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#AccessRWE

AccessPoint

News, views and insights from leading international RWE experts

A new wave of innovation for real-world evidence

80% of trials are delayed due to enrollment issues

RWI **accelerates** results in next-generation trials

See page 20 for details

Real-World Insights

QuintilesIMS™

AccessPoint

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"Today, we are energized by the technology-driven breakthroughs that are creating new possibilities for both RWE and RWI."

AccessPoint is a publication with its sights set squarely on "what's next?" for real-world evidence (RWE). Through articles and case studies from some of the world's leading RWE experts, we evaluate trends, introduce new applications and push ourselves to continually re-think the status quo.

We even evolve our own language. For example, we are seeing that real-world data (RWD) isn't just powering evidence for clinical decisions, it is also generating insights that are relevant across healthcare. Such real-world insights (RWI), developed from beyond the study environment, are expanding our perspective. Supporting better, more effective uses of medicine. Enhancing pharma's commercial engagement. Even improving the process and results of clinical development.

Today, we are energized by the technology-driven breakthroughs that are creating new possibilities for both RWE and RWI, some of which are discussed in this issue

- **Advances in data privacy technology and methodologies** which make possible new levels of sharing and collaborative learning, generating better evidence and delivering better treatments
- **Machine learning and data visualizations** which crack the code of Big Data in healthcare and give data scientists, researchers and clinicians a faster path to useable insights

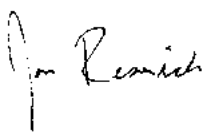
We are also witnessing fundamental changes in the way evidence is generated and used, driven in part by technology but also by the increasing demand to be more efficient and effective in the R&D process

- **New uses of RWE** which overcome critical hurdles in trial design, planning and operations – defining the next generation of clinical development
- **Pragmatic trials** which increasingly complement randomized clinical trials (RCTs), highlighting the value of a wider range of data sources
- **The growth of digital health** and subsequent patient-generated data which adds new depth to R&D programs, and places new demands on pharma to capture its value

Certainly, the companies that can embrace these trends – the evolution of technology and technology-enabled analytics, and the rise of new avenues to bring in data – are the ones that will gain advantage from RWE innovation.

It is in this context that we made the decision to merge two organizations at the forefront of clinical research and data-driven commercial and real-world expertise, forming QuintilesIMS. By bringing together our collective expertise and expanding our perspective, we believe we can better support practical, agile, technology-enabled solutions that improve the way healthcare functions and that provide new answers to "what's next?"

We hope you enjoy this issue of **AccessPoint** as you continue to deepen your understanding of RWE and drive the future of healthcare forward.



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A new wave of innovation for real-world evidence

Trend report: Accelerating RWI

The future of real-world insights (RWI) is being propelled by the combination of increasingly abundant data (supply) and rising stakeholder requirements for deeper insights (demand). And the needle is moving. As value is becoming clearer and regulators are playing a greater role, we are seeing demand emerge as a key accelerator of innovation and evolution.

BIG DATA

Patient-generated data, genomic information, unstructured data, PROs and integrated data sources – an unprecedented amount of data is available to pharma.

Empower data scientists. Embrace privacy and integration apps. Establish data governance. Leverage broad organizational knowledge to find the right data for the right question.

ADVANCED ANALYTICS

New analytic approaches are unlocking RWI, increasing the value of data: machine learning, natural language processing, predictive modeling and phenotype vectors are making waves.

Determine which tools and capabilities to build vs. outsource. Know which analytics will reveal the most meaningful insights.

STAKEHOLDER COLLABORATIONS

Payers and providers are working together on new payment programs, data integration and co-creation of RWE. This is resulting in greater transparency but also competing sources of truth.

Develop a disciplined engagement approach to participate in these collaborations, beginning with disease-level evidence early in development. Invest in the adoption of tools to enable greater transparency.

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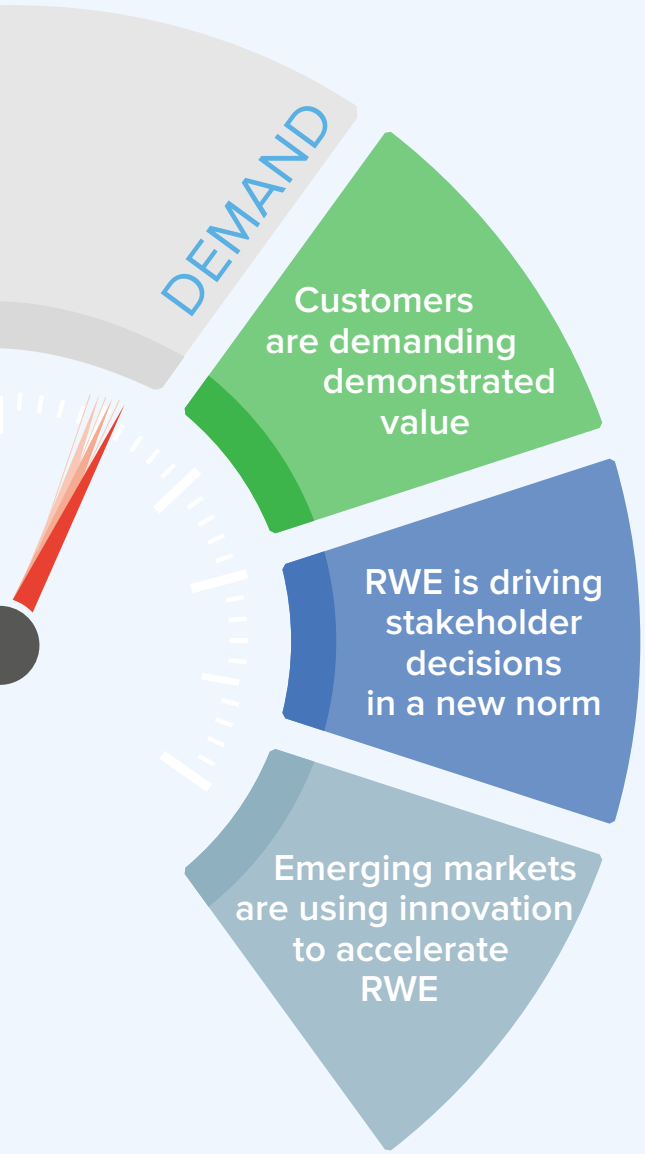

SPOTLIGHT ON VALUE

Increased competition, public pricing pressures and a brighter spotlight on value assessments are driving payers and providers to demand greater transparency and risk sharing from pharma.

Generate rigorous brand evidence aligned to customer priorities. Understand cost offsets from their perspective. Stress test RWE with them before generating evidence.

EVIDENCE EVERY DAY

Payers and providers are using RWE more frequently to monitor quality metrics and make prescribing and treatment decisions.

Ensure ongoing understanding of current customer needs across functions. Achieve fluency in RWE trends and capabilities across functions – be able to walk the talk.

EMERGING MARKETS

Supply and demand are increasing in countries like Brazil and China, and the need for technology and analytic solutions is creating new opportunities to deepen stakeholder understanding of treatment value.

As capabilities grow, account for the accelerating evolution of RWE and growing local insight.

PHARMA'S BIG DECISION

INNOVATION IS GREAT... IF YOU KNOW WHAT YOU'RE DOING!

Too-much, too-soon investment in the latest technological breakthrough without sufficiently defining its value and practical application creates doubts within pharma around RWE and its value.

Establish a well defined process for technology investment, including use case assessment and valuation, proof of concept requirements, and a disciplined pilot approach.

Step by step: Leveraging wearables in clinical trials

Regardless of geography or therapeutic area, wearables offer an important, exciting opportunity to better understand patients and improve their experience at each stage of their journey. Today, wearables are demonstrating real potential to transform data collection for clinical trials and accelerate the role of technology in clinical development. But to get there, pharmaceutical companies must take a disciplined approach and focus on five critical actions to succeed.

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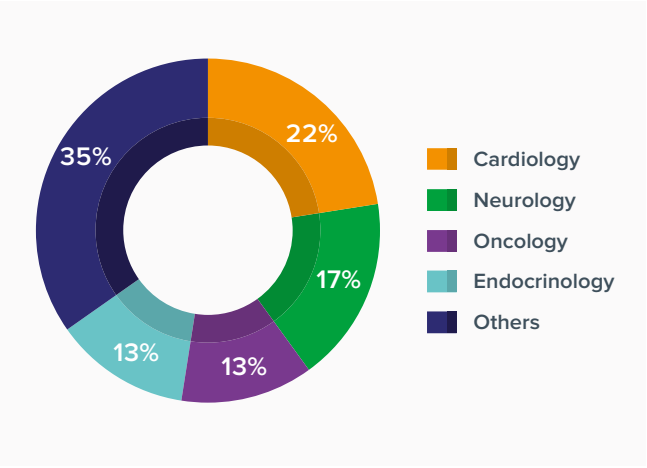
How can pharma confidently generate evidence from wearable technologies?

Wearables (devices that capture continuous health and activity data from individuals) have technically been around for a long time; in 1960, the first continuous ECG data was collected from patients. However, the real watershed moment for wearables came in 2007, when Fitbit® entered the market and the concept of a wearable device to monitor personal health information was introduced to consumers.[1] Since then, the use of wearables has been increasing throughout healthcare, including in clinical trials.

Statistics from the National Institutes of Health (NIH) show that by the end of 2015, approximately 300 clinical trials incorporated some kind of wearable device.[2] Looking at 2016 NIH data,[3] it is also clear that the concept is relevant across therapeutic areas (see Figure 1).

Figure 1: Utilization of wearables in clinical trials by disease area in 2016[3]



That said, a myriad of conflicting studies have been published in the last 24 months that alternately tout the benefits of wearables[4,5,6] or dismiss them as hindrances in the delivery of quality medical care.[7,8,9] Such contradictions have left many in the industry struggling to determine when and how wearables should be used, if at all, in the development of pharmaceutical products.

Closer evaluation shows that even negative studies provide valuable learnings and shine a light on emerging best practice.

Some of the observed pitfalls include

- Insufficiently defined endpoints (e.g., sustained weight loss with limited interventions)
- Multiple influences on patient behavior (e.g., observation, incentives)
- An excess of factors to measure with varying relevance

Despite these challenges, there is growing recognition that wearables and other digital technologies are here to stay. Continuous developments in technologies are helping pharmaceutical companies dive deeper into digital health.[10] Bayer is expanding its incubator Grant4Apps program;[11] EMD Serono is partnering with Big Data firm Palantir across discovery, patient experience and the global supply chain;[12] and Novartis has publicly stated its intention to take "a greater leadership role" in this area.[13] The imperative, then, is for pharma to proactively figure out how to make the best use of these devices in R&D and how to incorporate even negative data.

Outsiders come in

With the increased attention on leveraging new digital health technologies, companies outside of the healthcare space are paying closer attention to the trial setting and trying to help provide the tools necessary for using wearables in trials. Apple, for instance, is continuing to invest in ResearchKit, an open source framework for the creation of mobile applications that support medical researchers by gathering robust and meaningful data.[14] A second example is Qualcomm, which has been selected by Novartis as a global digital health collaborator for its Trials of the Future program. This program will leverage Qualcomm Life's 2net™ Platform to serve as a global connectivity platform for collecting and aggregating medical device data during clinical trials.[15] The type of data collected by each of these platforms is shown in Figure 2.

