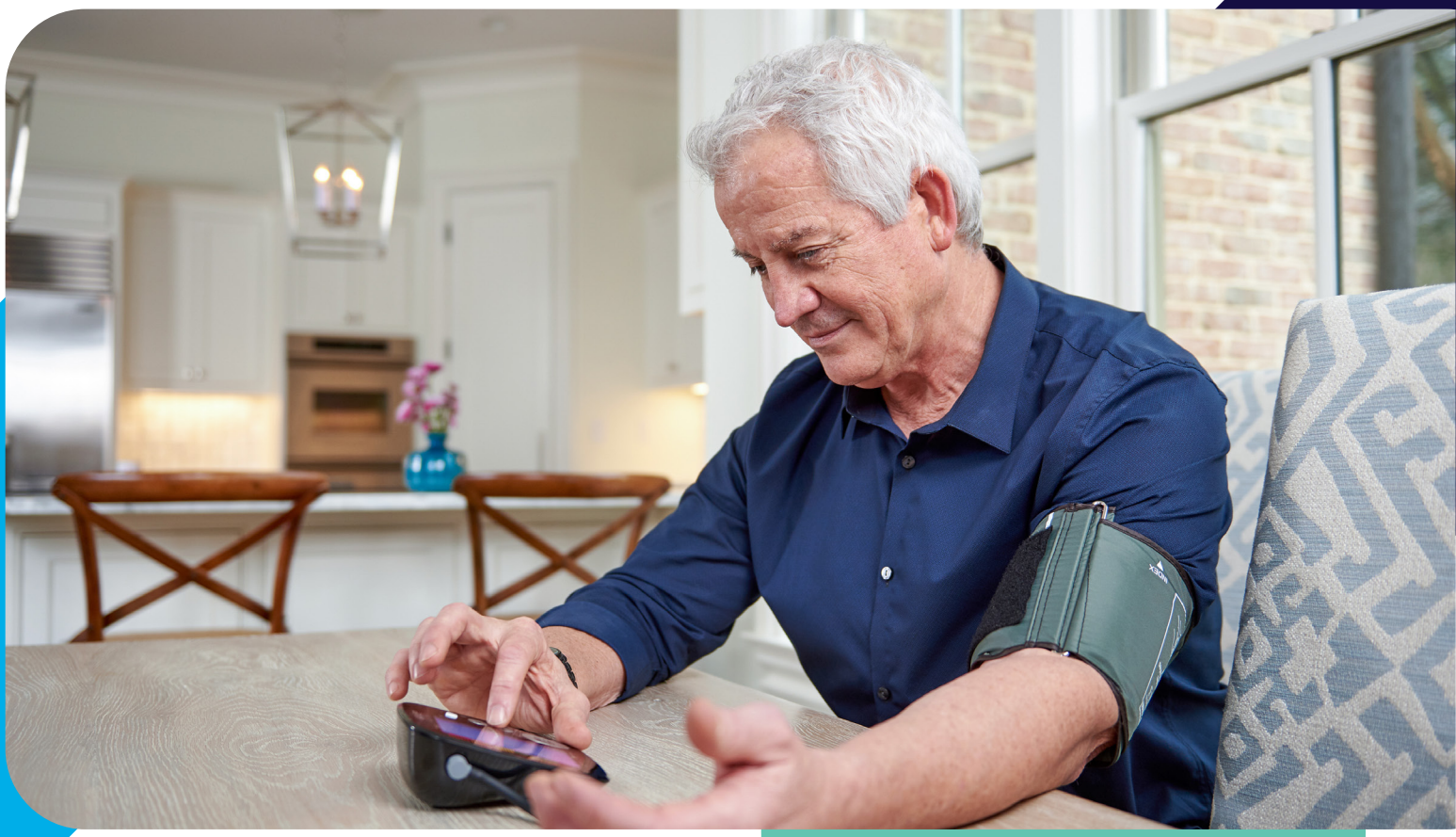
White Paper

Clinical Trials Moving From Site To Home - Lessons Learned From Digital Health Technologies

Evidence-based guidelines for optimizing the use of connected devices for home-based clinical trials.



