MINIMIZING UNCERTAINTY AND RISK IN CLINICAL RESEARCH

Proven Technologies Provide a Confident Path Forward
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GO BEYOND THE STATUS QUO

The stakes are higher than ever in clinical research. The clinical development marketplace has become more competitive, with stricter regulatory standards and greater emphasis on trial oversight and patient safety. Study designs are becoming more complex, needing more endpoints to demonstrate product value. In fact, the average number of clinical endpoints collected in oncology trials increased 71% between 2002 and 2012,² to an average of 12 per trial.

All this means more data, more data sources and more systems in an environment where budgets and people are ever more strained — often leading to underwhelming performance and unnecessary risks. Less than 10% of trials end on time, and nearly half of all sites under-enroll study volunteers.³

So the question is: Why are so many industry leaders still willing to collect, aggregate, manipulate and report clinical trial data using outdated — and in many cases manual — approaches when automated, centralized solutions have been proven to streamline operations and yield better results?

In this guide, we discuss 10 tech-driven, easily implemented approaches that give trial leaders confidence in meeting their clinical development goals and help them achieve higher quality data, lower costs and shorter study timelines.
EXPAND THE VIEW OF POTENTIAL SITES FOR ENROLLMENT

An investigative site’s ability to enroll and retain patients can significantly affect a trial’s timeline and costs. Many sponsors make site enrollment decisions based only on how a particular site has performed for them in the past — an approach that leaves out viable options that may yield better results.

A better approach is to identify sites based on their performance history across all studies from numerous sponsors. Algorithms based on behavioral and performance data can score a site’s historical performance relative to other sites using criteria integral to each study. These criteria should include patient enrollment scores, site quality scores, site operational efficiency scores and overall site scores with indication and phase specificity.

Site-specific study data across multiple sponsors can be used to highlight which sites have a proven track record for enrollment and patient retention for a given therapeutic area, giving sponsors the robust insight needed to make informed site selection decisions — even benchmarking their own sites against others. Current technology can serve up this data in a highly visual, interactive manner, allowing trial leaders to interpret results easily and identify which sites will position the study for success in the shortest and most cost-effective manner possible.

Learn more by reading this article on how to optimize site performance in four easy steps.
Many sponsors have clung to the use of paper-based patient diaries to collect Patient-Reported Outcome (PRO) and Clinical Outcome Assessment (COA) data based on an outdated notion that they are less expensive than electronic methods (ePRO/eCOA). Today, that’s simply not the case. The cost of poor quality data gleaned from paper collection and transposition — not to mention the risk and cost of waiting for study results — far outweighs the cost of collecting data from patients, clinicians and caregivers using proven electronic methods.

There’s also patient preference to consider: even when experiencing painful conditions and manual dexterity challenges, patients prefer electronic methods over paper. In one study, 86% of patients with rheumatoid arthritis preferred electronic, touch-screen methods over paper and the majority of them rated touch-screen highly for ease of use.4

Learn about the additional benefits of eCOA by reading “Improving Patient/Physician Interactions through Electronic PRO/COA.”
Medical Device Integrations: Ensure Regulatory Compliance and Improve Efficiencies

Objective measures can be collected wirelessly and integrated with ePRO/eCOA data for greater efficiencies. Medical device data — such as spirometry tests, electrocardiograms and imaging results — are often interpreted at sites and then entered manually into EDCs, a time-intensive process that can introduce inconsistencies in interpretation, as well as transcription errors, which jeopardize data integrity, clinical outcomes and patient safety.

By integrating medical device data with eCOA, these objective measurements can be wirelessly uploaded to the study database as eSource, without patient or clinical staff manipulation. Device data outside the customized range can trigger patient safety alerts. This generates quantitative, reproducible and objective data — obtained with less manual intervention in less time, and with lower costs.
ELIMINATE UNNECESSARY COMPLEXITY IN EVERY STUDY

The inefficiencies of paper-based data collection are especially stark when it comes to complying with FDA and EMA regulations that clinical data be attributable, legible, contemporaneous, original, authentic, complete, consistent, enduring and available (ALCOA). Regardless of study size, electronic collection of PRO or COA data will ensure regulatory compliance and minimize operational complexity.