While Apple and Qualcomm offer very different technologies, both are key tools in incorporating wearables into trials: ResearchKit provides researchers with tools to create apps that enable customer data collection; the 2net™ Platform allows for the secure storage and accessibility of continuously collected data, and it provides a way to connect data from various sensors and link it to a single patient.

continued on next page

> "Companies seeking to maximize the value of digital health and wearables in R&D can gain significant ground through the use of proof of concepts"

Figure 2: Data collected by ResearchKit and 2net™ Platform programs

Platform	Program	Target	Type of Data Collected
ResearchKit (Apple)	mPower	Parkinson's disease	Dexterity, balance, gait, memory
	Autism & Beyond	Autism	Emotional reactions
	EpiWatch	Seizures	Heart rate, movement
	Concussion Tracker	Concussion	Heart rate patterns, physical and cognitive function
	StopCOPD	Chronic Obstructive Pulmonary Disorder (COPD)	Physical activity, heart rate, sleep patterns
	GlucoSuccess	Diabetes	Movement, food intake, medication compliance
	C Tracker	Hepatitis C	Heart rate, activity level
	Mole Mapper	Melanoma	Photography of moles
	PPD ACT	Postpartum depression	Saliva (DNA) sample
	SleepHealth	Sleep health	Daytime alertness, sleep pattern, sleep quality
2net™ Platform (Qualcomm Life)	Breezhaler	Chronic Obstructive Pulmonary Disorder (COPD)	Inhaler usage including the duration of the patient's inhalation

Finding the right path

Direct experience helping pharmaceutical companies navigate this difficult terrain shows that the industry is only starting to understand how and when to test wearable technologies and take advantage of them in the clinical trial setting. Many have yet to learn the art of 'win fast, fail fast' or how to leverage proof of concepts (POCs) vs. larger pilots. A measured, practical approach to adopting new technologies has been proven to yield better ROI, more efficient use of time and resources, and valuable learning opportunities.

Case Example 1: Big hopes. Big disappointments.

Recently, a company new to mobile patient devices incorporated Fitbit® into a trial to explore its potential for a respiratory indication, without sufficiently clear clinical endpoints. The trial encountered various challenges, including a lack of clarity around the desired endpoints for defining success, and did not have the security of running a smaller POC. As a result, the inconsistent frequency and quality of the data being collected led to multiple protocol amendments, increasing the administrative burden. In the end, the trial could no longer be justified from a financial perspective and was canceled.

The reality here was that much of the trial's cost and many of its shortcomings might have been avoided had the company invested in a small POC to quickly gain knowledge of how to use the technology before incorporating it into a larger trial.

Case Example 2: Winning with POCs

Diabetes studies provide a number of early examples of success with wearables. In one case, incorporating a wearable glucose monitor into POCs allowed for both concrete data collection and the establishment of the data infrastructure to support future, larger trials and pilots. The wearable was used not only to measure glucose levels over multiple years but also, importantly, to put in motion the processes, capabilities and systems to

- Determine inter- and intra-patient glucose variation
- Advise on dosing schedules
- Set standards for ongoing surveillance and management
- Identify measures for managing drug adherence in future trials
- Measure the impact of activity and other patient characteristics on overall patient care

As these examples demonstrate, companies seeking to maximize the value of digital health and wearables in R&D can gain significant ground through the use of POCs. This approach will help them better evaluate technologies, identify appropriate opportunities for using wearables, set up the required capabilities and partnerships, and learn what works well and what does not.

Five steps to success

Against this background, companies should focus on five critical components of success.

1. **Embrace 'win fast, fail fast' with POCs.** As indicated, POCs provide a necessary and valuable approach for pharmaceutical companies to test confidently and practically the feasibility of new technologies (see Figure 3). For example, if a company is interested in using telehealth to monitor patients in a clinical trial, POCs can serve to test the prioritized technologies, understand their associated UI/UX (user interface/user experience), and ensure the capabilities required for set-up, partnering, support, etc.

   As a result, companies can save significant time, money and resources by deploying a POC compared to simply selecting one telehealth vendor and implementing a trial. POCs are the best way to learn how to use and maximize value from wearables and other technologies – especially in an industry unaccustomed to such an expedited approach.

   Of course, if a technology is already well understood (in terms of security, user interface, back-end data collection, geographic constraints, etc.) and all the data, systems and procedures are in place (e.g., appropriate platforms with required security for data aggregation, alerts and notification algorithms, pharmacovigilance requirements, etc.), then companies may be well suited for going direct to pilots.

2. **Be clear about who owns the POC and how it will be funded.** Testing the use of a new technology in a clinical trial has multiple implications and uncertainties. It changes the way the protocol should be written, incurs additional cost and may raise unanticipated questions from regulators – hence the hesitancy in assessing wearables or new technologies for use in trials. Best practice companies dedicate funding and an independent team to drive innovation in R&D, with the ability to test technologies quickly and cascade the learning through the broader organization.

3. **Start outlining a foundational data strategy.** Particularly in the case of wearables, the amount of collectable data can often be overwhelming and not always necessary. Take this simple example: a company wishing to use total sleep time as an indirect indicator of activity decides to use a validated actigraph (wearable). Theoretically, collecting sleep time should be easy. In reality, there is much to consider, including

   - How is sleep defined?
   - How is the sleep data displayed?
   - How will physicians see the data?
   - What will they do with the data?
   - Is there a requirement for thresholds to trigger medical visits or calls?
   - Who will triage the data?

   There is also a wide range of additional (but likely irrelevant) data that the wearable will collect (e.g., number of steps). Having a clear data strategy upfront is essential, impacting everything from informed consent to protocols and data security.

4. **Go outside your firm – involve key stakeholders, including patients and physicians, early and often.** Clinical trial protocols cannot be developed in isolation, especially when it comes to incorporating wearables or other digital health innovations. Viewing patients as technology *consumers* rather than as *patients* is critical. For example, understanding how patients will interact with the technology on a daily basis, how often they are likely to wear it, in what conditions (e.g., exercising, sleeping, showering, etc.), and what they consider to be incovenient, is extremely important when designing a trial protocol that incorporates wearables. Failure to consider these factors runs the risk of poor data and lack of compliance.

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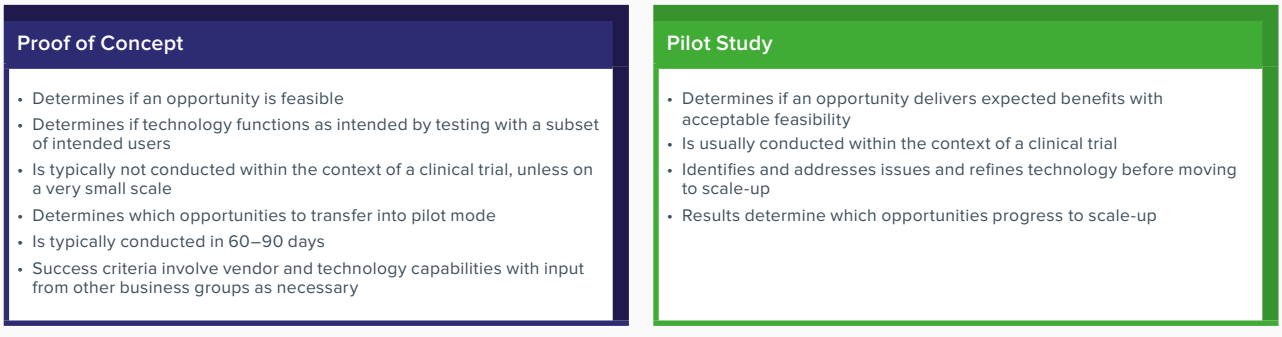
Figure 3: Key attributes of POCs vs. pilot studies



5. **Ensure that stakeholder-specific KPIs and learning goals are incorporated.** When considering incorporating wearables into a clinical trial, it is important to know exactly what endpoints are needed, how they will be analyzed and who will use them (e.g., payers, regulators, physicians, others).

Figure 4: POC learning goals should have broader application to other opportunities

Evaluation Questions	Success Factors
Was the vendor suitable?	Selected vendor was identified as a good partner and met timelines, milestones and service agreements
Did the technology work?	Technology was available, performed for a specific use/function, and was validated (if validation was required)
Were risks proactively identified and addressed?	Risks were identified during the course of the POC and mitigation tactics were developed
Were the scope and goals clear?	Key endpoints were captured and POC was completed in a timely manner
Are learnings (good and bad) useful and replicable?	POC learnings can be applied to other opportunities across the organization

Clear KPIs can include

- Time for technology installation
- Frequency of user errors
- Number of customer support calls

Most companies have now become adept in this area. However, just as important is having a clear idea of learning goals from a trial or POC. Even if trials or POCs fail to demonstrate usability of a technology, the learnings can and should serve to inform other opportunities (see Figure 4).

Moving forward

As the development of digital health technologies continues to accelerate, so do the opportunities to enrich R&D programs with patient wearables. To capitalize on this potential, there are certain key steps pharmaceutical companies can take to evaluate the relevance of technologies to their trials and build the competencies required to leverage them to best effect. First and foremost is a pivot to a 'win fast, fail fast' model that embraces POC as a catalyst for better learnings and more deliberate progress.

Ensuring dedicated funding and an independent team, defining a clear data strategy upfront, engaging early with key stakeholders, and establishing specific KPIs and learning goals are also fundamental to success. Certainly, companies that can bring together clinical trial and digital technology expertise will be the ones to confidently and sustainably plan, scale and implement wearables in R&D.

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Innovation delivering "what's next" now

At QuintilesIMS, we are using cutting-edge technology to power better problem solving for healthcare.

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- **Predictive analytics** to identify unmet need, facilitate treatment breakthroughs and enable critical commercial efficiencies
- **T-Shaped Evidence Networks (T-SENs)** to create complete disease views built on broad national datasets and deep, clinically rich information

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Getting on the fast track

In Europe, the concept of 'adaptive pathways' offers a faster route to critical medicines for patients with highest unmet needs through an iterative process of early and continuous evidence generation. Despite some criticisms, increased cross-stakeholder interest, including ongoing initiatives led by MIT, may provide a clearer path for this controversial approach. If successful, adaptive pathways could streamline the broader drug development process for the benefit of all parties – especially in rare disease treatments where niche populations and limited data can be a major barrier to access.

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Adaptive pathways are creating win-win scenarios for patients and pharma

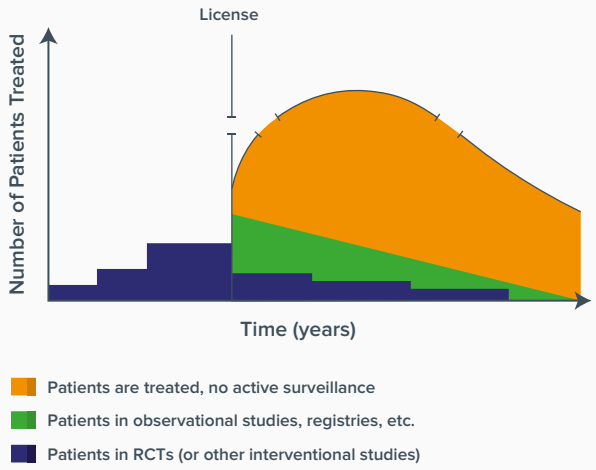
Advances in gene therapy and personalized medicines mean that many innovative treatments are targeting small patient populations. This has major implications for cost. As a result, stakeholders face the daunting task of balancing the growing expense of drug development against having enough proof of safety and value to ensure access. Collectively, these forces are accentuating the imperative for a new approach (see Figure 1).

To date, efforts to improve the drug development paradigm have looked for ways to give earlier access to patients with the most need while evidence of safety and value develops. Although compelling, this notion of 'adaptive pathways' to treatment has created controversy with some critics who believe it will lead to a lowering of evidential requirements and standards, and compromise patient safety.

Mind the gap

Although clinical trials are traditionally accepted as the gold standard of evidence, stakeholders – including regulators – are increasingly concerned about their shortcomings in being able to predict how a drug will perform in normal clinical practice. This gap in evidence has been highlighted by the European Medicines Agency's (EMA) Senior Medical Officer, Hans-Georg Eichler and co-authors: *"Even with these advances in clinical trial designs, randomized clinical trials (RCTs) will always leave significant uncertainty about benefits, risks, real-life utilization and performance of new drugs; RCTs are often designed to remove confounding factors such as comorbidities or exclude elderly, frail patients. 'Confounder cleansing' increases the ability to detect a drug effect if it is there, but reduces external validity. Progressive reduction of those uncertainties will need to be achieved by way of the use of data from observational studies."*[3]

Figure 2: The 'magic moment' of authorization in drug development [4]



In reality, earlier access may be the key to generating the real-world evidence (RWE) stakeholders need to inform broader access decisions. Developing knowledge of a drug's safety and effectiveness in actual practice could supplement standard clinical trial information that is often based on small samples for niche populations. It would give regulators better insights when broadening authorizations for medicines. It would also address their long-held concerns about the 'magic moment' when a medicine is authorized and no longer subject to the controlled environment of the trial (see Figure 2).

