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Clinical Researcher™

The Authority in Ethical, Responsible Clinical Research

January 2019 (Volume 33, Issue 1)



Data and Technology Trends You're Already Part Of

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Clinical Researcher™

Association of Clinical Research Professionals

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EXECUTIVE DIRECTOR'S MESSAGE

Firming Up Our Foundation

Jim Kremidas

“Training is everything. The peach was once a bitter almond; cauliflower is nothing but cabbage with a college education.” — Mark Twain



While I suspect his knowledge of clinical trials was limited, author Mark Twain understood the importance of the workforce. New technologies are exciting, new best practices are eye-opening, but the foundation of it all is a well-trained workforce with a clear career path and an understanding of expectations and the definition of success. It's called the human factor, and its impact cannot be overstated.

Enlightened focus on the workforce in clinical trials is long overdue. Nurses and pharmacists have clear roles, responsibilities, and standards to use as a professional template. Clinical trial professionals don't. That must change, and I think 2019 is the year to make it happen.

Throughout 2018, I gave you updates in this space about initiatives your Association was either spearheading or supporting. For example, we worked with others to establish competency frameworks for clinical research associates and clinical research coordinators. We're doing the same with principal investigators in 2019.

Via our conferences, our publications, and our speaking engagements, ACRP is beating the drum about the importance of standards and certifications as part of a clear career path. Thanks to you, our messages are powerful—and resonating. A wide array of healthcare organizations has joined

forces with us in several initiatives (many are outlined in John Neal’s “Chair’s Message” for this issue), and the U.S. Food and Drug Administration has begun taking steps with us to help advance the professionalism of the clinical trial workforce.

We’re also working with a wide swath of the industry to come up with innovative ways to attract new entrants into the workforce. I’ve been frankly surprised to learn how few young people are even aware of clinical trials as a career option. As part of our efforts to help craft meaningful career paths, we’re also working to identify and create the knowledge and standards that will help potential new entrants thrive in our industry.

Yes, there’s lots going on already; but I’m hoping our ACRP 2019 meeting and expo in Nashville in April serves as a launching pad for even greater heights. I hope to see you there.

Here’s to an exciting, productive 2019!

Jim Kremidas (jkremidas@acrpnnet.org) is Executive Director of ACRP.

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MANAGING EDITOR'S MESSAGE

The Future Has Arrived: Data and Technology Trends You're Already Part Of

Gary W. Cramer

The secret of your future is hidden in your daily routine. — Mike Murdock



I was struggling to think of how to introduce 2019's first issue of *Clinical Researcher* in a way that wouldn't mention that this is the year in which the first *Blade Runner* movie (the one released in that impossibly long-ago era of 1982) was set. Well, you can see how far my resolve got me...it's my favorite movie of all time, after all.

But wait! There's a connection to be made between the fictional, very dystopian future seen in *Blade Runner* and the real, very promising future of clinical research. At least...I hope I can convince you there is, if you'll bear with me.

In the movie's timeline, the collapsing ecosystem of Earth has prompted anyone who can afford it to emigrate to off-world colonies, where the quality of life is supposedly far better due in part to the slave labor provided by artificial humans (replicants) with limited life spans. Although it is not explicitly shown in the film, one gathers that replicants are treated as highly regulated, disposable tools, despite the most advanced models having developed authentic emotional responses to their experiences.

No Time Machine Required

As my mind makes the (possibly tortured) leap from science fiction to science fact, I recognize that the snowballing revolution we are experiencing in all things data- and technology-related has made—not without some bumps and bruises along the way—what in past decades would have seemed astonishing advancements in the practice of research part of our daily routines. As may be gleaned from the words of contributing authors in this issue, in many respects within the clinical research enterprise, we blinked—suddenly it’s 2019—and the future has arrived.

Although our environment hasn’t totally tanked (yet), we don’t have flying cars (yet), and replicants who can’t be distinguished on sight from us real folk don’t walk among us (yet?), we are already in the future foreseen by the more cautious prognosticators of the data and tech world nearly 40 years ago. In many cases, we’re not waiting to catch up to the trends we’ve long been told would change our lives; how we handle our daily home and work chores right now *is* the trend. We’ve made it! But we won’t be standing still.

Making the Future a Place You’ll Want to Live

In the quest to conscientiously utilize the best capabilities delivered to us via data and technology breakthroughs for the betterment of all, our clinical research enterprise will only thrive in this future we have awoken to if we keep a constant focus on the very real people who make it work. This translates not only to carefully crafted professional development opportunities that bolster the core competencies of the research workforce, but to the fostering of consistent and compassionate care for the volunteer participants in our studies.

Far from being treated as anonymous datapoints in a medical research realm motivated by profit and prestige—as mere replicants whose value is derived from limited terms of service—I hope that whatever the ongoing march of our technical prowess allows us to achieve, the flesh and blood people who have made it possible will always be cheered as “more human than human.”



Gary W. Cramer (gcramer@acrpnnet.org) is Managing Editor for ACRP.

CHAIR’S MESSAGE

Change is (Still) in the Air

John P. Neal, CRCP



As the clinical research industry continues to change quickly, I am fortunate to take the reins as Chair of the Association Board of Trustees for ACRP this month, following what was a successful year of firsts for ACRP in 2018.

As I had predicted at the ACRP 2016 Meeting & Expo, and subsequently in a series of blog postings titled “[Change is in the Air](#),” we are experiencing consolidation of companies across the spectrum (sponsors, contract research organizations, institutional review boards, and sites) at record rates. Concurrent with that, under the leadership of U.S. Food and Drug Administration Commissioner Scott Gottlieb, MD, a record number of drugs and devices were approved in 2018, bringing new hope to millions of people as these new therapies come to market. It is an exciting time to be involved in clinical research, while at the same time being challenged with the rate of change.

What Has Been...

In keeping up with ACRP’s mission to Promote Excellence in Clinical Research and to be the leader in defining the competencies, training, education, and certification options for our industry now and into the future, your Association successfully launched several programs in 2018 and expanded others, including:

- In May 2018, ACRP announced a new subspecialty designation program for certified individuals, the [ACRP Project Manager](#), or ACRP-PM.

- In June 2018, as a result of the work of our [Workforce Innovation Steering Committee](#) (WISC), the WISC and ACRP announced a new initiative to create the clinical research industry's first comprehensive set of [Core Competency Guidelines for Clinical Research Coordinators \(CRCs\)](#). Focused on hiring entry-level CRCs, these guidelines were released in December.
- In August 2018, ACRP unveiled the [Partners in Workforce Advancement](#) initiative, which is designed to raise awareness of clinical research as a career option and grow the workforce.

What's to Come...

The year ahead will be equally exciting. One of ACRP's goals for 2019 is to bring together—via conferences, educational webinars, training seminars, and publications—sponsors, resource providers, and sites in order to raise the quality of clinical trials. [ACRP 2019](#), taking place in Nashville, Tenn. this April, affords clinical research professionals in all disciplines the opportunity to stay up to date, expand their knowledge, and network with their peers from around the globe.

Additionally, in 2019 the WISC and ACRP will publish competency standards for principal investigators—a first for the industry. Through a variety of industry partnerships throughout 2019, ACRP will launch several additional initiatives, so stay tuned. I expect 2019 to be yet another successful year of firsts for ACRP.

I hope to see you in Nashville this April.

John P. Neal, CRCP, is Founder and Chairman of PCRS Network, LLC, and the 2019 Chair of the Association Board of Trustees for ACRP.

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PEER REVIEWED

How Can Real-World Data Support Clinical Trials and Medical Research?

Manfred Stapff, MD, PhD; Jennifer Stacey



Drug development is a long and complex process. A drug's life cycle is not limited to the results of clinical trials in Phase I through Phase IV—it also includes research about the cause and natural history of diseases, clinical outcomes, long-term safety, tolerability, optimal treatment targets, and new indications.

