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POSITION PAPER

Leveraging patient-centric sampling for clinical drug development and decentralized clinical trials: Promise to reality

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Abstract

Advances in the technologies to enable patient-centric sampling (PCS) have the potential to improve blood sample collection by enabling clinical trial participants to collect samples via self-collection or with the help of a caregiver in their home. Typically, blood samples to assess pharmacokinetics and pharmacodynamics of a drug during clinical development are collected at a clinical site via venous blood draw. In this position paper by the International Consortium for Innovation and Quality in Pharmaceutical Development (IQ), the potential value PCS can bring to patients, to the clinical datasets generated, and to clinical trial sponsors is discussed, along with considerations for program decision making, bioanalytical

feasibility, operations, and regulatory implications. With an understanding of the value of PCS and considerations when implementing during clinical drug development, we can bring the promise of PCS closer to reality and enable decentralized clinical trials.

INTRODUCTION

As part of drug development, blood samples are often collected from clinical trial participants for assessment of pharmacokinetics (PK) and pharmacodynamics (PD). The current standard practice requires participants to travel to a clinical site to have blood drawn using a needle and vacuum collection device by a healthcare professional. However, a patient-centric sampling (PCS) approach could improve clinical trial participants' experience of how, where, or when samples are collected without compromising the objective of trials and quality of bioanalytical data generated from the collected samples. Sample collection can be considered more patient-centric if it is less invasive, less painful, requires lower blood volume, and/or if the collection could occur remotely (i.e., not at the clinical site, via self-collection by the trial participant, or with the help of a caregiver or at-home nurse). This novel approach has been strongly recommended by patient advocacy groups and encouraged as well by health regulatory authorities.[1–3]

The origins of PCS and microsampling techniques date back to the early 1960s when Dr. Robert Guthrie used dried blood spots (DBS) obtained from heel or finger pricks to measure phenylalanine in newborns for the detection of phenylketonuria.[4] This early application revolutionized screening for metabolic diseases in this vulnerable population. Starting more than a decade ago, the pharmaceutical industry gradually adopted the approach of collecting small volume biological samples (microsampling) in nonclinical studies to reduce animal use.[5] Building on the work done in the nonclinical space, the industry recognized that microsampling techniques, in addition to reduced sample volumes, could have major practical and logistical benefits in clinical studies. When applied to clinical trials, these approaches are now more commonly referred to as PCS. Innovation in sample collection devices continues to address challenges associated with sample collection convenience, sample quality, and patient discomfort. Newer sample collection technologies include devices that allow a patient to self-collect a capillary blood sample from their arm with the push of a button as well as advanced microsampling approaches that can be used with a fingerstick. The utility of these devices has been demonstrated in large-scale phase III clinical trials to quantify drug and biomarker concentrations.[6]

With the disruptions caused by the coronavirus disease 2019 (COVID-19) pandemic, there has been an increased interest in and demand for decentralized clinical trials (DCTs) and PCS approaches.[7] The interest in DCTs extends beyond pandemic responses, as these approaches can be used to shorten clinical trial timelines, improve trial participant recruitment and retention, increase diversity in clinical trials, improve data accuracy, and reduce participant's burden.[8] PCS is an enabling technology for DCTs, as the collection of biological samples is always a critical component of clinical research.[6]

In this position paper, we highlight the value of PCS to patients, to PK/PD datasets, and to clinical trial sponsors. Herein, we discuss approaches for implementation of PCS, including considerations for program decision making, bioanalytical feasibility, operations, and regulatory implications (Figure 1).

VALUE PROPOSITION OF PATIENT-CENTRIC SAMPLING

Value to patient

PCS can improve the clinical trial participant experience. When trials require repeated blood draws, the participant may be required to travel to a clinical site multiple times and/or wait for extended periods for collection of multiple timed samples on a single day. This poses a significant and perhaps underappreciated burden to study participants and caregivers, especially if participants are not geographically co-located with clinical sites. Time away from work, school, and family can also be a significant hurdle for patients' ability to participate in clinical trials. Because many PCS technologies enable remote collection by a person without medical training, PCS could greatly reduce this burden, especially for trial participants in rural locations. As demonstrated during the COVID-19 pandemic, when ~1200 trials were delayed or paused,[9] clinical visits are not only burdensome but may be potentially hazardous for some trial participants. Lowering the burden of participating in a clinical trial may translate not only to greater

