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DIGITAL CAPABILITIES FOR CLINICAL TRIALS IN AFRICA

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EXECUTIVE SUMMARY

As advancing digital technologies provide capabilities to transform clinical trial operations, their application in emerging regions offers unique opportunities. In mature research environments, adoption of available digital technologies is proceeding gradually as novel approaches are integrated into traditional practice and infrastructure. In emerging regions, the lack of traditional infrastructure offers a more "blank-slate" environment in which to build new digital research models that can be designed and implemented holistically across all trial operations rather than adapted piecemeal into existing models. The efficiencies of such a digital platform could not only expand medical research in underserved populations, but also pilot high-efficiency models to advance clinical trials worldwide. Africa, which hosts only about 0.9 percent of global clinical trials, is an ideal venue for the implementation of "right-by-design" digital trials. This paper presents an operational framework for conducting digital trials in Africa based on applications of existing technologies.

INTRODUCTION

In "Turning the World Upside Down", Baron Crisp, former chief executive of the United Kingdom's National Health Service, argues that "rich countries can learn a great deal about health and health services from poorer ones and that combining the learning from rich and poor countries can give us new insight into how to improve health."[1] Knowledge transfer in clinical drug development has followed the well-worn path from developed countries of North America and Europe to emerging countries. Digital research technologies could well turn the tables, giving emerging regions the opportunity to pioneer novel, high-efficiency operational models for 21st century clinical trials.

The ever-increasing investments of time and cost required for traditional drug development research—estimated to exceed $2 billion per approved product for major pharma companies--are unsustainable.[2] Current efforts to identify and implement more informative, efficient clinical trial methodologies are advancing, enabled by digital technologies that improve data quality and operational efficiency while reducing research costs.

In the 2000s, electronic data capture (EDC) together with Internet connectivity enabled new capabilities as well as efficiency gains. The dramatic growth of health databases and the development of integrated real-time data management platforms now support advances including adaptive trial design, remote and risk-based site monitoring, and the use of simulation to improve trial design and execution.

Drug developers and regulators are currently evaluating the utility of digital technologies in a wide range of clinical trial operations. Social media offers new approaches for patient recruitment. Numerous "remote" and "direct-to-patient" studies are testing Internet-based approaches including patient recruitment and self-enrollment,[3] patient-directed interventions,[4] and remote data collection and monitoring.[5] The recent rise of low-cost, wearable mobile devices to collect health data offers expanded capabilities for real-time, continuous data collection and reporting.

While sponsors gain experience applying and integrating these digital capabilities in the context of traditional clinical trials, emerging regions offer a two-fold opportunity: 1) to develop digital clinical trial platforms, encompassing all study operations, in a blank-slate environment that enables a "right-by-design" approach; and 2) to expand clinical research in underserved populations where lack of infrastructure has made traditional research models unfeasible.

PPD, a recognized technology leader, is advancing digital technology applications through its pioneering real-time data management platform. This paper presents a collaborative view of an operational framework for the conduct of digital trials in Africa using proven technologies that are available on the market today.

THE OPPORTUNITY IN AFRICA

The globalization of clinical trials has increased dramatically during the 2000s, driven by the need to access study patients, accelerate research timelines and address burdens of global disease. By 2008, emerging nations including China, India and Korea, hosted nearly 30 percent of global trials compared to 15 percent in 2000.[6] The first wave of this growth in clinical research has been supported by the expansion of emerging economies, greater investment in health care and growing markets for pharmaceutical products—a virtuous circle that invites research and delivers therapeutic innovation. The second wave, now poised to expand clinical trials in Africa, is driven by the rise of non-communicable diseases in the undeveloped world.

Africa is home to roughly 15 percent of the world's population, but hosts only an estimated 0.9 percent of global clinical trials.[7] Historically, Africa's lack of medical

and research infrastructure has made clinical trials cost prohibitive. But Africa's research landscape is changing, due both to economic development and the rise of diseases more typical of the developed world.

Africa's population of 1.1 billion is projected to rise to 2.4 billion by 2050.[8] Non-communicable diseases including cancer, diabetes, hypertension and cardiovascular diseases are projected to account for 65 percent of mortality in Africa by 2020.[9] The demand for novel therapeutics to treat chronic diseases is increasing just as the region's economic growth is accelerating.