Over the past decade, key performance metrics in the clinical trials area have been constantly disappointing, and even worsening.^{1,2} As the complexity of clinical trial protocols increases, the feasibility to conduct them and the percentage of sites fulfilling the enrollment goal decreases.^{3}

Clinical research, especially as applied to drug development, is a very data-driven industry. Biostatistical methods and the interpretation of study results based on p -values dominate the scientific decision-making processes. However, in planning and operating clinical research, objective data and metrics are not used to the extent to which they are available today.

For example, healthcare data have been available in electronic format in recent years. The digitalization of the U.S. healthcare system, driven by the 2014 “Meaningful Use” legislation, can be considered almost complete. By 2015, 96% of all hospitals in the United States had already adopted certified electronic health records.^{4} However, the electronic data thus far have been locked in various systems, are scattered in many locations, and follow different standards of ontology, units, and other characteristics. These electronic data issues, together with the lack of a consumable, user-friendly visualization platform, made the use and interpretation of this vast amount of medical information difficult.

The following is intended to provide an overview of how electronic health data can currently provision the design and conduct of clinical trials, as well as support other medical research areas.

Electronic Medical Records Versus Claims Data

The two major sources for real-world data (RWD) in medical research are electronic medical records (EMRs) and insurance claims data. EMRs can be considered as the more “medical” component of patients’ health information. They contain data about diagnoses, examinations, and treatments as documented by a provider who applies healthcare to a patient.

A patient’s EMR data from a specific healthcare provider may be blind to information collected by other providers. For instance, another hospital visited (or physician consulted) by a patient may not have access to the patient’s prior EMR information, as these records may be in separate repositories unique to each treating healthcare organization.

Meanwhile, claims data represent the more “administrative” part of a patient’s health history. They originate from the interaction between provider and payer, and could include documentation which have been submitted or adjudicated or remitted for payment. Because of the original billing related intention, claims data may be limited to information supporting reimbursement (see Table 1).

Table 1: Claims Data Compared to EMR Data

	Claims Data	EMR Data
Scope of data	Broad: Information from all doctors/providers caring for a patient	Limited: Only the portion of care provided by doctors using the specific EMR of a provider organization
Contained diagnoses	Limited to diagnoses supporting a claim	Complete set of conditions and comorbidities
Included patients	Payers' covered population, U.S.-employed socioeconomic group	All patients of a healthcare provider, including uninsured
Medication	All prescriptions that were filled, including dates of refills	Knows only that a physician prescribed a drug, but not if it was filled
Longitudinality of data	Payer/employer-based: As long as a patient stays with the same insurance	Provider-based: As long as the patient stays with the same healthcare provider
Richness of data	As necessary for reimbursement (diagnoses, procedures, treatments)	More complete medical picture (diagnoses, laboratory results, vital signs, problem list, etc.)
Timeliness	Lag time, delay from submit to close	Often real time, as soon as entered/coded

As a rule of thumb, one can assume that claims data better support studies about the economic effect of a therapy or the cost burden of a disease, while EMR data better capture natural disease history, efficacy, safety of a drug, or the outcome of a disease. Ideally, both data sources, used together on a patient level (also known as “linked data”) and cleaned for duplicate information, would provide an optimal dataset for all applications.

Incorporating additional data sources can enhance patients' health histories and clinical characteristics beyond standard medical coding practices. For example, data from tumor registries often contain tumor stage at diagnosis, histology, and other cancer-specific factors; a genomics database may include details on sample sites tested and variant types. Such sources can open the world of personalized medicine in a data context.

How Can RWD Support Clinical Trials?

The success rate of drug candidates making it all the way from Phase I to launch remains low (approximately at 10%).^{5} Meanwhile, the complexity of clinical trial protocols, notably expressed by number of patient eligibility criteria requirements, is increasing, and this leads to significant enrollment challenges.^{6} Less than 30% of protocols do not need to be amended; 70% need two to three changes over the course of the study, which is an inefficient trend causing damages in terms of costs and time.

Study results are only taken seriously if there is a p -value below 0.05 or an appropriate confidence interval. However, in conducting clinical research, data and analytics are not used to the extent they are available.

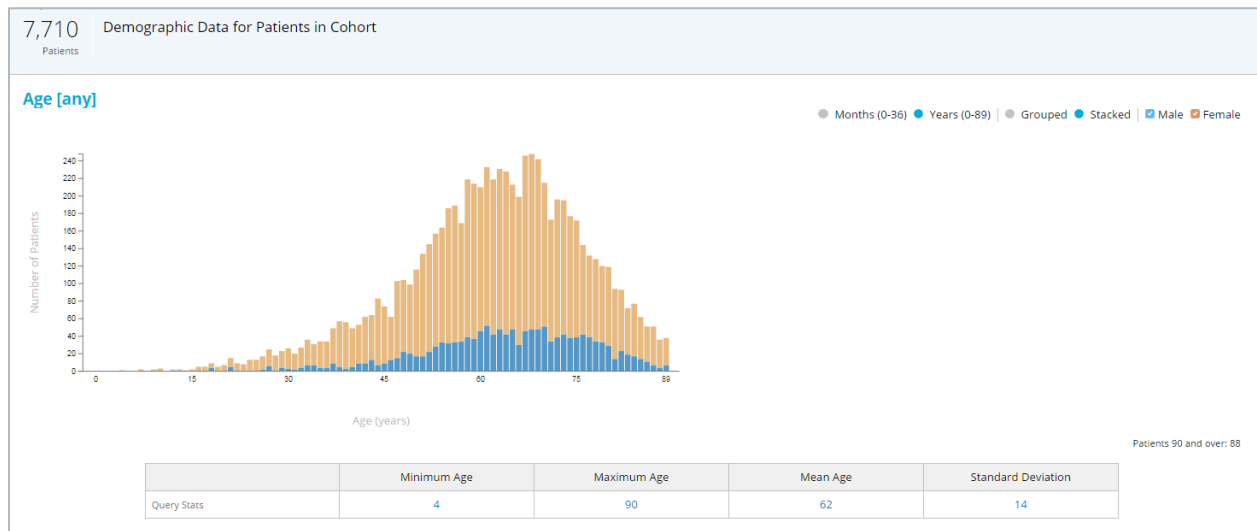
When determining the target population for clinical trial protocol design—from eligibility criteria to whether an amendment would improve a study—protocol authors traditionally rely on literature, experience, or expert opinion. They often do not have access to or use the extensive amount of RWD available in ways which would propel this decision-making process into a more objective and real-world scenario. Many costly and time-consuming amendments could be avoided by proper data-driven strategy planning.^{7}

Where in the Clinical Trial Process Can We Use RWD?

Trial design: Protocol authors need reliable and real-world information about patients, diseases, comorbidities, and concomitant treatments from routine medical practice (i.e., how patients present themselves in a true medical setting). RWD allow these authors to design clinical trial protocols in a realistic manner, including creating a feasible set of eligibility criteria.

A very simple example: It is a well-known fact that elderly patients and minorities are usually underrepresented in clinical trials. {8} Upper age limits are introduced in trial protocols for safety reasons, but often shift the demographics of the population toward younger patients. A quick look at RWD and the age distribution of patients with the target indication helps to quantify the discrepancy, and to set the age limit to an optimal value with the best balance between safety and representativeness (see Figure 1).

