Digital biomarkers decision making process working group

ISCTM Spring 2024
7:30 AM, February 23rd

Co-chairs:

- Vikas Mohan Sharma
- Anzar Abbas

Disclosures

- Anzar Abbas
  - Employee, hold stock in Brooklyn Health
  - Former employee, hold stock in AiCure

- Vikas Mohan Sharma
  - Full-time employee, Fortrea GmBH
  - Independent Ethics expert at the European Research Council

Agenda

7:30-7:45	Introduction to session
7:45-8:05	Opening presentations by sub-group leaders
8:05-8:50	Allocated time for subgroup discussions
8:50-9:10	Summary updates by the sub-group leaders
9:10-9:15	Session closeout and the next steps

Sub-group recap

Glossary

Clinical validation

Clinical operations

Regulation

Sub-group recap

Glossary

Biomarkers: What is available and what does it all mean

Biomarker: Resource Synthesis and Glossary Workgroup

J. Cara Pendergrass, PhD: work group leader

Disclosures: Founder and CEO of Avanti Clinical Research Consulting
Consultant with EMA Wellness, BioXcel, Newronika

Resource Synthesis Objective

- Gathering, reviewing and synthesizing existing resources about digital biomarkers, with a focus on CNS use cases
  - Focus on biomarker use in CNS clinical trials
  - Including key references and info about biomarkers in other areas when informative and relevant

- Status: actively compiling available information (description with sources and links when available)

Resource Synthesis: Domains

- Agencies, organizations, and committees
  - Links to websites and agency documents and guidances
- Educational resources
  - Existing glossaries and libraries of digital endpoints
- Key review articles
- Other available information: best practices and available support
  - Journals with focus of biomarkers
  - Symposiums, conferences, and meetings
  - Webinars, presentations, panels, discussion

Resource Synthesis: Plan

- Goal:
  - May 2024: available on ISCTM website
  - Ongoing: Will be actively maintained with newer, updated information added

Terminology Glossary Objective

- Identifying and compiling list of key terms relevant for digital biomarkers, with a focus on CNS use cases
  - Recognize that cannot include all terms or replicate work (i.e., Biomarkers, EndpointS, and other Tools (BEST) Glossary by FDA-NIH Biomarker Working Group)

- Status: actively identifying and reviewing information for key terms

Terminology Glossary: Plan

- Plan:
  - Beginning to organize outline and sections/classifications of relevant biomarker terms

- Goal: Review paper
  - Draft of review paper: working on summer 2024

  - Review paper in submission form: by end summer/Sept ISCTM meeting

Sub-group recap

Clinical validation

Disclosures

Subgroup lead: **Marc Aafjes**: Shareholder and CEO of Deliberate AI, which generates revenues from CNS trial sponsors and healthcare providers, and receives federal funding from the NIH, FDA, and DARPA.

Core group:

- **George Doffner:** Shareholder and part-time employee of The Siesta Group GmbH.
- **Felix Menne**: Employee of ki:elements, which generates revenues from CNS trial sponsors, and receives private and public funding from the Gates Foundation and German Federal Ministries.
- **Leif Simmatis**: supported by a Mitacs Elevate fellowship, employee and shareholders of Cove Neurosciences, which generates revenues from CNS trial sponsors and vendors, and receives funding from the Ontario Brain Institute and the Ontario Centre for Innovation.
- **Katie Aafjes-van Doorn**: employee and shareholder of Deliberate AI, which generates revenues from CNS trial sponsors and healthcare providers

Since meeting last, it has become clear **existing Clinical Validation of Digital Biomarkers is lacking quality and consistency**

1. Validation study reporting is highly variable

2. Many studies, specifically in CNS, have undergone limited peer review
   – Many are published in (lower quality) open-access journals or as conference proceedings

3. Replication studies or prospective confirmatory trials are lacking

4. Limited to no adoption in regulatory settings (e.g. pivotal trial endpoints)

5. Lack of clear definitions on Context of Use (CoU) and Concept of Interest (CoI)
   – And COI are often not necessarily ‘meaningful’ for FDA

6. Confusion about what is a Digital Biomarker, a Digital Clinical Outcome Assessment (COA) and an endpoint

We seek to **clarify standards for Clinical Validation (CV)** and then demonstrate those by evaluating the current research of a subfield

