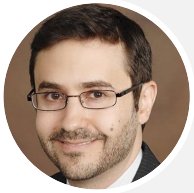
DIGITAL MEDICINE SOCIETY

Death by Pilot

How solid evidence can help digital health vendors achieve scale

October 26, 2021 at 12-1pm ET



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SVP, Scientific & Clinical Affairs
ICON
Moderator

Housekeeping

- **This session will be recorded**
  - Slides and recording will be available on DiMe's webinar page after the session

- **Ask questions!**
  - **'Raise your hand'** in the Reactions and the moderator will unmute you, or
  - **Type your question** in the chat box

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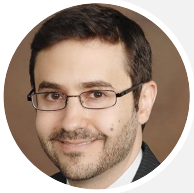

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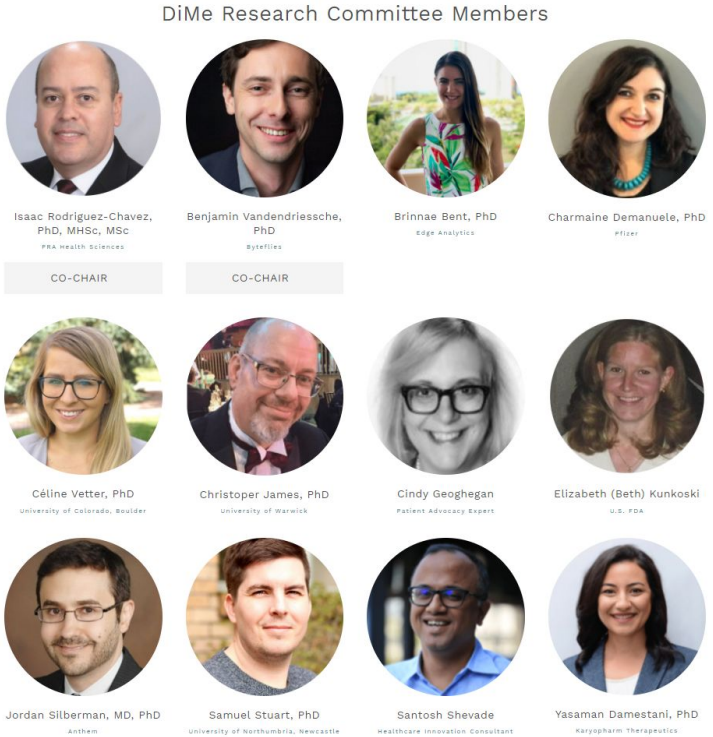
DiMe Research Committee



Source: https://www.dimesociety.org/research/dime-research-committee/

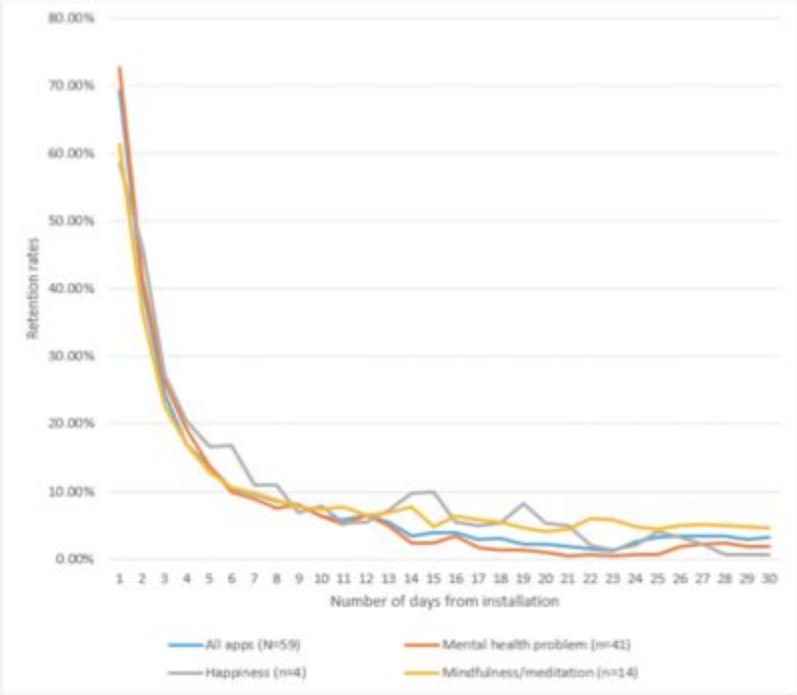
Why is evidence **quality** critical for digital health interventions?

