EVERYTHINGALS
CARE TO CURE

A Roadmap to Incorporating Digital Endpoints in Clinical Trials

How Citizen-Driven Research & Open Innovation Will Enhance Clinical Trials in ALS

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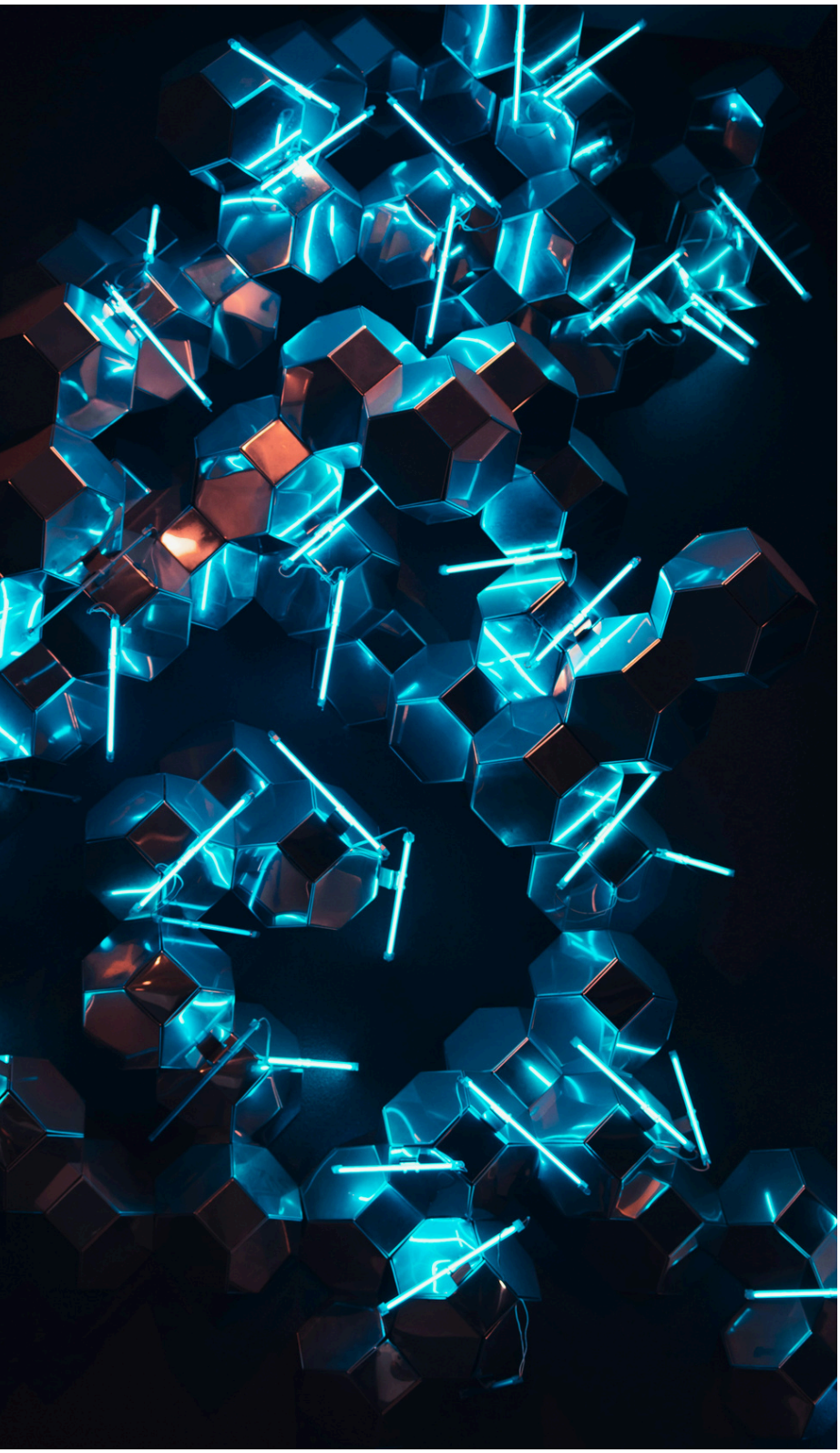


Executive Summary

This paper advocates for integrating digital health technologies (DHTs) into Amyotrophic Lateral Sclerosis (ALS) clinical trials to improve efficiency, accessibility, and patient centricity. Traditional trial endpoints remain burdensome, leading to high attrition rates and lengthy trial durations despite advancements in ALS research. DHTs offer solutions by enabling remote, continuous, and quantitative patient monitoring.

The EverythingALS Industry Consortia, a diverse network of biopharmaceutical professionals in cutting-edge research and development, aims to accelerate DHT integration into ALS trials. Its goal is to reach more people living with ALS (pALS) where they are, recognizing that until a cure is found, gathering insights and understanding the needs of pALS through their data is the next-best approach. Timely integration of new findings and innovations into trials is essential to keep pace with the rapid progression of ALS.

Governing Principles for Integrating DHTs in ALS Clinical Trials

Self-efficacy
Innovations in consent, privacy, and physical participation are critical for establishing and protecting participant self-efficacy in trials, fostering understanding and satisfaction.

Information utility
DHTs should generate clinically meaningful data by ensuring "fit for purpose" assessments. This involves remote data capture to better reflect pALS experiences and reliably measure intervention effects.

Agility of insight capture
Continuous data collection and insight generation in dynamic environments are essential. Relying solely on fixed collection points extends study duration and increases the risk of misinterpretation.