Stronger economies. Africa is expected to join the world's fast-growing economies over the next 20 years, with GDP rising from $2.4 trillion in 2013 to $3.3 trillion in 2020. According to a 2015 McKinsey report, Africa's pharmaceutical market, valued at $20.8 billion in 2013, will be worth as much as $60 billion by 2020.[10] Robust markets for chronic disease therapies can be anticipated in view of innovative economic collaborations like the GAVI Alliance, which has introduced more than 140 immunization programs across Africa, helped to develop sustainable markets and catalyzed a renaissance in the global vaccine industry.[11],[12]

Expanding research capabilities.
The pharmaceutical industry's investment in African research has focused almost exclusively on HIV, tuberculosis and malaria. Africa's rising incidence of non-communicable diseases underscores the importance of expanding African-based clinical research. There continues to be a compelling need to innovate therapies for infectious and parasitic diseases for African populations. Factors including immigration and climate change also make these diseases—and new ones like Ebola—significant threats to global health. The pharmaceutical industry has an important opportunity to advance scientific knowledge and global health by expanding clinical research in Africa.

Africa's research capabilities and infrastructure are expanding through collaborations like The World Health Organization's Special Programme for Research and Training in Tropical Diseases (TDR) and the European and Developing Countries Clinical Trials Partnership (EDCTP). EDCTP was created in 2003 to develop capabilities for Phase II/III trials in sub-Saharan Africa. A 2007 EDCTP report identified qualified clinical sites in 19 countries with expertise and equipment to conduct trials in TB, malaria and HIV.[13] Developing capabilities now sustain studies like Wyeth's 2009 river blindness trial in Ghana, Liberia and Democratic Republic of Congo,[14] and a decade-long TB trial published in 2014 that was co-sponsored by TDR and involved 1,800 patients across five countries.[15]

As expertise and qualified study sites increase, the implementation of digital clinical trial platforms has the potential to create a fully capable clinical research environment in Africa, while at the same time, piloting novel trial methodologies for worldwide application.

DIGITAL-BASED TRIALS IN AFRICA: CONSIDERATIONS AND OBJECTIVES

Africa offers more of a "blank-slate" type of environment that has important advantages for advancing digital research methodologies. Integrating novel digital approaches into traditional study designs faces daunting challenges in mature research settings. In Africa, research sites have little legacy environment in terms of research technologies and processes to accommodate. Rather than integrating digital approaches with existing systems, remote data-driven approaches can be designed across study operations and tailored to specific regional environments and research objectives.

Taking such a right-by-design approach, PPD technology experts undertook, as a first step, the review of available digital technologies to propose an operational framework that could support African-based studies across clinical trial operations, from site initiation and patient enrollment

through study conduct, data collection and site closeout.

In conceptualizing such a platform, three fundamental requirements must be considered:

+ Regulatory acceptance and strict compliance with ethical regulations and quality guidelines for digital approaches and technologies.
+ Availability of cost-effective digital technologies and devices capable of supporting clinical research operations conducted across study sponsors, collaborating service providers and investigative sites.
+ Digital infrastructure requirements, primarily reliable electrical power and Internet connectivity.

THE REGULATORY ENVIRONMENT: USE OF DIGITAL TECHNOLOGIES

Regulatory acceptance of digital technologies is encouraging implementation of digital trials, although formal regulatory guidance often lags the rapidly advancing digital capabilities. Recent regulations and standards support the use and wider adoption of digital technologies for data collection in clinical trials. These include the U.S. Food and Drug Administration's (FDA) 2013 guidance on the use of electronic source (eSource) data[16]; standards for eSource data defined by the Clinical Data Interchange Standards Consortium (CDISC)[17]; and the European Medicines Agency's (EMA) 2010 reflection paper on eSource data and EDC tools.[18]

One of the important considerations for use in a digital trial platform is the regulatory definition of a medical device. The recent and rapid introduction of mobile monitors and sensors poses questions regarding the regulatory acceptance of these technologies for use in clinical trial data collection. The FDA and EMA may or may not categorize such a mobile health (mHealth) technology as a "medical device" patient to regulatory review and approval. In 2014, FDA issued a draft guidance on its intention to exempt certain medical devices from premarket notification requirements[19]; further clarification is provided in the 2015 guidance on mobile medical applications.[20]

