BEYOND COVID-19: MODERNIZING CLINICAL TRIAL CONDUCT

TransCelerate BIOPHARMA INC.
ACCELERATING THE DEVELOPMENT OF NEW MEDICINES

ABSTRACT

The COVID-19 pandemic required swift implementation of innovative solutions to protect participant safety and enable clinical trial continuity. The pandemic catalyzed the expansion and acceleration of existing continuity solutions as well as the establishment of new ones. These continuity solutions should be extended beyond the pandemic to retain the benefits for participants and modernize clinical trials. This white paper describes the broad categories of continuity solutions utilized, the challenges related to their use, and the factors that made implementation successful. Also presented are the opportunities and justification for further implementation and normalized use of continuity solutions in the post-pandemic world. Utilizing these solutions can enable better clinical trial conduct without compromising participant safety or the integrity of clinical trial data for all therapeutic agents under development. TransCelerate attributes regulatory flexibility as one of the most important factors enabling success of clinical trial continuity solutions and will work with industry stakeholders to ensure their ongoing use where appropriate.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a newly recognized infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Zhou et al, 2020). The outbreak started at the end of 2019 and quickly spread across the world. On 30 Jan 2020, the pandemic was declared a Public Health Emergency of International Concern by the World Health Organization (WHO). Since then, COVID-19 cases and deaths have skyrocketed worldwide even as the pandemic's epicenters have moved geographically, most notably from China to Europe to the Americas, other parts of Asia (Middle Eastern countries and India), and Africa. Counter measures consist of shutdowns, lockdowns, and stay at home orders to keep people at home as much as possible. Facial masks and social distancing, including avoiding crowds, working from home, and delaying non-essential medical appointments, have become common practice. These pandemic mitigation measures have been practiced with varying degrees of success as evidenced by the fluctuating number of cases over time in various countries. As of 17 July 2020, the reported worldwide case count is over 13 million and the death toll is over 0.5 million (COVID-19 Case Tracker, 2020) and it's predicated that the case count will continue to increase for some time to come.

The pharmaceutical industry and its regulators, investigators and clinical trial sites, clinical trial participants, vendors, and other partners were forced to adjust rapidly to adapt to the COVID-19 pandemic. Shutdowns, social distancing, and avoidance of non-essential travel and medical appointments, combined with vulnerable participant populations in many clinical trials, made it impossible to continue with traditional trial methods that require participants, site personnel and sponsor personnel to travel to clinics for treatment. Industry had to implement changes quickly, according to regulatory flexibilities permitted by health authorities, to be able to start, continue, and closeout clinical trials.

The continuity solutions implemented in this time of crisis represent significant steps towards patient-centricity and a reduction of the burden for clinical trial conduct. Both of these are ideals that the pharmaceutical industry has recognized it must move towards. Continuity solutions implemented during these times should be extended beyond the pandemic to facilitate the modernizing[1] of clinical trials. This white paper describes broad categories of selected continuity solutions, the associated challenges and lessons learned, the factors that made implementation successful, and proposals for establishing these solutions in the modern post-pandemic world.

[1] Modernizing clinical trials, for the purposes of this paper, refers to employing patient-centric technology solutions and alternatives to on-site trial operations.

INTENT OF CLINICAL TRIAL CONTINUITY SOLUTIONS

Some of the most common continuity solutions implemented by large pharmaceutical companies appear to fall into several categories: telemedicine, electronic informed consent (eConsent), digital data collection tools, remote site monitoring, direct to patient shipping (DtP), home health visits, and local community-based laboratory utilization.

Broadly speaking, these solutions are intended to do the following:

- Protect trial participants and minimize COVID-19 infection risk by reducing the need for in-person interactions in a time of shutdowns, quarantines, travel restrictions, social distancing, and crowd avoidance.
- Ensure trial product availability for participants.
- Reduce the burden of clinical trial participation.
- Reduce the number of essential personnel needed at the study site.
- Streamline or automate the collection of data while maintaining levels of quality for submission to health authorities.
- Further advance the concept of risk-based approaches, focusing on the critical study elements that have been stated via health authorities and the International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use's Good Clinical Practice standards.

TransCelerate has actively begun to collect specific case studies of continuity solutions implemented during the pandemic from its membership and have published a select few in partnership with this paper. As additional case studies and information become available, the data will be provided to health authorities to grow the body of knowledge to support their prolonged use. Published cases can be found on TransCelerate's Modernizing Clinical Trial Conduct initiative web page.