The Wild West

- Overpromising is common.
- Evidence is our best tool to predict effectiveness
- Evidence quality is critical

Digital Health Products Without Evidence: Impact on Mental Health Outcomes

- What proportion of DH interventions are effective?
- Clinical data are not available for most DH interventions.
- Market research data
- Median engagement rate at 15 days = 3.9%.[1]
- If a DH product doesn't engage users for > 15 days, it's unlikely to provide clinical benefit.
- *Without peer-reviewed evidence, DH products targeting mental health may be unlikely to provide meaningful benefit.*



Engagement: popular DH products in mental health[1]

1. Baumel A, Muench F, Edan S, Kane JM. Objective user engagement with mental health apps:: Systematic search and panel-based usage analysis. *J Med Internet Res*. 2019;21(9):e14567.

Why is Evidence Quality Critical for Digital Health Interventions?

1. Digital health practices today - the “Wild West”

2. It’s likely that the majority of digital health interventions available today do not provide clinically meaningful benefit. Finding those that do requires careful evidence assessment.

Why is Evidence Quality Critical for Digital Health Interventions?

1. Digital health practices today - the “Wild West”

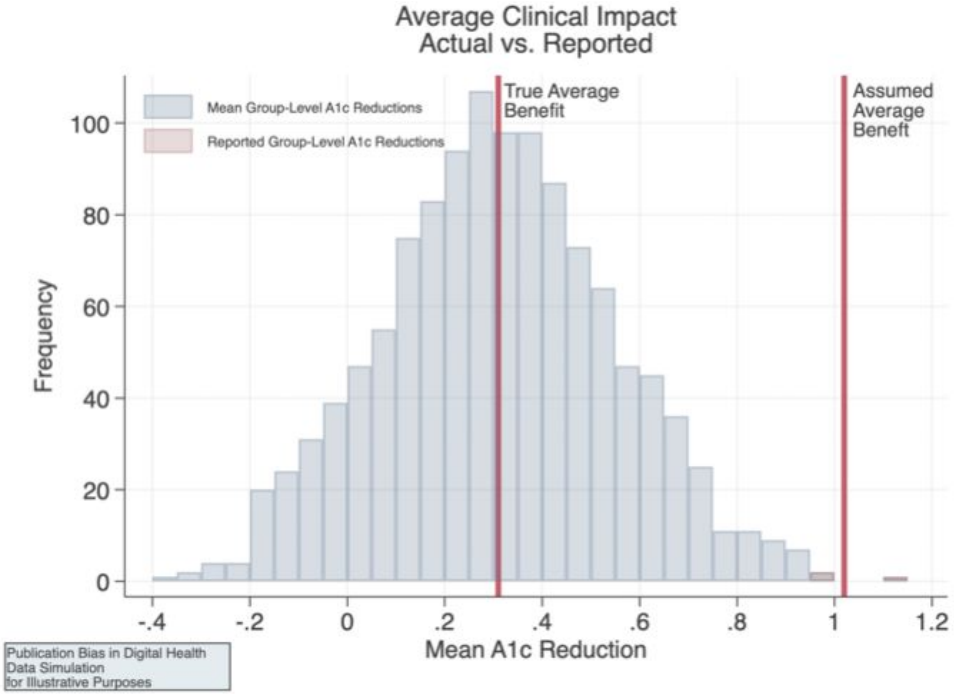
2. It’s likely that the majority of digital health interventions available today do not provide clinically meaningful benefit. Finding those that do requires careful evidence assessment.

3. Low-quality evidence often causes overconfidence in DH interventions.

A Few Examples...

