Data science and digital health in clinical development and operations: impact, challenges, and calls to action for the drug development ecosystem

April 2023

MDMi
Medicines Development Modernization Initiative

CONTRIBUTING AUTHORS

(listed alphabetically)

Ginny Beakes-Read, JD, BSN, Executive Director, Global Regulatory and R&D Policy, Amgen

Kyle Beauchamp, PhD, Senior Director of Data Science, Tempus

Meenakshi Chatterjee, PhD, Principal Scientist, Janssen Research & Development[1]

Claire Cravero, MPH, Head of Public Sector, Datavant

Danielle Friend, PhD, Director, Regulatory Policy and Intelligence, Janssen Research & Development[1]

Rachele Hendricks Sturrup, DHSc, MSc, MA, Research Director, Real-World Evidence, Duke-Robert J. Margolis, MD, Center for Health Policy

Najat Khan, PhD, Chief Data Science Officer Global Head, R&D Strategy and Operations, Janssen Research & Development[1]

Andrew Kress, CEO, HealthVerity

Mehdi NajafZadeh, MSc, MA, PhD, Senior Director, Medidata Link, Medidata AI, Medidata Solutions, a Dassault Systèmes company

Matthew Reynolds, PhD, Vice President, Scientific Affairs Real World Solutions, IQVIA

Akiko Shimamura, MBA, Vice President, Medidata Link, Medidata AI, Medidata Solutions, a Dassault Systèmes company

ACKNOWLEDGEMENTS

(listed alphabetically)

Martha Azer, PharmD, Associate Director, Global Regulatory Policy and Intelligence, Janssen Research & Development[1]

Catherine Lee, Associate Director, Regulatory Policy and Intelligence, Janssen Research & Development[1]

Deborah Ricci, PhD, Senior Director, Data Science Portfolio Management, Janssen Research & Development[1]

Kristopher Standish, PhD, Principal Data Scientist, Janssen Research & Development[1]

ABOUT THE MEDICINES DEVELOPMENT MODERNIZATION INITIATIVE (MDMI)

The Medicines Development Modernization Initiative (MDMI) is a multi-stakeholder and interdisciplinary initiative that brings together leaders and experts in the medicines development space who have a common interest in developing strategies and solutions that can optimize the medicines development process and, ultimately, bring medicines to patients more efficiently. MDMI is focused on making the medicines development process more efficient and less resource intensive by achieving the full potential of medicine development tools (MDTs).

[1] This individual is an employee of The Janssen Pharmaceutical Companies of Johnson & Johnson and may hold company stock or stock options

TABLE OF CONTENTS

Medicines development today is a lengthy, complex, and costly process, with a high degree of uncertainty that a drug candidate will succeed in clinical trials and ultimately reach the market. The high failure rate of clinical trials creates significant inefficiency in the industry and, at times, prevents potentially life-changing therapeutics from reaching the market. A recent Biotechnology Innovation Organization report found that over the last decade, the likelihood of candidates entering Phase I ultimately receiving FDA approval was 7.9%, with an average time to approval of 10.5 years (Biotechnology Innovation Organization, PharmaIntelligence, Quantitative Life Sciences, 2021). Estimates of the cost of bringing a successful medicine to market vary widely depending on, among other factors, which research phases are included in the analysis, and can exceed $2 billion when including the cost of the thousands of compounds that failed to proceed to the next stage of the clinical development process (Berdigaliyev & Aljofan, 2020) (Schlander, 2021). Further, the medicines that do make it to market despite the enormous investment of time and resources may face a lack of understanding of the precise patient populations that would most benefit from a novel therapeutic.

Maintaining or accelerating the pace of biopharmaceutical R&D requires new tools (methods, strategies) to overcome these challenges. Fortunately, we are at an inflection point in the development of new innovations in R&D, which may lead to faster, less expensive trials for therapies that are more effective and safer for patients. For the purposes of this paper, we will call these innovations medicines development tools (MDTs). How novel MDTs are defined is broad and evolving. It includes both technologies (e.g., artificial intelligence and digital health) and approaches like model-informed drug development, biomarkers, endpoint definition, responder/non-responder signatures, and patient-focused drug development. In the U.S. regulatory environment, these are commonly referred to as "Drug Development Tools." We have adopted the more global phrase "medicines development tools." In clinical development, MDTs can potentially mitigate many challenges to bringing new, life-changing therapies to market.

In this paper, we discuss how three MDTs - artificial intelligence (AI) and machine learning (ML) algorithms, digital health tools (DHTs), and augmentation of randomized controlled trial (RCT) data with real-world data (RWD) - can be applied to transform clinical development. The use cases discussed in the upcoming sections illustrate how novel MDTs can help redefine how the biopharmaceutical research sector conducts clinical study design and operations, resulting in tangible impact across a broad set of stakeholders in the healthcare ecosystem. They also highlight outstanding challenges to realize the full potential of MDTs in clinical development and the considerable opportunity that exists to modernize medicines development further. Integrating MDTs in an ecosystem that recognizes and supports the public health benefits of innovation will generate better medicines for patients while reducing the time and cost of development – allowing the best medicines to reach patients in need sooner.

MDTs can be applied end-to-end in R&D, from discovery through post-approval. This paper focuses specifically on use cases from clinical development to provide an illustration of both the impact that is possible and the challenges that remain to see value consistently and widely from their application. There are many use cases within clinical development. We selected a subset to show the range of MDTs and the impact that they can have on the major levers of R&D – time, cost, and value.

TRANSFORMATIVE POTENTIAL OF MEDICINES DEVELOPMENT TOOLS (MDTS) IN CLINICAL DEVELOPMENT AND OUTSTANDING CHALLENGES TO REALIZATION OF FULL VALUE

In this section, we define the three MDTs of focus (AI/ML, DHTs, and enhancement of RCT data with RWD), share a set of use cases for each MDT to illustrate how they are creating impact in clinical development, and describe the challenges that remain to full realization of value from these tools.

Artificial intelligence and machine learning models to improve study design and operations

AI/ML are emerging as crucial MDTs across the medicine development value chain, from target discovery to post-market research. In practice, much AI uses ML algorithms that allow computers to learn without explicit programming. Learning can be guided by a labeled dataset (supervised) or unsupervised. Unsupervised learning is most often used to cluster or segment datasets based on similar features within the data. Supervised learning, in contrast, uses labeled or annotated data to detect underlying patterns and relationships between input data and output labels, which can then be applied to new datasets.

There are many applications for AI/ML in R&D. Unsupervised machine learning can be used on databases to group by similarities to identify clusters that may represent key phenotypic features of the disease and differential responsiveness to treatment. Natural language processing (NLP), another subset of AI, can be used to organize and process EMR data to identify patients matching inclusion/exclusion criteria for clinical trials, potentially reducing enrollment timelines. As another use case, at-risk clinical trials can be remediated by using cluster analysis to identify the subsegments of patients that are most likely to be responsive to treatment.

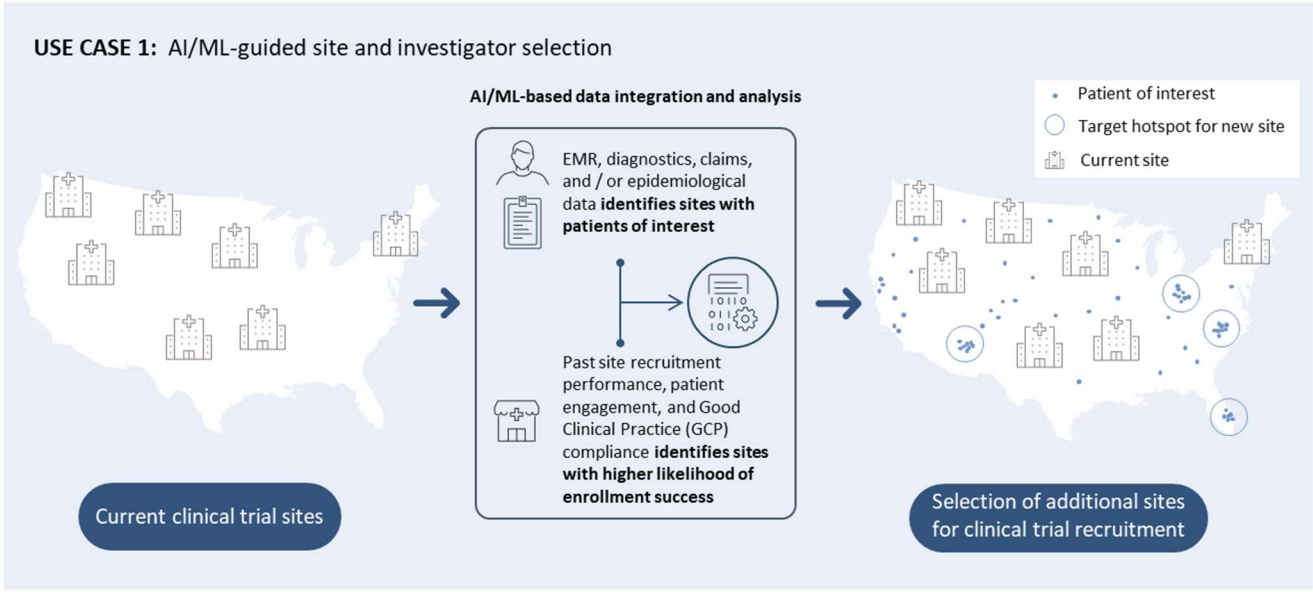
With the AI healthcare market forecasted to reach $44.5 billion by 2026, the biopharmaceutical industry is increasingly testing and scaling AI (Business Wire, 2022). We outline the impact AI/ML algorithms can have in clinical development and the cross-cutting challenges that remain to full implementation of these tools through two example use cases: site and investigator selection and patient identification and stratification.

Use case 1: AI/ML-guided site and investigator selection

Selecting high-potential sites with qualified investigators to recruit and enroll patients is critical to maintaining study timelines and producing high-quality evidence. A recent study found that of the more than 2,500 trials analyzed, approximately 1/5 were terminated for inability to accrue the required number of participants or were completed with less than 85% of the enrollment target (Carlisle, Kimmelmen, Ramsay, & MacKinnon, 2015). ML algorithms can greatly enhance the identification of suitable investigators and target sites through the analysis of curated data on past recruitment performance of sites, patient engagement, electronic health records (EHRs), and other predictive factors. It can also be used to identify sites with a good history of Good Clinical Practice (GCP) compliance.

AI/ML-guided site and investigator selection benefits the drug development ecosystem in several ways:

- (Bio)Pharma and tech developers can leverage or create algorithms to better understand concentrations of patient populations for more refined site selection efforts, potentially increasing recruitment rates. This can be particularly useful for infectious diseases with evolving epidemiology, or rare diseases with low numbers of potential participants.
- AI/ML applied to population demographics are helping to both identify higher concentrations of target patient populations and being applied to increase clinical trial diversity by identifying site locations with diverse populations that meet the clinical criteria for the trial.
    - In April 2022, the U.S. FDA released draft guidance on increasing diversity in clinical trials, recommending that trial sponsors include a plan for achieving diversity in their trials (FDA Takes Important Steps to Increase Racial and Ethnic Diversity in Clinical Trials, 2022). In February 2023 the FDA announced it will soon require late-stage clinical trials to include a plan to ensure diversity among clinical trial particants. (Kozlov, 2023)



AI/ML-GUIDED SITE AND INVESTIGATOR SELECTION IN ACTION

Tempus TIME trials network for the ELAINE II study

Tempus, an AI-enabled precision medicine company, is redesigning trial matching and site activation to significantly decrease standard timelines. Tempus uses next-generation sequencing results and information from health care provider medical records to match patients to industry-sponsored clinical trials in oncology (Tempus Clinical Trial Matching, 2022). Health data of patients is processed using a combination of expert staff and technology, including language-processing (NLP) models, in order to identify patients who appear to meet the key aspects of a trial's eligibility criteria. Patients who match are surfaced to their care team for further

review, and a novel activation model helps ensure that trials are activated at a patient's site of care about ten business days after the patient identified as being a match.