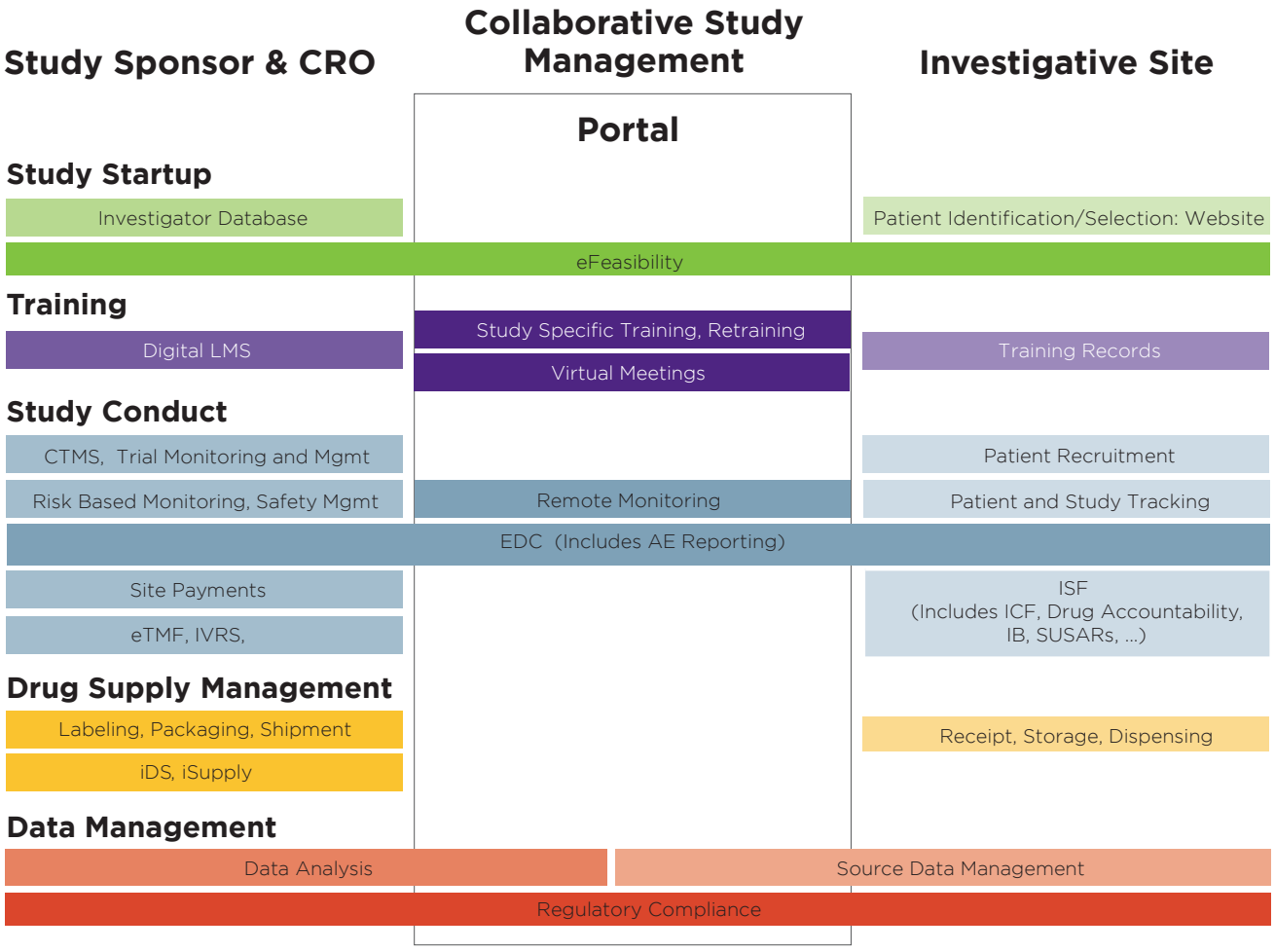
Africa's emerging regulatory environment varies country by country. In practice, sponsors conduct studies in compliance with FDA, EMA and global International Conference on Harmonization (ICH) standards[21] for research ethics and good clinical practice (GCP) and can look to these for evolving guidance on use of digital methodologies and eSource data. Standards specifically pertaining to Africa are taking shape. For example, the Swiss Tropical and Public Health Institute (Swiss TPH) has developed TRREE, a website that provides ethical guidelines, training and access to free distance learning programs and resources to support studies conducted in Africa.[22] The Pan African Clinical Trials Registry (PACTR) is building a platform to register trials and improve transparency.[23]

DEFINING A FRAMEWORK OF DIGITAL TECHNOLOGY CAPABILITIES

A constellation of digital technologies and devices must be integrated to collect and manage trial data and site operations. The availability and utility of existing technologies support the objective of designing a digital trial platform suited to research in African settings.