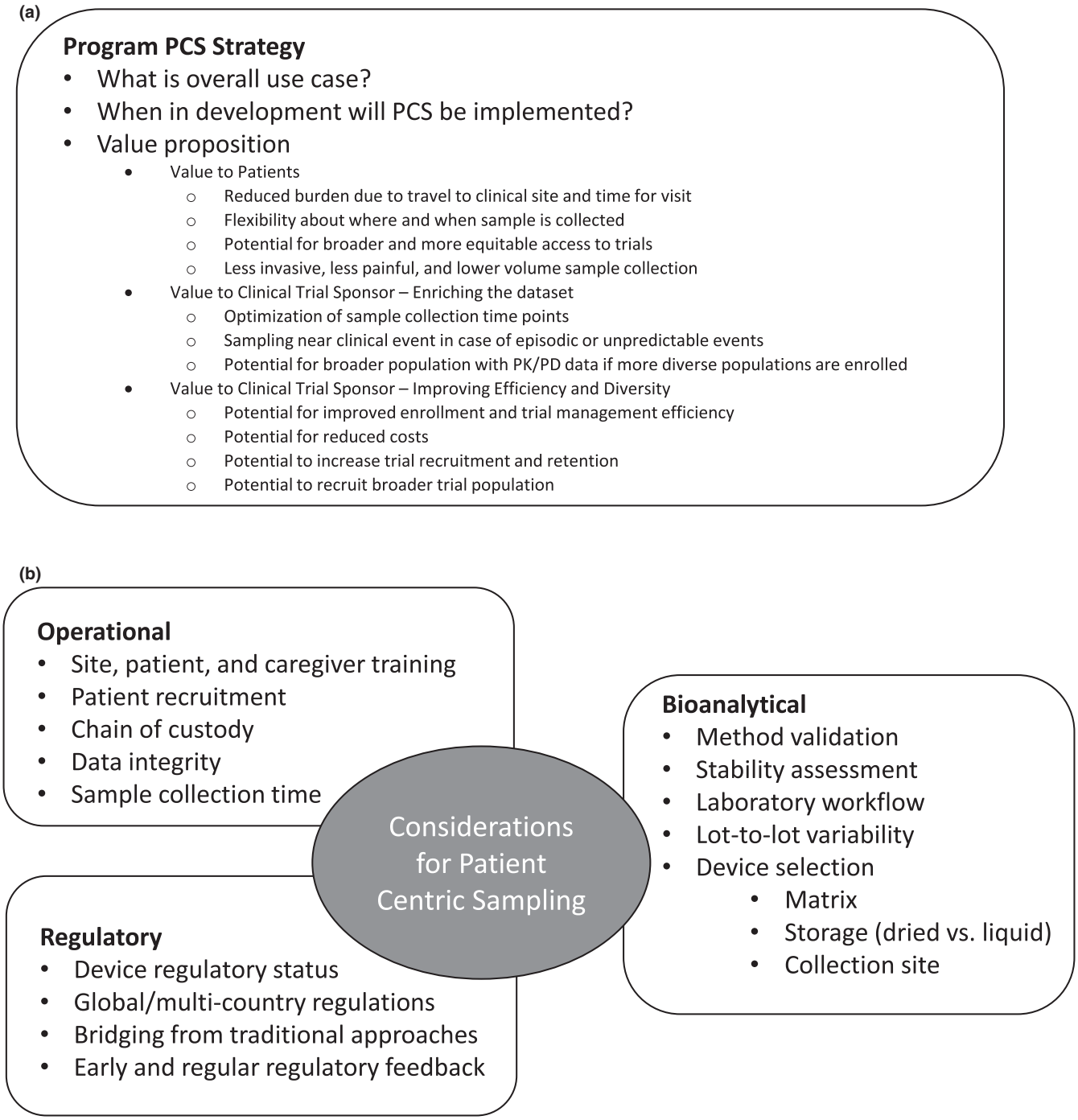

FIGURE 1 Considerations for patient-centric sampling including overall program strategy (a) and operational, regulatory, and bioanalytical considerations that may present challenges (b). PCS, patient-centric sampling; PD, pharmacodynamic; PK, pharmacokinetic

participant satisfaction, but it may also provide broader and more equitable access to investigational treatments in clinical trials.