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Introduction

Exciting change abounds in today's clinical trial ecosystem, and that's putting it mildly. Seemingly every day, we see, hear, or and read about novel innovations that have the potential to transform how clinical trials are conducted and optimize healthcare outcomes. The transformation we are witnessing is indeed remarkable, and was, of course, accelerated—if not catalyzed—by the seismic shifts brought on by the COVID-19 pandemic.

As is often the case throughout history, technology is driving the advancements, and the clinical trial ecosystem is no exception. Innovation is cropping up everywhere, across virtually every facet of clinical operations—including sophisticated centralized monitoring capabilities, finely tuned predictive analytics, the emergence of generative AI, and so forth.

One area where technological advancement is having a particularly significant impact is in the connected medical grade devices space, where the utility of these and other digital health technologies have rapidly gained acceptance for use in clinical trials. This dramatic increase in adoption has been driven by the evidence proving these technologies to be highly beneficial, particularly wearable connected devices that collect and transmit data with minimal patient or caregiver effort—referred to as *passive* data *collection*.

Subsequently, these devices and technologies have made it increasingly feasible to conduct successful clinical trials in the comfort of the patient's home, which can provide enormous benefits for medical research.

And in a carefully designed and successfully delivered decentralized clinical trial (DCT), everyone wins.

So… what does *winning* look like?

For patients and caregivers, the traditional burdens associated with site-based research are dramatically reduced—resulting in a more positive research experience. This positive experience in turn optimizes protocol adherence and enhances patient recruitment and retention. And from a data collection and analysis perspective, DCTs that use these novel digital technologies have opened up exciting doors of opportunity to produce more continuous, enriched, and higher quality data.

A note of caution, however: the more seamless the clinical trial experience becomes for patients in the remote setting, the more complex the moving parts within the operation.

Therefore, successfully moving clinical trials from the site to the home requires a combination of deep subject matter expertise in digital health technologies, biomarkers, and endpoints—complimented by the full breadth of end-to-end capabilities that would be expected of an experienced, finely tuned clinical research organization (CRO).

But first things first—let's review some important recent developments.

Shrinking size, growing opportunities: welcome to the paradigm shift

The journey began roughly twenty years ago, when electrocardiograms (ECGs) were still large, cumbersome machines that required patients to travel to an examination room or hospital to be assessed. In addition, a trained healthcare professional was required to administer the procedure.

Over time, improved technologies enabled ECG devices to become smaller and easier to use. Today, many clinical trials are utilizing relatively tiny, wearable ECG connected devices that are extremely light, noninvasive, and able to capture and transmit data remotely rapidly and accurately. This evolution in ECGs has become the prototype for *passive* data collection.

So it should come as no surprise that the same evolution towards more advanced, less burdensome technologies and reduction in size didn't stop with ECGs. In fact, the identical pattern emerged in other medical grade devices deriving a broader range of vital parameters—such as blood pressure and glucose monitoring, heart oxygen saturation, respiratory measurements that utilize at-home spirometry, and precision actigraphy—which has more than doubled in use since 2019.

Tipping point reached: at last, there is broad acceptance

Virtually every day, novel medical grade devices are launched within the industry that are much smaller, faster, and can passively collect quality physiological data in a manner that eases the patient and caregiver burden.

Now—at last—we have reached a tipping point where there is broad acceptance within the industry for using many of these devices and technologies in clinical trials. Currently, in fact, *there are more than 130 studies using wearable connected devices*—and we expect this number to increase exponentially moving forward.

And because extensive data and experience have now been amassed in successfully utilizing these digital health technologies, we can now clearly identify best practices derived from lessons learned.

And that means we are now able to construct an evidence-based blueprint for optimizing design and delivery of a clinical trial—conducted in the comfort of the patient's home—that harnesses the potential, at last, of these stunning technologies.