KEY SUCCESS DRIVERS

- ✓ Patient centricity
- ✓ pALS engagement and retention
- ✓ Interdisciplinary collaboration
- ✓ Agile trial design and implementation
- ✓ Alignment to clinically meaningful outcomes
- ✓ Regulatory compliance and data privacy

INTRODUCTION AND RATIONALE

Advances in ALS research, covering the disease's genetics, pathophysiological mechanisms, and preclinical models, have improved the potential for discovering new disease modifying therapeutics. Concurrently, novel trial designs enhance efficiency, facilitating the evaluation of multiple drugs (Paganoni et al. 2022; Mead et al. 2023). Yet, ALS trial endpoints have remained largely unchanged. Traditional ALS trial endpoints, such as the Revised ALS Functional Rating Scale (ALSFRS-R), vital capacity, strength testing, and survival, pose substantial burdens on people living with ALS (pALS). These endpoints often require in-clinic visits and are considered too challenging, costly, or inconsistent for remote monitoring, often resulting in missing data and reduced statistical power. This conventional approach of data collection in trials during single in-person clinical visits, poses a multitude of physical, emotional, logistical, and financial challenges for patients, caregivers, and researchers, particularly in neurologically debilitating conditions like ALS.

To address this challenge, innovative approaches for remote, continuous, and quantitative patient function monitoring are essential. Digital clinical endpoints, utilizing objective sensors and devices, bridge the data gap between clinical visits and offer a real-time insight into disease progression. This approach also reduces selection biases in clinical trials by including of a more diverse patient population.

Clinical heterogeneity, stringent inclusion criteria, and the progressive nature of the disease create a narrow window to diagnose, screen and enroll pALS into trials, which can significantly hinder patient retention. Dropouts in ALS trials occur due to various factors, including the burden of participation, failure to follow-up, perceived lack of efficacy, non-compliance, protocol deviations, attributing disease progression to lack of efficacy of the study drug, decisions made by physicians or investigators, and reaching protocol-defined stopping criteria (Wong et al. 2021). In turn, high attrition rates in ALS trials require larger sample sizes to maintain statistical power, further prolonging trial duration and inflating costs (Atassi et al. 2014).

Despite slower adoption in ALS, digital health technologies (DHTs) have seen growth across various disease areas. Digital clinical endpoints are increasingly integrated into pivotal phase 2 and 3 clinical trials (Digital Medicine Society (DiMe) Library of Digital Endpoints). These technologies can: 1) broaden trial accessibility by capturing a diverse participant pool, 2) optimize patient health status collection via direct and remote data acquisition, 3) enable more frequent or continuous real-world monitoring for a more accurate daily function representation, and 4) justify statistical exclusions from collected real-world data . As such, DHTs could provide more precise assessments, reducing the time and costs associated with conducting clinical trials.

Despite the potential benefits of remote monitoring and measurement technologies, the integration of digital tools into clinical trials is hindered by regulatory frameworks, financial constraints, and the inherent complexities of adapting them to the specific demands of neurological research. To overcome these challenges, it is crucial to foster interdisciplinary collaboration among clinicians, drug developers, and technology companies, while engaging with regulatory authorities and actively involving patient advocacy communities. These partnerships are essential not only to address regulatory hurdles but also to develop cost-effective implementation strategies, thereby facilitating the early and efficient integration of these technologies into ALS clinical trials.

THE VISION OF THE EVERYTHINGALS INDUSTRY CONSORTIA

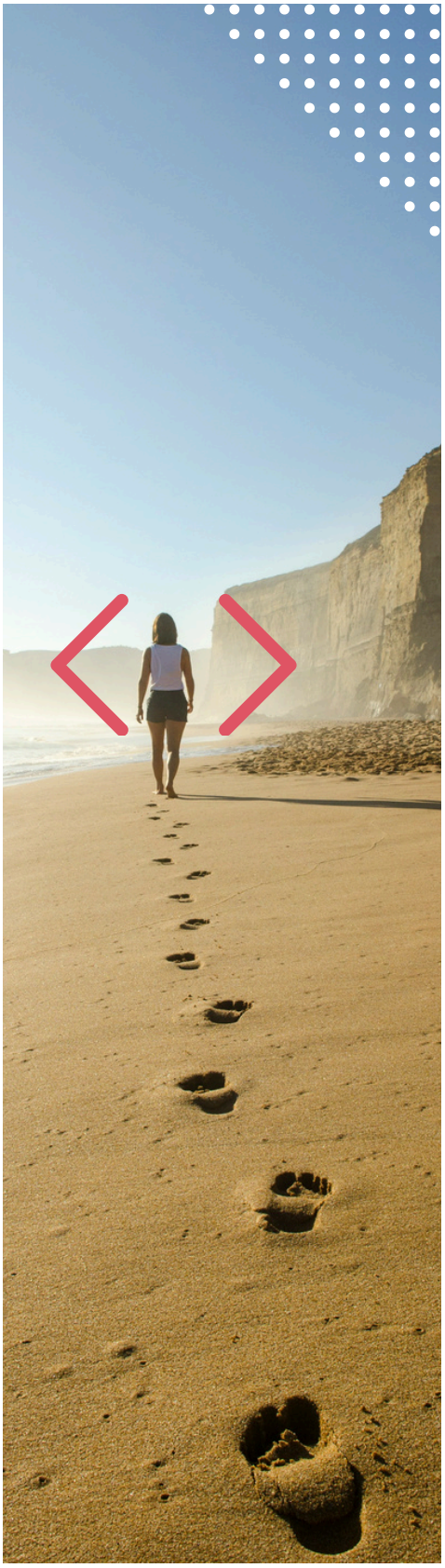
EverythingALS Consortia vision is centered on the transformative potential of digital endpoints in ALS clinical trials. These endpoints promise more efficient, frequent, and convenient real-world data collection, while enhancing trial access, participant diversity, and retention. Some DHTs have already demonstrated superior data yield in real-life settings (e.g., DiMe Library of Digital Endpoints; Vasudevan et al. 2022), drawing attention and support from initiatives such as NIH-sponsored think tanks and collaborative efforts, alongside new funding opportunities. However, critical gaps remain in enabling the seamless development, validation, interpretation, and regulatory acceptance of novel digital endpoints.

As professionals in biopharmaceutical research and development, members of the EverythingALS Consortia are committed to driving decision-making through establishment of a collaborative network. This network openly engages with key stakeholders, including pALS and caregivers (cALS), researchers, clinicians, and regulatory representatives, to address the gaps in ALS research and care.

EverythingALS Consortia goal is to fully integrate digitally captured endpoints and outcomes as foundational elements in understanding ALS disease progression and clinical study endpoints.

