Digital Measurement of Nocturnal Scratch: **New Developments**

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DIGITAL EVIDENCE ECOSYSTEM & PROTOCOLS

June 4, 11AM ET

Recent Regulatory Feedback

June 11, 11AM ET

Updates from R&D of Algorithms and Tools

June 18, 11AM ET

Processes, Validation and Adoption

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But first, housekeeping

- Please note: **today's session is being recorded**
    - Slides and recording will be available on DiMe's webinar page after the session
- To ask a question for discussion during live Q&A, please either:
    - **'Raise your hand'** in the Reactions and the moderator will unmute you to ask your question live, or
    - **Type your question** into the chat box

*** *Participants are not permitted to transcribe this webinar, violators will be removed from the session.*

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Genentech
A Member of the Roche Group

V3+ Framework Review

Tom Switzer M.Ed.
Genentech Research and Early Development (gRED)
Lead, Digital Health - Early Clinical Development

V3+ evaluation of digital clinical measures

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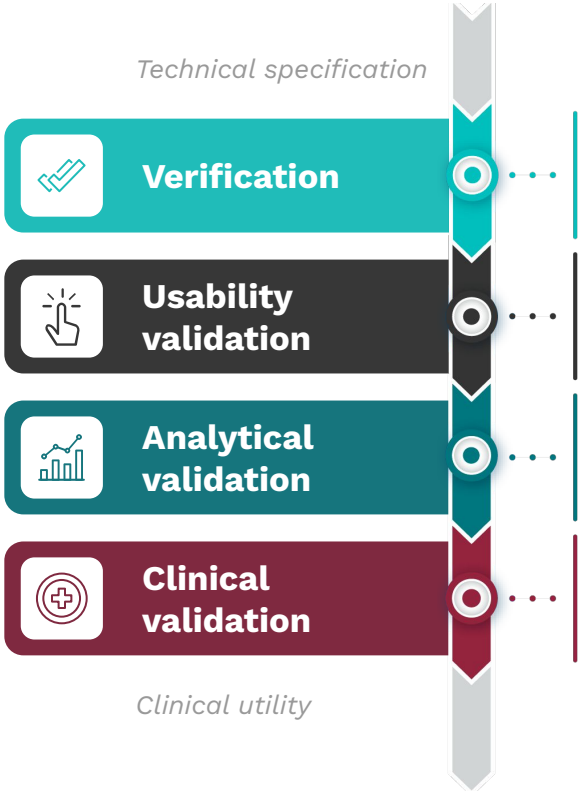

Evaluates and demonstrates the performance of a sensor technology within an **sDHT**, and the sample-level data it generates, against a pre-specified set of criteria

Evaluates whether an **sDHT** can be used to achieve specified goals with ease, efficiency, and user-satisfaction

Evaluates the performance of the algorithm, and the ability of this component of the **sDHT** to measure, detect, or predict physiological or behavioral metrics

Evaluates whether an **sDHT** acceptably identifies, measures, or predicts a meaningful clinical, biological, physical, functional state, or experience, in the stated context of use (which includes a specified population)

sDHT = Sensor-based digital health technology

Source: 1. NPJ Digital Medicine 2. V3+ framework

For sDHTs that are under development (pre-market), begin by developing a proposed intended use statement

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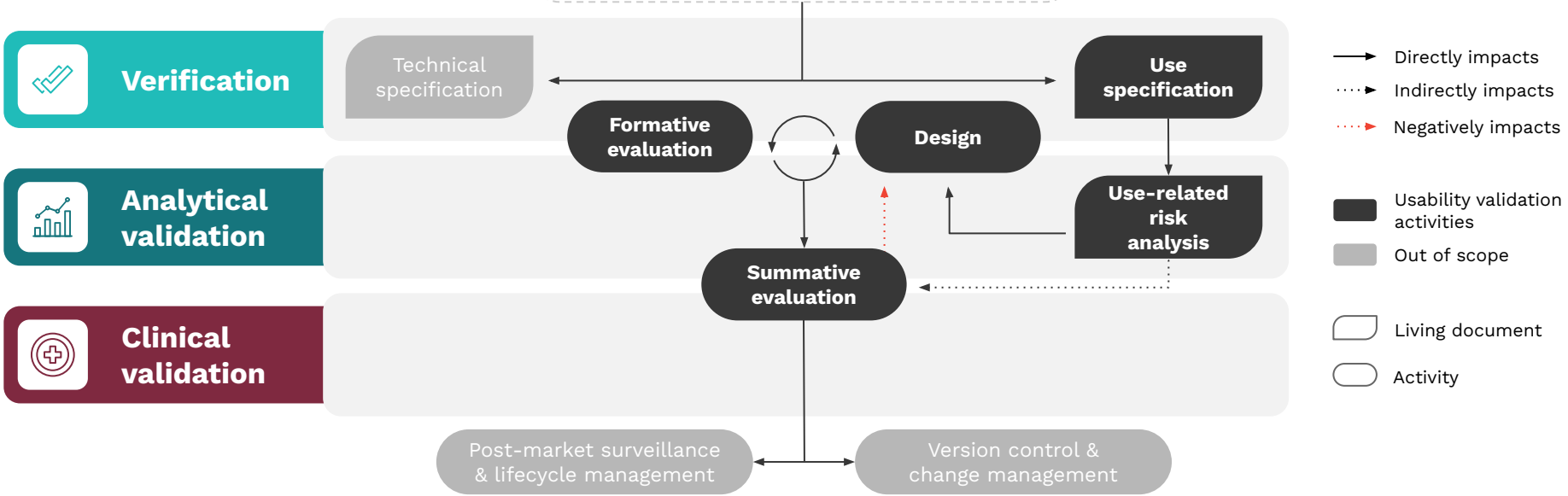
What does the sDHT do?
Who are the intended users?
Where should the sDHT be used?
When should the sDHT be used?
How should the sDHT be used?

