Digital Biomarkers

Tools and Devices - Review Article

Digit Biomark 2022;6:47–60
DOI: 10.1159/000525080

Received: November 5, 2021
Accepted: April 7, 2022
Published online: July 4, 2022

Considerations for Conducting Bring Your Own "Device" (BYOD) Clinical Studies

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Keywords
Bring your own device · BYOD · Digital health technology · DHT · Patient-generated health data · Biosensors

Abstract
Background: Digital health technologies are attracting attention as novel tools for data collection in clinical research. They present alternative methods compared to in-clinic data collection, which often yields snapshots of the participants' physiology, behavior, and function that may be prone to biases and artifacts, e.g., white coat hypertension, and not representative of the data in free-living conditions. Modern digital health technologies equipped with multi-modal sensors combine different data streams to derive comprehensive endpoints that are important to study participants and are clinically meaningful. Used for data collection in clinical trials, they can be deployed as provisioned products where technology is given at study start or in a bring your own "device" (BYOD) manner where participants use their technologies to generate study data. ***Summary:*** The BYOD option has the potential to be more user-friendly, allowing participants to use technologies that they are familiar with, ensuring better participant compliance, and potentially reducing the bias that comes with introducing new technologies. However, this approach presents different technical, operational, regulatory, and ethical challenges to study teams. For example, BYOD data can be more heterogeneous, and recruiting historically underrepresented populations with limited access to technology and the internet can be challenging. Despite the rapid increase in digital health technologies for clinical and healthcare research, BYOD use in clinical trials is limited, and regulatory guidance is still evolving. ***Key Messages:*** We offer considerations for academic researchers, drug developers, and patient advocacy organizations on the design and deployment of BYOD models in clinical research. These considerations address: (1) early identification and engagement with internal and external stakeholders; (2) study design including informed consent and recruitment strategies; (3) outcome, endpoint, and technology selection; (4) data management including compliance and data monitoring; (5) statistical considerations to meet regulatory requirements. We believe that this article acts as a primer, providing insights into study design and operational requirements to ensure the successful implementation of BYOD clinical studies.

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Introduction

Digital health technologies have been defined as "a system that uses computing platforms, connectivity, software, and sensors for healthcare and related uses [1]." Using technologies to collect data created and recorded by participants, known as "person-generated health data," has gained considerable interest and traction in clinical trials. These tools can collect patient data, enabling objective and frequent monitoring of physiology, behavior, and function compared to snapshot in-clinic assessments. In addition, the growth in digital health technology use in the general population has enabled the bring your own "device" (BYOD[1]) model. While this approach previously focused on using individuals' smartphones to capture electronic patient-reported outcome data, there is a growing interest in expanding the BYOD model to include personal digital health technologies.

The digital health technologies with the greatest potential to be amenable to BYOD studies are fitness trackers and smartwatches [2]. With intuitive and easy-to-use interfaces, embedded multi-modal sensors can derive various physiological measures, including physical activity, sleep, and vital sign data (e.g., heart rate, heart rate variability, pulse oximetry) [3–6]. Smartphones have increasing utility as digital health technologies with inbuilt sensors and technology such as accelerometers, global positioning system sensors, microphones, cameras, gyroscopes, and magnetometers. These sensors are used as a source of data for passive monitoring and to deliver functional assessments to study participants via mobile applications [7, 8].

The benefits of BYOD studies are multifarious; the approach allows participants to use their own technologies, leading to better compliance [9, 10] and, potentially, less chance of introducing biases, such as the Hawthorne effect, from monitoring technologies [11]. For participants, there is a familiarity with and access to the technology they use in their daily lives [12, 13]. Sponsors can design patient-centric studies with lower costs and burden on study sites [12–14]. The BYOD model potentially expands participation in clinical trials for populations with limited access to clinical facilities, e.g., older adults, people with disabilities, or living in remote locations [15]. Conversely, limiting eligibility to those with good health and digital literacy, internet connection, and the latest technologies may bias results with data not representative of the target population [15]. BYOD models may not be appropriate in all circumstances; the technologies required to generate study endpoints may not be readily available to the study populations. A model requiring provisioned devices for subsets of participants who do not possess the required technology may be optimal [15, 16]. A comparison between BYOD and provisioned device options is presented in Table 1.

The BYOD approach is feasible in non-interventional and interventional studies using observational, randomized controlled trials, pragmatic (practical) clinical trial designs, and real-world evidence studies (see Appendix 1, available online at www.karger.com/doi/10.1159/000525080, for study definitions, best practices, and checklists). Many observational and postmarketing research questions can be addressed with BYOD to collect data with minimal disruptions to daily life. For example, BYOD models have been successfully deployed in surveillance studies where sensor data from fitness trackers and smartwatches generate data on Flu and COVID-19 infections from 1.3 million [17], 200,000 [18], and 30,000 [19] individuals. These studies follow a typical BYOD approach where participants download a study-specific application to their smartphones to capture patient-reported outcomes, diagnostic test results, and data from connected technologies [13]. BYOD studies incorporating digital health technologies are beginning to emerge in interventional clinical trials [20–22]. Figure 1 showcases examples of different BYOD configurations utilized in clinical studies.

