Endpoint Strategy

Considerations to support endpoint strategy for clinical trials utilizing digital measurement of **nocturnal scratch**

NOCTURNAL SCRATCH

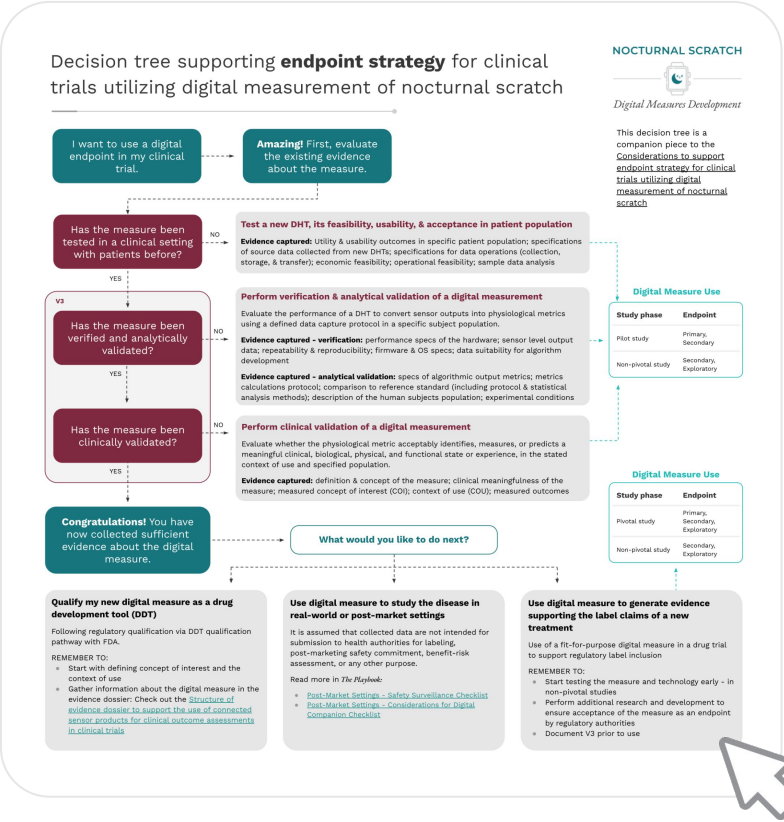
Digital Measures Development

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

A project by the DIGITAL MEDICINE SOCIETY

This is a companion piece to the *Decision tree supporting* ***endpoint strategy*** *for clinical trials utilizing digital measurement of nocturnal scratch*

The following list of considerations addresses the use of digital measurement of nocturnal scratch in different phases of medical product development.



Use of digitally measured nocturnal scratch in **NON-PIVOTAL TRIALS (Ph1, Ph2)**

Benefits of using digitally measured nocturnal scratch in non-pivotal trials

- Increased probability of success - better view on the efficacy effects of treatments
- Earlier go/no-go decisions (for a digital endpoint, but also a whole programme) in vulnerable populations (e.g. children)
- Ability to perform feasibility/pilot studies
  - One of the outcomes of the non-pivotal study may be evaluation of a digital measurement product
  - Pilot studies are a helpful way to assess tolerability, acceptability, and usability in the trial population and may also identify other, unanticipated issues with their proposed use in the specific context of the trial, such as poor wear-time compliance
- Part of COA development may be included in study design across non-pivotal and pivotal trials
  - Example approach: POC, analytical, clinical, or psychometric validation as a part of phase 2 study, then V3 before entering Phase 3, which would then be confirmatory of V3

Use of digitally measured nocturnal scratch in **NON-PIVOTAL TRIALS (Ph1, Ph2)**

Challenges of using digitally measured nocturnal scratch in non-pivotal trials

- Uncertainty when using digital endpoints and measures for the first time
- Lack of feasibility evidence and need to perform feasibility studies, increasing overall programme length and budget
- Lack of familiarity with devices, vendors, etc.
- Introduction of a digital measure impacting or biasing the study performance (slow recruitment) or study results (wearable triggering rash that is interpreted as lower efficacy or side effect)
- Risk of measuring a new aspect of the disease that will need to be re-evaluated in the context of the researched therapy

Use of digitally measured nocturnal scratch in **NON-PIVOTAL TRIALS (Ph1, Ph2)**

Consult *The Playbook:* What information about the DHT do I need if I want to use a **digital measure in non-pivotal trials**?