"Currently, there are more than 130 studies using wearable connected devices—and this number will increase exponentially moving forward."

Promoting collaboration to drive further innovation

Unlike before, regulating agencies across the globe are now actively encouraging pharmaceutical companies and manufacturers alike to work together to expand development of these innovative devices and technologies for use in clinical research.

At the same time, they are promoting this collaboration to develop novel endpoints and algorithms that benefit science as a whole; this includes facilitating greater diversity in trial populations by reducing the burden for sites and patients. These innovative technologies and digital endpoints will help all of us be more inclusive of groups that have traditionally been underrepresented in clinical studies.

"At IQVIA, we strive to ensure that all patients have an opportunity to participate in—and benefit from—important clinical research that improves healthcare outcomes."

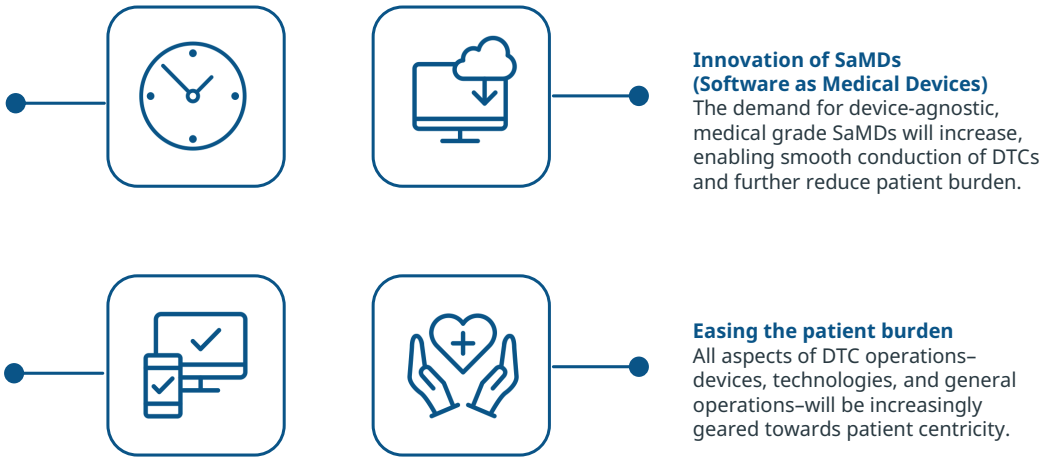
At the core, there are two interconnected capabilities that have been driving the paradigm shift in moving clinical trials from the site into the home.

The first, which we have already characterized, are the innovative connected devices themselves. These devices allow researchers to collect data directly from the patient in real-time with enhanced speed and accuracy—empowering researchers to make faster, better informed decisions throughout the trial journey.

The second is the advancement of remote data acquisition, which has also undergone a remarkable evolution. In addition to aggregating and analyzing data, remote centralized monitoring now includes capabilities such as detection of protocol deviations, rapid prediction and mitigation of risk, robust training and support to traditional sites or homes, and increased transparency that optimizes inspection readiness.

In addition, there are several high-priority considerations that sponsors will need to watch closely and leverage as the paradigm shift continues to unfold. These considerations will be critical in ensuring success (See Figure 1, below).

Figure 1: Key considerations when bringing clinical trials into the patient's home.



Defining digital biomarkers, digital endpoints, and SaMDs

The first step in optimizing a clinical trial conducted in the comfort of a patient's home is having a clear understanding of 3 key components: digital biomarkers, digital endpoints, and Software as a Medical Device (SaMDs).

A *digital biomarker* is any physiological parameter (such as heart rate, respiratory rate, or blood pressure) that is collected and measured by a medical grade device providing data in a digital format. Once digital biomarkers are used in a clinical trial to demonstrate a meaningful outcome, they are called *digital endpoints*.

A *digital endpoint* can be a single biomarker measured at different points in time—such as monitoring blood glucose levels before, during, and after a given treatment. Or, on the other hand, digital endpoints can combine multiple different biomarkers. For example, in infectious diseases, a digital endpoint may be a combination of heart rate, respiratory rate, temperature, and blood pressure in order to better determine disease progression.