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Figure 1: Something needs to change – drivers for improving drug development

Costs to develop drugs and gain marketing approval average $2.5B[1]

- Development costs are prohibitive for smaller companies/academic spin-offs
- Medicines with small target population potential may not be developed
- The increasing cost of drugs for patients and healthcare systems is unsustainable

Target populations are becoming smaller

- Many 'diseases' are in fact a collection of symptoms with different underlying pathologies
- Precision medicine is leading to more targeted therapies
- Authorization does not guarantee market access

Rare diseases are still a major cause of unmet medical need [2]

- More than 7,000 rare diseases have been identified
- 50% of sufferers are children
- Only 5% of diseases have effective treatment

> "In reality, earlier access may be the key to generating the real-world evidence (RWE) stakeholders need to inform broader access decisions"

A new proposal

Realizing that the current drug development paradigm is unsustainable, the Massachusetts Institute of Technology (MIT) Center for Biomedical Innovation (CBI) has been working for a number of years to address its biggest pain points.

The CBI's main initiative, known as NEWDIGS (**NEW D**rug Development Parad**IG**m**S**), brings together participants from all the major stakeholder groups – regulators, patients, payers, physicians and pharma. Together, they have developed the EMA's Adaptive Pathways or Medicines Adaptive Pathways to Patients (MAPPs), and Adaptive Biomedical Innovation, initiatives. These strive to address two core requirements: accelerated access for patients with urgent unmet need and a cohesive approach to the development of drugs.[3,5,6]

Adaptive pathways today

The premise behind adaptive pathways is that patients with a serious condition and unmet medical need might be prepared to accept greater uncertainty about the benefits and risks of a medicine in return for earlier access to treatment.

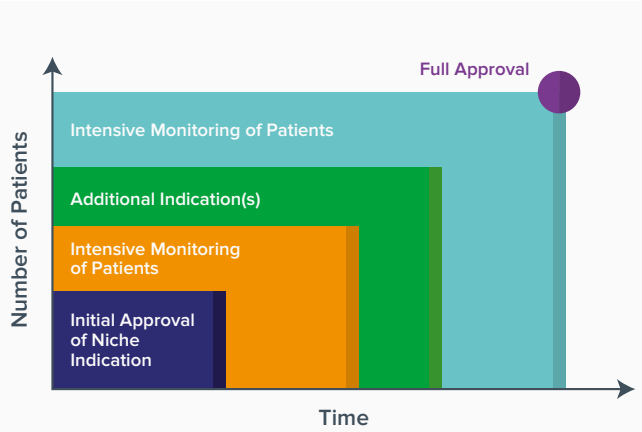
The neurodegenerative disease, amyotrophic lateral sclerosis, for example, typically causes death within 3–5 years of diagnosis. Individuals with such a life-limiting disease and short life expectancy cannot afford to wait 10–12 years for a full development program with the possibility of further delay for the drug to become available in the market. Furthermore, 30% of patients with rare diseases die before the age of five, so again, time is critical.[7]

Adaptive pathways propose earlier, but controlled, tiered market access. An early license is granted for patients likely to benefit most, and the majority of these treated patients are monitored closely in some form of observational study. Additional research, including further clinical trials, for expanded indications continues as do the observational studies.

As more information becomes known about the medicine, and the uncertainties around benefits and risks are reduced, the authorized indication is gradually widened to include those with lesser needs or other indications, until a full license is obtained (see Figure 3).

Critical to the program are strictly enforced control measures. At all times during the process the observed benefit-risk profile must be positive, requiring manfacturers to have market exit plans in place should this change. Access to the medicine must be sufficiently controlled so that only those patients who have the most to gain and are prepared to accept the higher levels of uncertainty are treated initially.

Figure 3: Schematic of adaptive pathways approach



To date, no drug following an adaptive pathway has been authorized. However, the EMA's report on its pilot program, published in 2016, confirmed that 62 proposals had been received and 20 accepted for an initial Stage 1 meeting. Of these, 18 entered Stage 2 discussions, with seven applying for formal joint health technology/scientific advice or scientific advice alone. Proposal rejections were mainly due to

- Lack of stated intention to use RWE
- Absence of unmet medical need
- Drug too far advanced in development, leaving little opportunity for innovation[8]

Bumps in the road

The introduction of adaptive pathways has not been smooth, with HTA bodies in some countries refusing to participate and critics deploring what they perceive as a lowering of standards and unacceptable risk to patients.[9] It is ironic that regulators, often regarded as being too cautious, are prepared to look at new ways of getting medicines to those who need them most but are being held back by other government agencies and payers. Coming at a time when expensive, innovative drugs are already straining healthcare budgets, this may reflect concerns that giving early access to drugs with less certainty of benefits and risks may come at the expense of access to proven treatments. Payers may also fear that once the genie (or in this case the medicine) is out of the bottle, it will not be possible to remove it from the market if it fails to live up to initial expectations.

Nonetheless, the fact remains that a drug available in five years time is of little help to patients with fewer years to live. If these individuals are fully informed and prepared to accept the risks, it is up to the industry, HTA bodies and payers to work out financial models to give adaptive pathways a chance.

> "The fact remains that a drug available in five years time is of little help to patients with fewer years to live... Adaptive pathways proposes earlier, but controlled, tiered market access"

Adaptive biomedical innovation

Apart from early market access, the concept of adaptive pathways also envisages adaptive development of the medicine itself. This 'adaptive biomedical innovation' utilizes very early engagement with all stakeholders (regulators, payers, providers and patients) to determine what evidence they need for optimal decision making (i.e., authorizing, reimbursing, prescribing or taking). The development plan for the drug encompasses all of these requirements, allowing a more cohesive approach rather than the more typical siloed one.

An iterative process

As evidence is generated, the development plan is revised, taking into account what has been learned and what questions remain. The optimal study design is then chosen for the next stage of evidence generation. In the case of a life-limiting rare disease with no effective treatment, a single arm study along with a disease registry or even historical controls, might be the choice for initial efficacy studies. This type of design was used for the gene therapy, Strimvelis, which although too early for the adaptive pathways program received a license based on efficacy data on just 12 patients.

Once the initial niche authorization and market access are granted, monitoring early access patients can also provide RWE to answer stakeholder questions and reduce uncertainty around benefits and risks. This review of all evidence and adaptive design is an iterative process across the product lifecycle. The emphasis here is on evidence generation changing from efficacy to safety and effectiveness. By considering all stakeholders' evidence needs from the start and optimizing the study design, a more efficient, streamlined development path is achieved.

Evidence generation over the lifespan of a medicine already exists in the form of post-authorization efficacy and safety studies (PAES, PASS). These can provide payers with both ongoing proof of effectiveness and critical safety information based on broader use.

Some payers, such as Cigna with Praluent, Repatha and Entresto, and the UK NHS with Velcade, are also utilizing 'pay for performance' systems to tie this data to reimbursement.[10,11]

Key potential to advance drug development

So where does this leave adaptive pathways? The concept is sound and the criticisms can be addressed. However, the approach will only work if

- Industry is prepared to accept lower initial pricing
- HTA/payers allow market access
- All parties accept that medicines which do not live up to their initial promise are either removed from the market or (if the risk-benefit trade-offs are still positive) are not given premium pricing

Adaptive pathways as a whole may or may not survive the critics, but some aspects will certainly endure. Adaptive biomedical innovation, in particular, presents an opportunity to revolutionize drug development. Not all medicines are suitable for early access but the principles of determining the evidence needs of all stakeholders and creating an adaptive development environment can be broadly applied.

An essential first step will be proactive development of meaningful plans which include the collection and analysis of RWE. The initial endpoints should be informed by both consulting with patients to understand what matters to them and engaging with other stakeholders to determine what evidence they need. Bringing the right drugs to the right patients at the right time and at the right price, safely and as quickly as possible, should be in everyone's best interest.

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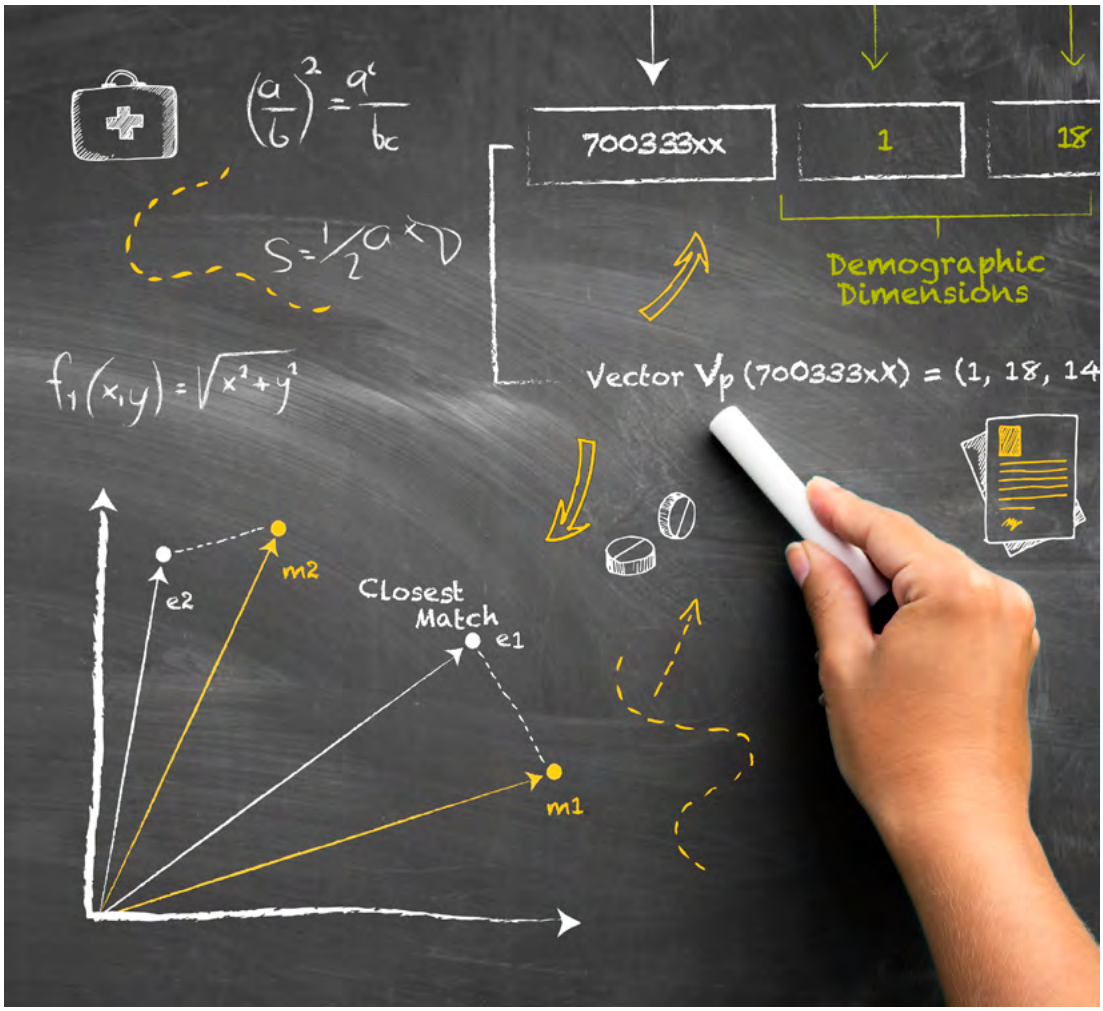
Taming Big (healthcare) Data

With pharma under pressure to achieve more from real-world data (RWD), data scientists are in growing demand. But they lack the tools to industrialize the onerous data wrangling that consumes 80% of their time. As companies increasingly turn to RWD to inform their research, an innovative approach leveraging phenotype vectors brings exciting potential to dramatically accelerate data science output and machine learning-based productivity and insights.