The **intended use statement***, which describes the specific clinical circumstance or purpose for which the sDHT is being developed and includes the indications for use, guides subsequent activities

***Note:** The intended use statement is a key component of the labeling of regulated medical devices. An equivalent statement should be developed for non-regulated sDHTs.*



Let’s start with verification

DATACC by DME

Is my sensor fit-for-purpose? 01

Is my sensor good or garbage? 02

Important concepts in verification

Sample-level data

Sample-level data refers to output data at the sample level from the sensor itself. It is a construct that holds clear and consistent meaning across all sDHTs. We prefer to use this term instead of “raw data,” which is often used to describe data existing in an early stage of the data supply chain and is often inconsistent across different technologies.

Performance goal

Performance goals are precisely defined and easily testable objectives that a sensor should meet to achieve the desired outcome. They are typically established by the manufacturer, based on the intended use of the technology, or by community standards for other familiar technologies.

Where can you find evidence of verification?

DATACC by DIME

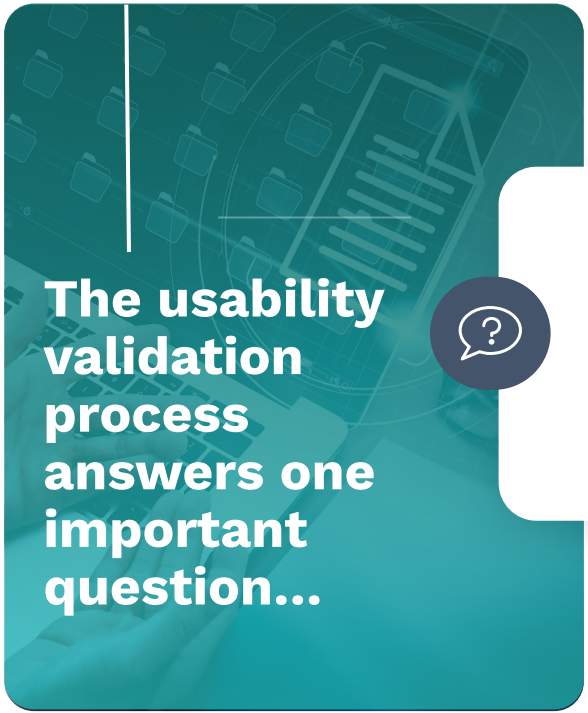
Performance specifications for the integrated hardware

Output **data specifications**

Overview of **software system tests**

Limitations to the verification testing, e.g., specific known items that were not tested during verification

Next, let's discuss usability validation



Can the sDHT be used to achieve specified goals with ease, efficiency, and user satisfaction, within the stated intended use which includes a description of all intended users?

01

Important concepts in usability validation

Use specification

- The intended use statement has a direct impact on the **use specification** of an sDHT. The use specification is a comprehensive description of who the intended sDHT user groups are; where, when, and how each user group will interact with the sDHT; and their motivations for doing so.

Critical tasks

- Critical tasks are user tasks that when not performed, or if performed incorrectly, would or could lead to **serious harm**.

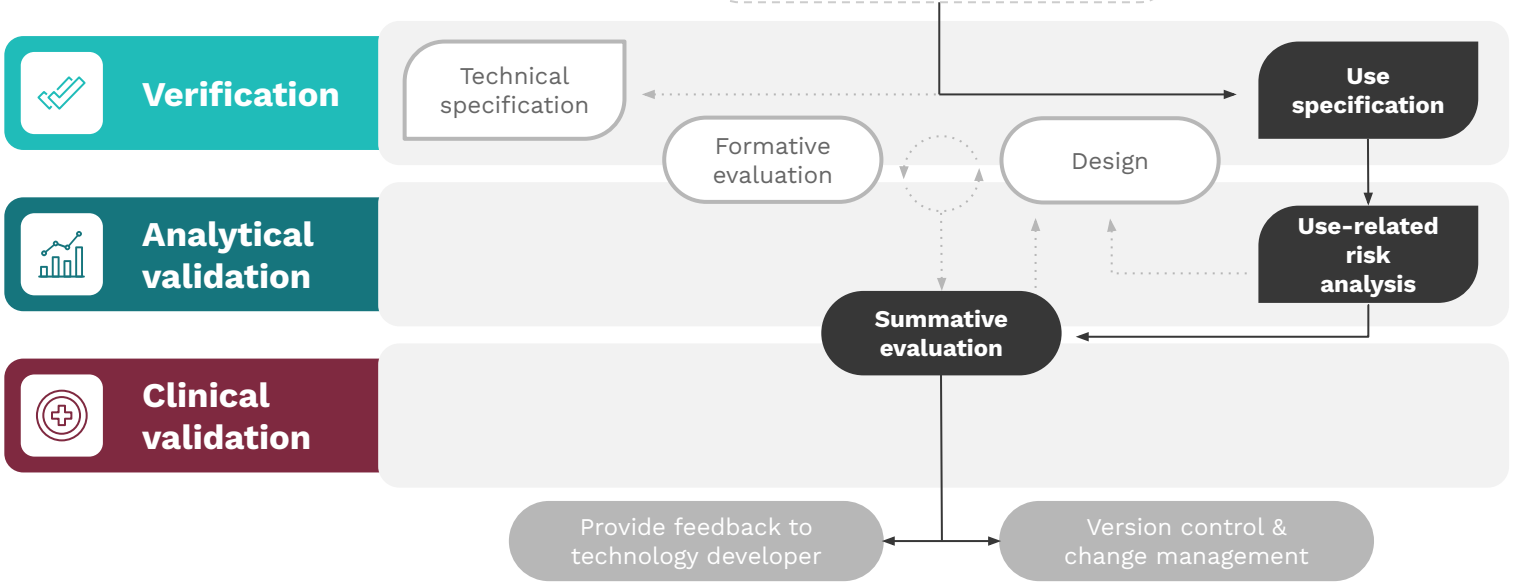
For sDHTs that are commercially available (post-market), begin by developing a proposed context of use statement

DATACC by DiME

What will the sDHT be used for?
Who are the intended population(s) of interest?
Where will the sDHT be used?
When will the sDHT be used?
How will the sDHT be used?

