Evidera | PPD

THE EVIDENCE FORUM

SPRING 2020

FOCUS SECTION ON
Digital Technologies

Topics include

- Leveraging Decentralized RWE Data Collection Strategies
- Simulation to Patch a Broken Trial
- Adopting eCOAs for Use in Clinical Trials
- FDA's Emergency Use Authorization
- *And Much More!*

TABLE OF CONTENTS

SPRING 2020

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A message from Evidera's President and its Leadership Team on the COVID-19 pandemic

Dear Valued Clients and Colleagues,

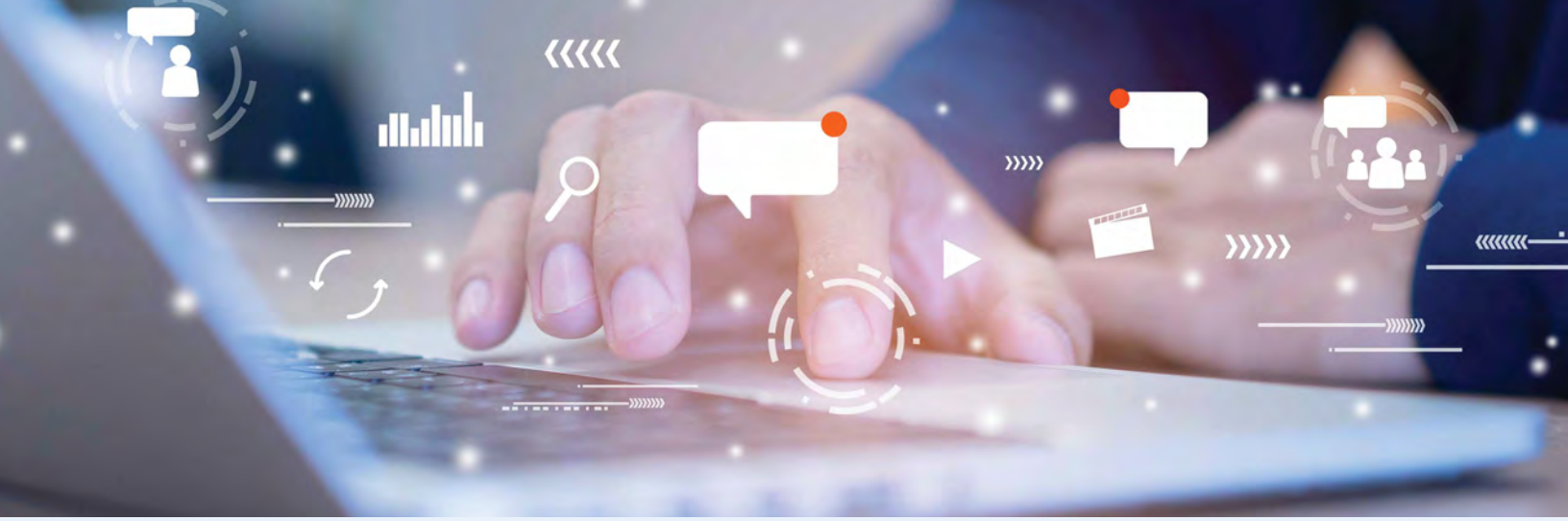
The COVID-19 global pandemic has fundamentally changed the way we work. But we are dedicated to both ensuring the safety of our employees, study participants, and clients and working closely with our pharmaceutical and academic partners to ensure the continuity of research programs and minimize disruptions and delays.

We are absolutely dedicated to working in this new world. While it will be challenging, we have the tools and, most importantly, devoted experts to keep your important work moving forward.

This issue of *The Evidence Forum* is focused on digital technologies which have become particularly relevant, offering potential solutions to overcome many of the study problems that are induced by COVID-19. As we work with clients to identify actions to maintain the conduct and completion of studies, we will continue to share our insights on ways to support and enhance patient safety while navigating the complexities of the current crisis.

For more information on how we are supporting clients during the COVID-19 global pandemic, please visit evidera.com/covid-19 for more information.

Sincerely,
Karen Kaucic
President of Evidera
On behalf of the Evidera Leadership Team
karen.kaucic@evidera.com



Digital Approaches in the Era of COVID-19

Interviews with **Science 37** and **Medable**

Recently Mariah Baltezegar, MBA, Executive Director and Head of Peri- and Post-Approval Virtual Trials with Evidera, and Niklas Morton, MSc, Senior Vice President and Global Head of Digital Services with PPD, spoke with leaders of Science 37 and Medable, two companies Evidera and PPD partner with for design and implementation in this space and are at the forefront of providing digital solutions to advance clinical research, about the effect of COVID-19 on perceptions and availability of digital approaches to clinical research.

How have, or do you think, patient perceptions/uptake of fully decentralized/virtual studies/technologies are changing in the era of COVID-19?

Jonathan Cotliar

Patients are typically not aware of all of the differences between traditional and virtual research, but in the current climate, it is difficult to keep patients motivated to participate in research using the traditional research model. Do participants want to travel to a hospital or doctor's office that places them at an increased risk of exposure to COVID-19? Is that even possible given the number of locations experiencing strict quarantine measures? So far, the answer has increasingly been "no." In our experience interacting with patients, the best way to motivate them is to simplify the research process and build it around their lives. If we can make research more convenient for them while mitigating some of the risks that the coronavirus presents, that's what we should aim for.

Michelle Longmire

COVID-19 has resulted in significant adoption of decentralized clinical trial methodologies. Given the site closures globally, virtual visits, remote data capture, and remote site monitoring have become a leading way to ensure participants are safe and research is moving forward.

What advice would you give drug developers who want to keep study continuity by deploying decentralized/virtual approaches to their real-world data collection strategies and/or studies?

Michelle Longmire

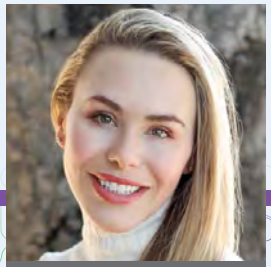
I would suggest leveraging patient-centric digital strategies that help collect real-world data. For example, mobile applications enable prospective data capture of outcomes, while also being an important tool for consenting for other types of digital data collection across diverse data sources such as claims, medical records, or mortality registries.

David Coman

The virtual approach makes the most sense in the current climate, and it has proven to be effective in providing some measure of continuity in the drug development process. In our experience, it helps for sponsors to have a clear idea of the protocol, schedule of assessments, investigator information, target geographies, and desired timelines as they consider a shift to a virtual model. From there,

David Coman, MBA
CEO, *Science 37*

Jonathan Cotliar, MD
CMO, *Science 37*



Michelle Longmire, MD
CEO, *Medable*

companies should look for partners that can help them virtualize their research with a platform that supports the entire clinical trial ecosystem.

What are the biggest challenges drug developers face in trying to pivot traditionally designed studies to a decentralized/virtual model?

David Coman
Many companies do not yet understand how to virtualize their upcoming or ongoing studies, which may mean reducing the number of in-person interactions or collecting endpoint data virtually, because it may be new territory for these organizations. We've conducted more decentralized or virtual trials than any other company, and one of our strengths is our savvy medical affairs team. These experts can assist drug developers with all aspects of virtualization, including study design and delivery, endpoint virtualization, and change management.

Michelle Longmire
The challenge relates to rethinking the trial strategy across endpoint data capture and safety data capture. The good news is that with an experienced partner, a trial can be changed in flight or pre-launch to accommodate a decentralized model. This is not to say that every trial or every visit can be done remotely, but a model that enables hybrid design is generally very achievable and can reduce participant burden and healthcare center exposure during this challenging time.

Are there certain types of studies (development phases, therapeutic areas, etc.) to which it is easiest to transition or apply decentralized/virtual approaches?

Michelle Longmire
We have seen that digital and decentralized approaches can benefit the aspects of trials that tend to be universal, such as screening and off-study visits in the first instance. These approaches can really improve patient centricity in screening and on-study care across phases and therapeutic areas. With planning and consideration of which are the most important data to collect, most studies can transition to some aspects of the digital approach.

Jonathan Cotliar
We are currently engaged in clinical trials in a variety of therapeutic areas with enrollment sizes ranging from dozens to hundreds of patients in a variety of phases, so we know that virtualization can be applied to studies in every major therapeutic area and phase of research. It usually depends on how many in-person, "hands-on" interactions are required between participants and the trial team, and whether a physician or other specialist needs to be present for the administration or assessment of a particular procedure.

Which digital solutions or strategies are going to be most critical to utilize as the industry looks to virtualize studies given the global pandemic?

Michelle Longmire
Telemedicine and remote patient monitoring have become a cornerstone of ensuring patient safety and continuation of trials. Additionally, site monitoring and eSource have gained importance due to site closures.

David Coman
The virtual research model has become the standard of clinical research in the current climate given the massive worldwide quarantine measures currently in effect and the need for those infected with COVID-19 to be isolated. When it comes to digital solutions, it's critical to employ a clinical trial platform that integrates systems, workflows, and processes for physician investigators, mobile nurses, and coordinators across the entire patient journey. This is especially crucial as study teams work across geographies. Comprehensive virtual trial platforms establish a centralized hub for trial activities such as electronic data capture, eConsent, electronic patient-reported outcomes (ePROs), telemedicine visits, patient notifications, and more.

How do you know which virtual/digital elements are the right fit for your study or patient population?

Jonathan Cotliar
These elements will depend on the study, but there are inherent advantages for many patient populations – think of patients with limited mobility, compromised immune systems, those who rely on others for transportation, or those with inflexible commitments such as work and childcare. The best thing for drug developers to do is consult with experts who can provide guidance on study design and delivery and endpoint virtualization. Science 37 works side-by-side with its clients to address these and other key trial aspects to come up with a trial design that maximizes efficiency, reduces time to market, and provides the necessary accommodations to ensure an optimal patient experience.

Michelle Longmire
Taking a look at what barriers exist in the traditional model and leveraging digital solutions to address barriers can help ensure that the digital strategy adds value and is a fit for the study. There is not a one-size-fits-all approach, so starting with barriers is key. Examining roadblocks to recruitment, screening, enrollment, retention, and evidence generation can help to identify the right fit for the study.

Tell us how telehealth can be used to conduct site visits virtually and the benefit telehealth presents for both patients and drug developers?

Jonathan Cotliar
Virtual trials, which are part of the telehealth landscape, reduce barriers to participation by bringing the research to the patients, which minimizes or eliminates the burden of making arrangements and traveling to a research site. Virtual trials have proven to reach and engage broader, more representative, and otherwise inaccessible populations of qualified candidates, which is a significant advantage for drug developers. For patients, the prospect of participating

David Coman, MBA, is the chief executive officer at Science 37 and is focused on furthering the company's mission to accelerate biomedical research by putting patients first. In pursuit of its mission, Science 37 makes it easier to participate by connecting patients with doctors and nurses through telemedicine visits and home health screenings, then managing trial logistics from an integrated, comprehensive platform. Science 37's decentralized model is reimagining biomedical research to get more life-enhancing medicines to patients faster. Prior to joining Science 37, Mr. Coman led the data and analytics business at ERT after serving as the company's chief strategy officer. He also previously worked for Quintiles (now IQVIA) as chief marketing officer and founder of its Digital Patient business. Mr. Coman earned his BA in advertising from Michigan State University and his MBA in marketing, entrepreneurship, and finance from the Kellogg Graduate School of Management at Northwestern University.

Jonathan Cotliar, MD, is the chief medical officer for Science 37 and was previously the vice president of medical affairs, where he contributed as an investigator on a number of virtual clinical trials in addition to his work in support of business development and regulatory strategy. Dr. Cotliar is board-certified in both internal medicine and dermatology. He serves as director of inpatient dermatology at Harbor-UCLA Medical Center, with previous full-time faculty appointments at the David Geffen School of Medicine at UCLA, Northwestern University Feinberg School of Medicine, and City of Hope National Medical Center, where he was chief of the division of dermatology. Dr. Cotliar received his BA from Trinity College, his MD from the University of Kentucky College of Medicine, and completed his training in dermatology and internal medicine at the David Geffen School of Medicine at UCLA. While at UCLA, he completed an NIH-sponsored K30 Fellowship in translational investigation.

Michelle Longmire, MD, is the co-founder and chief executive officer of Medable, a privately held, venture-backed company focused on building a unified platform for clinical trial execution, enabling patient generated data to drive clinical research and precision and predictive medicine. She is a trained physician and entrepreneur driven to improve human health through advances in technology. Dr. Longmire received her BS in biology and political science and her MD from The University of New Mexico. She did her residency and was a postdoctoral research fellow at Stanford University School of Medicine and was an attending physician at Stanford University. She is a board-certified practicing dermatologist. Dr. Longmire also holds the honor of being a Howard Hughes Research Fellow.

in a virtual trial – completing study visits within the comfort and convenience of home – means that trial participation can flex to their lives, which is undoubtedly an attractive option. Transforming the patient experience this way is reflected by improved retention: Science 37's virtual trials have an astounding 90% retention rate. Together, these factors help to accelerate enrollment and improve efficiency in clinical drug development without sparing quality.

Michelle Longmire

Telehealth enables efficiency and improved patient centricity. In clinical trials, telemedicine can facilitate screening, evidence generation, and clinical care. The benefits include patient convenience and retention as well as improved patient safety in times of site closures.

Do you think the current need to virtualize studies because of COVID-19 will permanently change the way in which clinical trials are conducted (i.e., moving towards more decentralized/virtual models permanently, etc.)?

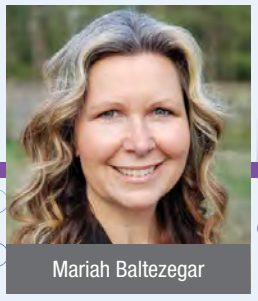
David Coman

As many are coming to realize, a virtual research model can help keep patients and study teams safe, support the wider public effort to slow viral spread, and provide business continuity during the COVID-19 pandemic. This approach may also reduce the burden on healthcare systems and personnel who are dealing with extraordinary circumstances due to the crisis. Going forward, the current situation will likely transform how the industry thinks about clinical trial execution and the inherent benefits of the virtual model. Patients already want research built around their lives – if we can make research more convenient for them while simultaneously mitigating some of the risks associated with a global pandemic, virtual trials seem like a logical way forward.

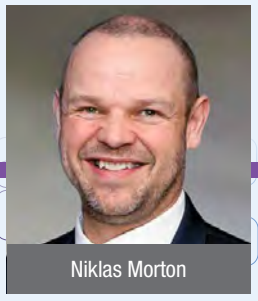
Michelle Longmire

I believe that current adoption will continue. Prior to COVID-19, we did not have as much evidence that decentralization was doable across therapeutic areas. Now, due to the necessity, we have a growing body of evidence that virtual and decentralized trial methodologies can be effectively applied at scale and across therapeutic areas. We are an industry driven by evidence and now that we have critical evidence, I anticipate we will see accelerated adoption. ■

Mariah and Niklas are leading experts in the design and oversight of decentralized/virtual study options across all phases of clinical trials and peri- and post-approval studies, with the ability to engage external partners when necessary to provide optimal solutions. These interviews were done to provide relevant and timely insights on how our clients' needs can be supported with digitally enabled solutions. For more information, contact godigital@ppdi.com.



Mariah Baltezegar



Niklas Morton

Leveraging Decentralized Real-World Evidence (RWE) Data Collection Strategies During the COVID-19 Pandemic and Beyond

Mariah Baltezegar, MBA
Executive Director and Head
Peri- and Post-Approval Virtual Trials
Evidera

The COVID-19 pandemic has washed over the world in waves and affected every aspect of life, including most obviously, healthcare. The impact is not only seen in relation to coronavirus patients and studies, but the ripple effect is also seen across all clinical and real-world studies. Several key factors have disrupted research efforts, including shelter-at-home mandates, limited access to healthcare facilities, patients' comfort level in participating in studies, and the shift in priorities and capacity of healthcare providers. These types of disruptions lead to some key challenges. For example, patients cannot visit sites to have their standard of care or protocol-defined safety assessments performed; patients' ability to visit sites for clinical or patient-reported outcome assessments are hindered; and there is a decrease in patient recruitment and retention rates. Patient safety is always the main priority of our industry, and we also need to continue to collect study dictated data as much as possible. To do this, we need to figure out ways to ensure patient safety in the current global scenario and mitigate the impact on study disruption.

How Regulators are Advising Stakeholders in These Dynamic Times

Globally, regulatory and data privacy guidance is evolving to address the current challenges faced by the industry. While specific guidance and actions may differ among regulatory agencies and ethics committees, it's clear that patient safety comes first. Guidance from the European Medicines Agency (EMA),[1] US Food and Drug Administration (FDA),[2] and Advarra,[3] a US Central Institutional Review Board (IRB), all mention the use of telemedicine and virtual visits to continue communication with patients and maintain engagement to ensure patient safety. The Italian Medicines Agency has allowed for a special provision for sponsors to directly engage specialized


Mariah Baltezegar

agencies such as home nursing to support management of patients that previously had to be contracted separately and directly with the Principal Investigator (PI).[4] Regulators continue to apply pragmatism to ensure continued care and patient safety.

Strategies to Bring a Study to the Patient

The continuum of data collection includes everything from the traditional brick and mortar approach, where a patient must go to a research site for all study assessments (posing the highest burden to patients), to a fully virtual, decentralized or metasite approach, where a patient never has to go to a research site for assessments (posing the lowest burden). Given the constraints COVID-19 is placing on the industry right now, the high burden brick and mortar approach is unachievable. Fortunately, virtual enablement approaches are available and solve many of the challenges the industry is currently experiencing.

While physical in-person visits to a study site may not be possible, there are alternate solutions possible to address each need, with some strategies being immediate and relatively short-term, while others are longer-term solutions.

- **Televisits** are available for patients who are unable to visit their healthcare providers to have standard of care, protocol-defined safety assessments performed. These visits enable healthcare providers to physically see a patient and perform assessments via video conference for both standard of care and protocol-defined assessments. This is being applied both to research activities as well as routine healthcare.
- **Remote e-signature consent** can be employed to acquire remote consent signatures for patients who do not have the appropriate consent in place or cannot visit sites to be consented. It is important to note that issues related to consent are continually evolving. For example, Advarra released additional guidance on 27 March 2020 noting that re-consent is not necessary unless the research challenge changes such that the original consent is no longer valid (e.g., re-consent is not necessary when changing from clinic visits to remote visits).
- **Direct to patient approaches, such as electronic clinical outcomes assessments (eCOAs), electronic patient-reported outcomes (ePROs), devices and wearables, and home nurses and phlebotomists** are options for patients who cannot visit their study site for clinical or patient-reported outcome assessments.
- **Direct to patient supplies** provide study medication or other supplies necessary to conduct study assessments via direct shipments to the patient's home when patients are unable to visit a site to replenish their clinical supplies.

It is possible to leverage individual solutions or bring these solutions together in a metasite model with a digitally enabled platform. With the metasite model, the burden is

Table 1. Solutions to Address Challenges Faced by Patients Unable to Visit Study Sites and Reduce Site Burden

CHALLENGE	eSignature Consent	Remote Consent + eSignature	Televisit	eCOA/ ePRO	EMR Extraction	Devices/ Wearables	Home Nurse/ Phlebotomist Visits	DTP Supplies	Metasite or Decentralized/ Virtual Model
Patients **cannot visit sites to consent to participate** or perform procedures remotely (where required) not detailed in the executed consent form	✓	✓							✓
Patients **cannot visit HCPs** to have SOC or protocol-defined safety assessments performed			✓						✓
Patient cannot visit sites for clinical or **PRO assessments**				✓		✓	✓		✓
Patient is running **low on clinical supplies** and cannot visit a site								✓	✓
Patient recruitment decreases, and retention rates are putting a study at risk									✓
Site staff do not have time to participate in **non-essential research**, identify patients, and enter medical record data		✓			✓				✓

eCOA = electronic clinical outcome assessment; ePRO = electronic patient-reported outcome; EMR = electronic medical records; DTP = direct to patient; HCPs = healthcare providers; SOC = standard of care

removed from the site staff who may be involved in frontline care during this pandemic and bring the study directly to the patient, allowing them to participate from the comfort of their homes. Table 1 summarizes these digital and other solution options.

Additional Strategies for RWE Data Collection

In addition to the solutions already presented, there are other strategies that minimize burden on patients, caregivers, and healthcare providers that may meet some of the needs brought on by COVID-19. *Electronic medical record (EMR) extraction* uses existing health information exchange (HIE) technology to connect clinical sites' EMR data and pre-enable them for research. This streamlined approach to accessing sites' rich EMR data answers specific research questions in a more rapid, automated, and repeatable manner and can eliminate the need for site staff to perform data transcription and free site staff to perform other activities while enabling continued data collection.

Alignment with *integrated delivery networks (IDNs)* allows recruitment of patients at the point of routine care versus traditional research centers. This strategy utilizes large healthcare delivery organizations that either own or manage multiple points of patient care (e.g., hospitals, physician practices, long-term care facilities), allowing for rapid feasibility as well as patient identification through centralized EMRs and enabling e-recruitment of potential patients or study participants. Existing registry data can also be leveraged to map study objectives, assessments, and measures across data sources. For example, the existing data sets being collected on COVID-19 in various geographies and formats and for various purposes can be used to answer research questions.

Real-World Examples of Study Engineering to Maintain Continuity of Data Collection

Case Study One

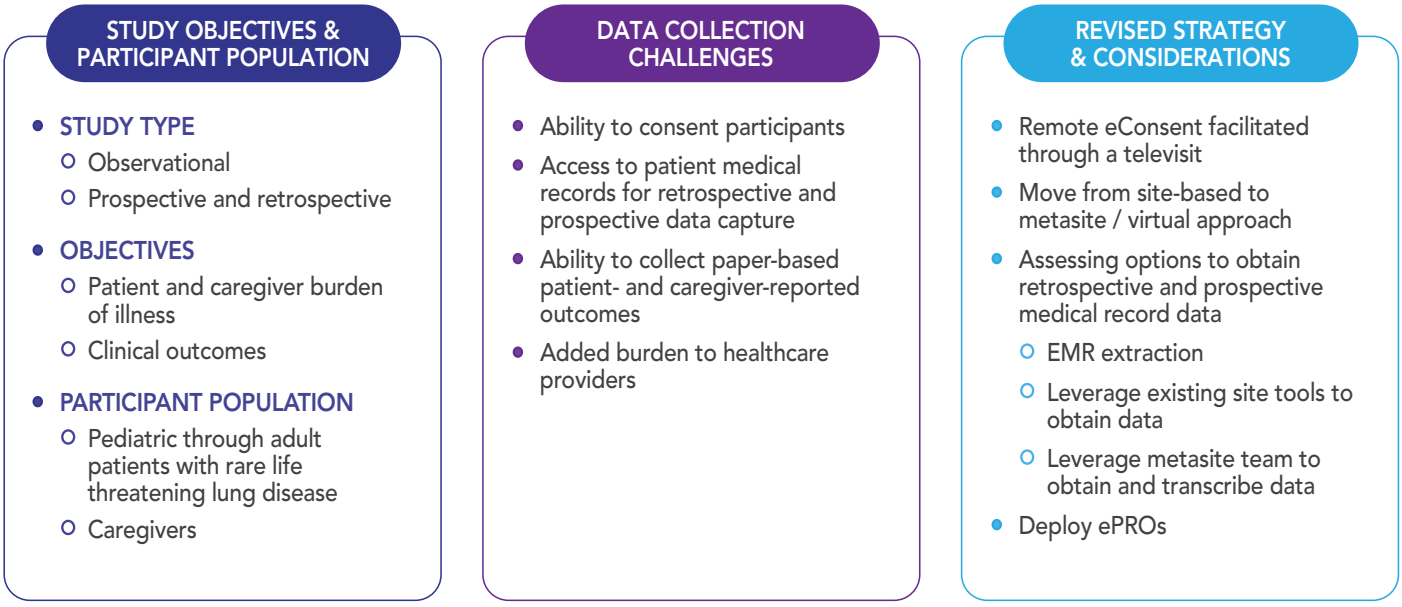
Concerns arose about the continuity of a current, ongoing observational study given the current pandemic and resulting shifts in priorities of healthcare providers, access to healthcare facilities, potential future local restrictions, and patient and caregiver preferences given the at-risk status of the patient population in the study. By evaluating the needs and using the options identified earlier in this article, a revised strategy was developed for this study. Figure 1 outlines the study objectives, challenges, and revised strategy to avoid study delays.