Figure 1: RWD Age and Gender Distribution of Patients with Rheumatoid Arthritis (RA) on Disease-Modifying Therapy

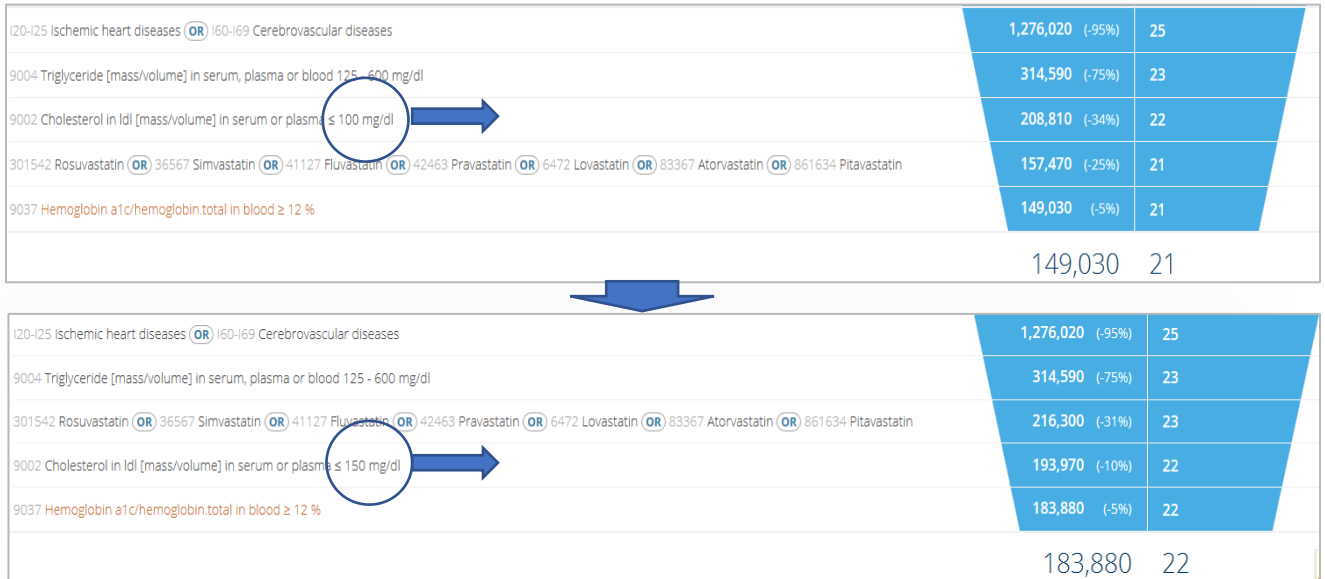


Note: If the upper age limit was set to 75 years versus 90 years, the study would miss almost 20% of patients with RA.

Study Feasibility: Clinical trial eligibility criteria are often compiled arbitrarily and carried forward through development phases by company standards (“tradition”), or come from individual(s) expert input(s). Nevertheless, they are rarely tested against RWD, especially in terms of their effects on the final percentage of eligible patients with all criteria taken into consideration together.

A simulation of a criteria analysis, or “patient funnel,” can help identify the most impactful criteria, predict recruitment hurdles, and test the effect on enrollment if criteria are changed (see Figure 2).

Figure 2: Automated “Patient Funnel” to Simulate Enrollment and Effect of Eligibility Criteria on Patient Availability (Based on RWD)



Note: Patients with cardiovascular events, with controlled hyperlipidemia, receiving statins, and with different cholesterol lab values were compared.

Site Selection: Once the protocol is designed, the study should be placed only in those sites where there is proof of availability of eligible patients. Traditionally, lengthy and time-consuming feasibility questionnaires are used to determine the number of potentially eligible patients at a site, and often this is estimated by an investigator. An RWD system which keeps the link from anonymized patient data back to the site—ideally with a built-in communication feature to the sites—allows the user to select sites with pre-screened patients. It also simultaneously addresses the Good Clinical Practice requirement {9} of the investigator to prove access to suitable study subjects.

Patient Screening: Data privacy regulations require that the collection of patients' health data happens in an anonymized, or at least pseudonymized, manner that makes re-identification of individuals impossible. A federated network structure, however, allows aggregated statistical counts to be obtained from the data source, keeping the original data at the source together with an identification key. Therefore, this enables the site via an "Honest Broker" to re-identify eligible patients (those matching inclusion/exclusion criteria) and potentially contact them (after respective institutional review board approval) for study participation.

Many vendors and data providers offer service or systems for different aspects of clinical trial optimization. The more steps of the process, from protocol design to patient enrollment, that can be addressed by the same system, the easier it will be for the corporate sponsor or the contract research organization it is using to implement such support from the procurement, budgeting, efficiency, and training perspectives.

From Randomized Controlled Trials to Real-World Evidence Studies

In decades past, randomized controlled trials (RCTs) represented the one and only gold standard for gaining scientific knowledge in drug development and in medicine in general.^{10} Only with the advent of EMRs has a new method, generally referred to as real-world evidence (RWE) studies, been discussed as reasonable and more representative alternative to RCTs.

RCTs are usually conducted in a very experimental and unrealistic setting. Nowhere in actual medical practice are patients so carefully selected, so closely supervised, and so well cared for as they are in a clinical trial. In some therapeutic areas, such as oncology, the expectations of study subjects achieving efficacy are quite high, and clinical trials are intensively promoted as best treatment options. Thus, a significant placebo effect can occur, and ethical questions are often raised.^{11}

Inclusion of patients who may be more likely to show efficacy and exclusion of patients with certain risk factors dramatically reduce the representativity of the study cohorts and their applicability to the general population.

On the other hand, RWE studies have their flaws, too. The main subject of criticism concerns the quality and completeness of the data, especially in terms of the trustworthiness of data analyses when there has been no randomization of the subjects. In comparative RWE studies, the susceptibility for confounding factors (bias) requires correcting or balancing methods, such as stratification or propensity scoring, to achieve comparable cohorts. See Table 2 for a summary of the general differences between RCTs and RWE studies.

Table 2: Main Differences Between RCTs and RWE Studies

RCT (experimental, “laboratory situation”)	RWE (data from real medical practice)
<ul style="list-style-type: none"> • Extremely selected population • Artificial experimental treatment • High expectation on efficacy by study subjects • Prospective randomization • Ideally, no confounding factors • Impacted by the scientific thinking of the protocol author • Average number of data points collected: 400,000 to 1,000,000 	<ul style="list-style-type: none"> • Population “as in medical practice” • Usual care • No significant placebo effect • Retrospective characterization • Very susceptible to significant imbalance and bias (e.g. physicians’ treatment decision) • Impacted by processes and documentation • Average number of facts in a typical RWD cohort: 500,000 to 900,000,000

The data from an RWE study cohort can contain much more information than the data from an RCT. This is mainly due to the much larger sample size, and often longer observation period, that can easily be achieved in comparison to RCTs with limited durations in which patients are willing to participate.

In RCTs, only a fraction of the available evidence is used. Estimates report that only about 2% of patients with cancer can enroll into a clinical trial, but we use 100% of the information from this highly selected small population for decision making about that specific oncology condition. {12}

Data in RCTs are perfectly validated against the source and checked for errors, as they are heavily regulated and monitored. Contrarily, RWE studies take the data as they are, reflecting actual medical practices. As such, they are influenced by patient characteristics (demographics,

comorbidities) and by provider characteristics (prescribing behavior and documentation completeness).

Meanwhile, it is sometimes the case that not enough discipline is applied in differentiating between RWD and RWE. In general, the “data” in RWD are related to the delivery or reimbursement of healthcare to a patient; they only become the “evidence” in RWE if adequate methods of collection, analysis, and interpretation of the data are applied. Only the combination of high-quality data collection and proper scientific methodology creates RWE out of RWD and makes this RWD/RWE combination “fit for purpose.”

The more accessible RWD become and the more valid RWE analyses are considered as researchers’ capabilities to do so develop and improve, the more questions will be raised over the extent to which RWE studies will one day replace RCTs. In our view, while RCTs are certainly complicated and costly, they will most likely never be replaced completely by RWE studies.

For drug development, especially in early phases when the knowledge about safety and efficacy of an experimental therapy is very limited, researchers may always need the experimental and relatively safe environment of a clinical trial. Yet in the advanced stages of clinical development—in Phase IV or perhaps even late in Phase III—RWE studies can be a much more cost-efficient tool for collecting the necessary knowledge based on a conditional approval for new indications or for long-term safety observations.

Proper Analyses Methods Needed for RWE Studies

Due to the ease of use and cost efficiency, it may be tempting to run repeated analyses on RWD until a desired result is found, and then take this result as scientifically proven. Terms like “data dredging,” “fishing expeditions,” “*p*-hacking,” and “selective publishing” are used to describe this undesirable practice. Therefore, it is extremely important to follow proper scientific methods from concept to planning regarding data collection, analysis, interpretation, and publication.