PCS allows for less invasive and less painful sample collection with lower collection volume.[10] Although not all PCS approaches are less painful than traditional venous blood collection, many PCS devices are less painful due to the size of the microneedles used and location of the sample collection. Surveys of patients have shown that patients prefer at-home sampling over in-clinic venous blood collections[3,11] and patients report less pain with upper arm capillary blood sampling devices compared to venous blood collection.[12,13] Diminished collection volumes result in significant reduction in the total amount of blood drawn per participant. This may be particularly beneficial in clinical trials in vulnerable populations (e.g., pediatrics, anemia, oncology, etc.), and making blood collection less painful is also likely important for participants.

Value to clinical trial sponsor

Enriching the dataset

Depending on the clinical trial design and the drug characteristics, restricting data collection to predefined study visits may result in loss of crucial PK/PD information. PCS can contribute to a more thorough understanding of disease and drug effects through optimization of sample collection timepoints.[1] PCS may particularly be beneficial where optimal PK collection times are not consistent with the timing of clinical visits for other study procedures, and where the number of conventional venous blood samples is limited by the total blood volume, as well as the potential in-clinic patient wait time. For example, PCS may be beneficial for drugs with long half-lives or with sustained release formulations, or to evaluate steady-state or time for drug washout. In addition, the time scale of biological response for biomarker assessments may not coincide with planned clinical visits.

PCS may also provide unique value for collecting data for clinical endpoints that are episodic and unpredictable (e.g., in migraine, asthma, erectile dysfunction, or the occurrence of adverse events). In these cases, gaining insights into PK and PD at the time of a clinical episode is critical in understanding the disease and drug effect. This would not be possible without sampling at the time of a potentially unpredictable clinical episode. For example, in the clinical development of ubrogepant, PCS was used to collect PK samples at the time of spontaneous acute migraine.[14] This enabled enriched exposure-response analysis and therapeutic drug monitoring refinement. PCS involving remote collection expands the window for access to such data. PCS has a significant potential for enriching population PK datasets at a lower burden for the trial participants.

PCS can be further coupled with technologies, such as smart packaging or electronic adherence monitoring to capture time of dosing, as was demonstrated in a phase I trial of healthy participants receiving once-daily sitagliptin.[11]

Improving clinical trial efficiency and diversity

In addition to the benefits to the dataset described previously, there may also be benefits to the clinical trial sponsor, including improved efficiency and cost reductions. Fees associated with staffing, site expenses, and participant travel costs, make the current model of site-based clinical trials costly for clinical trial sponsors. The current model also brings operational inefficiencies, such as loss of data due to participant dropouts, transcription errors, laborious data management and reconciliation, and costs associated with site monitoring. The ability to conduct a clinical trial with either partial or fully remote self-collection of PK/PD and other clinical laboratory data using PCS has multiple potential advantages for clinical trial sponsors. PCS can also increase enrollment efficiency, by using prescreening and reducing the number of subsequent screen failures.[15] Due to widely recognized under-representation of minority groups in clinical trials, increasing diversity has become an area of focus for regulators and sponsors.[16–18] PCS and its application in DCTs can reduce participant burden and improve accessibility and hence may contribute to recruitment of more diverse and broader participant populations,[6] including under-represented racial or ethnic populations, elderly, or disabled participants. From the perspective of clinical operations, PCS has the potential to improve clinical trial recruitment and retention of participants who may otherwise choose not to participate or may have withdrawn early from traditional clinical trials due to the burdensome requirements of time and travel.

IMPLEMENTATION OF PCS

Patient-centric sampling strategy

For the implementation of PCS, a careful strategy needs to be developed by taking into consideration the value it may bring to a development program, to individual clinical trials, and to clinical trial participants. The implementation strategy will need to be built early, likely when assets are transitioning from the nonclinical to the clinical stage. In addition to sample collection devices and procedures, technical, logistical, and operational issues need to be addressed for the conduct of individual trials and sample bioanalysis. Regulatory requirements may relate to both the status of a given device for use in clinical trials and the acceptability of the bioanalytical data generated for drug registration. Additional considerations may include how the data will be used (e.g., for an exploratory study or in a pivotal clinical trial), the need for bridging to demonstrate concordance with data generated from more traditional sampling approaches, and if samples will be collected unobserved or observed by a healthcare professional.

