PAR-25-170

Digital Health Technology Derived Biomarkers and Outcome Assessments for Remote Monitoring and Endpoint Development (UG3/UH3 - Clinical Trial Optional)

Webinar

December 11, 2024

National Institute of Neurological Disorders and Stroke

National Institute on Aging

NATIONAL CANCER INSTITUTE

National Institutes of Health
Office of Behavioral and Social Sciences Research

Webinar Agenda December 11, 2024

- Program Staff Contacts
- Background and Context for the Notice of Funding Opportunity (NOFO)
- Review of important terms:
  - Digital Health Technologies (DHTs)
  - Biomarkers, COAs and Endpoints
  - Concept of Interest (COI) and Context of Use (COU)
- Funding mechanism and research scope
- Specific requirements
- Non-responsive studies
- Participating IC areas of interest
  - NINDS
  - NCI
  - NIA
- Reminder: Data management and sharing plans
- Budget and prior approval
- Q&A with Program Staff

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Background and Context: Value of Remote Assessments

Remote assessments can improve clinical research by reducing the burden on study participants and caregivers

- Especially important for participants who must travel long distances to participate (such as those in rural communities), and
- participants who may not be able to travel due to their condition or from lack of sufficient resources (time, support, etc).

Remote assessments can be more sensitive to clinically meaningful changes over time due to more frequent assessments that are less susceptible to the variability from differences in an individual's state at the time of a single clinical visit.

PAR-25-170: Goals

Digital Health Technology (DHT) Derived Biomarkers and Outcome Assessments for Remote Monitoring and Endpoint Development

The goals of this NOFO are to:

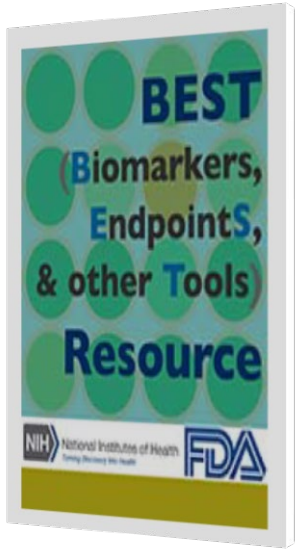
1) encourage collaboration across disease areas to pool expertise and resources, and
2) support research to generate the data needed for the development, analytical validation, and proof of concept clinical validation of DHT derived assessments and monitoring biomarkers, to be used as future endpoints in clinical trials for three or more disease areas.

Definitions used in this NOFO: Digital Health Technologies (DHTs)

Digital Health Technologies and **sensor-based digital health technology (DHT)** are a system that uses computing platforms, connectivity, software, and/or sensors for healthcare and related uses.

For the purpose of this NOFO, DHTs may refer to wearable sensors, mobile/app based cognitive or functional assessments, and in-home monitoring technologies.

Definitions used in this NOFO: Biomarkers, COAs and Endpoints



Biomarker: a defined characteristic that can be measured as an indicator of normal biological processes, pathogenic processes or responses to an exposure or intervention, including therapeutic interventions. – **FDA-NIH Biomarker Working Group BEST Resource**

Clinical Outcome Assessment (COA): a measure that describes or reflects how a patient feels, functions, or survives.

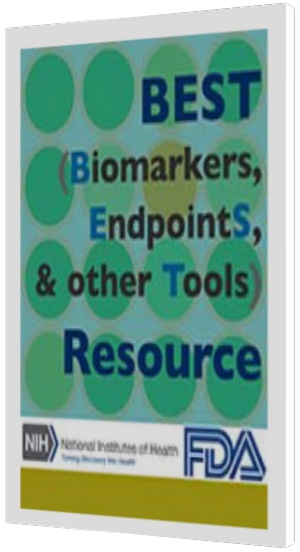
Types of COAs include:

- Patient-reported outcome (PRO)
- Observer-reported outcome (ObsRO)
- Clinician-reported outcome (ClinRO)
- Performance outcome (PerfO)/Functional outcome

Endpoint: A precisely defined variable intended to reflect an outcome of interest that is statistically analyzed to address a particular research question. A precise definition of an endpoint typically specifies the type of assessments made, the timing of those assessments, the assessment tools used, and possibly other details, as applicable, such as how multiple assessments within an individual are to be combined.

BEST Glossary: https://www.ncbi.nlm.nih.gov/books/NBK338448/#IX-E

Definitions used in this NOFO: Concept of Interest



Concept / Concept of interest (COI): the aspect of an individual's clinical, biological, physical or functional state, or experience that the assessment is intended to indicate or reflect.

Context of Use: A statement that fully and clearly describes the way the medical product development tool is to be used and the regulated product development and review-related purpose of the use.

BEST Glossary: https://www.ncbi.nlm.nih.gov/books/NBK338448/#IX-E

Definitions used in this NOFO: Validation

Validation: A process to establish that the performance of a test, tool, or instrument is acceptable for its intended purpose. This may include:

- **Construct Validation:** A process to establish, using quantitative methods, the extent to which the relationships among items, domains, and concepts of a clinical outcome assessment conform to a priori hypotheses concerning logical relationships that should exist with other measures or characteristics of patients and patient groups.
- **Content Validation:** A process to establish from qualitative research the extent to which the clinical outcome assessment instrument measures the concept of interest including evidence that the items and domains of an instrument are appropriate and comprehensive relative to its intended measurement concept, population, and use.

Analytical Validation: A process to establish that the performance characteristics of a test, tool, or instrument are acceptable in terms of its sensitivity, specificity, accuracy, precision, and other relevant performance characteristics using a specified technical protocol. This is validation of the test's, tool's, or instrument's technical performance, but is not validation of the item's usefulness.

Clinical Validation: A process to establish that the test, tool, or instrument acceptably identifies, measures, or predicts the concept of interest.

BEST Glossary: https://www.ncbi.nlm.nih.gov/books/NBK338448/#IX-E

Example (for illustration only)

	Concept of Interest:	Digital Health Technologies	Candidate Endpoint
Example:	Sleep disturbance	Wrist worn sensor Body worn sensor	Total sleep duration and number of wakeups [algorithm measuring biometric data from wearable sensors to determine sleep state; quantification of time asleep vs awake and number of wake-ups over 24 hours; number of days the assessment is made for a specified number of weeks or months).

***Examples* of the *types of questions that need to be considered to develop and validate an endpoint*:**

- How accurate are the **digital health technologies** at measuring the **concept of interest** relative to a gold standard?
- Are **DHT "A"** and **DHT "B"** both sufficient, or is only one sufficiently accurate/reliable? How is each measured (what is the algorithm of composite features that make up the measurement)?
- Are participants with condition X, Y or Z able to use **both DHTs** A and B? Do they prefer one over another?
- Is the accuracy of the measurement significantly altered by certain factors in the person's environment?
- Are there common comorbidities that influence the interpretation of the measurement?
- What amount of **change in the concept of interest** is **meaningful to participants** with X, Y or Z conditions?
- Does that amount of change predict/reflect a change in other established outcome assessments?
- Is the **digitally derived biomarker/COA** measured by the **digital health technology (DHT)** more sensitive/specific at detecting or predicting a meaningful change relative to the gold standard or established assessments?
- **What is the minimum sample frequency/duration needed** to measure the **biomarkers/COAs** to detect/predict a **meaningful change**?