IMPLEMENTATION CHALLENGES, LESSONS LEARNED, AND OPPORTUNITIES

This section presents the challenges encountered while implementing the clinical trial continuity solutions, the lessons learned from dealing with these challenges, and the opportunities that come with implementation. As many of these items were common across multiple continuity solutions, an overall summary is provided first followed by information specific to particular continuity solutions.

Note: It is not possible to present every challenge, every lesson learned, and every opportunity. Thus, this paper presents general themes and examples.

3.1 Challenges: The Big Picture

Implementing continuity solutions reactively and during a crisis (COVID-19 pandemic) inherently poses challenges, questions, and hurdles. This is true even for solutions/ideas that were employed pre-pandemic or considered by sponsors as ways to make clinical trial participation less burdensome and more patient-centric.

Challenges specific to implementation during the COVID-19 pandemic include:

- Retrospective protocol changes required expeditious execution, including changing protocol requirements in a crisis. This required researching solutions and vendors, amending protocols, modifying Informed Consent Forms (ICFs), creating new processes, training study staff and participants, and modifying data collection / clinical operations processes and plans.
- Global regulatory guidance for clinical trial conduct evolved throughout the pandemic and required interpretation and implementation for compliance.
- Study sites and institutions were primarily focused on managing and maintaining participant safety during the pandemic rather than implementing new technology to keep a clinical trial running.
- Sponsors needed to remain compliant with internal processes while expediting contracts with vendors.

Other challenges were more general and need to be considered when using these continuity solutions during non-pandemic times:

- Effective and efficient change management is needed for sponsors, vendors, sites, and participants to transition to and accept remote and digital solutions. This includes alignment and agreement across several functional areas within many organizations (e.g., a decision to use eConsent has implications for site monitoring, investigational review boards [IRBs], and database design).
- Implementing continuity solutions requires thorough evaluation of the solutions, assessing vendor capabilities, setting up new processes and/or equipment, navigating regulatory/legal requirements, updating monitoring/functional plans and study documents, and developing and delivering training for sites, participants, and others responsible for implementing the solutions (i.e., home health nurses, local community-based laboratories, couriers, etc.).
- Data integrity and flow (how to get traceable/auditable data from non-traditional sources into the electronic data capture [EDC] system) needs to be considered when using digital data collection tools, telemedicine, home health visits, and local community-based laboratories. System interoperability and data security are both factors. Considerations for selecting a technology platform (e.g., a wearable device that automatically takes and transmits vital signs) include the limitations of the technology and connectivity at the participant's home (Wi-Fi, cellular service,

etc.) as well as interoperability of the technology with other systems such as the EDC. Other important considerations related to digital data collections tools include, but are not limited to, statistical methodology implications, the steps necessary for regulatory clearance of a device for intend use (e.g., validation and verification of the technology), variability in the types of tools available, and potential data endpoints being captured.

- Variability in country/region-specific regulations can make it difficult to find a solution that works everywhere. For example, electronic signature requirements vary widely and may be a scan of a handwritten signature, a finger or stylus generated signature on a tablet, or a login/password combination, depending on the local regulations. Additionally, an ICF may require specific wording for solutions such as home health visits.
- Variability in institutional practices regarding participant privacy, remote access to information held at the site, cybersecurity, liability, technology platform differences, and ethics committee requirements can make uniform implementation of continuity solutions a challenge.
- Participant privacy regulations and ethical concerns must be considered. The more technology platforms that gather and transmit data, the more points of vulnerability are generated for the data to be hacked, stolen, or lost. The more vendors (e.g., technology platforms, home health practitioners, and drug supply couriers) with access to participant information, the more vulnerable the data.

It's also important to recognize that an increase of participant centricity and reduction of participant burden has to be balanced with any potential increase in burden on site personnel to implement the continuity solutions. Despite the enhanced trajectory of continuity solution use, sponsors must identify how to sustainably implement these solutions with all stakeholders in mind.

3.2: Challenges Specific to Certain Continuity Solutions

In addition to the general challenges faced by implementing continuity solution(s) that differ from traditional clinical trial practices, some continuity solutions faced unique challenges, both related and unrelated to the COVID-19 pandemic.

Examples of COVID-19 related challenges specific to certain solutions are shown in Table 1. These are not expected to be issues under normal (post-pandemic) situations when these continuity solutions are implemented, especially if the solutions are prospectively included during study protocol development. However, other challenges specific to certain solutions (Table 2) do not appear to be COVID-19 related and need to be addressed in order to use these solutions effectively in the post-pandemic world.