The **context of use statement*** fully and clearly describes the way the sDHT is to be used and the purpose of the use

***Note:** The context of use should be compared against the original intended use of the sDHT; this gap analysis will guide subsequent activities.*



Where can you find evidence of usability validation?

DATACC by DiME

Documentation of studies should include:

- Use specification
- Use-related risk analysis
- Regulatory submission (if applicable)

Summative study protocols, study reports and **white paper** and/or **Peer-reviewed manuscript** should also be made publicly available.

The **Institutional Review Boards'** (IRBs) or **Ethics Committees'** (ECs) **documentation** for the summative study should also be provided.

Now, let's move on to analytical validation

The analytical validation process answers three important questions...

How well does the algorithm perform in a potential target population? 01

Does the sDHT really measure the clinical concept it claims to measure as defined by a reference measure? 02

Can the algorithm acceptably measure, detect, or predict a clinical condition when that algorithm is applied to data captured by a verified sensor in accordance with a specific protocol in a particular population? 03

Important concepts in analytical validation

Reference measures for analytical validation

Algorithms that process sensor-generated data can create metrics that are behaviorally or physiologically meaningful, such as oxygen saturation, heart rate variability, or gait velocity. The metric produced by the algorithm must be evaluated against an **appropriate reference measure**; for example, oxygen saturation should be measured against a lab analysis of arterial blood samples, heart rate variability against electrocardiography, and gait dynamic against motion capture systems.

The best practices for choosing reference measures for analytical validation and avoiding poor methodological approaches should be **agreed upon and documented**. Guidance documents, consensus statements, and/or the peer-reviewed literature should be referred to as needed.

Where can you find evidence of analytical validation?

DATACC by DiME

Description of analytical validation studies conducted according to the requirements of Good Clinical Practice (GCP). This description can be in any one or more of the following forms:

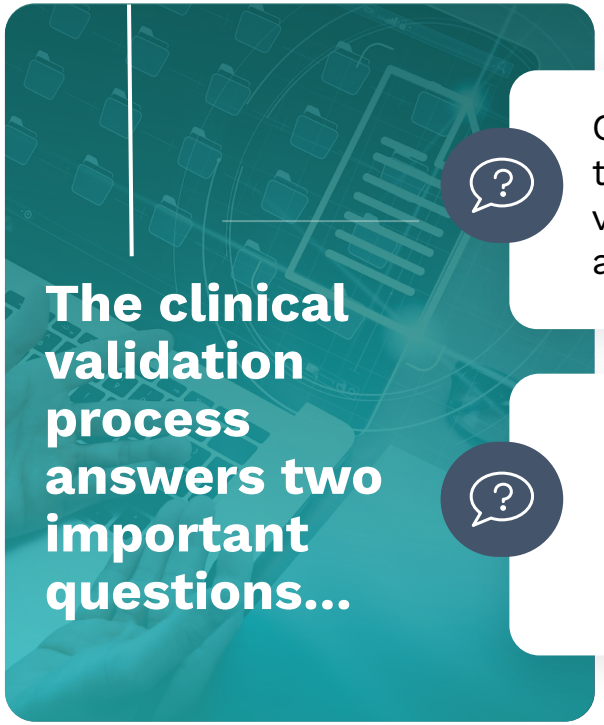
- Internal documentations
- Regulatory submissions (e.g., 510(k)s)
- White papers
- Published journal article

Documentation for every algorithmic output of system should include:

- Description of the output metric
- Overview of **how the metric was calculated**, including specific details where possible
- Which reference **measure** was used as the comparator to validate the metric
- **Results from a direct comparison** between calculated metric and reference measure, including statistical analysis methods
- Description of the **human subjects** population, experimental conditions, and protocol used in the aforementioned direct comparison testing

If this validation testing was undertaken as part of a clinical trial with human participants, then the **Institutional Review Boards (IRBs)** or **Ethics Committees (ECs)** documentation should also be provided.

Lastly, let's discuss clinical validation



The clinical validation process answers two important questions...

01

Can a sensor-derived outcome measurement that has undergone verification, usability validation and analytical validation be used to answer a specific clinical question?

02

Are the data clinically meaningful in the stated context of use?

PRO TIP

Clinical meaningfulness of the measure needs to be established **before** technology selection

This applies regardless of whether a digital clinical measure is being used to support *clinical research*, *clinical care* or *public health*.

Source: https://www.nature.com/articles/s41746-020-0260-4, Playbook team analysis

SPOTLIGHT

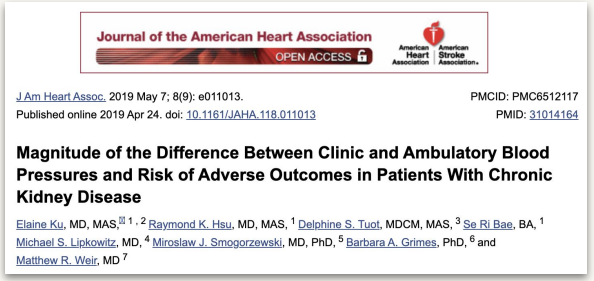
When an **existing clinical measure** is being digitized, clinical validation has mostly been completed.