Transitioning from paper to electronic collection doesn’t have to be disruptive. Current eCOA technology translates every protocol to study design requirements. Validated, modular components, rules and logic are employed for study design. As a result, screenshots are available in a timely manner for IRB/EC review.

Once the study design is approved, the unique study code can be deployed to a smartphone, tablet or browser, enabling universal data collection and saving considerable time. eCOA technologies can also streamline mid-study changes, making it easy to deploy amendments across multiple modalities, geographies and languages with a few simple keystrokes.
Real time, Easy Access to Global Data
Further Minimizes Risk

The use of eCOA greatly enhances reporting and analytics, using advanced algorithms to transform data into real time information that highlights areas outside the norm so site staff can address them. This centralized reporting enables 24/7 oversight of all operational and clinical data, from patient recruitment to study close-out — no more waiting until study close to understand what’s been happening.

Audits of study performance can easily be performed online 24/7 using near real time operational and clinical data. More sophisticated systems are even employing heat mapping for patient/site enrollment, compliance and trending, visit schedules and device inventories.

With these technologies, sponsors and CROs can enjoy not only greater control over the clinical trial process, but also improved scalability across geographies — facilitating better patient enrollment while incurring less risk.

Learn how to implement an eCOA strategy with this guide.
Cardiac safety concerns are among the leading reasons that promising drugs are halted in development and not brought to market. The ICH E14 Guidance for Industry requires every new drug to be tested for QT prolongation to predict the risk of Torsades de Pointes (TdP), a lethal arrhythmia. Digital data and ECG waveforms are required for submission, and centralized ECG analysis is recommended (whether assessing QTc in a Thorough QT study or in Phase I with concentration effect modelling, as now allowed under recent ICH E14 revisions).

Many trial sponsors still rely on site-managed ECGs that may produce questionable data quality, incorrectly include or exclude patients, increase study timelines and costs and — most importantly — place participants, trials and compounds at risk.

Although sites claim to be proficient at reading ECGs, a study of more than 900 physicians concluded that while QT experts correctly recognized a long QT 96% of the time, cardiologists and other physicians only got it right only 22% and 21% of the time, respectively. By taking this gamble with data quality, sponsors who rely on site-managed ECG analysis are jeopardizing their compounds due to inaccurate QT readings.

INACCURATE ECG INTERPRETATION OF LONG QT
The majority of physicians cannot recognize a long QT when they see one.

Learn more by watching the webinar replay of “Five Reasons to Rethink Paper ECGs.”
Impact on Patient Eligibility

Patient recruitment takes longer with site-managed ECG measurements. A 2015 analysis of 270,000 ECGs from oncology studies where patient eligibility was determined by site-managed ECG measurements concluded that as many as 45% of the patients excluded due to prolonged QTc were actually eligible for enrollment when correctly evaluated through centralized ECG measurement.6 In an environment where every day of clinical development averages $37,000 or more in operational costs, sponsors cannot afford to exclude suitable patients or incur delays in meeting recruitment goals and completing the trial.7

By centralizing ECG data collection through validated cardiac safety devices, including analysis by trained and experienced experts, trial sponsors gain confidence in ECG accuracy, overcome the challenge of inter-reader variability caused by site-managed readings and collect quality cardiac safety data from sites more efficiently.
Pharmaceutical and medical device developers are increasingly asked by regulators to include imaging analysis when evaluating clinical trial data. In fact, imaging in clinical trials has grown by an astonishing 700% since 2001.¹ While this phenomenal growth adds a whole new level of complexity and risk to clinical trials, trial sponsors need not fret about the inclusion of imaging in their clinical development programs.

However, trial sponsors who continue to take a traditional, de-centralized approach to imaging may be exposing their trial to unnecessary risk, as well as incurring delays and added expense. Traditional image collection, evaluation and management approaches are outdated — often based on paper case report forms (CRFs) and “one-size-fits-all” workflows that cause compliance and data quality issues throughout a trial. Lost images, missing time points and manually assessed images with arbitrary scoring generate subjective and variable data, requiring time-intensive staff reconciliation efforts before being submitted for regulatory review.

Automation and imaging technology solutions help sponsors overcome these challenges and bring myriad benefits to clinical studies, including objectivity, quality, consistency, transparency and compliance — all of which drive efficiencies and enable sponsors to make decisions about endpoints sooner.