ELAINE II is an ongoing clinical trial that leverages the Tempus TIME Trial network recruitment approach alongside traditional recruitment (Blau, 2022). The study evaluates lasofoxifene combined with abemaciclib in advanced or metastatic ER+/HER2- breast cancer patients with an ESR1 mutation. In total, there are six traditional and 10 Tempus TIME sites. Site activation timelines averaged ~200 days for traditional sites versus less than eight for TIME sites. In total, 16 patients were enrolled from traditional sites and 13 from TIME sites. These 29 patients were enrolled over eight months compared to an anticipated 12 to 18 months.

Machine Learning model to drive COVID-19 vaccine trial acceleration

In partnership with the Massachusetts Intitute of Technology (MIT), Janssen, the Pharmaceutical Companies of Johnson & Johnson, built a machine learning-based model with predictions 90%+ accurate for selecting high-incidence COVID-19 countries and trial sites, contributing to a highly rich dataset. The result accelerated development timelines by six to eight weeks and reduced Phase III sample size by 25%, with commensurate cost avoidance (Bertsimas D. L., 2023). Further, diversity, equity & inclusion surpassed the U.S. census, based on criteria including race as well as those over age 60. The modeling work was recognized as the winner of 2021's INFORMS Innovative Applications in Advanced Analytics Award and the finalist for the Franz Edelman Award in Operations Research.

Data-driven patient enrollment at scale

Yet another industry example of leveraging ML methods to identify and predict trial sites is at Amgen. There, the Analytical Trial Optimization Module project, or ATOMIC, uses data such as site-level historical clinical trial performance, key trial design characteristics, claims, and electronic health records to determine, systematically, which clinical trial sites are at the highest likelihood of high enrollment. Ultimately, ATOMIC generates a study-specific ranked list of sites, predicted enrollment rates, and other relevant data about the country, site, and investigators. The insights from ATOMIC have been applied to expedite trials in cardiovascular disease, atopic dermatitis, and gastric and lung cancer and are being scaled across the portfolio (Amgen, 2022).

Use case 2: AI/ML-driven patient identification and stratification

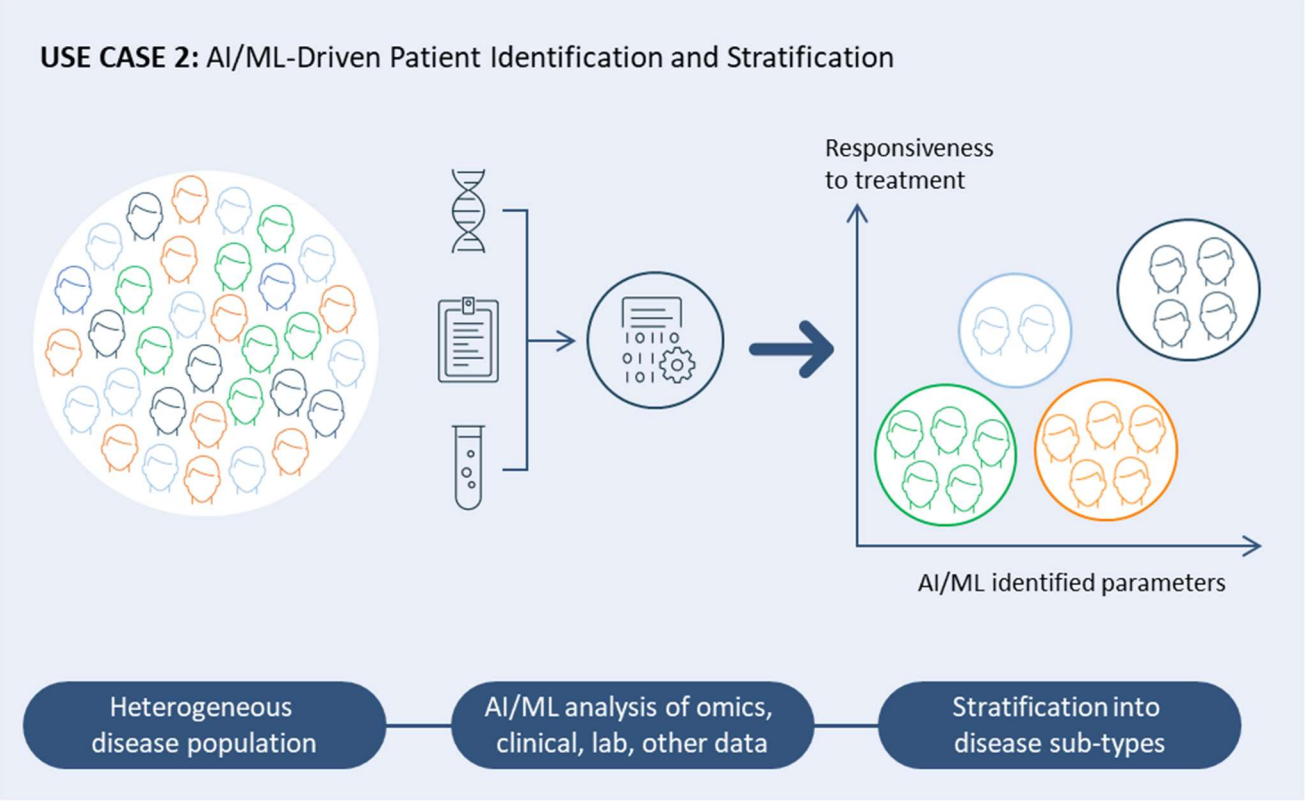
AI/ML algorithms can be applied to structured and unstructured data such as imaging, -omics[2], clinical, and laboratory data to recognize complex patterns and predict disease diagnosis and prognosis. These algorithms can be applied in R&D in several ways; for example, data acquired through sources such as registries or health system EHRs can be assessed against clinical trial eligibility criteria to match patients to studies, reducing the screening burden on providers for matching and stratification of patients in clinical trials, and in some cases,

[2] Most commonly, genomics, transcriptomics, epigenomics, proteomics, or metabolomics

helping patients in need enroll in trials at earlier or more optimal intervention points in their clinical treatment (Harrer, Shah, Antony, & Hu, 2019).

Applying AI/ML to identify and stratify patients has a clear, positive impact on sponsors, providers, and patients. AI/ML, for example, is helping sponsors accelerate matching patients to appropriate clinical trials by matching inclusion/exclusion (I/E) criteria to data typically found in an EHR, thus facilitating a critical pre-screening step and reducing the final screening burden on providers as well as accelerating patient recruitment timelines (Kolluri, Lin, Liu, Zhang, & Zhang, 2022).

Providers, in turn, benefit from ML algorithms completing initial screening and segmentation of their patients. ML algorithms, particularly those that are predictive or prognostic, can help identify patients earlier, or identify new treatment candidates who might not otherwise be considered for clinical trials. This helps ensure the right patients are matched with the right trials.



AI/ML-DRIVEN PATIENT IDENTIFICATION AND STRATIFICATION IN ACTION

AI-enhanced detection of patients with fibroblast growth factor receptor (FGFR) mutations

Up to 15% of people with advanced bladder cancer have FGFR mutations, however available FGFR molecular tests are very rarely ordered and take weeks to return results, leading to missed or late diagnoses and poor outcomes.

Janssen, in collaboration with Paige, an AI biotechnology company focused on cancer, has developed an AI-powered screening tool that uses hematoxylin and eosin (H&E) stained slides to identify patients likely to have an FGFR mutation. Changes in FGFR genes from a molecular test were analyzed with ML-based algorithms against H&E stained pathology slides to identify features predictive of FGFR mutations. Janssen's screening tool is able to analyze a slide within five minutes, compared to weeks, to receive results from a molecular test. Since the screening tool can detect FGFR mutants with over 60% accuracy, this can be deployed to determine which patients are more likely to have FGFR mutations (Loeffler, et al., 2022).

Janssen used this screening tool in its clinical trials to identify patients with FGFR mutations likely to meet the inclusion criteria. Bladder cancer patients were first pre-screened using the tool. As a result, they could screen patients from a much broader pool and identify an FGFR mutation-enriched cohort to then undergoes genomic testing. (Paige Announces Collaboration to Deploy a Novel AI-Based Biomarker Test for Advanced Bladder Cancer in Clinical Settings, 2022)

RWD and ML to guide precision medicine in vaccine trial: ExPEC vaccine study

Extraintestinal pathogenic E. coli (ExPEC) is a leading cause of bacteremia & sepsis worldwide, for which there is no existing vaccine. Janssen developed an ML-driven model that evaluates 100M patient lives to identify risk factors for ExPEC and stratify patients at high likelihood of invasive ExPEC disease (IED). This model validated known risk factors for IED and also identified novel risk factors, using an unbiased ML approach. As a result, the initial expert-driven trial design was transformed into a design that benefits more patients at risk. A generalizable ML-driven model is being scaled across the pharmaceutical portfolio with learnings and derived from this work. (Clarke, 2021)

Outstanding challenges to implementation of AI / ML models in clinical development

There are three primary challenges today to applying AI/ML in clinical development. While there are many examples of impact to date, the challenges below limit the scaling of these approaches across trials and broad adoption by the medicines development ecosystem.

- **Inconsistent data quality and challenges with standardization:** Data capture and reporting methods are not currently standardized across sources of RWD, and some sources may lack sufficient quality to drive AI/ML models.
    - Novel insights are gained through aggregation of datasets both by achieving scale and increasing the number of variables to assess patients and trial sites. The lack of a framework to capture and report data in a standardized way across data types inhibits the scale and diversity of inputs required for robust AI/ML models of adequate quality for regulators, impacting ability to phenotype patients or select better sites.
    - EMR documentation is fragmented at multiple levels. Different health systems will use different EMRs that are each highly customized to their needs. Providers can also have highly heterogenous approaches to EMR documentation depending on their specialty and personal approach to documentation. This results in the need for a labor-intensive manual review of extracted RWD to create clean datasets for accurate analysis.

- Lack of standardization can reduce transparency, making it difficult to ascertain a dataset's origin, fidelity, and key parameters about the included population. Data opacity is a persistent challenge which makes it difficult to aggregate and interpret data from multiple datasets.

What can be done?

Develop a comprehensive, consensus-driven set of standards and guidelines to guide RWD quality and feasibility for use in AI/ML models, building on guidance provided by regulators and other organizations. For RWD that is tied to EMR-specific content such as lab results, medications, and procedure codes, there are opportunities to standardize some of the data elements by using industry-specific crosswalks and identification codes. Standards should include requirements for transparency of models and provenance of underlying RWD to ensure other research groups can replicate and validate the results.