Figure 1 presents a framework of digital trial capabilities currently in use to conduct research operations in three spheres: operations conducted by the sponsor; operations conducted in collaboration with technology and service providers, primarily contract research organizations (CRO); and operations conducted by investigative sites. Across these spheres of responsibility, digital technologies enable pre-trial intelligence (study feasibility and identification/ recruitment of investigator sites); training for site personnel; study management; document management; drug supply management; and data management.

Figure 1. Digital Capabilities Framework for Clinical Trials
In the following sections we will discuss these digital capabilities as they apply to clinical studies conducted in Africa.



DIGITAL INFRASTRUCTURE REQUIREMENTS: ELECTRICITY AND INTERNET ACCESS

To support the digital capabilities described in this proposed framework, the sites conducting study operations must have access to essential infrastructure: electrical power and network Internet connectivity; physical security to protect study materials and data; and the ability to control access to essential study data.

Figure 2 details these infrastructure requirements as they pertain to three sites of study operations suitable for clinical trial conduct in African settings: the central study office; the study field offices; and field operations.

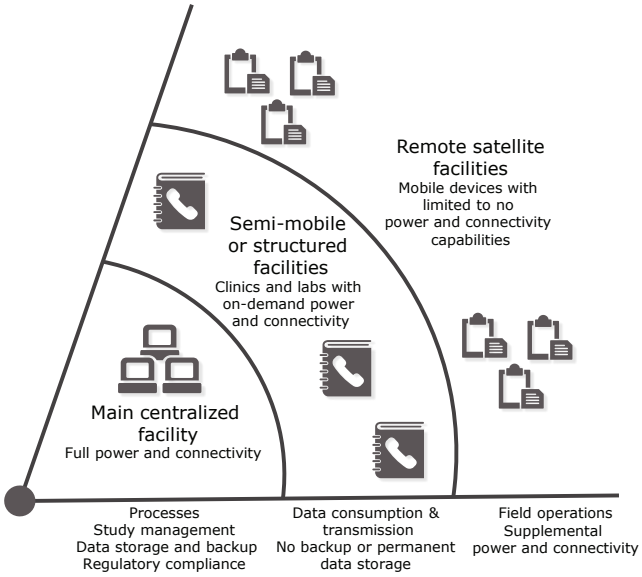
+ *Central Study Office:* Central location at the investigative site responsible for study coordination. For example, a project office at a university teaching hospital.
+ *Study Field Offices:* Locations where a subset of trial activities is conducted for multiple study patients. Examples include: a central laboratory conducting biomedical assessments; an imaging room using imaging devices; a primary health clinic that supports longer term patient treatment and follow-up. Field offices may be in the same building or campus as the central study office, or in remote locations.
+ *Field Operations:* Locations where a small subset of study tasks is performed for a small set of patients. Examples include: an individual patient responding to a survey or measuring vital signs in the home; or a community health worker collecting data during a visit to a study patient.

Figure 2. Electricity and Internet Requirements by Sites of Study Operation

Location	Electricity	Network Connectivity	Security
Central study office	Need continuous power ensured by backup power supply to avoid loss of critical documents or data due to power loss.	Need continuous, reliable Internet access to support transmission of a significant volume of data and documents between Central Study Office and sponsor.	Need physical security (locked office, locked cabinet, access management) to prevent loss or theft of digital equipment containing essential study data.
Study field offices	Need regular power; intermittent power access may be acceptable. Study equipment used at this location (imaging, lab) may require power backup.	Need access to regular but not necessarily continuous power. Intermittent power may be acceptable for regular transfer of primary study data.	Need physical security (locked office, locked cabinet, access management) to prevent loss or theft of digital equipment that may contain essential study data.
Field operations	Need at least daily access to electricity for charging mobile devices.	Need at least daily access to mobile network for transfer of study data.	Implement access management to control access essential study data.

It is important to note that different levels of infrastructure are required for different operational sites. Only the central office, at the highest level, is required to have continuous access to power and connectivity. For field offices and field operations, daily but intermittent access is sufficient to support study tasks. Figure 3 illustrates relative infrastructure requirements.