Objective

This paper provides considerations for designing and deploying a BYOD model to capture data for clinical studies. These considerations address: (1) early identification and engagement with internal and external stakeholders; (2) study design including informed consent and recruitment strategies; (3) outcome, endpoint, and technology selection; (4) data management including compliance and data monitoring; and (5) statistical considerations to meet regulatory requirements (Fig. 2). This paper is framed using the Agency for Health Research and Quality guidelines for real-world evidence study design [23]. These guidelines have been broadly adopted and selected as an overarching guide to develop our approach to support sponsors and researchers in designing BYOD studies across diverse patient populations and therapeutic areas. Such considerations are intended for a broad audience, including academic research, drug developers, and patient advocacy organizations.

[1] BYOD is a colloquial term and not associated with regulated devices as defined in Section 201(h) of the Federal Food, Drug, and Cosmetic Act.

Table 1. Comparison of the BYOD and provisioned technology options when designing a clinical study

Comparison parameter	BYOD	Provisioned technology
Participant compliance	Expected to be higher because participants are familiar with technologies and already own a device.	Can be lower, as participants may need to use two sets of digital health technologies (and potentially, distinct corresponding smartphones).
Hawthorne effect (changes in behavior due to awareness of being monitored)	Potentially very low as participants already monitoring themselves prior to enrolling in a study.	Potentially higher than the BYOD option as participants may modify their behavior in response to being monitored.
Technology cost	Cost-saving for sponsors since participants use their technology; extra cost for sponsors may be incurred due to technology evaluation; reimbursement costs to participants to cover the costs of study data transmission.	Sponsors need to budget for the cost of provisioned technology and data plans.
Participants preselection biases	May limit the study population to participants with higher technology literacy and ownership of technologies and access to the internet.	Less likely to be biased due to ownership of technologies though some degree of technology literacy is required to manage participation and data collection.
Study type applicability	Best suited for observational and postmarketing studies.	Any study.

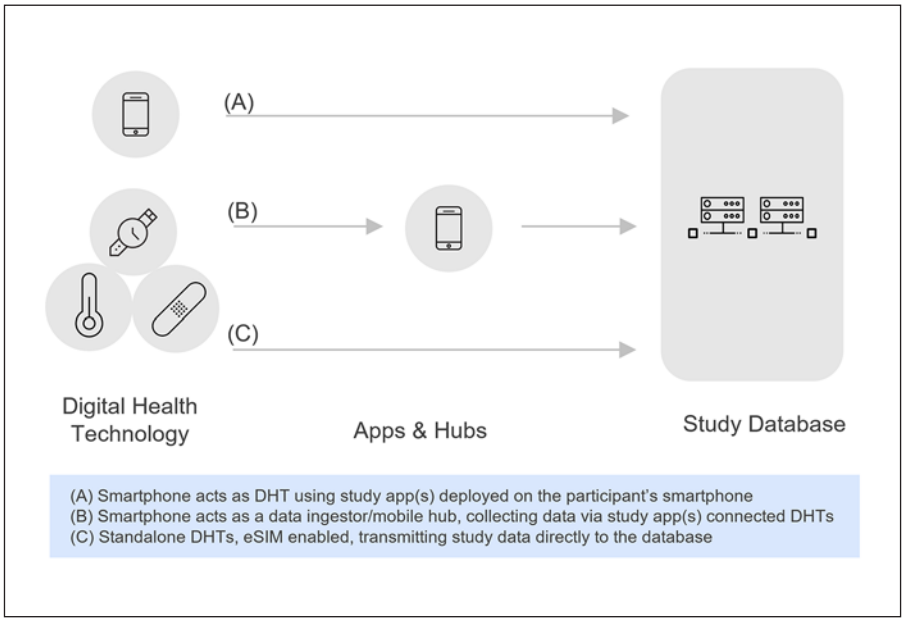

Fig. 1. Examples of possible BYOD configurations: (A) smartphone acts as DHT using study app(s) deployed on the participant's smartphone to collect a variety of data, including (i) electric patient-reported outcomes; (ii) diagnostic tests; (iii) active performance outcome assessments (PerfO) where participants are guided by the app and carry out physical assessments, e.g., a timed tapping assessment, walking task, or guided sit to stand test; (iii) passive data generated by the smartphone sensors without deliberate, intentional input from study participant, e.g., steps, global positioning system, weather, and voice sentiment. (B) Smartphone acts as a data ingestor/mobile hub, collecting data via study app(s) connected via Bluetooth or Wifi to one or more DHTs; (C) standalone DHTs, eSIM enabled, transmitting study data directly to the database. Adapted with permission from DIME [55].

Section 1: Early Identification and Engagement with Internal and External Stakeholders

Understanding the needs, concerns, and impact of the BYOD approach on stakeholders can improve the quality and efficiency of the study. Therefore, the proposed steps in the overarching approach are as follows; (1) stakeholder mapping to identify both internal and external stakeholders, (2) stakeholder engagement, a bidirectional interaction to gain understanding, and (3) stakeholder management to facilitate the smooth operationalization of BYOD in the clinical trial.

