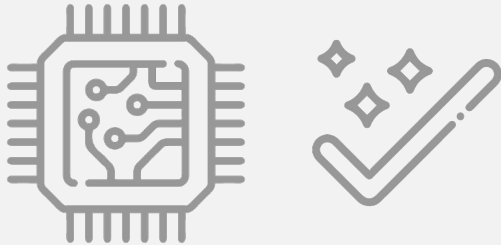


Evidence considerations

for selecting digital
tools for measuring
nocturnal scratch



NOCTURNAL SCRATCH



Digital Measures Development

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

A project by the



Introduction: What is "validation"?

What is the first step when deciding whether the DHT will be suitable for my trial?

According to the latest [FDA guidance](#):

- *Sponsors should ensure that a DHT is fit-for-purpose = i.e., that the level of validation associated with the DHT is sufficient to support its use and interpretability in the clinical investigation*
- *In the submission, the sponsor should explain why the DHT is fit-for-purpose for use in the clinical investigation*

What does it mean that a digital measurement technology is "fit-for-purpose"?

A **fit-for-purpose** DHT is a DHT that:

1. Fulfills sufficient levels of validation
 - Measures what it claims to measure (verification & analytic validation)
 - Is appropriate for the target population (clinical validation)
 - [The Digital Measurement Product "Validation" Flowchart](#) best describes how to evaluate if a digital measurement product is validated
2. Fulfills additional requirements of a fit-for-purpose DHT
 - Related to security, safety, utility, usability and economic feasibility

*Source: [The Playbook](#), [An evaluation framework for fit-for-purpose digital sensing products](#) and [Modernizing Evaluation Frameworks](#)

Introduction: What is "validation"?

What does it mean that a digital measurement technology is "cleared"?

- A **cleared device** is a medical device (or Software as a Medical Device, SaMD) that obtained FDA 510(k), De Novo, or PMA authorization



Note from DiMe: FDA clearance of a technology and/or the presence of a CE mark should not be used in place of the evaluation to determine if the technology is **fit-for-purpose** in the selected context of use

*Source: [The Playbook](#)

Must the device be cleared to be used in clinical investigation of new drugs?

According to the latest [FDA guidance](#):

- *Devices intended for use in clinical investigations are exempt from most requirements applicable to devices, including premarket clearance or approval, as long as the investigation complies with applicable requirements under 21 CFR part 812.*

This misperception is one of the most common. Mobile technologies for data capture in clinical trials do not necessarily need to be approved or cleared as a medical device by FDA 510(k), De Novo, or PMA authorization when used in clinical investigations.

*Source and more information: [The Playbook](#)

Introduction: What is "validation"?

Does a device need to have a CE-mark as a medical device to be used in a clinical trial?

A commercial technology likely does not require a CE mark as a medical device if it is:

- Being used as a research tool in drug development, and
- Not intended for commercialization associated with any medical claim

**Source and more information: [The Playbook](#)*

Verification considerations

for selecting technology measuring nocturnal scratch

All used sensors in the digital health technologies should be verified

Look for performance specifications for the integrated hardware. Manufacturer should provide documentation for:

- Performance specifications for the integrated hardware
- Output data specifications
- Overview of software system tests
- Limitations to the verification testing

How is source data defined?

Can be sample level data (e.g. accelerometer readouts) or aggregates (already pre-processed data). **Both may be acceptable;** however, the technology manufacturer should define and describe what constitutes the source data & how it was generated and verified

Data quality

Verification will also provide the necessary information to help you decide whether the sample level data produced by the sensor is suitable for use as input data to your algorithm.

- For example: accelerometer frequency required to detect finer scratch movements. Decide based on the level of scratch movement resolution you want to achieve

*Source: [The Playbook, p. 91](#) and the [V3 Framework](#)

Analytic validation considerations

for selecting technology measuring nocturnal scratch

Analytic validation confirms that the data collection protocol and the algorithm perform well together and are correctly measuring the outcome of interest.

Comparison to a "ground truth" or a "gold standard" measurement method is an independent confirmation of the measurement output of the selected technology

- However, this comparison will have the same limitations as the "gold standard" measurement method and can only confirm the new method to the degree of its own performance

Source: [V3 Framework](#)

Analytic validation considerations

for selecting technology measuring nocturnal scratch

Analytic validation is part of **overall validation** together with clinical validation in the target population. In such cases, it is often a **joint effort** between manufacturers and sponsors or researchers.