Table 1: COVID-19 Related Challenges Specific to Certain Continuity Solutions

Continuity Solution	Challenges
Direct to Patient (DtP) Shipping	Delays in retrospective DtP shipping set up during a pandemic led to some participants discontinuing some trials.
	Shipments from site to participant still required on-site staff presence to package the shipments.
	It was a challenge to find available certified couriers for products that require refrigeration and temperature monitoring.
eConsent	Some participants were not comfortable using the same stylus and tablet as the previous participant even if the hardware was sanitized in between participants.
Home Health Visits	Some participants were apprehensive about having study personnel visit their homes during a pandemic.
	There were availability challenges regarding hiring nurses for home health visits when hospitals needed nurses for COVID-19 units and other healthcare demands.
	Obtaining personal protective equipment (PPE) for use during a home health visit was challenging due to high demand and limited resources.
	Site closures sometimes prevented the accessibility of laboratory kits by site personnel for use during home health visits, resulting in cancellation of planned visits.
Remote Site Monitoring	Some sites could not complete necessary procedures (remotely and under expedited timelines) to enable remote access for site monitors, and some health authorities may require post-pandemic re-monitoring (on-site) of some data.

Table 2: Inherent Challenges Specific to Certain Continuity Solutions

Continuity Solution	Challenges
Digital Data Collection Tools	Set up requires time and training of sites, participants, and possibly other people involved in the study. Technology can malfunction, and participants or site staff might not remember how to use it when they need it.
	The tools need to be qualified and validated. If used for primary or key secondary endpoints, it is necessary to ensure prospectively that health authorities will accept the data collected through a particular tool(s).
	There is a need for enhanced monitoring of safety data in case of safety issues for individual participants and the implementation of processes and frameworks to review live data in a timely manner (supporting site teams) during the study.
Direct to Patient (DtP) Shipping	DtP shipping does not work for all investigational products (IP) including IP that cannot be administered at home (e.g., continuous intravenous [IV] infusions) and those that cannot be stored at home (e.g., those requiring specialized storage conditions such as a -70□C freezer).
	Couriers need to be specialized and/or trained if the IP needs to be maintained under specific conditions during transit.
	Participant privacy concerns mean that clinical trial supplies need to be packaged so that they cannot be identified by the courier or anyone else as an IP. This may unintentionally decrease access to medications in certain populations (e.g., urban dwelling participants may not have a secure delivery point).
	Countries and states have different laws and requirements for navigating drug shipment across borders which can require different models (e.g., site to participant, depot to participant, etc.).

Continuity Solution	Challenges
eConsent	eConsent means different things to different people and needs to be clearly defined for a study.
	The electronic signature requirements and amount of material required to be submitted to ethics committees differ according to local legal requirements and sometimes even between individual committees under the same jurisdiction.
	The eConsent platform instructions may not be available in the same language as the informed consent form (ICF).
	There are pros and cons to having participants use their own devices or provisioned devices.
Home Health Visits	Some investigators are not comfortable delegating participant examinations to a potentially unknown, external provider.
	Some sites view this as a revenue loss, or at a minimum, a complicating factor.
	Some health authorities for some protocols allow home health visits only after a specific point in the protocol's schedule of visits (e.g., after the first 6 visits are done in-person).
	Both visiting nurses and participants need to be told what to expect during these visits and what may be required (e.g., if a table is needed, it would be helpful if the participant had one available and ready).
	Not all drug administration methods can be easily completed as part of a home health visit (e.g., IV infusion).
	Local requirements could impact the activities performed by a visiting provider (e.g., certification for use of dry ice for specimen sample).
Local Community-based Laboratory Utilization	Laboratories must be properly certified and approved by sponsors to process and analyze participant samples.

Remote Site Monitoring	Providing documents for remote monitoring can add to site burden if the site does not provide/permit remote access to electronic records.
	Local regulations and institutional policies on what documents and information can be accessed remotely by a study monitor vary greatly.
	Systems and tools for this approach are still in their infancy and support from regulators is needed.
	There are differences between sites in terms of the types of source data - electronic, paper, or a mixture of both.
Telemedicine	There are legal and privacy concerns as well as participant acceptability issues (e.g., some participants are not comfortable with pictures and/or video being taken).
	Telemedicine means different things (phone call to specialized platform or app) to different people and needs to be clearly defined in each study protocol.
	The technology used must include a method for verifying the identity of the participant and site personnel conducting the assessment, especially if the entire trial is being conducted remotely (i.e., the participant has never been at the study site).
	Different sites have varying requirements for utilization of technology based on application/platform security, integration capabilities, etc.
	It can be difficulty to ensure equivalent experiences across global geographies with different local languages and requirements/regulations.
	For certain indications (e.g., wound healing), the telemedicine platform may not provide sufficiently high-resolution video.