To ensure collective progress in ALS, we have united to produce a paper prioritizing key recommendations. These recommendations aim to accelerate the change management needed in research and care, establishing a new paradigm in clinical research design, oversight, and regulatory review.

Leadership from EverythingALS, core members of its Scientific Advisory Board, representatives from the Consortia, and additional advisors from regulatory and patient advocacy bodies have joined forces to develop this body of recommendations and priorities. Divided into four workstreams represented in the four sections of the paper's recommendations (Priority 1-4), Consortia members bring their expertise and deep knowledge of the challenges and opportunities within each phase and function of the product life cycle in research and development across the full range of company types. These recommendations also outline the planned implementation activities in 2024 and 2025 by the EverythingALS staff, collaborators and funders to support the advancement of the listed priorities.



IDENTIFIED PRIORITIES

Key Strategic Priorities for Integrating DHTs in ALS Clinical Trials:

- **Priority 1:** Navigating regulatory, data compliance, and ownership considerations to update frameworks regarding data ubiquity, consumer consent, and a patient's right to access their data for maximum self-efficacy.
- **Priority 2:** Unlocking the potential of digital endpoints and biomarkers to improve ALS clinical trials.
- **Priority 3:** Utilizing agile methodologies for DHT testing in neurological diseases, in open, integrated platforms through citizen-driven research and change management recommendations.
- **Priority 4:** Optimizing the clinical trial experience for pALS and cALS by maximizing participant access and retention through thoughtful trial design.

Priority 1

Navigating Regulatory, Data Compliance, and Ownership Considerations

Efforts to incorporate DHTs as foundational design elements and insight capture tools require clearer definition and potential innovations in regulatory, data privacy and consent requirements. These concepts should directly involve potential participants in the research and development process by embracing evolving sentiments about data privacy and the protection of personal data. Stakeholders must address challenges in implementing expansive consent models, including ethical concerns about data openness, accessibility, and potential future utility, while ensuring consent frameworks evolve to meet this rapidly changing landscape.

Defining outcomes, endpoints and clinical data requires stringent clarity to avoid confusion or devaluation of terms. Standardizing definitions is crucial for facilitating effective communication in clinical and regulatory discussions. Biomarkers and clinical outcome assessments measure distinct concepts, while both can be facilitated DHTs (Vasudevan et al. 2022). The term "biomarker" refers to a characteristic that can be measured reliably and accurately as an indicator of a biological process, whether that process is normal or affected by a disease (NIH BEST Resource). Digital biomarkers, a subset of biomarkers collected via digital devices, are relevant in remote monitoring in real-world settings. Conversely, "outcomes", such as how someone feels, functions or survives, are collected using COAs.

Ethical considerations and practical challenges in integrating DHTs in clinical trials need to balance scientific advancement with participant benefit.

Depending on the assessor, a COA can be a Patient-Reported Outcome (PRO), a Clinician-Reported Outcome, or an Observer-Reported Outcome. The capabilities of DHTs may not neatly align with the existing categories (e.g., COAs) and frameworks, as they can serve as endpoints or biomarkers depending on their applications and alignment with direct measurements or surrogate indicators. Nevertheless, DHT development and validation are expected to advance therapeutic progress while concurrently improving patient care.

Ethical considerations and practical challenges in integrating DHTs in clinical trials need to balance scientific advancement with participant benefit. Issues such as informed consent, patient access, and blinding in studies require careful consideration to embrace a participant-centric approach that respects autonomy and acknowledges the evolving perspectives of participants.

Considering the potential psychological risks of data disclosures, sponsors could provide counseling for participants during result interpretation and ensure clear communication throughout the study.

Another ethical concern revolves around the intricacies of participants' understanding of data usage, value generation, potential earnings, and trust implications with study investigators and sponsors. Effective communication in the consent processes and throughout the study, coupled with comprehensive participant education on data collection and safety, especially with the rising prevalence of genetic testing, remains essential for ethical considerations.

Obtaining appropriate consent is critical to data sharing and to reuse in future research.

STEVE K.

Diagnosis

As a person living with sporadic ALS, I have committed myself to research over the past 6+ years. Through my participation in clinical trials, I have provided lots of clinical research data to help diagnose ALS more quickly, find treatments, and someday hopefully find a cure.

Since ALS is a highly heterogeneous disease (perhaps not a singular disease but a syndrome), it is critical that clinical research data - participant data - not be viewed as intellectual property (IP) held tightly by researchers, but open sourced to the world.

In my opinion, the entirety of ALS clinical trial data collected over the many decades, shared in a well crafted ecosystem, would unleash tremendous potential for fostering new scientific discoveries and informing future decision-making. Advanced technology tools today allow for computers and machines to simulate human intelligence, problem-solving capabilities and far more complex calculations of contributors to ALS than we've been able to process in decades past.

My concern is that artificial intelligence (AI) will be utilized in a siloed fashion and not holistically analyzed. This will continue to foster the same barriers to understanding the causes or enablers of sporadic ALS.

Obtaining appropriate consent is critical to data sharing and to reuse in future research. Many major US funding agencies (i.e. NIH, NSF, etc.) now strongly encourage data sharing and reuse. Similarly, many academic publishers also encourage data sharing. Do pharmaceutical companies share clinical trial results? Currently, the pharma data sharing landscape is fragmented in many ways, but together, they can set industry standards to do so.