Check out our blog for a more in-depth look at the benefits of tech-driven imaging and where the industry is headed.
Drive Better Imaging Results with Objectivity

These solutions empower quantitative and objective image analysis that is more accurate and verifiable than subjective and time-consuming scoring systems. While software-guided reads are becoming an important part of trial design and independent review manual (IRM) development by helping to ensure all images are read uniformly and consistently, strategically deployed human reads are still required to obtain optimal imaging results in many studies.

Through this powerful combination of advanced technology and human expertise, data quality improves, timelines shrink and variability is eliminated.

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Managing risk and generating high quality respiratory data is notably difficult due to complex protocols, lack of training and inconsistent data collection and analysis. Sponsors and CROs who rely on a traditional, decentralized approach to respiratory data collection may face uncertainties about patient safety, compound efficacy and a patient’s eligibility to participate in a trial.

With centralized diagnostic spirometry and pulmonary function testing (PFT), trial leaders can improve patient/site performance and increase protocol compliance for optimized respiratory data quality and improved study efficiencies. This is accomplished through the use of advanced, standardized equipment, along with reliable training and custom workflows that both guide clinicians to follow protocols precisely and help them better coach patients to perform correct maneuvers.

Precision and coaching are important throughout the study, but are most critical in the beginning. Trials need to reduce variability among responders, which begins with baseline readings that enable subsequent active indication management. An inaccurate baseline can artificially inflate drug efficacy — or significantly underrepresent its impact.

### ACTIVE INDICATION MANAGEMENT ENABLES GREATER CONFIDENCE IN THE DRUG EFFECT

**TRADITIONAL METHODS**

- **Patient Response:** Declining lung function?
- **160M decline**

**ACTIVE INDICATION MANAGEMENT**

- **Same Patient Response:** Efficacy Established
- **110ml increase**

**Sites:**

- **Traditional Methods:** limited consideration of research objectives; individual visit assessments reviewed in isolation according to minimum ATS/ERS standards; limited control of core drivers of variability
- **Active Indication Management:** focus on drivers of variability and holistic review of patient data while patient is present at site; move from acceptable ATS/ERS data to optimal data for each test session per patient; site selections and training based on past quality attainment levels

**Results:**

- **Traditional Methods:** reduced statistical power and limited ability to accurately identify responder patients
- **Active Indication Management:** research-grade quality data, greater study power, reduced variability, greater responder determination
Respiratory Trial Oversight & Data Visibility

Respiratory trials — such as those in Asthma, COPD, Cystic Fibrosis and Idiopathic Pulmonary Fibrosis — further benefit from integrated spirometry, FeNO, DLCO, LCI, ECG and eCOA data, which improve trial oversight and data visibility while making it easy for investigative sites to enroll the right patients at trial start-up. Near real time inclusion and exclusion alerts, along with central over-read, further reduce variability for virtually 100% acceptable data.

These benefits apply whether spirometry data is being collected for a respiratory or non-respiratory trial. Many sponsors are now measuring lung safety in inhaled compound trials in which the lungs serve as the entry route into the body — such as diabetes treatments, pneumonia vaccinations and antibiotics — or as a consequence of pulmonary toxicity associated with systemic drug exposure. Accurate respiratory data can speed up the regulatory approval process in these instances, and may eliminate the need to conduct additional trials.

Read how a global pharmaceutical company achieved near-perfect data acceptability in an asthma study.
GAIN GREATER INSIGHT THROUGH INTEGRATED mHEALTH / eCOA DATA

There is increasing interest in incorporating data from mHealth and wearable devices — e.g., activity and sleep trackers, heart rate monitors, and smartwatches — into clinical trials. This is mainly due to the advantages sponsors, sites and patients can recognize from their wireless recording of objective measures to better quantify a treatment’s effect on the participant. Investigative sites can use that data to monitor the patient’s health and engagement, and patient safety is increased with customized safety data range alerts to the patient and clinician.