Current regulatory efforts include, for example, the U.S. FDA issued final guidance on the use of RWD (FDA, 2022); EMA has published a draft Data Quality Framework that applies to RWD and is also developing a reflection paper on the use of AI in medicines regulation (due to be finalized in 2023, following public consultation) to be followed by the publication of guidance; and, the International Coalition of Medicines Regulatory Authorities (ICMRA) statement on international collaboration to enable RWE in regulatory decision making promotes the concept of common principles for RWD quality.

Establishing universal rigor and ethics in development of AI-based models

- Throughout design and testing, algorithms must be evaluated for bias. Bias in algorithms can have several root causes, including biased or incomplete training data, or incorporation of human biases. Once deployed, algorithms require ongoing maintenance to avoid 'algorithmic drift,' where the accuracy of an algorithm no longer meets standards set during the design phase. Algorithm drift can not only decrease accuracy, but also introduce new bias. There are established approaches to design, maintain, and monitor accurate, ethical algorithms, but employing them requires active, sustained effort on the part of the organizations developing the algorithms.
- Broad acceptance and use, including for regulatory decision making, of AI/ML models as supplements or replacements for traditional methods of patient identification & stratification and site selection requires confidence in both the models and the outputs. Lack of transparency in data provenance, analytical methods, and modeling methods can create a lack of trust from providers, sponsors, and CROs, resulting in underutilization of these novel tools.
- Data provenance and analytical methods are often not reported today for AI/ML models used in clinical development and other clinical settings.

What can be done?

Sponsors and tech companies should stand up internal governance and operating models to guide AI/ML design, development, monitoring, maintenance, and audit of algorithms. This can be supported by development of recommended SOPs to address potential issues like bias and algorithmic drift.

- **Criticality of hospital and health system partnership in the development and deployment of algorithms relying on patient data:** AI models for patient identification and stratification are developed and trained on patient data, often with the input of clinical key opinion leaders (KOLs). Hospitals and health systems provide irreplicable access to the data, KOLs, and real-world algorithm testing environments that are necessary to create robust and accurate AI/ML algorithms.
    - Additionally, there is no standardized way to integrate AI/ML into clinical systems or workflows across trial sites, making implementation at each site bespoke and time-consuming. This creates challenges to rapid scaling and deployment once validated through the clinical development process.

What can be done?

Partner with pioneering health systems to set rigorous data stewardship recommendations for AI/ML that uses patient data. Foster industry-wide conversations to address provider-level concerns with robust data security practices that ensure underlying patient-level data will remain privileged and the privacy of patients will be safeguarded.

Digital health tools for innovation in disease understanding, study design, and execution

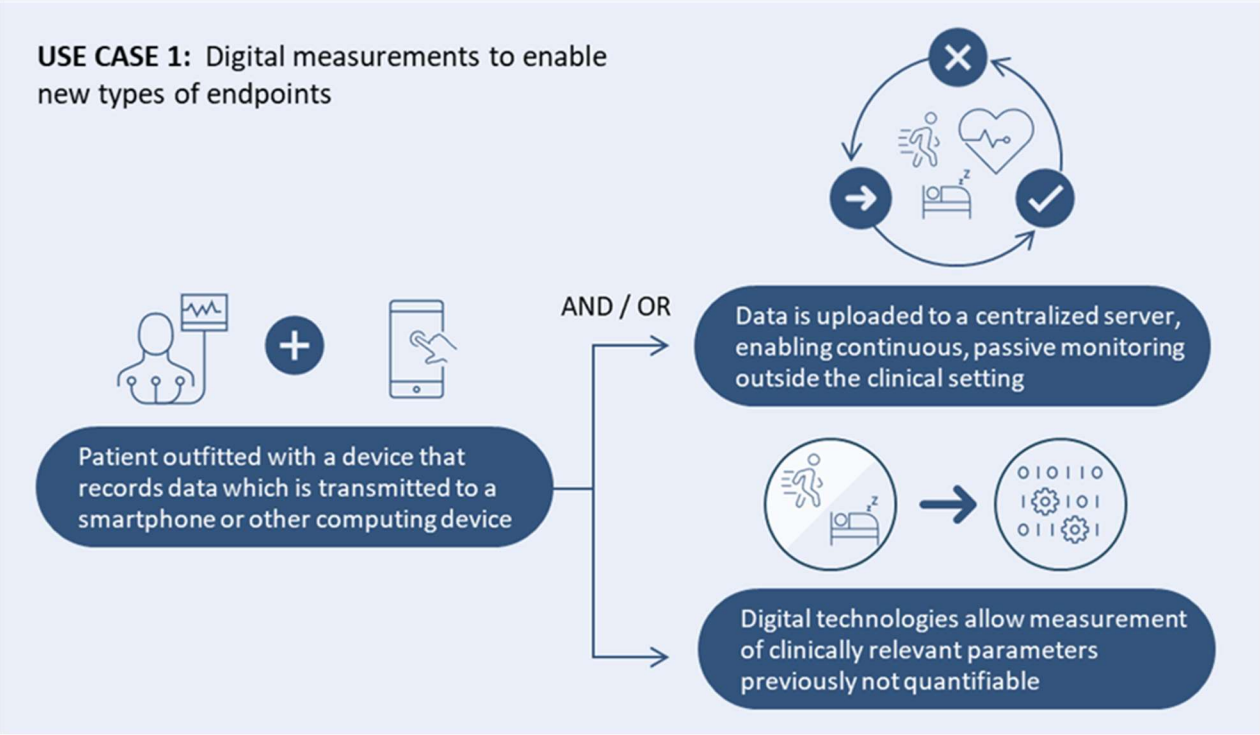
As information technology advances have accelerated, computing platforms, software, sensors, and the connectivity they enable have become invaluable tools in the diagnosis, treatment, and monitoring of disease. The term digital health tool (DHT) refers to the use of these technologies as medical products, in medical products, as companion diagnostics, or as adjuncts to other medical products (devices, drugs, and biologics), including patient/disease monitoring.

DHTs have application across therapeutic areas – from heart failure to neurodegenerative disorders and skin diseases (Digital Health Resources Library, 2022). DHTs integrate real-time measurement and data collection tools (accelerometers, cameras, heart rate monitors, patient-led questionnaires and assessments) with devices for storing, processing, analyzing, and sharing data (smartphones and computers). The speed and frequency of data capture, combined with powerful analysis often based in AI/ML, are important factors enabling many DHTs.

These technologies have also been adapted for use in R&D. The phrase 'digital health technologies' encompasses the use of digital technologies by patients but also in R&D applications, including digitally derived endpoints in clinical trials, electronic patient-reported outcomes (ePROs), devices, and platforms that enhance patient adherence to protocols, and digital platforms and digitally enabled approaches (e.g., virtual or hybrid clinical trials) that enable access to expanded patient populations (FDA, Digital Health Technologies for Remote Data Acquisition in Clinical Investigations, 2021).

Use case 1: Digital measurements to enable new types of endpoints

As a general principle, the best endpoints are those that are relevant to the patient and measured in the real world. Real-world measurement is particularly important, as RWD studies are not possible if the measurement of choice is never made. Digital measurements can play a key role in enabling such measurement, allowing RWD to be practiced routinely and enabling evidence collection well beyond the end of an RCT. Furthermore, DHTs that continuously measure, monitor, and evaluate a wide range of clinical parameters facilitate the inclusion of digitally derived endpoints in clinical trials. Digitally derived endpoints include sensitive, passive, and remote monitoring outside the clinical setting to measure a variety of vitals, symptoms, and behaviors. Remote collection of biomarkers and clinical outcome assessments can potentially reduce the number of patients needed for a clinical trial due to the availability of continuous data, which can be used to develop individualized thresholds to measure comparative effects (Dodge, et al., 2015). Continuous data also enables new types of digitally derived endpoints, such as the ability to assess the impact of a therapeutic on physiological outcomes (e.g., heart or respiration rate, gait, sleep) over time. Recent advances in digital health, including wearable devices and smartphone applications, not only enable novel clinical trial designs but can be paired with advanced computational techniques to paint a holistic understanding of disease and/or patient progression. (Gold, Amatniek, Carrillo, Cedarbaum, & Czaja, 2018)



Digital health tools can enable novel measurements for understanding and quantifying disease, particularly in the real-world setting, giving sponsors access to a broader range of potential endpoints. With the significant increase in experience and comfort across sponsors, PIs, sites, and patients, digitally derived endpoints can reduce some of the complexity of clinical trials for patients and providers, particularly where endpoint data can be collected passively or remotely. Finally, digitally derived endpoints are also creating a new body of evidence upon which to evaluate reimbursement decisions.

DIGITAL MEASUREMENTS TO ENABLE NEW TYPES OF ENDPOINTS IN ACTION

Digital endpoints of fatigue and sleep in neurodegenerative and immune-mediated inflammatory diseases

IDEA-FAST is a public-private consortium of 46 industry and academic partners across 15 countries in Europe and the U.S. and funded by the Innovative Medicine Initiative (IMI). The goal is to use multimodal biosensor measurements of activity, sleep, physiology, and neurocognition to identify and validate digital endpoints that can reliably, objectively, and sensitively quantify fatigue and sleep disturbances in patients with neurodegenerative diseases such as Parkinson's Disease and Huntington's Disease and immune-mediated inflammatory diseases (IMID) including Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus (SLE), Primary Sjogren's Syndrome (PSS), and Inflammatory Bowel Disease (IBD) (IDEA-FAST Project, 2022). The ambition of this study is to seek regulatory qualification for their widespread use as new clinical trial endpoints.

Remote assessment of disease and relapse in disorders of the central nervous system

Another IMI consortium, RADAR CNS, involving 22 industry and academic partners across Europe and the U.S. aimed to identify new ways of remote monitoring of major depressive disorder, epilepsy, and multiple sclerosis using multimodal measurements from wearables and smartphone sensors (such as sleep, physical activity, stress, mood, sociability, speech patterns, and cognitive function) to assess current clinical state and predict negative clinical outcomes (Matcham, et al., 2019) (Bruno, et al., 2020). For example, in patients with epilepsy, it was shown that measurements from wearable accelerometers could be a biomarker of post-ictal immobility, which is known to be associated with potentially life-threatening complications and sudden unexpected death in epilepsy (SUDEP) (Bruno, et al., 2020).