Bridging studies

A bridging or comparative study comparing the PCS approach with an equivalent conventional sampling technique has quickly been established as a regulatory expectation and is frequently reported in publications

of PCS approaches. The need for a bridging study may depend on the planned use case and may also evolve as PCS use becomes more commonplace. Typically, bridging studies are designed to demonstrate the integrity and consistency of data from PCS in a controlled environment prior to implementation in large-scale clinical trials.[19–21] Ideally, the bridging study would have samples collected by both methods at the same timepoints in a similar patient population, so a direct correlation can be drawn. In cases where the techniques are not directly comparable, appropriate correction factors may be used with proper justification (e.g., blood to plasma ratio).[22] If there is a difference in timing of when samples were collected to be compared, a PK modeling approach could be used to adjust for timing and enable comparison. Alternatively, if a bridging study is not feasible due to patient or sample availability, such as for pediatric studies, the bridging study may be performed in a different but relevant population (e.g., healthy subjects or adult patients) prior to applying it to the specific patient population.[23] Once the sampling approach has been successfully demonstrated in a bridging study, and regulatory agencies have provided positive feedback, it may be operationalized for use in a clinical trial as the sole collection method for the investigational analyte of interest.[24]

Use of novel sampling approaches for PCS often raise the question of how to appropriately compare PK/PD data of a drug candidate between different blood matrices (e.g., whole blood or plasma), different collection sites (e.g., peripheral/capillary versus venous blood), different stored matrices (e.g., dried vs. liquid blood), and when samples are collected with novel sampling devices.[19,25] Most of the experiences to date have been on bridging plasma to dried blood, for which various statistical approaches have been described to determine the concordance between blood and plasma data and decide on the sample size needed.[26] The majority of cases can be adequately described by linear models.

BIOANALYTICAL CONSIDERATIONS

Patient-centric sampling devices

Multiple PCS devices are commercially available and in development (Table 1). Choosing the most appropriate device can be dictated by multiple factors, including the specifics of the clinical trial,[6] patient group, matrix, and analyte. For example, a clinical trial in relatively healthy participants may allow a different collection device compared to a pediatric or oncology trial, including differences in sample volume or device size. Operational aspects, such as device availability over the duration of the study in the selected countries, can also be an important consideration.[26]

Bioanalytical method development and validation

PCS approaches have already been demonstrated for small molecule drugs, biologics, and other large molecule drug entities and have enabled collection of samples for mass spectrometry[27,28] and ligand binding methods.[29,30] Use of PCS often involves a new matrix (e.g., dried blood instead of plasma) and the development of a new assay.

Method development and validation experiments need to include the potential for the collection process to impact assay results. Experiments may be needed to understand nonspecific binding, partitioning, hematocrit effect, or sample stability.[31–34] A common example is concentration bias associated with individual hematocrit levels when DBS has been used for PCS.[35–37] By ensuring a controlled volume of blood is analyzed, hematocrit effects can be overcome.[38–40] Regardless of the specific device and assay type chosen, the main goal is to generate reliable results free of bias from PCS approaches.

Regulatory agencies worldwide have established guidelines for validation of bioanalytical methods, and many reference new technologies, such as DBS and other PCS approaches.[41–43] These efforts have been supported by agencies in the recent past. However, evaluations directly related to PCS may be required to validate the robustness and reliability of the data relative to more traditional sample collection approaches. These evaluations can range from studying the consistency of sample collection to the establishment of stability procedures relevant to the sample transport, storage, and processing.[44] With an increasing number of devices becoming available for PCS, validations must be tailored to the device and collection method, rather than solely focused on the traditional evaluations for established matrices, such as plasma or serum. As described in the previous section, use of novel sampling technologies is likely to require a bridging study with clinical samples, for which sponsors should seek regulatory feedback early on.