(Only Scratching the Surface)

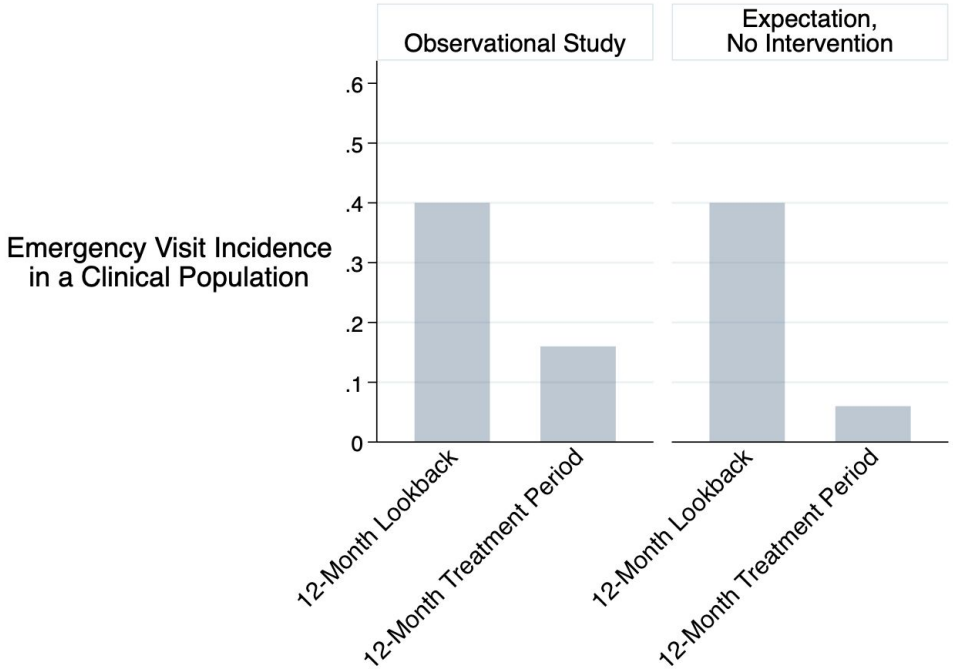
Example 1. Reporting bias.



Data simulated for illustrative purposes.

- Given market-driven messaging, competitive landscape, funding pressures, and regulatory context, DH product claims may often reflect only the most favorable sliver of a product's true effect distribution.
- Solutions include: study registration, prospective designs

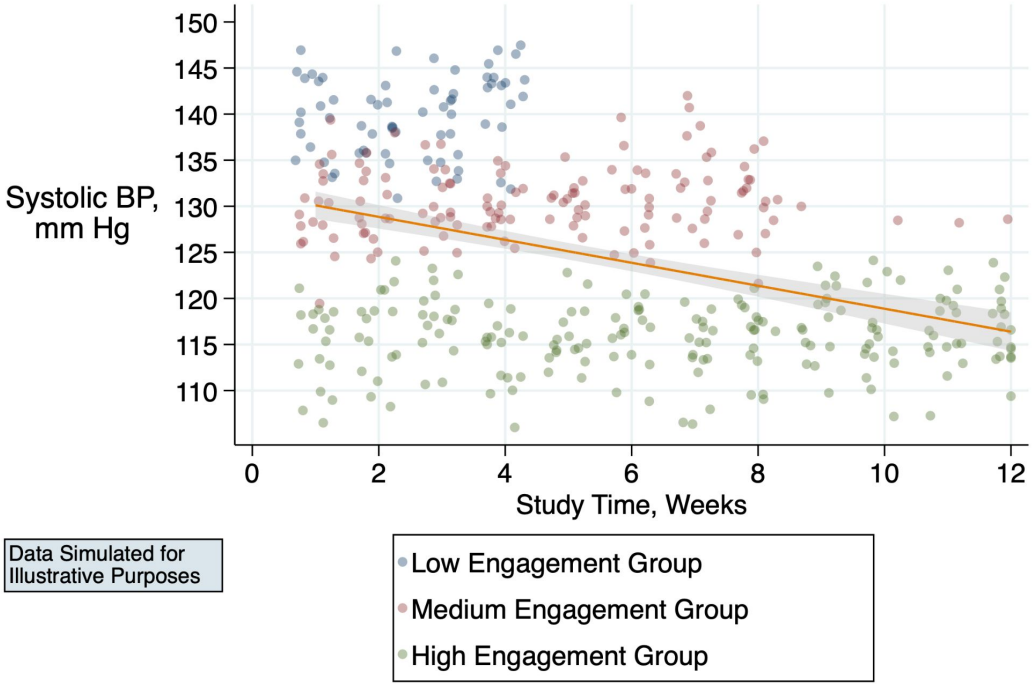
Example 2. Regression to the Mean.