PAR-25-170 is a UG3/UH3 phased cooperative agreement

PAR-25-170 - Digital Health Technology Derived Biomarkers and Outcome Assessments for Remote Monitoring and Endpoint Development

Applications must include both phases

Mechanism	Phase	Length *	Budget **
UG3	Phase I	Can be 1-2 years	Not limited but must reflect the actual needs of the proposed project
UH3	Phase II	Can be 3-4 years	Not limited but must reflect the actual needs of the proposed project

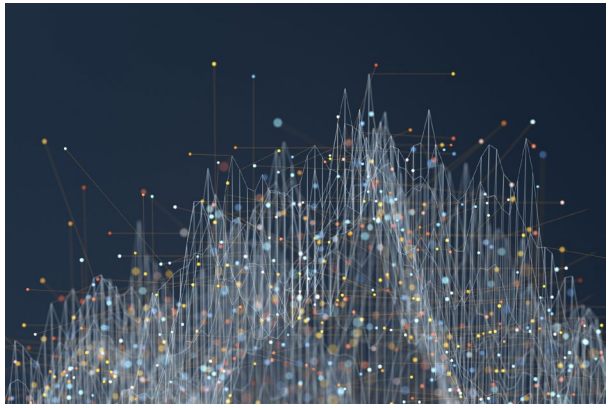
**The maximum project period is 5 years*

*** Not limited but requires prior approval (see next slide)*

Activities in the UG3 phase may include, but are not limited to:

First Phase (UG3; 1-2 years):

- **Device selection** and **analytical validation pilot studies** to optimize the algorithms to measure the **concept(s) of interest** against gold standards in the target patient populations which may include **construct and/or content validation.**
  - **May include head-to-head comparisons of different DHTs** to select the best performing or evaluate the generalizability across devices in preparation for use in the second (UH3) phase.
- **Evaluate factors that may interfere with the precision and accuracy of the data and measurement(s)** made from the DHTs in real world environments.



- Optimize and **finalize protocols** to ensure standardization across the sites and target populations; take into consideration missing data, amount of wear/use time needed for planned analyses in the prospective longitudinal clinical validation study (UH3 phase)
- **Establish the final statistical analysis and data management plans** for the UH3 phase.

Activities in the UG3 phase may include, but are not limited to:

First Phase, continued (UG3; 1-2 years):

- ❑ Develop **user-informed consent and training materials** for the UH3 phase with input from individuals with lived experience from diverse backgrounds
  - ❑ See the ***Informed Consent for Research Using Digital Health Technologies: Points to Consider & Sample Language document from NIH***: https://osp.od.nih.gov/wp-content/uploads/2024/05/DigitalHealthResource_Final.pdf.

- ❑ Conduct **outreach activities* and establish collaborations with communities that are historically underrepresented in clinical studies** including racial and ethnic minorities, individuals in rural populations, and individuals with limited English proficiency.

**Addressed in the Community Engagement Plan (see Other Attachments)*

Activities in the UH3 phase may include, but are not limited to:

Second Phase (UH3; 3-4 years):

- Conduct a **prospective longitudinal study** to determine the statistical relationships between the **digital monitoring biomarker** or **clinical outcome assessment** with established biomarkers, clinical outcome assessments, and consumer/patient informed quality of life metrics.

- *Evaluate the digitally derived biomarkers or COAs response to a therapeutic or behavioral intervention.

if evaluated as part of standard of care or as an ancillary study to an existing clinical trial [see non-responsive criteria**]*

- Obtain regulatory input such as through a Critical Path Innovation Meetings (CPIM) and/or submission of a letter of intent to one of the FDA's Drug Development Tools qualification programs [https://www.fda.gov/drugs/novel-drug-approvals-fda/critical-path-innovation-meetings-cpim]

PAR-25-170 Unique Elements and Specific Requirements

Applications must include the following elements:

Part of the research strategy:

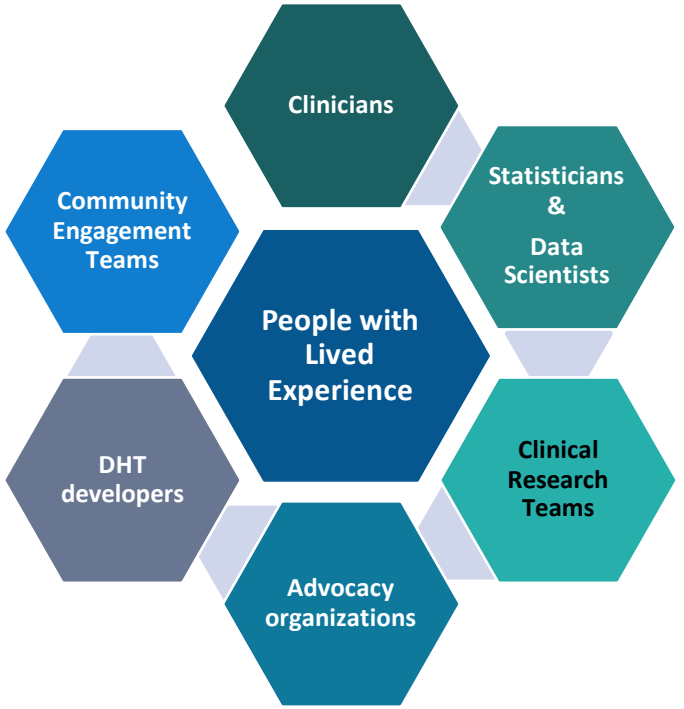
- ✓ Include partnerships with patient advocacy organizations and people with lived experience (PWLE)
- ✓ Propose to develop and validate the DHT derived biomarkers in three or more diseases/conditions
- ✓ Propose to develop and validate remote assessments for the purpose of filling an unmet need as a primary or secondary endpoints in clinical trials using digital health technologies
- ✓ Include a Context of Use statement

Separate required documents to be provided in the Other Attachments (Section IV):

- ✓ A community engagement plan (CEP)
- ✓ Timeline, annual milestones, and UG3/UH3 transition milestones
- ✓ Team management plan

Partnerships with patient advocacy organizations and PWLE

Partnerships with patient advocacy organizations and
people with lived experience (PWLE) are required to inform study design, endpoint selection, and increase community uptake.



Three or more diseases/conditions

<u>Three</u> or more diseases/conditions are required to encourage standardization of remote monitoring assessment and endpoint development, and to promote collaboration and pooled resources for successful translation.

For purposes of this NOFO, applicants *should reference the criteria used to define the disease/condition* which may include definitions from clinical practice guidelines or consensus papers, or similar standardized definitions.

Disease/condition: *A disorder of structure or function, which may have a known cause and a distinctive group of symptoms, signs, or anatomical changes. How a disease or condition is defined may evolve along with the biological understanding of the etiology or symptomatology.*

Goals must be to develop remote assessments for use in CTs

- ✓ Propose to develop and validate remote assessments for the purpose of filling an unmet need **as a primary or secondary endpoints in clinical trials** using **digital health technologies**

- ✓ A **Context of Use** statement(s):
  - ❑ How would these remote assessments be used in clinical trials?
  - ❑ What types of clinical trials? [*therapeutic drug/biologic/device development? Rehabilitation studies? Behavioral interventions? Others?]*
  - ❑ Why are they needed? [*what is the limitation of existing assessments/what problem(s) would having these remote assessments solve?]*

List of Other Attachments in PAR-25-170

- ❑ **Timeline and Proposed Milestones** (required; 3 pages maximum)
- ❑ **Team Management Plan** (required; maximum of 3 pages).
- ❑ **Community engagement plan** (required; 2 pages maximum)
- ❑ **Associated clinical trial protocols and consent forms** (required if applicable; no page limit)
- ❑ **Intellectual Property Plan** (*if applicable*)
- ❑ **Letters of Support** (*if applicable*)

These are included as "Other Attachments" (these do not go into your 12-page research plan)

Timeline and Milestones - “Other Attachment”

Timeline and Proposed Milestones (required; 3 pages maximum):

Milestones should describe **project decision points with quantitative metrics for go/no-go decision making** throughout the funding period. Clear deliverables with corresponding Go/No-Go milestones should be included at the end of the UG3 phase and annual quantitative milestones are required for each year of the UG3 and UH3 phases as indicators of a project's continued progress or emergent difficulties. Milestones will be used to monitor project progress as part of the evaluation for continued funding by the Program Official and Project Scientists.