Internal Stakeholders

A cross-functional team approach is required, including, but not limited to, representatives from the following groups: data management, medical affairs, biostatistics, data science and data engineering, clinical operations, regulatory affairs and safety (Table 2). Consultation is es-

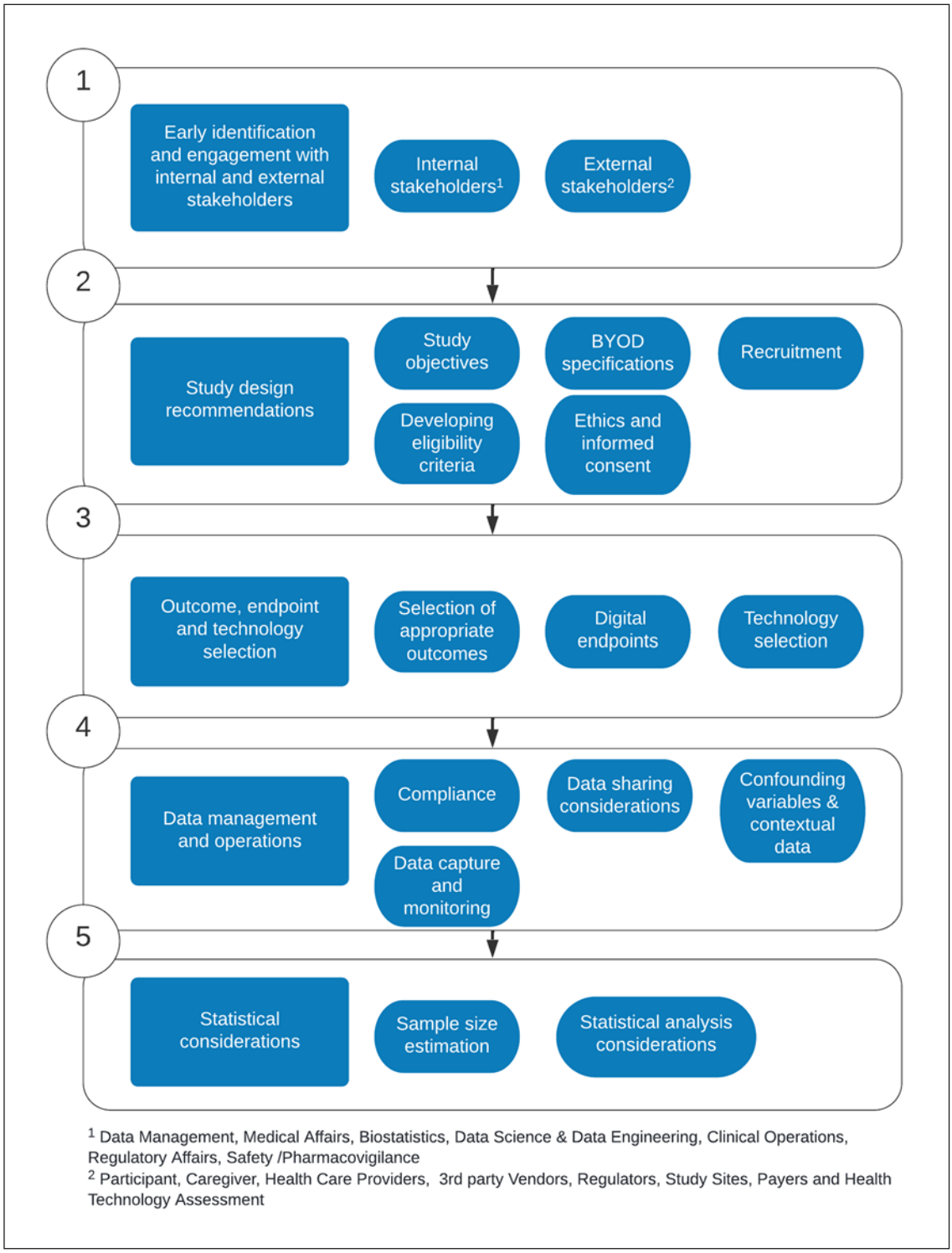

Fig. 2. Framework for deploying a BYOD model in clinical studies.

Table 2. Internal stakeholders to engage when developing a BYOD study and considerations from their perspectives

Internal stakeholders	Requirements for BYOD study design
Data management	• Design and implementation of trial-specific data collection tools from selected BYOD. • Map the data flow from device to study database: this may require the development of study-specific API with BYOD manufacturer's cloud and development of tokenization system to enable authorization process to facilitate collection of data from participants' own devices. • Develop ongoing data monitoring, querying, and cleaning plans. • Implement the team's compliance-monitoring strategies.
Medical affairs	• Determine the acceptability of study assessments and endpoints for remote data collection via suitable digital health technology. • Confirm a required level of ownership of the selected digital health technology among the population of interest. • Plan medical oversight and decision-making during the study where near-real-time data from BYOD technologies is available.
Biostatistics	• Develop and implement a statistical analysis plan that addresses the unique requirements of BYOD data (e.g., data heterogeneity across different digital health technology types allowed in the study, strategies to deal with missing data across the different digital health technologies). See Section 5.
Data science and data engineering	• Derive digital endpoints from digital health technology data. • Deploy these algorithms at scale across the different BYOD technologies allowed in the study. • Develop pipelines to visualize the different data types.
Clinical operations	• Interact with and manage study-specific third-party vendors. • Assess the need to supplement the BYOD model with provisioned devices if required. • Ensure usability (e.g., is the study app easy and intuitive for participants to install on their own?) • Develop patient engagement and support plans. • Develop compliance-monitoring strategies. • Develop training and Frequently asked Questions (FAQs) that are BYOD specific for the sites encompassing the different technologies allowed in the study. • Train sites to support study participants, including providing technology if required.
Regulatory affairs	• Manage interactions with regulatory authorities on trial design and approval. • If novel assessments are deployed via the digital health technology, develop, collate, and prepare an evidence dossier.
Safety/ pharmacovigilance	• New procedures may be required to address near real-time safety signals from BYOD and which may need to include additional processes for contacting site personnel.

sential to understand the potential impact of BYOD on the different work-streams [24].