Understanding prognostic vs predictive value of endpoints

It is also important to clarify the distinction between two categories of endpoints in terms of the value they provide in clinical trials: prognostic endpoints and predictive endpoints. Both are extremely valuable in different ways.

- **Prognostic endpoints** generally focus on evaluating the level of disease progression. For example, extremely elevated PSA values measured at the time of a prostate cancer diagnosis would suggest more aggressive disease.
- **Predictive endpoints** focus on what transpires after taking a given course of action. Think of a wristwatch, for example, that uses sensor technology to warn a patient that they are about to fall—this would be a *predictive endpoint* derived from passive data collection.

Prognostic and predictive endpoints can be exploratory in nature, or designed to demonstrate the commercial opportunity of a potential treatment.

"Today's novel devices allow researchers to collect data directly from the patient in real-time, with enhanced speed and accuracy."

Another innovation having a dramatic impact on moving clinical trials from the site into the home is the device-agnostic *Software as a Medical Device* (SaMD). Put simply, SaMDs can be defined as any software, platform, or mobile application that has the capability to provide information which can then be used to derive diagnostic or treatment decisions independently.

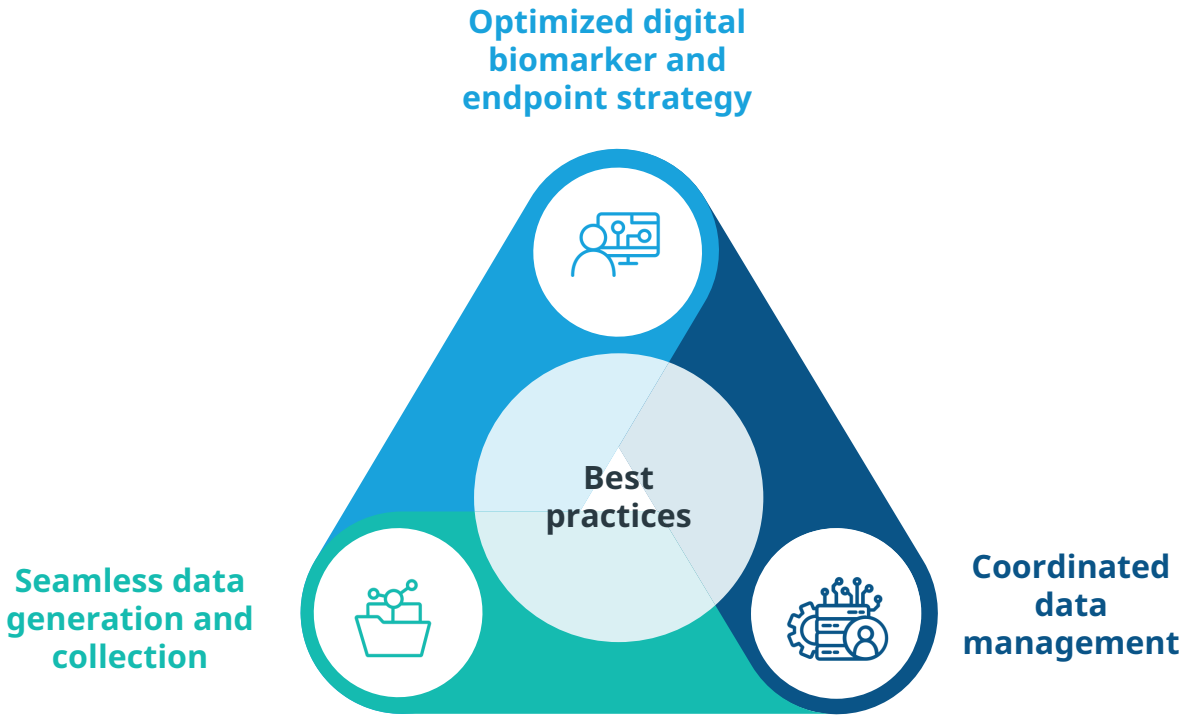
SaMDs work to accelerate discovery, management and treatment across a wide range of medical issues—automating certain aspects of care to save time. And due to their ability to rapidly collect large amounts of data, the use of SaMDs will undoubtedly continue to grow rapidly in the months and years ahead.