Case Study Two

In this example, a prospective Phase III study using an interventional oral therapy in dermatology needed to develop a rapid solution given a six-day lead time. This need was in a geographically sensitive area where patients had primary endpoint visits in the very short term. The primary endpoint is assessed via a scale that can only be performed visually, but the country is on complete lockdown, so face-to-face assessment was not possible. With time of the essence, this scenario required existing capabilities and partnerships, close relationships and alignment with all key stakeholders, and immediate mobilization for a successful outcome. Figure 2 identifies the study details, challenges, and solutions implemented.

While it is important to understand the available technology and how that technology can be deployed, it is equally, if not more important, to understand the relationships, processes, and limitations that support successful implementation.

Figure 1. Observational Study Continuation



EMR = electronic medical records; ePROs = electronic patient-reported outcomes

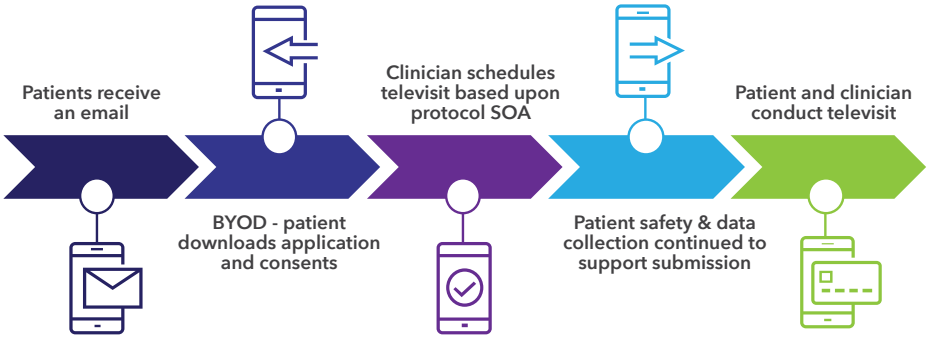
Figure 2. Phase III Study Strategy to Ensure Continuity of Primary Endpoint Data Collection

PATIENT POPULATION & STUDY CHALLENGES

- **STUDY TYPE**
  - Interventional oral therapy
  - Prospective Phase III study
  - Dermatology
- **CHALLENGES**
  - One site in Italy, five primary endpoint patient visits within next two weeks
    - Scale that can only be assessed visually
  - Country lockdown - visits cannot occur and primary endpoint data collection is at risk
  - Six-day lead time to solution

KEY CONSIDERATIONS & SOLUTIONS

- Need collaboration with pre-existing data collection processes
- Prioritize safety and primary endpoint data collection
  - Leverage a televisit
- Dynamic strategy development over short period of time
  - Close connections with regulatory, internal CRO team members, site staff, PI, and site privacy officer



CRO = contract research organization; SOA = schedule of assessments; BYOD = bring your own device

Conclusion

We need to be thoughtful and practical around collecting data in the current environment, while at the same time considering novel and alternative options to ensure clinical and real-world studies can continue. Regulators and other stakeholders are supportive of pragmatism while maintaining patient safety, both from a study data collection and virus exposure and risk minimization perspective. Decentralized solutions have been prioritized across the industry to address immediate needs for COVID-19 studies and other studies disturbed by the effects of the pandemic, but these solutions hold longer term potential. Outside of the current, urgent needs that digital solutions are helping to alleviate, these strategies offer the future standards for study development and allowing greater patient access and interactions that will expand the possibilities for future research. ■

For more information, please contact Mariah.Baltezegar@evidera.com. or godigital@ppdi.com.

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A Systematic Approach to Assessing Real-World Research Questions Supported by Digital Enablement

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Real-World Evidence, Evidera

Teresa Wilcox, PhD
Vice President
Real-World Evidence, Evidera

Multiple strategies, each with their individual advantages and drawbacks, may be employed to answer a research question, but determining the optimal strategy – the one that will bring you to your answer in the most effective and efficient way possible – that is the true challenge in our industry. Identifying that optimal strategy requires the synthesis of science, operations, and increasingly, technology. That synthesis, with its balance and integration of so many elements, cannot be achieved with a scattershot approach. Our systematic approach allows us to consider all these elements, to create that required synthesis, and to find that optimal strategy for each research question. This comprehensive process engages and considers the needs of cross-functional and multi-stakeholder subject matter experts (SMEs), including internal client stakeholders, study design experts, healthcare providers, external partners, other potential stakeholders, and most importantly, patients and their caregivers.

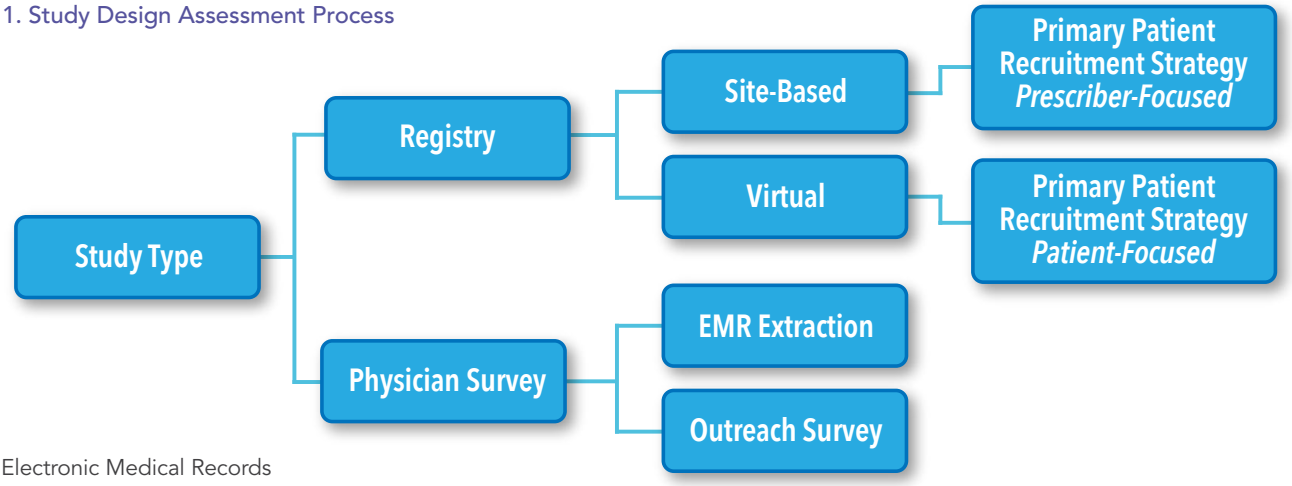
Our approach focuses on three key steps, including a two-step feasibility assessment and then a strategy confirmation.

1. **Level One Feasibility**: An assessment of possible strategies to answer the research question(s) of interest, including:
   - Detailed and specific scientific considerations and questions
   - Review of what is vital to the return on investment (ROI) assessment (e.g., regulatory requirements, critical assessments, length of data collection, patient retention, budget constraints)
   - Assessment of the optimal data collection method


Mariah Baltezegar


Teresa Wilcox

Figure 1. Study Design Assessment Process



EMR = Electronic Medical Records

2. **Level Two Feasibility**: Refinement of strategy informed by stakeholder feedback, including:
   - Analysis of study design options
   - Assessment of execution options
3. **Strategy Confirmation**: Specific recommendations

The two-step feasibility assessment considers the benefits of digital enablement at each point of the evidence generation process. While technology enablement uses a tool to produce an outcome, digital enablement is choosing the right technology to elevate and advance, in this case, evidence generation.

Level One Feasibility
Assessment of Approach to Answer Research Questions

In Level One Feasibility there are key questions and possible frameworks to be considered for each study. Figure 1 illustrates the flow of how we assess the study design process. Table 1 and Table 2 list the examples of the key questions for assessing study design and operations options, and whether digital enablement can contribute.

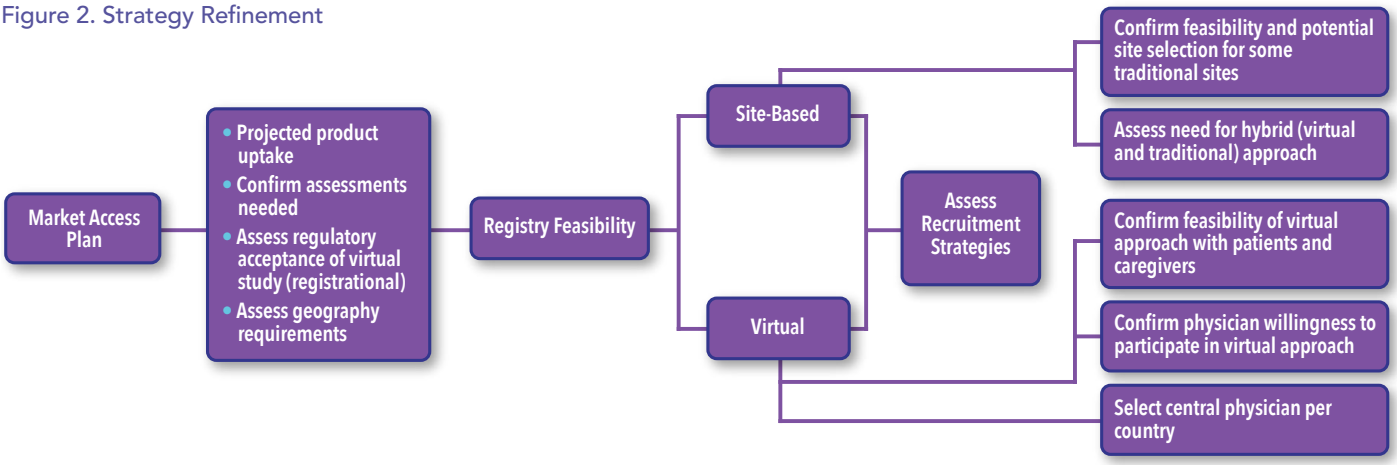
Table 1. Examples of Key Questions to Assess Study Design Options

Study Design Questions	Is Digital Enablement Available / Applicable?
Are there specific research questions/evidence requirements being requested by key decision makers?	N/A
Where is the point of care for the patient and for the dispensing/provision of the intervention (if applicable)?	Yes
Is the study data required for registration or regulatory purposes?	Yes
Do patients need to be recruited and/or can data be extracted from electronic medical records (i.e., assessments considered standard of care)?	Yes
In what geographical areas will this study be conducted?	Yes (digital enablement varies by geography)
Is data on multiple participants needed (i.e., pregnancy registry patient and newborn)?	Yes
Can some visits/procedures be decentralized?	Yes

Table 2. Key Questions to Assess Operational Options

Operational Questions	Is Digital Enablement Available / Applicable?
What sources are available for the cohort of interest?	Yes
Does the data collection plan account for the long-term follow-up (i.e., continuity of care, relocation)?	Yes
Can the report of measures be completed by the patient/caregiver? Is clinician confirmation required?	Yes
Where/how will patients be recruited? Are they recruited at sites or somewhere else? Where is follow-up being performed?	Yes
Could a virtual site be used?	Yes
Does electronic informed consent (eConsent) make sense?	Yes

Figure 2. Strategy Refinement



Level Two Feasibility

Refinement of Strategy Informed by Stakeholder Feedback

In Level Two Feasibility our study approach is assessed based on key features of each study and considerations based on answers received from the Level One Feasibility, ultimately informing the recommended approach. The next step is scientific and operational assessment of a series of questions and factors that inform the final design and operational strategy (See Figure 2).

Critical Features to Assess

The following critical areas must be assessed when determining the best study design to answer a research question:

- Acceptability to Regulators, including 21 CFR Part 11 Compliance[1]
- Alignment to the European Union's General Data Protection Regulation (GDPR)[2]
- Representativeness
- Country-Level Factors
- Availability of Measures
- Appropriate Data Reporter (Clinician, Patient)
- Patient/Caregiver Burden
- Site Burden
- Recruitment and Retention
- Timelines
- Cost
- Challenges and Opportunities

Considering Decision Maker Needs in Solution Development

Example: Regulatory Guidance Regarding Use of RWE to Address PASS

Should the key audience for the study findings be a regulator(s), the evidence generation approach must consider their requirements.

- The European Medicines Agency's guideline on good pharmacovigilance practices (GVP)[3] acknowledges real-world evidence (RWE) approaches for post-authorization safety studies (PASS) for both primary and secondary data. Most PASS are observational studies and increasingly introduce other objectives, such as real-world utilization (in particular, to describe exposure in groups that have not been exposed in clinical trials) and effectiveness outcomes, on top of safety outcomes, drug utilization (42%), and effectiveness (30%).
- In the US, the use of RWE for regulatory decision making was mandated in the 21st Century Cures Act[1] of December 2016, and a framework for its incorporation into decisions is provided in the Framework for FDA's Real-World Evidence Program[4] of December 2018. Although additional regulatory guidance documents are under development, the Cures Act and FDA RWE Framework provide sponsors with an array of study design options for the post-approval setting.
- Beyond Europe and the US, which have been followed closely by Canada and Australia, Asian countries such as South Korea, India, Japan, and mainland China also now request post-marketing, real-world evidence to observe drug effects both in routine practice conditions and in larger and more diverse populations.

Engagement of the Patient in Solution Development

The 21st Century Cures Act has expanded the focus on patient centricity by introducing "Patient-Focused Drug

Development" and developing a plan to issue guidance on how to include the patient experience in drug development and regulatory decision making. The inclusion of patient centricity in drug development can involve a multitude of activities. One aspect is the use of patient-reported outcomes (PROs) to collect patient experiences; however, this remains infrequent with a recent study showing that only six out of 30 registries collected data on measures of quality of life.

A virtual approach to study execution potentially reduces timelines and cost, enabling patients and caregivers across the globe to participate in a study while minimizing burden. Through the virtual model, the emphasis on sites and in-person monitoring can be foregone for remote data collection and electronic communication between physician and patient. This provides the researchers, patients, caregivers, and other stakeholders and data providers the flexibility to ease trials into their everyday work and life.

Case Study Example

Overview of Study Design

In this hypothetical case study, we outline the above approach for a study with these characteristics:

- A non-interventional registry study
- Evaluating long-term safety and effectiveness of a medication as used in routine clinical practice in adult patients (18 years of age or older)
- Designed specifically to meet a post-approval safety commitment

Strategy Recommendations

For this study, we recommend a virtual approach to collect study data outlined. This approach provides:

- Involvement of fewer countries and sites
- Reduced burden of participation for sites and patients
- Long-term engagement and retention of sites and patients

Other designs discussed in Level One Feasibility: Assessment of Approach to Answer Research Questions were considered. While database analytics is acceptable to regulatory bodies for assessment of long-term safety risks, other key decision makers may be interested in comparative treatment effectiveness, which is not feasible using data analytics alone since current databases rarely have continuity over extended time periods. The clinician and patient assessments of treatment effect are rarely recorded in the medical record, neither as defined fields nor in text fields.

Table 3. Example of Critical Features Study Design and Operations Options

Critical Feature	Site-Based Registry	Fully Virtual Registry
Acceptability to Regulators - 21 CFR Part 11 Compliance	Acceptable	Minimal to no risk given data is collected as standard of care
Representativeness	Participant mix highly dependent on participating sites	Highly representative given patients do not have to be in proximity to a brick and mortar site to participate
Country-Level Factors	Standard approval based on country regulations	For each country, we need to assess virtual feasibility and selection of a virtual site investigator
Measure Availability	Measures available from standard of care visit data from participating physician	Measures available from standard of care visit data from participating physician and available by medical records release for patients at the virtual site
Site Burden	No additional burden as data will be collected from visits scheduled as part of routine clinical practice	Reduced burden as virtual sites will take on activities for many brick and mortar sites
Recruitment and Retention	High level of site motivation and effort required to enroll patients and keep them engaged over 10 years	Recruitment and engagement managed through technology; close follow up with patients/caregivers by virtual site staff
Timelines	Lengthy contracting and site activation processes can delay timelines	Fully virtualizing reduces to a single site per country equating to shortened total start-up timelines

Virtual Model

Given the procedures are all standard of care in this case study example, we proposed conducting the study as a fully virtual study. This provides:

- Reduced country footprint
- Reduced site footprint
- Reduced patient, caregiver, and healthcare provider burden
- Increased potential patient pool given a patient's ability to participate from anywhere
- Increased patient engagement through digital enablement of engagement strategies and data collection

Conclusion

Real-world evidence research questions can be answered in a myriad of ways. Each solution has benefits and risks that must be weighed. Whether it is the quality or quantity of the data or cost of the procurement of the data, these risks and benefits need to be methodically assessed. This assessment must include scientific study design questions, operational execution questions, and align patient centricity and digital enablement. When assessment is underpinned by experience and strong capabilities, the resulting solution ensures a well-thought out, key stakeholder engaged approach. ■

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Virtualizing this study + applying the model assumptions above = a 55% reduction in budgeted costs

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Leveraging Simulation to Patch a Clinical Trial Broken by COVID-19

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Introduction

The basic structure of a randomized comparative clinical trial is quite simple. A candidate population that meets the admissibility criteria is recruited. Each candidate who consents to participate is randomly allocated to an experimental treatment or to one or more "controls." The participants are followed and data are collected until a pre-specified ending criterion is met. To ensure the integrity and usefulness of the trial, it is important that there be sufficient numbers of participants, they be followed as specified without losses, and all desired data be collected. Failure to do so increasingly threatens the informativeness of the trial, and if the losses are biased in some way, the validity of the trial can also be jeopardized. Medical research has become quite adept at meeting the design and operational challenges posed, but the COVID-19 pandemic has inflicted unexpected damages to ongoing trials. The enormous investments involved and the substantial adverse consequences of failing to gain the desired information from these trials put enormous pressure on our field to find ways of patching the broken trials. In this brief paper, we provide one novel solution to these problems: using simulation to attempt to rescue these studies and make up for the lost data.

What is the Problem?

COVID-19 impairs the process of randomizing people, following them over time, and collecting their data by making it more difficult for participants to carry on with their study visits, increasing reluctance of study personnel to carry out required activities, and in the extreme, removing people altogether if they become ill. For trials that are still recruiting participants, their identification and enrollment may be considerably impaired. Thus, trials are suffering from patients who leave the study early, cannot complete their scheduled data collection, or have significant missing data; some trials are even losing power to determine the planned endpoints because there are fewer participants to randomize.

J. Jaime Caro

One Powerful Solution

The essence of the solution comes from understanding the purpose of the comparator arm in a clinical trial. The idea is that we want to compare what happens to participants in the experimental arm to what would have happened if they had been left alone without receiving the experimental intervention. The control group fulfills this purpose – it provides information on what happens to similar people who do not receive the intervention (but are otherwise observed in a similar way).

In the early days of clinical research, there was a need to actively collect these comparator data because that information was scarce or non-existent. Now, after many decades of research, a great deal is known about the course of most diseases given the standard of care interventions, and data continue to accumulate. While not as good as data obtained optimally in a contemporaneous clinical trial, the existing data can be leveraged to respond to the question: what would have happened to these patients if they had completed the trial on the given comparator arm?

One way to accomplish this, which has been gaining credibility, is to find a suitable dataset, identify patients who would have been admissible to the trial in question, extract their data, and analyze their recorded outcomes. Various statistical techniques are then used to improve the likelihood that the selected patients do indeed reflect those who would be in the trial's control arm. This method, dubbed a "synthetic control arm," increasingly leverages the real-world data collected for other purposes. Regardless of the data employed, however, these types of studies are restricted to the "matching" patients found in the dataset and are limited in terms of controlling for the differences between the dataset and the trial.

A novel alternative that can overcome these limitations is to use a simulator to recreate the missing information.

What is a Simulator?

All of us, particularly younger generations, are very familiar with simulators, even if not specifically with a disease simulator. Many of the most popular video games, for example, are simulators. In the context of the problems experienced by Boeing, we have heard much about flight simulators and their use in training pilots. Even in medicine, much of the "hands-on" training has been shifted from having students and residents practice directly on patients to "dummies" that don't feel pain and can be reused as many times as necessary.

These are all physical simulators – they try to replicate physical environments, even if they are imaginary ones as in the video games. To patch the broken trials, however, we need something a bit different – more like the weather simulators that predict the pathways a hurricane may take. These are mathematical models that compute the possible trajectories, along with their likelihoods. Although they make predictions about a natural phenomenon, they are not physical simulators – they do not create representations of the ocean, the shoreline, and so on, but rather use a large number of linked equations that can take inputs like water temperature, barometric pressure and so on to derive predictions of the trajectory of the hurricane.

> With this tool, it is possible to simulate what would have happened to patients in the control arms had they completed the trial.

Our disease simulators, likewise, are mathematical structures that provide detailed predictions of the disease trajectories – of what will happen – for a particular patient profile under a given set of circumstances, including standard interventions, and how these change over time. Interlinked equations are at the core of the simulation and these are implemented in a framework that enables modifying the inputs and exploring their effects. With this tool, it is possible to simulate what would have happened to patients in the control arms had they completed the trial. In fact, real patients enrolling in the trial can now be allocated preferentially to the experimental arm maximizing the information to be obtained there (where simulation cannot reach), and the now "missing" control patients can be generated via simulation, possibly even going to no further controls, nearly a single arm study.

How is the Simulator Constructed?

The key to building a good simulator is detailed understanding of the disease trajectory and its predictors. This requires expert clinical knowledge, a good grasp of the literature, but most important, obtaining sufficient data to develop the core equations for that disease. The data sources can be many and varied, coming from depositories of real-world evidence, previous clinical trials in the therapeutic area, registries and other cohort studies, and meta-analyses. There is no reason to limit the simulator to any particular type of data or single source – the more data the better.

These data are used to develop the predictive equations that capture the disease trajectory. These are very much parametric equations that try to describe what is happening over time in relation to the patient profiles, environment, behaviors, interventions, and anything else that may be predictive. The equations can be quite complex, and their development requires expert statisticians experienced in this type of work. It is very important to avoid simplification for its own sake.

Once the equations have been developed, they are deployed in a framework that integrates them into a calculational structure with modifiable inputs and reporting

> The COVID-19 crisis is forcing us to consider novel approaches to fix unexpected problems that have few other solutions.

of the required outputs. A very flexible and easy to work with approach is Discretely Integrated Condition Event (DICE) simulation. In such a model, the things that can happen are represented as tabulated Events and all the information, including the equations, is stored in Conditions.[1-3] Instructional materials and examples can be downloaded from https://www.evidera.com/dice.

The resulting disease simulator must be extensively validated. Just like the hurricane predictors, or any weather model, the simulator is valuable only if it makes reasonably accurate predictions. With the weather, the forecasts are validated soon enough, but with disease simulators it is necessary to actively validate their predictions because often they will not be enacted in reality. This is, of course, especially true when patching a broken trial as the whole point is to recreate what would have happened but no longer will. The disease simulators are validated by seeking other studies and data sets and attempting to predict, on the basis only of the starting circumstance, what happened. Often this is done employing the same data that were used to develop the core equations, but this only provides partial, dependent validation. Ideally, the validation extends to studies that were not used in constructing the simulator. As the simulator's predictions may drive serious, expensive decisions, it is crucial to ensure that it is predicting accurately.

