseline screening tool, patient phenotyping, pathophysiology evaluation, etc.

**Drug Development Tools (DDTs) are methods, materials, or measures that have the potential to facilitate drug development. Examples of DDTs may include, but are not limited to: a biomarker used for clinical trial enrichment, a clinical outcome assessment (COA) used to evaluate clinical benefit, and an animal model*

LINK1: Digital biomarkers: Convergence of digital health technologies and biomarkers

LINK2: Drug Development Tool (DDT) Qualification Programs

Agency feedback

- The tool being described by DiMe **does not appear to be measuring a biomarker**. *(FDA defines a digital biomarker to be a characteristic, or set of characteristics, collected from digital health technologies that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions.)* However, the definition (biomarker or COA) would depend on the context of use of the measurement in a specific trial, e.g. for enrichment, etc.
- **Scratch is a clinical endpoint** and trying to label it strictly as a biomarker can be confusing and may have limited utility. Using the term digital biomarker here may also contribute to confusion between the method of measurement and the thing being measured. This publication was recommended to elucidate the matter.
- Measuring nocturnal scratch may be most useful, if feasible, for the youngest **pediatric patients**. Although there is a limited amount of data for younger groups, better alternatives for measuring itch than scratch are not available in pediatric populations. Therefore, development work and appropriate validation for that patient population are encouraged.
- For clinical validation, it will be important to demonstrate that **scratching at night correlates with disease presence** and that **changes in nocturnal scratch correlate with treatment effects**.
- There have been approvals for pruritus associated with pediatric liver diseases that use PROs and caregiver-reported ObsRO assessments (as opposed to direct measurement technologies), for example, odevixibat and maralixibat.

Actions & next steps following the CPIM Meeting

- Conceptualize the measurement before the research begins. Once the measure is conceptualized, it is easier to talk about **context of use** and its definitions (biomarker or COA). However, digital measurement of nocturnal scratch seems to fit most to the description of clinical outcome assessment.
- Validate the measurement in **target populations** - both adult and pediatric.
- In regards to the discussion about connection between itch and scratch:
    - **Support research of connection between itch and scratch** and the underlying mechanisms affecting both concepts. This will help understand how, when and/or how much they correlate in atopic dermatitis patients.
    - With current understanding of the concepts, part of clinical validation evidence may involve using an itch-specific PRO and/or a direct observation method measure to anchor the change in nocturnal scratch.
- Demonstrate that reduction in scratching will result in **improvement of the disease**.

Critical Path Innovation Meeting Topic: Advancing Nocturnal Scratch as a Digital Endpoint for Atopic Dermatitis

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