Ideally, an RWE platform would require a predefined analysis plan to be uploaded and documented, and would have an audit trail which date stamps all analytical steps. This would

show that the pre-specified data analysis plan was followed, and no result-driven analysis was conducted.

Proper documentation of analytical steps is important for the overall credibility of the study, and for the use of RWE within the context of meeting regulatory expectations for validity of data comparable to what is seen from RCTs. Guidelines are being developed and standards are currently being defined by several organizations, including the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the International Society for Pharmacoepidemiology (ISPE){13}, as displayed in Figure 3.

Figure 3: ISPOR and ISPE Recommendations for Good Procedural Practices for Hypothesis Evaluating Treatment Effectiveness Studies

1. *A priori*, determine and declare that a study is a Hypothesis Evaluation Treatment Effectiveness (HETE) study or an exploratory study based on conditions outlined below.
2. Post a HETE study protocol and analysis plan on a public study registration site prior to conducting the study analysis.
3. Publish HETE study results with attestation to conformance and/or deviation from the study protocol and original analysis plan. Possible publication sites include a medical journal or a publicly available website.
4. Enable opportunities to replicate HETE studies (i.e., for other researchers to be able to reproduce the same findings using the same dataset and analytic approach). The ISPE companion paper lists information that should be reported to make the operational and design decisions behind an RWE study transparent enough for other researchers to reproduce the conduct of the study.
5. Perform HETE studies on a different data source and population than the one used to generate the hypotheses to be tested, unless it is not feasible (e.g., another dataset is not available).
6. Authors of the original study should work to publicly address methodological criticisms of their study once it is published.
7. Include key stakeholders (patients, caregivers, clinicians, clinical administrators, payers, regulators, manufacturers) in designing, conducting, and disseminating HETE studies.

Studies using RWD have not yet achieved the levels of credibility and sophistication credited to RCTs, with their very detailed guidelines and regulations. While the U.S. Food and Drug Administration has already issued guidelines for the use of RWD in the regulatory process of medical devices, similar guidelines for use in drug development are pending. Therefore, RWE studies will, for the time being, mainly focus on hypothesis-generating projects, signal detection in pharmacovigilance, and obtaining supportive data for new indications (see Figure 4).

Figure 4: Potential Use Cases for RWD in Medical Research and Drug Development

Clinical Development and Operations

Use in design and statistical planning (sample size, variability, event rates)

Test feasibility of eligibility criteria

Select sites with eligible patients

Pharmacovigilance and Patient Safety

Observe safety signals (e.g., previously unknown adverse events)

Identify subpopulations with unique risk profiles

Describe safety in real-world conditions, validate or disprove safety signals

General Medical Research

Generate new hypotheses about diseases, causes, and potential new therapies

Understand real patient demographics, comorbidities, comedication

Describe the natural history of diseases

Medical Services and Health Outcomes

Understand treatment patterns and pathways

Evaluate clinical effectiveness and patient outcomes over time

Discover auxiliary benefits beyond original indication

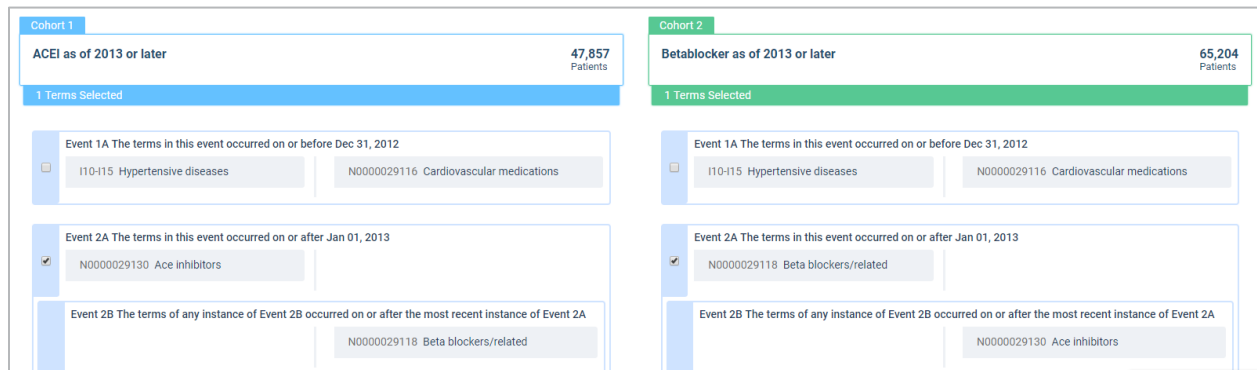
RWD and associated RWE may constitute valid scientific evidence, depending on the characteristics of the data and the analytical methods used. It will, however, take time for RWD guidelines to be established and the quality of RWD to achieve a high enough standard so that RWE studies can be used as a hypothesis confirming method, especially in the drug regulatory process. Nevertheless, RWD can now answer very important questions for which RCTs would be too time-consuming and costly for individual sponsors to conduct.

From RWD to RWE: An Example

After more than two decades of clinical trials conducted in hypertension, it is still unclear which antihypertensive class is better as first-line therapy for stroke prevention.^{ 14,15 } As most beta blockers (BBs) and angiotensin conversion enzyme inhibitors (ACEIs) are off patent and their clinical outcome results are unpredictable, it is unlikely that a sponsor would ever conduct a lengthy and costly clinical trial to compare BBs to ACEIs in stroke prevention. However, as seen in the following, RWD can provide valuable clinical insight to this comparative research.

The population to be evaluated is defined as having the ICD-10 code for hypertensive diseases (I10 to I15) and never having any cardiovascular medication before (taking either a BB or an ACEI as a first-line therapy). The ACEI group must have an ACEI but no BBs, and the BB group must have a BB but no ACEIs. To focus on relatively recent data, only patients with start of therapy after January 2013 are included (see Figure 5).

Figure 5: Cohort Definition Comparing ACE Inhibitors to Beta Blockers for First-Line Treatment of Hypertension



The start of therapy has been defined as the index event with a three-year observation period, starting 30 days after the index event (to exclude carryover effects from any diagnosis documented at the index date). The browser-based analytics platform then provides the results to a defined outcome (i.e., the risk of experiencing a cerebrovascular event [I60- I69] within the observation period) (see Figure 6).

Figure 6: RWD Results Comparing Risk of Experiencing Any Cerebrovascular Event Up to Three Years After Starting Antihypertensive Therapy with an ACEI or BB

Cohort		Cohort Statistics		
		Patients in Cohort	Patients with Outcome	Risk
1	ACEI as of 2013 or later	47,827	3,084	6.448%
2	Betablocker as of 2013 or later	65,152	6,805	10.445%

Risk Difference		Risk Ratio		Odds Ratio			
Risk Difference	95 % CI	z	p	Risk Ratio	95 % CI	Odds Ratio	95 % CI
-3.997%	(-4.318%, -3.675%)	-23.486	< 0.0001	0.617	(0.593, 0.643)	0.591	(0.565, 0.618)

Since retrospective RWD observations are not based on randomized patients, confounding factors with the potential for introducing bias must be considered. In this case, the BB group had a slightly higher percentage of patients with cardiac arrhythmias, heart failure, atrial fibrillation, and ischemic heart disease, but was otherwise comparable to the ACEI group.

There are several methods to balance for such confounding factors, with two of the most common being stratification and propensity scoring. Stratification was applied in this example, with two more analyses being performed. One subgroup contained only patients with at least one of these cardiac comorbidities; the second excluded all potential confounding cardiac comorbidities. Both strata delivered results comparable to those seen to the initial cohort, indicating that the cerebrovascular advantage of the ACEI may not be confounded by a slight imbalance in cardiac comorbidities.

More sophisticated cohort definitions and biostatistical methodologies may bring this simple example closer to a hypothesis-confirming study, rather than a hypothesis-generating one. This example also shows that the use of RWD in combination with user-friendly analytical tools can very quickly provide a picture about the therapeutic effectiveness of treatments in real medical practice, rather than in the artificial environment of an experimental and costly RCT.