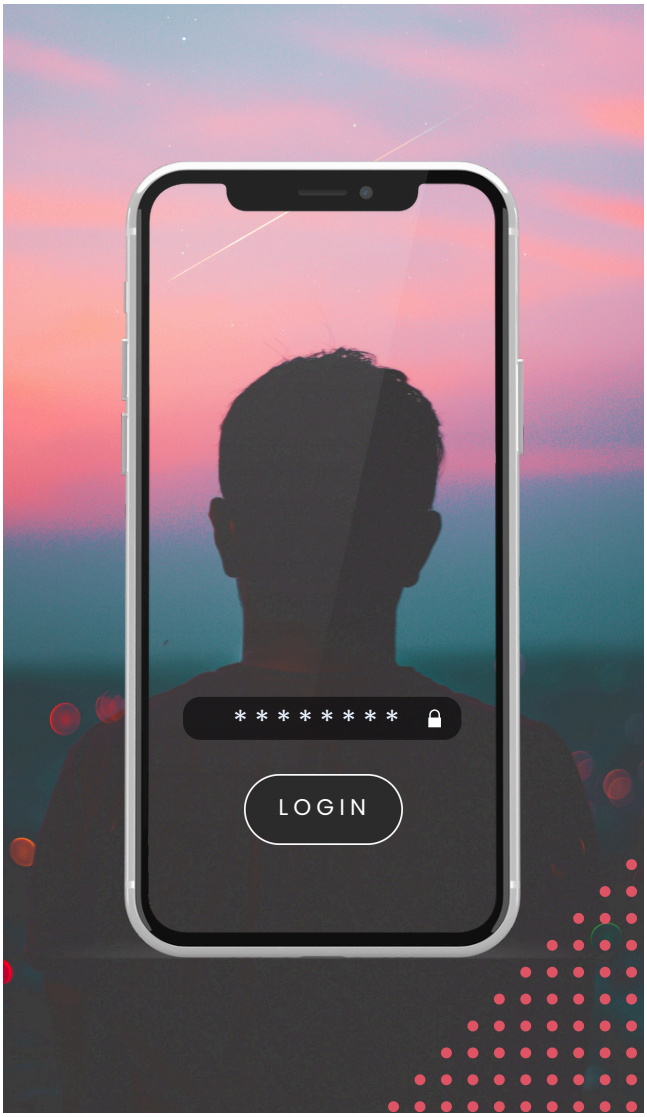
DHTs also allow for broader consent discussions, including data ownership, postmortem use, and international perspectives. Implementing extensive informed consent models poses challenges, especially regarding data openness, accessibility, and future use. To globalize DHT adoption, regulatory stakeholders must address these complexities and prioritize adaptability and collaboration.

Efforts to integrate DHTs into clinical trials have gained support from Congress, the FDA, and industry, notably through PDUFA VII reauthorization. However, sponsors incorporating DHTs still face significant regulatory risks due to the lack of a consistent FDA standpoint. While recent FDA guidance is a positive step, further advancements are needed, including clear pathways for FDA feedback on proposed DHTs and their validation approach.

Standardization efforts encompass not just technical aspects but also ethical considerations like security controls and the Health Insurance Portability and Accountability Act (HIPAA) compliance. While standards may evolve, advocating for interoperability and meeting specific standards during technology vetting ensures consistency and reliability across platforms, establishing a robust digital infrastructure in clinical trials.

Regulatory frameworks, data privacy protocols, and consent procedures should prioritize participants' needs and engagement, mandating a departure from traditional approaches. By embracing the dynamic nature of consent and its patient centricity, regulatory and ethical considerations can foster a research environment promoting transparency, trust, and participant engagement, rather than just compliance. This proactive approach addresses the unique needs of individuals involved in clinical trials, contributing to a participant-friendly and ethically robust landscape for integrating DHTs into research and development processes.

As the industry grapples with challenges related to decentralized methodologies, data generation, and patient-centric experiences, adherence to industry and government standards becomes paramount.



KEY RECOMMENDATIONS

Clinical trial designers, regulators, and researchers should consider the following:

Data requirements for regulatory approval:

- Incorporate insights from the lived experiences of pALS,
- Quantify and integrate patient-reported and clinically meaningful perspectives into data collection,
- Define "clinically meaningful" endpoints based on patient experiences and align efforts accordingly.

Regulatory pathways and standardization efforts:

- Identify regulatory pathways for data review (e.g., program-specific, qualification pathways),
- Support measurement standardization of digital endpoints and foster interoperability,
- Develop standardized criteria for validating DHTs in clinical trials, ensuring clarity on the evidence required for validation and aligning with FDA guidelines.

Consent and data use / access:

- Ensure consent serves both participant goals and study objectives,
- Maintain consistent consent language across centralized or localized Institutional Review Boards (IRBs).
- Adhere to global guidelines for consent,
- Obtain consent for data creation, contribution, and future access,
- Establish protocols for postmortem data management to ensure continued access.

Privacy and risk management:

- Evaluate the storage and anonymization of HIPAA-protected voice prints,
- Examine the collection methods of social media, voice, likeness banks, and other identifiable biometric data, ensuring consumer and patient control over data.

Priority 2

Unlocking the Potential of Digital Endpoints and Biomarkers to Improve ALS Clinical Trials

Despite their potential, remote monitoring and measurement technologies in neurological clinical trials are still under-utilized due to regulatory, budgetary or implementation complexities. It's essential to successfully integrate these technologies as they enable participants to engage in studies more frequently and safely, thereby lowering the risk of injury and participant attrition. Innovations in research involving physically vulnerable people require prioritizing safety and ease of participation as a foundational principle in research design and clinical assessment. This involves utilizing standardized, enhanced tools for objectivity and sensitivity, while making them accessible to as many stakeholders as possible to facilitate open dialogue and shared, patient-driven decisions.