Lessons learned: newfound clarity around best practices

As the saying goes, there is no substitute for experience. Now that the industry has—at last—amassed a significant body of evidence around the opportunities and challenges in conducting clinical trials in the home setting, our understanding of critical success factors, pain points, and best practices have crystallized.

We at IQVIA have identified 3 key characteristics that are shared by highly successful clinical trials conducted in the home setting. And these considerations need to be considered best practices and firmly adhered to (Figure 2, below).

Figure 2. Characteristics of best practices in clinical trials conducted in the home setting.



The *right* endpoints for the *right* trial: keys to optimizing a digital endpoint strategy

There is an important reason why we've defined digital biomarkers and digital endpoints so clearly in this article: simply put, deciding which digital biomarkers and endpoints to target in a clinical trial is pivotal in determining success or failure—particularly in the home setting.

The digital biomarkers, endpoints, and devices chosen for the home setting must be in perfect alignment with the study objectives, regulatory requirements (as per the participating countries), and labeling considerations.

Like the foundation of a house, which needs to be properly built to ensure the home is sturdy and suitable to withstand changing elements over time, an optimized digital endpoint strategy requires a carefully-planned blueprint and subject matter expertise in order to ensure successful outcomes.

"Optimizing a digital endpoint strategy requires meticulous planning and expertise in order to determine which biomarkers, endpoints, and devices best align with the study objectives."

As mentioned earlier, the list of innovative technologies becoming available is constantly expanding, ushering in new and exciting biomarkers and devices that help advance medical science. But at the core, a digital endpoint strategy can only be successful when the digital endpoints and biomarkers answer 3 simple but critical questions:

- Are they the best fit to support the objectives of the study?
- Will they be able to satisfy regulatory requirements?
- Will data be provided and analyzed in a manner that conforms to study objectives and labeling?

An optimized protocol requires these answers to be precise, evidence-based, and actionable. The study objectives *must* be carefully mapped to the physiological measurements; the feasibility around the quantity, duration, and frequency of the desired data collection must be carefully scrutinized; and the regulatory implications must be thoroughly understood and solved for—well before the biomarkers and endpoints are finalized.

From strategy to fruition: achieving operational excellence in the home setting

Once a solid foundation has been built to succeed with a well-honed endpoint strategy, the same rigorous planning must be applied to operationalizing. Implementation, however, must be customized for the home setting to ensure success. The first key step is to select a vendor wisely, which, once again, requires meeting customized criteria tailored to the home setting.

Choosing a device: critical success factors

Prior to selecting a vendor, the first order of business is ensuring 3 critical criteria are met in regard to the device being proposed for use in the home setting. These criteria are outlined below (see Figure 3).

Figure 3. Three key critical success factors for optimizing vendor and device selection.

- **User-friendly technology.** If a device is simple and easy to use, it lessens the burden placed on patients and caregivers. Reducing the technology burden helps facilitate higher quality, continuous data collection, while helping to create a more positive patient experience—which in turn enhances recruitment and retention.
- **Clearing regulatory hurdles.** In the home setting, every link in the chain of events within a trial—including logistics—will likely involve regulatory compliance in some shape or form. Depending upon the trial design, regulatory clearance could involve a range of different countries with highly specific requirements—all of which must be known and fully accounted for well in advance. Therefore, clarifying *intent of use* at the outset is critical.
- **Performing a risk-based vendor evaluation.** A vendor must be well-equipped to meet the unique needs of performing a clinical trial in the home setting. Does the vendor have the ability to overcome complex logistical and regulatory challenges while safeguarding patient privacy? Are they financially stable? Can they scale to meet the needs of a Phase 3 clinical trial? The benefits of the device become irrelevant if the vendor cannot meet the full range of nuanced requirements for success in the home setting.