How is the Simulator Used?

Once the simulator is validated, we can start repairing the gaps in the broken trial. Patients with missing data or shortened follow-up in the control arm and those who are still to be randomized can now be recreated in the simulator, rescuing much of the sample size and enabling conclusions to be drawn from the broken trial. To do this, the user does not need to be a simulation expert as the simulator is implemented in MS Excel®. What is required is a good understanding of the disease, the broken trial, the product indication, and the patient profiles enrolled in the trial. The user works with the simulator through a graphical interface where they can enter their various inputs, specify scenarios, and incorporate uncertainty. The interface sends the entries to the DICE engine where all the logic, equations, and analytics take place. After executing a simulation, the results are output to the interface. There is no need for the user to understand the workings of the simulator, but the models are very transparent and can easily be examined if there is interest.

Although fixing broken trials has not been a major objective of disease simulators (mainly because our field tries very hard not to have broken trials), simulation has been used to create simulated control arms for single arm studies and the results have been looked on favorably by regulatory agencies.[4] In addition, these simulators are being used to design new trials and extend the results to other populations or contexts.

Advantages and Limitations

Compared to synthetic control arms, the simulator can leverage data from many sources, incorporating as many predictors of the trajectories as possible. These are not only patient characteristics, but also features of the study protocol, context, environment, country, etc. Aspects particular to the broken trial, such as discontinuation, visits, and testing frequency can be simulated. This frees up the trial to redirect its efforts to the experimental arm and maximize power.

Although the focus here is on the clinical trial primary endpoint, and possibly some of the secondary ones, the simulator can produce any number of outputs including other health aspects, economic predictions, quality of life outcomes, and so on, and over longer periods than may be necessary for the trial itself.

The simulator is entirely dependent on the quality of the linked equations, and, thus, on the data used to develop them. If those data are very messy and incomplete, then the simulator will not yield good predictions. Beyond the data, the construction of the simulator itself is straightforward and can happen very quickly.

One aspect that can be difficult to incorporate into a simulator is the placebo effect and the related Hawthorne effects. Humans respond differently when they know they are under observation or they think they are receiving effective treatment. These responses are unlikely to be reflected in data collected routinely for other purposes but can be incorporated using information from previous trials. In any case, the validation against other trials can assess the extent to which unexpected effects occur in prospective studies and whether the simulator is capturing these.

While the simulator can patch the control arms, it is not able to simulate the experimental arm. That is precisely the knowledge the trial is supposed to generate and true *in silico* testing of products remains a remote hope.

There is also a psychological challenge to deploying disease simulators. While other fields have been doing it for decades, our field has been very slow and late to adopt simulation. For many people, there is a reluctance to jump into a new method; they worry that time and money invested in this approach may be wasted. Will anybody buy it? Will anybody believe it? The COVID-19 crisis, however, is forcing us to consider novel approaches to fix unexpected problems that have few other solutions.

Conclusion

Clearly, the COVID-19 era is threatening the conduct and completion of clinical trials. Simulation is a very powerful tool that can help overcome these difficulties – it helps fix the broken studies. Judicious leveraging of these novel approaches can answer the question: what do we predict would have happened to these patients if they had completed the standard of care or comparator arm? We need to accelerate the deployment of these unique – and possibly industry changing – strategies. ■

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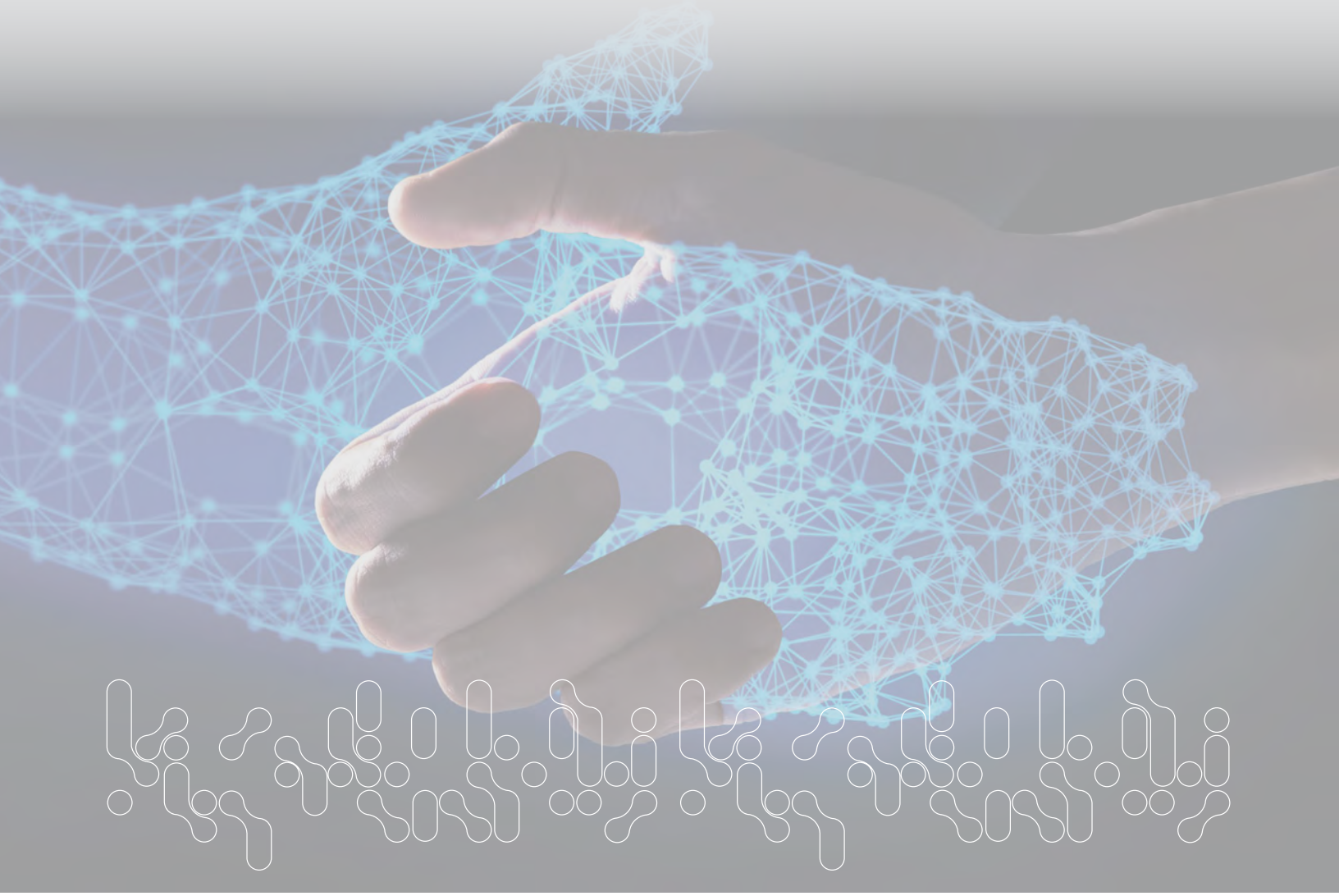

Evidence Generation Using Innovative, Technology-Driven Data Collection

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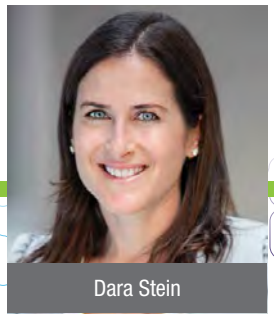
Background

Real-world evidence (RWE) is becoming increasingly more important across the pharmaceutical product lifecycle, from advancing the understanding of disease and informing clinical guidelines to supporting regulatory and outcome-based reimbursement decisions.[1] The landscape continues to rapidly shift towards the need for richer and more comprehensive sources of health outcomes.[1] To keep up with the growing demand for RWE there is a need to devise innovative methods to access data and generate robust and reliable evidence.

Electronic medical records (EMR) are now widely implemented in healthcare organizations,[2] and health information exchange (HIE) technology has been widely used to link patient information across different electronic sources. This offers an opportunity to connect to and communicate with EMR systems to extract data in an automated, repeatable, and secure manner for research purposes. Using enhanced HIE-based technologies to extract information from hospital EMRs, researchers get the best of both worlds by ensuring direct access to a rich source of clinical data while removing manual data entry labor, reducing site burden, and maintaining scientific rigor.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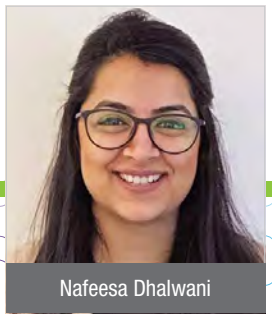
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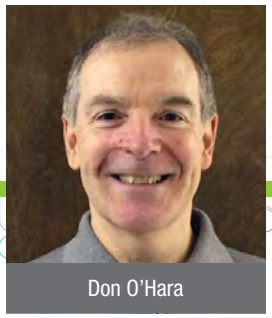

Don O'Hara

In the Fall 2019 issue of *The Evidence Forum*, we discussed key operational considerations to successfully implement technology-driven solutions for hospital EMR data collection based on our experiences[3] using this approach. The focus of this article is on the advantages, guiding principles, and best practices for using enhanced HIE-based technology to systematically extract data from hospital EMR systems in light of the need for rapid, repeatable, and automated data collection.

What is Technology-Driven Data Collection?

The focus here is on the use of technology to directly identify and extract patient-level data from hospital EMR systems for research purposes. Data extraction software is securely configured to the hospital EMR systems, all the while ensuring that industry best practices for patient privacy and data security are met at all levels. Once configured, the software user interface at the sites communicates securely with the site EMRs and off-site software user interface accessed remotely by researchers (See Figure 1). This allows authorized remote researchers to query multiple hospital EMR systems simultaneously to identify potentially eligible patients for inclusion in research studies, subsequently extract data, and generate queries to clarify ambiguities for enrolled patients. This step replaces the traditional method of having a person manually review and enter data from the EMR into an electronic data capture system.

Advantages of Technology-Driven Data Collection

Technology-driven data collection offers many advantages to traditional methods for capturing data in observational studies. While the use of existing administrative claims and EMR databases is rapid and cost-effective, many databases have inherent limitations due to long time lags between data recording and availability, limited capture of inpatient prescribing and disease-specific biomarkers, and incomplete recordings of risk factors and outcomes.[4,5] The traditional methods of collecting data via manual chart review and data entry by local hospital staff into an electronic case report form (eCRF) overcome some of the limitations of EMR databases, however, this approach is very labor intensive and prone to human error.[6] Additionally, for each new chart review study, a new or updated eCRF needs to be implemented and requires manual data entry by site staff, which is time consuming. The careful selection of key outcome measures is essential to limit site burden, leading to compromises between desired versus feasible data elements to collect in a given timeframe.

> Technology-driven data collection offers many advantages to traditional methods for capturing data in observational studies.

Figure 1. Technology Driven Data Collection Overview

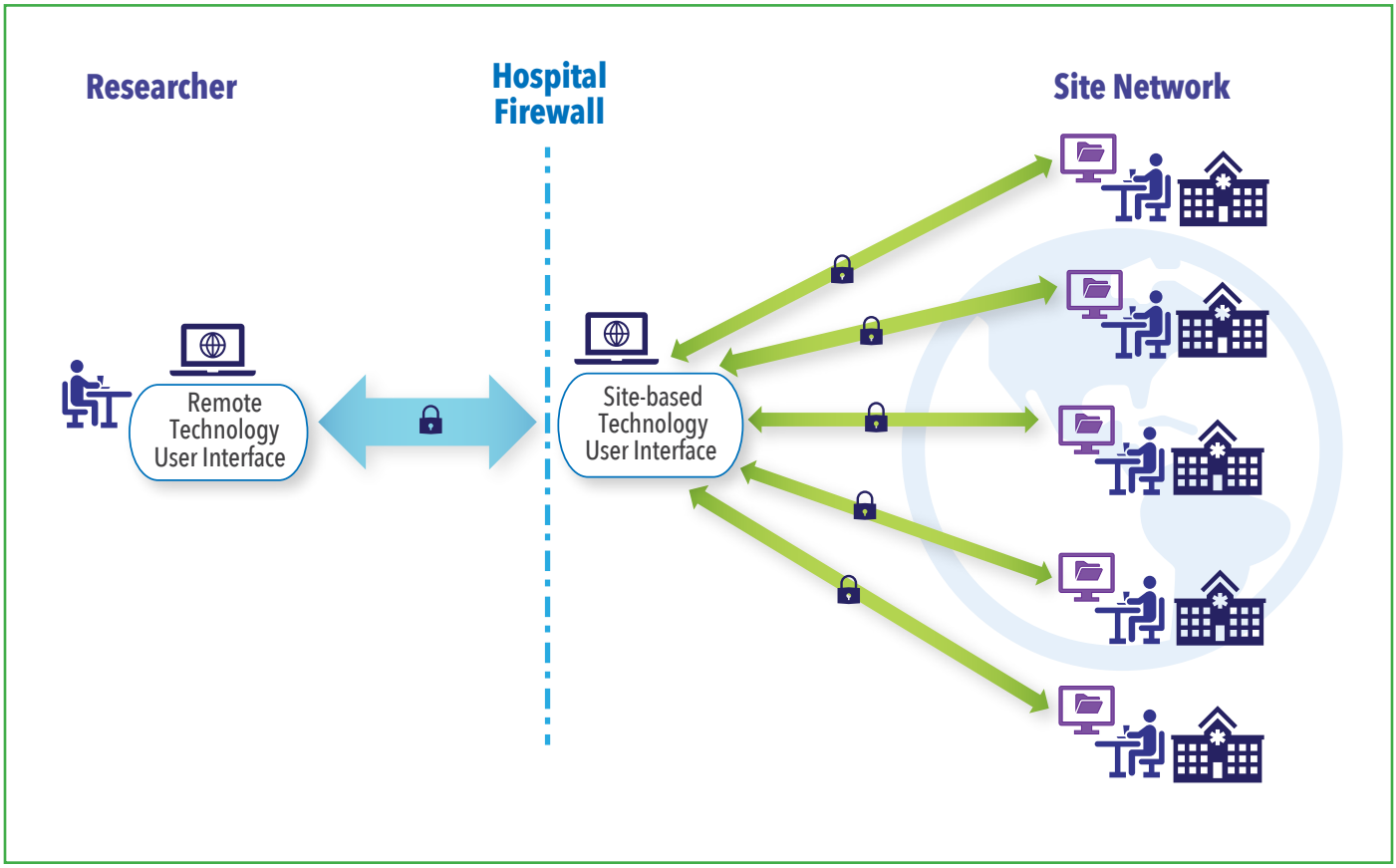
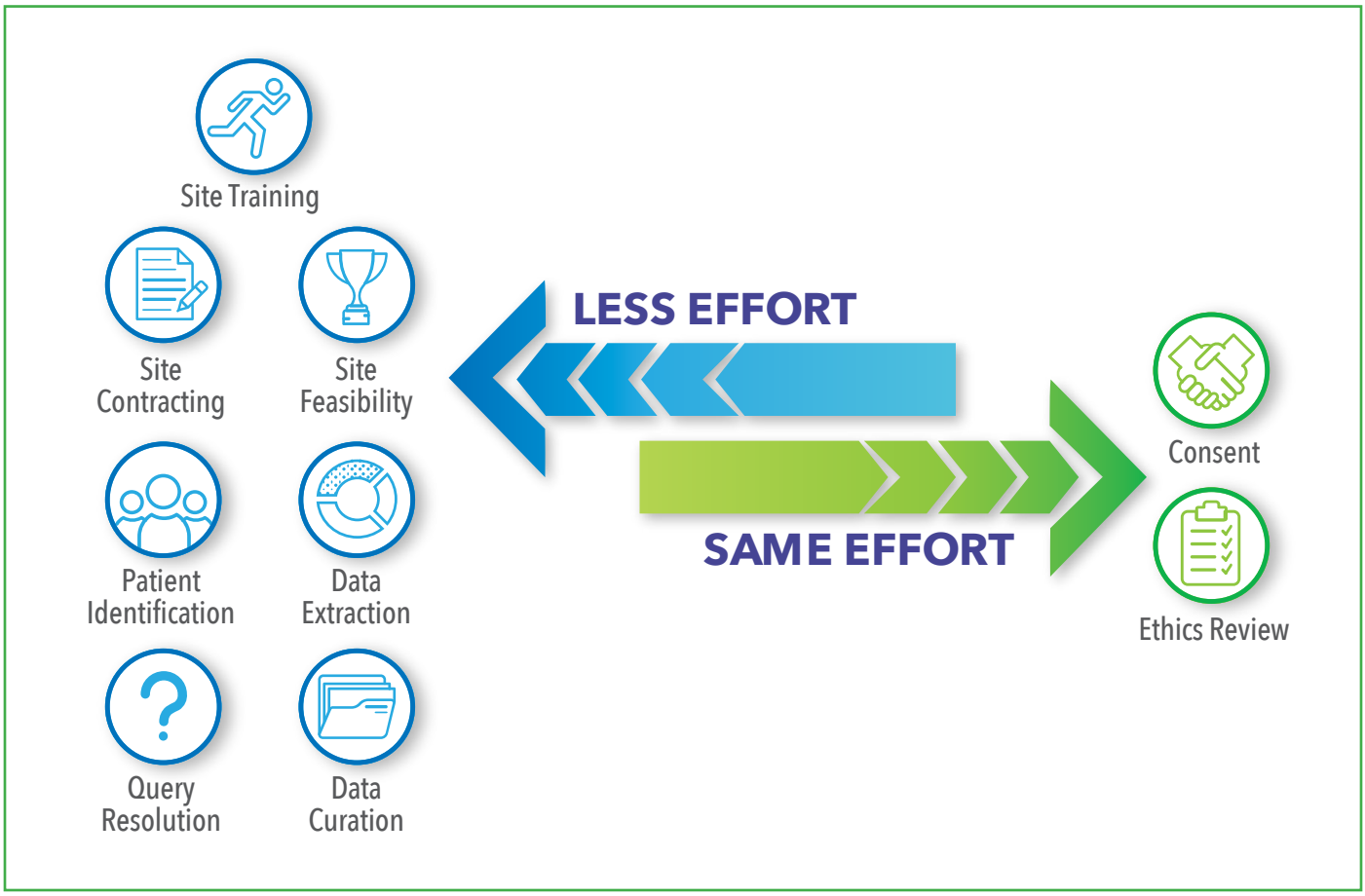


Figure 2. Comparing Level of Effort between Technology-Driven Extraction via Established Site Network vs. Traditional Chart Review Outside Site Network



In comparison, technology-driven data collection facilitates extraction directly from the source to minimize data entry errors, thereby reducing the volume of data queries. It also streamlines data collection, curation, and cleaning processes, as data are extracted directly into standard formats conducive to analyses. The same ethical considerations as chart review studies apply to technology-driven data collection approaches, ensuring the same level of scientific rigor and integrity. Using technology to automate data extraction also allows for the capture of a more rich and deep set of outcome measures in larger patient populations without increasing site burden and workload. It is particularly valuable in prospective studies with the need for future data refreshes because, if the sites are already configured, the process of repeat extractions is simplified. This allows for more streamlined and efficient study set-up and roll-out periods, as well as quicker results. Figure 2 compares the level of effort for study tasks required in technology-driven data collection studies within a pre-established site network with traditional chart review methods. While studies can include extractions at one single timepoint, capturing historical data, greater value comes from the ability to automate repeated extractions at pre-specified, future time-points (e.g., every six months or more frequently). Repeated data access facilitates the evaluation of the changing treatment landscape, as well as long-term clinical and safety outcomes, which cannot always be adequately accomplished in databases with time lags or chart review studies.

While technology-driven data extraction brings several benefits, it is not without its limitations. The main hurdle is finding suitable sites for configuration that also cover large catchment areas and provide comprehensive care to avoid gaps in data on patient care and treatment patterns/outcomes. Furthermore, not all site EMRs may be compatible for setting up the extraction technology. In addition to these limitations, patient privacy and concerns over cyberattacks and the misuse of patient data have been at the forefront of several media outlets in recent months,[7,8] adding further skepticism and scrutiny as a major barrier to technology-driven data collection.

Data Security and Patient Privacy Considerations

Data security must be implemented by means of end-to-end controls embedded into all layers of an application to ensure the protection of information assets: hardware, software, people, and data.[9] All application users and system support staff are trained on information security best practices, and all users are strictly required to follow the policies, procedures, and controls put in place to ensure data security.[10,11] In addition, hardware specifications

> In addition to keeping patient data secure while the data are in motion or at rest, the application needs to be compliant with all local and regional patient privacy regulations.

and software requirements are defined to ensure data are protected, kept confidential, untampered with, and accessible to only authorized users. The application should implement the continuous monitoring of applications to detect and circumvent intrusion or data alteration attempts. Site users and support staff need to have a complete understanding of how the application components are installed and configured in the site infrastructures. Sites must be actively involved from the initial planning phases through configuration, installation, day-to-day operation, and system retirement.[12] All security concerns and mitigation steps are discussed, agreed upon, and signed off on before any solution is implemented.

In addition to keeping patient data secure while the data are in motion or at rest, the application needs to be compliant with all local and regional patient privacy regulations, such as the Health Insurance Portability and Accountability Act (HIPAA)[13] in the United States (US), and the General Data Protection Regulation (GDPR)[14] in the European Union (EU) and United Kingdom (UK). A dedicated de-identification module within the application ensures that all patient identifiable data are transformed into pseudonymized patient data before leaving the site; key data elements and identifiers that could be used to identify a patient are removed from the extracted data.[15] The pseudonymized patient data includes a key-code identifier that can be used only by authorized site users to access the patient identifiable data by means of a look-up table that remains on the site infrastructure. No patient identifiable data are transferred outside the hospital firewall.