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The power of vectors to streamline data science and accelerate insights

According to Davenport and Patil, writing in Harvard Business Review, being a data scientist is "the sexiest job of the 21st Century."[1] While not everyone would agree, there is no doubt that demand for data science is outstripping supply: data science and Big Data engineering are predicted to be the two fastest growing areas for technology jobs in 2017, and healthcare and financial services are the leading industries driving high-tech job growth. Clearly there is intensifying demand for output from data science in healthcare – not surprising given the wealth of untapped information that companies are keen to unlock from real-world data (RWD).

Data scientists are highly skilled individuals, "better at statistics than any software engineer and better at software engineering than any statistician."[2] Paradoxically, however, the anecdotal reality is that data scientists spend only 20% of their time on 'real' data science. A staggering 80% is devoted to 'wrangling the data,' i.e., cutting the subset of data required for a study from source databases and creating a 'research-ready' format that can be used as input to the algorithms and calculations of data science. Thus, at a time when companies are more reliant than ever on extracting the maximum value from RWD, they are in fact spending significant time and resources on basic, low-level data manipulation. However, by using tools powered by phenotype vectors, such as QuintilesIMS E360™, it doesn't have to be that way.[i]

Accelerating insights

One of the data wrangling activities that is so effort intensive is converting RWD to 'phenotype vectors' as the fundamental raw material of RWD-based data science. By designing algorithms and systems around these vectors, it is possible to largely industrialize the data wrangling process. In doing so, companies can position themselves to fuel a dramatic increase in data science output: flipping the 80/20 rule would realize a four-fold increase in capacity. Perhaps of even greater value than the pure increase in capacity is the potential increase in velocity – automated tools can cut the time to generate research-ready data to minutes from the current weeks of programming.

A valuable side-effect of this approach are algorithms that are more portable across datasets. Such agility could drive significant gains in output, productivity and velocity.

So, what are phenotype vectors, why are they so pivotal in data science, machine learning and predictive analytics, and how can systems be designed to enable their production?

First, what's a vector?
A vector is something with scale and direction, usually drawn as an arrow. When placed into a coordinate system (i.e., axes), it can be represented as a series of individual variables or coordinates – one for each dimension. It can also be seen as representing a point in space – the endpoint of the vector if it were drawn from the origin. Two vectors can be considered 'close' if the distance between these endpoints is small.

Since a vector can have any number of dimensions, a single vector can be used to encode multiple values for a single object. It can then be thought of as either a sequence of values or as a position/arrow in (n-dimensional) space.

Where do vectors sit in data science and machine learning?
Vectors are no strangers to data science. Analyzing patient-level data, for example, requires multiple variables to be manipulated for a single person (e.g., age, gender, BMI, presence of diabetes, etc). This effectively describes the patient as a vector, the variables being its dimensions.

In fact, all data science is grounded in some underlying formal mathematical theory which is almost entirely vector-based. Examples of algorithms in common use that rely on vectors as inputs are cohort matching, regression analysis and clustering (see Figure 1). The key point for each is that in order to leverage the necessary mathematical theory into data science, the data must first be converted into vectors. The same is true of RWD.

RWD and portability
RWD is typically transactional and time-based (or longitudinal) and consists of two primary classes of entity

1. **People** (patient, enrollee)
2. **Events** (diagnoses, therapies, procedures, etc)

Converting RWD into a research-ready, vector-based structure is where data scientists spend so much of their valuable time. Even when the code is developed to be specific to a native data structure, the work is still not portable.

continued on next page

[i] For further information on QuintilesIMS E360™ see page 48 of this issue

> "At a time when companies are more reliant than ever on extracting the maximum value from RWD, they are in fact spending significant time and resources on basic, low-level data manipulation – but it doesn't have to be that way"

However, by defining the all-important data science algorithms (such as those shown in Figure 1) against standardized vector formats, the possibility exists for vectors to become the pivot point to overcome the issue of dataset portability.

This, of course, raises a key question: in seeking to perform data science on RWD, how are vectors created and how can their dimensions be defined in a portable manner?

Realizing the potential of phenotype vectors

A phenotype can be defined as "the set of observable characteristics of an individual resulting from the interaction of its genotype with the environment."[3] The focus here is on a specific implementation that enables rapid, generalized phenotype-vector production from RWD databases.

In the case of EMR data, for example, an initial, very simplistic view of a phenotype could be a single code list, such as 'does a patient take metformin.' This might expand to around 1,000 individual different codes but ultimately it is a single phenotype that will be represented as a single dimension in the phenotype vector for the patient, indicating their use of metformin.

Once created, a phenotype vector can inform multiple analyses. The example shown in Figure 2, for instance, could feed into a cohort-matching algorithm to find individuals with a particular outcome for ADHD treatments against those with a different outcome. Looking at regression analysis, it could be used to predict the risk of particular outcomes given its dimensions. For clustering, the phenotype vector would allow individuals with similar positions to be identified along with their drug treatment.

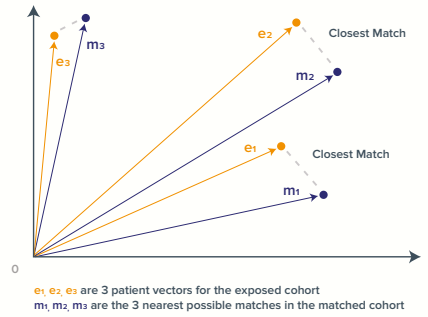
More generally, a phenotype may be defined as an arbitrary Boolean combination of demographic information, code lists or lists of values representing conditions, drugs, observations, procedures, etc. Each code or value list may include some absolute or relative time constraints. Time relationships between individual lists may also be specified (e.g., people who have a severe asthma diagnosis after being diagnosed with ADHD). So, in this subtly more sophisticated definition

Phenotype =
Boolean and time-related combination of
- Lists of conditions (optionally time-bound)
- Lists of drugs (optionally time-bound)
- Lists of observations (optionally time-bound)
- List of procedures (optionally time-bound)
- ***Phenotypes*** (optionally time-bound)

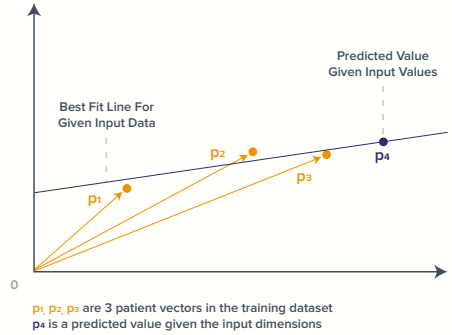
The last clause provides a recursive definition, a classic approach in computer science to represent infinite complexity with beguiling simplicity. This simple definition allows arbitrarily complex phenotypes to be defined by consuming and combining definitions of other phenotypes to any level of depth.

Figure 1: Uses of vectors in data science

1. **Cohort matching:** A technique for observational studies to determine, for example, the risk of a treatment causing a particular disease by comparing a quasi-control group against a given exposed patient cohort. Matched patients are identified by looking for patient vectors 'nearest in space' to each patient in the exposed group.



2. **Regression analysis:** Used in predictive analytics to estimate the risk of a particular disease given the presence of different variables, by finding a best fit mathematical equation for the points in space represented by the input vectors.



3. **Clustering algorithms:** Used in predictive analytics to determine, for example, potential markets for products. The distance between points in space represented by vectors identifies close neighbors, generating clusters of subjects that may be regarded as 'alike.'

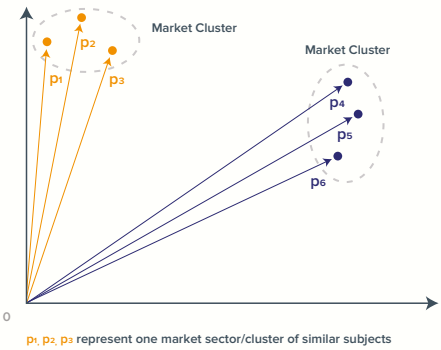


Figure 2: A sample phenotype vector created from an EMR database

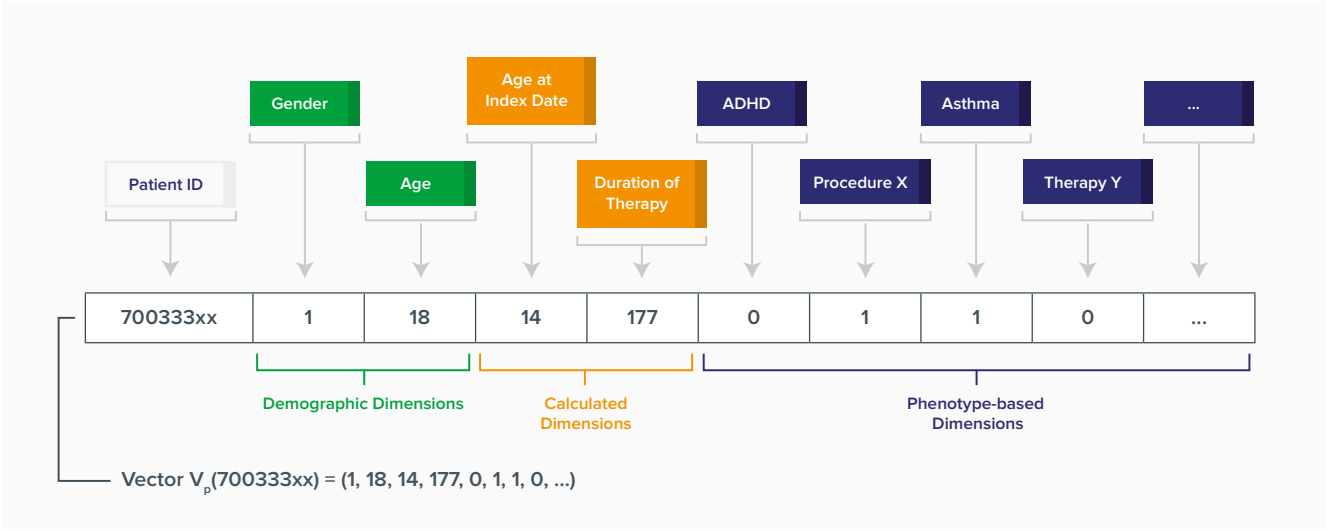
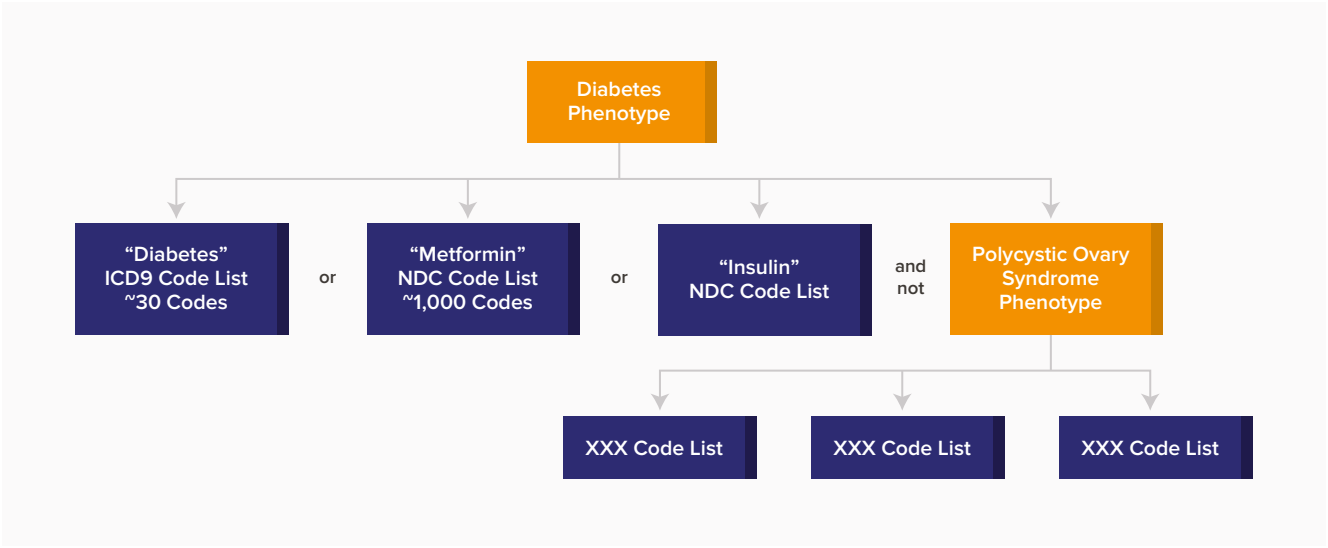


Figure 3: Building a diabetes phenotype



However, the use of phenotype vectors is philosophically very different from a traditional SAS-based Boolean logic approach in that

- The phenotype defines 'real-world' observations/conditions such as 'has diabetes' independently of any dataset or data model. These conditions can then be recursively combined to create new, more nuanced phenotypes. Once defined, these atomic and complex phenotype definitions can be ported across datasets.
- Phenotype definitions can be used both for record selection (inclusion/exclusion criteria) and for dimension definition for the phenotype vectors.