Scientific Use of “Big Data” in Medical Research: General Considerations

Discussions about the use of healthcare data for research are often motivated by two fundamental questions:

1. Which is the optimal source of data?

- RCTs are a very exact methodology to evaluate a treatment in isolation, under ideal conditions, and in a highly selective population. The results depend on patient eligibility criteria and on the details of the study protocol, providing insights to scientists on the effects of a molecule in development.
- RWE studies represent the collective experience from thousands of physicians treating millions of patients. They provide a complete view at the actual use of a product, its effectiveness, and related adverse events in a real medical setting. The results are influenced by treatment standards, physicians’ prescribing behavior, pharmaceutical company marketing, and documentation quality.
- A third data source is gaining more and more attention: patient-reported outcomes (PROs), including those communicated in social media. Here, the “voice of the patient” comes into play, and the information can be considered as if coming from an expanded focus group whose members are providing unfiltered, spontaneous feedback toward an overall view of the treatment’s reputation.
- While very sophisticated and scientific mentalities may still consider RCTs as the only gold standard in clinical research, one must admit that only together with RWE and PRO can a holistic picture about a treatment—its efficacy, tolerability, and effectiveness—be achieved. These three methods should not be viewed as competitive, but rather as complimentary.

2. Who can use a patient's medical data?

This question can be approached from an ethical standpoint or from a legal definition of “ownership.” The legal aspects, such as those related to privacy, data forwarding, or the analyzing process, must obviously be considered when using patient data for any research purposes. Compliance with every applicable law is a must, and the use of data created by one organization and used by another requires a contractual agreement.

The ethical and scientific views add nuance to this issue. A look at the life cycle of a study from data collection to publication shows that every step in the process adds value in advancing clinical research (see Figure 7):

- The patient allows the healthcare provider to document her or his health data
- The provider joins a data network, so healthcare information can be shared and analyzed by researchers
- These researchers analyze the data and publish the results

Only then can progress in medicine be achieved toward helping patients with the same condition.

Figure 7: Data Value Chain



All participants and steps in this circle make valuable contributions to data-driven medical progress. Patients who will suffer due to a medical condition in the future should be able to benefit from the information obtained from those who suffer the same medical condition today. To define an ethical “data ownership” is rather difficult, but the use of patient data should be available to researchers aiming to improve how clinical research is conducted.

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PEER REVIEWED

Risk-Based Strategies and Technology: Streamlining Site Activities

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In the past several years, clinical trials have continued to increase in number and complexity. Site infrastructure must acclimate to technology and create adaptive coping methods to meet these demands.^{1} Resource adaptation within changing protocol requirements is a critical skill, particularly as technology advances in the global clinical market.^{2} The streamlining of processes requires embracing new technology and new applications of current technology for best practices in training, reporting, and documentation.

The challenges and advances of the 21st century are a give-and-take system, accommodating both the increasing detail of research and providing technological solutions for excellence in safety and quality.^{3} By using a risk-based approach to site operations that is rooted in technology, site staff can be supported by best practice clinical trial conduct.^{4}

While current literature is abundant on risk-based monitoring application for sponsor/contract research organization (CRO)–level processes, the use of these strategies at a site level has not

been fully explored. This discussion outlines essential considerations for small and/or inexperienced sites using a two-pronged approach: using technology to streamline site activities, while also reallocating resources to the areas of highest risk.

The Site Role

Implementation of a risk-based approach to site processes is key in smaller practice trials, where funding for complex software aids and specialized staff may be lacking. Within practices of one to three investigators, research support staff often maintain numerous roles to accommodate the protocol requirements. Crucial skills of a research coordinator include “...organizational skills, attention to detail, interpersonal skills, and computer and database experience.... They can make or break the clinical trial.”{5}

When communicating complex situations, site-provided details create the data story. An accurate story allows downstream data managers/statisticians to correctly categorize and interpret adverse events, relationships, and investigational product comparisons. The information must be reliable in detail and well-representative of the real-life situation.{6}

The site focus should be on crucial success factors for growing and maintaining a clinical research team: proper knowledge, practical skills, and appropriate attitude. These skills allow site staff to effectively work in teams, stay motivated for self-directing tasks, and accurately handle information.{7}

Resource Allocation in Trainings—Strategic Use of Recorded Sessions

Rather than conveying a complete spread of equal resources to each aspect of a study, a risk-based approach has been shown to improve data quality at a lower cost.{8} As outlined by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), a risk-

based strategy identifies the areas of greatest risk for each specific protocol and allocates the highest priority and resources to those high-risk areas.{1,9}

It may be necessary to first discuss the purpose and rationale for risk-based strategies with site staff in order to prevent negative assumptions.{10} While larger and experienced sites may afford risk-based software, smaller and/or inexperienced sites will need to tackle trainings from a simplified, risk-based perspective.

With the amount of protocol/procedural education required in clinical studies, sites should consider recording narration of slides for minor trainings and for staff self-review purposes. While major trainings may require scheduling live presenters, recording such sessions allows for simple refreshers as needed.

Creating Visibility with Documentation

It is the sponsor's responsibility to ensure the quality of study data reported from each site. Inaccuracies or inadequacies in case report forms (CRFs) have been one of the most common reasons for FDA Warning Letters to clinical investigators.{6} Good documentation practices (GDPs) aim to prevent these types of violations by reducing/eliminating queries within the patient record. Once a site's risk areas are identified, transparent procedures can be built into daily activities.

In novice research sites, insufficient documentation could be due to a lack of training and/or experience.{6} Examples of essential GDP training include attention paid to documentation of Good Clinical Practices, study protocols and related procedures, and standard-of-care practices onsite. Evidence of these trainings should be tracked in dedicated electronic logs or forms, to create transparency and enhance reporting.

Note the difference between the task quality and procedure of documentation. In this case, “quality” refers to training completeness, while the documentation “procedure” refers to the correctness or detail of the associated log.

Figure 1: Example of a Log with GDP Elements

Version number and date. V1.0 15April2016

Name of site and contact information. Dr. Smith's General Practice
1234 Street Road
Boston, MA
555-555-1234

Information on each person who participated as well as a confirmation signature.

Description of log. The following staff members employed at Dr. Smith's General Practice participated in a training session.

Name	Title	Signature	Date	Comments
Suzy Adams	Trial coordinator	<i>Suzy Adams</i>	4/20/17	none -
 				
SA 4/20/2017				

Date of training (dd mmm yyyy): 20 April 2017

Training completed by (name, title): Dr. Smith, Medical Director

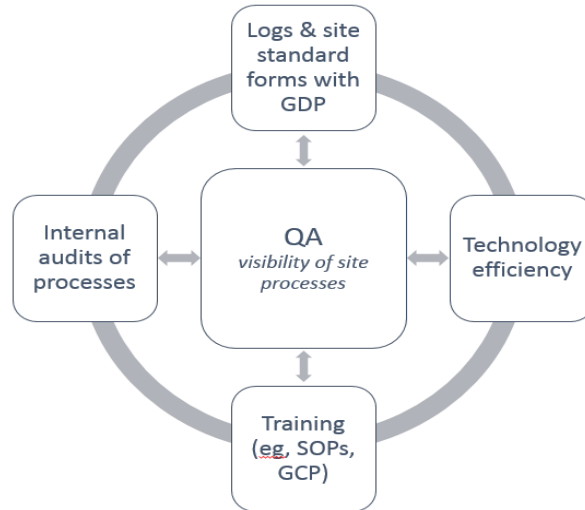
Training Topic: Training covered good clinical practice guidelines and ICH guidelines current as of April 2017. The session lasted approximately 2 hours and included time for questions.

Signature of individual completing training: Dr. Jane Smith

Description of training, with date and name/signature of person who completed training.

Figure 1 illustrates a well-constructed log using GDP elements. Two common research adages are worthy of memorization by site staff: “What is not documented is not done” and “Document what is done, as well as what is not done.” These phrases are excellent reminders to improve the visibility, providing a preventative and ongoing feedback loop for quality management. {6}

Figure 2: Interactions Between Site Process to Ensure Quality Assurance



When determining the interaction between site processes, Figure 2 may provide clarity.