Figure 3. Relative Infrastructure Requirements



DIGITAL CAPABILITIES FOR PRE-TRIAL INTELLIGENCE

To be selected to participate in clinical trials, African investigational sites need to be identifiable by sponsors seeking sites with the necessary capabilities and interest. In the search for and pre-qualification of investigative sites, sponsors typically look for the following information:

+ *Access to patient population:* To what extent the investigative site has access to the population that is targeted in the study.
+ *Qualifications of principle investigators*: Their training and clinical and research experience.
+ *Staff availability:* Training and qualifications of staff able to conduct study procedures.
+ *Facilities and infrastructure:* Capabilities to support specific study procedures, such as laboratory facilities, imaging equipment or biosample shipment. Availability of general facilities for clinical examination, resuscitation and space for monitoring visits.
+ *Drug supply management capabilities:* Special attention is given to assessments of facilities to support storage, management and dispensing of medicinal products.
+ *Electricity and Internet connectivity:* Systems in use at the site that can provide electricity, Internet connectivity, and document and data storage.
+ *Regulatory experience:* Knowledge and experience with local regulatory processes, especially interactions with institutional review boards (IRB) and knowledge regarding their usual response timelines.

Digital resources support both development of effective site profiles and their publication for easy access by sponsors. Guidance is available to African sites interested in developing site profiles, for example, at Forte Research.[24] Sites can review examples of site profiles at INDEPTH Network, a global network of health and demographic surveillance systems that supports development of research capabilities.[25] Site profiles can be published online using a website such as CenterWatch.[26] Another option is to use third parties that facilitate collaborations between investigative sites and study sponsors. These include the Malaria Clinical Trials Alliance,[27] the Global Health Network Site Finder [28] and TB research databases like the Working Group on New TB Drugs.[29]

DIGITAL CAPABILITIES FOR TRAINING

There is an important need to build research capabilities and expertise at research sites in Africa in order to increase participation in clinical research and to gain more rapid access to innovative treatment for the changing health needs of local populations. Novel digital methodologies offer important opportunities to assist in building human capabilities through powerful new learning techniques.

Chief among these is the concept of mobile learning, or mLearning, which focuses on providing education through mobile devices. This allows for distance learning at the time and in the context of ongoing activities. For example, if eSource tablets are being used to capture data for trial activities, that same tablet can deliver focused refresher training on that specific study activity—a "visit manual" for the clinical trial delivered through the same device used to record data on trial visits. Such mLearning does not replace traditional classroom training. Instead, it provides continuing training and amplifies the impact of classroom learning.

Clinical trial mLearning technologies are available, but not yet commonplace. Because they are relatively costly, they typically are considered for larger, more complex study protocols. More mature digital capabilities are commonly available to support computer-based training and "virtual classroom training." Digital tools also are available to manage and track compliance with mandatory training curricula through learning management systems. Standards for developing training content, such as SCORM (Shareable Content Object Reference Model), facilitate delivery of content through various digital channels and devices.

As these technologies evolve, it is important to assess the opportunity of using existing digital learning capabilities to support and enhance training for clinical trials in Africa—as a complement to and to increase the impact of traditional classroom training.

DIGITAL CAPABILITIES TO MANAGE STUDY ENROLLMENT AND PROGRESS

Over the past decade, a significant investment has been made in Africa to deploy broad networks of community health workers (CHW) to provide health services in underserved communities. The CHW network continues to grow. In the context of conducting clinical trials, these networks can contribute to community-based screening, as well as to strong patient adherence to clinical study protocols and patient retention in trials.

For example, the Kombewa Health and Demographic Surveillance System (HDSS) employed an existing network of community health workers, equipped with mobile devices used for surveillance to conduct a Phase III randomized controlled trial of a malaria vaccine in Kenya. Retention rates for pediatric therapeutic and vaccine trials supported by the HDSS platform have ranged from 90-100 percent in trials lasting as long as four years.[30] The Kombewa HDSS study demonstrates both the feasibility and value of implementing digital approaches in Africa-based trials.

DIGITAL CAPABILITIES TO MANAGE STUDY DATA

Data collection and management is subject to strict rules and regulations aimed at ensuring the highest level of data quality and reliability in clinical trials. The system by which data are first captured, whether it is paper or electronic, is called the "source system." It is essential that source data are under sole control ("sphere of influence") of the investigator and not the study sponsor. The sponsor does have both a right and obligation to monitor source data to ensure the study is being conducted in compliance with GCP, which includes source data verification.

Data are then transcribed, manually or electronically, from the source system into the case report form (CRF), which can be either paper or electronic (eCRF). The process

of transcribing data from the source to CRF must be validated to ensure that no errors are introduced. Source data verification, in which monitors compare source to CRF data, is part of this validation process.