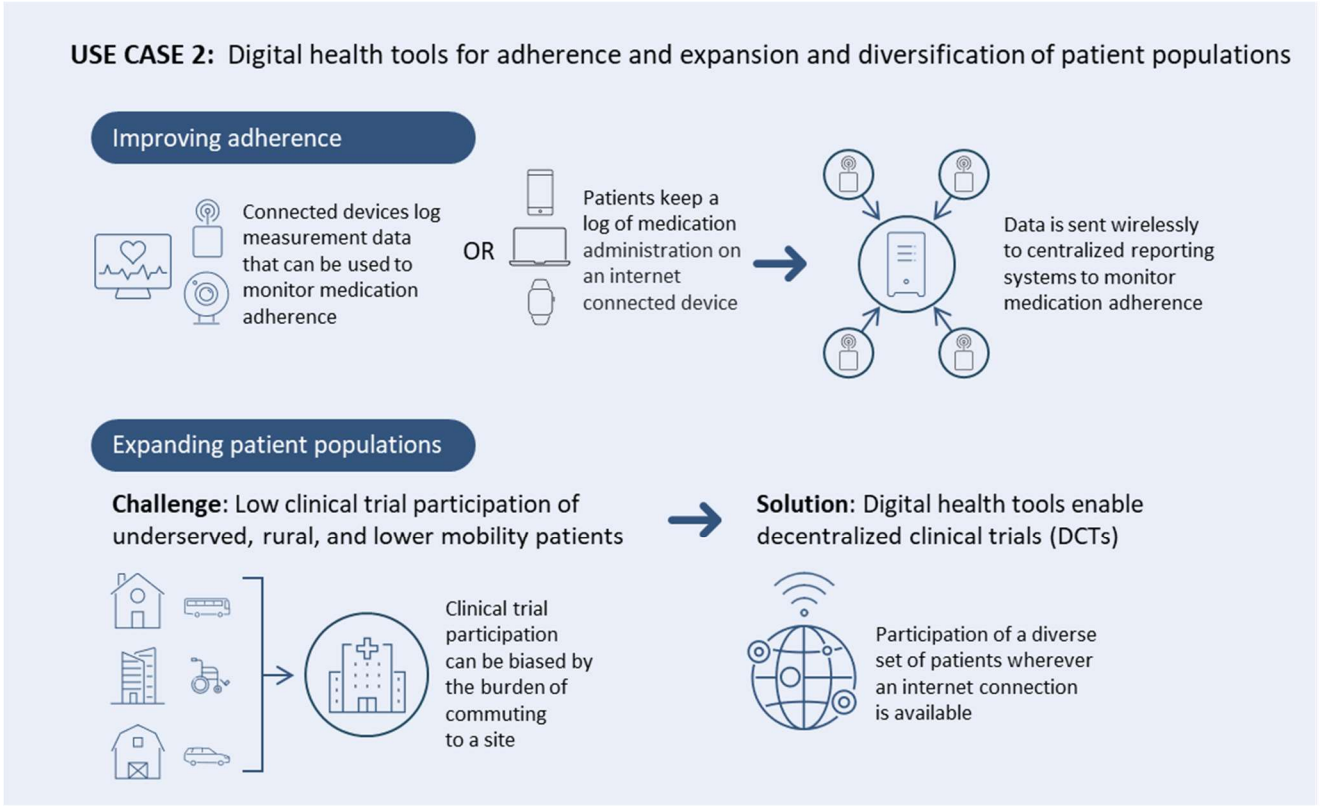
Janssen Autism Knowledge Engine (JAKE®) for monitoring clinical outcomes in autism spectrum disorder

Janssen Autism Knowledge Engine (Ness, et al., 2019) is a clinical research outcomes assessment system developed to monitor and measure treatment outcomes and identify subpopulations in autism spectrum disorder (ASD). Biosensor measurements such as eye tracking (Manyakov, et al., 2018), facial expression (Bangerter, et al., 2020), actigraphy (Bangerter, et al., 2020), electrocardiography, and electrodermal activity collected in a large observational study demonstrated differences between Typically Developing (TD) and ASD individuals and correlated with ASD symptoms.

Use case 2: Digital health tools for adherence and expansion and diversification of patient populations

Patient adherence to study protocols and retention of trial participants throughout the course of a clinical study are necessary to establish the robust safety and efficacy profiles required by regulators. DHTs have the potential to improve patient adherence, for example, by connecting medication administration technologies to centralized reporting systems to monitor medication adherence or facilitating passive measurements. A reduction or elimination of the need to visit trial sites can also enhance patient diversity by recruiting patients from a wider population than limited to a certain distance of a participating site (Ali, Zibert, & Thomsen, 2020). Digital health tools can therefore enable the inclusion of underserved, rural, and lower mobility patient populations.

The impact of digital health tools for improving adherence and expanding potential patient populations is more nascent than other categories of MDTs. However, the ecosystem has seen the potential value, and is testing DHTs to capture benefits for stakeholders across the ecosystem.



DIGITAL HEALTH TOOLS FOR PATIENT ADHERENCE AND EXPANSION OF PATIENT POPULATIONS IN ACTION

AARDEX is tracking dosing data from Sanofi's insulin pens via Bluetooth, eliminating the need for patient diaries to track medication adherence

AARDEX group and Biocorp were involved in a joint initiative to take part in the Phase IV study RADIAL in collaboration with Sanofi and Trials@home The goal is to create a digital solution to optimize insulin management. The Phase IV study will utilize Biocorp's Mallya pen injector add-on, a device that collects the dose and time of each injection from an attached Sanofi Solostar insulin pen. The data is transferred seamlessly via Bluetooth to AARDEX Group's medication adherence software MEMS AS to understand patient behaviors, including medication adherence, during the course of the study. This technology potentially replaces the patient diaries that are used to track adherence with a more reliable and objective digital measure. (Trials@Home - Decentralized Trial Centre of Excellence, 2022).

A total of 600 patients across 63 sites in six countries will be enrolled, with 150 site-based, 150 hybrid, and 300 participating remotely. Since many patients are participating remotely, in addition to providing real-time, continuous adherence data, this technology enables a decentralized trial (DCT) approach.

A decentralized clinical trial utilizing DHTs for atrial fibrillation monitoring increases participation from groups underrepresented in clinical trials

A trial was conducted to examine the reliability of the Apple Watch and companion smartphone application in correctly identifying an episode of atrial fibrillation (AF) from an irregular pulse notification (Perez, et al., 2019). The use of a digital platform for measuring, collecting, and analyzing data enabled a DCT approach. In this case, the result was a significant increase in participation from underrepresented groups, including racial and ethnic minorities, as well as patients 65 years of age or older. Rather than requiring participants to attend a clinic, 419,297 participants were enrolled that could participate remotely using the smartphone app platform.

Participants without AF wore an apple watch monitored by a companion app on their phones. If an irregular pulse notification algorithm identified AF, a telemedicine visit was initiated, and an ECG patch was mailed to the participant to be worn for up to 7 days.

34% of patients who received irregular pulse notifications had AF on later ECG patch readings. Among patients who had already received an ECG patch, 84% of subsequent irregular pulse notifications concurred with atrial fibrillation readings (Perez M. V., 2019). This decentralized trial also demonstrated the utility of DHTs in identifying patients likely to experience AF based on a point-of-care (PoC) test administered to a large and diverse patient population. In this case, participants included groups typically underrepresented in clinical trials. 32% of participants were non-white, 10% were 55-64 years old, and 5.9% were 65 years old and above. DHTs will potentially benefit trials across various conditions, allowing PoC testing at scale and in a diverse pool of participants.

Outstanding challenges to implementation of digital health tools in clinical development

- **Regulatory guidance to ensure use of DHTs in clinical development for regulatory decision making:** While regulatory agencies like the U.S. FDA have issued guidance and offer support for sponsors seeking to integrate DHTs into their trials, there are remaining gaps and challenges.
    - The U.S. FDA's Center for Devices and Radiological Health (CDRH), Center for Drug Evaluation and Research (CDER), and Center for Biologics Evaluation and Research (CBER) have issued guidance on DHTs. However, the level of evidence that must be generated to demonstrate a DHT is fit-for-purpose in a clinical trial is still unclear and there is a risk that expectations will be overly burdensome, hindering the ability to employ DHTs in clinical trials at scale.
    - While these advances are encouraging for the use of DHTs in clinical development, sponsors of pharmaceutical products desiring to use DHTs in their trials often need to be knowledgeable and proactive in navigating CDER/CBER and CDRH to have sufficient engagement to successfully leverage DHTs in clinical development (FDA, 2021).
    - Guidance is still needed to determine whether a DHT is considered a device, and under what circumstances device requirements or design controls apply.
    - Finally, while the FDA and some EU countries, including an EU recommendation paper on decentralized clinical trials (EMA, 2022), have provided guidance on digitally enabled clinical trials (FDA, 2021), there is no harmonized global guidance today, making it challenging for sponsors operating global trials.

What can be done?

Continue to create channels for regulators and sponsors to learn from one another. Specifying regulatory guidance will be critical to accelerating the ability to create value from DHTs in trials.

- **Analytical validation and technical quality assurance of digital measurements:** Today there is insufficient guidance on quality standards and quality assurance processes in place to ensure that the hardware and software enabling digital health tools and the resulting data is reliable, accurate, and compliant with standards for privacy and security. The U.S. FDA has issued draft guidance on standards for remote data acquisition, but it does not address all the outstanding questions pertaining to use of DHTs. Organizations like the Digital Medicine Society (DiMe) seek to fill some of the gaps through frameworks and recommendations but there is an outstanding need for official, harmonized guidance from regulators.
    - DHTs that enable digital measurements and remote patient monitoring require robust hardware and software. The absence of quality standards for hardware and software can reduce confidence in the data, particularly when only processed outcomes, rather than raw data, are reported by the DHT developers. Sponsors may also not have the ability to understand the implication of DHT software updates on the data, creating challenges ensuring measurements are comparable when software updates occur.

- A lack of standardization in data structures and analytics leads to a high level of validation required for any DHT deployed in clinical development. Data structures vary at multiple levels, from the metadata used to identify key data elements to the file formats in which data is stored. Algorithms are similarly diverse, both at a core functional level, but also operationally—languages and coding practices vary. The resulting lack of interoperability is a challenge for deploying validated DHTs at scale across research groups.
- Developing standardized methods for validation and quality assurance remains a critical roadblock. Once standards are in place, there must be education and outreach to communicate these standards to sponsors and CROs across the industry.
- The regulatory pathways to support the use of DHTs in clinical development need to be further clarified and streamlined to ensure timely adoption and acceptance of DHTs in clinical development and regulatory decision making.

What can be done?

Continue to establish forums for stakeholders – regulators, biopharma sponsors, and DHT developers – to jointly address complex questions in the DHT space. Consortiums with regulatory participation, building on the model of organizations like the Digital Medicine Society (DiMe), IMI IDEA-FAST, IMI MOBILISE-D, IMI RADAR-AD/CND, IMI Trials@Home, and C-Path projects are a potential path forward.

- **Experience and comfort with DHTs:** Sponsors need to weigh taking the established path of traditional clinic-based trial designs and endpoint collection with incorporation of DHTs.
  - Using DHTs is still novel, particularly in registrational trials. It requires both investment and risk to sponsors opting to use DHTs such as decentralized models or digitally derived endpoints over more traditional approaches. Finally, without accruing experience, sites and clinical trial participants may find DHT-based trial elements challenging to implement. Patients need to be trained to use the tools and there may be technical challenges (outages, system integration) and use of DHT-base elements may require more effort from patients than more traditional approaches (*e.g.*, due to the need to continuously wear devices).

What can be done?

Encourage industry-wide innovation and collaboration through a test-and-learn approach based on regulatory guidance. The convenience of DHTs for patients and providers should be a focus, as well as accelerating comfort with DHTs among PIs, patients, and regulators. Comfort with DHTs across stakeholders is critical to realizing the potential of DHTs in clinical development.