Example: Blood pressure

It's well known that blood pressure is important; we don't need to prove it just because we're using a digital tool to measure it.

When a **clinical measure is novel** or being captured in a new environment, much **more** comprehensive clinical **validation is needed**.

Example: Blood pressure at home


Journal of the American Heart Association
OPEN ACCESS
American Heart Association | American Stroke Association

J Am Heart Assoc. 2019 May 7; 8(9): e011013. PMCID: PMC6512117
Published online 2019 Apr 24. doi: 10.1161/JAHA.118.011013 PMID: 31014164

Magnitude of the Difference Between Clinic and Ambulatory Blood Pressures and Risk of Adverse Outcomes in Patients With Chronic Kidney Disease

Elaine Ku, MD, MAS,[✉1,2] Raymond K. Hsu, MD, MAS,[1] Delphine S. Tuot, MDCM, MAS,[3] Se Ri Bae, BA,[1] Michael S. Lipkowitz, MD,[4] Miroslaw J. Smogorzewski, MD, PhD,[5] Barbara A. Grimes, PhD,[6] and Matthew R. Weir, MD[7]

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6512117/, Playbook team analysis

Where can you find evidence of clinical validation?

DATACC by DME

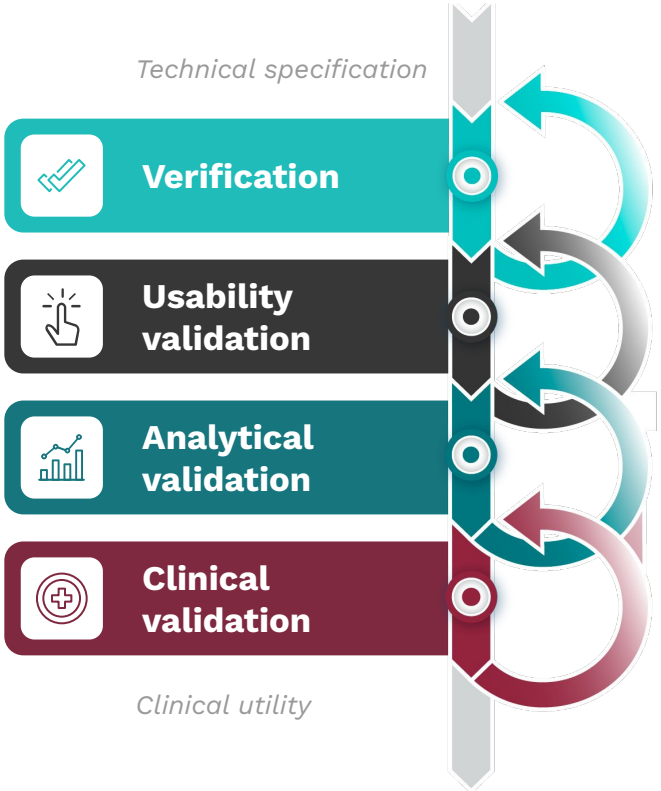
Documentation of studies should include one or more of:

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

Protocols and **study reports** should also be made publicly available.

The **Institutional Review Boards'** (IRBs) or **Ethics Committees'** (ECs) **documentation** for the study should also be provided.

V3+ is a modular evaluation process



Changes to hardware/firmware?

- *Reverification, or*
- *Documentation of back-compatibility*

Changes to use specification?

- *Repeat usability validation, or*
- *Documentation of generalizability*

Changes to software that change algorithm?

- *Repeat analytical validation, or*
- *Documentation of back-compatibility*

Expansion to a new patient population?

- *Repeat clinical validation if usability and analytical validation in new population is documented, or*
- *Repeat usability and/or analytical validation in addition to clinical validation*

Source: 1. NPJ Digital Medicine 2. V3+ framework

Relevant resources

- Resource: V3+ Framework
- Resource: Analytical Validation Library
- Publication: Evaluation, Acceptance, and Qualification of Digital Measures: From Proof of Concept to Endpoint
- Publication: Unlocking the full potential of digital endpoints for decision making: a novel modular evidence concept enabling re-use and advancing collaboration
- Publication: Incorporating digitally derived endpoints within clinical development programs by leveraging prior work
- Publication: Digital health technologies and machine learning augment patient reported outcomes to remotely characterise rheumatoid arthritis
- Publication: Walk, talk, think, see and feel: harnessing the power of digital biomarkers in healthcare

DEEP | Accelerating Digital Measures

A DEEP enabled collaboration to advance validation and qualification of digital measures

Tuesday June 18, 2024

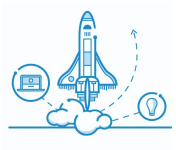
John Batchelor, Science Liaison
john@deepmeasures.health

What is DEEP?

DEEP Accelerates Digital Measure Development

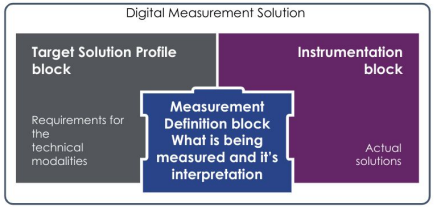
DEEP is built with input from cross-stakeholder experts and integrates several relevant standards and best practices into a single tool

DEEP



Understand the disease or condition
Conceptualize clinical benefit
Define measures & standards
Evaluate measurement properties
Interpret meaningful change
Engage in dynamic regulatory review

The DEEP Stack model and cloud platform provide a structured validation blueprint and simplified process that developers of patient centred digital measures can follow.