Objective for 2 Papers

1. **Develop EVIDENT: a (CNS) digital biomarker evaluation framework [June 2024]**
   - EVIDENT: Evaluation and Validation Indicators for Digital biomarkers and ENdpoints in Trials
   - Goal1: Provide a framework to evaluate evidence
   - Goal 2: Provide reporting guidance for future papers
   - Optional: Provide suggestions on how to address criterion validity when comparables are lacking (i.e. no 'gold standard')
2. **Demonstrate EVIDENT: a scoping review of validation in targeted area [Aug 2024 – date TBC after ISCTM]**
   - Evaluate scientific evidence of digital biomarkers (by indications or type of digital biomarkers, TBC)

Agenda for Break-out

1. **Feedback on EVIDENT framework draft**
   - Rank framework indicator agreements to identify consensus and disagreements
   - Identify any additional missing areas of framework for consideration
   - Brainstorm counterfactuals that any CNS Digital Biomarker with a relevant COI has an ML component
   - Discuss any other special considerations for CNS
2. **Open discussion on addressing 'criterion validity' when comparables are lacking (i.e. no 'gold standard')**

Publish 2 papers in 2024:
1) Methodological Paper & 2) Scoping Review

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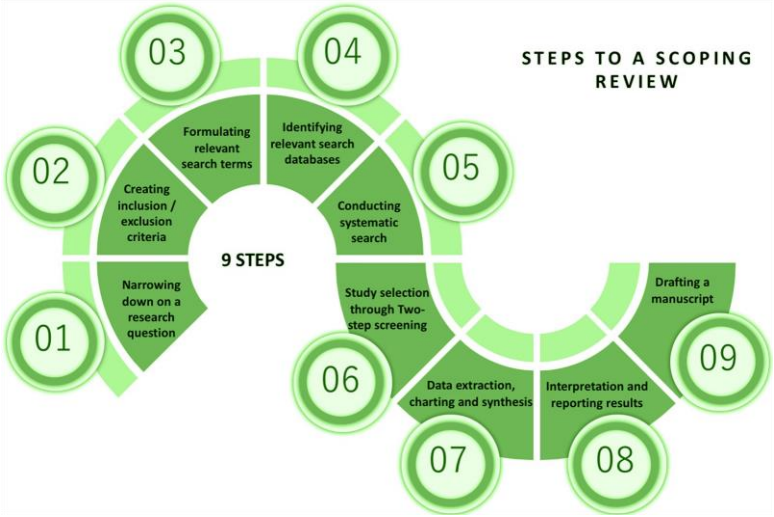
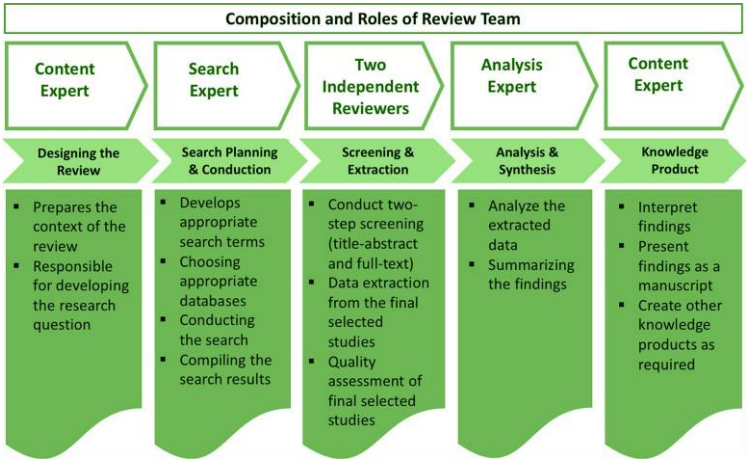
Our scoping review will follow an **iterative process**, following PRISMA guidelines, and then its application





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Sub-group recap

Clinical operations

Subgroup on clinical operations

Evaluating the operational excellence of digital health technologies in clinical trials