Raising the bar on RWD through RCTs, while enhancing RCTs with RWD-driven insights

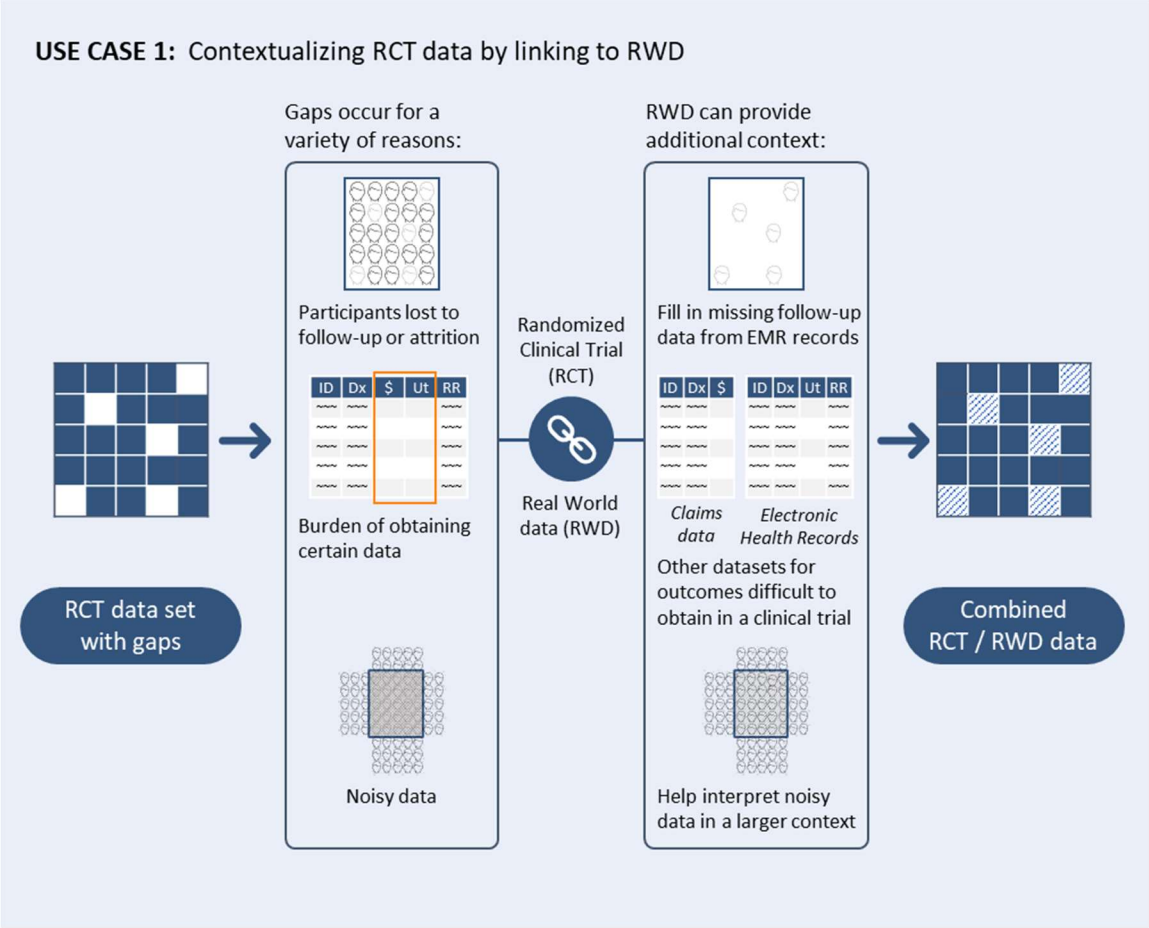
One of the challenges of utilizing RWD is the validity of propensity scores. Direct comparison to an RCT trial will in principle allow validation or adjustment of the propensity scores: if the external control resembles the actual RCT control, this supports high confidence in the RWD methodology (or conversely, flags potential issues). Likewise, insights drawn from RCTs and subsequent regulatory submissions can be enhanced by supplementing RCT data with RWD (data collected outside of the traditional clinical trial settings, including claims and billing activities, EHRs, labs, disease registries, mortality, and data collected from mobile / wearable devices) (Makady, de Boer, Hillege, Klungel, & Goettsch, 2017). The evidence produced by RCTs demonstrates the efficacy of an intervention on a study population often selected based on strict inclusion / exclusion criteria under a controlled experimental setting. These restrictions can make study results difficult to generalize to the heterogenous patient populations that exist in the real-world, non-experimental setting.

Additionally, RWD can enhance RCT data by validating or contextualizing findings or supplementing where there are gaps in data (e.g., missing clinical encounters, inability to safely or ethically randomize to a control group). The linkage of RCT data to RWD is typically facilitated by tokenization, an advanced analytic technique that transforms protected health information (PHI) through creation of unique identifiers, or "tokens", that are de-identified and can be used for linkage across different data sources without the need for exchanging PHI (Polinski, Weckstein, & Batech, 2022). The benefit that RCT-RWD linkage can provide to stakeholders in the healthcare ecosystem can be significant when it comes to augmenting RCT data, tracking follow-up, and external control arms. However, as the following cases demonstrate, numerous challenges to implementation in clinical development remain.

Use case 1: Contextualizing and validating RWD methodologies by linking to RCTs

In many cases, RCTs can have limitations such as missing data from loss to follow-up or attrition. Often key outcomes or variables might have not been collected because of feasibility and/or additional burden on study sites and patients (e.g., cost and utilization data). Additionally, some RCT data can be noisy and need to be interpreted in a larger context (*e.g.*, patient-reported outcomes (PROs)), subjective clinician notes, missing data). In those cases, linkage with RWD can provide complementary evidence and help contextualize RCT results (Cohen, Greenberg, Harnett, Madsen, & Smith, 2021), potentially generating a more robust package for

submissions. Conversely, RWD studies can benefit from comparison to an RCT (*e.g.*, in a Phase II or III study), for validation or correction of propensity scores, over time elevating the standard of rigor for RWD.



CONTEXTUALIZING RCTs THROUGH RWD IN ACTION

Alliance for Clinical Trials in Oncology Foundation is a collaboration with leading RWD vendors to augment clinical oncology trials with patient electronic records through the Integrating Clinical Trials and Real-world Endpoints (ICARE) data study

The Alliance for Clinical Trials in Oncology Foundation partnered with Dana-Faber Cancer Institute/Brigham and Women's Hospital, the American Society of Clinical Oncology, and the MITRE Corporation to conduct a study in which RWD is collected alongside an RCT (ICAREDATA, 2019). Additionally, the mCODE standard (an open-source standard for data infrastructure and capture) is being developed and piloted through this study to capture higher-quality electronic health record-based treatment data. Patients enrolled in prospective RCTs will have study data obtained using standard electronic case report forms, while treatment response and toxicity data is also sourced directly from the EHR using the mCODE format. This will allow for the comparison

of endpoints collected from EHR data to results obtained from standard electronic case report forms (mCODE, 2022).

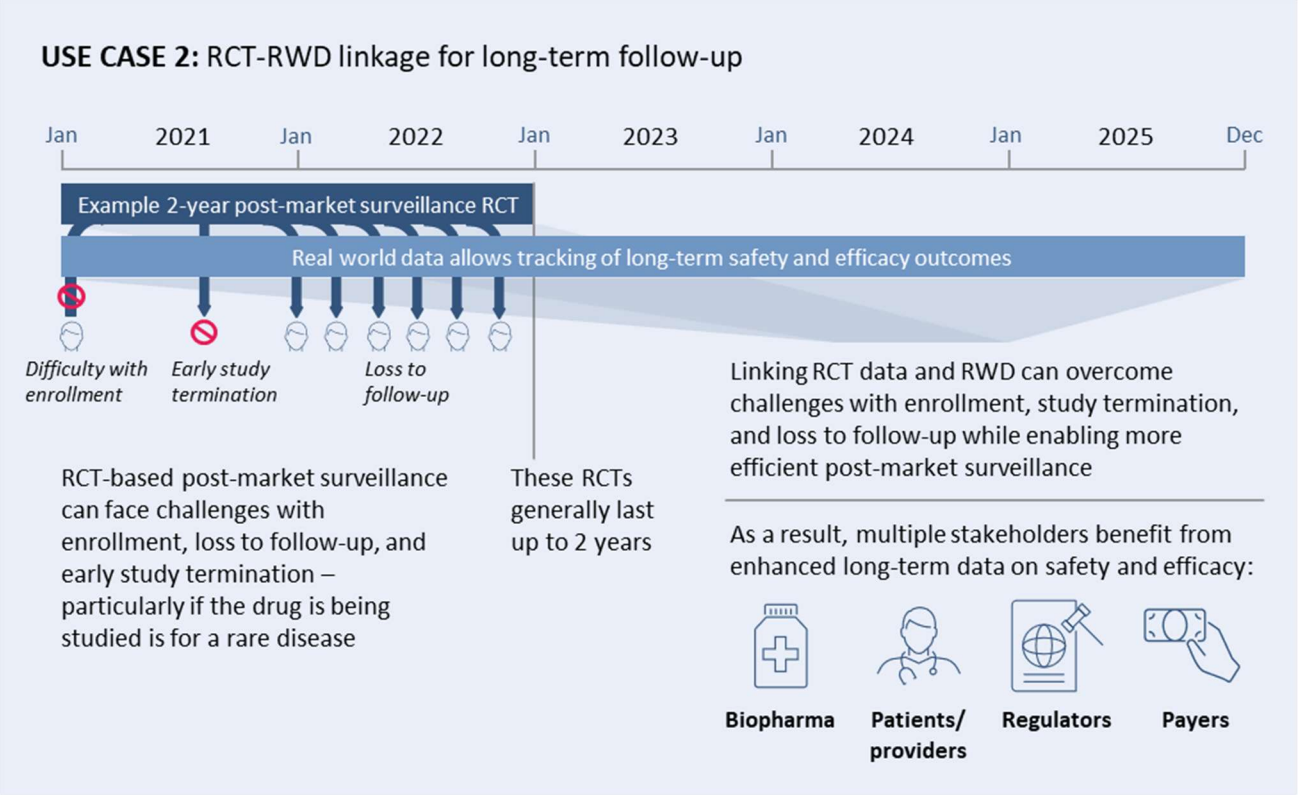
The Alliance seeks to assess the correlation between randomized trials and RWD by initially focusing on disease progression and toxicity with plans to expand to a broader set of data in future clinical trials. The hope is that EHR data will allow the evaluation and comparison of numerous parameters and patient subgroups and yield insights into the understanding of cancer and the design of future clinical trials. Currently, Alliance trials are being run for a variety of indications, including cutaneous squamous cell carcinoma, chronic myeloid leukemia, advanced renal cell cancer, and rare genitourinary tumors.

Use case 2: RCT-RWD linkage for long-term follow-up

Sponsors and regulators are often required to or interested in tracking long-term safety and efficacy of new drugs in clinical trial participants. Long-term extension studies using traditional RCT methods can be difficult to implement and be expensive for sponsors and burdensome to patients. (Burcu, Manzano-Salgado, Butler, & Christian, 2022). RWD for trial participants, on the other hand, are being routinely collected outside of traditional clinical studies, including data from insurance claims, EHRs, registries or wearables and can be leveraged to capture long-term outcomes for specific clinical outcomes of interest.

Linking RWD to RCT data to enable long-term follow-up has benefits across the ecosystem:

- **Biopharma:** Linkage of RCT data to RWD for clinical trial participants can provide sponsors with a view of long-term outcomes, including enhanced data on long-term safety and efficacy, possibly sooner than post-marketing surveillance studies. Participant consent to RCT-RWD linkage, or linkage of de-identified RCT data with de-identified RWD data through tokenization, can also enable sponsors to track patients who have dropped out of trials.
- **Patients/providers:** Enhanced data on long-term safety and clinical outcomes can provide patients and providers with increased confidence in the effectiveness and safety of investigational and newly approved drugs.
- **Regulators:** RCT-RWD linkage could facilitate collection of post-marketing surveillance data, especially from patients who could have otherwise been lost to follow-up if a traditional RCT had been conducted.
- **Payers:** Enhanced data on long-term safety and clinical outcomes from linking RCT participants to RWD enables payers to identify the safest and effective, and cost-effective treatments for managing the disease.