As wearables and mHealth devices mature and as new products enter the market, the possibilities for their use in pharmaceutical research seem endless. But in order to fully leverage the objective data provided by a device, it must be certified by global regulators as collecting clinical-grade data. Integrating clinical-grade objective data and subjective ePRO/eCOA endpoint data in a single study portal enables researchers to achieve study power more efficiently than with disparate databases. Even better, this approach further simplifies the data collection/transfer process, making it easier for patients to stay engaged in clinical trials.
The Enormous Potential of mHealth Data

Regulatory bodies are taking notice. The FDA has expressed its interest in digital health — defined as mHealth, health information technology (IT) and wearable devices — in a statement: “The use of technologies such as smartphones, social networks and internet applications is not only changing the way we communicate, but is also providing innovative ways for us to monitor our health and well-being and giving us greater access to information. Together these advancements are leading to a convergence of people, information, technology and connectivity to improve health care and health outcomes.”

The FDA established its Digital Health Program to “better protect and promote public health and provide continued regulatory clarity by fostering collaborations and enhancing outreach to digital health customers, as well as developing and implementing regulatory strategies and policies for digital health technologies.”

The future of mHealth has arrived. Clinical leaders who are slow to adopt it in development strategies may be missing opportunities to better engage with patients, gain greater insight into therapeutic effects, accelerate research and reduce development costs. The challenge now is to leverage meaningful insights from that data — and to do that requires incorporating mHealth applications as part of a trial’s core data strategy and revisiting the study infrastructure to ensure the proper technology solutions and data integration processes are in place.

Check out this article to understand the scientific and operational considerations of wearables in clinical trials.
Clinical trial teams must rely on a number of data capture systems — an average of 7-10 per trial — to manage trials in their entirety. Because today’s commonly used clinical data collection systems, such as EDC, IRT and ePRO, are not designed to “talk” to one another, the information that trial managers need is locked in silos and maintained in an assortment of spreadsheets, emails and various extracts. The problem is exacerbated when other data sources, such as labs and mHealth, are in the mix. This lack of integration burdens study teams with manual data aggregation and compilation that are time-intensive and prone to human error. It can take weeks to filter out the noise and identify legitimate issues and risk indicators to act on — leading to slow, reactive trial management that extends timelines and increases costs.

A recent ISR survey found that “better integration of the data between EDC software and other systems” was the solution that most respondents thought would “have the biggest impact on reducing the time needed to conduct a trial.” Fortunately, there are now data-agnostic, cloud-based solutions that can amalgamate all necessary data into one repository. These solutions can integrate data from any number of key eClinical systems, with access controlled by role-based permissions.

“Proactive oversight requires real time — or at least near-real time — and accurate clinical information to support timely and effective decision-making to guide the course of a trial.”

- Andrea Ochoa, Premier Research Executive Director Project Implementation
Untapped Opportunity: Proactive Trial Oversight

By automating data collection through centralized trial oversight technologies, sponsors and CROs can achieve near-real time visibility into trial performance and risk indicators, including:

- Up-to-the-minute enrollment and study progress for each site and across the entire trial
- Queries that are being opened
- Outstanding site deviations
- Other parameters that indicate potential risks and concerns — so you can remediate issues immediately

And because integrated, transparent views of trial data are always available, a centralized platform improves collaboration between sponsors, CROs and other trial stakeholders — freeing up time to focus on strategy, risk mitigation and other key activities, rather than routine information exchange.

Sponsors and CROs that have invested in these solutions reduce the risk of human error in their data management processes, improve operations and dramatically reduce trial times and costs. One CRO saved approximately 200 operational hours per month across 10 studies by integrating data from five different data capture systems into a single trial oversight solution.

MODERN CLINICAL DATA ECOSYSTEM

Advanced oversight solutions provide a 360º view of the many moving parts that make up today’s clinical trial architecture.

Learn how to leverage today’s clinical trial management solutions to create efficiencies and increase transparency in this article.
MODERNIZE REPORTING & ANALYTICS

In any trial, data is king. Using data for different applications at varying points of the trial will provide a distinct competitive edge for sponsors. But not all data reporting/analytics platforms are the same.

In order to meet the needs of today’s and tomorrow’s clinical trials, the platform should enable thorough lifecycle management for validated devices that support the capture of clinical measures in both home and clinical settings. It should also enable seamless integration and amalgamation of clinical trial workflows and data silos, regardless of the data source (application, device, etc.), frequency or size.

An optimal data collection and reporting platform will scale and adjust to accommodate clinical trial complexities through systematic automation of repeatable processes while enabling risk based monitoring, real time analytics and endpoint adjudication to position trials for success.