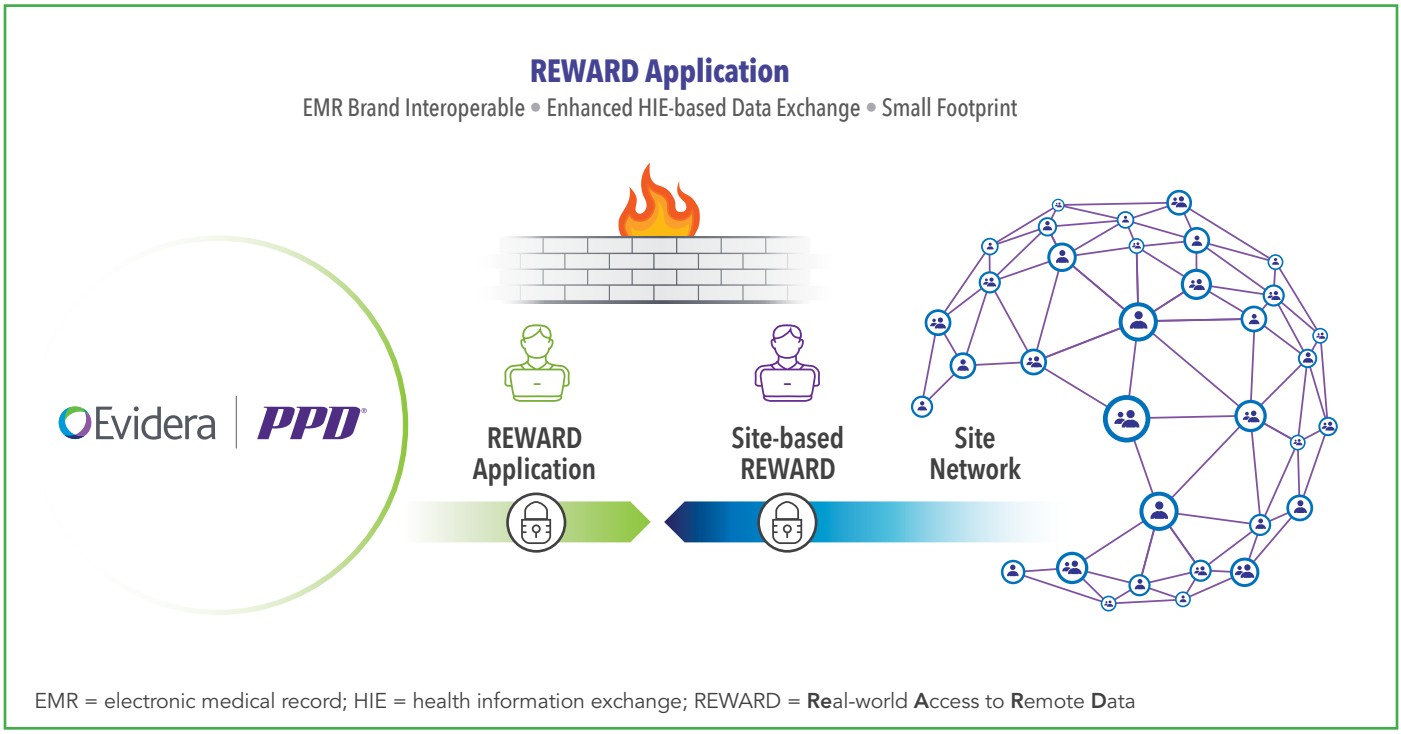
In addition to hardware and software controls used to ensure information security and patient data privacy, healthcare applications must give sites the tools to remain in control of their data. Sites should be allowed to choose the studies in which they would like to participate via an opt-in/opt-out mechanism; within a particular study, sites must have the ability to approve or deny queries from researchers asking for patient counts; and, sites need to be able to approve or deny all patient-level data being extracted. No data aggregate or individual-level pseudonymized patient data can leave the site without site permission. Patient consent should always be requested, where applicable, and study-specific ethics approval will always be sought.[16]

REWARD: Our Approach to Technology-Driven Data Collection

Real-**W**orld **A**ccess to **R**emote **D**ata (REWARD) is Evidera's solution to technology-driven data collection (See Figure 3).

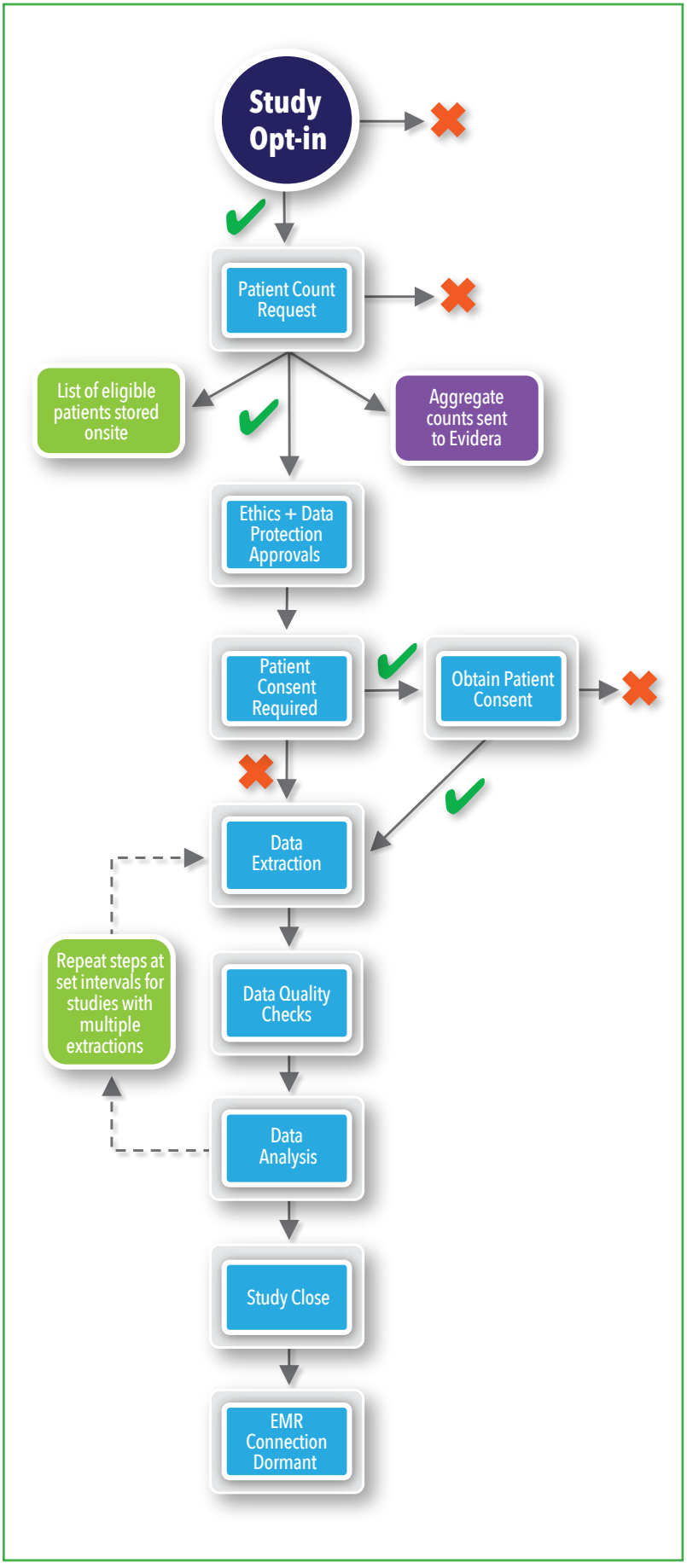
REWARD employs a systematic approach to technology-driven data collection with built-in checkpoints at each step of the study lifecycle. Through REWARD, hospitals

Figure 3. Overview of REWARD



EMR = electronic medical record; HIE = health information exchange; REWARD = **Re**al-world **A**ccess to **R**emote **D**ata

Figure 4. Data Extraction within REWARD



keep control of data access and flow, while the application safeguards patient privacy and securely stores data. Once configured, sites are invited to participate in each study through the REWARD site application and can opt-in or opt-out of the study. If sites opt-out of the study, no further contact is made in relation to that particular study. If sites opt-in, then the Evidera user issues a patient count request within the REWARD application to identify potentially eligible patients and obtain initial patient counts. Sites have to approve the request before any active linkage with the site EMR is made and any aggregate counts can be shared with Evidera. Once the request is approved, the REWARD application links to the EMR data and returns aggregate counts to Evidera. REWARD also creates a list of potentially eligible patients and stores that information within the site application; this list, however, is not shared with Evidera. Following ethics approval, sites confirm patient enrollment and consent (when required) using this pre-stored list via REWARD. Sites then approve the data extraction request, at which point data extraction and patient data de-identification is undertaken via REWARD. If subsequent extracts are required, sites will be prompted to approve this within REWARD beforehand. Any queries regarding extracted data are sent to the site for review and comment. Once data extraction and curation is complete, the site becomes dormant until a repeat extract is requested in prospective studies, or the site opts-in to participate in another study.

Summary

Implementation of technology-driven data collection using a systematic approach to research that has checkpoints, safeguards patient privacy, and ensures data security can address a breadth of research questions pertinent to drive drug approvals and improve patient care. In order to build trust, it is integral that hospitals remain the gatekeepers to their patients' data and be in control of data access through all steps of the research study. Short-cuts should not be taken, and full transparency regarding the process is essential for success. ■

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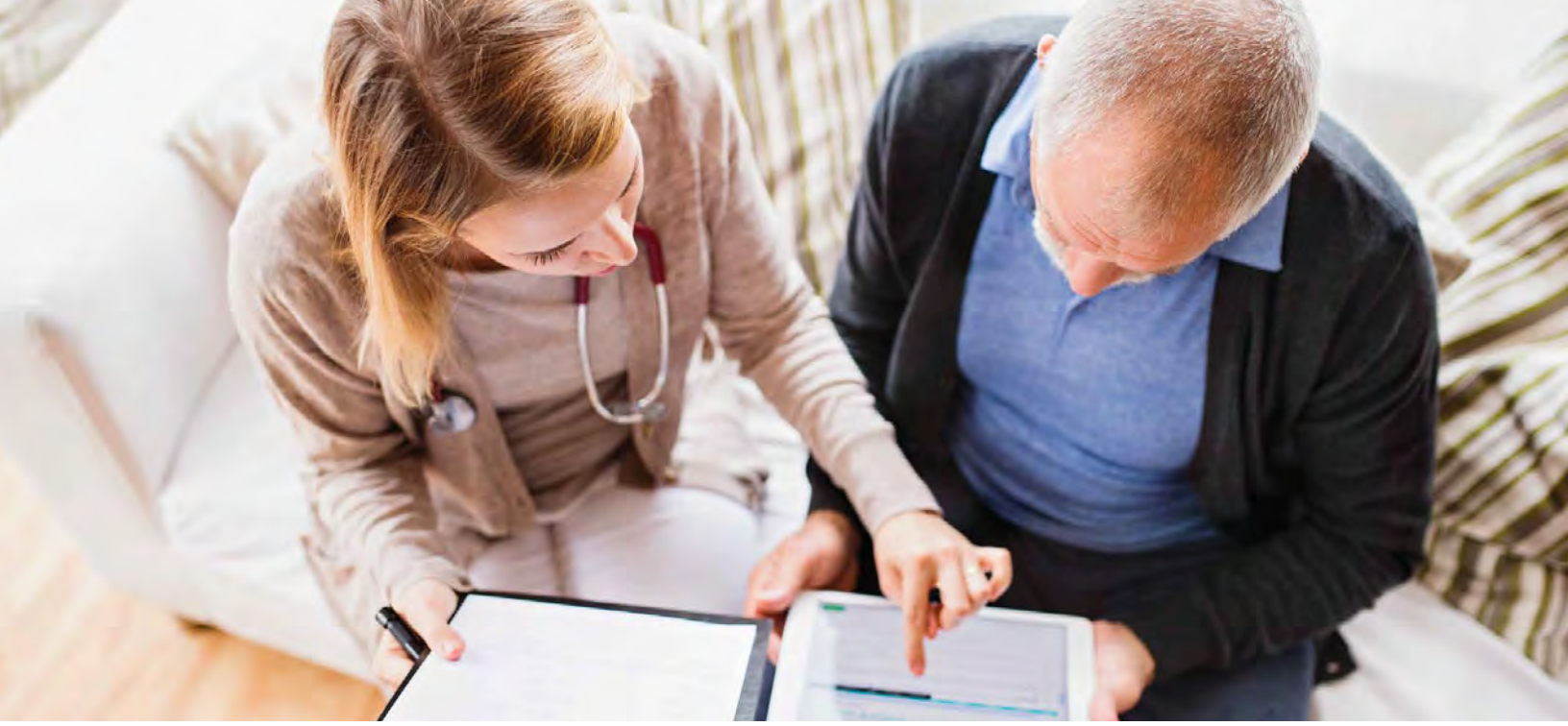

Surprises You Don't Want When Adopting eCOAs for Use in Clinical Trials

Cautions for Decision Making and Planning

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Introduction

The surge in the digitalization of communications over the past ten years is not only shaping our day-to-day lives but is also seeping through to scientific methodology such as clinical outcome assessment (COA) data collection methods in clinical trial research. COA tools are used to measure symptoms, health status, or impacts of a disease or condition on functioning.[1] A COA can be a standardized measure with multiple items or domains, or an individual item. COAs include patient-reported outcomes (PROs), clinician-reported outcomes (ClinROs), observer-reported outcomes (ObsROs), and performance-based outcomes (PerfOs) measures.

Adoption of electronic COAs (eCOAs) for clinical trial data collection is happening at a faster rate than ever before and many pharmaceutical and healthcare organizations (hospitals, clinics, etc.) are now switching efforts to move away from paper data collection methods.[2,3] The types of COAs available for use is getting more varied with electronic modalities such as smartphones, tablets, wearables, interactive voice response systems (IVRS), web-based software, and device apps like Bring Your Own Device (BYOD). Currently, the most popular modalities are smartphone, BYOD, web, and tablet, while IVRS use is on the decline.[4,5] It is projected that in the next five years alone eCOA revenue will grow by almost 20%—with the market reaching $160 billion by 2027.[6]

eCOA Advantages

There are numerous advantages to using eCOAs in clinical research. Evidence demonstrates that the use of eCOAs improves data accuracy and site and user compliance. They

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have the added benefit of significantly reducing missing data.[7,8] Moreover, eCOAs allow users to receive reminders to complete their assessments and provide the flexibility of data completion from anywhere (e.g., home, clinic, or hospital). Regulatory bodies like the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) appear to support the use of eCOAs as electronic data can be easily tracked, time stamped, are confidential, and allow for centralized data monitoring.[9-11] Since 2012, many medicinal products approved by the FDA and EMA include an electronic format of a PRO, and especially daily patient diaries.[12]

Beyond their overall acceptance by the industry and regulatory bodies to date, eCOAs allow for implementation of branching logic of questions, reducing the length of questionnaires, and patient burden. Skip patterns can be more effectively used to give patients a better personalized and user-friendly experience.[13] Finally, their use has been shown to improve patient willingness to answer sensitive questions that they otherwise may not be comfortable answering.[14]

eCOA Logistical Considerations

Although there are advantages to using eCOAs, there are also planning steps, hurdles, and detailed technical requirements to think through (summarized in Figure 1). It is not reasonable to expect to buy the product off the shelf from an eCOA vendor and have it work well in the trial. It is crucial to assure the goal of your study is going to be well supported by the eCOA you select, and be sure you have appropriate buy-in from your internal stakeholders. There are a number of logistical, decision making, and tailoring considerations that must be arranged before, during, and after you decide to use eCOAs.

Implementing electronic modalities usually requires added time and funding in the early stages. The initial search for a suitable eCOA vendor should include more than investigating budget for services; it should scrutinize the potential vendor's ability to meet the study specifications and study goals with their services and not present limitations in programming, platforms, or other services that would hinder the successful accomplishment of study goals. The eCOA vendor costs can vary dramatically depending on required logistics and selected devices (e.g., BYOD versus tablets; leasing versus buying devices; global versus country-specific) and complexities (e.g., length of study assessment, COA length and branching logic, type of modality). eCOA vendors know these territories well and will offer options beneficial to their own efficiencies, but it is also important to involve a scientific expert well versed in eCOA to guide this planning phase to be sure the scientific requirements are being properly considered. Some eCOA vendors offer this kind of scientific expertise to assist project design while others do not and are more focused on operationalization of the devices and programming. You will want to consider the scientific input as a key step so that the study design is not compromised later due to implementation, technical, or user issues.

Once it is determined that implementing an eCOA is the right fit for a study and the project specifications are finalized, conducting due diligence in vendor selection is critical. The level of experience and resources that a vendor has with clinical trials is critical, including how experienced

Figure 1. Cautions about Using eCOA

1. Many COAs are originally developed on paper and require migration to an electronic format before use
2. Permission from COA developer may need to be sought ahead of use and migration
3. Can take more time and money upfront (migration, validation, equivalence)
4. Not enough is known about modality differences: one size does not fit all
5. It may look more flexible, but it is not always (Title 21 CFR Part 11 compliance important)
6. If not programmed well, it may add significant burden to site or patients
7. Careful considerations must be made depending on population and geography (e.g., remote areas)
8. Special considerations must be made for international studies and across languages; missing data issues
9. Health authorities/regulatory bodies still exploring eCOA and do not always provide specific guidance
10. Newer technologies like wearables and health technology apps still need to be tested and validated

they are with the study intricacies, including CFR Part 11 compliance, which is a regulatory requirement in many clinical trials.[1] The juxtaposition with Title 21 CFR Part 11 Compliance requirements is that, to date, it is not as flexible as it appears to be, as it requires a certain infrastructure in place (guidance on establishing security controls, backups, system maintenance, and data integrity).

If an eCOA is being used to support an endpoint for a labeling claim in a clinical trial and in order to adhere to regulatory requirements, the best option is usually to use a provisioned device (devices provisioned by the sponsor or site that are specific device models that have undergone study customization). Drawbacks with provisioned devices, however, is that they lack the flexibility or user-friendliness that a BYOD app may provide. Provisioned devices also require device shipping, training, and setup by the user; will have limited device functionalities; and, may add the burden of carrying another device in the respondent's pocket or purse.

eCOA training is important especially for target populations that are not as familiar with technology or older populations who did not grow up using electronic devices or apps. Although research suggests that older populations are able to successfully use eCOAs, there is often a learning curve that requires initial device training. Another example of how an eCOA implementation may falter is if the login or setup process is too complex or time consuming for the patient or site. This can deter user engagement dramatically and lead to a loss of critical data for trial success.

Additionally, an important consideration to make during the planning phases is knowing your target population. If for a neurodegenerative disease, for example, patients have upper extremity difficulties (e.g., difficulty with writing and typing), an eCOA solution that includes the need to type or sign might be a major design flaw. The application of eCOAs can be used across a broad range of therapeutic areas and indications, including oncology, rheumatology, dermatology, gastroenterology, rare diseases and beyond, but with caution.

In short, if the implementation phases and programming are not well executed, they may add significant burden to those taking part, including sites, the study team, patients, and caregivers, and can fail, especially in the case of multi-national, longitudinal trials that require more than one time point for data entry.

Completion of eCOAs should also be weighed carefully when combined with other data collection case report forms or electronic modalities. It is considered good practice to match as much as possible with other electronic modalities during that trial to provide the end user with a seamless experience.[15] Reducing mixed modes in a trial and using only one device, for example, to complete all data collection would be the ideal scenario, but this depends on the study design, the status and type of instruments being used, the phase of drug development in which the study occurs, and the overall available funding. Often, eCOA implementation is not well thought through, and the patient, for instance, is expected to complete her/his case report forms on a tablet, while their daily diary is on a smartphone. This can be jarring and confusing, leading to lower compliance rates and engagement with the trial. Such issues should be considered and resolved with the expert research scientist, eCOA vendor, and study investigator during project planning phases.

Cross-Cultural and Geographic Issues

When it comes to international trials and deployment of eCOAs across countries and languages, special additional considerations must be made regarding the migration of COA instruments to electronic formats. Such issues include the number of words per question across languages, which often differs and can impact the of the size of the screen that must be used. The programming structure of response options across languages will also require detailed scrutiny as languages are conjugated differently and some can be substantially longer than the source document's character count. Screen size and programmable character count should be considered early to assure the electronic PRO (ePRO) vendor can support the language and COA needs. Another example is the use of English keyboards in international trials; they can create confusion, data quality issues, and decreased patient engagement.

More problems may arise in translation programming. Some vendors do not have the capability to implement Zulu, for instance, a South African language, or Cantonese characters in Chinese.

Cross-cultural issues are relevant not only within global trials, but also within one country where more than one language is spoken (e.g., English and Spanish in the US). Such considerations can have budget implications and need to be thought through well in advance.

Geographic locations of the study population must also be considered. For example, if the study population is mainly in rural areas and patients do not have access to WIFI, yet the device relies on a WIFI connection, the data for that group is at risk. This can result in major study catastrophes on data generalizability and may decrease power from the statistical analyses and result in significant cost burden and delays.

Additional Scientific Issues

Other considerations are scientific in nature. Text placement on the screen can make a big difference to user engagement. Text that is centered versus crowded in the top left corner is preferred as it has been shown in cognitive interview work to be easier for patients to read. Word wrapping is another consideration. Where words break can totally change the meaning in some languages. Text should not extend out to the same margins as the item numbers,

Table 1. eCOA Validation and Equivalence (Adapted from Fuller et al., 2016)

Classification	Rationale	Examples	Level of Evidence
Functionality Adaptation	Change is made solely for adaptation to computer format.	1. Non-substantive changes in instructions (e.g., use of radio buttons rather than circling a response, addition of comment boxes to capture information).	Usability testing
Instruction Adaptation	Addition of instructions from administration guidelines or study-specific conventions that are not included in the paper scale.	1. Addition of previously established guidelines (e.g., instruction from scale manual informing clinician to read question verbatim).	Usability testing
Minor Modification	The modification can be justified on the basis of logic and/or existing literature. No change in content or meaning.	1. Minor changes in format (e.g., use of bold vs italics) 2. Minor changes in wording in text intended for the administrator or subject that do not alter interpretability (e.g., using "select item" instead of "underline item").	Cognitive debriefing usability testing
Moderate Modification	Based on the current empirical literature, the modification cannot be justified as minor. May change content or meaning.	1. Changes in item wording or presentation that are more significant and might alter interpretability.	Equivalence testing: usability testing
Substantial Modification	There is no existing empirical support for the equivalence of the modification, and the modification clearly changes content or meaning.	1. Substantial changes in item response options. 2. Substantial changes in item wording.	Full psychometric testing, usability testing

and response options should have adequate space between their start and the stem item. Both issues have been shown to cause patients to skip reading the items fully because the screen area is visually congested. If users begin to skip reading parts of the message and assume an incorrect message, this can have an impact on the data, the validity of an instrument, and the findings.

It is important to note that the majority of standardized COAs were originally developed on paper and require migration to an electronic format before use. In those cases, working closely with the COA developer or license holder and the study investigators will be important. Many of the license holders do not yet have clear guidelines for eCOA implementation, so it is important to allow ample time for these tasks to be accomplished as they require longer periods of coordination.

Validation research must also be conducted before using an eCOA in a study if the instrument is to be an endpoint to support a medical label claim.[16] Although equivalence of paper and electronic has been shown to be highly correlated, it is still recommended to consider validation.[17,18] This type of research can be divided into three categories and will depend on the level of modification from paper to electronic as shown in Table 1.[19] The type of research includes usability testing for minor modifications, cognitive testing for moderate changes and equivalence/full psychometric testing for major change or de novo instruments.

Conclusion

We are in a time where technology is rapidly advancing, making new options interesting and attractive. While collecting data by varied electronic platforms opens up the potential for research that increases accuracy, timeliness of reporting, and the types of variables that can be captured, the electronic modality itself must be approached with a variety of cautions in order for the marriage of eCOA data collection and scientific research to be effective.

As different electronic modalities become available, more needs to be known about their individual validity and comparative difference between modalities. Pre-planning

logistics, costs, and limitations in programming should be researched in great detail in order to be clear what will be required of an ePRO vendor before making the selection.

New technology must not be used simply because it can be; it needs to be chosen with an eye to providing the best fit for the study needs with the data objectives, the required logistics, the population characteristics, impacts of the therapeutic area, and overall patient burden well thought out in advance of the final decision. Careful pre-planning and extra awareness will go a long way towards avoiding surprises that nobody wants. ■

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Digital Therapeutics
Past Trends and Future Prospects

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Introduction

Digital therapeutics (DTx) are a digital health category defined by the Digital Therapeutics Alliance as products that *"deliver evidence-based therapeutic interventions to patients that are driven by high quality software programs to prevent, manage, or treat a medical disorder or disease."*[1] DTx are distinct from digital medicines or "smart pills," which combine a prescription medication with an ingestible sensor that is designed to communicate with a software application to track compliance.

Advances in and the increasingly dominant role of mobile technology and artificial intelligence (AI) in our everyday lives have broadened the role of DTx in healthcare. Although, historically, interest in developing DTx was mainly confined to academia and technology companies, the potential to use DTx in conjunction with medicines to improve health outcomes has sparked the interest of big pharma, who have started to venture into the DTx space through investments and strategic partnerships with tech companies.[2] This exciting advancement will create opportunities to increase patients' awareness of their health and their ability to play a more active role in managing their


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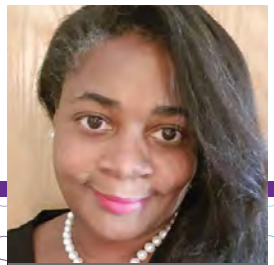
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Andrew Bevan

disease, thereby creating the potential to improve health outcomes and reduce the demands on healthcare systems compared to traditional pharmacological interventions alone.[3,4] The DTx market is expected to grow tenfold in the next three to five years, with a projected market value of $9 billion (USD) by 2025.[5] However, this presents challenges in terms of how the technology is regulated, how healthcare providers (HCP) respond to this paradigm shift, and how these technologies are reimbursed.