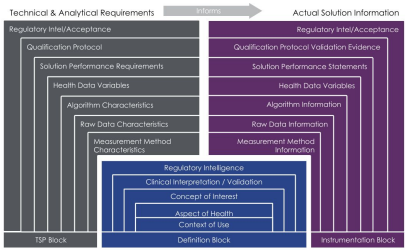
Knowledge is findable, accessible, interoperable & reusable (FAIR). These principles allow structured evidence to support multiple qualification pathways.

How does DEEP support new ways of working

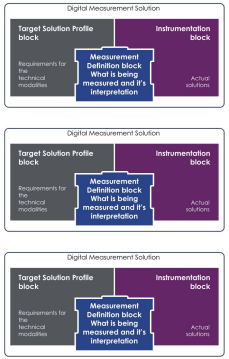
DEEP simplifies the development and qualification process for digital measures

Academia | PPP's | Regulators | Pharma | Patients | Tech | Payers | HTA bodies

Builds transparency and alignment between multiple stakeholders, fostering collaboration.



Enables content re-use and automation for more efficient development.



Promotes comparison and harmonization of digital measures that are meaningful to patients.

The DEEP-EFPIA pilot with the European Medicines Agency

Case study: Nocturnal scratch

Following the work started with the Digital Medicines Society (DiMe), a multi-stakeholder applicant consortium including 7 Pharma companies partnered with DEEP and EFPIA to participate in the pilot and seek EMA regulatory advice for:

- Nocturnal Scratch as a measurable concept
- Using a technology standard for measuring Nocturnal Scratch to validate new or updated Digital Measurement Solutions, and
- Extendability of the evidence for Nocturnal Scratch in Atopic Dermatitis to Psoriasis.

Pfizer

GSK

ucb

sanofi

Johnson&Johnson

abbvie

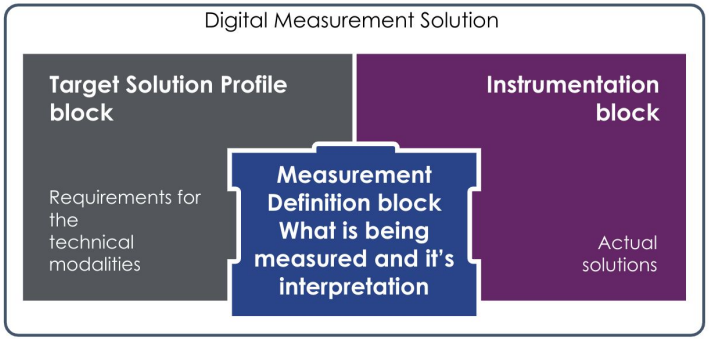
Lilly

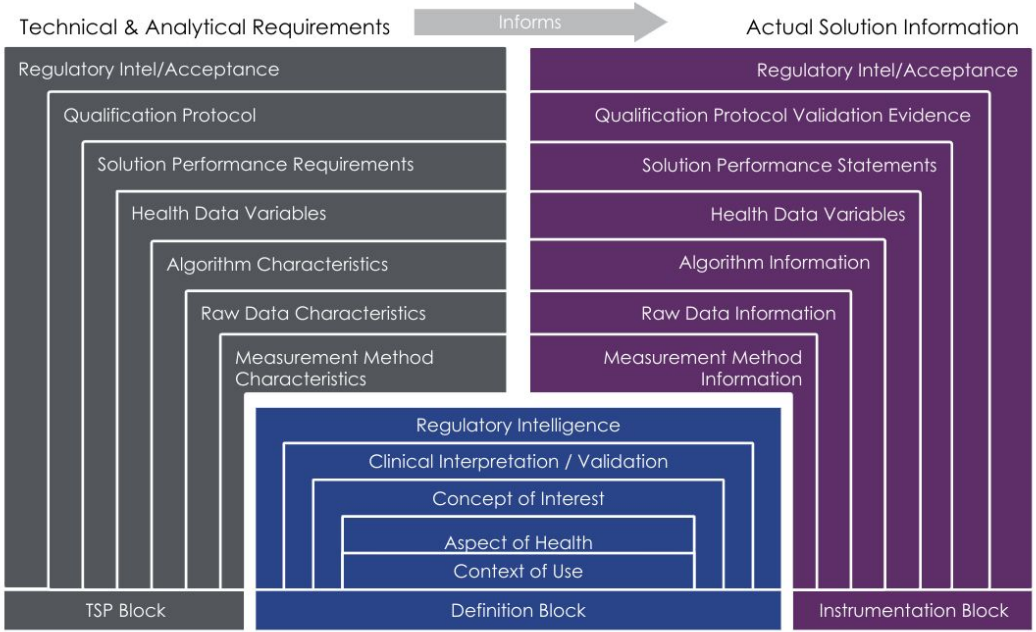
FInal ITF meeting notes are available at www.deepmeasures.health/nocturnalscratch

The Stack Model

Each block within the stack has several layers that have individual re-use and harmonization potential.