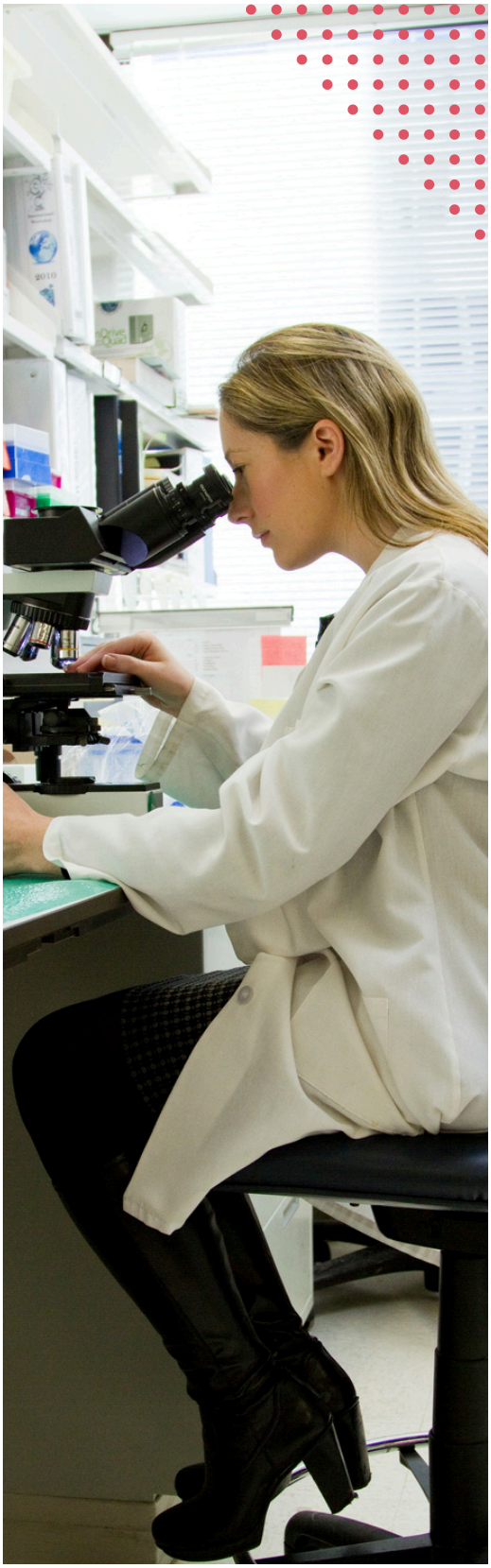
Additionally, commonly used outcome measures such as the ALSFRS-R have scientific limitations that hinder their clinical and research utility, including lack of unidimensionality (Fournier, James, and Glass 2022) and insensitivity to detect subtle changes (Franchignoni et al. 2015; Rooney et al. 2017). Shortcomings from the patient perspective further reinforce the need for more sensitive, objective, and accessible outcome measures for effective monitoring and treatment evaluation (Boyce et al. 2023). For instance, pALS concerns about accuracy and ability to capture pALS functioning, alongside practical, linguistic challenges, and administration inconsistencies, hinder ALSFRS-R efficacy (Boyce et al. 2023).

Researchers and clinicians are in pursuit of more granular, simple, accessible tools to diagnose, monitor and predict disease course.

In contrast, DHTs offer the unique ability to collect objective measurements of real-world functions both passively or actively, while potentially adapting to the patient journey and disease stage. Furthermore, digital tools are uniquely suited to enhance the quality and quantity of longitudinal data collection, by streamlining the process and reducing human bias.

Nonetheless, as we explore novel and potentially more accurate DHTs, rigorous fit-for-purpose validation alongside established measures is necessary to ensure clinical relevance and sensitivity to disease progression. For inclusion in trials as potential endpoints and outcomes, digital measures need to be clinically meaningful for both clinicians and patients. This clinical relevance can enable clinicians to make quicker decisions about treatment efficacy, accelerating regulatory approval and expediting the development of treatments for pALS. Meanwhile, patient experience data can inform medical product development, addressing specific patient needs and enhancing regulatory decision-making processes.

By leveraging remote monitoring tools, wearable sensors, and mobile applications, DHTs can enhance participant engagement, facilitate real-time data collection, and broaden the geographic reach of clinical trials.

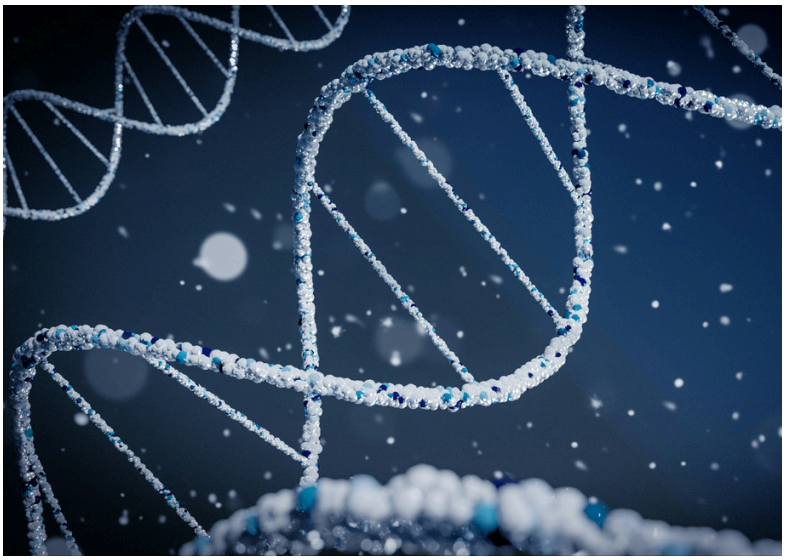


Accelerated ALS clinical studies are critical for all stakeholders involved. In particular, pALS require timely insights into disease progression, facilitated access to potential interventions, and enhanced patient care. Simultaneously, researchers and drug developers benefit by improving effective risk management and reducing costs associated with prolonged trials, leading to streamlined drug development process, resource optimization, and expedited translation of research findings into tangible clinical outcomes.

The shared goal of biopharma companies to expedite clinical trials, with fewer participants, while increasing predictability and understanding of outcomes, comes with a challenge. With a smaller participant pool, each dropout or instance of non-adherence to the protocol carries greater weight within the study, heightening the risks of two leading drivers of clinical trial failures: participant dropout and site protocol deviations. DHTs have the potential to address both these aspects effectively. They can broaden patient populations by integrating flexible protocol designs allowing remote monitoring or home health visits, while also enhancing the patient experience and improving study adherence through frequent touchpoints.

DHTs can help further advance the paradigm of decentralized clinical trials. By leveraging remote monitoring tools, wearable sensors, and mobile applications, DHTs can enhance participant engagement, facilitate real-time data collection, and broaden the geographic reach of clinical trials. They promote inclusivity in research by facilitating outreach and integration of diverse and underrepresented populations, while reducing the monitoring requirements of traditional onsite activities

Utilizing DHTs for gathering data to support clinical trial endpoints faces a number of challenges for the development of digital biomarkers, clinical outcome assessments (COAs) and novel endpoints, including security and privacy issues, the amount of data collected, data complexity, and relevance to patients. These challenges remain to be important for further clarification among the EverythingALS Consortia and the stakeholders involved in the advancing this field.