For each milestone, provide a **brief description of the success criteria and justification for those criteria**.

Quantitative milestones are dependent on the project but should include but are not limited to:

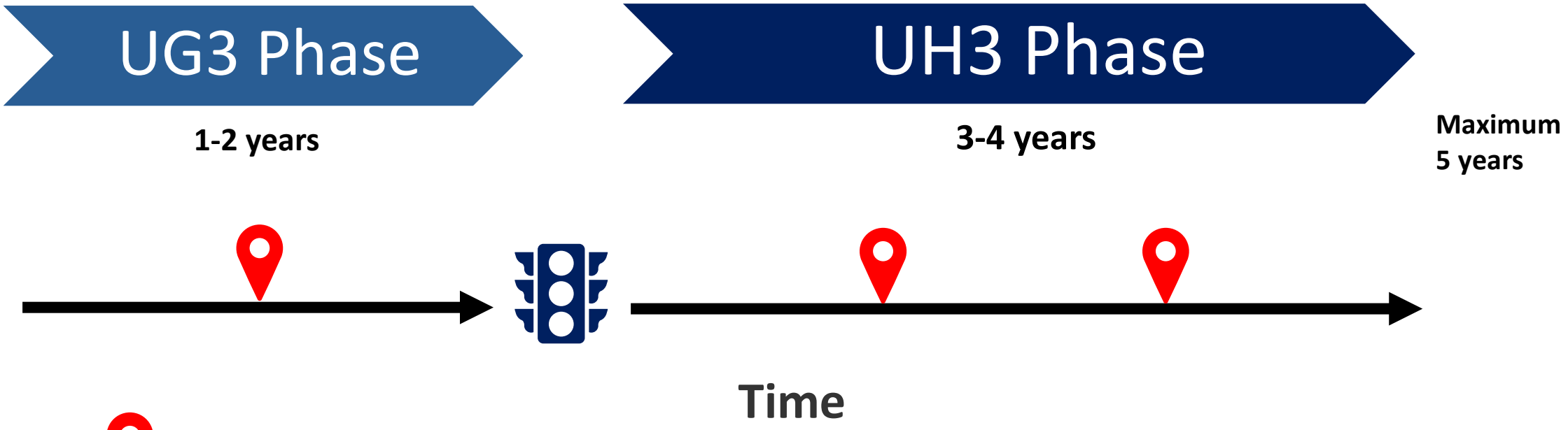
- ✓ Progress metrics such as evidence of community engagement, obtaining user feedback, reaching enrollment and data collection goals, etc.
- ✓ Performance metrics such as demonstrating data quality and completeness, reaching target analytical sensitivity, specificity, precision and accuracy thresholds, etc.

A Gantt chart for the timeline of attaching each milestone is strongly encouraged.

The Timeline and Milestones are added as an “Other Attachment” (see Section IV).

Timeline and Milestones

NOTE: Continuation to the UH3 phase is contingent on meeting both the annual milestones and Go/No-Go milestones



Annual Milestones (UG3 and UH3 Phases: to demonstrate continued progress towards deliverables)

Go/No-Go Milestones (transition point between UG3 and UH3 Phases to achieve UH3 deliverables/readiness & feasibility for UH3 phase)

Recommendation is to propose ~2-4 milestones per year

Timeline and Milestones: UG3 Example

Timeline and Proposed Milestones (required; 3 pages maximum):

Example of an UG3 Phase Annual Milestone*:

Progress Milestone: Complete feasibility study and obtain input from people with lived experience to collect input on device selection, study protocol and consent forms.

Success criteria:

- Complete 2-month feasibility study in X number of participants from conditions X, Y and Z [described in application]
- Complete data collection on qualitative study [described in application] to incorporate feedback from participants on digital health technologies used, burden of assessments, and clarity of consent forms.

Justification: Qualitative input from participants is required to inform adjustments to protocols and consent language. Analyses and revision to protocols will be completed in year 2.

Recommendation is to propose ~2-4 milestones per year

The Timeline and Milestones are added as an "Other Attachment" (see Section IV).

Timeline and Milestones: Go/No-Go Example

Timeline and Proposed Milestones (required; 3 pages maximum):

Examples of a UG3 to UH3 Transition Go/No-Go Milestone*:

Performance Milestone: Determine which of the digital health technologies tested in the UG3 phase meet the performance criteria to be used in the UH3 phase.

Success criteria:

- Useability: >X% of participants were able to wear/use the device as planned meeting the minimum adherence requirements needed [amount of time/sessions, frequency of use, etc]
- Accuracy: >X% of __ events in >Y% of participants, were correctly detected as ___, relative to the reference standard [__]
- Reliability: Intraclass correlation coefficient (ICC) on __ tests exceeded __.

Justification: [*brief description of the success criteria and performance thresholds selected***]**

Recommendation is to propose at least 3 Go/No-Go milestones

The Timeline and Milestones are added as an "Other Attachment" (see Section IV).

Timeline and Milestones: UH3 Example

Timeline and Proposed Milestones (required; 3 pages maximum):

Example of an UH3 Annual Milestone*:

Progress Milestone: Recruit [#] of total [#] of participants and obtain baseline data that meet data quality performance metrics.

Success criteria:

- Complete baseline data collected on all participants [list any assessments or procedures run in addition to the DHT data collected]
- Data collected from DHTs meet pre-specified data quality metrics established in the UG3 phase

Justification: This is the minimum number of participants needed in year __ to meet the recruitment goals with the acceptable data quality needed for the planned analyses.

Recommendation is to propose ~2-4 milestones per year

The Timeline and Milestones are added as an "Other Attachment" (see Section IV).

Not in Scope of PAR-25-170

Non-responsive studies:

- Clinical trials or clinical research where the primary intent is to develop therapeutic agents or devices,
- Clinical trials or clinical research to evaluate a therapeutic agent or device's clinical safety, efficacy, effectiveness, and/or clinical management,
- Pre-clinical research using animal models or in vitro models,
- Applications where the primary intent is to develop diagnostic or risk assessments or biomarkers rather than for monitoring/endpoint development,
- Applications that do not include a statement titled "contexts of use" that specifies how the proposed endpoints will fill an unmet need for the diseases/conditions specified, and clearly defines the three or more diseases/conditions to be included,
- Applications that are proposing to develop a device or app rather than using existing devices/platforms,
- Applications that do not include milestones,
- Applications that do not include diseases/conditions within the participating NIH IC missions.

Non-responsive applications will be administratively withdrawn without review.