3.3 Lessons Learned

Reflecting on lessons learned provides an opportunity to strategize and proactively plan to handle future challenges. One of the recurring challenges experienced by clinical trial sponsors was the difficulty with retrofitting a continuity solution to a protocol that was developed without the solution in mind. Thus, the overarching lesson learned was the desirability of pre planning which may include the following:

- Prospectively setting up future protocols and corresponding ICFs to include the option to use certain continuity solutions.
- Building the necessary functional plans and ensuring that sponsor systems (e.g., EDC) can accept data from all planned sources as well as incorporating time to provide training for sites, participants, and others as needed.
- Collecting and sharing solution assessments and vendor performance across various functions or therapeutic areas within a sponsor company.
- Considering study team and site capabilities for operationalizing the use of continuity solutions during study feasibility discussions and site selection.
- Setting up service contracts with solution providers before a solution is needed.
- Prospectively discussing digital data collection tool(s) with health authorities to ensure acceptability of data collected.
- Considering the pertinent and critical data that is required to be collected during the trial.
- Identifying the data elements that are priority and the solutions available to collect and monitor data remotely.
- Having pandemic preparedness built into protocols to allow for supplementary estimands for key efficacy endpoints to understand the impact of changes in data collection on the interpretation of endpoints.
- Identifying and utilizing available best practice aides, guides, or tools within industry to assist with solution planning and implementation. For example, assets from TransCelerate's Risk-Based Monitoring (RBM) and Quality Management System (QMS) initiatives were mentioned by some sponsors as helpful during utilization of remote monitoring continuity solutions.

For digital data collection tools and other technology platforms, technical challenges were a recurring theme amongst participants and sites. This challenge may also vary with the participant population (e.g., an older population may be less adept with technology). Planning for the use of technology-based solutions should include the following:

- Building in time to train sites, participants, and other key stakeholders that might be impacted by or involved with this new technology (e.g., caregivers, family members).
- Including an in-person training visit (at clinic or participant's home) during which a device can be set up and the participant can be trained to use it (remote training can be difficult).
- Providing technical support (e.g., helpdesk and service telephone number) to participants, sites, and other stakeholders in the event that they experience difficulties with study required technology.

TransCelerate also believes that finding efficiencies in the protocol schedule of assessments, by grouping in-clinic assessments into as few visits as possible (e.g., having an echocardiogram and pulmonary function tests on Day 11 rather than an echocardiogram on Day 9 and pulmonary function tests on Day 10), would be beneficial to participants and sites. This efficiency and consolidation of in-clinic visits would further support the use of telemedicine or home health visits in between the required clinic visits.

3.4 Opportunities

Although the pharmaceutical industry, regulators, sites, and vendors were compelled to respond swiftly during the COVID-19 pandemic to keep clinical trials running, the continuity solutions adopted during the crisis represent a positive shift towards improved clinical trial conduct. Namely, the intent to protect participant safety and data quality while minimizing burden. Continuity solutions, when used either independently, or together, present numerous efficiencies and can enable momentous change in the shift towards the ideal modernized clinical trial.

eConsent, as an illustrative example, may improve recruitment and retention of participants in clinical trials by providing a more participant friendly and interactive explanation of trial participation requirements. eConsent can be set up with videos, animation, and knowledge reviews to provide a vivid picture of the clinical trial requirements and test if a prospective participant understood the material. This may be favorable compared to a clinician explaining a lengthy document and answering questions. More informed participants may make better decisions about trial participation by better understanding the benefit/risk profile and participation burden (Simon 2018). When combined with telemedicine, there are additional opportunities for patient-centric enhancements in understanding study details during the consent review process, such as live question and answer sessions with investigators or delegates. It logically follows that this can then lead to increased participant retention as fewer participants will find themselves surprised by study requirements after beginning the study.

When implemented together, continuity solutions may provide opportunities to accomplish broader goals. For example, let us consider the recruitment of a more geographically diverse participant population. The use of remote visits by combining solutions such as telemedicine, home health visits, and local community-based laboratories (when appropriate for the investigational product [IP] and indication) reduces the travel burden for the participant. Participants may inherently save time, effort, and money due to remote visits. Use of remote visits can reduce geographic barriers to participation and allow for recruitment of a larger pool of participants, especially those in more remote (non-urban) areas and/or those who do not drive and/or have easy access to transportation. Larger participant pools enhance probability of increasing diversity. In a survey of over 800 participants enrolled in clinical trials during COVID-19, 35% of respondents reported spending less time going to research visits at sites or hospitals versus before the pandemic (CTTI 2020).