RCT-RWD LINKAGE FOR LONG-TERM FOLLOW-UP IN ACTION

Janssen and HealthVerity partnered to create the first RCT to RWD registry using data tokenization

Tracking long-term follow-up outside of a clinical trial setting has historically been challenging, with many patients lost to follow-up. Janssen, in collaboration with HealthVerity, developed a first-in-industry clinical trial and RWD registry to track COVID-19 vaccine patients. The registry links RCT data with RWD (*e.g.*, claims, EHR, lab data) to create a robust, longitudinal dataset on outcomes.

HealthVerity's RWD platform ensures HIPAA-compliant linkage of patient data through tokenization, in which the patient information is used to generate a unique token that does not reveal the underlying data or compromise privacy. These tokens can be linked across multiple sources of health data to create a single record for each patient across time and sites of care.

Intercept Pharmaceuticals worked with Komodo Health to link claims, lab, and mortality data via Datavant tokenization for a comparative effectiveness study of Ocaliva in primary biliary cholangitis (PBC)

Ocaliva was granted accelerated approval for PBC in 2016 based on a reduction in alkaline phosphatase (ALP), a marker suggestive of reduced liver injury (Intercept Pharma Press Release, 2022). As part of the drug's accelerated approval, there was a post-marketing requirement to evaluate clinical outcomes in patients with advanced PBC. Post-marketing studies like these are challenging due to the ethical dilemma and difficulty of

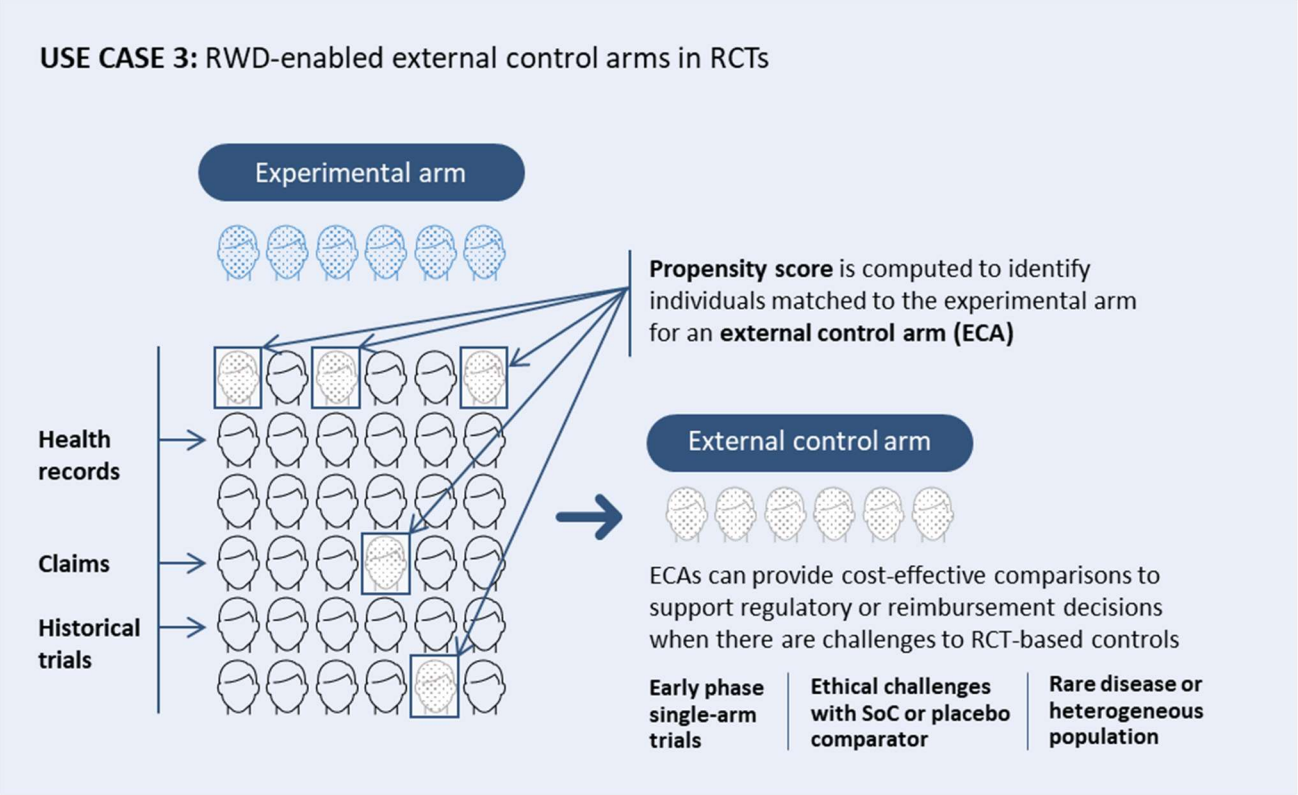
enrolling patients in a placebo arm when there is an on-market drug to treat the condition. Ocaliva was faced with this challenge when COBALT, a Phase IIIb/IV confirmatory study for Ocaliva, was terminated early due to challenges in enrolling and maintaining patients. At the time of termination, the study was only 80% enrolled, and more than 50% of patients discontinued the study prior to meeting the endpoint.

In order to augment the regulatory filing for Ocaliva, Intercept Pharmaceuticals is conducting two retrospective real-world studies in partnership with Komodo Health and Datavant. The two real-world analyses will provide greater insight into the impact of Ocaliva on clinical outcomes for PBC patients to be compiled along with the data available from COBALT. HEROES-US, the first retrospective real-world analysis, used U.S. claims data from Komodo, linked via Datavant tokenization to Quest and LabCorp laboratory data and the Social Security Death Index to compare clinical outcomes in a group of patients with PBC treated with Ocaliva and a group of PBC patients who met the trial criteria but were not treated with Ocaliva. A statistically significant reduction in all-cause death, liver transplant, and hospitalization for hepatic decompensation was found among treated patients (Intercept Pharma, 2022).

Use case 3: RWD-enabled external control arms in RCTs

Clinical trials usually rely on the randomization of patients into treatment and control groups to provide an unbiased estimation of treatment effects (Ventz, et al., 2019). Single-arm trials (SATs), where all participants receive the intervention, often have difficulty establishing sufficient evidence for treatment effects without adequate control (Grayling, Dimairo, Mander, & Jaki, 2019). The increased availability of data from historical trials and RWD from sources such as EHRs and insurance claims has enabled the creation of external control arms (ECAs) (Corrigan-Curay, Sacks, & Woodcock, 2018). Linking patients in SATs to RWD allows for direct comparison of SAT patients with external patients on an 'apples to apples' basis, ensuring controls and SAT patients are as similar as possible in terms of their clinical and demographic characteristics. The linkage, therefore, improves the quality of matching SAT to external controls by using consistent RWD-based measurements of variables.

External controls, particularly when substantiated through RWD-RCT linkage, provide new options for contextualizing the results of RCTs. They give sponsors the ability to include a control group in trials where it may otherwise not have been feasible, and if used to evaluate an investigational product against the standard of care (SOC), may save costs of traditional RCT formats. For regulators and payers, ECAs can provide expanded data to assist in interpreting RCT results to support regulatory or reimbursement decisions. Although promising, external controls can be challenging to execute and must be carefully designed to incorporate calculable and comparable endpoints across real-world and experimental arms.



RWD-ENABLED EXTERNAL CONTROL ARMS IN RCTs IN ACTION

LIBRETTO-001 phase I/II clinical trial of selpercatinib used RWD to create an external control arm

Data from LIBRETTO-001, a single-arm phase I/II trial of the RET inhibitor selpercatinib, was augmented using RWD and control data from other clinical trials to generate a synthetic external control arm to compare clinical outcomes (Rolfo, et al., 2022). The data included patient-level data from a de-identified real-world database and the control arms of two clinical trials, KEYNOTE-189, and REVEL. The study first aligned the RWD control arms to the trial arm by restricting the trial I/E criteria. The data were then matched using analytic techniques, including entropy balancing, doubly robust method, and propensity score approaches.

This analysis allowed a comparison of the treatment arm, selpercatinib, to treatment naïve RET+ non-small-cell lung cancer patients. Analyses showed highly consistent statistically significant improvements in clinical outcomes, including objective response rate (ORR), progression-free survival (PFS), and post-progression overall survival (O.S.) due to selpercatinib treatment. The study validated RWD approaches to generating comparator data in single-arm trials, allowing early-phase single-arm trials to serve as powerful exploratory and hypothesis-generating investigations prior to Phase III trials (Rolfo, et al., 2022).

Outstanding challenges to implementation of augmentation of RCT data with RWD in clinical development

- **Industry-wide mindset shift around RWD and RWE:** As the use of RWD gains acceptance and both the data and access to data improves, an evolution in the mindset of sponsors, tech companies, and regulators will help increase the value of its use. RWD, particularly when used to generate RWE, had in the past been viewed as a potential replacement for traditional RCTs. While there is still promise in these applications, such as for label extension, or the various efforts to understand whether RCTs can be fully replicated using RWD, there should be recognition that the value today includes a broader set of use cases. The most impactful use cases today, like those highlighted in this paper, involve enhancement of RCTs with RWD to ground RCT design and analysis in what is happening in the real world and the use of RWD to augment trials beyond scenarios where an internal control is not feasible or ethical (*e.g.*, for rare diseases and oncology indications).

What can be done?

Promote an industry-wide mindset shift to a pragmatic and inclusive view of "RWE AND RCTs": the many ways in which RWD can improve clinical development as an adjunct, rather than a replacement, for RCTs. Broad and consistent application of RWD to design better trials, enhance operations, and contextualize the results of RCTs can contribute significant value to clinical development today and help to foster buy-in from regulatory authorities.

- **Inconsistent data quality, availability, and structure:** Though many parts of the drug development ecosystem are working together to rectify data quality issues, there are still inconsistencies in RWD quality that lead to challenges in applying it for clinical research and regulatory purposes.
    - Developing novel insights by linking RWD to RCT data requires the RWD to meet high standards for quality. For some sources of RWD, there is a lack of quality standards. There is no method for enforcement today for those data sources with existing standards (*e.g.*, Fast Healthcare Interoperability Resources (FHIR) standards for EHRs). As described earlier in the paper, the U.S. FDA has released several draft guidances on RWD quality and fitness for regulatory use, and other institutions like the Duke-Margolis Center for Health Policy also provide resources for sponsors. However, it will require ongoing effort from all stakeholders to ensure consistent quality of RWD applied in clinical development.
    - Depending on the source of RWD, sponsors and tech developers may not have access to individual patient-level data. There are two implications – (1) that linkage is not possible for these data sources, and (2) that the data may not be able to be used for regulatory purposes if regulators require access to patient-level data in their assessment of the regulatory package.

What can be done?

Similar to what is needed for AI/ML models, develop a comprehensive, consensus-driven set of standards to guide RWD quality and feasibility for use in enhancing RCTs, building on guidance provided by regulators and other organizations (*e.g.*, academic groups).