Figure 3 shows a simple example of building a diabetes phenotype through a combination of code lists, and referencing a separate phenotype for polycystic ovary syndrome. In this case, it may also include the prescription of metformin or insulin, hence the need to exclude such events as an indication of diabetes.

Vectors are thus the raw material of generalized data science, with phenotypes providing dimensional definition to enable the conversion of RWD to vectors. As such, phenotype vectors are the raw material of RWD-based data science. A library of such phenotype definitions provides the core templates for both data selection (through use as inclusion and exclusion criteria) and for vector production (through use as dimension definitions).

Developing a phenotype execution engine

Completing the picture requires systems, such as QuintilesIMS E360™, that allow data scientists to create and share phenotype definitions and then execute those phenotype definitions against large datasets, both to

1. Rapidly cut data from databases using phenotypes as inclusion/exclusion criteria
2. Build patient vectors for the selected data using phenotypes as dimension definitions

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Figure 4: Using phenotype definitions to build inclusion/exclusion criteria

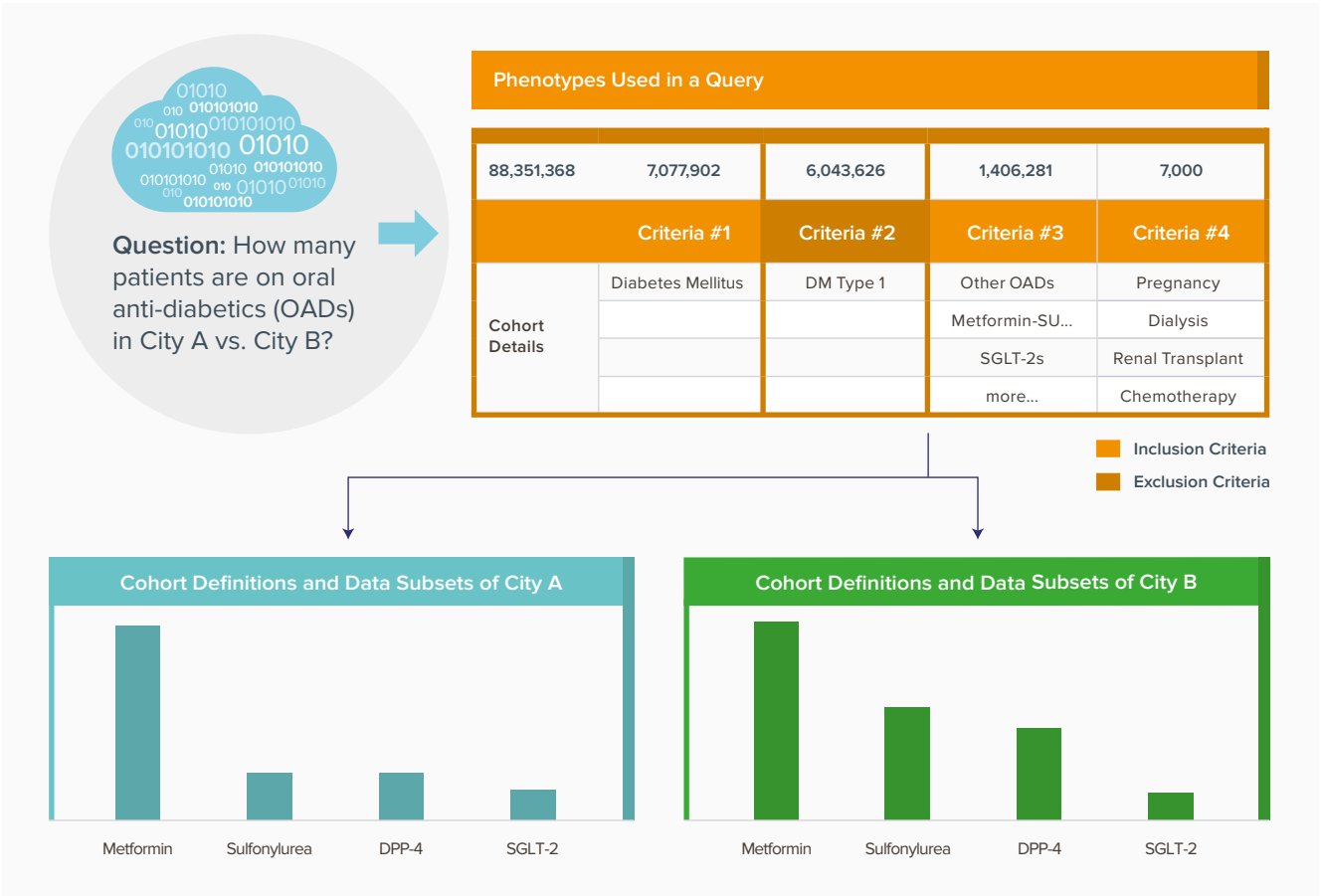

Figure 4 depicts the use of database-independent phenotype definitions to build inclusion and exclusion criteria. These cohort definitions can be applied across multiple-source RWD databases to produce data subsets for subsequent data science-based research.

However, at this point the data is not research-ready, being still notionally structured in its native format or a Common Data Model such as OMOP. Figure 4 also shows the second stage of processing. This again uses the same library of database-independent phenotype definitions but this time to define vector dimensions. Once the real-world data subsets are passed through this process, they are converted to a research -ready vector format for use as input to data science routines.

Achieving rapid, high-value insight generation

As demand for data science in healthcare continues to escalate, there is a growing need for solutions to address a critical shortfall in the expertise required to derive the maximum value from RWD. Data scientists have a rare combination of skills in advanced statistics and computer science. Paradoxically, however, they spend the greater part of their time on basic data wrangling – driven by the lack of industrialized tools to transform native data formats into the vector-based format required by the mathematics underlying data science theory.

Within RWD-based data science, phenotypes offer a fundamental atomic building block that enables both data subset creation and vector creation. Delivering research-ready data, they allow companies to significantly expand the capacity of their skilled resources, increase the output of data science and drive additional productivity gains through dataset portability. This is achieved by

1. Separating data wrangling activities and algorithmic development, and positioning phenotype vectors as the pivot between them
2. Building a strong phenotype definition library that can be ported across source datasets, enabling greater value to be extracted from data science algorithms
3. Developing algorithms that act at phenotype level, not against source RWD
4. Deploying systems and processes that can efficiently execute phenotype definitions for converting RWD to phenotypical vectors to inform faster derivation of insights

As companies increasingly seek to leverage RWD to fuel research and near real-time insights across the spectrum of drug development and commercialization, taking steps to close their skills gap using phenotype vectors could be the answer to more rapid, high-value insight generation.

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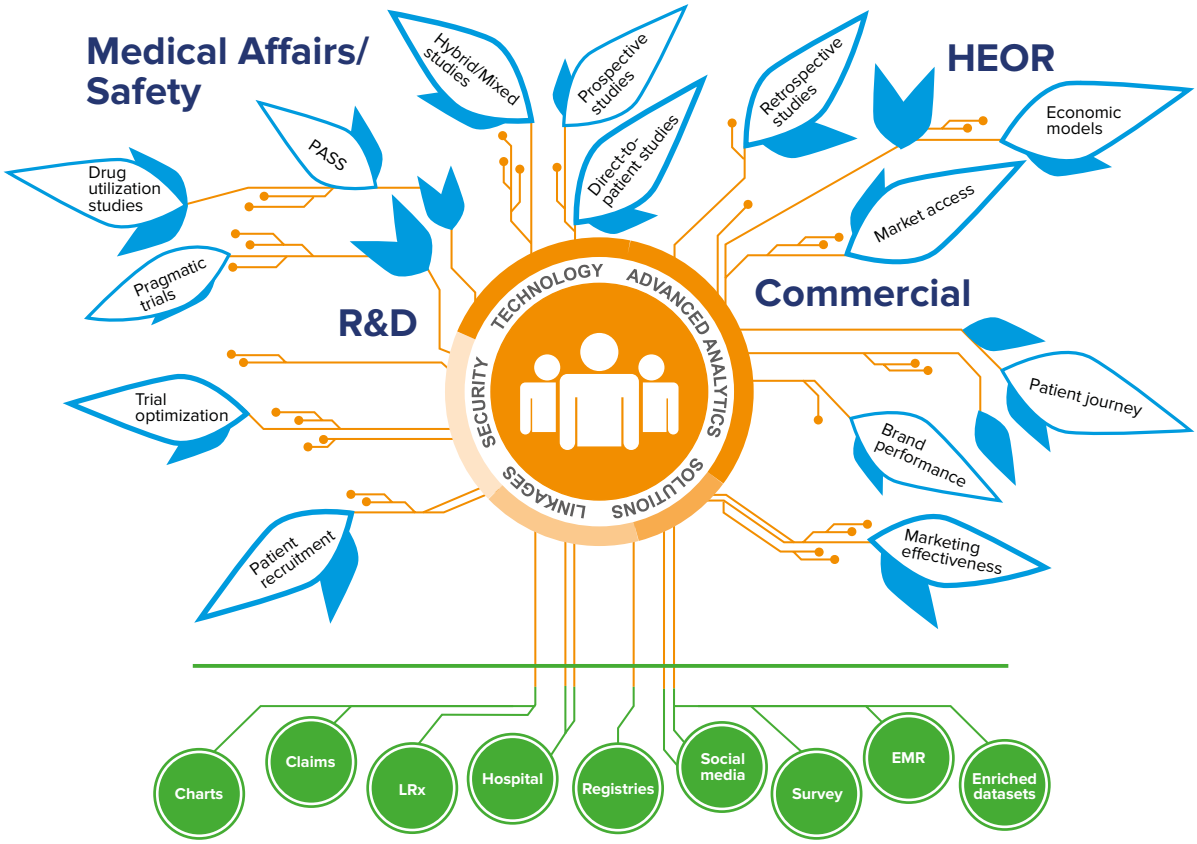
Breaking new ground with RWE



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A better, faster trial

As manufacturers face the increasing challenges of ever more costly and complex clinical development, the combination of more accessible real-world data (RWD) and advanced analytics is demonstrating growing potential as a powerful enabler of significant and valuable efficiencies. Signaling a new era of accelerated, evidence-informed trial design, planning and operations, its innovative use combined with experiential data is now driving opportunities to transform every aspect of the drug and clinical development lifecycle.

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The next generation of clinical development will be powered by real-world evidence

Biopharmaceutical and Contract Research Organizations (CROs) are bringing a wide array of medical products to market in increasingly sophisticated and innovative ways. However, the growing specificity and complexity of modern clinical development presents challenges. The statistics are telling: 60% of clinical trials have protocol amendments;[1] nearly 80% of trials are delayed by enrollment;[2] almost half of trial sites are unable to reach enrollment targets; and patient dropout remains very high.[3]

Many organizations are embracing insights from real-world data (RWD) and its increasing merit in clinical development planning and operations. Innovations in analytics, such as predictive modeling, and new visualization tools now allow organizations to leverage healthcare data on a global scale. Through these approaches, they can better understand the risks, inform clinical program decisions, predict success, and identify avenues to control time and cost.