- Common yet underappreciated.
- "Ignoring regression to the mean is a great way to show that your intervention 'works.' "[1]
- Solutions may include: control arms; matched designs; prespecified, defensible targets (devil in the details).

1. Roland M, Abel G. Reducing emergency admission: are we on the right track? *BMJ*. 2012;345:e6017

Example 3. Attrition Bias.



- Common issue in DH evidence.
- DH study data are often modeled assuming that data are missing completely at random (MCAR), despite strong reason to doubt this assumption.
- In DH (“Wild West”), high attrition rates often go unquestioned.
- More motivated patients may show both favorable clinical outcomes and longer retention in trials.
- This can create an illusion of effectiveness.
- Solutions may include: aggressive data chasing, appropriate diagnostics, imputation, sensitivity analyses, others. (Devil in details)

Details matter.

Evidence in Digital Health: Target Future State

1. DH evidence standards are clear and consistent.
2. DH evidence quality is actionable consistently.
3. Trust is established with DH vendors. Resistance to scaling is reduced.
4. A clear path is established for DH vendors to scale.

How we get there

Key steps may include:

1. **Aligned standards defining actionable quality evidence.**
2. Clear standards for measurement in digital health.
3. Statistical standards for biometric monitoring technologies.
4. Innovation in trial designs to accommodate the dynamic nature of digital health interventions.

DiMe Research Committee Work Group

The Evidence DEFINED Framework: A Rigorous, Rapid Approach to Assess Clinical Value for Digital Health Interventions

- Evidence DEFINED (Evidence in Digital health for EFfectiveness of INterventions with Evaluative Depth) is a novel framework under development by a DiMe Research Committee work group.
- This Framework differs in its inclusion of unique elements designed for rigor and speed. Specifically, enhanced rigor is achieved by incorporating:
  a. Evidence quality criteria unique to digital health.
  b. Evidence quality criteria warranting enhanced vigilance in “Wild West” context of digital health.
  c. Established frameworks designed to assess non-digital interventions.
- Achieves efficiencies by:
  a. Screening steps
  b. Deprioritization of info gathering that’s unlikely to impact assessments

Evidence DEFINED may help accelerate progress toward consistently actionable evidence in digital health.

How we get there.

Key steps may include:

1. Aligned standards defining actionable quality evidence.
2. **Clear standards for measurement in digital health.**
3. **Statistical standards for biometric monitoring technologies.**
4. **Innovation in trial designs to accommodate the dynamic nature of DH interventions.**

EVIDENCE Checklist

Evaluating Connected Sensor Technologies Checklist

a DiMe Tour of Duty

Digital Biomarkers

NODE – Review Article

Digit Biomark 2021;5:127–147
DOI: 10.1159/000515835

Received: January 25, 2021
Accepted: March 10, 2021
Published online: May 18, 2021

EVIDENCE Publication Checklist for Studies Evaluating Connected Sensor Technologies: Explanation and Elaboration

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Source: https://www.dimesociety.org/tours-of-duty/evidence/

DiMe Research Committee Work Group

Statistical Considerations for Analyzing and Interpreting Data from Biometric Monitoring Technologies (BioMeTs) in Clinical Trials