- **Data linkage complicated by the limited view of data provenance and lineage:** Execution of the use cases highlighted in this paper depends on linking multiple data sources without revealing privileged identifying patient information. Adoption depends on prioritizing data security and confidentiality while simultaneously allowing traceability for auditing and validation.
    - Most approaches today depend on tokenization, in which an algorithm processes a patient's health data into a token, a surrogate string of characters that reflects the underlying data, while securely concealing the content of that data (Clinical Leader, 2021). Tokens are statistically matched across multiple sets of data, identifying tokens that are similar but not identical and likely come from the same patient. While there is precedent for the successful use of tokenization, including in many financial applications, it introduces the possibility of false linkages.
    - Different groups may have different practices for traceability of the data's provenance and lineage—its origin and history (EU Support Centre for Data Sharing). This can complicate efforts to validate matching success and the underlying data used in research projects. EMA has published a list of metadata from RWD catalogs (Jun 2022) for RWD sources and studies and a draft Good Practice Guide for using the Metadata Catalogue (Sep 2022) for public consultation.

What can be done?

Biopharmaceutical sponsors should establish common practices for embedding metadata tracking the provenance, lineage, and pedigree of health data. Traceability is critical to demonstrating that false matches are improbable and increasing confidence in data linkage approaches.

- **Lack of scalability of infrastructure:** Today, linkage is often done in a bespoke manner that is not scalable across clinical trials.
    - Relevant sources of RWD often vary trial-by-trial based on the best source for the diseases, study population, and geographies involved, and as data formats by source are not standardized, many analyses require significant data manipulation and cleaning to supplement RCT data with RWD. This makes it harder for sponsors to scale up data linkage across multiple clinical trials.

What can be done?

While data sources are likely to remain fragmented for the foreseeable future, biopharmaceutical sponsors should partner with tech developers to create scalable infrastructure and algorithms that reduce the complexity of linking RCT data and RWD for different trials.

- **The need for the proactive and consistent design of RWD-enhanced RCTs:** There are several elements of RWD-enhanced RCTs that must be clear and aligned across relevant stakeholders.
    - RWD-enabled study elements should be proactively written into study protocols. Adding elements where RCT data is augmented with RWD is significantly more challenging mid-study.
    - This extends to the informed consent process. While there are good examples of informed consent forms (ICF) that have been used to allow patients to opt into RWD collection and tokenization, there is currently no standardized language or timing. Writing a robust ICF for collecting RWD and collecting consent simultaneously with primary consent for the trial is not always practiced, but it is important to enable the use of RWD in the context of an RCT and protect patients. Although RWD collection or use can occur through a process that does not involve informed consent (such as the use of previously de-identified data, or through a waiver of consent provided by an institutional review board), where it does involve informed consent, these principals should be given due consideration.
    - When designing a study that includes RWD enhancement of RCT data, there are critical questions to answer early on in the study design. For example, how will RWD be collected and stored securely, and how will PHI be secured?

What can be done?

Sponsors should establish an organizational culture of broad and meaningful use of RWD and proactive planning for RWD-based elements in studies by building consideration and design of RWD-based elements into the governance for protocol design – or even earlier, into clinical development plan design.

WHAT IS NEEDED FROM THE ECOSYSTEM TO ACHIEVE THE FULL IMPACT OF MDTS IN CLINICAL DEVELOPMENT?

The approaches and examples above only scratch the surface of the innovative ways that sponsors and tech developers are creating and applying MDTs to facilitate the delivery of novel medicines for patients. AI/ML facilitates more precise patient identification and stratification and guides site and investigator selection towards concentrated and/or diverse patient populations. DHTs enable new types of endpoints and can enhance participant adherence and access to broader populations. Augmentation of RCT data with RWD, either through formal linkage (*e.g.*, tokenization) or supplementally, can contextualize RCT results for a more robust understanding of findings, enabling external control arms to provide comparative effect in RCTs or provide a new mechanism for long-term follow-up on safety and efficacy.

Innovative MDTs, like AI/ML, DHTs, and augmentation of RCT data with RWD, have significant potential to make clinical development more efficient in terms of time and cost and less burdensome for all involved – sponsors, CROs, sites and PIs, and patients. The level of resources put into R&D today is unsustainable, and it is imperative that ecosystem participants make R&D more efficient – both to bend the time and cost curves and to enable new medicines to be delivered to patients faster. There are MDTs beyond those discussed in this

paper, such as AI/ML applied to disease understanding and target discovery, that also holds promise to accelerate the delivery of more personalized medicines for patients.

There are unique challenges to advancing and scaling each MDT. However, two common challenges will require participation from across the ecosystem to resolve and allow for the impact of MDTs to be maximized:

Continued investment in MDT-based approaches to gain confidence and experience: Organizations will inevitably face pressure to cut programs before they are fully mature, particularly in today's difficult budgetary environment. Though some of the MDT approaches described in this paper are nascent, it is beneficial for sponsors and enabling peers (*e.g.*, tech developers, CROs, data partners) to continue to invest the time and cost to gain experience in applying MDTs and create scalable use cases and tools.

- Industry stakeholders must increase the maturity, rigor, and standardization of MDT-based techniques to ensure that they can be applied consistently and valuably to clinical development. Setting a high bar for rigor is critical across all three approaches described in this paper, ensuring that one bad actor does not set back progress across the industry. Standards should ensure accuracy, prevent bias and algorithmic drift in AI/ML algorithms, uphold high standards for the selection and validation of DHTs, and ensure the quality and fitness of RWD sources and analytic approaches.
- Increased experience and rigor with MDTs will consequently increase confidence in MDTs and their outputs for all who are impacted by their use, including providers using models and interpreting clinical evidence and the patients at the center of clinical research (both participants and those that will benefit from new medicines).
- Building a body of experience will also help ecosystem participants and stakeholders identify the best way to scale MDT-based approaches – enabling them to become more ingrained in the medicine development process.

Continued guidance and a path to increased acceptance from regulators: Regulators like the U.S. FDA have taken important steps to facilitate the use of MDTs in clinical development, such as engaging the industry, establishing centers of excellence, and developing guidances on many novel MDTs.

- It is critical that regulators continue this effort and engagement to resolve outstanding challenges in leveraging MDTs, as well as to clarify existing regulatory pathways for company sponsors without the scale or existing know-how to use MDTs as they seek to bring new medicines to patients.
- To increase regulatory familiarity and comfort, it is also incumbent upon sponsors to be willing to bring forward digitally acquired data, novel endpoints, and robust RWD-enhanced RCTs early and often for regulators as they gain familiarity with MDTs and the utility they can have in clinical study design and operations.
- Both regulators and sponsors must cultivate talent "bilingual" in medical science and data science. Further, all players must be aware of the continued change management effort required on the part of all parties in the understanding, development, and adoption of MDTs, and provide opportunities to share successes and learnings to drive acceptance.

REFERENCES

Alexander, W. (2013). The Uphill Path to Successful Clinical Trials. *Pharmacy and Therapeutics, 38*(4), 225-227.

Ali, Z., Zibert, J. R., & Thomsen, S. F. (2020). Virtual Clinical Trials: Perspectives in Dermatology. *Dermatology, 236*, 375-382.

Amgen. (2022, October 12). *Data-driven machine learning model, ATOMIC, is accelerating clinical trials, bringing medicines to patients more quickly.* Retrieved from Science & Innovation: https://www.amgen.com/stories/2022/10/follow-the-data

Bangerter, A., Chatterjee, M., Manfredonia, J., Manyakov, N. V., Ness, S., Boice, M. A., . . . Pandina, G. (2020, May 11). Automated recognition of spontaneous facial expression in individuals with autism spectrum disorder: parsing response variability. *Molecular Autism, 11*. doi:10.1186/s13229-020-00327-4

Bangerter, A., Chatterjee, M., Manyakov, N. V., Ness, S., Lewin, D., Skalkikn, A., . . . Pandina, G. (2020, Mar 24). Relationship Between Sleep and Behavior in Autism Spectrum Disorder: Exploring the Impact of Sleep Variability. *Front Neurosci., 14*(211). doi:10.3389/fnins.2020.00211

Baune, B. T., Sluth, L. B., & Olsen, C. K. (2018). The effects of vortioxetine on cognitive performance in working patients with major depressive disorder: A short-term, randomized, double-blind, exploratory study. *Journal of Affective Disorders, 229*, 421-428.

Beck, J. T., Vinegra, M., Dankwa-Mullan, I., Torres, A., Simmons, C. C., Holtzen, H., & Urman, A. (2017). Cognitive technology addressing optimal cancer clinical trial matching and protocol feasibility in a community cancer practice. *Journal of Clinical Oncology, 35*(15_suppl), 6501.

Berdigaliyev, N., & Aljofan, M. (2020). An overview of drug discovery and development. *Future Medicinal Chemistry*.

Bertsimas, D. L. (2023). Data-Driven COVID-19 Vaccine Development for Janssen. *INFORMS Journal of Applied Analytics*, 70-84.

Bertsimas, D. L. (2023). Data-Driven COVID-19 Vaccine Development for Janssen. *INFORMS Journal of Applied Analytics*, 70-84.

Biotechnology Innovation Organization, PharmaIntelligence, Quantitative Life Sciences. (2021). Clinical development success rates and contributing factors 2011-2020.

Blau, S. (2022, June 15). Operational metrics for the ELAINE II study combining a traditional approach with a just-in-time model. *J Clin Oncol, 40*. Retrieved from Paige Announces Collaboration to Deploy a Novel AI-Based Biomarker Test for Advanced Bladder Cancer in Clinical Settings: https://www.businesswire.com/news/home/20220615005063/en/Paige-Announces-Collaboration-to-Deploy-a-Novel-AI-Based-Biomarker-Test-for-Advanced-Bladder-Cancer-in-Clinical-Settings

Brasier, N., Osthoff, M., Iso, F., & Eckstein, J. (2021). Next-Generation Digital Biomarkers for Tuberculosis and Antibiotic Stewardship: Perspective on Novel Molecular Digital Biomarkers in Sweat, Saliva, and Exhaled Breath. *J Med Internet Res., 23*(8).

Bruno, E., Biondi, A., Böttcher, S., Vértes, G., Dobson, R., Folarin, A., . . . Richardson, M. (2020, Dec 16). Remote Assessment of Disease and Relapse in Epilepsy: Protocol for a Multicenter Prospective Cohort Study. *JMIR Res Protoc., 9*(12). doi:10.2196/21840

Burcu, M., Manzano-Salgado, C. B., Butler, A. M., & Christian, J. B. (2022). A Framework for Extension Studies Using Real-World Data to Examine Long-Term Safety and Effectiveness. *Therapeutic Innovation & Regulatory Science volume, 56*, 15-22.

Business Wire. (2022). Global Healthcare Artificial Intelligence Market (2021 to 2026) - Rising Investments In Advanced Drug Discovery & Development Processes Presents Opportunities - ResearchAndMarkets.com. Dublin: Berkshire Hathaway.

Carlisle, B., Kimmelmen, J., Ramsay, T., & MacKinnon, N. (2015). Unsuccessful trial accrual and human subjects protections: an empirical analysis of recently closed trials. *Clinical Trials, 12*(1), 77-83.

Cavasotto, C. N., & Filippo, J. I. (2021). Artificial intelligence in the early stages of drug discovery. *Archives of Biochemistry and Biophysics, 698*, 108730.