Consider including description of analytic validation studies conducted according to the requirements of Good Clinical Practice (GCP), if performed as a part of an interventional study (ICH GCP does not apply if validation is performed as a part of non-interventional study). This description can be in any one or more of the following forms:

- Internal documentations
- Regulatory submissions (e.g., 510(k)s)
- White papers
- Published journal articles

Documentation for every algorithmic output of system should include:

- ✓ Description of the source data (input data for the algorithm) and how they were generated
- ✓ Description of the output metric
- ✓ Overview of how the metric was calculated, including specific details where possible
- ✓ Which reference standard was used as the comparator to validate the metric
- ✓ Results from a direct comparison between calculated metric and reference standard, including statistical analysis methods
- ✓ Description of the human subjects population, experimental conditions, and protocol used in the aforementioned direct comparison testing

Analytic validation considerations for selecting technology measuring nocturnal scratch

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Commercial technology manufacturers often focus on developing generic algorithms with broad applications to a wide variety of subject populations in order to market their products to the widest possible consumer base. These algorithms (step count, walking speed, heart rate and heart rate variability, falls, sleep, muscle activation, etc.) could be applied to subjects with a variety of health conditions and under a variety of circumstances. However, commercial technology manufacturers may only conduct analytical validation for their algorithms using a small cohort of healthy subjects in a controlled laboratory setting. The manufacturer may or may not document the results of these studies in order to demonstrate the analytical validation of all the algorithms in their product. Sponsors of new medical products (drugs, biologics, or devices) choosing to use commercial technology will typically need to conduct their own analytical (and then clinical) validation.”

Clinical validation considerations

for digital measurement of nocturnal scratch

Clinical validation

Evaluates whether the physiological metric acceptably identifies, measures, or predicts a meaningful clinical, biological, physical, or functional state or experience in the stated context of use and specified population

There are differences between existing clinical measures being digitized vs. novel clinical measures

- When an **existing clinical measure** is being digitized, clinical validation has mostly been completed (e.g. blood pressure)
- When a clinical measure is **novel** or being captured in a new environment, much more comprehensive clinical validation is needed (e.g. nocturnal scratch)

Evidence of clinical validation can be documented in:

- ✓ Clinical study report (CSR)
- ✓ Regulatory submission (FDA or EMA)
- ✓ White paper
- ✓ Published conference proceeding
- ✓ Published journal article

*Source: [The Playbook, p. 61](#) and the [V3 Framework](#)

Clinical validation considerations

for digital measurement of nocturnal scratch

Clinical validation of nocturnal scratch

Should digitally measured nocturnal scratch correlate with traditional COAs (such as IGA, EASI, PRO measures)?

NO and YES. On one hand, digitally measured nocturnal scratch is a novel measurement category, where inter-correlations between the measures can be variable:

- Observation: Appearance of skin (signs and symptoms)
- Perception: Subjective sensation (itch)
- Experience: Personal experience (QoL, sleep)
- **Behavior: Objective actions (nocturnal scratch)**

On the other hand, it is expected that the symptom of scratching correlates with the overall state of the disease in AD patients and some correlation can be observed.

How should the clinical validation of nocturnal scratching be approached?

- First, by conducting analytic validation by comparing the measurement of scratching activity against a standardized method (such as infrared, thermal, or other of type videography) within the selected AD population
- Second, by providing evidence of clinical validity of the novel outcome measure/endpoint measurement properties for AD drug development (such as content validity, construct validity, reliability, and ability to detect change)

Clinical validation considerations

for digital measurement of nocturnal scratch

Clinical validation of nocturnal scratch

How should we validate this new endpoint?

Based on our **project learnings**, we can make a few assumptions:

- Nocturnal scratching should at least somewhat correlate with the standard measures and COAs (IGA, EASI, SCORAD, POEM, etc.), as it is assumed that scratching gets worse for patients with increased disease severity, and can show measurable changes in response to treatment.
- Analysis of correlation with specific items, or singular NRS for itch or scratch, should be evaluated and could also add important evidence.
- A plan for validation would require a bit more of the dedicated research and analysis of the explored domains evaluated in atopic dermatitis.
- Work on clinical validation is best advanced as a collaborative effort.
- Incorporating regulatory feedback on planned studies is always optimal. Reference [The Playbook Regulatory Quick Start Guide](#) for a summary of processes for interacting with the US Food and Drug Administration (FDA) regarding novel endpoint development.

Clinical validation considerations

for digital measurement of nocturnal scratch

Clinical validation of digital measurement of nocturnal scratch in AD populations is a multidisciplinary and multi-stakeholder effort

Collaboration between sponsors, clinical experts, regulatory bodies, and technology manufacturers is required to establish context of use and validation thresholds

- For example, what percentage of scratching movements is meaningful for the patients to capture by a selected measurement technology?
- What is the description of target populations and subpopulations? (e.g. *age, disease severity, etc*)

For measurement of nocturnal scratch, the **consensus regarding what's "good enough"** (in terms of specificity, sensitivity, accuracy across populations, and disease severities, etc.) is only recently emerging, emphasizing a strong need to publish the results & collaborate.