- ✓ Checklist to support use as exploratory endpoint
  - Exploratory endpoints may be included to explore new hypotheses
- ✓ Checklist to support use as other secondary endpoint
  - Defined here as an endpoint that is pre-specified, included in the statistical analysis plan, and required to be listed on clinicaltrials.gov, but not used to inform power calculation or affect multiplicity adjustment
- ✓ Checklist to support use as early efficacy endpoint
  - Early efficacy endpoints are endpoints that measure efficacy of a drug that may be considered by regulatory authorities
- ✓ Checklist to support use for internal decision making
  - This checklist pertains to digital clinical measures that will inform internal go/no-go decisions regarding whether to advance a investigational new drug forward for further testing in a pivotal trial

Use of digitally measured nocturnal scratch in **PIVOTAL TRIALS (Ph3)**

Current State

Commonly used **primary** endpoints in AD drug trials:

- ClinROs: IGA score, EASI

Commonly used **secondary** endpoints in AD drug trials:

- ClinROs: EASI, SCORAD
- PROs: DLQI, Pruritus NRS, Sleep Loss Due to Pruritus, and others
    - Patient-reported outcomes are not a part of primary end points of clinical trials for AD.[1]

The FDA Guidance for Industry for clinical trials for treatment of AD recommends the primary end point of treatment success to be based on the IGA score at the end of the treatment compared with the start of the study [2]

[1] Wei, Erin X.; Kirsner, Robert S.; Eaglstein, William H. (2016). End points in dermatologic clinical trials: A review for clinicians. Journal of the American Academy of Dermatology, (), S0190962216013177–. doi:10.1016/j.jaad.2016.01.052

[2] http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DermatologicandOphthalmicDrugsAdvisoryCommittee/UCM436605.pdf

Use of digitally measured nocturnal scratch in **PIVOTAL TRIALS (Ph3)**

Am I required to use only **qualified** COAs for clinical trials?

No. While FDA believes there are benefits to using qualified COAs, you are not required to use a qualified COA to support a clinical trial endpoint. FDA encourages discussion with the appropriate FDA review division as early as possible regarding use of COAs in an individual drug development program.[3]

"**COA qualification**" is a regulatory conclusion that FDA finds the COA to be a well-defined and reliable assessment of patients' symptoms, overall mental state, or how they function.[3]

- *An example of a manufacturer of a DHT measuring scratching following this pathway can be found here: Clinical Outcome Assessments (COA) Qualification Program DDT COA #000120: Scratch Sensor*

[3] https://www.fda.gov/about-fda/clinical-outcome-assessment-coa-frequently-asked-questions#Consideration1

Use of digitally measured nocturnal scratch in **PIVOTAL TRIALS (Ph3)**

Rationale for using measure of nocturnal scratch as a secondary endpoint in pivotal trials

Using Sleep Loss Due to Pruritus as secondary endpoints - points to itch and sleep disturbance already making way to the secondary endpoints

- Commonly used secondary endpoints: EASI, DLQI, Pruritus NRS, Sleep Loss Due to Pruritus

Addition of a novel measure of nocturnal scratch as a secondary endpoint can bring **important benefits** to treatment efficacy evaluation:

- DHT-based measurement in home environments can provide richer data over prolonged period of time without the need to rely on the clinician's, patient's, or caregiver's perception or observation
- The inclusion of both PRO and DHT will give a more complete picture about a key aspect of the disease and of how patients function
- DHT-based measurement may be less prone to biases seen in PROs and ClinROs such as patient background, accuracy of recollection, recall bias, bias related to data collection mode, proxy-caregiver bias (relevant in pediatric AD population)
- *For more in-depth description of benefits of measuring nocturnal scratching in clinical trials, refer to the toolkit document: Case study: Defining value and identifying benefits of integrating digital measurement of nocturnal scratch into clinical studies*

Use of digitally measured nocturnal scratch in **PIVOTAL TRIALS (Ph3)**

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

For additional information about value of digital measurement of nocturnal scratch, refer to toolkit document: Case study: Defining value and identifying benefits of integrating digital measurement of nocturnal scratch into clinical studies