Disclosures

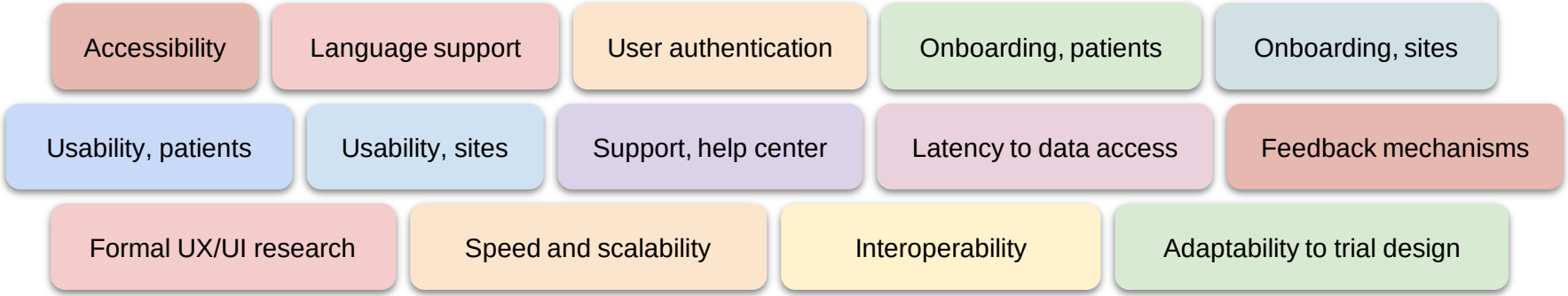
- Employee, hold stock in Brooklyn Health
- Former employee, hold stock in AiCure

Background

- Formed organically last spring
- Goal to formally evaluate effect of a digital health technology on trial operations
- Improve experience for patients and sites while avoiding adding risk to study
- Important considerations unrelated to scientific validity, regulatory acceptability, etc.
- Sponsors already asking these questions; subgroup meant to standardize evaluation criteria
- Help vendors developing technologies have goals on user experience, design, etc.
- Final output is a **rubric** with items evaluating different aspects of a digital health technology

DHT ClinOps Rubric

- Currently has 15 items
- Need feedback on items, what is considered poor / acceptable / good on each item
- Will be presenting rubric as a poster in the fall ISCTM to get more feedback
- Will then submit a manuscript on operational excellence of DHTs in clinical trials



Example of items

01 – Accessibility Score

How accessible is the technology for all users, including those with disabilities?

1	No special considerations have been made for accessibility	
3	Basic accessibility features have been integrated, such as simple and clear language, the option for larger text , color correction, or voice control	☐
5	Technology is compliant with the Web Content Accessibility Guidelines (WCAG) and has features to support a range of disabilities	

Example of items

02 – Language support Score

Can the tool support multiple languages and be deployed globally?

1	The technology is only available in the original language; no additional language support
3	The technology can support multiple languages and the vendor has capacity to expand the number of supported languages given sufficient time
5	Language support has been built from the ground up and the tool has been formally validated for required languages

Example of items

03 – User authentication Score

How protected is access to the tool by the users?

1	The tool, once installed and set up, can be accessed without authentication
3	Basic authentication using a code or username and password has been implemented
5	Advanced authentication through use of biometrics, multi-factor authentication, or other means has been implemented

We need members!

Come join us

Sub-group recap

Regulation

Disclosures

Travel and/or consulting fees: WCG Clinical Services, Lundbeck, Acadia, Otsuka, Sumitomo, Karuna, Minerva Neurosciences, Guidepoint, and Decision Resources Group. CEO and part owner of Quantic Innovations, which provides services related to digital phenotyping.

What is the current state of regulatory acceptance of biomarkers in CNS drug or device approvals?

Objective: The purpose of the regulatory stream is to develop the regulatory section of the workgroup tool.

Method for first product: eCOA regulation

- Review regulatory agency documents
- Interview participants in industry/regulatory discussions of proposed eCOAs
- Review the results of applications for approval

Deliverable: an article that will

- Review kinds of eCOAs
- Summarize the FDA & EMA qualification programs
- Review experience to date of qualification applications
- Integrate this information as recommendations

Members: Margaret Moline, Luca Pani, Cara Pendergrass, Corey Reuteman-Fowler, Louisa Steinberg, Brian Kirkpatrick

Subgroup meeting: first article & beyond

Article

Introduction
- eCOAs as the present focus of deliverable
- Types of eCOAs, why apply for qualification, various uses

The qualification process: FDA & EMA
- The agencies' documents, including recommendations for navigating the process
- Agency responses to specific applications (especially problems with the applications)

Discussion
- The cost/benefit of the qualification process

Discussion of future steps