Log/form standardization, training, and technology efficiency are dynamically involved with each other to ensure quality assurance (QA) at the site. With documentation of the research activities, specific movement of staff, patients, and data throughout the practice becomes measurable.

Consider an alternate application of technology to facilitate mandatory staff training, thereby allowing visibility within site process; for example, staff are required to review slides on a minor protocol amendment. Upon completion, staff are instructed to complete a brief electronic quiz on SurveyMonkey® to demonstrate understanding. After the training due date, the quiz results are downloaded and filed, along with the slide deck.

A QA reviewer of the quiz will report any concerns about individual results to management, and a discussion on future risk mitigation could commence—fulfilling certain safety requirements and guidelines established in 21 CFR Part 50 (Protection of Human Subjects) in the *Code of Federal Regulations* and in the International Council for Harmonization’s E6(R2) guideline on GCP.{11,12}

Specific strategies on documentation should be integrated into operational site processes, enabling routines to support FDA compliance. This coupling of corrective/preventative action is the best practice for efficient and high-quality site management.{1,12}

Integrating GDPs into Your Site

The specific mechanism of action to establish visibility is outlined through GDPs. Per GCPs, GDP standards should be integrated into mandatory site standard operating procedures (SOPs). The FDA ensures data quality with the acronym ALCOA, which stands for attributable, legible, contemporaneous, original, and accurate.{13} The EMA later enhanced ALCOA with four new elements (complete, consistent, enduring, and available) when considering electronic documentation, changing the acronym to ALCOA-CCEA.{9} These aspects are wholly grounded in the traceability of data origination, which are more readily examined from electronic sources.

A second document that is often required for clarity at a clinical research site is a memo- or note-to-file (MTF or NTF). These are documents included to explain errors or issues that have occurred. M/NTFs should not be used as a cover-all on deviations, but as a tool to explain exceptions to total protocol compliance. They allow for clarity on the accidental deviations that

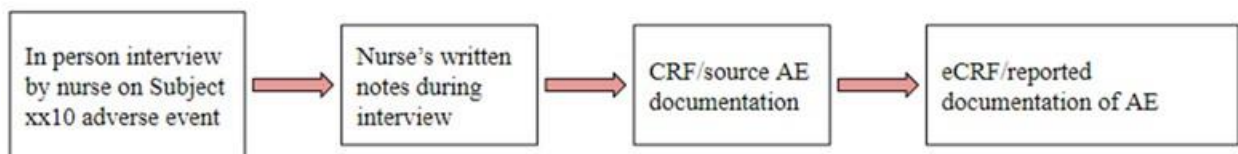
can be expected within real-world clinical trials. Additionally, original source pages or visit notes should be amended where possible to prevent unnecessary documentation. {6,14,15}

Technological Advantages within GDPs

Technology is a broad category of advancements that can be applied within various categories of clinical trials at the site level. Consider the use of paper source documents versus a low-cost, Internet-capable tablet. For the former, Figure 3 shows an example workflow for moving patient adverse event (AE)-related information reported at visits to electronic CRFs (eCRFs) in the electronic data capture (EDC) platform. The three sequential arrows represent the transcription of information from one form into another, with each having the potential for increased error rates.

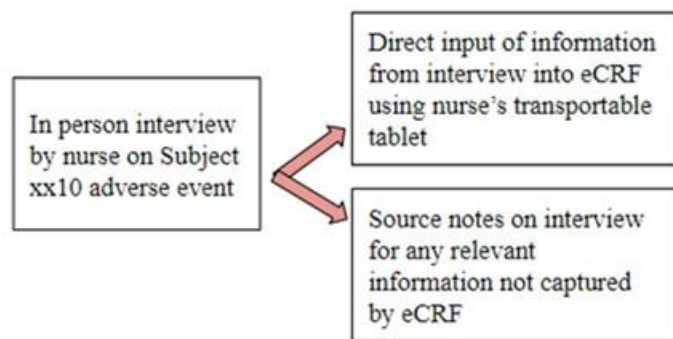
Unnecessary handling of data introduces risk and increases with the number of added variables, such as the number of staff members involved or dependent actions. In this example, a clinic nurse completes the patient interview, a research assistant transcribes notes from the clinic chart to participant binder, and a study coordinator enters information into the eCRF. Within part of the workflow, an error could occur and be repeated/exacerbated in dependent steps. {16}

Figure 3: Example Workflow of Newly Reported AE, Without Application of Technology



Now consider Figure 4, which uses a tablet for the same scenario. The nurse is able to effectively enter the information directly while interviewing the patient. This has the minimum amount of risk, with a single transformation of data from the verbal patient report into the relevant eCRF as original data, without the need for a paper copy. Instead of a physical paper trail, the site process would be supported by the site SOP explaining this streamlined data collection process and rationale in risk mitigation.

Figure 4: Example Workflow of Newly Reported AE, With Use of Technology



With the tablet in use, workflow is immediately shortened by staff EDC data entry. Duplicate collection of information via secondary paper documents is removed from the equation, providing two benefits: 1) time-intensive creation/validation of paper source documents becomes unnecessary, and 2) information entry is completed only once between source and eCRF for each piece of data.

Tablet usage also allows the staff members completing patient interviews to be the ones entering data, eliminating the concern for data misrepresentation. Finally, there is also easy transportation

of the exact, protocol-required eCRF entry fields, ensuring that all necessary information is collected without extraneous or unessential details.

Considerations for Technology Use in Documentation

While embracing technology, it is important to note the requirements for security when utilizing software and digital site files. Title 21 CFR Part 11 outlines the specific requirements of electronic systems and how to translate the previous requirements for physical documents into the e-version of these pages. This FDA regulation also verifies that the use of electronic records is acceptable in place of physical records. Just as hard copies of patient information must be in restricted access areas, the e-versions of trial files must be located in protected workflows, with unique, confidential passwords for each employee.

The same requirements also apply in terms of audits, such as e-files being easily accessible to the FDA. For electronic items, there should be an audit trail to provide evidence of all changes, username of the change initiator, the date, and the changes made. Unique identifying passwords can act as the signature electronically and create an appropriate imprint to verify the authenticity of the user inciting any changes or approvals. Further, records retention is essential; much of the good practices for clinical trials pertains to the accuracy and assurance of the records.{17}

Sites should also consider how systems already used onsite could be expanded for documentation in clinical trials. For example, Microsoft® Office 365® aims to comply with 21 CFR 11 requirements, and has options for audit trails and cloud-based storage.{18} Adobe™ Acrobat™ can be used for more than document viewing, and includes e-signature capabilities.{19} Identifying existing programs that show FDA compliance with electronic

documentation can be a cost-saving technique to improve efficiency of technology according to GDPs.

Conclusions

Technology and risk-based considerations in site management pair productively with data management to enhance site output quality. Understanding the interaction between site activities in order to create visibility and measurability promotes risk management. Tactical application of the aspects described herein allow for optimization of site and study success in the new era of technology fluency.

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PEER REVIEWED

Opinion: A Futurist View on the Use of Technology in Clinical Trials

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The clinical research organization (CRO) I work for doesn't provide source documentation for studies, so every site we work with does things a bit differently. The variations in source data formats and quality create inconsistencies in data capture and increase the monitoring burden by forcing the clinical research associate (CRA) for any given multisite study to learn how each site operates.

Even for a small Phase III trial with only about 50 research sites in the U.S. and Canada, the hassles to a monitor of conducting visits and capturing data that are collected according to myriad site-specific standard operating procedures can be overwhelming. Phase III studies are sophisticated operations and are increasing in complexity,^{1} so the chances that 50 different sites perfectly capture all the data we need are close to zero. In addition to complexities of the study itself, these 50 sites may have been trained by 10 or more different CRAs on a protocol that has been amended multiple times before the study even started—so we must focus on capturing just the minimum data we need to have the test product approved.

This is not a criticism of my employer. I have worked for one small CRO and two of the largest CROs, and they are all essentially the same. Not providing source documentation to sites for consistent data capture is an industry standard practice.