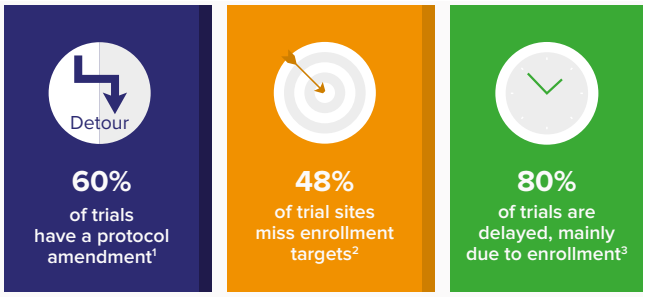
Transforming clinical development using RWD and advanced analytics

The use of novel applications of RWD, statistical analysis, machine learning and predictive modeling creates potential to improve a clinical development and operations process that still relies heavily on key opinion leaders (KOLs), historical experience and assumptions. It can serve to validate or refute these historical inputs with evidence about patient journeys, standards of care, disease progression and drug access, to bolster understanding and reduce the risk of protocols emerging with inherent flaws.

This article considers three major focus areas where RWD coupled with experiential data can change the nature of clinical development, and outlines an approach for enabling the relevant capabilities. These areas are

1. **Accelerated site identification and activation** using new models and analytics that quickly tier high-performing sites and investigators based on quality, prior performance, participation and delivery of data collected from previous studies
2. **Evidence-driven design** that lowers the risk of protocol and execution amendments by leveraging real-world evidence (RWE) to support decision making across clinical design and planning
3. **Faster patient access, recruitment and engagement** using tools that enable site teams to act on patient availability and access data that informs discussions and strategies for engagement, enrollment and referrals

Clinical development challenges



1. Accelerated site identification and activation

Finding patients tied to investigators and medical practices is fast becoming the norm in the US. Many vendors offer access to claims and electronic medical records (EMR) data, albeit with wide ranging breadth, scale and potential biases. Such access and the application of claims, prescription and hospital data have been instrumental in the identification of sites with appropriate patient populations.

Of course, the fact that patients with the right diagnoses can be tied to particular sites does not mean they are appropriate for the trial or that the associated investigators will perform as required. Additional insights are required about the standard of care and investigator capabilities in terms of quality and performance. These insights come from advanced models that associate therapeutic standard of care and past performance data to further define patient cohorts and the likelihood of success for the associated investigators.

The following two examples illustrate how these advanced insights, combined with historical clinical trial experience, can be used to glean insights into cohort characteristics and investigator performance.

Example 1: Determining site-specific patient cohort characteristics (Crohn's disease)
It is important to understand that site-level data can be misleading. Further, while patients are usually located based on diagnosis they are far from uniform, comprising different ethnic groups, comorbidities, standards of care and lines of therapy. The ability to distinguish at this level is invaluable but requires more than just claims and EMR data.

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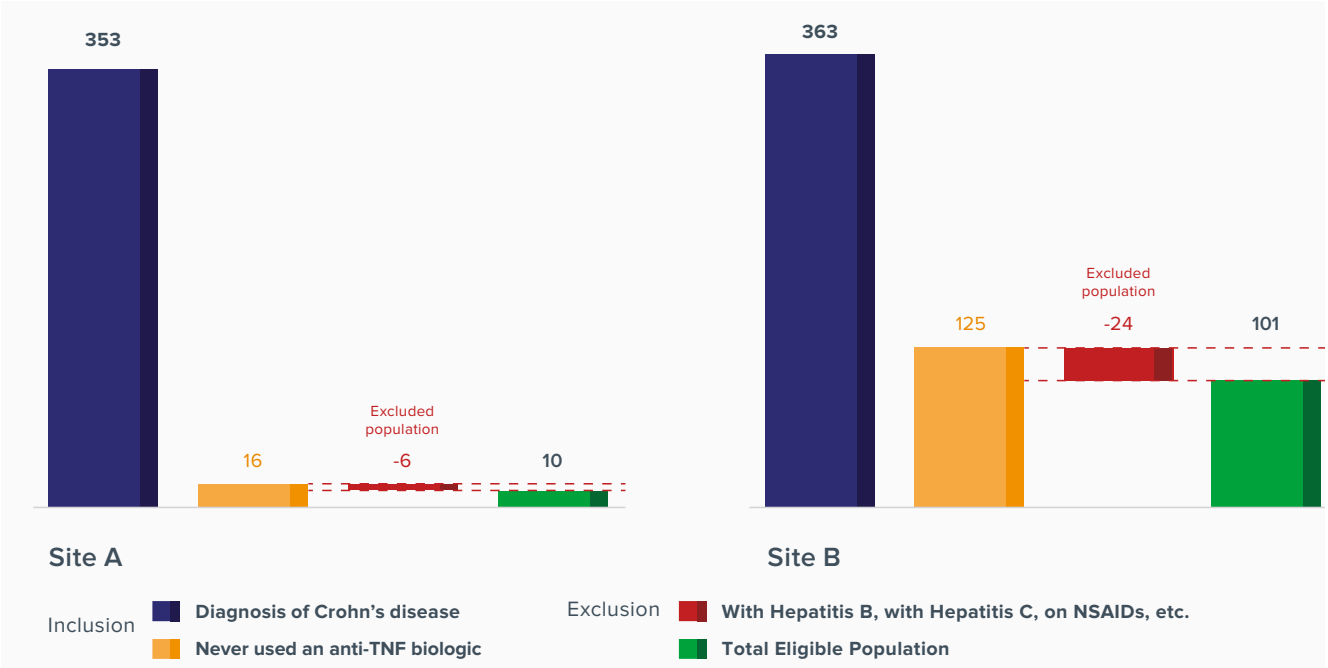
> "Innovations in analytics, such as predictive modeling, and new visualization tools allow organizations to leverage healthcare data on a global scale"

Figure 1: Using advanced insights to size patient cohorts at site level



Two sites have similar originating cohort sizes for diagnosis but dramatically different patient populations based on standard of care. In this example, Site A would be unable to enroll based on the lack of biologic-naïve patients as evidenced by the use of anti-TNF treatment.

The addition of prescription, lab and demographic data as well as other potential sources can enable critical insight at both the site and patient level.

Figure 1 illustrates two investigator sites. While both have more than 350 patients diagnosed with Crohn's disease, the respective cohorts have been exposed to a very different standard of care. Site A clearly engaged anti-TNF biologics earlier, meaning that only ~5% of their Crohn's patients are biologic-naïve vs. ~34% at Site B.

Thus, while each site has a large number of Crohn's diagnosed patients, initiating both centers would create risk of delays if the search was for patients who have never used a biologic. In that case, Site B would be the choice as Site A would struggle to recruit patients into screening.

It is therefore vital to be able to distinguish cohorts at the site level. Next-generation site identification can provide this view by pulling together the composite RWD to delineate their respective patient populations.

Example 2: Expanding the pool of high quality investigators (ulcerative colitis)

Enabling compliant and successful trials requires more than just identifying investigators with appropriate patient cohorts. It is also critical to ensure that the investigator and clinical research associate (CRA) are fully engaged and committed to the study and its outcome. In terms of performance, delivery and quality, not all investigators and CRAs are equal. The next generation of feasibility analytics can both assess past performance of sites and investigators and identify predictive traits to determine their likelihood of success for future trials.

RWD can tie patient cohorts to sites and investigators but commercial datasets cannot provide insights into past investigator performance. Such knowlege is built on decades of investigator performance data drawn from the execution of prior clinical trials. This data can be used to study protocol deviations as a measure of quality assurance, enrollment rates as a measure of performance, and the successful completion of trials as a measure of delivery – appended to hundreds of thousands of investigators globally. These tiers allow sites and investigators to be quickly assessed to ensure a continued focus on those that are known and high performing.

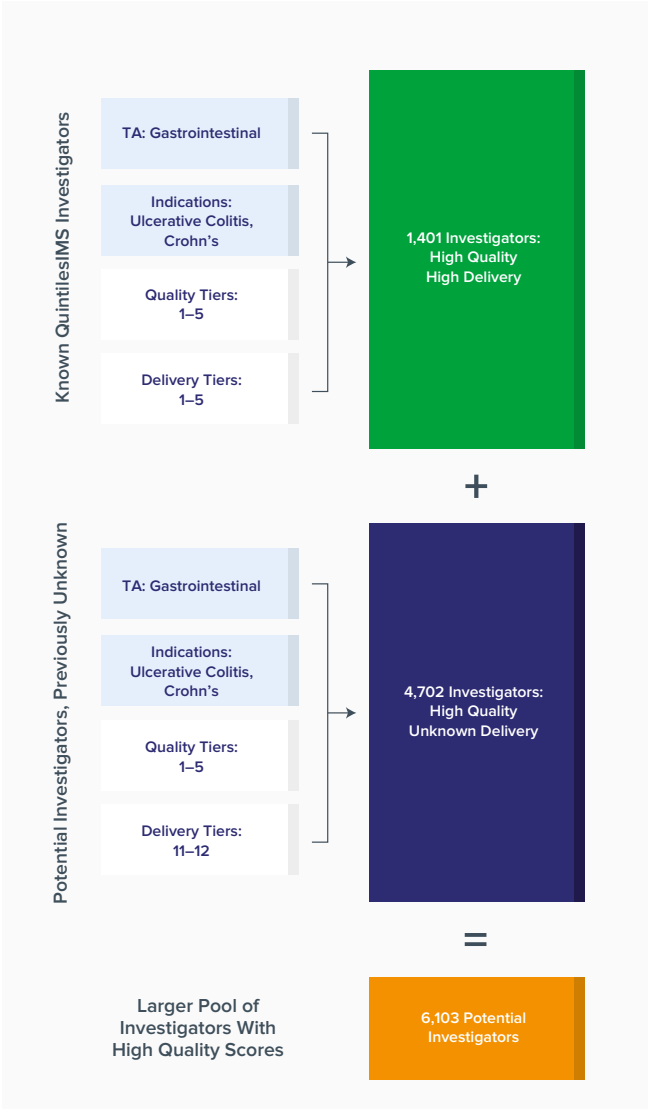
To date, QuintilesIMS has developed four such tier models

1. **Quality.** Assessed risk for quality issues based on prior history in clinical studies
2. **Performance.** How investigators have performed on prior studies based on start-up times, enrollment and other metrics
3. **Participation.** Whether investigators are appropriate for consideration
4. **Delivery.** How to differentiate investigators based on ability to perform on clinical trials, combined with appropriateness for participation

The application of these models has dramatically improved the identification of top-performing investigators, with particularly significant benefits for highly competitive studies.

Figure 2 shows a cadre of over 1,400 investigators who have strong Quality and Delivery Tiers (1–5) based on clear evidence of prior performance and quality, and a history of delivering on clinical research. In the case of large or very competitive studies, where a higher number of investigators is required to enable the trial, the potential pool can be extended by modifying the criteria to include investigators

Figure 2: Application of Quality and Delivery tier models to increase investigator pool



with high quality scores and those for whom there is insufficient data to derive a score. These are investigators who have engaged in trials with a high level of quality but may not have fully completed a study or met the other criteria to receive a complete delivery score. They are likely to be good, potentially only requiring additional CRA support, and can serve to substantially increase the overall investigator pool for consideration.

The example shown in Figure 2 demonstrates how this approach enabled the addition of 4,700 investigators, bringing the total to a robust pool of more than 6,000 with proven or strong inferences for quality and delivery.

2. Evidence-driven design

Typically, CROs are given access to study protocols only after completion by the sponsor, with the Target Product Profile (TPP) and Clinical Development Plan (CDP) developed in isolation using KOLs, disease experts and historical experience in the therapeutic area.