In this article, we will review the trends in the development of DTx over the past decade, the current landscape, future prospects, and some of the challenges faced by companies looking to commercialize DTx applications.

Trends over the Past Decade

Study titles containing the word "digital" that were registered between January 2010 and December 2019 were searched on clinicaltrials.gov. Of the resulting 557 studies, 182 were determined to be interventional trials of DTx applications based on protocol title and type of intervention. Out of those 182 studies, 167 trials (92%) were registered with clinicaltrials.gov in the past five years, during the time when the number of DTx application trials increased more than five times from 12 in 2015 to 58 in 2019 (See Figure 1).

With respect to therapeutic areas (TA) under investigation, the highest percentage of trials have been conducted in psychiatric indications (25%) – and there is strong evidence supporting digital cognitive behaviour therapy's (DCBT) efficacy in this area[6] – followed by cardiovascular (11%), endocrine (10%), addiction (10%), neurology (8%), and respiratory (7%) (See Figure 2). Seventy-seven percent of DTx trials conducted over the past 10 years have been sponsored by academia, which has dominated research across all TAs apart from respiratory, where 50% of trials have been sponsored by industry. Although traditional cognitive behaviour therapy (CBT) has been effective in improving health outcomes in chronic nephrology[7] and gastroenterology[8] indications, there has been very little research to investigate the effectiveness of digital modalities in these TAs.[7,8]

Future Prospects for DTx

A pipeline review of nine leading DTx companies (See Figure 3) revealed the development of therapeutic applications for a diverse range of neuroscience indications, such as attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), schizophrenia, depression, and bipolar disorder, dominates commercial research and development (R&D), which follows the trend seen in the analysis conducted for the clinicaltrials.gov trials. Furthermore, a focus on the development of solutions for cardiovascular disease (CVD) such as hypertension, hyperlipidemia, and acute coronary syndrome (ACS) is consistent with trends seen in clinical trials over the past decade. However, the focus on developing DTx solutions for gastrointestinal diseases, such as irritable bowel syndrome (IBS), inflammatory bowel disease (IBD),

Figure 1. Trends in Interventional Digital Therapeutics Trials Over the Past Ten Years

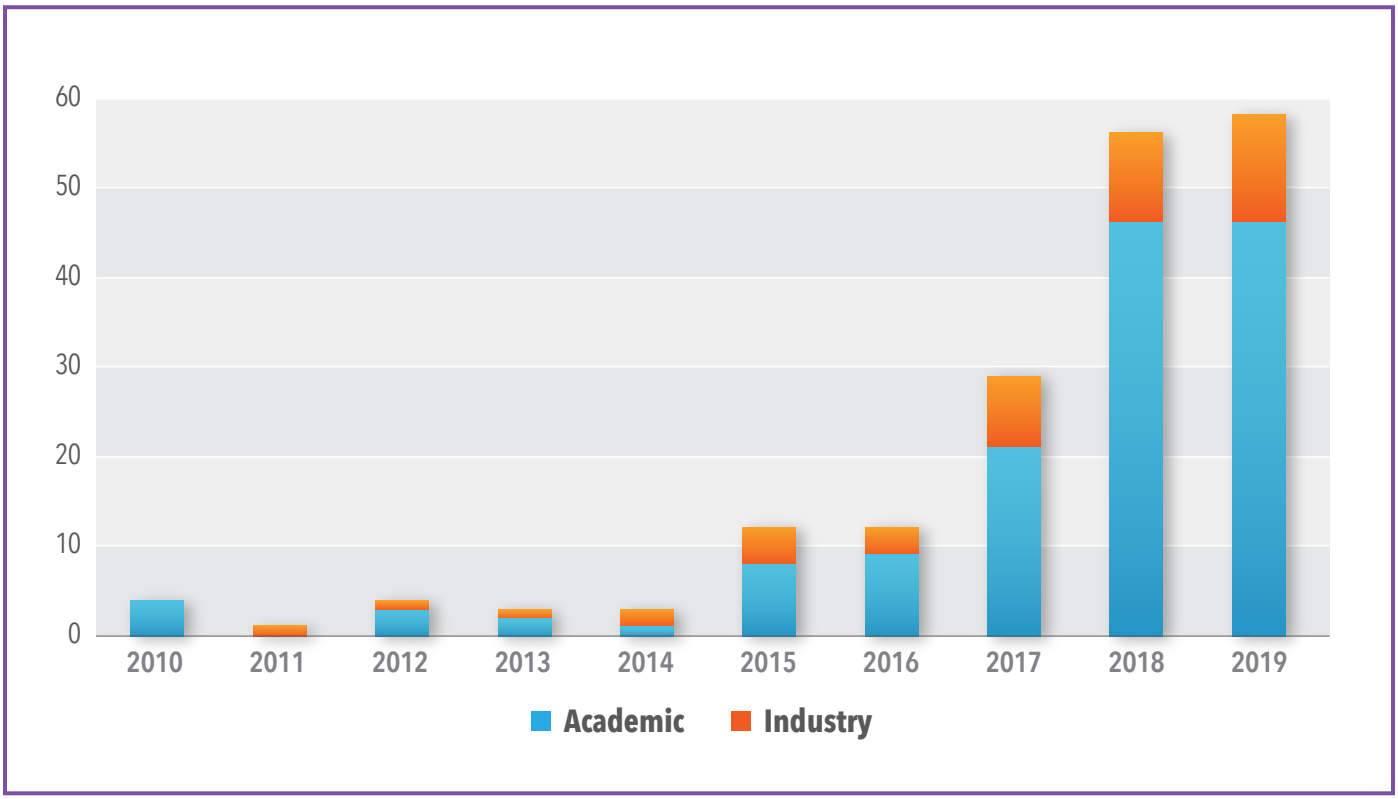
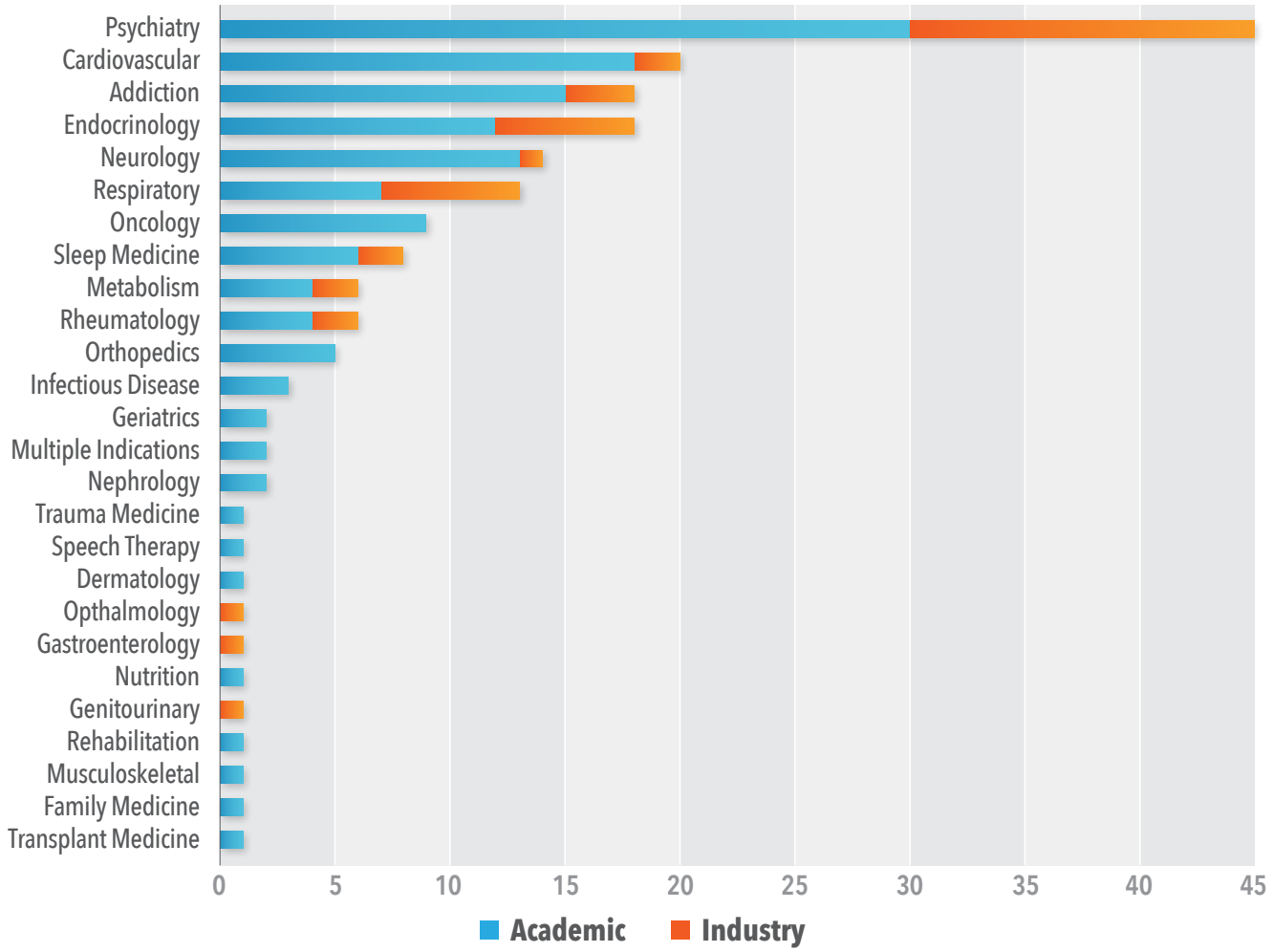


Figure 2. Trends in Digital Therapeutics Trials by Therapeutic Area Over the Past Ten Years



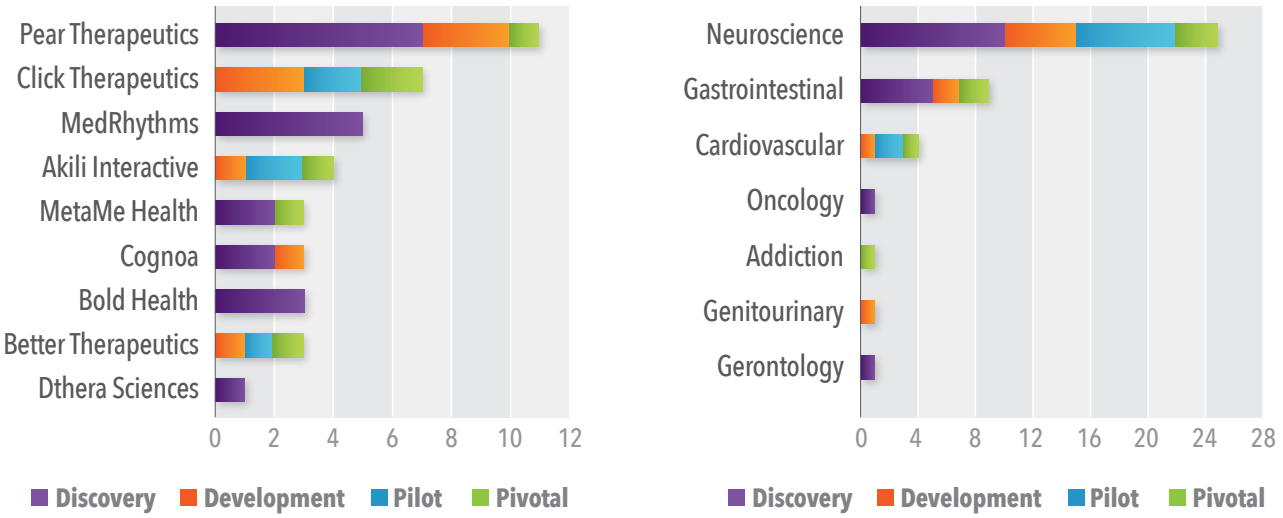
and gastroesophageal reflux disease (GERD), bucks the trend seen over the past decade. This suggests that DTx companies are looking to diversify their pipelines by adding new indications were there is currently unmet need, including chronic kidney disease (CKD),[9] and where the potential for DTx to improve health outcomes has been highlighted.[10] Pediatrics is another area with a high degree of unmet medical need, to the extent that in 2003, the Pediatric Research Equity Act (PREA)[11] was introduced in the United States (US) specifically to address the lack of approved pharmaceutical treatment options available for children. Furthermore, in the United Kingdom (UK), there have been challenges ensuring mental health provision for children and young adults due to difficulties engaging this population and issues with lack of funding[12] and treatments. However, DTx represents a unique opportunity to engage this population with the aim of improving health outcomes since UK statistics indicate that more than 95% of individuals aged 16 to 34 own a smartphone[13] and many also own tablet computers and/or game consoles.

The 21st Century Cures Act[14] (Cures Act), which became law in the US on December 13, 2016, is paving the way for tech companies to streamline the development of new technology that improves the treatment of serious diseases that have unmet medical needs. The law includes several important regulatory changes designed to facilitate advances in DTx. One such change is the introduction of the FDA Breakthrough Devices Program[15] that offers manufacturers an opportunity to interact with the experts at the Food and Drug Administration (FDA) and efficiently address topics as they arise during the premarket review phase to make timely and agreed upon adjustments based on FDA's feedback. An additional benefit is that manufacturers also receive prioritized review of their submission. The goal of the program is to provide patients and healthcare providers with quicker access to medical devices, and since its introduction, several manufacturers have been given breakthrough designation for their leading DTx products.[16-18]

There exists a dichotomy between the "move fast and break things" philosophy of the tech industry and the need for robust evidence-based health solutions. However, the DTx industry has established core principles and best practices (See Box 1) to ensure that tech companies provide

Figure 3. R&D Pipeline Overview for a Selection of Leading DTx Companies

Number of Indications and Stage in Development by Company and Therapeutic Area



evidence to support claims of safety, efficacy, equality of performance, and quality of their DTx products. Although these are not currently stringent regarding the burden of evidence required for a medical product or device, regulatory authorities are implementing frameworks in order to rigorously assess DTx.

Creating Formularies for DTx

The increasing DTx options present patients and providers with a challenge for selecting the relevant application for a given disease.

In May 2019, Express Scripts started developing the first Digital Health Formulary to support HCPs in identifying treatments with the greatest overall value for patients. The first release of the Digital Health Formulary included 15 applications that aid in the management of the country's eight most common chronic conditions: diabetes, prediabetes, hypertension, asthma, pulmonary disease, depression, anxiety, and insomnia (See Table 1). The formulary will be reviewed and additional solutions will be added in 2020.[20]

In addition to the Express Scripts initiative, National Health Service (NHS) England is working with the National Institute for Health and Care Excellence (NICE) to support a new digitally enabled therapy assessment program to expand the provision of psychological therapies under the NHS's Improving Access to Psychological Therapies (IAPT) and Improving Access to Digital services as set out in the Five Year Forward View for Mental Health and the NHS Long Term Plan.[21] NHS England is managing all stages of this project, including selection and assessment of technologies, supporting development of technologies, and testing them in practice. NICE is responsible for the technology supplier

BOX 1.

Core Principles For All Digital Therapeutic Products[19]

- Prevent, manage, or treat a medical disorder or disease
- Produce a medical intervention that is driven by software and delivered via software or complementary hardware, medical device, service, or medication
- Incorporate design, manufacture, and quality best practices
- Engage end users in product development and usability processes
- Incorporate patient privacy and security protections
- Apply product deployment, management, and maintenance best practices
- Publish trial results inclusive of clinically meaningful outcomes in peer-reviewed journals
- Be reviewed and cleared or approved by regulatory bodies as required to support product claims of risk, efficacy, and intended use
- Make claims appropriate to clinical validation and regulatory status
- Collect, analyse, and apply real-world evidence and product performance data

Source: www.dtxalliance.org

Table 1. The First Cohort of Solutions in the Express Scripts Digital Health Formulary*

Clinical Category	Sub-Categories	Digital Health Formulary	
Diabetes	Type 1 diabetes Type 2 diabetes	PREFERRED:	Livongo® Health for Diabetes
		ALTERNATIVES:	Omada Health for Diabetes LifeScan's OneTouch Reveal® Plus, powered by Welldoc's BlueStar® platform
	Diabetes prevention	PREFERRED:	Livongo® Health for Pre-Diabetes
		ALTERNATIVES:	Omada Health for Pre-Diabetes
Cardiovascular	Hypertension	PREFERRED:	Livongo® Health for Hypertension
		ALTERNATIVES:	Omada Health for Hypertension
Pulmonary	Asthma COPD	Propeller Health	
Mental Health	Depression Anxiety Insomnia	Learn to Live Cognitive Behavioral Therapy SilverCloud Health Cognitive Behavioral Therapy	
ADDITIONAL SOLUTIONS COMING 2020			

**Released in December 2019, the formulary includes 15 solutions, including remote monitoring services and digital therapeutics that aid in the management of eight of the US's most common chronic conditions.*

Source: Express Scripts Website

selection and assessment, the IAPT assessment briefing report, and the production of the final evaluation for each digital therapy product. To date, NICE has provided IAPT assessment briefing reports for 14 digital therapy products, which will be assessed for use in NHS.[22]

Regulatory Challenges

The regulatory landscape for DTx is still evolving, and while the ultimate goal of regulation is to ensure that DTx applications are safe and effective, the FDA's Center for Devices and Radiological Health (CDRH) has acknowledged, through its Digital Health Innovation Action Plan,[23] that the *"FDA's traditional approach to moderate and higher risk hardware-based medical devices is not well suited for the faster iterative design, development, and type of validation used for software-based medical technologies."* The plan, which follows the imperatives established by the Cures Act, describes the FDA's steps to reimagine their policies, processes and tools to align with the needs of emerging technologies, and highlights three focus areas for the FDA:

1. New FDA guidelines on the regulation of digital therapeutics, especially with respect to multi-functionality (i.e., products with some software functions that fall under the FDA medical device oversight and others that do not), software changes to an existing device, and the clinical approach to Software as a Medical Device (SaMD).
2. The development of a Software Precertification Program (Pre-Cert) aimed to replace the need for a premarket submission for certain products and allow for reduced submission content and/or faster review of the marketing submission.
3. An increase of digital health expertise in the CDRH by hiring new staff who have a deep understanding and experience with software development and its application to medical devices or chemical and biological entities to improve the quality, predictability, consistency, timeliness, and efficiency of decision making for individual products and developers.

In 2019, the FDA began a test phase of the program with a limited number of organizations, applying both the Pre-Cert model and the traditional review process to each premarket submission, with the intent to confirm that the framework provides a reliable equivalence in terms of assuring safety and effectiveness for SaMD as the mainstream review

pathway. This retrospective testing achieved its objective in identifying the feasibility of the streamlined review package and excellence appraisal summary as sufficient to conduct a premarket review of SaMD. Next steps will be to confirm these early results with prospective testing outcomes.[24]

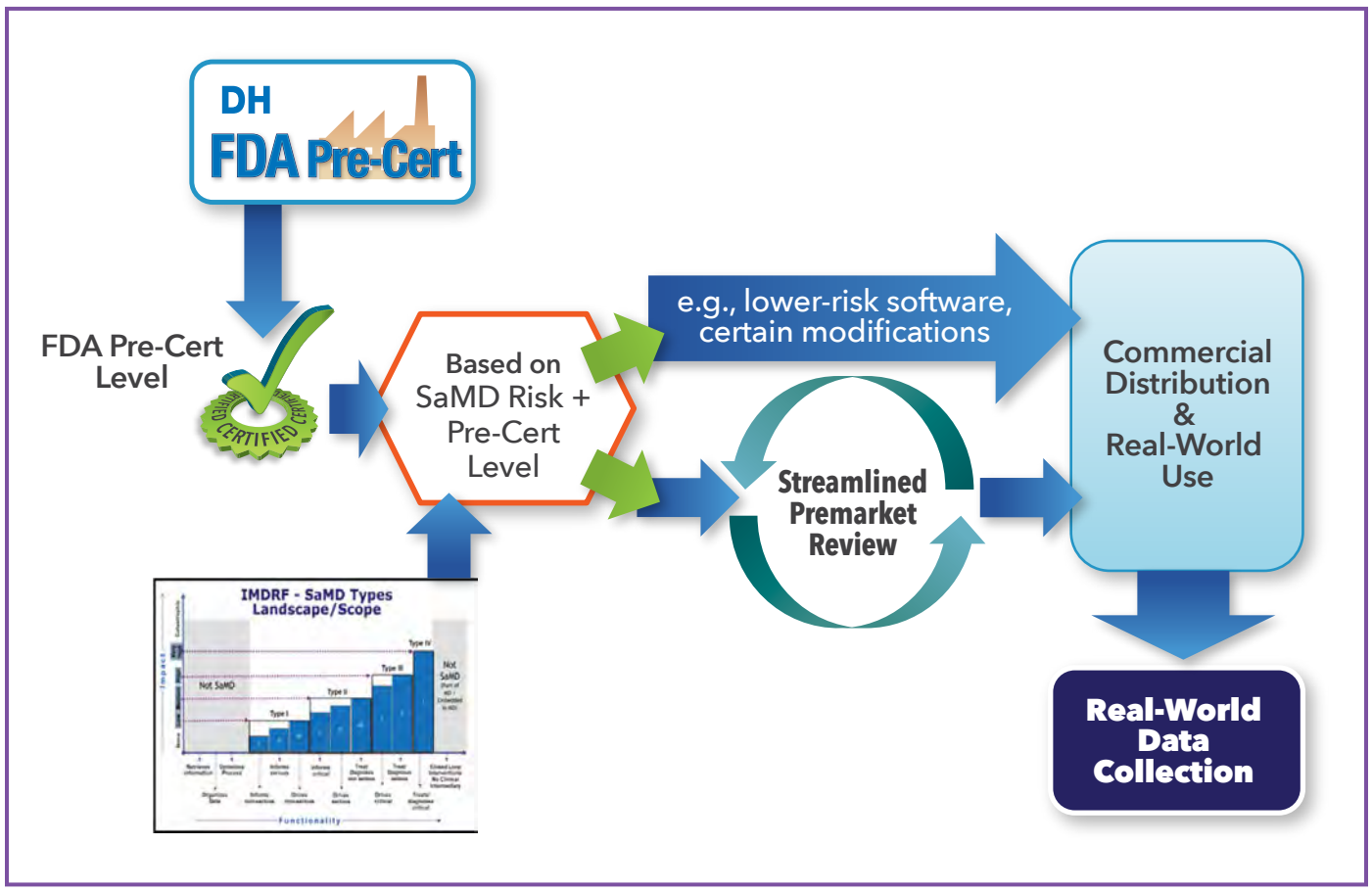
The FDA's vision for the future is that companies taking advantage of the Pre-Cert program will also be able to utilize the National Evaluation System for health Technology (NEST) system.[25] This aims to generate better evidence for medical device evaluation and regulatory decision making across the device lifecycle by collecting post-market, real-world data in order to affirm the regulatory status of the product and support new applications of the technology (See Figure 4). This aligns with the FDA's wider effort to establish guidelines to incorporate real-world evidence (RWE) in the regulatory decision-making process.[26]

The FDA is also part of an international effort to accelerate the harmonization of medical device regulations, including SaMD, through the International Medical Device Regulatory Forum (IMDRF), which includes medical device regulators from Australia, Brazil, Canada, China, European Union (EU), Japan, Russia, and Singapore. In 2017, the IMDRF SaMD Working Group published a technical document for planning the clinical evaluation process of an SaMD[27] for a harmonized global approach (See Figure 5).