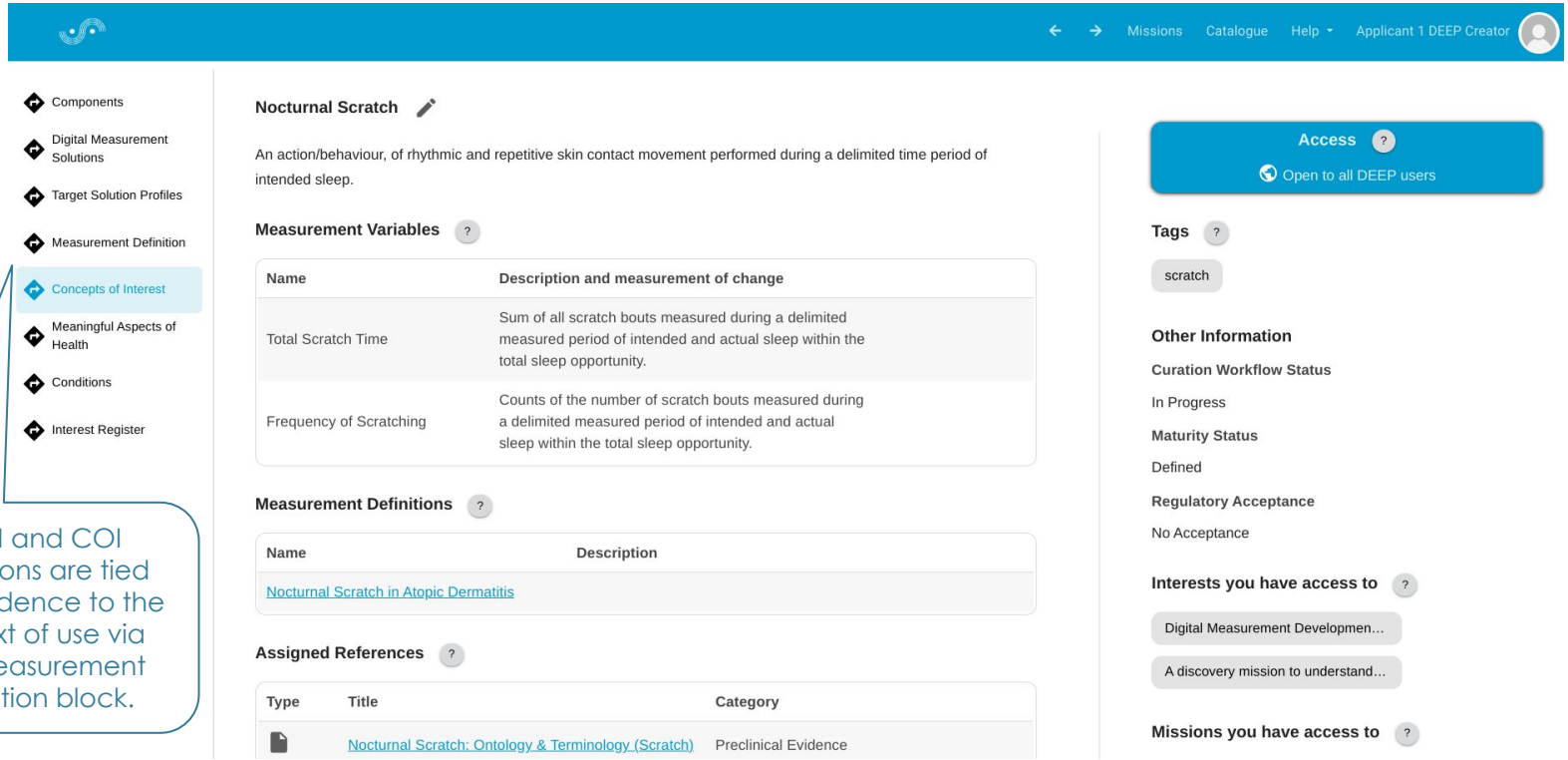
This is an efficient and scalable way to structure information and enable network effects to accelerate the ecosystem.





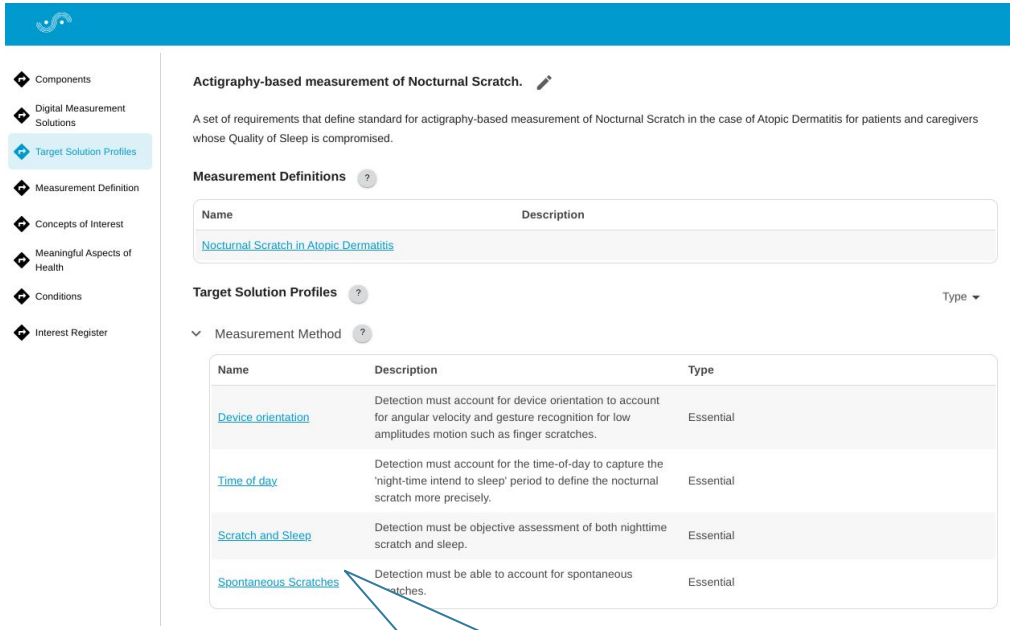
The DEEP **stack model** enables **standardisation** and **re-use** of digital measure components