When designing approaches to clinical validation in mild/moderate/severe AD populations, consider:

- Fluidity of the disease between the severity levels and within individuals
- Evaluating experience of flares at the time of the assessment
- The nature of severity descriptions, which might reduce the complexity dimensions of the disease as a whole (e.g. even a patient with mildly severe AD may still scratch with high frequency or intensity)

Beyond V3: Other considerations for selection of fit-for-purpose technology measuring nocturnal scratch



Quality Requirements

- Explore quality control process of the software vendor - Audit each supplier's quality assurance, quality control, and distribution standard operating procedures (SOPs), paying close attention to how they manage protected health information (PHI)
- Require risk analysis on the device, firmware, companion, apps and algorithms



Cybersecurity Measures

- **Minimum threshold:** Does the company have a Coordinated Vulnerability Disclosure (CVD) Policy and what does it contain?
- **Desired threshold:** Does the organization track and share a Software Bill of Materials (SBOM)*?
- **High quality threshold:** Does the organization publish its security support lifetime and issue secure, prompt, and agile software updates once security issues are discovered?



Data Rights, Privacy, & Governance

- **Minimum threshold:** EULA, ToS, ToU and PP exist, are comprehensive, and are publically accessible online
- **Desired threshold:** Documents are comprehensible by broad audiences, documents are accessible (e.g., 508 Compliant) for people with disabilities
- **High quality threshold:** Human-centered principles are applied to health data and users can opt-in or opt-out of third party transfer/use of their data; data retention policies are clearly laid out and deletion is standardized

Beyond V3: Other considerations for selection of fit-for-purpose technology measuring nocturnal scratch



Utility & Usability

Evaluate considerations such as:

- Human factors (*e.g., patient experience, acceptability, tolerability, site on body, specifics of patient population (e.g. pediatric, elderly, etc.)*)
- Battery life
- Form factor of the device
- Materials used
- Water-resistance
- Electrical safety
- Interoperability
- Firmware, operating systems
- Patients' familiarity with the systems
- Availability of technical support
- Ease of use



Economic Feasibility

Economic evaluation analysis can include:

- Budget impact
- Cost-consequence
- Cost-effectiveness
- Cost-utility
- Cost-benefit

*Source: [The Playbook](#)

Structure of evidence dossier to support the use of a mobile sensor to provide data to derive clinical endpoints to support regulatory decision making

Refer to this resource
from *The Playbook*



SPOTLIGHT

Considerations for development of an **evidence dossier** to support the use of connected sensor product for clinical outcome assessments in clinical trials

The Playbook / Customize by context of use / Clinical research



Figure 1. **Structure of evidence dossier** to support the use of a mobile sensor to provide data to derive clinical endpoints to support regulatory decision making.

1. Executive Summary	
2. Intended Goal	
2.1 Endpoint Definition	
2.2 Endpoint Positioning	
2.3 Meaningful Aspect of Health Intended as Clinical Benefit from Treatment	
2.4 Target Label Claim	
3. Concept of Interest for Measurement	
3.1 Concept of Interest for Measurement and Rationale	
3.2 Conceptual Framework	
4. Context of Use	
5. Content Validity Documentation	
6. Construct Validity and Ability to Detect Change	
6.1 Construct Validity	
6.2 Reliability	
6.3 Ability to Detect Change	
7. Clinical Interpretation	
8. Technology-Specific Plans Related to Use Affecting Clinical Trial Design and Data Analysis	
9. Description and Supporting Evidence of the Mobile Sensor Technology	Clinical validation of the measure FDA Center: CDER/CBER
9.1 Mobile Sensor Technology	
9.2 Verification and Analytical Validity of the Mobile Technology	
9.3 Algorithm Description and Validation	
9.4 Usability Testing and Feasibility Research	
9.5 Safety	
9.6 Data Storage and Transfer Methodology	
10. Key references	Analytical validation of the technology FDA Center: CDRH
Appendix A. User Manuals (including training for sites and patients)	
Appendix B. Supportive Evidence	
Appendix C. Study documents (e.g., protocols, analysis plan, interview guide, other data collection forms used)	

Source: <https://pubmed.ncbi.nlm.nih.gov/32087341/>, Playbook team analysis

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Additional Relevant Resources:



- **The Playbook:** [Digital Measurement Product “Validation” Flowchart](#)
- **The Playbook:** [Is FDA clearance \(e.g. 501k\) or CE mark required to use a digital sensing product?](#)
- **The Playbook:** [Regulatory acceptance versus qualification of a digital clinical endpoint](#)
- CTTI: CTTI recommends that a mobile technology’s regulatory status not be the sole driver in sponsors’ decisions about which technology to use. ([Selecting Mobile Technologies for Data Capture in Clinical Trials](#))
- [EU-U.S. and Swiss-U.S. Privacy Shield Frameworks: 14. Pharmaceutical and Medical Products](#)
- FDA Guidance: [Digital Health Technologies for Remote Data Acquisition in Clinical Investigations](#)
- Article: [Considerations for development of an evidence dossier to support the use of mobile sensor technology for clinical outcome assessments in clinical trials](#)

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