Reimbursement and Market Uptake

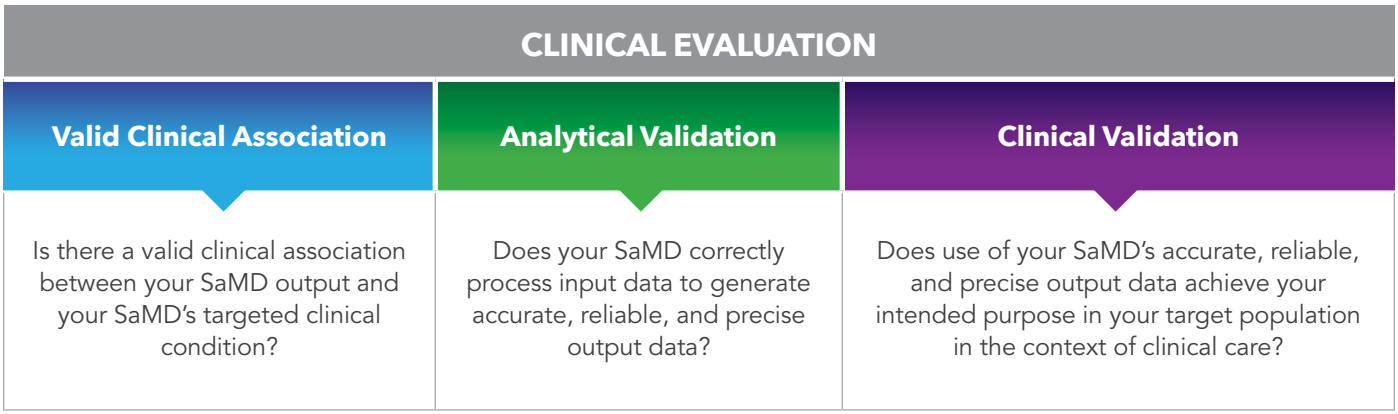
In addition to the regulatory challenges, the DTx industry also faces pricing and reimbursement challenges as the traditional pricing and payer reimbursement models, where providers are paid based on the amount of service they deliver, are not well suited for DTx. Until recently, direct-to-consumer (DTC) approaches, with users paying subscription fees to access DTx applications, has been the main channel for reimbursement in the industry. However, it is generally acknowledged that this is not a sustainable long-term market strategy, and therefore, DTx companies are exploring other channels to generate revenue, including the business-to-business-to-consumer (B2B2C) approach of selling products through online retail outlets.[28] In theory, a value-based healthcare delivery model where providers are paid based on patient health outcomes would appear to be a viable path for reimbursement, but this is dependent on robust RWE being available to support claims and demonstrate value. This emphasizes the importance of digital health formularies, such as what Express Scripts has developed, to increase the awareness of and confidence in evidence-based DTx solutions among HCPs and payers alike to help drive market uptake. Ultimately, payers need evidence of the clinical and economic benefits of DTx for these products to receive market access and be successful in the marketplace. A recent study conducted by McKinsey

Figure 4. High-Level Concept of the Reimagined Approach Using FDA Pre-Cert for Software



Source: FDA Digital Health Innovation Action Plan

Figure 5. Clinical Evaluation Process for SaMD



Source: Software as a Medical Device (SaMD): Clinical Evaluation. IMDRF, 2017

in partnership with the German Managed Care Association (BMC) estimated that up to €4.3 billion in potential healthcare savings could have been realized in 2018 if the German healthcare system had adopted all of the available digital solutions for patient self-treatment and patient self-care.[29,30] This demonstrates DTx's potential to reduce healthcare costs.

Conclusion

The rapid growth in research into DTx over the past decade has resulted in the commercialization of evidence-based applications that are set to become major disrupters to healthcare markets over the next decade. As DTx's reach in terms of therapeutic use and market penetration increases, so does its potential to positively impact public health and reduce healthcare costs. This will force a paradigm shift among regulators, payers, and providers to revaluate their approaches to ensure that they are fit for purpose. While progress is being made in the area of regulation and health technology assessment, progress with reimbursement pathways is lagging partially due to the need for RWE generation for DTx applications to demonstrate value. As a result, tech companies are looking to other channels such as the B2B2C selling model in order to increase market penetration and generate more sustainable revenue streams. ■

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US FDA's Emergency Use Authorization (EUA)

Applicability for Marketed and/or Investigational Products for Treatment of Coronavirus Disease (COVID-19)

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Brief Overview of EUA Regulatory Path

The Emergency Use Authorization (EUA) is a statutory authority which allows the US Food and Drug Administration (FDA) to help strengthen the nation's public health protections against chemical, biologic, radiological, or nuclear (CBRN) threats by facilitating the availability and use of medical countermeasures (MCMs – i.e., drugs, biologics, vaccines, diagnostic tests, etc.) during public health emergencies.[1] The EUA allows for the unapproved use (i.e., off label use) of an approved medical product (drug, biologic, vaccine, or device) or the use of an investigational/unapproved product in order to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by CBRN threat agents when there are no adequate, approved, and available alternatives.

The EUA for a medical product is issued by the Commissioner of the FDA, following the declaration by the Secretary of Health and Human Services (HHS) of an emergency or threat justifying the issuance of such an EUA. The process requires a Pre-EUA Consult Meeting (following the submission of an adequate meeting package), followed by the submission of a formal EUA Request to the FDA. The recommended content of the Pre-EUA Consult Meeting package and the EUA Request are defined in the FDA's Guidance for Industry and Other Stakeholders: Emergency Use Authorization of Medical Products and Related Authorities.[2] The FDA processes Pre-EUA Consults and EUAs in as expedited a manner as feasible, with EUA applications being prioritized based on a multitude of factors, such as:

Kusuma Mallikaarjun

- Seriousness of the public health emergency
- Urgency of the need for medical countermeasure interventions
- Plausible mechanism of action of the product
- Extent of proof of activity/safety
- Stage of development

However, there are no mandated timelines in place for this process. A successful Pre-EUA Consult will have the potential to lead to the issuance of an EUA within hours to days, once the formal EUA Request is submitted.

The decision to approve/issue the requested EUA for a medical product will depend on multiple factors, including answers to key questions such as:

- Do the data show that the product "may be effective" in achieving the intended use to diagnose, treat, or prevent the serious or life-threatening disease or condition?
- Do the known and potential benefits of the product outweigh the known and potential risks, looking at the totality of the scientific evidence? Such evidence may include (but is not limited to): results of domestic and foreign clinical trials, in vivo efficacy data from animal models, and in vitro data.
- Would other regulatory paths, such as developing a clinical study protocol under an existing Investigational New Drug or Device Exemption (IND/IDE) or granting access to the investigational product under an Expanded Access IND/IDE authority, be more appropriate?

The FDA can impose conditions and requirements for authorized EUAs pertaining to sourcing of the product, fact sheets for healthcare workers and patients, adverse event monitoring/reporting, etc.

Authorized EUAs generally remain in effect from the date of the authorization to the date the emergency declaration by the HHS Secretary is lifted. The state of the declared emergency can periodically be reviewed by the FDA, who can revise or revoke an EUA based on such review.

Status of EUAs for the COVID-19 Pandemic

The Secretary of HHS declared a public health emergency for the COVID-19 pandemic on February 4, 2020, effectively authorizing the FDA to issue EUAs for unapproved devices, drugs, and biologics, or for unapproved uses of otherwise approved products, that may be effective medical countermeasures to combat the COVID-19 pandemic. Subsequently, the FDA has issued a large number of device EUAs, with the first one being issued on the same day as the declaration of the public health emergency by HHS. Device EUA statistics as released by the FDA on May 1, 2020, are as follows:

- 54 device EUAs issued to test kit manufacturers and laboratories
- 23 device EUAs issued for high complexity, molecular-based laboratory developed tests (LDTs)
- 9 device EUAs issued for personal protective equipment (PPE)
- 12 Device EUAs issued for ventilators, re-processing/sterilization units for PPEs and other miscellaneous devices to be used in the COVID-19 pandemic
- 380+ test developers who have interacted with the FDA stated that they will be submitting EUA requests for tests that detect the virus
- 235+ laboratories have notified the FDA that they have begun testing under the policies set forth in the Policy Guidance for Diagnostic Tests for Coronavirus Disease-2019 during the Public Health Emergency[3]

The FDA has issued two drug EUAs to date. The first EUA covered hydroxychloroquine phosphate and chloroquine sulfate, both of which are to be supplied from the Strategic National Stockpile (SNS) for distribution and use for certain hospitalized patients with COVID-19. These drugs will be distributed from the SNS to states for doctors to prescribe to adolescent and adult patients hospitalized with COVID-19, as appropriate, when a clinical trial is not available or feasible. The second EUA was issued on May 1, 2020, for Gilead's investigational, antiviral drug remdesivir, to be used for the treatment of suspected or laboratory-confirmed COVID-19 in adults and children hospitalized with severe disease. Under this EUA, remdesivir is to be distributed in the US and administered intravenously by healthcare providers, as appropriate. Severe disease is defined as patients with low blood oxygen levels or needing oxygen therapy or more intensive breathing support such as a mechanical ventilator. This EUA has been issued based on the data released by the National Institute of Allergy and Infectious Diseases (NIAID) on April 29, 2020, from NIAID's Adaptive COVID-19 Treatment Trial (ACTT), which is described as:

- A randomized, controlled trial evaluating remdesivir compared with placebo in 1063 patients
- Involving 68 sites (47 in the US and 21 in countries within Europe and Asia)
- Including patients with advanced COVID-19 who exhibited evidence of lung involvement, such as:
  - Rattling sounds when breathing with a need for supplemental oxygen, or
  - Abnormal chest X-rays, or
  - Illness requiring mechanical ventilation.

The NIAID press release stated that the patients who received remdesivir had a 31% faster time to recovery than those who received placebo ($p<0.001$). Specifically, the median time to recovery was 11 days for patients treated with remdesivir compared with 15 days for those who received placebo. Results also suggested a survival benefit, with a mortality rate of 8.0% for the group receiving remdesivir versus 11.6% for the placebo group ($p=0.059$). It is important to note that no EUAs have been issued to-date by the FDA for biologics or vaccines. This does not imply that no such requests are being submitted or are under review.

Recommended Regulatory Strategy

Many pharmaceutical companies are examining whether they have assets that could be of use to combat COVID-19, and if so, what are the next steps in moving forward with EUA designation. The key elements companies should consider for potential COVID-19 programs include:

- Evaluate your approved and/or investigational assets which may be useful for the treatment of COVID-19 for EUA path feasibility
- Engage with the FDA via the Pre-EUA Consult or Pre-IND Meeting mechanism **as soon as possible**, depending on the outcome of EUA feasibility assessment
- Engage relevant external consultant experts to assist with the EUA and/or the IND path for your COVID-19 program
- Submit either an EUA Request or an IND in an expedited manner to the FDA

The issuance of an EUA serves to aid the public with immediate and urgent drugs and devices to combat health emergencies. Therefore, the process to apply for this designation should be undertaken swiftly to ensure relevance to the immediate need. Seeking guidance from experts who understand the intricacies of the process and can provide counsel on the best path forward can save a great deal of time in preparing the submission. EUAs for approved products can be issued within days if the need is great, especially since product information is already available in existing approvals or submissions. It is important to note that products receiving EUA designation do not automatically receive permanent approval for the emergency use, and normal approval processes must be continued for long-term use once the EUA has expired. However, products seeking approval through normal channels can offer hope to many people during a crisis, and exploring the issuance of an EUA is something to consider and act upon expeditiously to include your product in the list of those making a difference in fighting COVID-19. ■

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Integrated Scientific Advice during the COVID-19 Pandemic

Matthew Bending, PhD
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The process of seeking scientific advice from regulatory agencies and health technology assessment (HTA) bodies has expanded in recent years and more pharmaceutical companies are looking to take advantage of the opportunity. The most prolific providers of this scientific advice is the European Medicines Agency (EMA) and the European Network for Health Technology Assessment (EUnetHTA) in Europe. They offer two different parallel consultation pathways – Consolidated Parallel Consultation and Individual Parallel Consultation – in which the EMA provides advice alongside multiple HTA bodies from different European countries (coordinated by EUnetHTA). This advice is intended to enhance manufacturers' clinical development and plans for economic assessment, and there are 11 monthly slots available for submissions.

The COVID-19 pandemic, however, has affected EUnetHTA's ability to participate in Parallel Consultation due to the heavy involvement of healthcare practitioners and bodies in aiding those affected by the pandemic. As a result, EUnetHTA had to temporarily suspend/reduce their input into the Parallel Consultation procedure for submissions made in March and April of 2020. The organization is assessing on a monthly basis based on the status of the pandemic and is updating their website accordingly (https://eunethta.eu/eunethta-response-to-covid-19).

In the meantime, companies are still seeking counsel on scientific advice to keep their products moving forward in the drug development process, and there are still options available.

1. National bodies such as the National Institute for Health and Care Excellence (NICE) in the United Kingdom still have time slots available for 2020 with an expected timeline of approximately 18 weeks, and others such as the Federal Joint Committee (G-BA) in Germany are already booking slots for 2021, with openings now for the end of Q1.

2. Evidera can alternatively assemble a panel of national HTA specialists who can provide advice on the basis of your briefing package if you are no longer able to submit through formal scientific advice procedures and have limited time to inform your development program.

Although the pandemic continues to have far reaching consequences, both within the healthcare industry and more broadly, there are still avenues that exist to allow our work to continue. The reduced availability and consequent delays of formal procedures do not mean companies have no recourse. There are alternative means to understanding the expectations of regulators and HTA bodies early in planning to position your products for overall success. While the current pandemic may be making things more challenging, it has not blocked your access. Resources and experts are still available who can help navigate the path and optimize your drug development program. The important thing is to continue exploring those avenues to reach your ultimate destination. ■

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Matthew Bending

Trends in Medical Device Purchasing, Evaluation of Value, and Advice for Manufacturers

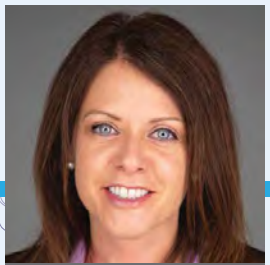
Interview with Patrick Vega

Consulting Director, Advisory Solutions, Vizient

In his role at Vizient, a leading healthcare performance improvement company, Patrick Vega supports member hospitals, health systems, and physicians in musculoskeletal services with a focus on high-value care, aligning cost, and quality. He brings over 20 years of achievement in service line and business development for hospitals, health systems, and physician practices. His broad expertise in assessment, planning, and implementation coupled with highly developed physician relations abilities has resulted in a history of successes in the most challenging environments. Patrick consults, writes, and speaks on topics regarding the spine, orthopedics, and neurosciences, specifically in the areas of strategic assessment and planning, program development, and center of excellence development. He has more than 35 national conference presentations and published articles.

This interview was conducted by Ann Menzie, MS, Senior Director, Evidence Synthesis, Modeling & Communication, Evidera, in conjunction with ongoing efforts to provide relevant and up-to-date information to help our clients develop and execute their evidence generation and market access strategies.

Ann recently spoke with Patrick about the evolution of the medical device industry, maturation of hospital value analysis programs, and driving value in healthcare by improving outcomes and quality while reducing costs. While this interview focuses on the changing medical device landscape and hospital purchasing dynamics in the US, formal value analysis through health technology assessments (HTAs) or tenders is well established ex-US. Many countries in Europe, for example, have implemented evidence-based, decision-making strategies to drive quality of care in a cost-constrained environment. By encouraging manufacturers of medical devices to consider the clinical and economic value of new products and the evidence strategies to support differentiating value propositions, there is substantial opportunity to address key stakeholders'



Ann Menzie

needs in all markets. While presented from the perspective of the US, the ideas expressed in this interview have global implications for clients looking to develop successful market access strategies worldwide.

What trends have you observed over the past five years regarding changes in the medical device industry and the dynamics of surgeons and hospitals as key decision makers of medical technologies?

Historically, the process of selling medical devices to hospitals was often informal. If a physician expressed interest in a product and believed it to be safe and effective, then the hospital approved it for purchase with minimal consideration of cost. In today's environment where reimbursement rates are flat or declining, hospital purchasing decisions follow a process of value analysis that evaluates both price and performance.

Relative to purchasing, where the hospital/physician relationship was once defined by rising tensions, there is now a need to establish collaborative partnerships in acquiring new devices and technologies. This evolution is largely driven by a need to evaluate service-line performance by sharing data as well as a growing understanding of a co-dependency of physicians and their affiliated hospitals in order to thrive, or at times simply survive, in a challenging hospital environment.

Please tell us more about the value analysis programs being used by hospitals to evaluate medical devices and technologies.

Most hospitals apply the process of value analysis to address product efficacy, clinical outcome, quality of care, and safety (for both patients and staff). Focus areas for value analysis include improving outcomes, appropriate vendor standardization, pricing optimization, and implementation of cost-saving initiatives. Many hospitals also incorporate lean initiatives into their value analysis programs to aid in the identification and elimination of waste, redundancies, and inefficiencies.

Value analysis teams (VATs) are comprised of multi-disciplinary professionals including physicians, clinicians, and purchasing staff. Additional members of VATs may include nurses and representatives from finance, supply chain, infection control, central processing, and data informatics. The strategic aim of a VAT is to select products and services that promote the highest standard of care - not always at the lowest cost, but at the greatest value. The value-based procurement process followed by a VAT for medical devices is not unlike the process followed by a pharmacy and therapeutics (P&T) committee.

VATs are used by hospitals as well as hospital networks of all sizes, including integrated delivery networks (IDNs), and are typically established for each hospital service line (e.g., cardiology, orthopedics, and general surgery). Larger hospital networks may implement system-wide value analysis programs that make decisions impacting multiple facilities. Group Purchasing Organizations (GPOs) also have well-developed value analysis processes to support their members. GPOs utilize VATs that include representation from member health systems to assess the value of products and services across the continuum of care using a collaborative approach benefiting member hospitals by helping them achieve their high value, quality outcome, patient care strategies.

What is the process for bringing a new medical device to a VAT?

Physicians submit the medical device to a VAT for evaluation, typically using an online system, and may be asked to present the product to the VAT. VAT meetings are frequently closed to vendors, including medical device manufacturers; however, they may be invited by the VAT to provide additional information if needed. The VATs evaluate requests for products and services and critically evaluate the influence on clinical outcomes, safety, processes, and total cost of care compared to what is currently being used.

Medical device manufacturers may provide physicians with evidence-based materials to help them prepare for VAT meetings and advocate for the new medical device. These materials communicate "value" [Value = (Quality + Outcomes)/Cost] and may take the form of evidence reviews; value briefs; or dossiers, economic models, etc.

It is not uncommon for VATs to conditionally approve a new medical device with a trial period before fully approving it for use. Hospitals may wish to test the impact of the product within their system to evaluate if claims of improved outcomes and/or cost savings are fully realized before committing to purchasing the product. To be successful with VATs, medical device manufactures must seek and deploy a strategic understanding of their customers, both physicians and facility, that blends price, product efficacy, and patient functional outcomes.

What do VATs use to inform their decision making?

VATs leverage a wide range of inputs to inform their decision making, including the following:

- Physician evaluation of clinical efficacy and safety
- Evidence published in peer-reviewed journals – often independent, outside services may be leveraged to assess the strength of the evidence base
- Reimbursement coding, coverage, and payment - Is the medical device reimbursed using existing coding? Does the reimbursement payment for the procedure adequately cover any incremental costs?
- Manufacturers' brochures, evidence briefs, white papers
- Economic models that show cost savings, cost effectiveness, and/or cost offsets resulting from using the medical device or technology

- Data collected through electronic medical records (EMR) and other internal sources evaluating surgical site infections, transfusions, readmissions, costs, and patient satisfaction to assess unmet needs for new products or services

VATs evaluate the medical device or technology in comparison to existing products. Therefore, it is imperative that materials supplied by the manufacturer demonstrate meaningful differentiation from existing products, and that these claims are supported by evidence.

There is variation in the level of sophistication of VATs within US hospital systems that is related to the level of clinical supply integration. VATs that are less sophisticated do not have a rigorous, evidence-based process for reviewing requests and are more of a "rubber stamp." Those that are more sophisticated are physician led and use financial, clinical, and operational data to drive their decisions. Many VATs fall somewhere in between the two and are looking to continually evolve in order to increase their level of sophistication.

Many manufacturers are looking beyond medical devices, such as surgical implants, and are developing robotic and digital platforms. How do hospitals evaluate these new technologies that often add cost to the system without incremental reimbursement or long-term data showing improvement in patient outcomes?

To date, the evidence supporting long-term clinical outcomes of robotic-assisted procedures is limited. Published studies have varying designs and report a range of outcomes making it challenging to draw meaningful conclusions from the literature. Many papers report improvements over open procedures, but evidence is mixed compared to minimally invasive procedures using existing technology. Manufacturers have developed brochures and white papers reporting short-term clinical outcomes with a strong focus on cost improvements from implementing robotic programs. Making evidence-based decisions regarding robotics programs is challenging given variation in costs and opportunities for improving efficiencies between different hospital systems.

Value analysis of robotic programs often extends beyond the traditional VAT to include additional hospital stakeholders responsible for strategic purchasing decisions related to return on investment. Physicians will evaluate robotic programs based on intra-operative and clinical improvements, such as enhanced visualization, less blood loss, faster recovery, and the potential for better outcomes. Service-line leaders and hospital C-suite executives may evaluate robotic programs based on the ability to grow market share by attracting patients seeking robotic technology. Physicians may be attracted to hospitals that offer advanced technology as well by building their practice and referral base through leveraging their expertise in and access to robotics. Hospitals may also invest in robotics programs to build their residency programs to train the next generation of surgeons using the most advanced robotics technologies available.

Robotic programs introduce additional costs to the system through capital equipment, disposables, maintenance contracts, etc., often with no incremental reimbursement. However, the expectation is that the increased volume will drive revenue. This demand for advanced technology by patients and physicians coupled with clinical evidence purporting the procedures are equivalent in safety and efficacy often drives hospital decision making in favor of establishing a robotics program.

What advice would you give to manufacturers looking to approach a hospital with a new medical device or robotic technology?

Develop a robust go-to-market strategy for ***both*** physicians and providers, specifically:

- Develop an advocate (most often a physician) who will champion the product on behalf of the manufacturer to the VAT
- Be transparent regarding all costs, including non-product costs, such as disposables, maintenance, and additional equipment
- Develop a VAT strategy and evidence-based tools that communicate clinical and economic value (e.g., value analysis briefs, cost calculators)
- Demonstrate an understanding of the reimbursement landscape for the procedure and/or product and the impact on the hospital contribution margins
- Offer product trials, as needed
- Invest in evidence generation to substantiate differentiating value propositions and claims
- Seek a strategic partnership between vendor, hospital, and physician by approaching hospitals as key stakeholders
- Consider pricing strategies that reflect the clinical and economic value the product delivers to providers and patients, not just covering costs of manufacturing and factoring in a profit
- Build capabilities within the field organization to facilitate evidence-based discussions with hospitals and develop a trusted relationship

The opportunity for vendors in an increasingly sophisticated purchasing environment lies in not just serving physicians but also understanding more holistically the many buyer considerations: price, performance, differentiation from current products, and long-term value. This level of understanding is not easily acquired, requiring manufacturers to develop and deploy a strategy that addresses all key purchasing elements. ■

Patient Preference Studies in HTA Decision Making
A NICE to Have?