Clarke, E. G. (2021, July 29). Identification of Risk Factors for Invasive Extraintestinal Pathogenic Escherichia coli (ExPEC) Disease. *Antimicrobial Stewardship & Healthcare Epidemiology, 1*(S1), S22. doi:10.1017/ash.2021.40

Clinical Leader. (2021, July 13). *Trial Tokenization: Building a bridge between clinical trial data and real-world data*. Retrieved from Clinical Leader: https://www.clinicalleader.com/doc/trial-tokenization-building-a-bridge-between-clinical-trial-data-and-real-world-data-0001

Cohen, S. B., Greenberg, J. D., Harnett, J., Madsen, A., & Smith, T. W. (2021). Real-World Evidence to Contextualize Clinical Trial Results and Inform Regulatory Decisions: Tofacitinib Modified-Release Once-Daily vs Immediate-Release Twice-Daily for Rheumatoid Arthritis. *Advances in Therpay, 38*, 226-248.

Corrigan-Curay, J., Sacks, L., & Woodcock, J. (2018). Real-world evidence and real-world data for evaluating. *Journal of the American Medical Association, 320*(9), 867-868.

de Kraker, M. E., & Harbarth, S. (2018, Dec 15). Optimizing the Design and Analysis of Clinical Trials for Antibacterials Against Multidrug-resistant Organisms: A White Paper From COMBACTE's STAT-Net. *Clin Infect Dis., 67*(12), 1922-1931.

Digital Health Resources Library. (2022). Retrieved from Digital Medicine Society (DiME): https://www.dimesociety.org/communication-education/digital-health-resources-library/

Dodge, H. H., Zhu, J., Mattek, N. C., Austin, D., Kornfield, J., & Kaye, J. A. (2015). Use of high-frequency in-home monitoring data may reduce sample sizes needed in clinical trials. *PLoS One, 10*, e0138095.

Dombernowsky, T., Haedersdal, M., Lassen, U., & Thomsen, S. F. (2019). Criteria for site selection in industry-sponsored clinical trials: a survey among decision-makers in biopharmaceutical companies and clinical research organizations. *Trials, 20*(708).

EU Support Centre for Data Sharing. (n.d.). *Data provenance & lineage*. Retrieved from EU Data Sharing: https://eudatasharing.eu/technical-aspects/data-provenance-part-1

FDA. (2021). *Digital Health Technologies for Remote Data Acquisition in Clinical Investigations.*

FDA. (2022). *Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products Guidance for Industry.*

FDA Takes Important Steps to Increase Racial and Ethnic Diversity in Clinical Trials. (2022, April 13). Retrieved from https://www.fda.gov/news-events/press-announcements/fda-takes-important-steps-increase-racial-and-ethnic-diversity-clinical-trials

Girman, C. J., Ritchey, M. E., McNeill, A. M., Sundell, K. A., & Meyer, R. J. (2021). Demonstrating that Real World Evidence Is Fit-For-Purpose to Support Labeling: Parallels to Patient Reported Outcomes in the Pursuit of Labeling Claims. *Therapeutic Innovation & Regulatory Science, 55*, 561-567.

Gold, M., Amatniek, J., Carrillo, M. C., Cedarbaum, J. M., & Czaja, S. J. (2018). Digital technologies as biomarkers, clinical outcomes assessment, and recruitment tools in Alzheimer's disease clinical trials. *Alzheimers Dementia (NY), 4*, 234-242.

Grayling, M. J., Dimairo, M., Mander, A. P., & Jaki, T. F. (2019). A review of perspectives on the use of randomization in phase II oncology trials. *Journal of the National Cancer Institute, 111*, 1255-1262.

Harrer, S., Shah, P., Antony, B., & Hu, J. (2019). Artificial intelligence for clinical trial design. *Trends in Pharmacological Sciences, 40*(8), 577-591.

Health, M. (2022). *mCODE*. Retrieved from MITRE: https://health.mitre.org/mcode/

Health, M. (n.d.). *mCODE*. Retrieved from MITRE: https://health.mitre.org/mcode/

Health, M. (n.d.). *mCODE*. Retrieved from MITRE: https://health.mitre.org/mcode/

ICAREDATA. (2019, July). Retrieved from Alliance for Clinical Trials in Oncology: https://www.allianceforclinicaltrialsinoncology.org/main/public/standard.xhtml?path=/Public/News-ICAREdata-Jul2019

IDEA-FAST Project. (2022). Retrieved from idea-fast.eu: https://idea-fast.eu/

Intercept Pharma. (2022, June 3). *Intercept announces new clinical trial and real-world outcomes data for Ocaliva in PBC*. Retrieved from Intercept Pharma: https://ir.interceptpharma.com/news-releases/news-release-details/intercept-announces-new-clinical-trial-and-real-world-outcomes

Intercept Pharma Press Release. (2022, June 3). Retrieved from https://ir.interceptpharma.com/news-releases/news-release-details/intercept-announces-new-clinical-trial-and-real-world-outcomes

Kang, C. (2021). Fosdenopterin: First Approval. *Drugs, 81*(8), 953-956.

Kim, Y., Jiang, X., Giancardo, L., Pena, D., Bukhbinder, A. S., Amran, A. Y., & Schulz, P. E. (2020). Multimodal Phenotyping of Alzheimer's Disease with Longitudinal Magnetic Resonance Imaging and Cognitive Function Data. *Scientific Reports, 10*, 5527.

Kolluri, S., Lin, J., Liu, R., Zhang, Y., & Zhang, W. (2022). Machine Learning and Artificial Intelligence in Pharmaceutical Research and Development: a Review. *AAPS J*.

Kozlov, M. (2023, February 16). *FDA to require diversity plan for clinical trials*. Retrieved from Nature: https://www.nature.com/articles/d41586-023-00469-4

Kraus, A. L., Yu-Kite, M., Mardekian, J., Cotter, M. J., Kim, S., & Decembrino, J. (2022). Real-World Data of Palbociclib in Combination With Endocrine Therapy for the Treatment of Metastatic Breast Cancer in Men. *Clinical Pharmacology & Therapeutics, 111*(1), 302-309.

Landers, M., Dorsey, R., & Saria, S. (2021). Digital Endpoints: Definition, Benefits, and Current Barriers in Accelerating Development and Adoption. *Digital Biomarkers, 5*, 216-223.

Li, X., Dunn, J., Salins, D., Zhou, G., & Snyder, M. P. (2017). Digital Health: Tracking Physiomes and Activity Using Wearable Biosensors Reveals Useful Health-Related Information. *PLOS Biology*.

Loeffler, C. M., Bruechle, Jung, Seillier, Rose, Laleh, . . . Kather. (2022). Artificial Intelligence–based Detection of FGFR3 Mutational Status Directly from Routine Histology in Bladder Cancer: A Possible Preselection for Molecular Testing? *European Urology Focus, 8*(2), 472-479.

Mahta Jahanshahi, K. G. (2021). The Use of External Controls in FDA Regulatory Decision Making. *Therapeutic Innovation & Regulatory Science*, 1019-1035.

Makady, A., de Boer, A., Hillege, H., Klungel, O., & Goettsch, W. (2017). What Is Real-World Data? A Review of Definitions Based on Literature and Stakeholder Interviews. *Value in Health, 20*(7), 858-865.

Manyakov, N. V., Bangerter, A., Chatterjee, M., Mason, L., Ness, S., Lewin, D., . . . Pandina, G. (2018, Nov). Visual Exploration in Autism Spectrum Disorder: Exploring Age Differences and Dynamic Features Using Recurrence Quantification Analysis. *AutismRes., 11*(11), 1554-1566. doi:10.1002/aur.2021

Matcham, F., Barattieri di San Pietro, C., Bulgari, V., de Girolamo, G., Dobson, R., Eriksson, H., . . . Hotopf, M. (2019). Remote assessment of disease and relapse in major depressive disorder (RADAR-MDD): a multi-centre prospective cohort study protocol. *BMC Psychiatry, 19*(72).

Minchom, R. A., Girard, N., Bazhenova, L., & Ou, S.-H. I. (2021). Amivantamab compared with real-world therapies in patients with NSCLC with EGFR Exon 20 insertion mutations who have progressed after platinum doublet chemotherapy. *Journal of Clinical Oncology , 9052*(15_suppl), 39.

Ness, S. L., Bangerter, A., Manyakov, N. V., Lewin, D., Boice, M., Skalkin, A., . . . Pandina, G. (2019, Feb 27). An Observational Study With the Janssen Autism Knowledge Engine (JAKE®) in Individuals With Autism Spectrum Disorder. *Front. Neurosci.* doi:https://doi.org/10.3389/fnins.2019.00111

Paige Announces Collaboration to Deploy a Novel AI-Based Biomarker Test for Advanced Bladder Cancer in Clinical Settings. (2022, June 15). Retrieved from Businesswire: https://www.businesswire.com/news/home/20220615005063/en/Paige-Announces-Collaboration-to-Deploy-a-Novel-AI-Based-Biomarker-Test-for-Advanced-Bladder-Cancer-in-Clinical-Settings

Perez, M. V. (2019). Large-Scale Assessment of a Smartwatch to Identify Atrial Fibrillation. *The New England Journal of Medicine*(381), 1909-1917.

Perez, M., Mahaffey, K., Hedlin, H., Rumsfeld, J. S., Garcia, A., Ferris, T., . . . Lee, J. (2019, Nov 14). Large-Scale Assessment of a Smartwatch to Identify Atrial Fibrillation. *N Engl J Med, 381*(20), 1909-1917.

Plackett, B. (2020). Why big pharma has abandoned antibiotics. *Nature*.

Polinski, J. M., Weckstein, A. R., & Batech, M. (2022). Durability of the Single-Dose Ad26.COV2.S Vaccine in the Prevention of COVID-19 Infections and Hospitalizations in the US Before and During the Delta Variant Surge. *JAMA Network Open, 5*(3), e222959.

Rolfo, C., Hess, L., Jen, M., Peterson, P., Li, X., Liu, H. L., . . . Summers, Y. (2022). External control cohorts for the single-arm LIBRETTO-001 trial of selpercatinib in RET+ non-small-cell lung cancer. *ESMO Open, 7*(4).

Schlander, M. H.-V. (2021). How Much Does It Cost to Research and Develop a New Drug? A Systematic Review and Assessment. *PharmacoEconomics*, 1243–1269.

Schultz, A., Saville, B. R., Marsh, J. A., & Snelling, T. L. (2019). An introduction to clinical trial design. *Paediatric Respiratory Reviews, 32*, 30-35.

Seyhan, A. A. (2019). Lost in translation: the valley of death across preclinical and clincal divide - identification of problems and overcoming obstacles. *Translational Medicine Communications, 4*, 18.

Tang, J., Atrache, R. E., Yu, S., Asif, U., Jackson, M., & Roy, S. (2021). Seizure detection using wearable sensors and machine learning: Setting a benchmark. *Epilepsia, 62*(8), 1807-1819.

Tempus Clinical Trial Matching. (2022). Retrieved from Tempus: https://www.tempus.com/oncology/clinical-trial-matching/

Trials@Home - Decentralized Trial Centre of Excellence. (2022, July 19). Retrieved from AARDEX Group: https://www.aardexgroup.com/2022/07/19/trials-at-home/

Ventz, S., Lai, A., Cloughesy, T. F., Wen, P. Y., Trippa, L., & Alexander, B. M. (2019). Design and evaluation of an external control arm using prior clinical trials and real-world data. *Clinical Cancer Research, 25*(16), 4993-5001.