At-home sampling considerations

A setting away from a clinical trial site, such as a trial participant's home, does not provide the same level of

TABLE 1 Examples of patient-centric sampling devices

Product	Company	FDA 510(k)?	CE marked?	Location of collection	Storage format	Type of collection	Volume of collection
BD Microtainer	BD	Y	Y	Finger prick	Liquid	Whole blood, plasma, serum	Up to 600 µl
Haiim	Winnoz	N	Y	Finger prick	Liquid	Whole blood	150–500 µl
HemaPEN	Trajan	Y	Y	Finger prick	Dried	Whole blood	Four samples of 2.74 µl
HemaXis DB10	DBS System	N	Y	Finger prick	Dried	Whole blood	Four samples of 10 µl
HemaXis DX	DBS System	N	N	Finger prick	Dried	Plasma, serum	Unknown
Mitra	Neoteryx, LLC	Y	Y	Finger prick for blood samples	Dried	Blood, serum, plasma, urine, tears, cerebral spinal fluid, synovial fluid, saliva	Up to 30 µl per tip
qDBS	Capitainer	Y	Y	Finger prick	Dried	Whole blood	Two samples of 10 µl
TAP	YourBio Health	Y	Y	Upper arm	Liquid	Whole blood	100 µl
TAP II	YourBio Health	N	Y	Upper arm	Liquid	Whole blood	Up to 250 µl
Tasso+	Tasso, Inc.	Y	Y	Upper arm	Liquid	Whole blood	Up to 600 µl
Tasso-M20	Tasso, Inc.	Y	Y	Upper arm (adults and adolescent), lower back (babies)	Dried	Whole blood	100 µl
Tasso-SST	Tasso, Inc.	N	N	Upper arm (adults and adolescent), lower back (babies)	Liquid	Whole blood without anticoagulation	Up to 300 µl

Abbreviations: CE, acronym for the French "Conformite Europeenne"; DBS, dried blood spots; FDA, US Food and Drug Administration; PCS, patient-centric sampling.

control or facilities as a clinical site, and the sampling may be performed by a caregiver or the trial participant themselves. Consequently, variables, such as temperature, processing times, and how carefully sampling instructions will be followed, need to be proactively addressed in the method validation, stability assessments, and planning for the sampling including detailed trial participant instructions. In addition to clear instructions for the trial participants, at-home sampling may require patient logs or other data capture methods to record sample collection date and time, and additional procedures to ensure data quality and integrity. Pilot studies with a PCS device prior to implementing PCS in a larger clinical trial may provide valuable experience and indicate additional factors that need to be addressed.

Correct storage and handling of novel PCS devices prior to use may also require additional attention if the devices will be stored in an uncontrolled environment, such as a trial participant's home with high humidity or temperature. For example, exposure to high humidity or temperature might degrade a device prior to use, as could opening a sealed package too far ahead of intended sampling. Parameters for correct use of a novel device will likely be derived from a combination of information from the device manufacturers themselves (e.g., shelf life), and validation work performed by the bioanalytical laboratory using the device for a specific analytical method.

Devices for dried blood collection have particularly been studied due to the potential logistical advantages for this most commonly sampled biofluid. Two areas of particular concern for sample stability are drying times and shipping conditions. Many of the PCS devices available rely on volumetric collection of blood onto a substrate, which is then dried for storage and shipment. However, it has been observed that, in some cases, variation in drying time can significantly impact sample stability, and that a humid environment, insufficient desiccant, or premature sealing of the device in a closed container can lead to sample degradation.[45] In addition, specialty couriers and overnight carriers have historically been relied upon for biological sample shipping to avoid extended shipping times. A truly patient-centric approach, on the other hand, would allow patients the convenience of using their local mail carrier, which typically does not provide a controlled environment or rapid shipment. Temperatures during ambient shipping can become very high, as found in a 2013 study using temperature data loggers in shipments between several US cities where average shipment temperatures mirrored the external temperature (~26°C), but, in some cases, spikes of up to 50°C for 12 h were observed.[46]