External Stakeholders

Early engagement with participants, caregivers, vendors, site personnel, and other external stakeholders (Table 3) will maximize value and minimize the burden during study development. These are novel study designs; therefore, clear communication, education, support, and training are essential for a successful study to ensure that the sites and investigators are appropriately trained in the study objectives and the considered technology. Participant materials need to be informative, addressing any participants' concerns with respect to data privacy, mobile data costs, and the consenting process. Gauging the digital literacy of potential study participants during these initial activities will allow for planning and developing appropriate training supports (e.g., videos, a support line) to mitigate differences among participants in how they engage with the technology. Developing a partnership approach with the technology vendor is important so technical issues and mitigation strategies can be jointly developed.

Section 2: Study Design Considerations

Study Objectives

The first set of questions are: Are digital health technologies appropriate to address the study objectives and research questions? Does a BYOD study design minimally provide equivalent data to traditional approaches, and add value, providing insights not derived via standard approaches?

BYOD Specifications

Study teams creating the evidence dossier to support specific digital health technology and digital endpoints should consider the data context: data generated by participants' technology contrasts with a provisioned approach where the team has complete control of the technology. Study applications should capture information

Table 3. External stakeholders to engage when developing a BYOD study and considerations from their perspectives

External stakeholders	Requirements for BYOD study design
Participant	• Collaborate with representatives of individuals with condition(s) being studied to ensure outcomes and endpoints represent unmet patient needs. • Assess availability, acceptability, and accessibility of the digital health technology and internet connection. • Provide additional accommodation for health and technology literacy and support. • Address data privacy and security concerns, particularly concerning using the participant's own digital health technology. • Obtain input on the study concept. • Confirm that the study concept (e.g., study app) works as intended when tested by participants using patient group engagement. • Use the end-of-study questionnaires to get feedback and obtain recommendations for improvement.
Caregiver	• Address training and educational needs of those supporting participants with compromised health who require assistance with daily life and management of the digital health technology, including the study app.
Health care providers (e.g., clinicians, primary care physicians, specialists, nurses, technologists, pharmacists)	• Provide study-specific material for the participants' community healthcare providers to ensure they are aware of and support participation in research and recognize that their patients may not get to see the study data collected by their own digital health technology.
Third-party vendors	• **Technology vendor**: Establish a relationship to understand their strategy on obsolescence and end of life (EOL) policies of the digital health technology and software, the planned rollout of new technology versions and software, firmware updates, and compatibility with existing versions. (While not all vendors may be willing to share sensitive market information, most will share critical insights under confidentiality agreements.). • **Application developers**: Design and deploy the study app at scale in required languages and publish in app stores. • **Data analytics vendors**: Manage data capture and storage from the app and connected digital health technologies, requiring managing multiple devices and providing a dashboard for compliance monitoring. • **Technical support**: Depending on the magnitude and complexity of the study, a technical support hotline and call center may be required to provide technical assistance to participants and must be able to troubleshoot multiple BYOD technologies (e.g., multiple smartphone operating systems, different types of connected digital health technologies such as fitness trackers). • **Equipment and logistics**: If provisioned devices are required to supplement the BYOD approach, vendors may be needed to procure and ship additional technology for the study.
Regulators	• Ensure the digital outcome measure and endpoints are relevant. • Assess the appropriateness of data analysis methods utilized by the study team, including strategies that address the added complexities and heterogeneity of BYOD data. • Recognize that BYOD data collected may not represent the population with the condition and may be skewed towards patients with access to technology and openness to using consumer apps or wearables. • Ask: In a study that uses a mix of provisioned and BYOD models, is there evidence supporting the pooling of these two data sources? Moreover, does compliance and missing data vary between the two, impacting the robustness of the findings?
Study sites	If sites are used in the study, they need to be made aware of the additional BYOD requirements and be adequately trained and supported by the study team. In addition, sites need to be familiar with the BYOD selected for the study and trained (often in collaboration with third-party vendors) in the following: • Download and set up the study app on participants' phones. This may require assisting the participant with resetting their Google and Apple passwords. • Understand and verify operating system requirements. • Set up a study app password for authentication. • Monitor compliance dashboard and contact participants in cases of noncompliance. • Be aware that participants may call with concerns about the study app and the collected data. • Provide first-line technical support (using a technical cheat sheet or FAQs provided by the study team) if a technical hotline is not available. • Have details of second and third line technical support if required.
Payers and Health Technology Assessment (HTA)	Determine if BYOD data: • Provides insights into the clinical effectiveness of the intervention under consideration. • Provides insights into the aspects of quality of life and activities of daily living in the real-world. • Is generated in a cost-effective manner.

about the data source, i.e., technology specifications (e.g., model, version, manufacturing date), to inform the data analysis and interpretation. Study teams must define the minimum technological requirements necessary to generate the required digital endpoints, such as the operating system, the model, firmware, and data storage requirements. Once minimum requirements are established, study teams may further restrict the technology type for a more targeted study or proceed with more flexibility and specify analysis sets [16].