Device planning in the home setting

Device planning, of course, is a pivotal component of conducting a clinical trial in the home setting. To achieve best practices, there are 5 rules of thumb that need to be carefully considered.

1. **Create a clear, collaborative, and transparent vendor partnership.**
   The same rigor and foresight put into vendor selection must be applied to vendor management. Clearly articulated contracts, including Master Service Agreements (MSAs), must leave no room for ambiguity. Exactly what are the liabilities and who is accountable? Who owns the intellectual property? Who owns the data? In addition, predetermined metrics and key performance indicators (KPIs) must be locked into place to ensure proper governance and performance, including explicit language around continuous improvement and sharing of new technologies.
2. **Develop a well-informed and realistic logistical plan.**
   One of the most significant differences between traditional site-based trials versus home-based trials is that devices must be shipped directly to patients—often in different parts of the world.—in a timely, patient-friendly manner. This is no simple task, requiring extensive experience and institutional knowledge from a provider with a global reach in order to avoid common traps (ie, customs delays) and ensure smooth delivery.
3. **Accommodate differences in country requirements.**
   Keep in mind, import requirements can vary greatly between countries—including device approval processes, documentation requirements, and licenses—which must be factored realistically into timelines well before shipment initiates. Country differences also impact replacement devices, supplies, and resupply shipments.
4. **Ensure proper handling of biomedical waste.**
   Another key component of the paradigm shift in moving trials from the site to the home is the disposal of biomedical waste. Once again, success is achieved through careful planning and *clarity*. Participants in a clinical trial likely do not fully understand the nuances of proper disposal and handling. Therefore, clear demarcation of biomedical waste is essential, with highly prescriptive instructions written simply to ensure rapid comprehension.
5. **Secure study data, materials, and other sensitive information.**
   Provisioning the lockdown of phones, laptops, and other supplementary devices is crucial in the home setting in order to prevent any misuse or accidental encounter with dangerous websites. To secure sensitive trial information and mitigate risk, effective remote management must ensure that all trial participants and vendors only have access to the portals, URLs, websites, or software updates specific for use in that particular trial.

Collecting & generating quality data in the home setting

Once the process for vendor selection and device planning has been carefully mapped out, including, of course, granular scenario planning, the focus turns the core objective of the study: generating and collecting high quality data in the home setting.

As mentioned previously in this article, we now have the benefit of analyzing best practices over a duration of time, so we can turn to evidence-based guidelines that helps ensure the data being collected and generated is of the highest quality. And that begins, of course, with ensuring proper use of the device.

Ensuring ease of use in device management

In the previous section, we covered the importance of choosing a device that is easy to use and simple to operate—as reducing the technology burden helps ensure the data being collected and generated is of the highest quality. But it is also important to keep in mind that *ease of use* must apply to all aspects of the device. Calibration checks, general maintainance, and sterilization requirements should also be simple and intuitive.

Utilizing device-agnostic software—ideally a state-of-the-art, remotely managed eSource platform—is another means of reducing patient burden by eliminating the need for multiple logins while seamlessly collecting data.

An eSource platform requires stable connectivity, achieved only by having a sound grasp of the infrastructure within the geographical location where the data is being collected. To ensure uninterrupted data collection and transfer, risks to connectivity need to be anticipated and accounted for globally. This in turn allows the devices—including laptops, tablets, and other supporting devices—to be sent to the subjects well in advance of the trial.

"Utilizing device-agnostic software—ideally a state-of-the-art, remotely managed eSource platform—is another means of reducing patient burden by eliminating the need for multiple logins."

Remember, ease of use in and of itself does not guarantee a device will be used properly, which is why providing training and around-the-clock, readily available support (what we at IQVIA refer to as *just in time* support) is absolutely essential.

Training content—regardless of channel—must be adaptable to align with the sensibilities and culture of the location, communicated to patients in a quick and easy to understand manner. As a general rule of thumb, incorporating visuals and avoiding long, dense documents optimizes retention of instructional training.