Product strategy and clinical development have always been considered the organizational 'crown jewels'. Nevertheless, 60% of trials still require protocol amendments.[1]

How can inherent flaws in protocols that make it through the design stage be prevented? The next generation of clinical development enables sponsors to validate opinions, assumptions and historical experience by using RWD to back-test assumptions made in the CDP. This can directly translate into better TPPs, better CDPs, and protocols that have had their key hypotheses tested using RWD. Sponsors can thus feel confident that

- **Study objectives are fully aligned** to the outcomes and endpoints of the study
- **Study procedures have the lowest possible patient burden** by removing non-core procedures and decreasing the overall number of procedures where possible
- **Enrollment strategies have been back-tested** with similar studies and account for patient prevalence, standard of care and geographic distributions of sites, investigators and patients

Further, sponsors can calculate the probability of technical success, likelihood of approval and even the net present value (NPV) of the asset to inform major decisions prior to huge capital outlays for studies.

Developing the right CDP requires a detailed understanding of the disease, patient populations and addressable market for the drug, but also a deep knowledge of the required components of the study. What kinds of studies and endpoints are required to be differentiated in the market? What will these product differentiations mean for market value? How will the unique aspects of the drug affect the timeline and cost of the studies? Does the value of being unique in the market outweigh the additional development costs? Will it lower the probability of success for the trials and the overall CDP?

The next-generation approach uses clinical, commercial and performance data to challenge the assumptions of KOLs through the application of advanced modeling techniques. This involves creating various clinical development planning scenarios based on a variety of assumptions and a wide range of development approaches and options. For example, decisions around various endpoints impact the cost and timeline of development – so each scenario is modeled for impact against the requirements for cost, timeline and feasibility.

Scenario development

For each scenario, the NPV of the asset is calculated based on the anticipated development costs associated with the CDP assumptions and the likelihood of approval and market access based on historical precedents. The risks associated with each of the decisions and assumptions are identified and the probability of success calculated based on similar trial strategies and constructs. This now extends far beyond just influencing the execution of a clinical protocol to the key decisions that have to be made about the strategy of an overall program.

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Figure 3: Evaluating clinical development scenarios

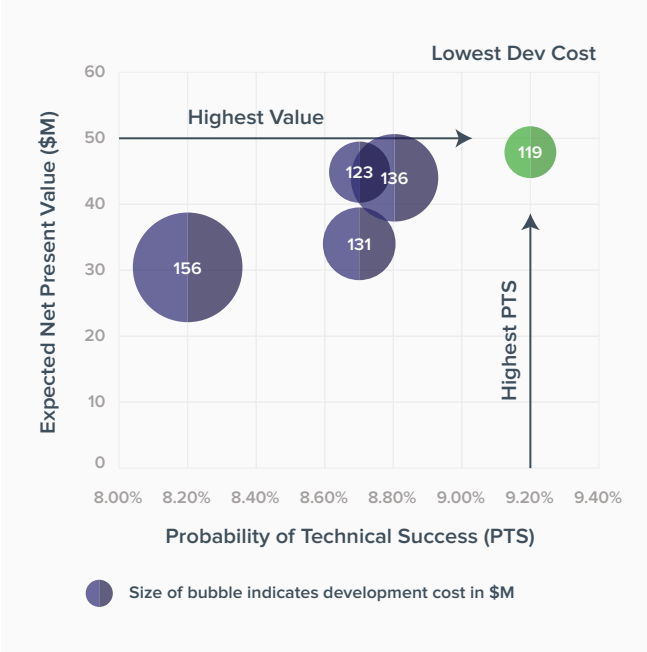


Figure 3 plots five unique clinical development scenarios showing the expected cost of development, the probability of technical success for the CDP and the expected NPV of the asset. These calculations are then plotted for discussion. The green ball represents a hypothetical scenario where the probability of technical success is the greatest, the NPV is the highest and the development costs are the lowest.

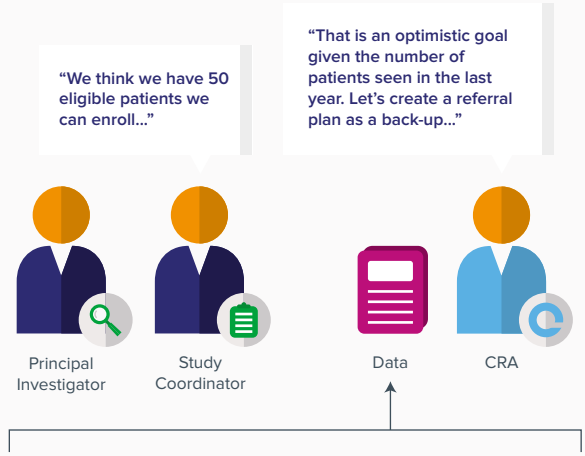
However, experience shows that most of the time, trade-offs of these measures are required for best results. For example, the sponsor might be willing to accept higher development costs if it means a more differentiated product with a higher NPV in the market.

3. Accelerating patient recruitment and engagement

RWD is profoundly changing the way clinical trial sites are initiated in terms of patient recruitment and engagement. It is also advancing the interaction between the CRA and site investigators. Setting enrollment targets, patient targeting and expanding patient access are all opportunities to more effectively plan and manage trials after the site has been initiated.

Highly competitive trials in particular can directly benefit from these solutions to maximize the productivity of a site, set fact-based and pragmatic goals, and enable alternate approaches when patient recruitment and enrollment fail to meet expectations. RWD can enable greater proactivity with sites to identify issues faster and ensure that mitigation plans are in place before an issue even exists.

Figure 4: Recruitment commitment call or site initiation visit



Illustrative Example

Physician	Institution	Est. # of Patients
Dr. Jones	ABC Hospital	15
Dr. Smith	DEF Hospital	<5
Dr. Perry	GHI Practice	45

Three major categories of capabilities have been identified where RWD can be used to deliver this value to the study, the sites, the investigators and the CRAs

1. **Predict**. *Enabling predictability in site enrollment.* Using RWD and site-specific data about existing and available patient populations can inform the recruitment action plan based on facts and data about the investigator and practice. This will eliminate common errors tied to over-promising and under-delivering patients to the study. Figure 4 shows a sample vignette between the Principal Investigator, Study Coordinator and CRA that illustrates how data can be used to validate or refute site claims for enrollment before a plan is completed and the targets obligated. Over-estimating site enrollment is one of the most common root causes for enrollment delays which could be better addressed through this data.
2. **Prevent**. *Creating site enrollment trigger reports.* Another common site issue is investigators who are not actively engaged and miss opportunities to enroll presenting patients, perhaps due to competing studies or lack of interest in the trial. Having periodic (weekly or monthly) snapshots of site-level patient activity is an indispensable tool that can identify these situations early in the process rather than allowing sites to slide slowly into a deficit that may not be recoverable.

> "RWD can enable greater proactivity with sites to identify issues faster and ensure that mitigation plans are in place before an issue even exists"

Figure 5: Generating critical visibility through trigger reports

Illustrative Example

Dr. Jones, ABC Hospital	Wk. 1	Wk. 2	Wk. 3
Potential Patients (per report)	0	3	5
Actual Screened Patients	0	0	1

Figure 5 shows a hypothetical example of trigger reports in practice, allowing CRAs to come on site knowing how many qualifying patients the investigator has seen vs. enrolled. This will ensure a more productive CRA visit focused on understanding the situation and implementing remediation plans.

3. **Boost**. *Building patient referral site networks.* It is essential to have alternate plans in place where patient enrollment issues persist. Another RWD-driven capability enables insights into nearby providers with eligible patients, referral patterns and institutional relationships. In situations where an initiated investigator under-enrolls, the Boost capability can bring insights around patient densities and other investigators or physicians who could be leveraged to build a referral network or engage sub-investigators who can contribute patients to the study. This could provide tremendous value to the study by avoiding a need to move immediately to costly site expansion.

Driving the next generation of clinical development

Innovative new methods are rapidly emerging to create and apply data-driven insights across the entire drug and clinical development lifecycle. The combination of historic clinical trial and investigator performance data, and global RWD enables remarkable insights that directly address some of the most important issues in clinical development. As the adoption of this approach expands, capturing the value will be a key step to demonstrating definitive proof points for reducing protocol amendments, improving site performance and productivity, and engaging investigators and patients. Together, these accomplishments will enable and empower a new era of clinical development.

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[1] Tufts CSDD Impact Report, 2016, January/February; 18(1)

[2] InfoWorld, "Bots Will Change Workplace Research Sooner Than You Think," Feb. 1, 2017 Available at: http://www.infoworld.com/article/3163148/business-intelligence/bots-will-change-workplace-research-sooner-than-you-think.html Accessed 24 March 2017

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Applications for the next generation of clinical development with late phase research

In addition to clinical trials, key applications for the next generation of clinical development are **non-interventional studies (NIS)** and **observational studies**. These also benefit from a more comprehensive understanding of the standard of care, disease prevalence, and patient pathways, in order to increase predictability, reduce timelines and maximize the value of the treatment or intervention under study.

As discussed in the main article, **evidence-driven design** can inform and shape real-world studies through a greater understanding of their requisite components. Similar to randomized clinical trials (RCTs), the impact of inclusion/exclusion criteria, recruitment strategies and enrollment planning are all key considerations for NIS.

Palliative care is one area where RCTs are often insufficient or inappropriate. In this case, studying variations in access to care, the use of treatments and interventions, and the quality of care delivered most often requires the use of observational methods.

The next generation of clinical development is well suited to inform the planning of these studies, yielding insights into standards of care, adherence, and the duration of medication use. When paired with qualitative feasibility information from patients and/or their clinicians (e.g., pain and quality of life), these insights can further refine and shape the design of a fit-for-purpose study. In palliative care, they can help studies avoid protocol deviations because they better reflect the real-world circumstances. Being able to view this level of detail at the investigator, site and country level provides critical guidance for observational study designs.

A more complete picture of health

Randomized clinical trials (RCTs) often run to hundreds of millions of dollars and dramatically impact the end price of the product. Pragmatic randomized clinical trials (pRCTs) can deliver robust, actionable information at costs that are at least 50% lower than classical RCTs. This article looks closely at pRCTs, their benefits and their value in driving new ways to generate evidence in this evolving, cost-conscious environment.

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Enriching evidence through pragmatic randomized clinical trials (pRCTs)

The 21st Century Cures Act of 2016 calls upon the US FDA to evaluate the use of real-world evidence (RWE) to support approval of new indications for previously approved drugs and to support or satisfy post-approval study requirements (see news article on page 44). The idea of leveraging RWE for expanded indications is a game-changing notion for many, but especially for classical clinical trialists.

Randomized clinical trials (RCTs) have long been held up as the leading – and indeed only – way to generate clinical evidence that is sufficiently robust for market authorization of label expansions. They are also considered the best source of information for developing clinical guidelines and evaluating how well treatments work, for which patients, in what situations, and at what cost. But they have their limitations.

Classical RCTs are narrowly defined and expensive

When new products are being developed, they are tested using RCTs – highly controlled and rigorously monitored conditions with a thorough adjudication of events to ensure accurate and reliable results. RCTs focus on narrowly defined groups of patients who are treated according to a randomization schedule and clinically assessed in optimal settings by experts. New treatments are compared to placebos. And all at considerable expense. An RCT can cost tens, even hundreds, of millions of dollars and may take years to complete.

However, once a product is on the market and used more broadly, the information obtained from these artificial settings and homogenous patients studied prior to market authorization is of little use in predicting a) how well the treatment will perform in the diverse patients encountered in everyday clinical settings and b) how its risks and benefits compare to current treatments (that were not in the RCT), including less expensive alternatives.

Pragmatic clinical trials: Randomization with real-world data

The limitations of RCTs have spurred interest in pragmatic randomized clinical trials (pRCTs). These retain some elements of the classical RCT but offer more broadly applicable results at much lower cost. In a pRCT, once physicians and patients agree to participate, treatment is assigned at random according to the protocol, rather than by a clinical evaluation of each patient. Follow-up visits and data collection occur as they would in everyday medical interactions.

As a result, pRCTs offer unique insight into the effectiveness (rather than the efficacy) of a treatment in routine clinical practice; they are designed to reflect real-world variations between patients. Often, pRCTs also include comparisons to one or more treatments that are used in a given region, rather than to placebos. The results thus reflect the consequences of real-world practice, not the artificial constraints of trial environments (see Figure 1). In real-world practice, for example, physicians may choose to use a treatment at a lower dose than recommended in the package insert, or patients may decide to take a medication more or less frequently than prescribed, according to their tolerance and perceived benefit.