Developing Eligibility Criteria

In any protocol, the eligibility criteria define the population of interest [23]. When establishing eligibility criteria for BYOD studies, the potential limitation of BYOD specifications needs to be considered [19].

Eligibility criteria considerations affect the generalizability of the results, may bias the collected sample, and impact inclusion and diversity in clinical studies. Ownership of a specific technology or internet connection, as part of the eligibility criteria, may bias the study cohort towards individuals of higher socioeconomic strata and deter the participation of those with limited access to technology and the internet [25]. Participants may not feel comfortable with the sponsor accessing study data from their technology where their personal information is stored [26]. Technology should never limit study participation. Mitigation strategies that provide these participants with stand-alone technology or internet service promote broader inclusivity [15]. The Critical Path Institute's electronic patient-reported outcome Consortium recommends provisioning devices for participants who do not own the technology required for the study [27]. This helps address gaps due to low socioeconomic status.

Recruitment

BYOD studies could potentially limit participation to those who own digital health technologies; therefore, ensuring that the study sample represents the population of interest is essential. A recruitment plan, even for BYOD studies heavily reliant on technology, should incorporate a variety of methods such as broadcast and clinic advertisements and targeted outreach. Recruiting solely through social media can exclude participants with no or limited access to the internet, such as those living in rural areas and with low socioeconomic status [28, 29]. Participants may own the required technology to enroll in the study (e.g., a smartphone) and may be willing to participate but lack other resources such as reliable internet connection and research awareness. Such practices nurture the digital divide and limit the ability to understand the needs of historically underrepresented communities.

Ethics and Informed Consent

The consent process in BYOD studies includes training that may require face-to-face interaction to explain the study's aim, scope, and risks [30]. In studies deemed as "low risk" (e.g., observational, non-interventional studies collecting nonidentifiable information), online consent could be used [31], depending on local regulations. Procedures must ensure participant and technology user verification (e.g., identity and meeting eligibility criteria), mitigating data privacy and security risks [32]. The process for withdrawing consent and disengaging their technology from the study needs to be straightforward. Study software installation also needs to be simple, responsive, and intuitive. Technologies must comply with local regulations, e.g., the Health Insurance Portability and Accountability Act or the General Data Protection Regulation. Local institutional review boards should be consulted and study protocols approved as necessary [30].

Communications need to be tailored for health and technical literacy. Consent materials should be explicit and appropriate so participants can understand their responsibilities, the study data collected by their technology, the method and duration of data storage, the data usage, privacy and sharing, and how it aligns with the research goals. Participants need to be aware of the importance of not changing their technology during the study without alerting the study team and have information related to technical support should their technology malfunction or have issues with the study application.

Section 3: Outcome, Endpoint, and Technology Selection

Selection of Appropriate Outcomes

Despite the convenience and potential cost savings of a BYOD model, the same approaches used for outcome selection in traditional clinical trials should be applied [23]. Sponsors should select measures that are meaningful to the population being studied [33–35]. The United States Food and Drug Administration (FDA) recognizes that the clinical meaningfulness of digital outcomes can impact regulatory decision-making [36]. It is essential to consider the multiple stakeholders (as in Tables 2, 3), study scope and objectives, and the intended application of the outcomes [23].

Table 4. Key considerations for analyzing data collected by BYOD models

Data consideration	Methodology examples
Confounding factors	Address remaining sources of bias in the data in the statistical modeling whenever possible. E.g., the percentage of missing digital health technology data may correlate with age and socioeconomic status. This is due to the possibility of older/lower SES participants having intermittent Wifi access, resulting in systematic data loss; the different BYOD technologies allowed in the eligibility criteria may not be balanced across study arms.
Variability across the various platforms and devices	(i) Determine the validity and accuracy of the derived digital endpoints across the technologies allowed in the study using either data collected in methodology studies, data provided by the technology manufacturer, or published in the literature as comparators (Section 3). (e.g., using intraclass correlation coefficient, correlation analysis, and Bland-Altman plots). (ii) Consider including information about device specifications (e.g., type of operating system, size, version) and model as confounding factors. (iii) In studies using BYOD and provisioned devices, assess the impact on compliance and data quality, the demographic data of these two cohorts, and their distribution across study arms. (iv) Conduct subgroup analyses when appropriate.
DHT compliance and missing data	(i) Consider that many factors can impact compliance, e.g., compliance can vary by demographics such as age, education, and overall health literacy; by study group; and by the different DHTs allowed in the study (e.g., participants using one type of wearable device that requires bi-weekly charging may wear it more continuously than devices requiring daily charging). (ii) Determine a priori and specify the planned methodology for dealing with missing data and any appropriate data thresholds used for analyses in the statistical analysis plan. E.g., studies on physical activity with actigraphy use concepts of "valid days" and "valid week." Days with 10 or more hours of data are considered "valid." A valid week consists of 5 or more valid days and is included in the analysis [53].
Sensitivity analyses	Investigate the robustness of the findings against analysis choices such as data imputation methods, outlier definitions, and compliance thresholds [48]. Sensitivity analyses may investigate the impact of the different technologies allowed in the study by the eligibility criteria.
Causal relationship or association between the digital endpoints and baseline variables	Assess the causal relationship between the digital endpoints and baseline variables such as patient characteristics, comorbid conditions that can be risk factors, and study arms using randomized controlled trials (e.g., randomization between drug interventions or dosage levels) [75]. The association may also be more commonly evaluated through pragmatic clinical trials (e.g., randomization BYOD vs. non-BYOD or usual care) or real-world evidence studies (e.g., BYOD-related healthcare resource utilization).