KEY RECOMMENDATIONS

Digital biomarkers and endpoints hold the potential to improve ALS clinical trials by enabling:

- A comprehensive understanding of the context of use of a therapeutic candidate and the concept of interest early in the study design phase,
- Efficient quantification of a pALS ongoing experience during the trial, utilizing their own recorded progression and baseline data,
- Proactive data harmonization for real-time analysis, facilitating rapid assessments of response sub-populations and predictive analytics,
- Early identification and monitoring of patient cohorts through remote clinical studies and observational research, ensuring continuous patient stratification over time,
- Insight capture of pALS and cALS perspective to align their treatment goals and priorities with measurable outcomes,
- Conducting cross-sectional and longitudinal studies to detect changes across different cohorts and onset timings,
- Remote participant recruitment and observation (through outreach and existing registries), minimizing transit-related risks and study disengagement and thereby enhancing data collection frequency, particularly in open label extension and expanded access studies.

Priority 3

Utilizing Agile Methodologies for DHT Testing in Neurological Diseases, in Open, Integrated Platforms

Agile methodologies are critical to ensure a viable environment for platform-based data collection that can be deployed to support platform-designed studies. These methodologies involve testing products, collecting user feedback, and iterating based on insights captured more frequently during clinical trial design and implementation.

In the dynamic landscape of DHTs, the need for a robust evaluation platform is of paramount importance. Adopting agile methodologies in clinical trial design and implementation is critical to create an environment conducive to validated and fit-for-purpose approaches for data collection. The successful deployment of such digital tools hinges on emphasizing the consensus, understanding the context of use, and the concept of interest.

Aligning data collection strategies with clinically meaningful outcomes upfront is crucial. This lays the groundwork for seamless integration and interoperability across diverse digital health devices and technologies. Additionally, by engaging with pALS, digital platforms such as smartphone applications can capture their perceptions of what is important to them and what impacts they wish to see from treatments and care. This patient-centric approach bridges the gap between subjective experiences and measurable outcomes, aligning the study with the real needs of the affected population.

My quality of life would be enhanced with knowledge of how to prepare for the next level of disease progression

JOHN H.

Diagnosis

As a pALS and a usability tester of digital health technologies, I value their potential to assist me gain objective, quantified, predictive information that I could add to my personal subjective observations.
As the course of ALS is so variable in individuals, I would like to have a series of measures that can help me track, and hopefully predict, the rate of progression as well as which areas may become affected next. My quality of life would be enhanced with knowledge of how to prepare for the next level of disease progression - and how it might also affect my primary caregiver(s) - by keeping focused on what is happening to me now and in the next months, rather than trying to cover all contingencies (bulbar, lower extremity, upper extremity, pulmonary) all at once.

Clinically meaningful measures can be implemented on a large scale and among a more cohesive population through trial and digital platforms.

Feedback loops built into the system ensure a continuous improvement cycle. By aligning with regulatory standards and compliance, the platform not only accelerates the evaluation process but also enhances the credibility and reliability of the gathered data.

Such alignment is pivotal for providing regulatory bodies with the necessary evidence to support the efficacy and safety of digital health technologies.

A PLATFORM / AGILE APPROACH TO ENSURING SUCCESS OF DIGITAL ENDPOINTS IN ALS

Collaboration among sponsors, academia, and biotech companies is essential to share both positive and negative findings on open-access platforms like PRO-ACT, maximizing data utilization within the scientific community and preventing its stagnation in industry archives or on laboratory shelves. Given the value of this data in light of the history of unsuccessful trials, such collaboration and sharing are critically important.
In such cases, sponsors can optimize data utilization and prevent the creation of irreproducible datasets by validating new vendors or testing less standardized endpoints within a platform ecosystem.

KEY RECOMMENDATIONS

Using an agile framework to ensure success of digital endpoints in ALS research:

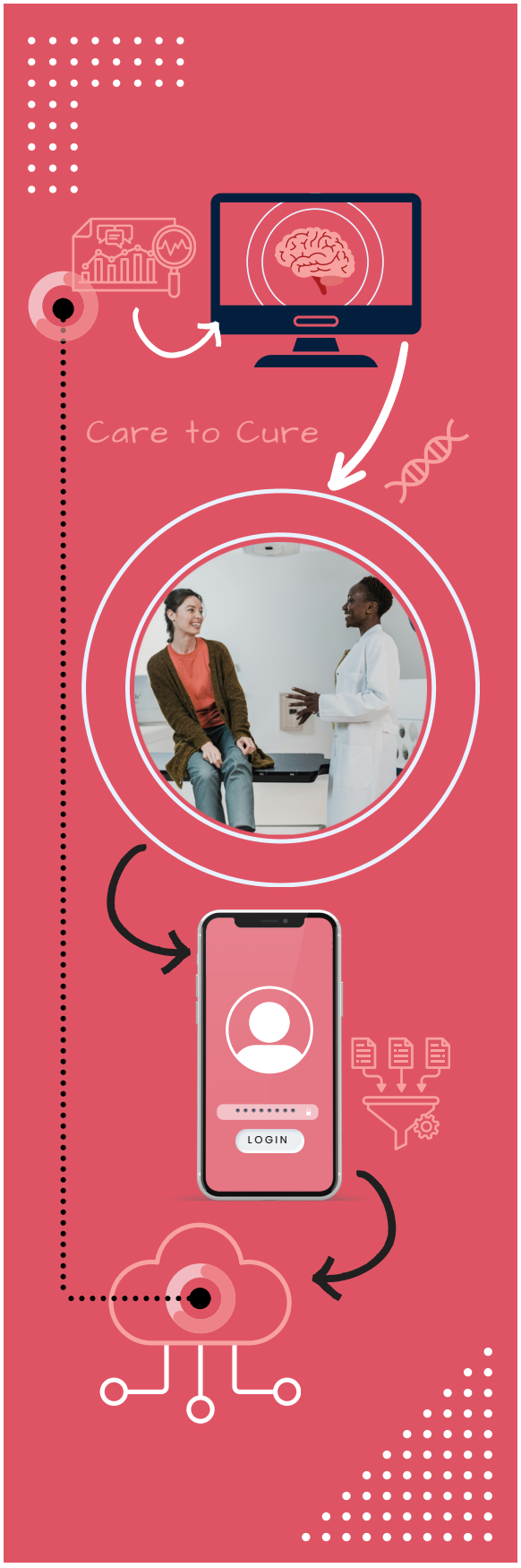
- Expand the use of platforms beyond just trial recruitment and onboarding. Develop a larger ecosystem that includes education for more transparent authorization and increased portability of baseline multi-modal DHT data and clinical history.
- Commit to the full digitization and objective capture of meaningful components of the ALSFRS-R and activities of daily living (ADLs), such as:
  - Speech,
  - Fine motor (e.g., texting, typing),
  - Gross motor (e.g., walking, exercises),
  - Respiration (e.g., spirometry),
  - Cognition (e.g., ECAS - Edinburgh Cognitive and Behavioural ALS Screen).
- Embrace Diversity, Equity and Inclusion in clinical trials:
  - Ensure trials are more diverse, like the Radcliff study, which is more diverse than other ALS studies,
  - Provide language support and remote proctors (potentially using AI translation),
  - Reach rural areas and underrepresented populations through decentralized clinical trials, as highly suggested by the FDA,
  - Improve recruitment, follow-up, and retention.