Concept of interest (COI) view - Measurement Definition Block

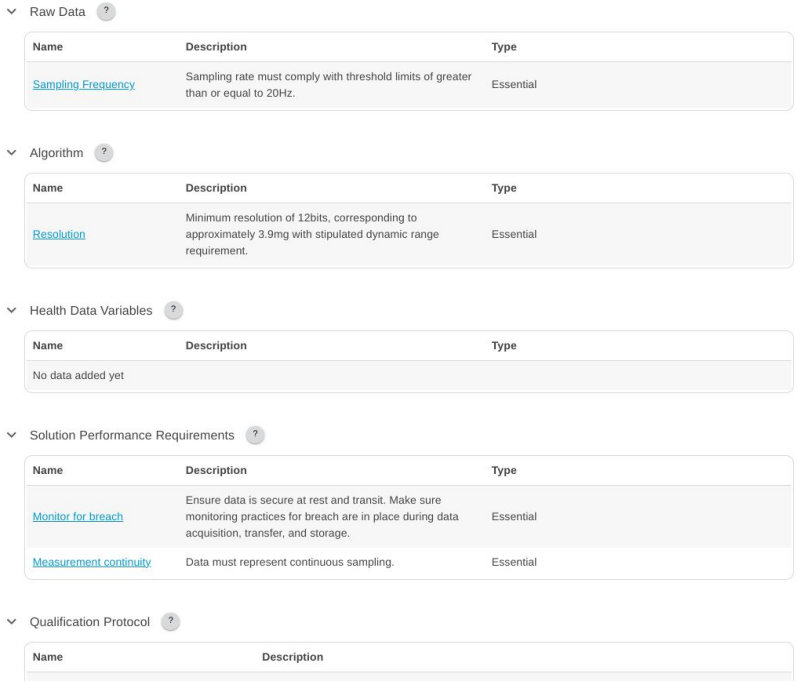


MAH and COI definitions are tied with evidence to the context of use via the Measurement Definition block.

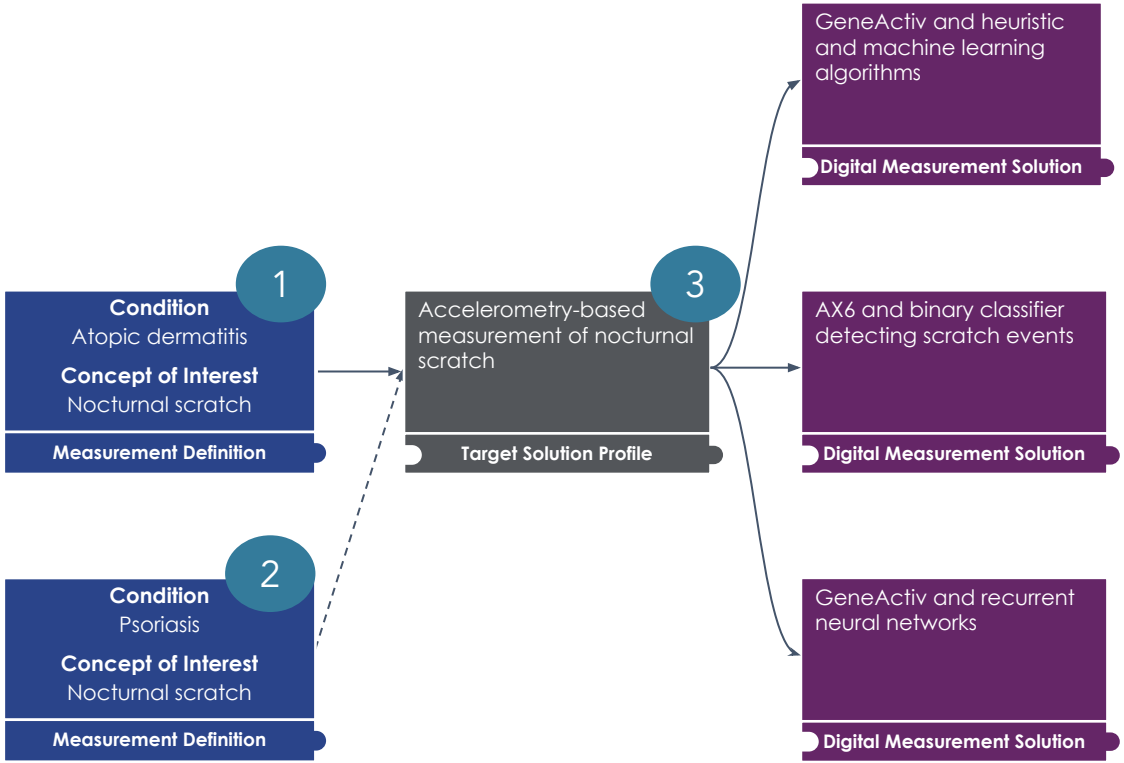
Target Solution Profile (TSP) view



Technical, analytical and usability standards (incorporating V3+ etc..)



Catalog in the ITF Procedure

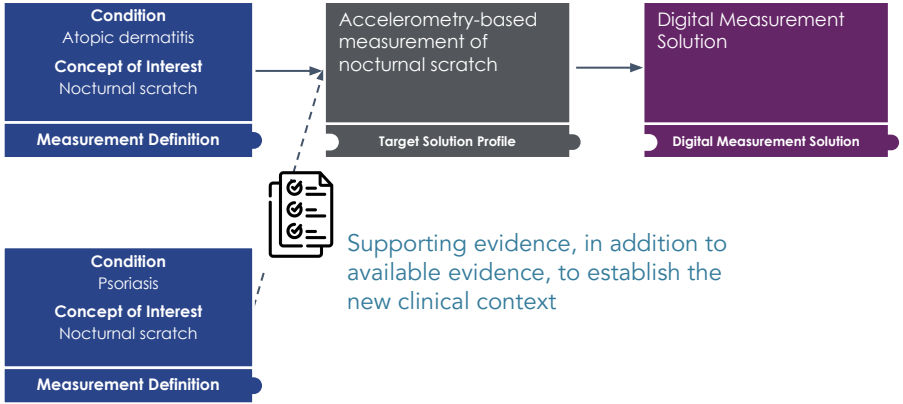


The Catalog provided structured evidence for the Questions in the Briefing Document focused on