Digital Endpoints

Endpoints need to be reliable and accurate, measure the treatment effects, validated against an appropriate reference standard, and assess the population under consideration [37–40]. A fundamental challenge of BYOD models is ensuring the equivalence of digital endpoints captured or derived from different technologies. As discussed below, study teams should rely on published literature or conduct methodology studies in the population of interest to establish differences in endpoints derived from data collected by the different technologies under consideration. Estimating measurement errors and data reliability should also be addressed in the analysis (Table 4).

Technology Selection

Teams should consider the proportion of study participants who may have access to the proposed technology and develop plans to provision technologies to those who have not. The selected technology needs to be "fit for purpose" [41]. Digital health technologies can be used to collect digital measures directly, such as heart rate, [42] and to derive novel endpoints such as resting tremor [43] or scratch and sleep quantification [44]. The selection process is impacted by the sampled data quality, such as the signal-to-noise ratio that impacts the downstream derivation of the endpoints [45], the battery life, which can affect compliance, and the ability to deploy the study app.

Digital health technology selection must consider the analytical and clinical validation of the endpoints, using frameworks such as the V3 framework, encompassing device verification, analytical and clinical validation [38], security practices, data rights and governance, utility, usability, and their economic feasibility [46]. The EVIDENCE (EValuatIng connecteD sENsor teChnologiEs) checklist can be used to support technology performance evaluation [47].

Pretrial feasibility studies to evaluate suitability, establish measurement errors, and test equivalence of different technologies under consideration may be needed [38]. Feasibility studies can be expensive and time-consuming. Secondary data sources such as vendor quality documents and peer-reviewed literature validating the tech-

nologies and establishing data accuracy can be an alternative solution [48]. Published studies and publicly available datasets, preferably combining data from multiple digital health technologies, can be leveraged to compare technologies [46]. Identifying systematic measurement errors and data limitations is crucial for interpreting BYOD study data (e.g., different wristbands can impact the sensor-skin interface and, subsequently, the derived endpoints) [49]. It also informs endpoint-selection and estimates the expected data variability, which helps estimate sample size and develop the analysis plan.

Deliberation is required regarding the data capture capabilities of the technology, including the (a) *type of data output* (e.g., will the device provide raw data, epoch level data, summary data, or endpoint level data?); (b) *the data ingestion and transfer* (e.g., is this enabled via WiFi or Bluetooth, does it need a dedicated mobile hub?); (c) *data storage capacity* (e.g., data generation based on the chosen sampling rate, data storage before data transfer initiation, and memory characteristics); (d) *data security*: appropriate and up-to-date cyber security processes and procedures [46]; (e) *system validation* – this should include computer system validation according to international best practice [50].

Section 4: Data Management and Operations

Compliance

BYOD models have the advantage that participants carry their technology for personal use and regularly interact with it – this can be leveraged to engage participants and provide information and motivation alongside data capture. Different strategies can be deployed to maintain compliance, e.g., alerts via the study application, automated reminders, or direct text messages and phone calls from the study team. Compliance reminders can be incorporated as part of the study intervention to manage adherence to a medication or therapy as successfully deployed across several therapeutic areas, including cardiovascular [51] and respiratory disease [52]. Ongoing data monitoring strategies based on study-specific compliance algorithms can be used to alert study teams to noncompliant participants and help optimize interaction with participants and technical support. As in any study, compliance thresholds, e.g., a "valid" day consists of 10 h of wear time every 24 h [53], must be outlined a priori in the protocol and the statistical analysis plan [54].

Data Capture and Monitoring

Technology and user-related issues may affect data quality in a BYOD study. Connectivity can affect data quality and cause errors in the capture and synchronization of the data [15]. Participants may lose or change their DHTs, or the software may be upgraded during the trial, adding to potential variations in data quality. Incorrect usage (e.g., charging, updating, or non-wear/use) adds to the challenges of adequate data capture and data loss [15]. It is therefore essential to implement an automated and centralized data monitoring system [50].

Data Transmission. In contrast to studies with provisioned technology where data capture falls under the auspices of the study teams who provide sim cards, data plans, and mobile hubs where appropriate, BYOD studies rely on the participants' own connectivity. Internet access required for data transfer may be problematic: participants may have limited data allowance, restricted by their data plan. International travel during the study could impose roaming charges or disabled data plans. Consideration should be given to contingency plans such as data uploads configured to use WiFi as the primary preference to reduce participant costs and mitigate data loss. Reimbursement plans should consider expenses associated with data transmission [26].