This is a criticism of the industry. There are two reasons I have identified for why CROs don't provide source to site:

1. It means less work for the CRO.
2. It addresses the issue of liability—if there is a deficiency in a site's source data, it is the site's fault instead of the CRO's.

The Case for Standardized Source

I believe a CRO is hired for its expertise in clinical trials, and should be responsible for providing adequate source documentation to ensure the study goes as smoothly as possible by promoting consistency in data capture. Adopting and providing standardized source to sites reduces the workload not only on research sites, but also on the CRO's own staff of CRAs.

By having to familiarize myself with each site's method of source data capture, I not only eat into my limited time onsite, but also am less likely to recognize any trends across my sites, since they all capture the data differently. Noticing trends is a crucial part of clinical research monitoring, and is vital to patient safety and good data quality.

The Case for Technology in Patient Consent

The consent form lists out the possible benefits of the study, side effects of the treatment, and any alternative treatments. It also informs the patient that he/she can withdraw at any point and provides contact information in case they have questions.

The consent form is usually around 20 pages long, but can vary depending on the complexity of the study. A patient must be consented prior to the completion of any study procedures. {2} The consent process is a critical element of any legitimate research study, and ensuring proper consent is main priority for a CRA. Proper consent protects patients by keeping them informed of risks and alternatives.

When I monitor the consent process, I check that each page of the most recently approved consent form is present in the patient's chart and that the signature date matches the patient's

first visit date. Hopefully, the site jots down a note with some details about the consent conversation with the patient, or at least uses a checklist that hits the bare minimum points.

I can never truly know by simply checking a signature and a note if the proper consent process happened; there is no way to know if the dates on the signature are accurate. Even if the date is accurate, I have no way of knowing if the consent process happened before any other study procedures that day. As for the note about the consent conversation with the patient, it does not take a monitor long to notice that sites use standard language. I suspect many sites have become much more proficient in documenting a proper consent process than actually performing proper consent.

I can ask site staff to clarify their consent process if I am having trouble believing the accuracy of the standard language consent notes, but if they say none of the subjects had any questions, I don't have any evidence to the contrary. I am forced to accept the industry standards for documenting consent.{2}

India recently addressed the consent issue by requiring the consent process to be captured on video.{3} Filming consent is much more effective at ensuring the process was followed, since a monitor can easily re-watch the entire process. However, the revised video consent process has been met with resistance. Some doctors in Indian clinical trials argue that the requirement for being videotaped makes a patient less likely to enroll in a trial and hurts enrollment.

As an industry skeptic, I believe the push-back from doctors and the decrease in enrollment rates due to video consent have a different source: fraud.

It is much more difficult to fabricate patient data and entire patients when video consent is required. The truth is likely somewhere in between, but ample evidence exists across the globe proving that some patients are fabricated.{4,5} As a monitor, I have seen patient fabrication first hand, and suspect there have been instances I missed.

Industry leaders may argue that a video consent process carries the potential of unblinding patient data or increasing the time of monitoring. To those experts I pose the following questions:

1. Does adaptive and remote monitoring not address the issue of taking too much time to monitor the full consent process?
2. Are you willing to risk patient safety, rights, and well-being by not having a complete video consent process in the interest of saving time/money and expediting enrollment?

Currently there are no video consent requirements in the U.S. or for U.S. Food and Drug Administration (FDA) submission, so I am forced to accept paper documentation at face value.

The Case for BYOD

Clinical trial managers now routinely use eDiary software that is provided to patients to complete some assessments, though it does not track dosing or side effects. Both dosing compliance and side effects are essential data, so not capturing them as accurately as possible in real time can be problematic.

As a CRA, I have witnessed these problems first hand. During an HIV study I worked on, I noticed at a patient's last visit how she had returned almost all of her study medication unused. There were 30 days between each study visit and the patient returned 28 pills. Proper dosing is once a day, so there had been an obvious noncompliance in dosing with no way to determine exactly when the patient stopped properly dosing. The site reported that the subject stopped dosing two days after her previous visit, and that the site was not aware until the patient came in for her most recent visit 30 days later.

If the study recorded patient dosing electronically, the system could have been set up to automatically notify the site of dosing noncompliance, and the site could have followed up with the patient in real time. Noncompliant dosing is particularly dangerous in studies such as HIV, as it can cause the patient to develop resistance to the treatment and potentially to future treatments. {6}

I read on to determine why the patient stopped taking her medicine. At her Day 30 visit, the patient reported that 28 days earlier she felt that the medicine was making her nauseous. This side effect isn't uncommon in the study, but can require some follow up. In this instance, it will require a lot of follow up.

The site performs a pregnancy test at each visit, and this patient's most recent test was positive. Her nausea was not due to the medicine, but caused by her pregnancy. Now the site has a pregnant woman at risk of developing resistance to HIV treatment for both herself and her unborn child. All of this could have been avoided if the eDiary reported dosing and side effects to the site in real time. The patient, site, and CRO would have been aware of the pregnancy in three days, and the patient would have had continued treatment.

At this point, many sites and CROs are familiar with some kind of electronic clinical outcomes and assessments (eCOA) device, but current solutions present their own challenges. Supplying a large volume of sites with adequate diaries in a study with unpredictable enrollment can result in supply shortages. There is an adage in clinical trials that 80% of study enrollment will come from 20% of the sites on the study. With such a discrepancy in enrollment between sites, it can be difficult to forecast accurately to ensure adequate supply of product and supplies. Study supply shortages delay enrollment and greatly increase the costs of the study. {7}

The tactic of "bring your own device" (BYOD) mitigates the problems associated with supplying sites with an eCOA device. Critics of BYOD will argue that many patients in clinical trials are economically disadvantaged and are unlikely to have a smartphone necessary for BYOD. However, data suggests 50% of U.S. adults making less than \$30,000 per year own a smartphone. {8} Further, critics of eCOA argue that older patients have difficulties utilizing smart devices, but research shows 73% of U.S. adults 50 to 64 own a smartphone. {8}

BYOD should further mitigate concerns with patients being unable to correctly capture eCOA by allowing them to use the devices they are already familiar with. Not having to carry two smart devices also improves the chance of patients remembering to complete their assessments as required.

However, BYOD is not without its own challenges. Any BYOD application needs to have a tested and proven user interface to ensure a diverse patient population will be able to complete all required assessments. While data suggests most patients do have access to the required smartphones for BYOD, it is crucial to not exclude patients who do not own a personal

smartphone. The best clinical trial management system should incorporate both BYOD and sponsor-supplied diaries to ensure all potential patients can enroll.

While eCOA does not yet have the capability to send out real-time alerts, early adoption of this technology is a step in the right direction. A workaround to temporarily solve real-time alerts could be [text-message reminders](#) sent directly to your patients, alerting them to take the medication and fill out their diaries. Patients can respond to these text messages if they are experiencing any side effects, such as nausea, which will result in follow-up visits.

The Case for eSource

I will spend the bulk of my day going through every datapoint the site has collected for each subject. I verify that the information is complete, accurate, makes logical sense, and was properly entered into the electronic data capture (EDC) system. When the EDC is properly set up prior to the study start, this process can be as simple as just checking to make sure the numbers on the page match what's in the EDC system.

However, it is seldom this easy. In my experience, sites rarely have a fully functional EDC with good data validation and system queries in place prior to study start. Due to poor study foresight, tight timelines result in the implementation of deficient study management systems. The CRA is responsible to work with the site to mitigate the errors incurred as a result of any shortfalls. Errors are compounded by the fact that sites often enter data into the EDC several days after patient visits occur. It is not uncommon for a site to miss crucial study datapoints at the beginning of enrollment.

The need for onsite monitoring of early study data is crucial to ensure research sites are capturing all required data. Industry standards tend to require a visit within the first two weeks of enrollment. Unpredictable enrollment and a large site load can make it difficult for a CRA to meet this crucial requirement. With delayed EDC entry and required onsite monitoring, it can be anywhere from several days to months before a research site is even aware of a data deficiency, which could potentially affect all of a site's patients up to that point.

The worst part is that this problem can be easily avoided.