Laura Holmes-Haddad, a former clinical trial participant and cancer survivor, provided her experiences on the burden she and her family endured while frequently traveling to the trial site for her protocol required visits (Interview of Laura Holmes-Haddad): “One of the most difficult parts of participating in a clinical trial was traveling for treatment. Traveling by plane every week was physically, emotionally, and financially draining. Protocol required that I receive my bloodwork and scans at the trial site, rather than at the hospital closer to my home (where my oncologist practiced). If I could have had the weekly bloodwork performed at a lab near my home instead of traveling that would have alleviated so much stress.” Laura is just one of many participants who experienced the inconvenience and discomfort of traveling when dealing with critical conditions. Had the trial Laura participated in offered options such as telemedicine or local laboratories for blood sampling, she could have avoided unnecessary discomfort and pain.

DtP shipping as a solution can also reduce burden to participants as the majority of IP re-supply visits occur in-person at the clinic. The use of DtP shipping of IP reduces travel burden for participants by allowing them to receive drug at their home or residence.

Opportunities for greater efficiencies also exist for sponsors and sites as key stakeholders of continuity solution implementation. Establishing interoperability of EDC systems, electronic health records (EHRs), and digital data collection tools can reduce the amount of source data verification (SDV) required by study monitors. This is because a greater proportion of study data can be accessed and reviewed without human transcription and the associated chances of error. This interoperability increases efficiencies for sponsors and sites and provides participants with reassurance that their data is managed and maintained with

integrity and at a minimum risk of misinterpretation. Evaluating fit-for-purpose monitoring approaches and leveraging centralized monitoring in lieu of SDV further reduces traditional monitoring demands without negatively impacting data quality (Gough 2016).

Presumably, refinement of and prospective planning for continuity solutions will result in better clinical trials which may be modernized, flexible, decentralized, and patient-centric. Full realization of modern clinical trials will require the support of key stakeholders including participants and sites. While supporting data is still needed and being generated, early input from both stakeholders point to a desire for modernizing clinical trials via prolonged use of the referenced continuity solutions. A recent site staff survey (SCRS 2020) showed that staff recognize potential benefits of using technology in clinical trials. The key potential benefits cited by site staff were greater participation in and access to clinical trials. Sites considered the distance between the participant's home and the site and the frequency of site visits to be the biggest deterrents to clinical trial participation. These issues could be mitigated by telemedicine, home health visits, use of local community-based laboratories, and DtP shipping of IP. Site staff are also increasingly expressing dissatisfaction with current eClincial technologies as a result of disparate systems. This sentiment further supports the need for modern, adaptive, and integrated approaches to clinical trials. Importantly, it should be noted that sites perceived overall quality of study data and participant safety as challenges to decentralizing clinical trials. Sites and sponsors will need to work together to assuage these concerns as remote technologies become more commonplace.

Participants expressed similar sentiments to those shared by sites, further supporting the need for modernized trial conduct. A participant survey (CISCRP 2019) conducted before the pandemic found that 70% to 80% of participants (clinical trial participants and potential participants) found collecting all data at home, having home health visits for all study visits, and a hybrid approach of at home and in-clinic visits to be at least somewhat appealing compared with all in-clinic visits. In addition, participants who reported receiving their ICF in an electronic format reported the easiest time understanding the document. eConsent was also a top mention for "convenience enhancing solutions" for clinical trials. Another participant survey taken during the pandemic (CTTI 2020) found that 52% of the respondents who reported going to in-person visits to the research site or hospital before the pandemic, experienced changes to their clinical trial. Of that group, 50% reported changes having no impact to their participation experience while 19% reported an improvement to their participation experience and 31% reported a worsened experience. This is an important indicator that clinical trials utilizing continuity solutions are not worsening the participant experience in a majority of cases. While the results of this survey are promising industry should seek to understand the 31% of patients who reported worsened experiences. There is a clear need to uncover the root cause of any changes in experience to clinical trial conduct during the pandemic, and we are encouraged to continue engagement with patients to learn more.

While early data suggest support for extended use of continuity solutions, structured analyses of data (especially safety data) before and after implementing continuity solutions within a study during the COVID-19 pandemic need to be conducted. In addition, new data points may need to be collected to understand the effects of the pandemic on data integrity (e.g., sensitivity analyses). These analyses will be a crucial component to securing health authority support for modern approaches to clinical trials and shouldn't be overlooked.

IMPLEMENTATION FACTORS ENABLING SUCCESS

The successful implementation of continuity solutions during the COVID-19 pandemic depends on numerous contributing factors, both internal and external. One overarching success factor is the desire and determination of regulators, sponsors, sites, and vendors to minimize the disruption of treatment and care for participants.