IC Interest Areas: NINDS

National Institute of Neurological Disease and Stroke (NINDS)

NINDS is interested in applications that propose to develop assessments that meet an unmet need for neurological diseases and **conditions across the lifespan**. **NINDS recognizes that DHT derived measurements needed for use in pediatric or elderly populations may be substantially different than adult populations and require distinct efforts.**

This NOFO is aligned with the NINDS 2021-2026 Strategic Plan's priority areas of supporting the development and validation of biomarkers and outcome measures, as well as aiding in the efforts to **promote health equity by supporting representative validation efforts and by developing remote assessments that can reduce the barriers to participate in clinical trials**. Research activities outside of the NINDS mission or traditionally supported by another NIH Institute or Center that is not signed onto this NOFO will not be considered.

https://www.ninds.nih.gov/about-ninds/strategic-plans-evaluations/strategic-plans/ninds-strategic-plan-and-priorities

Related NOFOs: NINDS

National Institute of Neurological Disorders and Stroke

NOFO	Title
NSF-23-614 NOT-OD-23-165	Smart Health & Biomedical Research in the Era of Artificial Intelligence & Advanced Data Science (SCH)
PAS-22-196	Advancing Research on Alzheimer's Disease (AD) and AD-Related Dementias (ADRD) (R43/R44 Clinical Trial Optional)
PAR-22-076	Prospective Observational Comparative Effectiveness Research in Clinical Neurosciences (UG3/UH3 Clinical Trial Not Allowed)
Approved Concept	Clinical Trial Readiness for Rare Neurological and Neuromuscular Diseases

IC Interest Areas: NIA

National Institute on Aging (NIA)

Through this NOFO, NIA supports research that focus on

- Development and validation of remote digital monitoring biomarkers and digital clinical outcome assessments in age-related neurological disorders, such as Alzheimer's Disease (AD) and related dementias (ADRD). Examples of ADRD are Lewy body dementia (LBD), frontotemporal disorders (FTD), limbic-predominant age-related TDP-43 encephalopathy (LATE), Vascular contributions to cognitive impairment and dementia (VCID) as well as mixed dementias.

- Systematic collection, scientifically sound analysis, and interpretation of clinically meaningful health information to improve age-related outcomes, decrease health disparities and improve care delivery of older adults.

- This NOFO is aligned with NIA's strategic mission and the NIA/NAPA AD+ADRD Research Implementation Milestone 9 and 11, as well as joining the efforts to promote health equity by developing remote assessments that can reduce the barriers to participate in clinical trials.

Related NOFOs, NOSIs and Approved Concepts - NIA

National Institute on Aging

NOFO	Title
PAR-25-209	Analytical and Clinical Validation of Biomarkers for Alzheimer's Disease (AD) and AD-Related Dementias (ADRD) (U01 Clinical Trial Optional)
NOT-AG-23-004	Notice of Special Interest (NOSI): Small Business Digital Technologies for Early Detection, Characterization and Monitoring of Senescence-Related Changes
NOT-AG-21-048	NOSI: Notice of Special Interest (NOSI): Digital Technology for Early Detection and Monitoring of Alzheimer's Disease and Related Dementias
Approved concept	Translational Center for Accelerating the Use of Digital Technologies in Alzheimer's Disease and Related Dementias Research
Approved concept	Digital Technologies as Tools to Screen and Monitor Alzheimer's Disease and Related Dementias

IC Interest Areas: NCI

National Cancer Institute (NCI)

NCI is interested in applications aligned with the NCI mission and scientific priorities and focused on the development and validation of cancer-specific digital monitoring biomarkers, clinical outcome assessments, and endpoints. As cancer is a group of diseases, applicants may define each cancer type or subtype (including molecular subtypes) as separate diseases if scientifically justified. NCI is particularly interested in applications that:

- Address unmet needs of high-risk, understudied, and/or underserved cancer populations including but not limited to individuals with early-onset cancers, rare cancers, pediatric cancer survivors, older cancer patients with comorbidities, and rural patient communities,
- Develop and validate digital biomarkers to monitor cancer treatment related symptoms, sequelae, and/or outcomes (e.g., pain, cognitive impairment, adverse events, late effects toxicity),
- Develop and validate cancer-specific biomarkers using analyte data derived from electrochemical DHTs,
- Use DHTs to monitor physiological status and/or clinical outcomes associated with physical function, nutritional or dietary status, aerobic capacity, body composition, sleep/circadian disruption, and/or mobility, and
- Use DHT-measured physiological and analyte data to monitor treatment response and inform treatment selection, optimized dosing, and adaptive designs.

Related NOFOs: NCI

NOFO	Title
NSF-23-614 NOT-OD-23-165	Smart Health & Biomedical Research in the Era of Artificial Intelligence & Advanced Data Science (SCH)
PAR-21-166	Academic-Industrial Partnerships for Translation of Technologies for Diagnosis and Treatment (R01 - Clinical Trial Not Allowed)
NOT-CA-24-031	NOSI: Validation of Digital Health and Artificial Intelligence/Machine Learning Tools for Improved Assessment in Biomedical and Behavioral Research
NOT-CA-23-037	Notice of Special Interest (NOSI): Technology Development for Cancer Control and Population Science Research
NOT-EB-23-022	Notice of Special Interest (NOSI): Quantum Sensing Technologies in Biomedical Applications

IC Interest Areas: OBSSR

National Institutes of Health
Office of Behavioral and Social Sciences Research

OBSSR-Supported Notices of Funding Opportunities

The OBSSR participates in the following active funding opportunities. Please note that this is not an exhaustive list of all funding opportunities related to behavioral and social sciences research, but rather a list of those that OBSSR coordinates or has joined. **OBSSR does not award grants**.

Please contact the NIH Institutes and Centers (IC) Research/Scientific contact(s) listed in these notices for questions regarding IC funding interest in grant applications.

https://obssr.od.nih.gov/research-resources/funding-announcements

Budgets and Prior Approval - PAR-25-170

Application *budgets are not limited* but need to reflect the actual needs of the proposed project.

Requests of $500,000 or more for direct costs in any year requires prior approval.
See links below for Institute/Center (IC) specific requirements and timelines.