A relatively new solution has arrived on the clinical trials scene: eSource. eSource comes in many forms, and there currently isn't a one-size-fits-all solution; each study in clinical trials presents unique problems that require unique solutions. Recently, more complete eSource systems have emerged, with new systems seeking to eliminate issues caused by delays in CRA monitoring (and the costs they incur to both sites and CROs).

The site I am at on any given day may not utilize eSource, so I will be paging through multiple patients' visit binders all day. Each error I find—from simple mistakes like using the wrong year in a date to larger issues such as missing data—needs to be addressed by the site staff while I am physically onsite. However, the site staff have a regular workload while I am onsite—one that will be continuously interrupted throughout the day as I find new issues to be tackled. This creates tensions that often lead to poor relations between site staff and their CRAs, thus reducing the CRAs' ability to serve effectively.

A good eSource enters timestamps automatically for each datapoint, so the staff don't even have to enter a date as the audit log captures the required information. Timestamps that include user signatures go a step further. With unique user accounts, every datapoint is traceable back to its originator; site staff do not have to waste any time signing and dating, and can instead focus on performing patient visits as quickly as possible. Expediting patient visits is critical as the industry moves toward more patient-centric trials.

Effective eSource reduces the workload on sites by decreasing visit time and transcription errors, thus freeing up site overhead to take on additional studies. As I sit at the (typically small) desk in the makeshift office I am given during visits at most sites, pouring through pages of data to ensure the site does not have any transcription errors, it occurs to me that eSource renders this entire process obsolete.

The greatest benefactor of eSource is the CRO. Too often, a monitor's time is spent fixing transcription errors that do not exist when eSource is properly implemented. eSource enables the data to be pulled directly into the EDC. This process dramatically reduces the workload for sites by eliminating data entry and the need for quality control/quality assurance for the data entry process.

Source data validation can easily account for more than 80% of a monitor's time. After eliminating the need for source data validation onsite by making the source electronic, the monitor can focus on the larger issues of site enrollment, performance, and patient compliance, which can all be overlooked with a high source validation workload.

When I am at a site that does not utilize eSource, I will have to page through hundreds of pages of source documents to ensure nothing is missing or incomplete. As I scramble to ensure I checked the bare minimum amount of data before I need to rush off to catch my flight, only to do it all again tomorrow in another city, I am struck with this thought: I love being a CRA, but the role as it exists today is obsolete.

Conclusion

By adopting completely electronic systems, 95% of the issues I address currently won't exist. Say goodbye to transcription errors, say goodbye to follow-up calls for missing documentation; most monitoring issues should be eliminated. The future of monitoring will be to focus on educating sites on the latest available systems developed to reduce workload, improve patient safety, and increase patient engagement.

To the sites and CROs that haven't started to look at eSource, my advice is simple: Start today.

I believe in 10 years clinical trials will be completely paperless. Complete eSystems will eliminate the existing inefficiencies. Average study length will decrease, and study workload for sites and CROs will *drastically* decrease. Data safety and trends will be tracked in real time using advanced analytics, making investigative trials as safe as possible for our patients.

I believe the latest technology will significantly reduce the cost of bringing new treatments to market, and it is my sincerest hope that the savings generated by more efficient clinical trials will be passed onto the people who truly matter in clinical trials: Patients.

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Hindsight, Foresight, and Coming Full Circle

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My formative years in clinical research were guided by the wise words of my first clinical research associate (CRA) manager: “Clinical research is the biggest small world in which you will ever work. Don’t burn bridges. Always be professional!” My inexperience prevented the holistic perspective required to appreciate her message at the time; however, several years (and employers) later, I began to understand the meaning behind those words.

Career progression demands change that is historically accepted/expected in this industry; clinical researchers change companies/sites for increased salary, promotion, or academic opportunities. This trend increases the likelihood of future encounters with past and present colleagues, even if new duties take us far from familiar settings. Our present behavior is the strongest influencer of these future encounters, and it all comes down to professionalism.

Words of Wisdom, Ghosts of Jobs Past

That wise manager always advised me to remain professional no matter how trying the circumstance. To think before speaking, review before sending, and pause before reacting. She reminded me that when encountering a person/situation from our past, how much better to walk the bridge preserved than to scramble from the bridge burned. It was only when I faced the situation personally that the lesson had an indelible impact.

As a new CRA, I worked with an authoritative project lead; to his stern management style I could never relate. If I had made the effort to understand his behavior and the enormous pressure he was under, I would have been more empathetic than terse. That smallest courtesy may have helped me land the dream position for which he interviewed me several years later (I did not get it).

The far-reaching impact of professional courtesy on business relationships came full circle during a site evaluation visit many years ago. I was scheduled to meet with an oncology investigator and research nurse from a VA hospital. The evaluation visit included a trip to the site's research pharmacy to speak to its leader about investigational product (IP) preparation and storage. I was looking particularly forward to this meeting because this was the first large hospital to which I had ever been assigned to monitor (15 years prior). That two-year CRA assignment cemented my oncology monitoring skillset. I could not believe it had been 12 years since my last visit to the site.

Though I was not meeting with the previous investigative team, I hoped I would encounter the same lead research pharmacist as before. She had worked at the hospital for years and was a literal mainstay of that part of the site's research functions. She had a very specific influence on my developmental monitoring communication skills. Through our interactions, I learned two important things: how to effectively communicate with a diversity of personalities, and never to presume to form an opinion of someone based on a few superficial interactions, because that opinion will most likely be incorrect.

Getting to Know You...

The research pharmacist was a brilliant lady for whom I felt both admiration and intimidation. She was an oncology drug expert and deservedly confident with such expertise. She was quite reserved, until questioned, and then purported to become terse. If a CRA had an IP dosing query, they should ensure to be more than prepared with notes, calculations, and the pharmacy manual for reference. The most experienced monitor was often flustered by her accuracy.

Our first few drug accountability visits were uneventful; she provided the requisite accountability logs and any unused drug for reconciliation. The site had only enrolled a couple of patients. To

strengthen the relationship with the pharmacist, I attempted pleasantries that were met with a quizzical look and ensuing silence. I never really knew what she was thinking, so I was forced to guess. The conclusion drawn from my very green perspective was that she simply did not like to me.

She must have sensed my inexperience (as demonstrated from my fledgling first attempts at confirming infusion calculations), and resented my review when I clearly did not know what I was doing. I lacked the perspective and patience required when dealing with a more reserved personality, so I continued to feel uncomfortable around her.

My fourth monitoring visit to the pharmacy changed that dynamic when I discovered a study drug dosing error. I must have recalculated that mg/kg dosing formula a thousand times because I very much wanted to be wrong; regretfully, it was correct. I was reluctant to tell the pharmacist for fear of her reaction, but knew I must. My mind raced with a slew of possible negative outcomes, but I formulated a communication plan based on her demeanor. I would communicate the deviation in a manner most comfortable for her.

Her reaction confirmed that my initial presumption of her was not only incorrect, but unfair.

When the time came to report the dosing error to the pharmacist (though sweating bullets), I maintained composure as I explained the finding. She requested the pharmacy manual and accompanying source/drug accountability logs. After studying the documents intently for what seemed hours, she turned to me, and *thanked me* for discovering the error before it was repeated. You could have knocked me over with a feather for my shock. She informed me that she would complete corrections and institutional review board reporting immediately. I thanked her and turned to the monitoring area, when her next sentence made me smile inwardly for hours: “I am glad we have a monitor who knows what she is doing.”

That victory elated me.

Transitions and Thanksgiving

Over that two-year period as our relationship progressed, I learned how to best communicate findings, and study status, to her. We worked well together because I remained professional and made the effort to understand her.

Fast forward to the present-day evaluation visit, during which I discovered that it was that same pharmacist's last day after 20 years at the site. Her colleagues were throwing her a farewell party, and true to character, she had agreed to provide 20 minutes for the pharmacy tour despite the festivities.

When I entered the pharmacy, she recognized me immediately, and asked how I had been. We caught up briefly and then she returned to her party. As I watched her colleagues celebrate her valued contribution, I felt grateful that our past collaboration had ensured this future outcome.

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