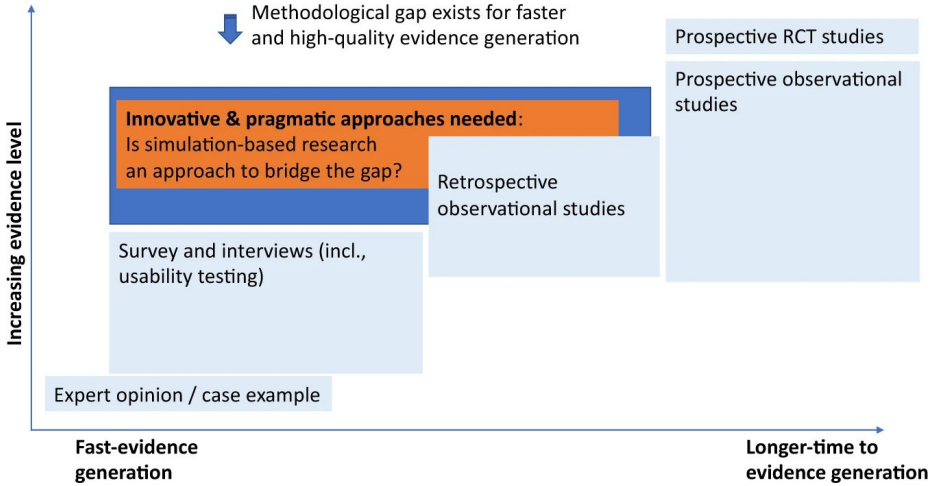
- **BioMeTs:** “Connected digital medicine products that process data captured by mobile sensors, using algorithms to generate measures of behavioral and/or physiological function that may ultimately result in the identification and deployment of digitally measured biomarkers”.

- As evident from the **Crowdsourced Library of Digital Endpoints**, there is a growing need for standardized methodologies to validate health-related digital measures.

- This paper provides considerations for statistical analysis planning to analyze and interpret large amounts of health-related digital data generated from BioMeTs in clinical trials, to support clinical validation of Electronic Clinical Outcome Assessment (eCOA) and digital Biomarkers.

Source:
https://www.google.com/url?q=https://ascpt.onlinelibrary.wiley.com/doi/10.1111/cts.12865&sa=D&source=editors&ust=1635170536310000&usg=AOvVaw0zM00WHAmze_xpLXeGl-u- | https://www.dimesociety.org/communication-education/library-of-digital-endpoints/

Innovative Methods to Accommodate Dynamic DH Interventions



Other approaches may include:

- N-of-1 trials
- Micro-RCTs
- Multiphase Optimization Strategy (MOST)
- Innovative adaptive trial methods
- Novel methods designed for DH interventions

Source: https://www.nature.com/articles/s41746-020-00314-2/figures/1

Assessment Domains Beyond Evidence (A Few of Many)

Quantifiable business value upfront with measurable success criteria for claims including

- Improve of patient health outcome
- Reduce healthcare spend
- Increase access to care
- Improve patient and/or care team experience

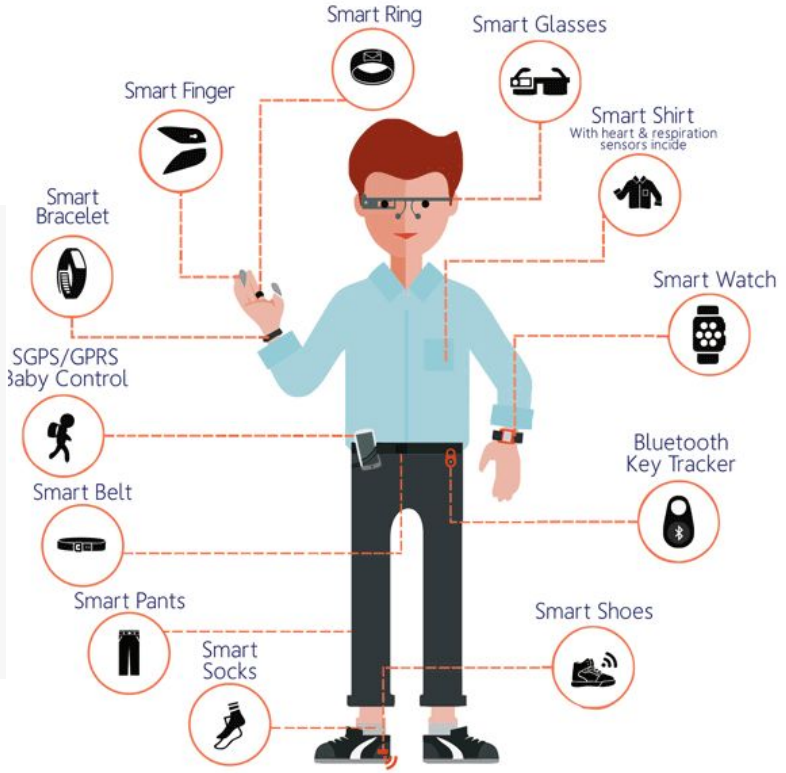
Alignment on operational metrics between healthtech startups and healthcare ecosystem including timelines, expectations, and the right capacity and agility for long-term execution