Lot-to-lot variation issues for blood collection devices

A number of PCS devices rely on precise collection of a small volume of blood, and lot-to-lot variation of the device can significantly impact results.[35] A common recommendation from device manufacturers and bioanalytical laboratories is to reserve an adequate supply of a single lot of devices to use for method development, validation, and all stability assessments. Similarly, it is recommended to use a single lot of devices for clinical sampling and preparation of standards and quality control (QC) samples during bioanalysis. Whereas lot control may be feasible for small- to medium-sized studies, for large or long-running studies, it may be impractical or impossible given the volume of supplies available and their validated shelf life. One proposed alternative is to deliberately source multiple lots during development and validation, so that lot-to-lot variability is already reflected in the method validation. Regardless of how lot-to-lot variability is handled during development and validation, it is important to track device lots used in clinical sampling to assess any lot-to-lot effects. In many cases, this will be a new or additional process for sites, laboratories, and sponsors.

Laboratory workflow considerations

Many novel PCS devices will deliver samples to the bioanalytical laboratory in an unfamiliar format (e.g., as a dried sample) and with different storage and labeling requirements. Consequently, new processes may be needed to successfully operationalize analysis of such samples. New sample types may need different storage racks or cabinets, additional storage space, and monitored, humidity-controlled room temperature storage. The location and type of label may be incompatible with sample management capabilities, or the labeled device may contain multiple subsamples that need to be relabeled when the device is opened in the laboratory. Novel devices may be incompatible with current automated processes and require time-consuming manual processes to open the device and remove samples; sample extraction and processing for dried samples may also require additional steps compared with common liquid matrices. Creation of calibrators and QC samples in dried sample formats may be challenging and labor intensive, and can require access to significant volumes of control matrices such as fresh whole blood which are more difficult to obtain. One way to circumvent this problem is to test if the cross-validation between wet and dried format is successful, possibly opening the feasibility to

measure dried samples against a calibration curve using easier-to-use liquid calibrators and QC samples. Many innovator companies rely heavily on contract research organizations (CROs) for bioanalytical scale, especially for later stage development studies, but CROs may have limited ability to analyze novel devices and sample formats. Many of these types of challenges existed for liquid matrices but time and innovative thinking have shown that these challenges are not insurmountable.

OPERATIONS

Operational aspects of clinical trials may be underestimated by those who receive biological samples for laboratory analysis. Sample handling procedures (e.g., collection, storage, and shipment) are prescribed in clinical protocols and study manuals and typically carried out by trained professionals, including drawing blood to access plasma or serum for analysis and collecting tissue specimens for pathological examination. PCS is likely to use technical procedures that are different from mainstream sample collection technology and will use different materials and devices, and in addition are frequently conducted in less controlled environments. Training and implementation strategies may need to include procedures for sample time stamps, patient reporting tools, material kits, instructions in various languages, and patient reminders to ensure data integrity and patient compliance.

Supplies

As clinical teams look to operationalize PCS, a strategy for supply of the PCS devices to clinical sites will need to be developed taking account of the availability, maturity, and regulatory status of the device. There may also be regulations for device import and usage that need to be considered for multi-country studies. Furthermore, management of device lots and expiration as described previously will need to be considered, including recording of the device lot numbers used for sampling and tracking of materials sent to clinical sites. Sponsors may need to work with central laboratories or specialty kit vendors to adapt processes and generate sampling kits for the sites, with special attention to kits intended to be used by trial participants or caregivers.

Sample integrity and chain of custody

When samples are collected outside of the usual clinical setting, it can be challenging to ensure appropriate sample integrity, identity, and quality. Sponsors, clinical sites, central laboratories, and CROs need to adapt processes for managing nontraditional sample collections. In large global trials, multiple couriers may be necessary depending on the countries involved in the trial. The ability to monitor the samples during storage and shipping may be required to ensure that samples remain within stability conditions established during assay validation. Technology that monitors temperature and humidity is evolving, as are best practices for implementation. As PCS with remote collection gains greater use, we may see more standardized monitoring practices. Trial participant privacy should also be considered when shipping from remote sample collection sites, including the participant's home; providing shipping materials with an alternative return address may be required to ensure trial participant confidentiality. Finally, labeling of PCS devices or storage containers is critical for ensuring chain of custody, but can be complicated due to sterility concerns when devices cannot be labeled until the time of use. In addition, the shape of some devices may not be compatible with typical label sizes. Appropriate training and clear instructions may be critical to ensure samples are collected and processed correctly.