Below are some additional considerations that have proven to be highly successful in home-based clinical trials:

- Not surprisingly, videos are the most effective tools for training, as they are readily available, easy to follow, and can be viewed at any time.
- Training materials must be properly pulsed for maximum effectiveness—providing materials either too far in advance or too close to the trial date presents a new set of risks.
- Creating kits that include training materials is optimal when shipping directly to patients, as it's been shown to be an effective way to ensure patients receive guidance for trouble-shooting.

Remotely safeguarding patient safety and privacy

It is helpful to step back for a moment and consider, once again, that one of the most important objectives when conducting a home-based clinical trial is replicating the same high level of governance typically seen in a site-based trial. This is particularly important in regard to patient safety and privacy.

Historically, the only mode of data transfer was either from the patient to the site, or from the site to either the pharmaceutical company or clinical research organization (CRO). But in a home-based clinical trial, of course, the patient's home *is* the site. The novel devices and software discussed in this article enable data to flow directly from the patient into the pharma company or CRO—as well as the potential for bi-directional data exchange.

Because of this direct path, patient safety and medical monitoring management is a highly important consideration for protecting data privacy, and ensuring adherence to other critical regulations.

Minimizing data loss through monitoring and metrics

As with any clinical trial, home-based studies can only be as successful as the quality of the data being collected. Trial data must therefore be carefully monitored and safeguarded at all times to ensure its quality, and standardized metrics must be put into place to recognize trends and ensure rapid course-correction, if necessary.

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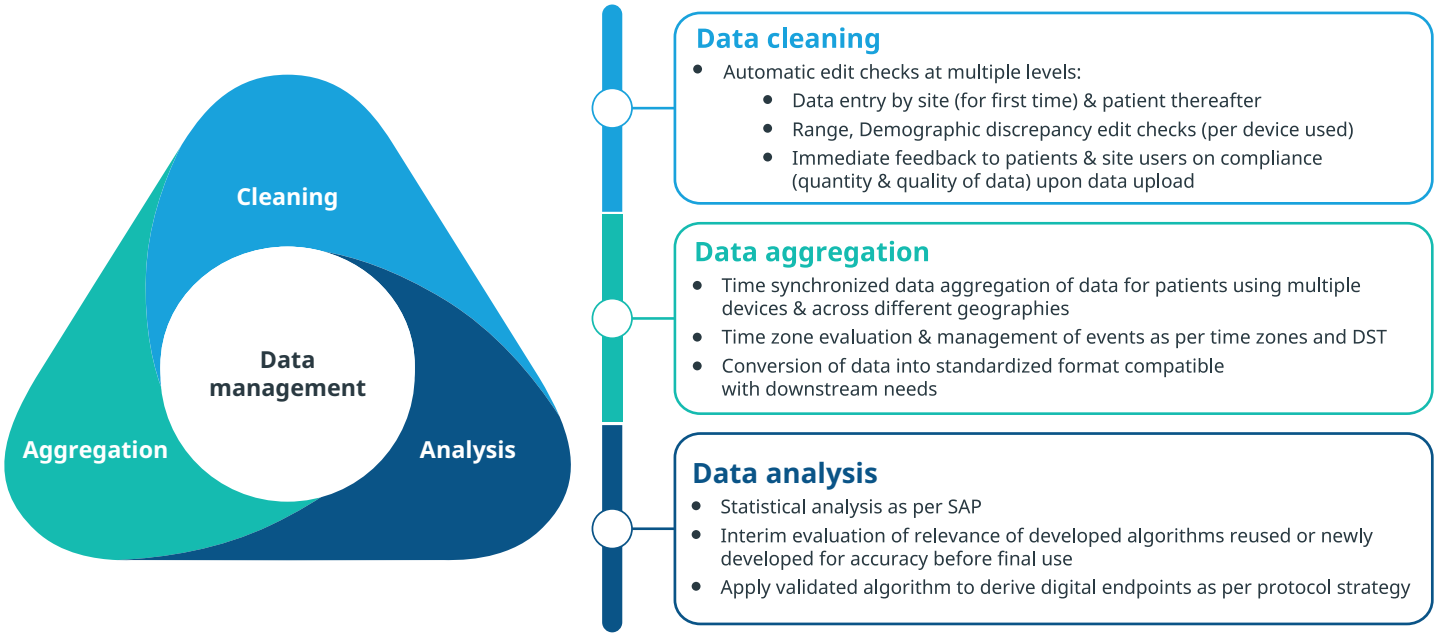
Once again, putting the right metrics in place requires rigorous planning and experience. Is the data being collected as per the device instructions? If not, is site or patient retraining required? Are data uploads occurring in a timely manner to avoid data loss and overwriting? Keep in mind, some devices store data before being uploading.