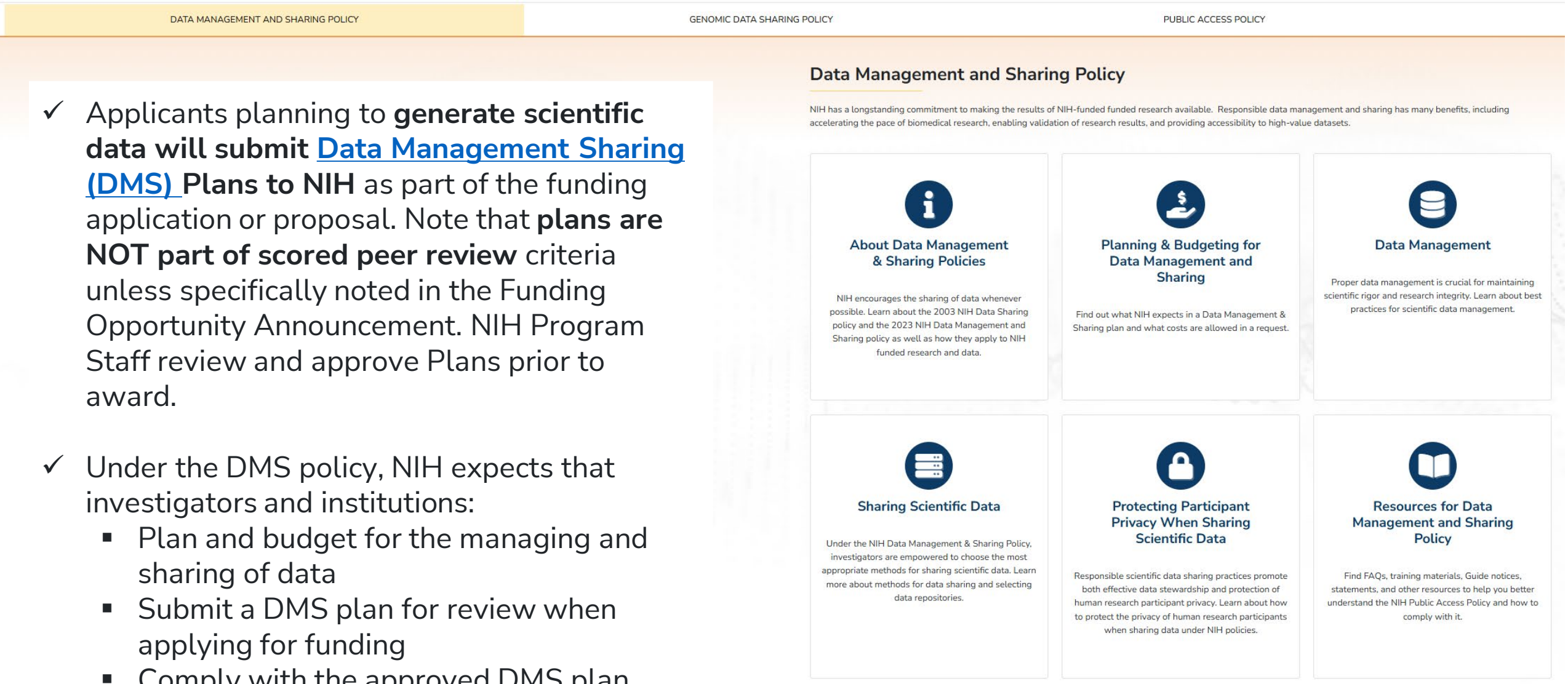
- **NINDS:** https://www.ninds.nih.gov/funding/preparing-your-application/application-process/pre-submission-approval-large-budget-500kyear-or-more
- **NIA:** https://www.nia.nih.gov/research/grants-funding/nia-guidance-awaiting-receipt-applications-ara-unsolicited-large-budget
- **NCI:** https://cancercontrol.cancer.gov/funding/submission-and-review/aras-for-large-budget-grant-applications-dccps-guidance

Please reach out to the IC Scientific Contact if you have questions.

NIH Data Management Sharing Policy

- ✓ Applicants planning to **generate scientific data will submit** [Data Management Sharing (DMS)](#) **Plans to NIH** as part of the funding application or proposal. Note that **plans are NOT part of scored peer review** criteria unless specifically noted in the Funding Opportunity Announcement. NIH Program Staff review and approve Plans prior to award.

- ✓ Under the DMS policy, NIH expects that investigators and institutions:
  - Plan and budget for the managing and sharing of data
  - Submit a DMS plan for review when applying for funding
  - Comply with the approved DMS plan



https://sharing.nih.gov/data-management-and-sharing-policy

Due Dates: First receipt date is February 21, 2025

Key Dates

Posted Date November 13, 2024

Open Date (Earliest Submission Date) January 21, 2025

Letter of Intent Due Date(s) Letters of intent are requested, but not required, 30 days before the application due date.

Application Due Dates			Review and Award Cycles		
New	Renewal / Resubmission / Revision (as allowed)	AIDS - New/Renewal/Resubmission/Revision, as allowed	Scientific Merit Review	Advisory Council Review	Earliest Start Date
February 21, 2025	February 21, 2025	Not Applicable	July 2025	October 2025	December 2025
June 20, 2025	June 20, 2025	Not Applicable	November 2025	January 2026	April 2026
February 20, 2026	February 20, 2026	Not Applicable	July 2026	October 2026	December 2026
June 22, 2026	June 22, 2026	Not Applicable	November 2026	January 2027	April 2027

All applications are due by 5:00 PM local time of applicant organization.

Applicants are encouraged to apply early to allow adequate time to make any corrections to errors found in the application during the submission process by the due date.

Expiration Date June 23, 2026

Question and Answer Session

Thank you for attending!

Questions?

Extra slides

Team Management Plan – “Other Attachment”

Team Management plan (required; 2 pages maximum)

All applicants must include a team management plan that describes the workflow of the team/key personnel.

Describe how the team will work together (e.g., data generation, reporting of data and integrated review across teams with various disciplines, decision-making, etc.) over the course of the project and include letters of support (below).

This section should be complementary to the “Multiple PD/PI Leadership Plan” leadership plan by *focusing on how the project will be managed across sites, PIs, co-Is and consultants*. Effective project management is a critical component of achieving the program goals, especially as the team size increases.

Elements to consider include:

- Organizational structure, team composition, and roles
- Shared vision, contributions, and distributed responsibility for decision-making
- Resource sharing and allocation
- Credit assignment
- Knowledge transfer
- Coordination and communication
- Intra-team data sharing, archiving, and preservation

The Team Management Plan is added as an “Other Attachment” (see Section IV).

A community engagement plan (CEP) – “Other Attachment”

A community engagement plan (CEP) is required that outlines how communities will be engaged throughout the research process.

The plan should identify relevant invested parties as collaborators at a level of involvement that is meaningful and feasible for the community partner(s) and appropriate for the project to enhance the impact of the research.

No specific community engaged research approach is required but please see the National Academy of Medicine’s Advancing Health Equity and Systems Transformation through Community Engagement strategy for assessing meaningful community engagement as a reference and to identify core principles to follow.

The CEP is added as an “Other Attachment” (see Section IV).

PAR-25-170 supports different types of validation in each phase

Can be addressed as part of the premise/supporting literature & in the UG3 phase

Validation: A process to establish that the performance of a test, tool, or instrument is acceptable for its intended purpose. This may include:

- **Construct Validation:** A process to establish, using quantitative methods, the extent to which the relationships among items, domains, and concepts of a clinical outcome assessment conform to a priori hypotheses concerning logical relationships that should exist with other measures or characteristics of patients and patient groups.
- **Content Validation:** A process to establish from qualitative research the extent to which the clinical outcome assessment instrument measures the concept of interest including evidence that the items and domains of an instrument are appropriate and comprehensive relative to its intended measurement concept, population, and use.

Analytical Validation: A process to establish that the performance characteristics of a test, tool, or instrument are acceptable in terms of its sensitivity, specificity, accuracy, precision, and other relevant performance characteristics using a specified technical protocol. This is validation of the test's, tool's, or instrument's technical performance, but is not validation of the item's usefulness.

Clinical Validation: A process to establish that the test, tool, or instrument acceptably identifies, measures, or predicts the concept of interest.

BEST Glossary: https://www.ncbi.nlm.nih.gov/books/NBK338448/#IX-E

PAR-25-170 supports different types of validation in each phase

Validation: A process to establish that the performance of a test, tool, or instrument is acceptable for its intended purpose. This may include:

- **Construct Validation:** A process to establish, using quantitative methods, the extent to which the relationships among items, domains, and concepts of a clinical outcome assessment conform to a priori hypotheses concerning logical relationships that should exist with other measures or characteristics of patients and patient groups.
- **Content Validation:** A process to establish from qualitative research the extent to which the clinical outcome assessment instrument measures the concept of interest including evidence that the items and domains of an instrument are appropriate and comprehensive relative to its intended measurement concept, population, and use.