Data Heterogeneity. This can arise unexpectedly during the study and must be addressed during data processing and analysis. Causes of data heterogeneity include (1) changes in the software such as upgrades to the operating system and internal signal processing algorithms; (2) variations in the digital health technology: participants may be wearing different versions of the same technology allowed within eligibility criteria that differ in size and wearability characteristics (e.g., different wristbands) which may impact the accuracy of sensors and battery life; and (3) participants may change technologies during the study due to loss, malfunction or for personal reasons. This information needs to be captured by the study application. The study team should determine whether it is appropriate to incorporate this data in the analysis based on their definition of a valid dataset prior to study start as outlined in the statistical analysis plan.

Data Privacy and Security. DHTs may store personally identifiable information and personal health information. These data need to be safeguarded in accordance with local data protection requirements. Study vendors (Table 3) need to provide evidence of how the software (e.g., firmware, cloud, and study apps) influences the functionality, and the data capture is adequately protected and up to date, ensuring the data is secure [46]. The Digital Medicine Society Playbook outlines key data privacy and security considerations [55]. The Clinical Trials

Transformation Initiative provides additional resources that outline approaches for securing data, including encryption, automatic backup, and user authentication [56]. Risk management plans should address data security breaches and potential interference of study tools with other applications on the participant's technology [50]. Before the study starts, investigators should use this information to define how the data will be transmitted, secured, evaluated for completeness, and establish analysis rules to address data heterogeneity [15].

Data Sharing Considerations

Although participants continue to have access to data routinely available from their technology, investigators and sponsors may choose to share study data with participants for transparency or because participants prefer it [57]. If this is deemed appropriate, the study team needs to determine which of the study-specific data (e.g., newly derived digital endpoints) can be shared, including the frequency, timing (e.g., during study participation or at the end of the study), and the mode of communication. The Clinical Trials Transformation Initiative has suggested a decision tree for this purpose [58].

Confounding Variables and Contextual Data

Confounding variables influence results and impact the interpretation of data and study findings. Thus, these variables must be collected and accounted for in the analyses. Specific to BYOD, technology ownership duration (in months/years), and usual wear time (hours/day) can help interpret compliance and other potential sources of bias [59]. Participants' digital literacy may be especially relevant in studies involving active assessment (such as conducting performance tasks via an app) instead of passive monitoring of activity with wearables [60].

Obtaining contextual data (i.e., relevant background information) can further assist in analyzing and interpreting the more heterogeneous BYOD data, e.g., when measuring physical activity, it is helpful to know what may impact participants' daily activity patterns. Contextual variables that can be obtained with minimum burden to participants include employment status (full-time employment vs. retired), periods of vacation time (documented in a participant diary), weekend/weekday, hospitalization, and if their location is known, weather and seasonality data [61]. Concerns for data and personal privacy remain of utmost importance – the collection of contextual data can be made optional to participants and requires the approval of the local ethics board.

Section 5: Statistical Considerations

Sample Size Estimation

Estimating the number of participants required to address the scientific objectives of the study is an essential part of any study design [23]. The study size rationale varies by study type, and corresponding checklists guide sample sizing (Appendix 1). To address the added variability in BYOD studies, one can predetermine the minimum sample size required for subsets of the data to address specific hypotheses (e.g., based on demographics or expected compliance, by technology) in addition to the overall total sample size [48].

Sample size estimation should also account for the expected attrition and noncompliance in technology usage [62], which can significantly impact study size and feasibility of BYOD approaches. Strategies to mitigate dropout rates include: (1) including the participants' perspective in the design of digital tools to optimize usability benefit; (2) incorporating comprehensive participant and site training; (3) having clear audio-visual instructions for every interaction; and (4) offering 24/7 technical support systems to participants and caregivers [63].

Statistical Analysis Considerations

The statistical analysis plan must include (1) detailed information on the derivation and analysis of the digital endpoints; (2) the thresholds and methods used to establish minimally clinically important differences [64, 65]; (3) multiple hypothesis testing; and methodologies to assess the accuracy, sensitivity, and specificity of any predictive models built on DHT data [48]. Specific BYOD data considerations are outlined in Table 4.

Conclusion

Today, a large percentage of the global population possesses the technology to generate health data – 85% of Americans now own a smartphone, and almost one in five regularly uses a fitness tracker [66, 67]. This presents an opportunity to use these technologies to objectively quantify human physiology, behavior, and function in the real world. How we harvest this data with the rigor required for clinical studies requires careful considerations and planning.

The BYOD model provides certain advantages over conventional studies that deploy provisioned devices, including familiarity among trial participants with their own technology such that the technology itself does not function as an intervention and the reduced burden of

carrying additional devices. However, its widespread use is hampered by a lack of commonly accepted methodologies describing critical success factors and an evolving regulatory landscape. Adopting the Agency for Health Research and Quality guidelines [23], we provide the following considerations on five key aspects of the design and deployment of BYOD studies for clinical research.