While it is virtually impossible for 100% of the data gathered to be used in the final statistical analysis of a study, it is critical to produce a sufficient volume of optimum data to ensure a robust analysis of the trial results.

Another critical component of ensuring high quality data is derived from a home-based clinical trial is making sure data management is optimized—which includes *data cleaning, aggregation*, and *analysis* tailored for success in the home setting (see Figure 4, below).

Figure 4. Key drivers of optimized data management in the home setting.



Incorporating automatic edit checks in data cleaning

In home-based clinical trials, data cleaning needs to be thorough, rapid, and occur unimpeded throughout the entire course of data collection—facilitated by automatic edit checks that are triggered upon data entry. This ensures that demographic discrepancies, potential device malfunctions, and other potential risks to data quality are identified immediately upon uploading.

At the same time, we need to ensure that subject identifiers are never shared, achieved by limiting the amount of alphanumeric characters and/or using other best-practices measures of protecting patient privacy.

Synchronizing and standardizing data aggregation

Another critical difference between conducting medical research in the home setting and traditional sites is the potentially extensive range of geographies generating data. Time zone differences *must* be taken into consideration and accounted for in order to ensure that the data being collected in different parts of the world is readily available and accurate.

Even within a single country, time zone variations—such as Daylight Savings Time (DST)—will undermine data quality if not planned for. Therefore, time synchronization of data—as well as converging the data into a standardized format—protects data quality and ensures alignment of the analyses that occurs downstream as specified in the trial protocol.

Incorporating interim evaluations into the statistical analysis

Throughout this article we have stressed the importance of having a well-planned, clearly articulated strategy for every step of a clinical trial conducted in the home setting. The final piece of this puzzle—statistical analysis of the data—is no exception.

Interim evaluations must be put into place in order to pressure test and verify the relevance of the algorithm designs currently in place, and provide an opportunity to potentially explore supplemental algorithms that can help derive the digital endpoints specified in the protocol design.

Summary: the next frontier of patient-centric clinical trials has arrived

When it comes to conducting clinical trials in the home setting, we as an industry finally have what we have been waiting for: breakthrough advances in passive data collection, broad regulatory acceptance, and most important of all, the breadth of experience necessary to make well-informed decisions.

The key to success is a well-planned, clearly articulated strategy for every step of a home-based clinical trial—which includes a finely-tuned digital endpoint strategy, robust device planning, and a data management roadmap uniquely tailored to the home environment.

The tipping point has been reached. And at last, the tide has turned.

Better data, better outcomes, and a significantly more positive research experience for patients has now come to fruition.

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With the background of medicine and clinical research education, Tapan has more than 18 years of experience working in the CRO industry managing centralized cardiac safety operations, data management, as well as creating end-to-end solutions for using data-generated using medical devices as part of the safety and efficacy endpoints for clinical trials.

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With over 12 years dedicated to pre-clinical and clinical trial research, Tracy has supported hundreds of trials in various capacities. Tracy has been with IQVIA for 4 years, and is currently managing a team in project management as well as supporting key clients as a strategic operations lead. In her current role, Tracy supports both strategic conversations around device selection, and develops operational processes.

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