There are special requirements pertaining to source systems. Regulatory inspectors must have the ability to retrace submitted data back to its source for multiple years after study completion. In practice, this means that a system must meet a number of strict functional requirements (audit trail, electronic signature, signature invalidated when data are updated, etc.) and operational requirements (password management, backup, physical security, etc.).

It would be unrealistic to expect that many research partners in Africa use electronic systems that meet these requirements. In absence of such systems, the only alternatives are the use of paper or eSource solutions.

These eSource solutions offer—quite literally—paper forms that sit on handheld tablets and meet all the requirements of a source system for clinical trials. Like a paper form, eSource tablets can be used by the investigative site to record source data. But unlike paper forms, subsequent transcription of the data to the sponsor's data management system is automated and validated.

In addition, eSource solutions provide many additional benefits for sponsors, investigative sites, regulators and study patients, including:

+ **Data quality.** Like the paper form, the eSource form is under the investigative site's sphere of influence. Investigators always have access to enter, edit or annotate source data. Data edits are recorded in an audit trail and confirmed with an electronic signature. Unlike paper forms, eSource forms also can implement "edit checks" at the source, that is, when data are being captured. This means that data can be checked for validity and consistency as it is being entered. For example, vital signs can be checked to be sure they are within the inclusion ranges of the study protocol. Implementing edit checks at the source can save considerable amounts of overhead. Data inconsistencies that are not captured by an edit check and discovered after the fact must be addressed through a data query using data clarification forms—a time-consuming process that puts a strain on both the study team and investigative sites, and often leads to delays in locking of the study database.

+ **Timely data access.** When using paper source forms, it is common practice to first assemble multiple paper forms from multiple study visits over a period of time, and then enter all simultaneously into the sponsor's EDC system. This can reduce the overhead of managing data for investigative sites, but it also may delay time between data collection and data availability to the sponsor by several weeks or more. When using eSource, source data is captured electronically, submitted by the investigator and automatically transmitted to the sponsor's data management system, giving the sponsor access to the data in real time. Real-time data access enhances the sponsor's ability to analyze and respond data. It also supports the implementation of adaptive trials and improves operations aimed at overseeing patient safety.

+ **Remote and risk-based monitoring.** Source data verification (SDV), an essential task in study monitoring, verifies source data against data submitted to the sponsor and ensures investigative sites are following appropriate procedures, such as adverse event reporting. If a paper source is used, study monitors are required to visit investigative sites to conduct SDV in person. If eSource is used, monitors can review source data and conduct monitoring tasks remotely, reducing the number of onsite visits. Results from eSource monitoring activities flow electronically into the risk-based monitoring system, which determines the level of monitoring oversight for each investigative site participating in the study. Use of eSource streamlines monitoring functions, making onsite visits more efficient and facilitating higher quality work while reducing levels of onsite monitoring.

In our experience, many investigative sites are very enthusiastic about using eSource in clinical trials because it helps reduce overhead by, quite literally, reducing paperwork. Making the electronic forms available on handheld devices allows data capture at the source, anytime and anywhere data is generated—at the bed side, in the lab, during clinical consultation. The only time investigative sites are less enthusiastic about eSource is when the use of these devices conflicts with or duplicates their internal source systems and data entry procedures. In Africa, where there are few or no options for using local systems to capture source data electronically, we believe eSource can drive important efficiencies in the overall study process, presenting a special need and opportunity to deploy these innovative eSource systems.

DIGITAL CAPABILITIES TO MANAGE STUDY DOCUMENTS

Investigative sites exchange a large number of documents with study sponsors during clinical trial preparation, study conduct and site closeout. Many of these documents must be archived for long periods—typically 15 years after study completion—to provide documentary evidence that the study was conducted in compliance with ICH-GCP guidelines.

The "essential documents" list, which cites the documents that should be collected, at minimum, during a clinical trial, is defined by ICH.[31] Many of these documents are provided by the study sponsor, including the Investigator's Brochure, the Clinical Study Protocol and Monitoring Visit Reports. Other documents are provided by the investigative site, including the investigator resume, documented approval of the local IRB and Independent Ethics Committee (IEC) and applicable medical, technical or laboratory procedures.

Both sponsor and investigative sites must collect and retain study documents. The documents that must be retained by the sponsor are collected in the trial master file (TMF), while those that must be retained by the investigator are part of the investigator site file (ISF).