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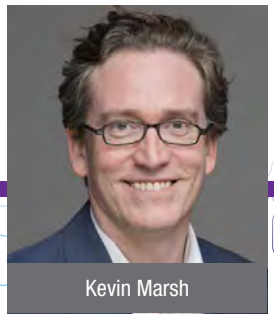
Overview

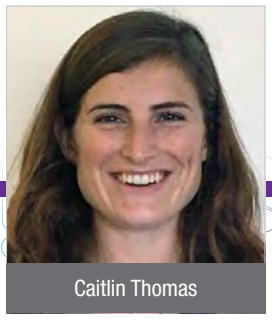
There has been a lot of recent discussion about the potential role of patient preference (PP) data in support of reimbursement decisions. In January 2020, the National Institute for Health and Care Excellence (NICE) published a paper[1] that provided more detail on the use of patient preference data. They emphasised their perspective on the importance of PP data and clarified how this can be used by their committees. This article summarizes the key takeaways from NICE's publication and what this means for sponsors' evidence generation strategies.

Introduction

PP data quantifies how patients make trade-offs involved in treatment decisions. Decision makers are increasingly interested in using quantitative PP data to support their decisions. For instance, the US Food and Drug Administration's (FDA) Center for Devices and Radiological Health (CDRH) encourages manufacturers to submit PP data to support its benefit-risk assessment.[2] Health technology assessment (HTA) often also involves the use of quantitative preference data. However, HTA agencies have tended to use general population preferences to estimate utility


Kevin Marsh


Jessica Griffiths


Caitlin Thomas

inputs for cost-effectiveness analysis.[3] While patient input is sought, it has often been in the form of qualitative insights on the burden of the disease, submissions from patient advocacy groups, or patient representatives being members of decision-making committees.[4] There has traditionally been little or no role in HTA for quantitative PP data.

However, agencies such as Sweden's Dental and Pharmaceutical Benefits Agency (TLV) and Germany's Institute for Quality and Efficiency in Health Care (IQWiG) have identified formal roles for PP data in their methods guides. Other HTA agencies have more recently also shown an interest in PP data, initiating consultations and pilots to explore how this data might support their decision making.[5,6] Notably, in 2019 NICE provided its first scientific advice on PP study design, specifically on how PP data might support the selection of endpoints in a COPD clinical study.[5,6] However, questions still remain about how PP data can be used in HTA. In its recent publication,[1] NICE begins to answer some of those questions and confirms that the use of PP data is one of NICE's nine priority research topics. Three main uses of PP studies are identified:

1. Clinical trial endpoint selection
2. Informing benefit-risk assessments for regulatory approval
3. Supporting reimbursement decisions

This article focuses on the use of PP data to support clinical trial endpoint selection and reimbursement decisions. What does NICE's article say about this use of PP data? What questions still remain? And what does this mean for sponsors' evidence generation strategies?

Why Does NICE Think There is a Benefit to Conducting a PP Study?

NICE's publication identifies four ways in which PP data can support their committees.

Ensuring a Representative Picture

NICE currently captures the views and experiences of patients through several routes. These include having lay members on NICE committees and patient organizations and patient experts providing written evidence and attending committee meetings to share their experiences of the condition and, if possible, the treatment being considered. However, NICE has acknowledged that there are limitations to the current approach for ensuring patient input into recommendations. Specifically, only a small subset of patients' opinions are included and not the wider patient population, which raises concerns that the input provided may not be representative. NICE suggests that PP data may provide a way to overcome this concern, especially if the sample is representative of the broader patient population. Furthermore, PP studies can provide insight on how preferences vary between subsets of patients.

> NICE has acknowledged that there are limitations to the current approach for ensuring patient input into recommendations.

Understanding How Patients Make Trade-Offs

Where therapies have quite different profiles, in terms of efficacy, safety, and convenience, PP data can help committees understand how patients make trade-offs when choosing between such treatments. NICE illustrates this with an example of cancer treatments, where chemotherapy, radiation therapy, and immunotherapy differ in modes and ease of administration, effectiveness, and the risk of serious side effects. In such cases, a PP study could provide important insights to a committee on how patients with cancer would make trade-offs between the different treatment options and the probability that patients would prefer one treatment over another.

Supplementing the QALY

NICE does not currently envisage PP data replacing the current method for calculating the incremental cost-effectiveness ratio (ICER) or being used to justify reimbursement of a drug that is not clinically or cost effective. However, they acknowledge that PP studies can supplement ICERs where attributes that are relevant to patients are not captured by quality-adjusted life years (QALYs). For instance, PP data can help committees understand the value that patients place on changes in mode of administration (MoA).

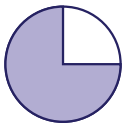
Justifying Endpoint Selection

PP studies can identify the endpoints that matter most to people living with the condition and therefore should be included in clinical trials. NICE's scientific advice team produced its first ever guidance on a COPD PP study in February 2019. Input was received to improve the design of the COPD patient preference study, inform evidence generation strategy, and collect certain outcome data alongside PP to help in correlating the PP results with current NICE processes for evaluating new treatments.[1]

Remaining Questions – Precisely How Will NICE Use PP Data?

NICE's publication provides valuable insight into how PP data can support their committees. However, there remains uncertainty as to precisely how NICE committees will use PP data. For instance, how will patient preferences for new modes of administration inform committee's decisions? NICE acknowledges that such process utilities (i.e., utility can be affected by the process of treatment, not just the outcomes of treatment) are not captured by the QALY and that PP studies can capture these and thus supplement the QALY. How exactly PP data can supplement the QALY is not clear.

Summary of NICE's Use of Patient Preference (PP) Data

Use of PP Data	When to Use?	Considerations*	Importance to Committees
Endpoint Selection	Lack of established quality of life or patient-reported outcomes (PROs)	PP study must be conducted in early phase of drug development	
Supplementing the QALY	When attributes are not captured by QALYs e.g., different MoA, impacts on acute pain	Uncertainty on how PP can supplement the QALY	
Broader Patient Perspective	Heterogeneous patient group	Ensuring PP sample is representative of broader patient population	
Understanding Patient Trade-Offs	Drug profiles differ in terms of efficacy, safety, and convenience	Designing PP study capturing all relevant attributes**	

*NICE scientific advice can help manufacturers address challenges associated with PP data collection and design
**Attributes should be understandable, operational, non-overlapping, minimal, and complete, using fundamental and absolute outcomes
QALY = Quality-Adjusted Life Year; MoA = Mode of Administration

Should estimates of process utility generated using PP data be incorporated into an ICER scenario analysis? If so, how should this be done? PP data can be used to express process changes in equivalent changes in health outcomes that can be captured by the QALY. For instance, the improvement in life expectancy that will give the same utility as changing mode of administration. Can these equivalent changes be added into the QALY calculation?

How does NICE reconcile the use of PP data with the priority given to general population preference data in its reference case? Can the above approach – estimating changes in terms of equivalent changes in life expectancy – be interpreted as capturing patient experience, which are still valued in the same way as other measures of patient preferences, in a manner consistent with the NICE reference case?

> It is important that sponsors seek scientific advice from NICE on methods for collecting PP data and the proposed use of the data.

If the insight from PP data should not be used within scenario analysis of the ICER calculation, how should committees incorporate this data into their decisions? NICE has stipulated that PP data cannot be used to justify the reimbursement of a treatment that is not cost-effective. Could a strong patient preference, for an attribute of a treatment not captured by the QALY, be evidence of uncertainty in the utility estimates included in the cost-effectiveness analysis, and thus a justification for adopting a different cost-effectiveness threshold?

Conclusion

NICE's publication confirms the importance of PP data to their committees. This is encouraging for sponsors who see patients' preferences as an important part of their value messages and provides support for them to include PP studies in their evidence generation strategy. However, inevitably there are still questions about precisely how this data will impact reimbursement decisions. Given this uncertainty, it is important that sponsors seek scientific advice from NICE on methods for collecting PP data and the proposed use of the data. ■

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Version 4.1 of the AMCP Format
Introducing a Trio of Dossiers to Support a Product Throughout its Lifecycle

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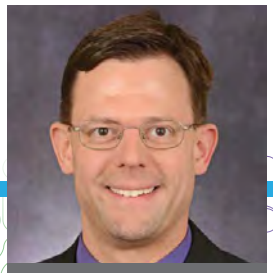
On December 23, 2019, the Academy of Managed Care Pharmacy (AMCP) released Version 4.1 of the AMCP Format for Formulary Submissions.[1] This new version of the AMCP Format describes three types of dossiers that manufacturers may choose to develop: Unapproved Product Dossiers, Approved Product Dossiers, and Unapproved Use Dossiers.[2]

Unapproved Product Dossiers provide information about a product that is not currently approved by the United States (US) Food and Drug Administration (FDA).[2] Manufacturers may use these dossiers to provide information about a product to healthcare decision makers (HCDMs) prior to FDA approval.[2]

Approved Product Dossiers present information about a product that has been approved by the FDA.[2] Manufacturers may use these dossiers to reactively provide information about a product to HCDMs in response to an unsolicited request after FDA approval.[2]

Unapproved Use Dossiers contain information about a product that is currently approved by the FDA.[2] However, this information focuses on a currently unapproved indication of the approved product.[2] Manufacturers may use these dossiers to inform HCDMs about an unapproved use of an approved product prior to FDA approval of the unapproved use.[2]

While developing Version 4.1 of the AMCP Format, the AMCP Format Executive Committee decided to focus their updated recommendations on Unapproved Product Dossiers and Unapproved Use Dossiers, and made minimal changes to the section on Approved Product Dossiers.[2] Therefore, a piece of good news for manufacturers is that converting an existing Post-Approval Dossier that follows Version 4.0 of the AMCP Format into an Approved Product


Donald Smith

Dossier that follows Version 4.1 of the AMCP Format is a straightforward process. For these reasons, this article will focus on Unapproved Product Dossiers and Unapproved Use Dossiers.

Why Develop an Unapproved Product Dossier or Unapproved Use Dossier?

Even though manufacturers are not required to develop Unapproved Product Dossiers or Unapproved Use Dossiers,[2] they can be very useful tools. Version 4.1 of the AMCP Format specifically states that "HCDMs need and are interested in receiving information from manufacturers about unapproved products and about unapproved uses of approved products for which FDA approval is being sought."[2] However, it is important to note that manufacturers may also benefit from developing dossiers that describe an unapproved product or an unapproved use of an approved product. For example, developing an Unapproved Product Dossier or Unapproved Use Dossier may be helpful if:

- The manufacturer is entering a new field and is not familiar with the disease and/or its key treatments
- The manufacturer wants to start work on an AMCP dossier for internal needs, but feels that it is too early to start work on an Approved Product Dossier
- The manufacturer wants to understand how the available literature supports their early, and often aspirational, value story and what evidence gaps exist
- The product will have an orphan or fast-track designation
- The product is not being launched outside of the US, and therefore there is no global value dossier, making the AMCP dossier the primary source for information related to the clinical and economic value of the product
- The clinical development plan for a product includes multiple indications or disease populations
- The manufacturer wants to share information with HCDMs prior to FDA approval of the unapproved product or the unapproved use

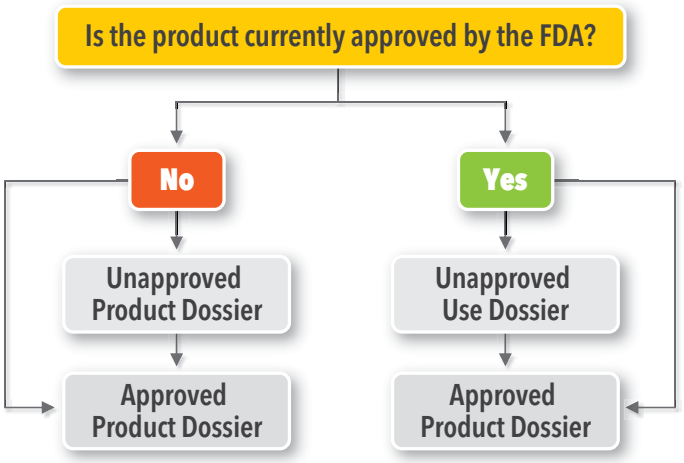
Finally, unlike Approved Product Dossiers, which can only be provided in response to an unsolicited request (i.e., reactively), Unapproved Product Dossiers and Unapproved Use Dossiers may be provided either proactively or reactively, at the discretion of the manufacturer.[2] However, many HCDMs want the information contained in these dossiers as early as possible so that they can more effectively plan for future drug approvals. Therefore, it is expected that many HCDMs will request Unapproved Product Dossiers and Unapproved Use Dossiers, and that most of these dossiers will be provided in response to an unsolicited request rather than in a proactive manner.

An Important Question

When deciding which new dossier type(s) to develop, it is important to ask whether the product of interest is currently approved by the FDA.

- If the product is not currently approved by the FDA, the manufacturer may develop an Unapproved Product Dossier and/or an Approved Product Dossier (See Figure 1). The manufacturer is not obligated to develop an Unapproved Product Dossier prior to developing an Approved Product Dossier.[2]
- If the product is currently approved by the FDA, the manufacturer may develop an Unapproved Use Dossier and/or an Approved Product Dossier (See Figure 1). There is no requirement for a manufacturer to develop both an Unapproved Use Dossier and an Approved Product Dossier.[2]

Figure 1. Dossier Types That Can Be Developed Based on a Product's Approval Status



FDA = Food and Drug Administration

Unapproved Product Dossiers and Unapproved Use Dossiers

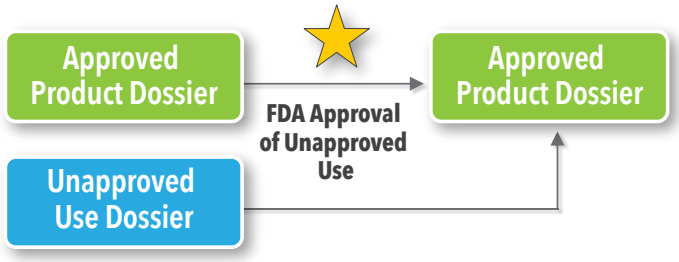
As shown in Figure 2, an Unapproved Product Dossier should be converted into an Approved Product Dossier when the unapproved product receives approval from the FDA.[2] An Unapproved Product Dossier and an Approved Product Dossier for the same product never exist simultaneously; a product is either approved by the FDA or it is not.[2]

In contrast, an Unapproved Use Dossier and an Approved Product Dossier may exist simultaneously; this depends upon the product and the goals of the manufacturer (See Figure 3).[2] However, the information in the Unapproved Use Dossier should be incorporated into the existing Approved Product Dossier after FDA approval.[2] Alternatively, an Unapproved Use Dossier could become its own Approved Product Dossier,[2] and the manufacturer could ultimately have multiple Approved Product Dossiers for a single

Figure 2. Unapproved Product Dossier Flow Chart

FDA = Food and Drug Administration
Reference: Adapted from Figure 1 in Version 4.1 of the AMCP Format.[2]

Figure 3. Unapproved Use Dossier Flow Chart



FDA = Food and Drug Administration
Reference: Adapted from Figure 1 in Version 4.1 of the AMCP Format.[2]

product, a practice that has existed for years. Interestingly, some of the information that appears in an Unapproved Use Dossier may originate in an Approved Product Dossier since Approved Product Dossiers may contain information about potential off-label uses and potential new indications under investigation.[2]

Per Version 4.1 of the AMCP Format, Unapproved Product Dossiers and Unapproved Use Dossiers should contain the same four main sections (See Table 1).

Section 1: Highlights and Overview

Unapproved Product Dossiers and Unapproved Use Dossiers begin with a Highlights and Overview section that consists primarily of a table and outlines some of the important general information about a product, such as its name, expected approval date, clinical trials, and expected indication.[2] There is no Executive Summary in an Unapproved Product Dossier because:

- "Manufacturers may not make claims about an unapproved product"[2]
- "Manufacturers may not make claims about an unapproved use of an approved product"[2]
- "No characterizations or conclusions should be made regarding the safety or effectiveness of the unapproved product or the unapproved use"[3]

Instead, the manufacturer should focus on providing information that is factual, objective, and unbiased.[2,3] Version 4.1 of the AMCP Format contains a table that provides guidance on the type of information that should be included in Section 1 of an Unapproved Product Dossier and Unapproved Use Dossier.[2] Some examples include the New Drug Application (NDA) or Biologics License Application (BLA) submission date, the Prescription Drug User Fee Act (PDUFA) or FDA approval date, information on Phase II and Phase III trials, the prevalence and incidence of the disease in the US, and information on product pricing.[2] Of note, the manufacturer is expected to include the current list price of the approved product in an Unapproved Use Dossier.[2]

Section 2: Product Information and Disease Description

In Section 2.1 (Product Description), the manufacturer should include general information about the unapproved product, such as its mechanism of action, the patient population being examined, projections related to patient utilization, and patient support programs.[2] Importantly, as is typically done for Approved Product Dossiers, the current version of the FDA approved prescribing information should be attached to an Unapproved Use Dossier.[2]

In Unapproved Product Dossiers, the manufacturer must include a clear statement that "the unapproved product is not FDA approved, and that the safety or effectiveness of the unapproved product has not been established."[2,3] Similarly, an Unapproved Use Dossier must include a clear statement that "the unapproved use of an approved product is not FDA approved, and that the safety or effectiveness of the unapproved use has not been established."[2,3]

In Section 2.2 (Disease Description), the goal is to describe the disease, including information on epidemiology, clinical presentation, and disease burden. At a webinar conducted by AMCP on January 23, 2020, a question was raised as to why including information on unmet need, treatment guidelines, and competitors/comparators in Unapproved Product Dossiers and Unapproved Use Dossiers is not specifically mentioned in Version 4.1 of the AMCP Format.[4] The answer given at the webinar centered around a reminder that no characterizations, conclusions, or claims may be made about a product that is not approved by the FDA or about an unapproved use of an approved product.[4] However, it was also mentioned that Unapproved Product Dossiers and Unapproved Use Dossiers may discuss the current state of the field in general.[4] For example, an Unapproved Product Dossier can discuss the current unmet need in a field, but it cannot state or imply that the unapproved product fulfills that unmet need.[4] Similarly, information from treatment guidelines and data on potential competitors/comparators can be included in an Unapproved Use Dossier.[4] However, the information presented must be factual and unbiased, and no characterizations, conclusions, or claims about the unapproved use of the approved product may be made or implied.[4]

Table 1. Main Sections of Unapproved Product Dossiers and Unapproved Use Dossiers

Unapproved Product AMCP Dossier	Unapproved Use AMCP Dossier
Section 1: Highlights and Overview	Section 1: Highlights and Overview
Section 2: Product Information and Disease Description	Section 2: Product Information and Disease Description
Section 3: Clinical Evidence	Section 3: Clinical Evidence
Section 4: Economic Information	Section 4: Economic Information

AMCP = Academy of Managed Care Pharmacy
Reference: Version 4.1 of the AMCP Format.[2]

Section 3: Clinical Evidence

In Section 3 of Unapproved Product Dossiers and Unapproved Use Dossiers, the manufacturer can discuss the clinical trial program that supports the unapproved product or unapproved use of interest. Information that may be included in this section includes publicly available information describing the design, patient population, and results of the studies.[2] Data on file that is not publicly available can be included at the discretion of the manufacturer.[2]

Manufacturers should focus on making a factual presentation that does not include claims, characterizations, or conclusions.[2] Therefore, a "Conclusions" section should not be included for the study summaries. However, whether the studies should be presented as text-based study summaries, evidence tables, or both is up to the manufacturer.[2]

Section 4: Economic Information

Unapproved Product Dossiers

The last section of an Unapproved Product Dossier, Economic Information, has generated a fair amount of discussion. This is mostly because it is uncommon for manufacturers to provide information about the potential price of a product prior to approval by the FDA.[2] The intent of this section is to provide HCDMs with information on pricing before FDA approval so that they can plan for future reimbursement decisions in a more informed manner.[2] While the AMCP Format Executive Committee "strongly recommends that manufacturers provide as much product pricing information as possible," the manufacturer is under no obligation to provide this information.[2]

If a manufacturer chooses to provide information on the potential pricing of an unapproved product prior to FDA approval, the price may be provided as a range.[2] In fact, Version 4.1 of the AMCP Format helpfully provides price ranges that can be used for this purpose.[2] However, even if an informed price range is provided by the manufacturer, it may not be possible to develop economic models prior to FDA approval.[2] This is because it is likely that economic models will include outcomes and/or assumptions related to the effectiveness and safety of the unapproved product in the target population.[2]

Unapproved Use Dossiers

The section on Economic Information in an Unapproved Use Dossier is more straightforward than it is for an Unapproved Product Dossier. This is because the manufacturer already has a known price for the approved product. The known price of the approved product should be included in Unapproved Use Dossiers.[2]

However, there may be times when the price of an unapproved use of an approved product may be different than the price of an approved use of the same approved product. For example, the unapproved use of an approved product may occur in a different patient population and/or have a different formulation that requires a different route of administration than the approved use of the approved product. Per Version 4.1 of the AMCP Format, any potential changes in cost between the unapproved use and the approved use(s) of the product should be mentioned.[2] For reasons similar to those described earlier, it may not be possible to construct economic models prior to the approval of an unapproved use of an approved product by the FDA.[2]

Relationship to the FDA Guidance on Communications by Firms to Payors Regarding Unapproved Products and Unapproved Uses of Approved/Cleared Products

Version 4.1 of the AMCP Format was created in response to the Final FDA Guidance on Drug and Device Manufacturer Communications With Payors, Formulary Committees, and Similar Entities that was published in June 2018.[2-4] In fact, in the sections of the AMCP Format that describe Unapproved Product Dossiers and Unapproved Use Dossiers, the AMCP Format specifies which sections of the dossiers arise from the aforementioned FDA Guidance and which ones are AMCP Format recommendations.[2] While the FDA Guidance does not specifically mention unmet need,

treatment guidelines, or economic models, it does mention information on product pricing and the manufacturer's ability to provide a "factual presentation of results" related to both placebo and active controls included in trials examining the unapproved product or unapproved use of interest.[3] The FDA Guidance also provides some useful examples that highlight some of the differences between providing a "factual presentation of results" from a clinical trial and making a characterization or conclusion about the safety or effectiveness of an unapproved product or an unapproved use.[3]

Other Considerations for Manufacturers

When developing Unapproved Product Dossiers and Unapproved Use Dossiers, a key factor that must be considered is the time needed for their review and approval. The information in these dossiers is often desired by HCDMs six to 24 months prior to FDA approval,[2] so some manufacturers may need to revise and/or optimize their current internal review and approval processes to account for these new types of dossiers, especially if they wish to provide them proactively.

The manufacturer should also think about when to update their dossier, if applicable. In the past, Approved Product Dossiers have been updated in response to a new indication, a new clinical trial, new recommendations from treatment guidelines, and/or the arrival of new competitors to market, among other things. If the initial version of an Unapproved Product Dossier or an Unapproved Use Dossier is completed far ahead of FDA approval, it may be valuable to update the dossier again prior to approval if data from an ongoing clinical trial is published, there is a change in the FDA review time, or information on patient support programs becomes available. For all three dossier types, the decision of whether or not to proceed with dossier updates is up to the manufacturer.[2]

Conclusions

Version 4.1 of the AMCP Format provides manufactures with guidance on generating a trio of dossiers that can help support a product throughout its lifecycle.[2] Even though manufacturers are not required to develop Unapproved Product Dossiers or Unapproved Use Dossiers, they can be useful tools for facilitating communications with HCDMs. We recommend that manufacturers review the options offered by Version 4.1 of the AMCP Format and consider which type of dossier will best meet their needs. Developing an Unapproved Product Dossier or Unapproved Use Dossier not only provides the manufacturer with an opportunity to prepare for the launch of new products and new indications, but also helps HCDMs plan for future FDA approvals. ■

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2. AMCP. The AMCP Format for formulary submissions (version 4.1). Guidance on Submission of Pre-approval and Post-approval Clinical and Economic Information and Evidence. December 23, 2019. Available at: https://www.amcp.org/sites/default/files/2019-12/AMCP_Format%204.1_1219_final.pdf. Accessed December 26, 2019.
3. FDA. Drug and Device Manufacturer Communications With Payors, Formulary Committees, and Similar Entities — Questions and Answers Guidance for Industry and Review Staff. June 2018. Available at: https://www.fda.gov/media/102683/download. Accessed January 29, 2020.
4. AMCP. AMCP Format v4.1: New Guidance on Evidence Requirements for Unapproved Products and Unapproved Uses. January 23, 2020. Available at: https://www.amcp.org/Resource-Center/formulary-utilization-management/amcp-format-v41-new-guidance-evidence-requirements. Accessed January 29, 2020.