AUTOMATIC REPEATABLE PROCESSES

1. RISK-BASED MONITORING
   A real time statistical method that looks for outliers in patient data to flag problem sites, advanced risk-based monitoring solutions analyze the quality of data collected to help CRAs determine which sites require intervention and/or additional training. The use of risk-based monitoring is expected to rise, as it is increasingly viewed as a requisite data management tool for all trials — a win-win in terms of complying with international regulatory guidelines and lowering the cost of CRA deployment.

2. REAL TIME ANALYTICS
   Greater interest in adaptive and discovery trials — particularly in oncology — is driving the need for real time analytics to help trials adjust throughout the study process. When data is integrated into EDC, real time analytics take progressive cuts of data and adjust parameters to enrich respondent populations in adaptive trials. Advanced solutions seamlessly integrate patient diary and other clinical outcomes data with commonly used EDC systems, greatly streamlining data management to enable a unified view of the patient and provide real time views of trial performance.

3. ENDPOINT ADJUDICATION
   Since endpoint adjudication is carried out near the end of the trial, when there is dissonance in the conclusions drawn from the data, CROs and sponsors must track clinical trial progress with greater frequency and ease, flagging discrepancies during the study without incurring high costs. Advanced systems are highly secure, capturing and storing data in a repeatable way that protects the patient, site and sponsor. Trial leaders should use a robust platform that can scale to accommodate new or different types of high-volume data from diverse sources, analytic and reporting needs or mid-study changes.
GET SERIOUS ABOUT PATIENT ENGAGEMENT

The role of the clinical trial patient has changed dramatically in recent years. Sponsors recognize the need to put patients at the heart of trials — from their recruitment and education to their ultimate care and safety throughout the process and beyond.

In the not-too-distant past, patient engagement was only considered when a trial wasn’t recruiting effectively. The concept of engaging patients was an afterthought, sometimes even a rescue process. Sponsors who continue to adopt this reactive approach are facing the consequences of poor patient protocol compliance and trial retention, which significantly impacts clinical development costs and timelines.

Today’s most efficient clinical studies focus on proactively engaging patients, not just retaining them. As such, managing the flow of information to and from patients has become critical to trial success.

Understanding of the patient experience and what’s important to them has fueled the development of technology solutions that allow sponsors and sites to interact directly with subjects. Tools such as online disease communities, interactive apps and games accessible online or via patients’ personal devices enable sponsors to tailor their outreach with clear instructions and alerts on what to do and when.

In this way, patients are better informed and engaged, which improves protocol compliance and retains them as active participants, keeping clinical trials on time and on budget.
PREPARE FOR THE FUTURE NOW

While many sponsors and CROs still rely on outdated, often paper-based data collection and management approaches, the pressure to improve trial efficiencies will bring about changes in how they approach these critical aspects of clinical development. Sponsors and CROs that are slow to adopt today’s centralized, technological advances in their clinical operations risk falling behind their more progressive and efficient peers now and in the future.

In order to keep up with evolving trends — a more competitive marketplace, stricter regulatory standards and the need for more complex study designs to demonstrate safety and efficacy — trial leaders will need to rethink their current processes and embrace proven approaches and technologies to accelerate research and reduce development costs. Only then will they remain competitive and positioned for success, confident that their trial is on a sure path forward.

EMBRACE PROVEN APPROACHES AND TECHNOLOGIES TO ACCELERATE RESEARCH AND REDUCE DEVELOPMENT COSTS
REFERENCES


ABOUT ERT

ERT is a global data and technology company that minimizes uncertainty and risk in clinical trials so that customers can move ahead with confidence. With nearly 50 years of clinical and therapeutic experience, ERT balances knowledge of what works with a vision for what’s next, so we can adapt without compromising standards.

Powered by the company’s EXPERT technology platform, ERT’s solutions enhance trial oversight, enable site optimization, increase patient engagement and measure the efficacy of new clinical treatments while ensuring patient safety. Since 2014, more than half of all FDA drug approvals came from ERT-supported studies. Pharma companies, biotech and CROs have relied on ERT solutions in 10,000 studies spanning more than three million patients to date. By identifying trial risks before they become problems, ERT enables customers to bring clinical treatments to patients quickly -- and with confidence.