Analytical Validation: A process to establish that the performance characteristics of a test, tool, or instrument are acceptable in terms of its sensitivity, specificity, accuracy, precision, and other relevant performance characteristics using a specified technical protocol. This is validation of the test's, tool's, or instrument's technical performance, but is not validation of the item's usefulness.

Tested in the UH3 phase

Clinical Validation: A process to establish that the test, tool, or instrument acceptably identifies, measures, or predicts the concept of interest.

BEST Glossary: https://www.ncbi.nlm.nih.gov/books/NBK338448/#IX-E

Information and Resources: Digital Medicine Society

The Digital Medicine Society: "The Digital Medicine Society (DiMe) is a global non-profit and the professional home for digital medicine."

"**The Digital Health Measurement Collaborative Community (DATAcc)** by the Digital Medicine Society (DiMe) is a collaborative community with the FDA's Center for Devices and Radiological Health. We provide a forum for collaboration where partners and experts from across the digital health field work to advance the use of digital health measures in research to improve lives.

https://datacc.dimesociety.org/
https://playbook.dimesociety.org/playbooks/the-playbook/
https://datacc.dimesociety.org/resources/

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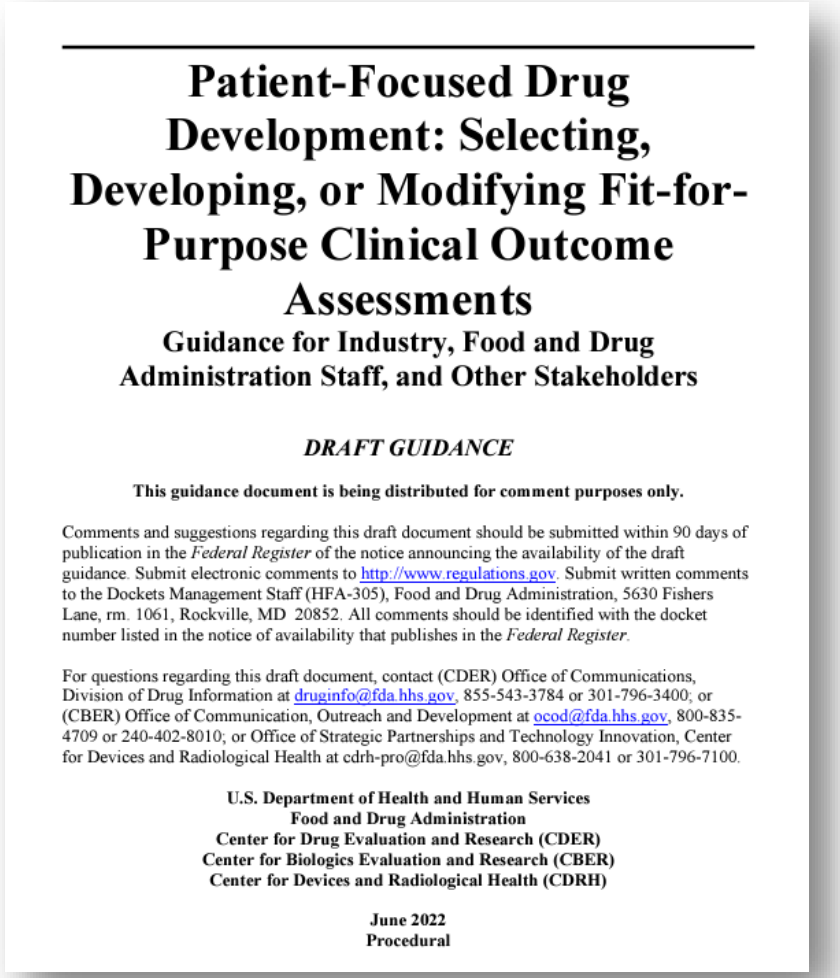
Information and Resources: FDA Guidance Documents



Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments

Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Office of Communications, Division of Drug Information at druginfo@fda.hhs.gov, 855-543-3784 or 301-796-3400; or (CBER) Office of Communication, Outreach and Development at ocod@fda.hhs.gov, 800-835-4709 or 240-402-8010; or Office of Strategic Partnerships and Technology Innovation, Center for Devices and Radiological Health at cdrh-pro@fda.hhs.gov, 800-638-2041 or 301-796-7100.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

June 2022
Procedural

Selection of FDA Guidance Documents

https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical

https://www.fda.gov/media/155022/download

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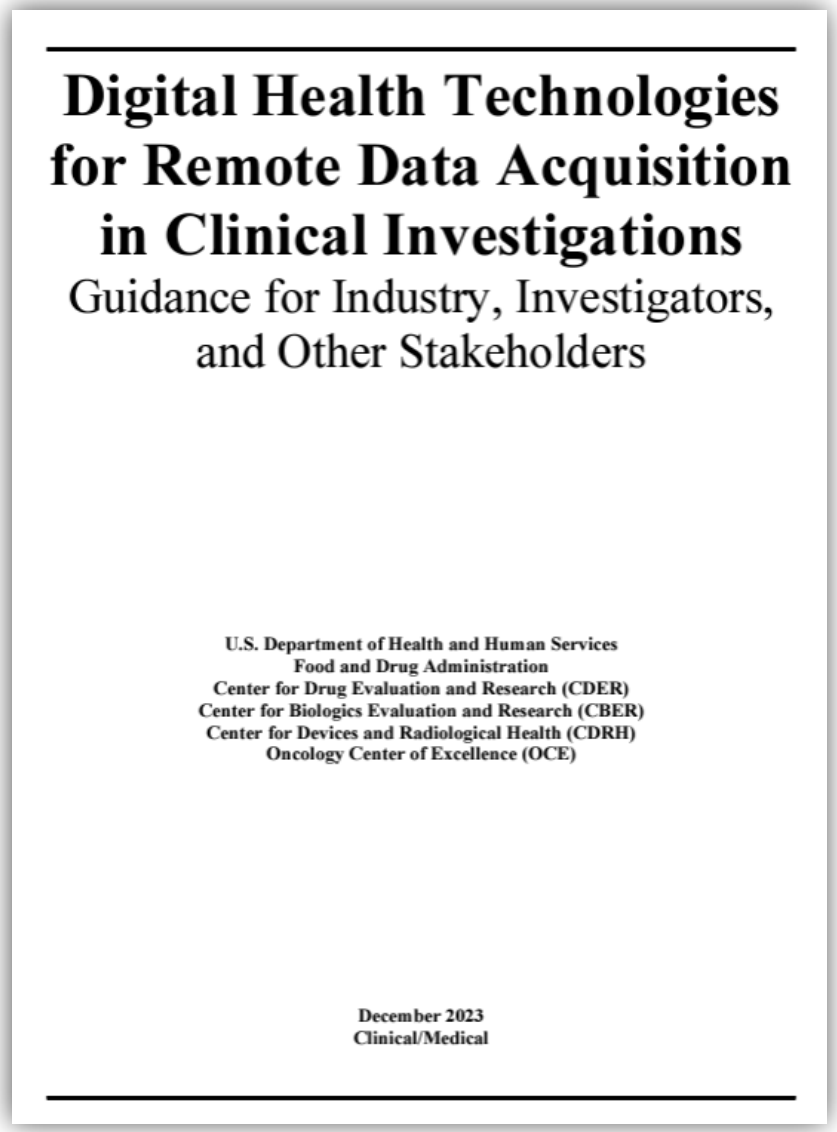
Information and Resources: FDA Guidance Documents