Accepted Presentations

Due to the COVID-19 pandemic, many conferences have either canceled or moved to a virtual format where all acceptances may not be virtually presented. To account for the rapidly changing status of conferences, we are a providing a list of all accepted presentations and the status of conferences as of the print date of this publication.

DIA MASC 2020

May 6-7, 2020 | VIRTUAL CONFERENCE

POSTER

Readability Assessment of Clinical Trial Information on Pharmaceutical Product Websites Intended for Patients and Caregivers

Watts R, MacIntyre B, Cash K

PODIUM

Readability Assessment of Clinical Trial Information on Pharmaceutical Product Websites Intended for Patients and Caregivers

Watts R

ISPOR US 2020

May 18-20, 2020 | VIRTUAL CONFERENCE

WORKSHOP

W2: We are Not All the Same: The State-Of-Practice in Accounting for Preference Heterogeneity

Marshall D, **Heidenreich S**, Boeri M

ISSUE PANEL

IP13: Can Patient Preference Information (PPI) Be Generated for Multiple Uses Across Different Treatment Comparisons and Associated Decisions?

Marsh KM, Muhlbacher A, **Gelhorn H,** Russo L

PODIUM PRESENTATIONS

ND4: Development of a Statistical Model to Predict EuroQol Five Dimensions (EQ-5D) Utilities in Parkinson's Disease

Chandler C, Franco-Villalobos C, Wang Y, Gal P, Folse HJ, Ward A

MS1: Validation of Modeled 5-Year Survival Outcomes among Patients with Cystic Fibrosis (CF) Treated with the CF Transmembrane Conductance Regulator Modulator (CFTRM) Ivacaftor Using US CF Foundation Patient Registry (USCFFPR) Data

McGarry L, Lopez A, **Chandler C, Pelligra C**, Alkhateeb Z, Rubin JL, Liou T

PR4: Impact of Clinically Meaningful Reduction in Dyspareunia on Health-Related Quality of Life among Endometriosis Patients: A Pooled Analysis of Two Phase III Clinical Trials

Agarwal SK, Soliman AM, **Pokrzywinski RM, Coyne KS**

POSTERS

PBI4: Evidence Requirement Trends for Single Arm Study Scenarios in Rare Disease and Oncology: What Are the Lessons for Value Demonstration?

Faulkner EC, Ringo MC, Mihos MC, **Berger A**

PND82: Conducting Clinical Trial Simulation to Study Heterogeneity of Trial Outcomes in Amyloid-Modifying Drugs

Tafazzoli A, Chavan A, Kansal A

PND84: Framework for Early Economic analysis of a Disease Modifying Therapy for Parkinson's Disease

Folse H, Chandler C, Gal P, Chavan A, Wang Y, Ward A

PCN15: Efficacy, Effectiveness, and Safety of Frontline Treatments for Peripheral T-Cell Lymphoma

Ashaye AO, **Panchmatia H, Burnett H**, Ovcinnikova O, Dalal MR

PCN90: Assessment of Utilities for Adverse Events (AES) Associated with Chimeric Antigen Receptor (CAR) T-Cell Therapy in Large B-Cell Lymphoma (LBCL)

Howell TA, Matza LS, Jun MP, Garcia J, Powers A, Maloney DG

PCN332: Patient Perceptions Regarding Multiple Myeloma and its Treatment: Qualitative Evidence from Interviews with Newly Diagnosed and Relapsed-Refractory Patients in the United Kingdom, France, and Germany

He J, **Duenas A, Collacott H**, Lam A, Gries K, Kobos R, Potthoff D, Guilmet C, Trevor N, **Tervonen T**

PMU18: Economic Evaluation of an NT-proBNP-Supported Diagnostic Strategy among Dyspneic Patients Suspected of Acute Heart Failure in the Emergency Department

Siebert U, **Milev S, Zou D, Litkiewicz M**, Gaggin H, Tirapelle L, Masson S, Januzzi J

PRO89: Symptom Experience of Patients with Generalized Pustular Psoriasis (GPP)

Skalicky A, Rentz A, Esser D, Thoma C, Gloede T

PGI23: Treatment Cost Analysis for Patients in the United States with Moderately-to-Severely Active Ulcerative Colitis Who Have an Inadequate Response or Who are Intolerant to TNF Blockers

Sardesai A, Milev S, Quon P, Bourret J, Peeples-Lamirande K, Salese L, Cappelleri JC, Sharma PP

PGI37: Thresholds for Meaningful Change for the EQ-5D VAS and EORTC QLQ-C30 Physical and Role Functioning Scale in Gastrointestional-Related Cancers

McHorney C, Cha E, Becker CC

PNS26: Protocol Design in Real-World Evidence: The Indispensable Link Between Strategic Need and Study Execution

Bassel M, Sayegh L, Fernandes S, Saragoussi D

PIH69: The Need for Person-Centred Care in Endometriosis Treatment: Results of a Qualitative Study

Mohan D, Scotland G, **Heidenreich S**, Ramsay C, Saraswat L, Pirie D

PMS34: Taltz® (Ixekizumab) For Treatment of Psoriatic Arthritis in The United States: A Budget Impact Analysis

Murage M, **Panchmatia H**, Patel S, Birt J, Gellett A, Sprabery T, Malatestinic W, Atiya B, Kern S, **Kadambi A**

EAN 2020

May 23-26, 2020 | VIRTUAL CONFERENCE

E-POSTER

Patient Attitudes and Valuation of Preventive Migraine Treatments: A Focus Group Study

Tockhorn-Heidenreich A, **Seo J, Thomas C**, Ford JH, Stauffer VL, Nicholson RA, Duffy KH, **Tervonen T**

ISCT 2020 Annual Meeting

May 28-29, 2020 | VIRTUAL CONFERENCE

POSTER

Shifting Clinical Trial and Value Demonstration Models for Cell and Gene Therapies: Present and Future Critical Success Factors

Faulkner EC, Theocharous P, Koh M, Morgese P

ASCO20 Virtual Scientific Program

May 29-31, 2020 | VIRTUAL CONFERENCE

ABSTRACT ONLY

Real-World Treatment Patterns and Clinical Outcomes of Advanced Melanoma Patients Following Disease Progression on Anti-PD-1-Based Therapy

Hernandez-Aya L, Burke M, **Collins J**, Earle D, Hamilton M, **Nordstrom B**, Zhang Y, Srivastava S

AADMD 18th Annual Conference 2020

June 4-6, 2020 | VIRTUAL CONFERENCE

POSTER

Impact of Possible TD on Caregivers: Results from a Prospective Real-World Screening Study (RE-KINECT)

Cutler AJ, Caroff SN, Tanner CM, Shalhoub H, **Lenderking WR**, **Wilcox T**, Franey E, Yonan C

ERA-EDTA Congress – 2020

June 6-9, 2020 | VIRTUAL CONFERENCE

POSTER

A Qualitative Study of Patients' Preference for the Treatment of Anaemia Associated with Chronic Kidney Disease

Alexandre AF, Morga A, **Marsh KM, Thomas C**

EHA25 Virtual Congress – 2020

June 11-14, 2020 | VIRTUAL CONFERENCE

ePOSTER

Comparison of Safety Management Costs across Chimeric Antigen Receptor (CAR) T Cell Therapies in Relapsed or Refractory Large B-Cell Lymphoma

Rivolo S, Xiao Y, Litkiewicz M, Saint-Laurent Thibault C, Patel L, Zhang Y, **Dorman E**, Liu F, Kuruvilla J

ABSTRACT ONLY

DREAMM-1: Patient Perspectives from the First-In-Human Study of Single-Agent Belantamab Mafodotin for Relapsed and Refractory Multiple Myeloma (RRMM)

Eliason L, Opalinska J, **Martin ML, Correll J**, Gutierrez B, Popat R

ADA 2020

June 12-16, 2020 | VIRTUAL CONFERENCE

ePOSTER

Utilization of Glucose-Lowering Drugs in Patients with T2DM and Established CVD in US

Ganz ML, Ustyugove A, Sawalhi-**Leckenby N**, et al.

DIA 2020

June 14-18, 2020 | VIRTUAL CONFERENCE

WORKSHOP

Qualitative, Quantitative, and Mixed Method Approaches to Capture the Patient Experience

Gelhorn H, Dashiell-Aje E, Knoble N, Freeman E

Patients as Partners US

September 20-21, 2020 | Boston, MA, USA

ISSUE PANEL

Creating and Executing an Outstanding and Inclusive Patient Experience from the CRO and Site Perspectives

Bechtel J, Andriote JM, Gray S, Prowisor E, **Latif E**

Precision Medicine Leaders' Summit 2020

October 20, 2020 | Research Triangle Park, NC, USA

PODIUM

Critical Success Factors for Addressing the Next Generation of Precision Medicine

Faulkner E

ISOQOL 2020 Prague

October 21-24, 2020 | Prague, Czech Republic

SYMPOSIA

Item Bank for your Buck: Successfully Harnessing the Power of Item Banks and Libraries to Assess Clinical Benefit from the Patient Perspective

Nelsen L, Cella D, **Gelhorn H**, Regnault A

The Application of Mixed Methods to Measure Health Outcomes in Clinical Trials, Clinical Practice, and Health Policy

Dias-Barbosa C, Ogunsanya M, Regnault A, **Martin M**, Barbic S

Recent Presentations

AMCP 2020

April 21-24, 2020 | VIRTUAL CONFERENCE

POSTER

Budget Impact Analysis of Galcanezumab for the Treatment of Adult Patients with Episodic Cluster Headache in the United States

Foster SA, Milev S, **Sardesai A**, Mason O, Samaan K, Hasan A, Marrone C, Hoog M

Advances in Alzheimer's and Parkinson's Therapies | An AAT-AD/PD Focus Meeting

April 2-5, 2020 | VIRTUAL CONFERENCE

POSTER

Clinical Trial Simulation to Support the Design of a Randomized Controlled Trial of a Hypothetical Disease-Modifying Treatment for Parkinson's Disease

Gal P, Folse H, Chavan A, Chandler C, Ward A

Crohn's & Colitis Congress - 2020

January 23-25, 2020 | Austin, TX, USA

POSTER

Content Validity of the Subcutaneous Administration Assessment Questionnaire (SQAAQ) in Adult and Adolescent Patients with Moderate to Severe Ulcerative Colitis

Naegeli AN, Hunter T, Delbecque L, **Karn H, Skalicky A**

Phacilitate Leaders World and World Stem Cell Summit – 2020

January 20-24, 2020 | Miami, FL, USA

PODIUM

Health Economic Impact Value Models - Developing a Robust and More Accurate Representation of Cell and Gene Medicine

Ruffin M, **Faulkner E**, Slotnik J, Smolinski I

AHA American Heart Association Scientific Sessions – 2019

November 16-18, 2019 | Philadelphia, PA, USA

POSTER

Cost-Effectiveness Analysis of Empagliflozin as a Second-Line Therapy Compared to Sitagliptin in Patients with Type 2 Diabetes in the United States

Reifsnider O, Kansal A, Pimple P, Aponte-Ribero V, **Brand S**, Shetty S

DIA Real World Evidence Conference

November 14-15, 2019 | Cambridge, MA, USA

CHAIR/SPEAKER

New Platforms for Clinical Research Purposes

Hao Y, **Schaumberg D**

ACR/ARHP Annual Meeting – 2019

November 8-13, 2019 | Atlanta, GA, USA

POSTER

Assessment of Fatigue in Adults with Moderate-to-Severe Systemic Lupus Erythematosus (SLE): A Qualitative Study to Explore What Patients Feel Should be Measured in Clinical Trials

Mannix S, Beyer A, Strand V, Hanrahan LM, **Abel C**, Flamion B, **Hareendran A**

ACAAI 2019

November 7-11, 2019 | Houston, TX, USA

POSTER

Patient Experience with the Asthma Impairment and Risk Questionnaire (AIRQ) in Clinical Practice

George M, Brown R, **Coyne K**, Lavoie S, Eudicone JM, Gilbert I, Gandhi HN, Reibman J

WSPID 2019

November 5-8, 2019 | Manila, Philippines

POSTER

Global Public Health Impact of the 13-Valent Pneumococcal Conjugate Vaccine (PCV13): 10 Years on, How Far Have We Come?

Chapman R, Sutton K, Dillon-Murphy D, Patel S, Hilton B, Rarkouh R, Wasserman M

ISCoS 2019

November 5-7, 2019 | Nice, France

POSTERS

Incidence of UTI and Other Catheter-Related Complications Following Initiation of Intermittent Catheterization: Experience of Two European SCI Centers

Berger A, Inglese GW, Vos-van der Hulst M, Hofstad C, Goldstine J, **MacLachlan S, Ross L**, Weiss J, Kirschner-Hermanns R

Potential for Selection Bias in Designing "Real-World" Comparative Effectiveness Studies of Brands of Intermittent Catheterization: Experience of Two European SCI Centers

Berger A, Inglese GW, Vos-van der Hulst M, Hofstad C, Goldstine J, **MacLachlan S, Ross L**, Weiss J, Kirschner-Hermanns R

AMCP Nexus 2019

October 29-November 1, 2019 | National Harbor, MD, USA

POSTERS

Budget Impact of Introducing Avelumab as a Treatment for Genitourinary Cancers, Including First-Line Treatment for Advanced Renal Cell Carcinoma and Second-Line Treatment for Locally Advanced Metastatic Urothelial Cancer in the United States

Kongnakorn T, Bhanegaonkar A, Zheng Y, Kim R, Phatak H

Elagolix Reduces Productivity Losses in Uterine Fibroids Patients with Heavy Menstrual Bleeding - Evidence from Pivotal Trials

Al-Hendy A, Wang A, Wang H, Owens C, **Coyne K**

Psychometric Evaluation of the Functional Impact of Migraine Questionnaire within the COMPEL Trial

Lipton RB, Knoble N, Gandhi P, **Bushnell DM**, Niu X, Viswanathan HN

Real-World Treatment Patterns and Costs of Oral Antipsychotics for Treatment of Schizophrenia in the United States

Bessonova L, **Martin A**, Doane MJ, O'Sullivan AK, **Cichewicz A, Snook K, Hughes R**, Harvey PD

Use of Glucose-Lowering Treatments among Patients with Diabetic Kidney Disease in the United States

Iyer NN, **Li Q**, Dang-Tan T, Gamble C, Bakris G

Use of Prostanoids for the Treatment of Pulmonary Arterial Hypertension in the United States: Results of Analyses of a Large, United States, Commercially Insured Population

Highland KB, Drake W, Nagao M, **Murphy B**, Pruett J, Tsang Y, **Berger A**

ACG 2019

October 25-30, 2019 | San Antonio, TX, USA

POSTER

Real-World Safety of Vedolizumab and Anti-TNF Therapies in Biologic-Naive Ulcerative Colitis and Crohn's Disease Patients: Results from the EVOLVE Study

Yarur A, Mantzaris GJ, Kopylov U, **Bassel M, Brett N**, Lissoos T, Lopez C, Natsios A, Kifnidi C, Saha S, Demuth D, Patel H, Bressler B

Southeast SAS Users Group 2019

October 20-22, 2019 | Williamsburg, VA, USA

PODIUM

Data-Driven Programming Techniques Using SAS Macros to Semi-Automate Generation of Descriptive Tables in Healthcare Research

Mercaldi K

ISOQOL 2019 26th Annual Conference

October 20-23, 2019 | San Diego, CA, USA

WORKSHOP

Clinical Outcome Assessment in a Multi-Cultural Context: Measurement Challenges and Solutions

Martin ML, Hudgens S, Regnault A, Eremenco S, McLeod L

ROUNDTABLES

Developing Clinical Outcome Assessments for Regulatory Purposes

Lenderking W

How to Peer Review a Paper

Feeny D, Revicki D

SHORT COURSE

Introduction to Patient-Centered Outcomes Research for the Pharma/Biotech Industry: Informed Decision Making for Regulators, Payers, Prescribers and Patients

Lenderking W

ORAL PRESENTATION

Understanding the Patient Experience in Follicular Lymphoma (FL), Relapsed/Refractory FL (R/R FL), and Relapsed/Refractory Diffuse Large B-Cell Lymphoma (R/R DLBCL)

Bell JA, Cherepanov D, Revicki D, **Speck RM, Swett L**, Stumpo K, Rong Y, Gordon LI

SYMPOSIUM

United States Utility Algorithm for the EORTC QLU-C10D and the FACT-8D: Multi-Attribute Utility Measures Based on Cancer-Specific Quality of Life Instruments

Revicki DA, Norman R, Viney R, Pickard AS, Mercieca-Bebber R, Shaw J, Cella D, King MT

UEG Week 2019

October 19-23, 2019 | Barcelona, Spain

POSTER

Clinical Effectiveness of First-Line Anti-TNFa Therapies and Second-Line Anti-TNFa Therapy Post-Vedolizumab Discontinuation in Patients with Ulcerative Colitis or Crohn's Disease

Bressler B, Yarur A, Kopylov U, **Bassel M, Brett N**, Lissoos T, Lopez C, Natsios A, Saha S, Kifnidi C, Demuth D, Patel H, Mantzaris GJ

CHEST 2019

October 19-23, 2019 | New Orleans, LA, USA

POSTER

Dual-Combination Maintenance Inhaler Preferences in Asthma and Chronic Obstructive Pulmonary Disease: A Patient-Centered Benefit-Risk Assessment

Martinez FJ, **Tervonen T**, Gilbert I, Eudicone JM, **Heidenreich S**, Hanania NA

European Society of Gynecology Congress – 2019

October 16-19, 2019 | Austria, Vienna

POSTER

Bremelanotide Provides Meaningful Treatment Benefits for Premenopausal Women with Hypoactive Sexual Desire Disorder

Koochaki PE, Revicki DA, Wilson H, **Pokrzywinski R**, Jordan R, Lucas J

Recent Publications

Ambavane A, Yang S, Atkins MB, Rao S, **Shah A**, Regan MM, McDermott DF, Michaelson MD. Clinical and Economic Outcomes of Treatment Sequences for Intermediate- to Poor-Risk Advanced Renal Cell Carcinoma. *Immunotherapy*. 2020 Jan;12(1):37-51. doi: 10.2217/imt-2019-0199. Epub 2020 Jan 29.

Anatchkova M, Brooks A, Swett L, Hartry A, Duffy RA, Baker RA, Hammer-Helmich L, Sanon Aigbogun M. Agitation in Patients with Dementia: A Systematic Review of Epidemiology and Association with Severity and Course. *Int Psychogeriatr*. 2019 Mar 11:1-14. doi: 10.1017/S1041610218001898. [Epub]

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Cherney DZI, Repetto E, Wheeler DC, Arnold SV, **MacLachlan S**, Hunt PR, Chen H, Vora J, Kosiborod M. Impact of Cardio-Renal-Metabolic Comorbidities on Cardiovascular Outcomes and Mortality in Type 2 Diabetes Mellitus. *Am J Nephrol*. 2020;51(1):74-82. doi: 10.1159/000504558. Epub 2019 Dec 6.

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Evidera Welcomes New Senior Experts

Martin Parkinson, MRPharmS
Principal Consultant, Market Access Consulting

Martin is a pharmacist with over 25 years' experience spanning roles in government, industry, and life sciences consulting. In his current role, he leads a wide range of strategic market access consulting projects. His areas of particular interest include the theoretical and practical issues surrounding outcomes-based contracting for medicines, health technology assessment (HTA) methods and approaches, healthcare and medicines policy, and innovative pharmaceutical commercial and medical models.

Martin started his career in a large university hospital before moving on to manage a regional medicines information service where he established a highly successful program used nationally in reviewing new medicines and developing formulary guidance spanning hospitals and family doctors. He moved into payer organizations where he was responsible for medicines strategy across the community, including multiple hospitals. Martin was a key member of several Drug Formulary committees and chaired the overarching Area Prescribing and Therapeutics Committee. Through this he led the development of one of the first medicines formularies across both primary and secondary care. Martin also led the development and implementation of clinical guidelines across a wide variety of therapy areas to improve patient care and chaired the Research Ethics Committee.

Following more than 10 years in the NHS, Martin moved into a market access and payer strategy role within Pfizer working across many of the blockbuster brands in the pain, cardiovascular, and respiratory categories. In addition to market access strategy he also developed and led several innovative, value-added collaborations with healthcare stakeholders and national policy and decision makers. He also led a European project for the leadership team to refine and optimize management of key accounts and payer engagement across markets.

Prior to joining Evidera, Martin's consulting career included management consulting for the life sciences industry and specialized market access consulting. He has a wide range of experience across the spectrum that includes the redesign of commercial organization functions such as market access capability assessment and builds, payer and funding flows, pharmaceutical pricing, and the design of a global decision making and governance process for outcomes-based contracting. Martin has also managed the construct of a global post-authorization registry for a rare disease medicine and engaged in HTAs.

Margaret 'Meg' Richards, PhD, MPH
Senior Research Leader
Non-Interventional Studies
Real-World Evidence

Meg has with over 30 years of experience as an epidemiologist and health services researcher in both the private and public sectors. She has held several senior level positions within the private sector, including executive director of scientific affairs at PRA Health Sciences in their real-world solutions business unit; vice president of data analytics and epidemiology/real-world strategy and analytics at Mapi Group (now ICON plc); and seven years as an executive director of epidemiology/real-world outcomes at PPD Inc.

Prior to her work in the clinical research organization environment, Meg served as director, global patient safety and risk management at Genzyme Corporation. At both Genzyme (now a Sanofi company) and Abbott Labs (now AbbVie), she managed the quarterly data mining and "signal" (safety issue) detection and evaluation programs for each company's post-marketed product line.

Meg's public sector service includes 10 years with the Rhode Island Department of Health, the Illinois Department of Public Health, and Quality Partners of Rhode Island (a Centers for Medicare and Medicaid Services quality improvement contractor).

She received her BS in nutrition from the University of New Hampshire and her MPH and PhD from the University of Illinois at Chicago's School of Public Health, after which she served a two-year tour of duty with the US Public Health Service as a member of the Centers for Disease Control and Prevention's Epidemic Intelligence Service.

Meg has managed every stage of a real-world study including design, data collection, analysis, reporting, and publication. She is also a skilled SAS programmer and is certified in focus group conduct.

Evidera Acknowledges Excellence with Senior Staff Promotions

Ruth Chapman, PhD
Research Scientist
Modeling & Simulation

Carla Dias Barbosa, MSc
Senior Research Scientist
Patient-Centered Research

Peter Gal, MSc
Research Scientist, Research Director
Modeling & Simulation

Jessica Griffiths, MEnt
Senior Consultant
Market Access Consulting

Barbara Hawkins
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Leyla Mohseninejad, PhD
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Katie Murphy, PharmD
Principal Medical Writer
Medical Writing and Healthcare Communications

Peter Quon, MPH
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