Viable business model resulting in financial ability and flexibility for all stakeholders to scale up or down as needed, as trial participants need to provide **explicit consent for data sharing**

Source: https://gdpr.eu/

Digital health technologies (DHT)

- Allows for a broader, holistic picture of how patients feel and function
- Can provide novel measurements, and more frequent or continuous data collection
- Able to move healthcare from the clinic to the patient
- Enhance data collection and enable decentralized clinical trials



Some DHTs meet the definition of a medical device — while others don't

Per Section 201(h) of the Food, Drug, and Cosmetic Act, a device is:
An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

1. *recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,*
2. *intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or*
3. *intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and*

which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes. The term "device" does not include software functions excluded pursuant to section 520(o).

Source: https://www.fda.gov/medical-devices/classify-your-medical-device/how-determine-if-your-product-medical-device

Is marketing authorization (premarket clearance or approval) required to use a DHT in a clinical investigation?

Devices intended only for use in clinical investigations are typically exempt from many requirements applicable to Devices – including premarket clearance or approval – as long as the investigation complies with applicable requirements under 21 CFR part 812

The CDRH Digital Health Center of Excellence (DigitalHealth@fda.hhs.gov) is a resource for questions on DHTs

21 CFR 314.216 Adequate and Well-Controlled Studies

- The purpose of conducting clinical investigations of a drug is to distinguish the effect of a drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation.

- Characteristics of adequate and well-controlled studies
    - Clear statement of the objectives of the investigations and a summary of the proposed or actual methods of analysis in the protocol and report of results
    - Study uses a design that permits a valid comparison with a control to provide a quantitative assessments of drug effect
    - Minimize bias
    - **Method of assessment of subjects' response are well-defined and reliable**
    - Analysis of the results adequate to assess the effects of the drug

If a DHT has marketing authorization (premarket clearance or approval), does that mean it is appropriate for use in a clinical investigation?

DiMe

DHTs used in clinical investigations should be ***fit-for-purpose****

Fit-for-purpose:

A conclusion that *the level of validation associated with a DHT is sufficient to support its proposed use.*

Clinical investigation ***endpoints**** should reflect an outcome of interest

Endpoint:

A precisely defined variable intended to reflect an outcome of interest that is statistically analyzed to address a particular research question…

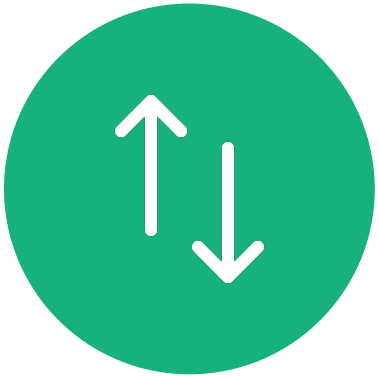
*Definitions adapted from FDA-NIH BEST Glossary. Available at https://www.ncbi.nlm.nih.gov/books/NBK338448/

When using data from a DHT to inform an endpoint, begin by treating the endpoint like you would any other endpoint

Definition

Justification

Type
(Safety, Effectiveness)



Positioning
(Primary, Secondary, etc.)

Definitions

Verification

Confirmation by examination and provision of objective evidence that the physical parameter that the DHT measure (e.g., acceleration, temperature, pressure) us measured accurate and precisely over time.

Validation

Confirmation by examination and provision of objective evidence that the selected DHT appropriately assesses the clinical event or characteristic in the proposed participant population.

Source: https://www.dimesociety.org/tours-of-duty/v3/

Engagement with the Agency

- Engage early with the Center responsible for the medical product being studied, to discuss use of DHTs in a specific clinical investigation
    - Submit a meeting request to the relevant review division
    - Select your endpoint and DHT in advance
    - Have evidence to support the endpoint and the DHT
        - Is the endpoint clinically meaningful?
        - Did you complete verification and validation of the DHT?
- Drug Development Tool (DDT) or Medical Device Development Tool (MDDT) Qualification Programs
- Digital Health Center of Excellence

Top 5 Steps to Accelerate the Transition from Pilots to Scale

1. Collect clinical data early.

2. Have internal experts develop your evidence strategy. Don’t assume higher quality evidence always costs more.

3. Talk to external experts in regulation and reimbursement.

4. Register studies. State publicly what you’ll do, then do it.

5. Generate the highest quality evidence that is feasible. Details matter.

QUESTIONS?