Digital Health Technologies for Remote Data Acquisition in Clinical Investigations

Guidance for Industry, Investigators, and Other Stakeholders

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Oncology Center of Excellence (OCE)

December 2023
Clinical/Medical

Selection of FDA Guidance Documents

- **Digital Health Technologies for Remote Data Acquisition** in Clinical Investigations
- Qualification Process for **Drug Development Tools Guidance** for Industry and FDA Staff
- Qualification of **Medical Device Development Tools**
- **Multiple Endpoints in Clinical Trials**

https://www.fda.gov/media/155022/download

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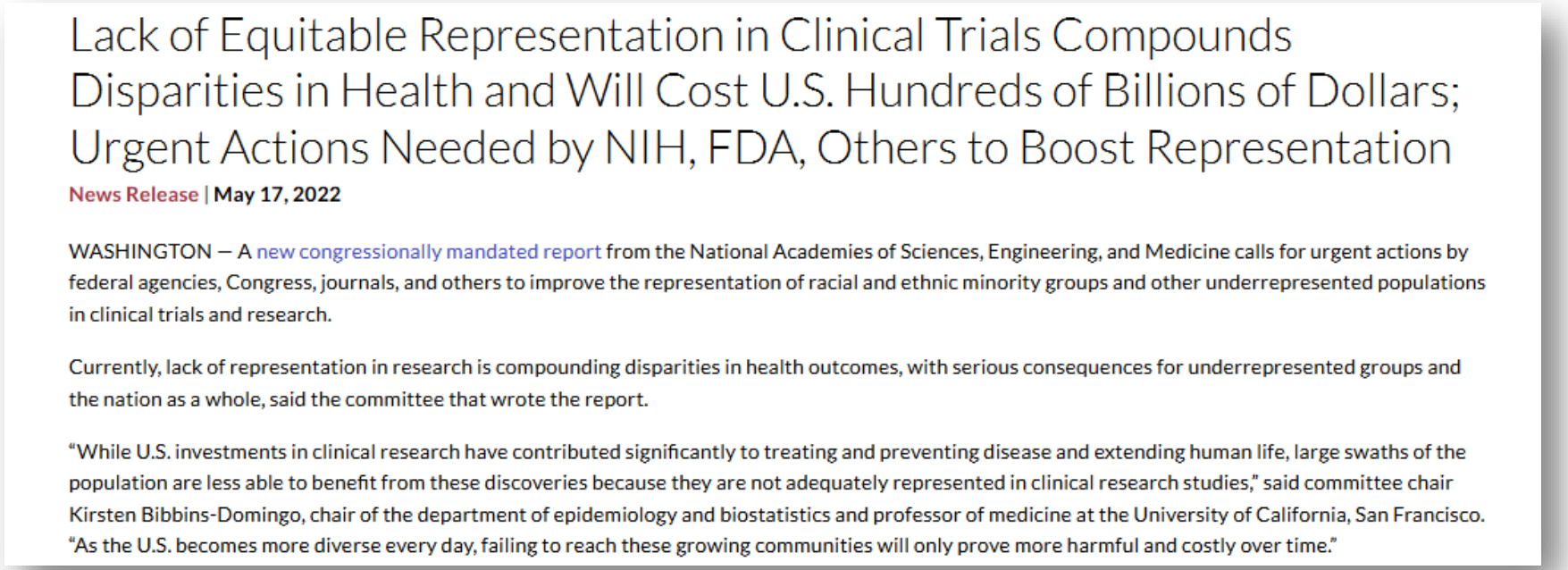
Background and Context: Increase Participation in Clinical Trials



Lack of Equitable Representation in Clinical Trials Compounds Disparities in Health and Will Cost U.S. Hundreds of Billions of Dollars; Urgent Actions Needed by NIH, FDA, Others to Boost Representation

News Release | **May 17, 2022**

WASHINGTON — A new congressionally mandated report from the National Academies of Sciences, Engineering, and Medicine calls for urgent actions by federal agencies, Congress, journals, and others to improve the representation of racial and ethnic minority groups and other underrepresented populations in clinical trials and research.

Currently, lack of representation in research is compounding disparities in health outcomes, with serious consequences for underrepresented groups and the nation as a whole, said the committee that wrote the report.

"While U.S. investments in clinical research have contributed significantly to treating and preventing disease and extending human life, large swaths of the population are less able to benefit from these discoveries because they are not adequately represented in clinical research studies," said committee chair Kirsten Bibbins-Domingo, chair of the department of epidemiology and biostatistics and professor of medicine at the University of California, San Francisco. "As the U.S. becomes more diverse every day, failing to reach these growing communities will only prove more harmful and costly over time."

Congressionally mandated National Academies report emphasized the value of improving participation in clinical trials:

https://www.nationalacademies.org/news/2022/05/lack-of-equitable-representation-in-clinical-trials-compounds-disparities-in-health-and-will-cost-u-s-hundreds-of-billions-of-dollars-urgent-actions-needed-by-nih-fda-others-to-boost-representation

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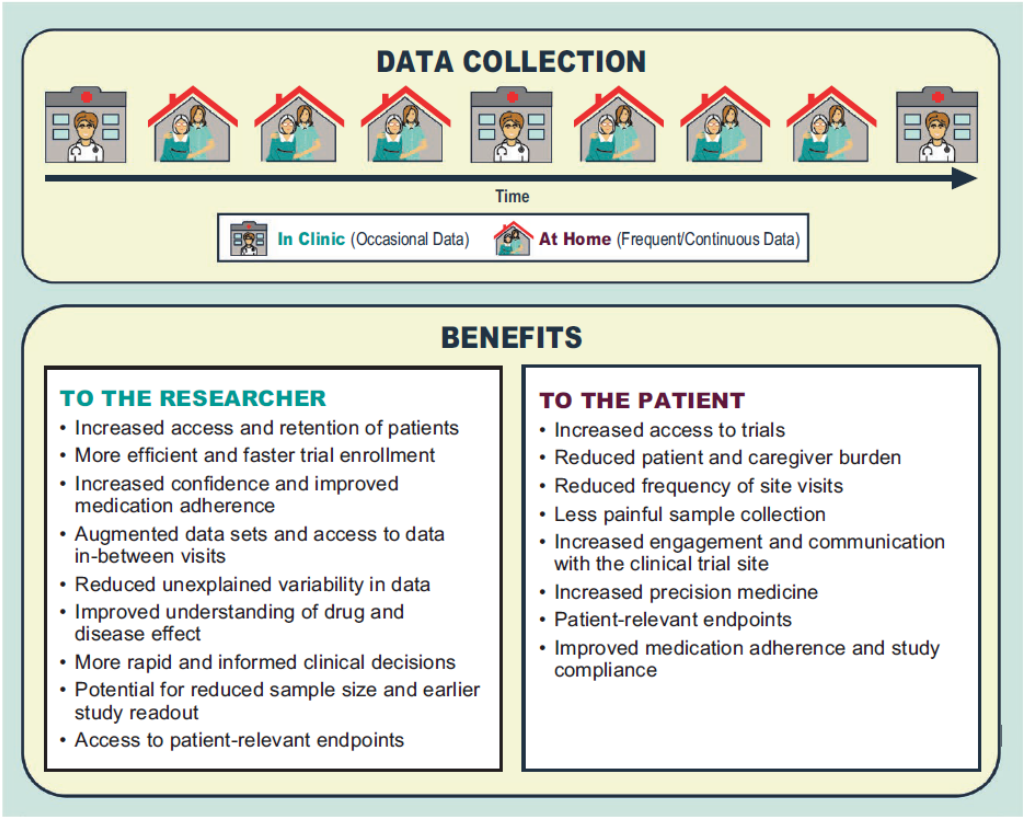
Background and Context

There are many benefits of remote data collection to patients and researchers.