Use of digitally measured nocturnal scratch in **PIVOTAL TRIALS (Ph3)**

Challenges of using digitally measured nocturnal scratch in pivotal trials

- Endpoint not "developed" enough - missing evidence on concept of interest or parts of V3 (verification, analytical or clinical validation)
- Lack of acceptance as a secondary endpoint by regulatory authorities (assuming this endpoint would not be used as a primary endpoint, as it does not cover all disease dimensions)
- Selected technology measuring new endpoint not established as fit-for-purpose
- Introduction of a digital measure impacting or biasing the study performance (slow recruitment) or study results (wearable triggering rash that is interpreted as lower efficacy or side effect)

Use of digitally measured nocturnal scratch in **PIVOTAL TRIALS (Ph3)**

Consult *The Playbook*: How to prepare for use of new digitally measured endpoints suitable for **label inclusion**

Please refer to this resource for full information

Who should use this?

Clinical development team including:

- Medical director
- Clinical trial medical lead(s)
- Regulatory personnel
- Health outcomes/Digital health lead
- Patient-centered outcomes researchers
- Biostatisticians

When?

- During clinical development planning, optimally before Phase 2.

Why?

- To determine the steps that need to be taken to demonstrate that the endpoint is fit-for-purpose for the context of use, and thus, for label inclusion
- To identify gaps in the evidence needed to demonstrate that an endpoint is fit-for-purpose so that steps can be taken to generate the evidence required
- To inform regulatory discussions for the suitability of the endpoint for label inclusion

The resource addresses:

- What questions should you be asking?
- What answers do you need?
- What do you do next?

Use of digitally measured nocturnal scratch in **PIVOTAL TRIALS (Ph3)**

Consult *The Playbook:* What information about the DHT do I need if I want to use a digital measure in **pivotal trials**?

✓ Checklist to support use as exploratory endpoint

Exploratory endpoints may be included to explore new hypotheses

✓ Checklist to support use as other secondary endpoint

Defined here as an endpoint that is pre-specified, included in the statistical analysis plan, and required to be listed on clinicaltrials.gov, but not used to inform power calculation or affect multiplicity adjustment

✓ Checklist to support use as key or gated secondary endpoint

A secondary endpoint in this case is one you would include in your multiplicity adjustment and submit to regulators to demonstrate additional effects on the disease or condition

Use of digitally measured nocturnal scratch in **POST-MARKETING SETTINGS**

Benefits of using digitally measured nocturnal scratch in post-marketing trials

- Enabling remote monitoring, better oversight, remote management
- Potential increased scalability and patient engagement by using BYOD devices
- Opportunity for differentiation of therapy from competitors

Challenges of using digitally measured nocturnal scratch in post-marketing trials

- Variability in BYOD devices (operating systems, form factors, firmwares, etc.)
- Variability in human aspects of technology use (larger, more varied group of patients/users with different preferences)
- Increased overhead connected to managing a large-scale trial

Use of digitally measured nocturnal scratch in **POST-MARKETING SETTINGS**

Consult *The Playbook:* What information about the DHT do I need if I want to use a digital measure in **post-marketing settings**?

- ✓ Checklist to support use as a digital companion product
  - Note: 1) integration of the digital tool with an existing drug or biologic requires a label change for the drug or biologic and 2) regulatory requirements may recognize digital tools coupled with a drug or biologic as a combination product
- ✓ Checklist to support use for safety surveillance
  - The checlist includes digital clinical measures that track the occurrence of adverse events in the post-market to monitor the safety of medical products

Additional Relevant Resources

- The Playbook: Benefits matrix
- The Playbook: Can this digital measure inform an endpoint suitable for label inclusion?
- The Playbook: Measurement dossier
- CTTI: Selecting Mobile Technologies for Data Capture in Clinical Trials - page 6: Feasibility studies
- FDA Guidance: Digital Health Technologies for Remote Data Acquisition in Clinical Investigations
- FDA Guidance: Atopic Dermatitis: Timing of Pediatric Studies During Development of Systemic Drugs Guidance for Industry
- DiMe Evidence Checklist
- Considerations for development of an evidence dossier to support the use of mobile sensor technology for clinical outcome assessments in clinical trials
- The Value of Exploratory Endpoints in Early Phase Clinical Trials
- Quantifying the Benefits of Digital Biomarkers and Technology-Based Study Endpoints in Clinical Trials: Project Moneyball

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