DIGITAL MEDICINE SOCIETY

Moving the Needle

ACRO toolkit to advance decentralized clinical trial technology

November 10, 2021 at 12-1pm ET

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Moderator: Ari Feldman
Vice President, Global Compliance and Strategy
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Virtual
Journal Club

Nov 17, 2021 at 11am ET

Show me the money!
Academic research is critical to building trust

The Playbook
Driving Adoption
a DiME Tour of Duty

Meet the Authors

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Jeanne Chung

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SLIDE GRAVEYARD

Source: https://www.dimesociety.org/research/dime-research-committee/ | https://www.dimesociety.org/communication-education/library-of-digital-endpoints/

How we get there

Key steps may include:

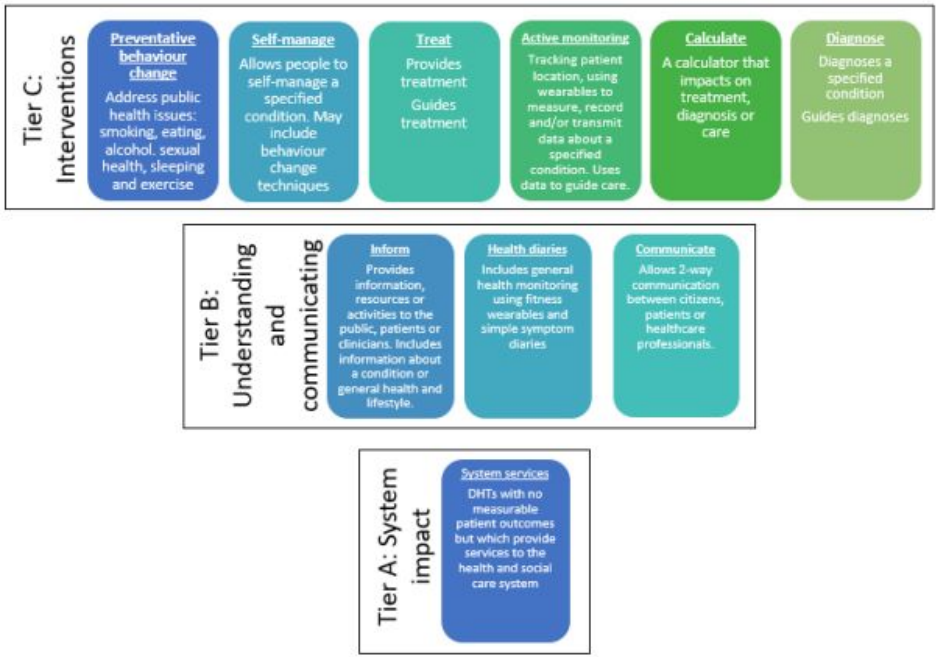
- Clear standards for measurement in digital health
- Clear statistical standards
- Aligned best practices to generate actionable quality evidence affordably.
- Aligned, concrete best practices to promote digital health equity.
- Aligned best practices around innovative study designs that accommodate the dynamic nature of DH interventions.

How we get there.

Key steps may include:

1. Clear standards for measurement in digital health
2. Statistical standards for biometric monitoring technologies
3. Aligned standards defining actionable quality evidence.

Evidence Standards Frameworks



DHTs classified by function and stratified into evidence tiers

- In 2018, the UK National Institute for Health and Care Excellence (NICE), in partnership with Public Health England, NHS England, NHS Improvement and others, developed an evidence standards framework (ESF) for digital health and care technologies (DHTs).

- The ESF was designed to provide a standardised approach to guide developers and commissioners on the levels of evidence needed for the clinical and economic evaluation of DHTs by health and care systems.

Source: https://journals.sagepub.com/doi/10.1177/20552076211018617