REVIEW

Digitally Enabled, Patient-Centric Clinical Trials: Shifting the Drug Development Paradigm

Marissa F. Dockendorf[1,*], Bryan J. Hansen[1], Kevin P. Bateman[1], Matthew Moyer[1], Jyoti K. Shah[1] and Lisa A. Shipley[1]



Clin Transl Sci (2021) 14, 445–459 DOI: 10.1111/cts.12910

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Background and Context

Digital Health Technologies (DHTs) are increasingly being used in clinical research studies.

npj | digital medicine

www.nature.com/npjdigitalmed

BRIEF COMMUNICATION OPEN

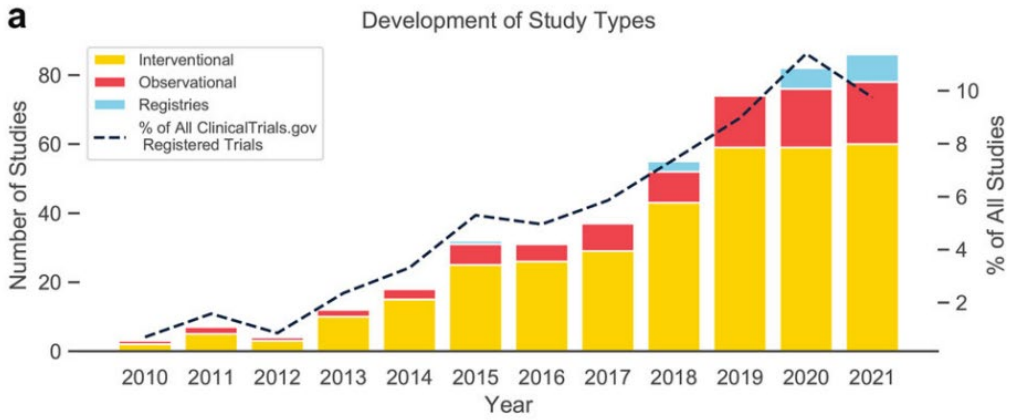
Check for updates

Evidence from ClinicalTrials.gov on the growth of Digital Health Technologies in neurology trials

Lars Masanneck[1,2], Pauline Gieseler[2], William J. Gordon[3,4,5], Sven G. Meuth[1] and Ariel D. Stern[2,6,7]

Digital Health Technologies (DHTs) such as connected sensors offer particular promise for improving data collection and patient empowerment in neurology research and care. This study analyzed the recent evolution of the use of DHTs in trials registered on ClinicalTrials.gov for four chronic neurological disorders: epilepsy, multiple sclerosis, Alzheimer's, and Parkinson's disease. We document growth in the collection of both more established digital measures (e.g., motor function) and more novel digital measures (e.g., speech) over recent years, highlighting contexts of use and key trends.

npj Digital Medicine (2023)6:23 ; https://doi.org/10.1038/s41746-023-00767-1



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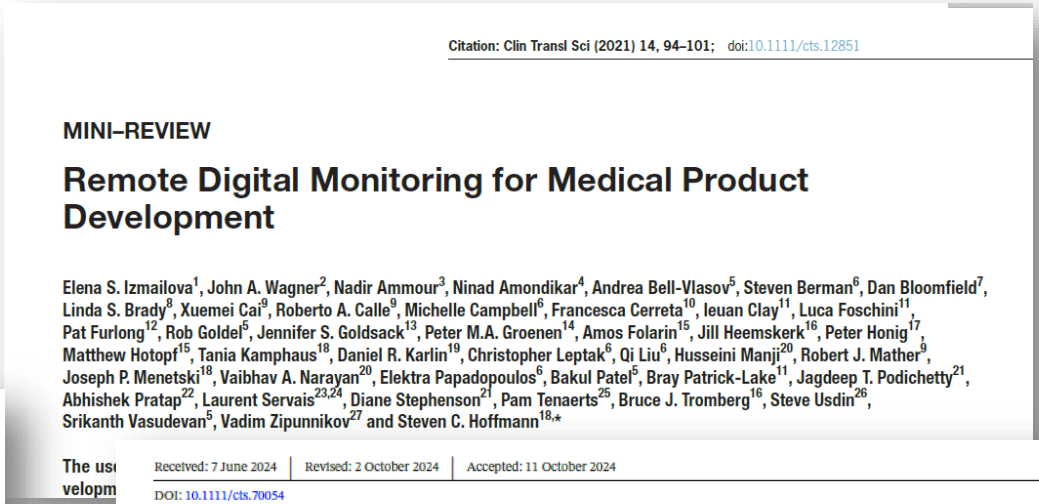
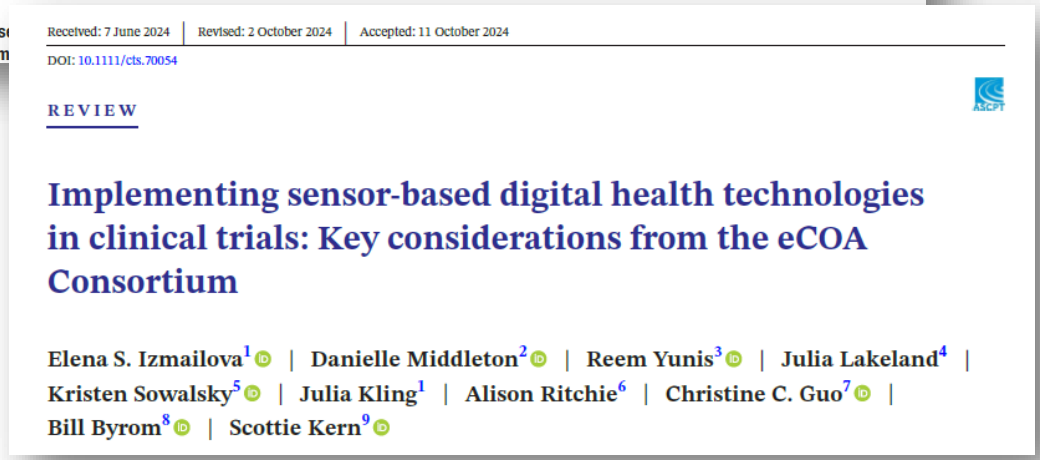
Background and Context: Fit-for-Purpose Validation is Needed

Generating the evidence required for validating endpoints that are ready for use in clinical trials remains challenging.





https://doi.org/10.1186/s12916-024-03590-x
https://doi.org/10.1111/cts.12851

https://doi.org/10.1002/cpt.3398
https://doi.org/10.1111/cts.70054

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Definitions used in this NOFO: Summary

	Concept of Interest:	DHT(s)	Candidate Endpoint
Example:	What do you want to measure?	What will you use to measure it?	HOW will you measure the Concept of Interest?

Context of Use
If you can accurately and reliability measure it, how will it be used?