In addition, successful stakeholders possess the following attributes which contribute to the overall success of these continuity solutions:

- Openness to modified ways of working to enhance infection control and promote more virtual, remote, or decentralized methods for conducting trials.
- Willingness to be creative and/or flexible without one size fits all solutions (e.g., allowing some participants/sites to have in-clinic visits and others to have telemedicine or home health visits).
- Desire to work together and prevent increased burdens from becoming too much for any one group (e.g., willingness to look for ways to reduce site burden).
- Recognition of the potential benefits and consideration of the work required to implement continuity solutions as an investment towards a better future.

Other success factors relate to actions rather than mindset. Some of these success factors are a result of industry's activity prior to the COVID-19 pandemic:

- Ongoing research/consideration of digital data collection tools and other technology platforms to modernize data collection and reduce the study monitoring burden.
- Ongoing research/consideration of other possible continuity solutions (regardless of disruption) to reduce the burden for clinical trial participation.
- Established use of RBM to identify the appropriate approach for monitoring critical data so that SDV or source data review (SDR) via remote monitoring can focus on key issues.

Lastly, some success factors are realized only after changes to clinical conduct were necessitated due to the pandemic. Examples of these success factors include the following:

- Effective change management plans are established to help everybody understand, communicate, and navigate upcoming changes. The development of training materials, tool kits, and working instructions for new technologies for both sites and participants enables these plans.
- Communication plans ensure that key stakeholders are aligned to changes in data collection and data reporting procedures, priorities, and expected study/site monitoring activities. Additionally, the use of communication channels makes sure everyone's concerns are heard and considered.

COVID-19 was a catalyst for sponsors, sites, and their partners to adapt to new ways of conducting clinical trials as there was a very strong incentive to find solutions. All parties involved in clinical trial conduct realized that it was necessary to adapt to new ways of working or risk participant safety and the integrity of trial data by pausing or stopping trial conduct altogether.

A major success factor that should not be overlooked was the timely response from numerous health authorities that published temporary guidance for conducting clinical trials during the COVID-19 pandemic (EMA 2020, FDA 2020). This can be seen in the global response by regulators to change policies and guidelines to allow remote site monitoring solutions. For instance, in the FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency (FDA 2020), the FDA declared that "Sites could upload certified copies of source records to a sponsor-controlled electronic system or other cloud-based repository that contains appropriate security controls." Similarly, the EMA's guidance (EMA 2020) states, "Centralized monitoring of data acquired by electronic data capture systems (e.g., eCRFs, central laboratory or ECG / imaging data, ePROs, etc.) that are in place or could be put in place provides additional monitoring capabilities that can supplement and temporarily replace on-site monitoring through a remote evaluation of ongoing and/or cumulative data collected from trial sites, in a timely manner."

BEYOND THE PANDEMIC: PROPOSALS FOR MODERNIZING CLINICAL TRIALS IN THE NEW NORMAL

The critical need for continuity of participant safety, study oversight, assurance of data integrity, and maintenance of IP supply in the face of a pandemic provided an impetus to accelerate towards the goal of modernized, patient-centric clinical trials. The industry has been working, testing, and piloting ways to make clinical trials more participant friendly, risk-appropriate, and decentralized, and some sponsors and organizations were already considering the risks of change:

- Will regulators accept data that was collected by a new technology and monitored differently?
- Will processes, sites, and partners be able to adapt?
- Why change from traditional approaches?

In most cases, before the pandemic, these risks were either greater than the benefits of changing or greater than the risks of continuing business as usual. The COVID-19 pandemic catalyzed an effect on the industry by altering the risk-benefit calculation. The risks of change decreased as regulators adopted stances more open to continuity solutions. The risks of not changing increased to unacceptable highs and industry rapidly altered how clinical trials are being conducted.

With these changes enabled by regulatory flexibility during the pandemic, all stakeholders need to re-examine the risk-benefit ratio of the changes and continue to employ those solutions that have either enhanced or not negatively altered participant engagement, participant safety, and data integrity. The benefits of the changes include:

- Reduced burden on participants by bringing visits, services, and supplies to them, leading to increased access to trials.
- Potential improvement of participant recruitment (e.g., geographic diversity of recruitment), adherence to protocol, and retention.
- Bringing needed new medicines and vaccines to participants faster.
- Utilizing RBM principles and leveraging technology to collect and manage data with reduced chances for human error.