Early Identification and Engagement with Internal and External Stakeholders

The input from a variety of stakeholders is key to successful technology selection and implementation. We identified internal (cross-functional team members responsible for study design, protocol development, and execution) and external (participants, caregivers, service providers, site personnel) stakeholders needed to provide input and facilitate the operationalization of BYOD models. Participants should be consulted during the study design phase when selecting outcomes, endpoints, and technologies to appropriately address their needs and preferences [68]. Focus groups [69] allow participants to test technologies before deployment and provide an opportunity to collect valuable feedback on the study design and usability of accompanying technology (e.g., study applications). This facilitates the early identification and mitigation of design and operational issues. End-of-study questionnaires that evaluate the participants' experience in the trial can be leveraged to optimize future studies [70].

Study Design Recommendations, Including Informed Consent and Recruitment Strategies

The technology of choice should be appropriate to address study objectives and research questions. The eligibility criteria should include technological requirements to generate the data stipulated in the study objectives. The generalizability of the results should be considered very carefully as it may be impacted by the preselection of participants with access to selected technologies. There can be potential inbuilt bias if recruitment is restricted to the latest technology model. Recruitment and consenting should include various options to engage broad socioeconomic strata in compliance with local regulations. Consideration should be given to digital literacy, health conditions, and education level of participants.

Digital health technology data collected from more diverse populations can reduce bias in pharmaceutical research by making clinical trials accessible to communities that are distant from traditional clinical sites [71]. However, the access to the internet and technology is limited in underrepresented communities [72]. Mitigation strategies, such as provisioned technologies and connectivity enabling approaches, ensure that BYOD studies do not exacerbate the digital divide to the detriment of participants [15]. Transparency regarding study methodology, design, and data limitations is crucial in improving BYOD strategies and advancing all-inclusive research and development.

Outcome, Endpoint, and Technology Selection

BYOD study outcomes and endpoint-selection are governed by the same principles as traditional clinical studies, including selecting appropriate digital health technologies to generate reliable, accurate, and clinically meaningful endpoints. In addition, the technology manufacturer's "end of life" or technology obsolescence strategy needs to be considered to ensure that the technology selected for the study does not restrict the inclusion of particular socioeconomic groups or regions where newer models may not be readily available, or older versions are no longer compatible.

The context of use is a crucial consideration because technologies are not universally optimized and some have been shown to not work as well in certain groups. E.g., the photoplethysmography sensors used to measure oxygen saturation and respiration rate are less reliable on skin types with high pigmentation [73]. Similarly, the accuracy of some wrist-worn devices to accurately measure levels of physical activity in older adults and those reliant on mobility aids have been questioned [74]. Such examples highlight the need to ensure the technology being considered has been validated in the population under consideration.

Data Management and Operations, Including Compliance and Data Monitoring

The BYOD approach needs to account for the specific challenges of data collection, including *data transmission*, which requires increased cooperation of participants; *data heterogeneity* as multiple technologies may be used along with unplanned software upgrades; and protection of personally identifiable information. As in conventional studies, participant compliance needs to be monitored with solutions to intervene if compliance falls below a defined threshold. Teams should determine appropriate strategies for sharing study data with participants.

Statistical Considerations to Align with Regulatory Requirements

The BYOD study's statistical analysis plan should assess potential biases in the study population, variability introduced by deploying more than one type of technology, variability arising from a mixture of BYOD and provi-

sioned technologies, and approaches to account for missing data and conduct fit-for-purpose sensitivity analyses.

In conclusion, this article aims to provide considerations for study design and technical, operational, and statistical considerations to successfully implement BYOD models in clinical research. Questions remain about the feasibility of the BYOD approach, e.g., does it provide the same insights as a provisioned device approach? Can this approach be fully operationalized in a pivotal global study? While the body of evidence does not yet exist, the field of digital health research is rapidly evolving, driven in part by the growing interest in decentralized and hybrid trials. This is exemplified by the declaration by the FDA in its 2021 draft guidance that sponsors should consider the appropriateness of participants' own technology to collect data [30]. We anticipate that future studies will showcase examples of BYOD deployment that help refine the concepts outlined in this paper, document key learnings, and include additional considerations stemming from emerging regulatory guidelines.

Acknowledgments

This publication is a result of collaborative research performed under the auspices of the Digital Medicine Society (DiMe). Special thanks to Jennifer Goldsack, Isaac Rodriguez-Chavez, Benjamin Vandendriessche, Elizabeth L. Kunkoski, and Amir Lahav for their detailed manuscript reviews.

Conflict of Interest Statement

Dr. Charmaine Demanuele and Pirinka Georgiev are employees and shareholders of Pfizer Inc. Dr. Elena Izmailova is an employee of Koneksa Health and may own company stock. Dr. Kelly H. Zou is an employee and shareholder of Viatris Inc. Ms. Marie McCarthy is an employee of Novartis Ireland Ltd. and may own company stock. Dr. Cynthia Lokker, Dr. Emre Sezgin, Dr. Krishna Jhaveri, and Mrs. Cindy Geoghegan have no conflicts of interest to declare. The views expressed are the authors' own and do not necessarily represent those of their employers.

Funding Sources

None of the Authors received funding in the preparation of data or the manuscript.

Author Contributions

Charmaine Demanuele, Pirinka Georgiev, Elena Izmailova, Kelly H. Zou, Marie McCarthy, Cynthia Lokker, Emre Sezgin, Krishna Jhaveri, and Cindy Geoghegan substantially contributed to the conception of this manuscript and played a role in drafting and revising the article. All authors approved the final version for publication.

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