In platform-centric ecosystems, organizations like EverythingALS are dedicated to balancing intellectual property rights while advancing science and breaking down barriers between organizations.

Smaller, faster, and more efficient studies (for internal decision making or regulatory approval) accelerate treatment to patients. Platforms that actively recruit and consent participants for studies tailored to their specific needs and disease progression can drive more efficient recruitment, consent, onboarding, engagement, and retention. This can shorten study timelines and potentially increase statistical power through higher retention, and deploy clinically meaningful measures at scale, interpreted within a more cohesive population. In discussions with Consortia members and pALS advisors, this can result in several key improvements:

- Patients, clinicians, and regulators all perceive greater clinical meaningfulness in how the measures represent the impact on a person's life,
- Greater predictability for detecting an intervention effect of 20%, and
- Enhanced understanding of therapeutic candidate impact within a multi-modal data collection platform spanning longitudinal tracking and studied sub-populations within a unified pALS population.

Focus should be on evaluating, selecting, and implementing tools that enable pALS and cALS to generate and utilize objective measurements while striking a balance between passive and active data collection methods. Objective data captured through sensors can enhance pALS understanding of their initial diagnosis and disease progression, empowering them to make informed decisions about their present and future. Consider these concepts as guidelines for individuals managing daily challenges while participating in studies. Think of remote DHTs as analogous to "Homework". Remote sensors and sessions function as tasks evaluating individuals in their home environment. However, it's important to provide support and guidance, similar to remote "tutors" or research proctors, along with practice exercises and feedback dashboards. Similar to how homework adapts with a student's development, the nature of these tasks should adjust according to the stage of the disease and the needs of the individuals.



Priority 4

Optimizing the Clinical Trial Experience for pALS and cALS

To enhance patient experience, sponsors, contract research organizations, and technology vendors must prioritize providing valuable clinical trial data directly to patients. This ensures their contributions are valued and offers insights to both patients and at-risk family members. Emphasizing accessibility and patient-friendliness in the pALS experience is crucial. When technological advances are integrated into clinical trials, this approach broadens the patient experience beyond technology functionality and convenience, encompassing the entire participant journey. Therefore, patient-centric design should factor in the diverse demographics, digital literacy levels, and potential challenges that participants might encounter, ensuring inclusivity and minimizing obstacles.

In pursuit of this commitment, the pharmaceutical industry should actively engage with and learn from consumer device companies, assimilating their design principles and accessibility features. Understanding their nuances and incorporating these lessons into medical-grade technologies can enhance usability and foster a sense of trust and respect for participants. This approach eases the adoption curve and contributes to a more intuitive and engaging patient experience.

Balancing intellectual property rights with pALS experiences and insights is challenging, but industry must remain dedicated to overcoming these obstacles.

When considering technological choices, clinical trial designers should pay special attention to the urban versus rural divide. In urban settings, Wi-Fi connectivity is abundant, so the emphasis may be on optimizing synchronization and updating processes to local clinical sites. In contrast, rural locations, often plagued by limited connectivity, demand potential supporting solutions such as Mi-Fi devices or lighter bandwidth-requiring approaches. The aim is to avoid creating technologies that are disproportionately advantageous in urban areas and unfeasible in rural settings, ensuring equitable access and participation. To extend the reach of clinical trials beyond academic and specialty areas, an AI-enabled concierge akin to a technology patient navigator could be a potential solution. Personalized support can address technical concerns and becomes a valuable human touchpoint for compliance and usability insight capture. There can sometimes be a delay between issue reporting and resolution, so ensuring that participants feel supported and understood while efficiently addressing their needs is crucial for a tailored approach.

The real experience sought is the one that combines technological sophistication with personalized, human-centric care.

In clinical research, there is a growing recognition of the patient burden to participate in the research studies. As such, technologies could promote a more empathetic and compassionate approach by incorporation of motivational elements after engaging in study visits and tasks. Completing surveys and daily diaries can be emotionally taxing for participants, and providing positive messages or affirmations at the conclusion of tasks could be a way to offer positive reinforcement. This shift from mere acknowledgment to active encouragement seeks to uplift participants, recognizing the difficulties they navigate and expressing gratitude for their invaluable contributions to the ALS research process. It's a nuanced strategy aimed at fostering a more supportive and positive pALS experience within the clinical trial landscape.