When sample collection is not performed by trial staff or medical professionals, it may be important for trial sponsors to consider how to ensure a sample is collected from the actual trial participant. Whereas DNA profiling can be and has been used to confirm participant identity in biological specimens, this is unlikely to be implemented broadly due to cost, logistical, and privacy concerns. Another approach may involve facial recognition technologies during sample collection, and similar technology is currently being implemented for adherence monitoring, whereas addressing trial participant privacy concerns. Using eDiary technology for both dose administration and sample collection can be an additional option to improve confidence in data and time recording.

Participant and caregiver training

One benefit of PCS is that trial participant samples can be collected at home. Effective training of trial participants or caregivers is clearly key to success and varying approaches have been taken, including training by clinical site staff, training by PCS specialists from device manufacturers, or provision of visual-audio recordings together with pictorial patient-facing materials and clear written instructions along with well-designed, easy to use sample collection materials. The ability to familiarize potential trial participants in a simple and meaningful way at the screening and consenting steps of the

trial is critical for acceptance of the PCS device by trial participants. Materials need to be available in multiple languages and produced considering trial participants or caretakers with disabilities, such as visual or hearing impairment. Another important consideration is to provide reminders for participants to take their samples, and this may include texts, telephone calls, refrigerator magnets, emails, or e-diary alerts. The final consideration for the participant is to ensure samples are correctly packaged and shipped, and again it is important to have clear instructions and easy to use materials such as prelabeled return packaging in the collection kits.

REGULATORY CONSIDERATIONS

For clinical trials intended to support drug registration application, regulatory considerations may relate both to the status of the PCS device itself and to the acceptability of bioanalytical data generated using PCS methods, as well as associated patient-reported data, such as sample collection time. Both of these considerations need to be addressed prior to study initiation.

Health authorities and independent ethics committees (IECs) or institutional review boards (IRBs) may question the safety of a PCS device which may have different regulatory statuses in each country. In the United States, devices have a class designation of class 1, 2, or 3 based on risk assessments. However, devices can be used for research use only purposes and can be approved through an IEC or IRB. In European Union (EU) countries, a CE mark indicates compliance with health, safety, and environmental protection standards for products sold within the European Economic Area (EEA). This designation can simplify utilization in clinical trials. However, it is best to anticipate potential health authority and IEC/IRB concerns during study initiation activities. Clinical trial sponsors may need to collaborate with device manufacturers to formulate responses to health authority and/or IEC/IRB questions and provide additional documentation around device risk assessments.

Engagement with regulators is important particularly prior to utilization of PCS approaches in pivotal registrational trials. Multiple touchpoints for regulatory feedback may be necessary as a program progresses through clinical development. Feedback can be used to develop bridging studies early in development and to shape the implementation plan for late-stage trials. Questions and company positions regarding the PCS strategy (possibly including data packages and analysis) should be considered and included as teams develop their regulatory strategy and meetings with health authorities are requested.

SUMMARY AND CONCLUSIONS

The industry is experiencing rapid advances in patient-centric approaches to clinical trials, including use of novel sample collection approaches with the potential to significantly enable further innovations in clinical trial conduct. Whereas PCS is becoming more mature, especially from the technical perspective, challenges remain in areas such as laboratory workflows, slow adoption, operational implementation, and internal/external stakeholder acceptance. However, the potential benefits may far outweigh the challenges in realizing the opportunity of these innovations. Therefore, pharmaceutical companies, academia, device manufactures, non-profit organizations, and regulators need to partner more effectively in driving faster and broader change. The COVID-19 pandemic has emphasized the need for novel sampling approaches, provided opportunities for demonstrating the unique value of PCS, and highlighted examples of successful implementations. Multiple member companies of the International Consortium for Innovation and Quality in Pharmaceutical Development (IQ) are exploring and applying this approach in clinical trials with positive outcomes. The front-line adopters will likely play an important role in leading others through sharing of case studies, best practices, and health authority interactions. PCS will be an invaluable component to the overall design of clinical trials of the future as the pharmaceutical industry moves away from traditional clinical trials and toward trials that place the participant needs front and center.

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The authors are all employees of and shareholders in pharmaceutical or diagnostics companies.

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