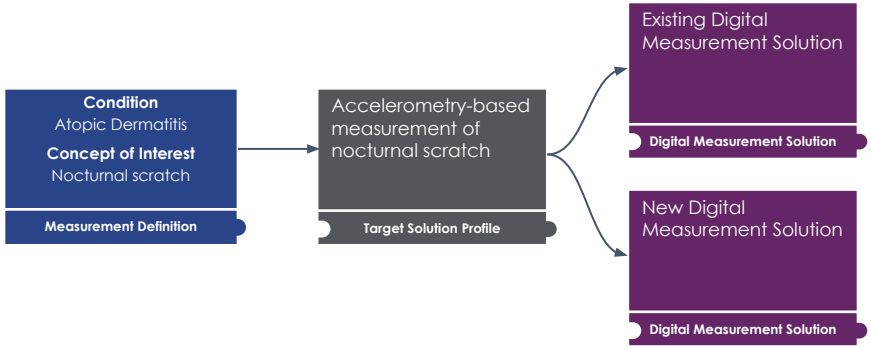
1. Body of Evidence Need for Regulatory validation of Nocturnal Scratch Measure
2. Development of new definition block for Psoriasis
3. Development of a new instrument block for current target solution profile (TSP)

Key Scenarios for Re-Usability

Scenario 1:
Extending the Measure to another Condition



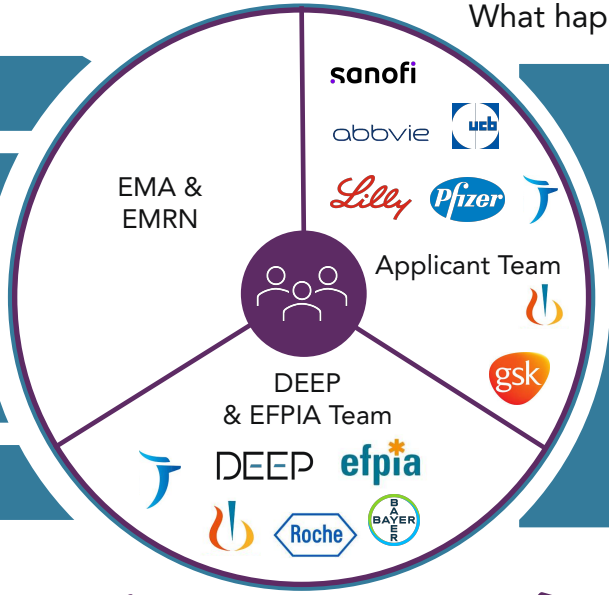
Scenario 2:
Developing a new instrument block for current target solution profile (TSP)



Pilot learnings from ITF feedback and future applicability

Exploratory Components

- Collaboration
- Standards for validation
- Content lifecycle management
- Targeted regulatory engagement
- Re-use cases: DHT and CoU



What happens after the pilot?

DEEP to continue developing the platform informed by the learnings of the pilot

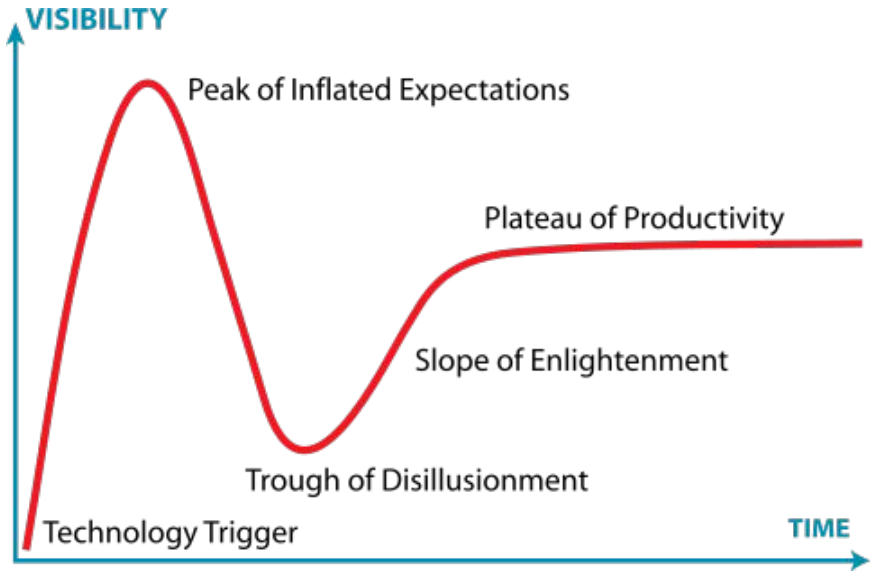
- Test on a full qualification procedure on a digital endpoint using the DEEP model across Contexts of Use
- Conducting pilots with other key stakeholders (Notified Bodies, other Agencies, HTAs)

Feedback from participants

- Structured approach has the potential to increase the quality of evidence submitted
- Reuse of evidence for new conditions showed large potential
- Technology agnostic digital endpoint development is appealing
- Pilot on a real use case provided feedback for further development

From promise to reality for the digital measures field

What can each stakeholder do to accelerate arriving at the plateau of productivity?



Collaboration

Meaningfulness and patient centricity

Validation and data standards

Regulatory acceptance

Re-use of evidence

Life-cycle management

Public Workshop

Using Patient Generated Health Data in Medical Device Development: Case Examples of Implementation Throughout the Total Product Life Cycle

FDA

DIGITAL MEDICINE SOCIETY

June 26, 2024 | 11am - 3pm ET

June 27, 2024 | 11am - 3pm ET