Regulatory flexibility is a major factor in enabling success for the clinical trial continuity solutions. Results and experiential data from COVID-19 affected clinical trials will ultimately determine whether participant safety and/or data integrity were negatively impacted or not by use of these continuity solutions. Because many trials using these continuity solutions are still in progress (versus completed and analyzed), there is a need to analyze trial data (when available) to determine the effect of using these continuity solutions. To achieve the goal of turning crisis-generated solutions into long-term improvements, TransCelerate supports the public statements made by health authorities at recent major conferences (DIA 2020) to examine where it is appropriate for pandemic guidance to transition and become permanent guidance.

In the current circumstances, we ask that health authorities harmonize regulatory policies as much as possible and improve the ability to use regulatory reliance pathways, especially when health authority resources are constrained, and the same regulatory dossier is under simultaneous review at multiple agencies. TransCelerate welcomes the opportunity to discuss inconsistencies in regulatory policy and their impact with interested Health Authorities.

We also appeal to research sponsors, investigators, clinical trial sites, and other partners in the clinical trial process to build upon the lessons learned from the implementation of continuity solutions during the pandemic. Specifically, the lesson learned to plan future protocols prospectively to accommodate flexibility for in-clinic, home health, and/or telemedicine visits; use of digital data collection tools, eConsent, EDC systems, and local community-based laboratories; leveraging of RBM for central and remote monitoring of only the critical data; and DtP shipments of drug supply.

Retreating to the traditional ways of running clinical trials would be a lost opportunity to modernize clinical trial conduct and may not even be an option. The environmental changes resulting from the pandemic are not yet over and may last for years to come. As discussed in the paper, the opportunities to use continuity solutions independently or in combination hold promise and their impact should be examined. We should strive to make the appropriate improvements to modernize clinical trials based on what participants tell us about their trial experience and other value-added lessons in order to overcome the threat the pandemic represents to impeding scientific and medical progress. We should not waste what we learn from this period of adversity but plan to build on its momentum instead.

TransCelerate plans to continue working with multiple stakeholders on these topics. The ecosystem is at the genesis of an iterative process of collecting data and case studies to continually learn as a community. This will ensure the implementation of fit-for-purpose solutions to serve the best interests of our clinical trial participants whilst protecting and promoting the highest evidentiary standards in our studies. TransCelerate will be collecting information to help advance the understanding of the impact of these solutions for further discussion with health authorities. We believe that regulatory flexibility was one of the most important factors enabling success of the COVID-19 clinical trial continuity solutions, and TransCelerate is committed to working with all stakeholders to ensure their continued use and success.

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APPENDIX

Table 1: Descriptions and Examples of Clinical Trial Continuity Solutions

Solution	Description and Examples
Digital Data Collection Tools	Hardware and/or software products can be used to support the practice of medicine via collection, measurement, and remote transmission of data from a variety of sources including laboratories and clinical trial participants themselves. Digital data collection tool is an umbrella term that includes tools for which a person must manually input data (e.g., a web-based app that the home health practitioner uses to enter a participant's pulse right after taking it) as well as tools that automatically collect and transmit data (e.g., wearable technology that collects and transmits a participant's pulse at specified times). Digital data collection tools include, but are not limited to, the following: • Wearable and connected devices that automatically collect and transmit participant data (collectively referred to as telemetry) • Apps that remind participants to do something and/or allow participants to manually enter data (e.g., study drug dosing reminder apps and participant diaries for adverse events and study drug dosing information) • Electronic clinical outcome assessments (e.g., web-based or app versions of questionnaires traditionally done on paper) • Technology that collects data while facilitating participation in a study (e.g. telemedicine platform) *Sources: TransCelerate Patient Technology (here) and Digital Medicine Society (here)*
Direct to Patient Shipping	Direct to Patient (DtP) Shipping requires an integrated supply chain system that enables participants to receive supplies (including investigational product) necessary for clinical trial participation at their own home, place of work, or local pharmacy. This includes the development of processes and approvals adhering to local requirements to implement the direct shipment of investigational product from the study site or clinical supply depot directly to the participant. The purpose of DtP shipping is to minimize in-clinic visits done primarily to re-supply the participant with investigational product.