There are important challenges associated with returning study data to participants. Addressing potential pitfalls in data delivery and disclosure methods, sharing information without appropriate context and support can have a significant emotional toll, and risks unblinding the study. As such, careful reflections to ensure that participants receive data in a manner that is both informative and supportive are essential. Examples could be study summaries or notes, balancing between providing meaningful insights and mitigating potential negative emotional impacts. The suggestion to move from real-time feedback to a summarized format speaks to the complexity of managing participant expectations and emotional well-being. This consideration is particularly pertinent in the context of conditions like ALS.

DAVE S.

Diagnosed in 2023 with Limb Onset ALS

As a professional technology finance strategist and someone living with ALS, I felt a strong drive to maximize my chances for longevity and, eventually, recovery. I motivated myself to learn everything I could about potential trial and treatment options. I also became committed to facilitating change within our community, advocating for tools and studies that prioritize what matters to me. [...] I don't really use the word "fighting" ALS. It seems like a losing proposition. I prefer the term "hacking" ALS, recognizing the urgent need for rapid, bold innovation and the willingness to challenge outdated paradigms that have not gotten us very far in the past 70 years. I believe in the importance of breaking ALS down into better-defined and understood subtypes to ensure that more effective therapies come to the market sooner.

Apps and interfaces supported by non-profit organizations like EverythingALS can be crucial to enhance patient experiences in study participation. These platforms can offer continuous education, support, and study engagement to maintain long-term relationships with pALS and study participants. Integrating these types of resources can be among the most important steps in research recruitment and, where implemented compliantly, remote study engagement. Specifically, key experiences from pALS and cALS advising this workstream have identified highly valued considerations to inform the protocol development and consent process for upcoming studies from the patient perspectives.

KEY RECOMMENDATIONS

Patient Experience Considerations for Implementing DHTs in Clinical Trials:

- Focus on patient experience when selecting technologies for remote monitoring.
- Leverage agility through rapid iteration cycles to:
  - Test products and support services with small "super-user" groups first,
  - Learn from the initial testing, then validate with a larger group,
  - Iterate with continuous feedback with patient satisfaction loops.
- Bolster home and remote health support by designing local ecosystems of engagement and resources. Understand the ongoing relationships and support networks that participants rely on in their local communities.
- Minimize physical handling of apps and interfaces through voice-activated experiences.
- Reduce assessment fatiguability and redundancy:
  - Replace survey questions with sensors whenever possible,
  - Collaborate to share trial data on open-access platforms like PRO-ACT, incorporating de-identified sharing language into consents for seamless data sharing,
  - Provide trial data directly to patients, recognizing their contributions and facilitating access to insights for themselves and their families, while balancing intellectual property concerns.
- Improve inclusivity by consenting study participants' partners:
  - Develop consent flows that include study partners and backup study partners, when participants require assistance for participating,
  - Provide a companion guide for study partners with clear technical instructions, education and study information.
- Provide motivation and self-efficacy through feedback:
  - As a design principle, start with asking the trial team, "What can we give back in return for pALS participation and data? What can we share back immediately that will keep them engaged and informed, and how can we accompany them on their care journey?"
  - Offer built-in professional consultation and support services if the provided data show disease progression. This could include:
    - Counseling support to help pALS and their loved ones navigate the implications of disease progression,
    - Facilitation of communication between participants, their care teams, and their support networks.

Looking Ahead and Conclusions

The Consortia: A roadmap for digital endpoints and biomarkers

The EverythingALS Industry Consortia has embraced the 4 priorities delivered in this paper as a series of unifying areas of activity. The recommendations provided in each section are the catalysts for ongoing conversations and areas of research and development to be undertaken by EverythingALS - in direct collaboration with the Consortia membership and with other key partners at regulatory agencies and with other non-profits and clinical practices.

2024 - 2025: Core Areas of Consortia Activity

Research sponsors, clinical collaborators and advocacy organizations form a triangular relationship in data generation. This relationship must be built on open and trustworthy engagement with each other. Ideally, consent should be governed by mutually agreed-upon considerations that prioritize the needs of present and future pALS and cALS at the core of study design and implementation.

1) **Facilitating Change Management:** Championing DHTs in ALS research through Expanded Access Programs (EAPs) and next-phase collaborations.

2) **Advancing AI in ALS Diagnosis and Progression Tracking:** Utilizing algorithmic and expert review of COAs and Patient Reported Outcomes (PROs) to create a common, open data repository consolidating all recent phases of ALS studies.

Research sponsors, clinical collaborators and advocacy organizations form a triangular relationship in data generation.

3) **From Radcliff to Healey and Beyond Platform Integrations:** Advancing new trial designs to maximize interoperability of data collection platforms, advancing the measuring of the ALSFRS-R, and exploring multiple interventions continuously, while also improving the assessment of ALSFRS-R through objective sensor-based measures.

4) **Evolving the Ethics of Consent in a Digital, Dynamic Era:** Adapting ethical frameworks and consent to address the complexities and rapidly evolving nature of data collection, sharing, and analysis and to embrace pALS-centric approach, with a focus on improving diversity, equity and inclusivity through multiple modes of consent.

Conclusions and Next Steps

The 2024-2025 EverythingALS Endpoints and Digital Biomarkers Summit will be focused on taking the next steps in using digital health to increase access to trials and improve disease progression tracking for care. We invite our manufacturers, regulatory representatives and the care delivery experts to join the effort to advance DHTs and implement them to improve standards of diagnostic and therapeutic care.

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MISSION

Advancements in digital health technologies provide versatility beyond their conventional application in drug development to various domains of the healthcare sector. Realizing their comprehensive potential requires a collaborative engagement among diverse stakeholders, including clinicians, researchers, technology developers, regulatory authorities, and patients. These collective endeavors should strategically address intricate challenges such as data privacy concerns and regulatory intricacies, requiring the establishment of standardized validation procedures and securing regulatory endorsement as pivotal milestones. The creation of a unified pre-competitive ecosystem is crucial for the facilitation of innovation and the seamless integration of digital endpoints across multifaceted healthcare realms. By collectively advancing in this trajectory, stakeholders can optimize the advantages offered by digital endpoints, enhancing the precision of healthcare interventions, and fostering improved patient outcomes.

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THANK YOU!