Some documents also require collecting evidence, or in this case acknowledgment, that the document has been received and contents have been understood. Such evidence is required, for example, when the sponsor shares with investigative sites documents that contain important information about the potential safety events related to the study protocol. Examples of these documents include updates to the investigator's brochure, or notifications of suspected unexpected serious adverse reactions (SUSAR).

There are many benefits to exchanging these documents electronically at the following times:

+ **During study startup.** Study startup involves exchange of a large number and wide variety of documents that must be reviewed and signed by multiple parties, posing challenges for tracking the status of individual documents. Typically, paper documents travel by couriers and their status is tracked in spreadsheets. When exchanging and signing documents electronically, the exchange is near real time and status can be tracked in automatically generated dashboards. Sites only may be initiated, and patients only may be screened for enrollment, once all essential documents for study startup have been exchanged and properly signed and executed. Electronic document exchange can help to prevent issues that may delay site initiation and patient recruitment.

+ **During study execution.** The study monitors need to regularly review source documents to ensure the study is being executed in compliance with ICH-GCP guidelines. As with the use of eSource data, the use of electronic source documents allows monitors to conduct more monitoring activities remotely. Higher quality management of source documents also can support reduced levels of monitoring oversight and drive further efficiencies in study management.

+ **During study closeout.** At the end of the study, a large number of study documents must be completed, signed and filed. As with study startup, exchanging these documents electronically may

greatly reduce the overhead and timelines associated with study closeout activities.

Digital solutions for document exchange in clinical trials have rapidly matured in the last 10 years, and reliable, compliant, proven solutions are available to support these capabilities. For investigative sites that lack local capabilities for document storage, these solutions also may support long-term archiving of the ISF.

Beyond the operational benefits and availability of digital solutions for document exchange, there is also a particular need for such technologies in the context of running clinical trials in Africa. The alternative—the exchange of paper documents by courier—not only may cause considerable costs to the study, but exchanging documents across countries and continents may result in unexpected and lengthy delays.

DIGITAL CAPABILITIES TO CONDUCT INFORMED CONSENT

Informed consent, a cornerstone of ethical research practice, poses special challenges for clinical trials conducted in Africa. Experience has shown that clinical standards and processes created based on the values of developed regions may not always be appropriate for African studies where research concepts are unfamiliar and often approached with caution. Reviews of study patients' understanding of informed consent information are driving clinical researchers to find new ways both to inform and consent study patients in Africa and other less developed regions of the world.[32]

The FDA's 2015 draft guidance, "Use of Electronic Informed Consent in Clinical Investigations," stipulates that informed consent includes providing potential patients adequate information about the study to allow an informed decision about participating and must include a "process that facilitates the patient's comprehension of the information …"; the use of electronic informed consent (eIC) must comply with regulations set in 21 CFR parts 11, 50 and 56 pertaining to electronic records, electronic signatures and informed consent practice.[32]

In consideration of the use of eIC in African-based studies, it is important to distinguish the two components of informed consent: informing the potential patient about the study; and obtaining the patient's consent to participate.

Informing the patient. The research environment in Africa poses a number of challenges surrounding informed consent, including low levels of literacy and education in general, lack of understanding about the clinical trial process, and, in many cases, lack of strong supporting relationships between study investigators and patients. Informed consent practice must ensure that patients understand key research concepts, their rights as research patients and the requirements for participation in the study.

To expand clinical research in Africa, it is essential for clinical researchers not only to develop appropriate tools that can adequately inform study participants, but also to measure informed consent comprehension. There is a critical need to standardize and simplify administration of informed consent—especially as it regards informing the patient—to ensure safety and ethical practice in African settings where cultural attitudes may influence patients to comply with authority rather than to weigh information and decide independently.

New technologies promise to play an important role in overcoming literacy and language barriers to improve informed consent practice. Electronic media offer new, effective ways to inform patient by targeting the auditory as well as visual learner to deliver information on study risks and benefits and the patient's rights—such as the right to withdraw from the study at any time. Electronic media offer the flexibility to customize educational content for a given study population, and to integrate comprehension criteria by using various types of delivery, design and languages to accommodate the age, ethnicity, nationality and other characteristics.

Obtaining consent. Just as necessary as informing the patient is the need to effectively support the administration, completion, collection and management of the informed consent process in compliance with FDA (21 CFR part 11)

and other regulatory standards. Management of the process and informed consent forms (ICF) is complex and prone to error, as evidenced by the fact that ICFs are a common subject of audit findings.