Solution	Description and Examples
Electronic Health Record & Electronic Data Capture	**Electronic Health Record (EHR):** An EHR is an electronic version of a participant's medical record that is maintained by the provider over time and may include all of the key administrative and clinical data relevant to that person's care under a particular provider. Such data include demographics, progress notes, problems, medications, vital signs, past medical history, immunizations, laboratory data, and radiology reports. This is source documentation for the participant and is present regardless of whether the participant is in a clinical trial or not. *Source: HealthIT.gov (here)* **Electronic Data Capture (EDC)**: The EDC system for a clinical trial is a computerized electronic system that allows users to collect (manually and automatically) clinical trial data originating from multiple sources (e.g., patient health records, patient reported outcomes, laboratories, digital data collection tools, etc.). As clinical trials implement telemedicine, digital data collection tools, use of EHRs, and more, it is critical that data from these other solutions can be integrated into the EDC.
Electronic Informed Consent (eConsent)	Electronic informed consent (eConsent) uses electronic media to provide information about trial participation, procedures, and risks that would normally be included in a paper informed consent form (ICF). The use of multimedia formats can be used to provide a more engaging and informative experience and offers flexibility for diverse learning styles. • eConsent includes a range of capabilities from having the participant print, sign, and scan the ICF to an interactive multi-media experience culminating with a digital signature using a login/password combination. • eConsent can be signed via tablet while at the clinic or from anywhere in the world with an internet connection. • eConsent is not meant to replace the important discussion between the trial participant, investigator, and site staff. Such a discussion should still occur and can be part of a screening visit (in-person, by telemedicine, or home health visit). *Source: TransCelerate eConsent (here)*
Home Health Visits	Home health visits allows the conduct of clinical trial assessments in the participant's residence or other location, decreasing the need for the participant to travel to the study site. This solution can be used in combination with a telemedicine platform if the investigator, in addition to the home health practitioner, also needs to attend the visit (e.g., to provide a real-time investigator judgment on whether the participant should be given study treatment based on a pre-dose assessment conducted by the visiting practitioner).

Solution	Description and Examples
Local Community-based Laboratory Utilization	When data is needed immediately to make a safety assessment, treatment, or randomization decision or when getting the participant to the study site is problematic or otherwise not ideal, use of local community-based laboratories that are close to the clinical trial participant may be an alternative to using a central laboratory. This capability supports the ability to leverage a convenient local laboratory while still having the data processed, queried, and analyzed in accordance with the requirements of the protocol and data management plan. The use of local laboratories requires processes for gathering data, collecting normal ranges from the local laboratories, and ensuring the clinical trial database reflects the local laboratory information. Ultimately, the goal of using local laboratories during a pandemic is to allow the participants to have laboratory / imaging performed in close proximity to their residences and reduce risk of exposure associated with traveling (to a study site).
Remote Monitoring and Sponsor Visits to Study Sites	Remote clinical trial monitoring utilizes digital tools for facilitating review of documentation and data to select, initiate, monitor, and close out clinical site activities from a remote location. This includes reviewing an electronic Investigator Site File (eISF) as well as conducting remote protocol training, site level contracting, and audits/inspections. Remote monitoring may be part of a broader risk-based approach that could also include central monitoring and on-site monitoring. **Central Monitoring:** Remote evaluation of accumulating data, performed in a timely manner, supported by appropriately qualified and trained persons (e.g., Data Manager, Statistician, or Monitor) **Remote/Off-site Monitoring:** Includes monitoring activities as defined either within process documents or in the monitoring plan (MP) that occur away from the study site location (e.g., at a Monitor's home or in a sponsor representative's office). Risk-based monitoring (RBM) identifies critical data and critical processes on which the monitor should focus. Remote clinical trial monitoring allows monitors to conduct source data review (SDR) (assessing how the data were collected and evaluating whether procedures were conducted per protocol) and can enable source data verification (SDV) of critical data to ensure it was reported accurately in the case report form (CRF). Use of other continuity solutions can complement or facilitate remote site monitoring by reducing the amount of data requiring SDV. For example, automated collection of EHR data eliminates the need for transcription of data to the CRF and so eliminates the need for some SDV. Remote clinical trial monitoring requires allowing the monitor to access site master file information such as inclusion/exclusion information for individual participants, consent forms, drug accountability data, and participant source data. Such access must be in compliance with local and institutional policies and regulations regarding participant privacy. Tools for providing remote access can be as simple as secure video and/or secure document / data exchange platforms.

Solution	Description and Examples
Telemedicine	Telemedicine is the use of telecommunications technology to deliver real-time healthcare interaction, that would traditionally be handled in an in-person visit, from a distance. In a clinical trial setting, an investigator in one location uses telecommunications infrastructure for two-way, real-time, interactive communication while administering healthcare to a participant and/or caregiver at a remote location (i.e., other than the designated trial site, institution, or clinic). Telemedicine can range from a simple phone call asking about adverse events during a post-treatment follow-up to a study visit via video component requiring login/password to authenticate the participants (investigator and clinical trial participant).