Electronic management of informed consent offers the potential for reduced error and greater efficiency. The use of mobile tablet applications represents the most promising opportunity to streamline and standardize the patient education and consent process while maintaining regulatory compliance. Mobile tablet applications supporting electronic ICFs may include benefits such as biometric or facial-recognition identification and signature. These functions may be influenced by local legislation and regulations. For instance, while ICH-GCP requires a "valid signature" on the ICF, local authorities determine what a "valid signature" is. For an effective eICF application, it is preferable to use role-based electronic and digital signatures and include robust form-field validation to ensure accurate completion of each IRB/IEC approved consent in any language in any country.

The eICF application also must report on the progress of each consent by version, subject, site, IRB/IEC, region, study and across studies in a completely paperless environment. Sites or monitors may elect to have consents emailed or, as is most likely in Africa, printed and handed to the patient. Centralized authoring and administration features eliminate the version control problems that are frequently experienced with paper-based processes. Verifying patients' comprehension of the expectations for their participation in the study helps to improve overall retention rates.

The decision to use electronic consent must be weighed in light of the eIC's potential benefits in meeting the challenges of informed consent practice. Particularly in the context of conducting trials in Africa, there is an important need to exploit the capabilities of advanced digital technologies to properly inform study patients about the study, participation requirements and the rights of study patients.

The benefits of electronic consent can outweigh the cost, connection challenges and logistics it requires—especially when the study involves research-naïve and possibly illiterate patients. Lack of compliance with informed consent processes accounts for some of today's most common audit findings. The use of eIC offers an important opportunity to avoid common pitfalls and conduct informed consent with optimal effectiveness and efficiency. Various eICF technology solutions should be considered, especially when a study is being conducted using a standardized, flexible delivery platform that improves the informing function as well as complying with regulatory requirements. Implementation costs can be partially offset by using the same digital infrastructure and devices that are used to collect study data. Efficiencies are improved through capabilities including electronic processing and monitoring of ICF documents.

DIGITAL CAPABILITIES TO MANAGE DRUG SUPPLY

Regarding opportunities for clinical trials in Africa, consideration should be given to the operational challenges facing pharmaceutical companies and CROs surrounding drug supply, management and reporting. African countries vary greatly in research capabilities and infrastructure. Many lack developed regulatory requirements governing drug management and the associated supply lines to meet the needs of clinical trials. Drastically different challenges in drug management are likely to be encountered, from cultural differences to varying import regulations. These include infrastructure limitations outside of major cities and lack of familiarity with technology to support drug management, as well as cultural and import regulations of drugs.

As drug supply and management operations are designed for African studies, identification of the differences between legislative requirements and study requirements is a priority. Sponsors and CROs must consider what is absolutely necessary to successfully manage the supply of drugs through the life cycle of the trial and adopt flexible, process-driven solutions supported by simple but effective technologies.

CONCLUSION

The operational framework proposed here for conducting digital-based clinical trials in Africa is intended as a starting point toward two important goals: expanding drug development research in Africa; and piloting digital technologies in Africa to accelerate their adoption and advance clinical trial methodologies worldwide. The technologies detailed in this paper are available now. Their utility and benefits have been demonstrated, and they are being used in clinical trials to improve research processes, including data collection and management, safety monitoring and informed consent.

Wide adoption of these technologies has been lagging due to legacy research systems and technologies in place in the mature research environments of North America and Europe. In Africa, where there are few legacy systems to impede implementation of new approaches, pharmaceutical sponsors and CROs can build digital research platforms that are "right by design" and then apply what they learn to speed applications in mature research venues. It is time to seize this enormous opportunity in Africa to turn the traditional clinical research world upside down. Let Africa be the springboard to pilot digital technologies for advanced clinical trials worldwide, and at the same time expand clinical research to meet the needs of Africa's underserved population.

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David Blackman is Business Innovation Director at PPD, where he has responsibility for aligning business needs with PPD innovation strategies. He is responsible for creating and developing differentiating business capabilities for PPD, together with its partners and clients, to accelerate clinical trial research. A graduate of the University of Johannesburg in South Africa, he combines his more than 20 years of technological experience in development, process and technology innovations with his commitment to implementing cutting-edge technologies in Africa as a platform to advance innovative technology solutions in clinical trials worldwide. He holds two patents and two patent applications for technology innovations.

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