Unlike pure observational studies, pRCTs use randomization to eliminate much of the selection bias that can occur when physicians and patients decide who receives a new treatment. For example, without randomization, patients who have failed on other treatments and choose the new drug as a last resort may be over-represented in the treatment group of interest. Therefore, they are more likely to experience poor outcomes simply because of the selection factors that drove them to try the new drug.

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Figure 1: Pragmatic trials blend RCTs and non-interventional or observational studies by offering randomization in a real-world setting

Attribute	Classical RCTs	Pragmatic RCTs	Non-Interventional and Observational Studies
Purpose	New molecular entity (NME), label expansion	Label expansion? RWE for clinicians, payers and patients	
Randomized	Yes	Yes	No
Study Population	Homogeneous	Heterogeneous	
Comparator	Placebo	Single marketed drug or 'standard of care'	
Endpoints	May include intermediate endpoints	Endpoints typically encountered in clinical care	
Follow-up	Mandated testing and visit schedule	Testing and care provided in natural settings	
Data Monitoring	Heavy	Light	

Significant advantages

The potential benefits of pRCTs in evaluating effectiveness and safety are considerable. They can serve to investigate clinical issues of importance to multiple stakeholders, including patients, providers and regulators; they can help providers make better treatment choices; and they can support policy-makers and payers in a variety of settings and healthcare systems. Pharmaceutical companies can, of course, also leverage them to answer market access questions definitively – and answer more of them, given the lower costs involved. The bottom line is a holistically better approach to addressing patient and system needs.

The caveats

Even with their lighter touch and use of naturalistic approaches, pRCTs are not without challenges, and there are trade-offs to be made when considering these study designs (see Figure 2).

- Unlike classical RCTs, which involve blinded treatments that are provided directly by the sponsor, pRCTs most often study marketed products that patients have to acquire themselves. This creates a need to address possible co-payment differences between the treatment of interest and the comparators, since randomization may assign a new treatment that has a much higher co-payment requirement. Patients should not suffer financial penalties for participating in a research study.
- Dropout rates may be higher with pRCTs if patients, being aware of which treatment they have been allocated to use, do not receive the treatment of interest.
- Use of standard of care as the comparator in pRCTs can make it more difficult to detect real differences between treatments even as it makes the findings useful for decision makers. This is because the true differences between two active treatments are often smaller than between an experimental treatment and placebo. Further, the more comparators of interest, the larger the study needs to be in order to detect meaningful differences between treatments.

It should also be noted that increased access to digital health data is making the pRCT design increasingly attractive. Such data offers inexpensive yet consistent ways to follow patients via electronic health records (EHR), prescription claims and other real-world health data sources (see article on wearables on page 4).
These existing data sources can be supplemented with targeted clinician- and patient-reported outcomes to develop a fuller picture of how well treatments work. Ultimately, supplementing pRCTs with the growing availability of digital health data allows investigators to evaluate the safety, effectiveness and benefits of a marketed treatment without the cost and complexity of an RCT.

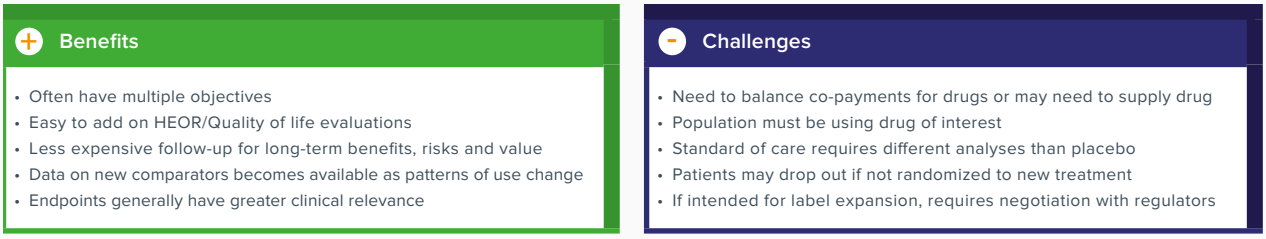
Growing interest

As the use of pRCTs expands and the quality and value of this approach becomes clearer, these trials will become an increasingly important tool for developing clinical guidelines and supporting value-based contracts for market access. Regulators have already expressed interest in using pRCTs for label expansions and post-marketing safety assessments. In a 2013 memo, Dr. Robert Temple, Deputy Director for Clinical Science at the FDA's Center for Drug Evaluation and Research (CDER) noted concerns about drug development studies that are "not representative of the people who will use the drug if it is approved," and referenced a call for "pragmatic" trials, which are more inclusive of the broader patient population.[1]

Examples in practice

Although pRCTs are a relatively new concept, examples already exist of how they can generate robust evidence at a much lower cost than classical RCTs. The ADAPTABLE study in the USA and the Salford Lung Study in the UK are two cases in point.

Figure 2: There are several trade-offs when considering pragmatic study designs



> "As the use of pRCTs expands and the quality and value of this approach becomes clearer, these trials will become an increasingly important tool for developing clinical guidelines and supporting value-based contracts for market access"

1. ADAPTABLE trial

PCORnet, the National Patient-Centered Clinical Research Network, recently funded a three-year pRCT called ADAPTABLE to determine whether low dose daily aspirin is more effective than higher doses of the drug in preventing heart attacks and strokes in high-risk patients.[2] A unique feature of this 20,000 person study is that follow-up will be performed by linking existing records, instead of using primary data collection. **The budget for a classical cardiovascular outcomes trial of similar size would be hundreds of millions of dollars, whereas this study is expected to cost less than $20M.**

2. Salford Lung Study

The Salford Lung Study in the UK used Electronic Health Records (EHR) and National Health Service (NHS) data to recruit and randomize treatments for 2,800 patients to examine the safety and effectiveness of a new drug for COPD in a real-world clinical setting.[3] Commencing prior to the drug's approval, the study was specifically designed to evaluate heterogeneous patients, including those who would be omitted from a traditional RCT (e.g., patients with comorbidities). The result is a clearer picture of how everyday patients interact with healthcare and use their medicines. Non-blinded treatments were provided through local pharmacies and patient follow-up was conducted through EHR and other linked data. The evidence generated from this study was used to satisfy regulatory commitments with regard to safety surveillance and demonstrate effectiveness and value for payers.

At this stage, pRCTs are still novel and there is no guarantee that regulators will allow their use as the basis for label expansions. As for any novel endpoint or new study design, companies interested in using pRCTs for label expansion should seek out regulators in advance to discuss the potential benefits of the study design and address any concerns.

A new paradigm for enhanced understanding

While RCTs will always hold an important role in pharmaceutical research, they are not the only option for generating reliable evidence. The industry can no longer sustain an environment that requires billions of dollars to answer individual research questions, particularly in the context of a growing focus on targeting smaller patient populations. As companies look to the next generation of clinical development, they should consider how more efficient study designs, coupled with digital health data, can enhance their ability to understand treatment heterogeneity and patient safety to promote intelligent, affordable and sustainable healthcare.

Pragmatic trials offer strong advantages in studying newly marketed medications and devices where uptake initially may be limited while payers are considering reimbursement or have allowed very restrictive access. These restrictions generally skew initial new product users to a smaller, sicker population than the broader target population for which the product is intended. In these cases, pRCTs can be particularly beneficial when trying to demonstrate the value of a product in a highly competitive market since randomization can minimize many of these biases. In doing so, they produce evidence that is considered more robust than a typical observational study while maintaining the real-world clinical relevance that is so important.

Thus, the benefits of these modernized approaches are too valuable to ignore.

> “The industry can no longer sustain an environment that requires billions of dollars to answer individual research questions, particularly in the context of a growing focus on targeting smaller patient populations”

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[3] Pioneering Salford Lung Study achieves world first. Available at: http://www.manchester.ac.uk/discover/news/pioneering-salford-lung-study-achieves-world-first Accessed 4 April, 2017

Trust, transparency and a turning point for medicine

The pharmaceutical industry is now sharing clinical trial data externally under a number of data release mechanisms for both structured individual patient datasets and clinical reports. This opens up tremendous opportunities for building knowledge, advancing research and strengthening trust through greater transparency. However, it also presents challenges for sustainable scalability, requiring action by multiple stakeholders to ensure that the benefits can be realized.

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Advancing research through responsible data sharing

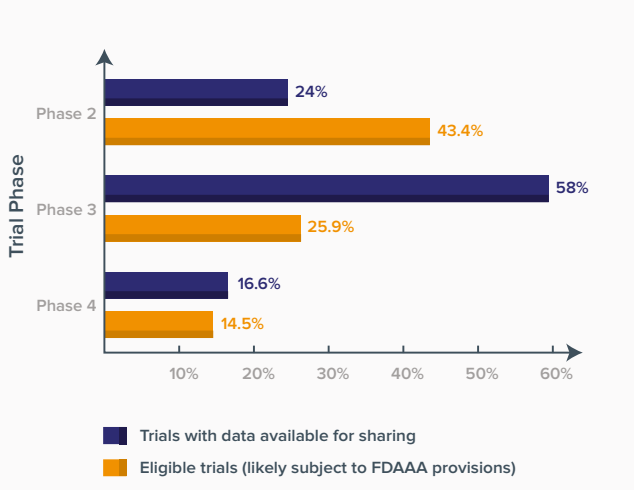
A recent accounting found that data from 3,255 Phase 1 to Phase 4 clinical trials is available for sharing.[1] Although this figure takes into account only the larger trial data-sharing efforts, there is still at least an order of magnitude difference between the number of datasets accessible for sharing and the number of trials conducted.[i] It is early days and sharing mandated by regulators is not yet widespread, leaving many trials for which no data has been made available.

Figure 1 compares trials by phase which have accessible data[i] with those on the clinicaltrials.gov website that are eligible for data sharing within the scope of the FDA Amendments Act (FDAAA).[2] The latter pertains to non-Phase 1 interventional trials of drugs, medical devices or biologics that must be registered on clinicaltrials.gov and where the sponsor is mandated to report basic summary results.

As Figure 1 shows, accessible data is significantly more prevalent for Phase 3 trials, suggesting that this is the type of study that researchers are more likely to demand for secondary analysis – or at least the type that sponsors believe they will demand.

In general, the narrative within the clinical trial data transparency community is that data sharing is going to increase in scope and magnitude over time.

Figure 1: Phase distribution of trial datasets that are shared compared to eligible trials[1,2]



NB: Covers trials that either completed or terminated between 1 January, 2008 and 31 August, 2012. For trials with data available for sharing, n=2487 (excluding Phase 1); for eligible trials n=13,327

Furthermore, it will eventually reach a point where it is the normal way of conducting business and is the default expectation of patients, sponsors, academics, trialists and regulators. The challenges that need to be overcome are

- Scaling up the data-sharing process to make it cost-effective
- Ensuring that the data being shared is useful and used
- Creating appropriate funding models to make clinical trial data sharing the norm for academic trials as well as industry-sponsored trials

Why are sponsors sharing clinical trial data?

A strong case has been made for sharing detailed clinical trial data to truly understand the effectiveness and safety profile of drugs already on the market.[4] However, providing access to this information also brings other multiple recognized benefits, including

- Allowing researchers to replicate the analysis in published studies
- Facilitating novel secondary analysis of individual trial data as well as pooled trial data
- Supporting meta-analysis using individual patient data
- Providing transparency into the decision making of regulators approving new medications or indications
- Offering potential to help improve study designs for different therapeutic areas[ii]
- Making data available for educational purposes and training new analysts and scientists
- Avoiding duplication of studies by reducing the chances of unnecessarily enrolling patients in similar trials and exposing them to risks

These benefits accrue to academic researchers, the trial sponsors themselves, and society as a whole.

What are the drivers for data sharing?

Clinical trial data can be shared under four main scenarios

1. **When sharing is mandated by regulators.** The European Medicines Agency (EMA) has mandated the public sharing of clinical trial reports once it has decided on a submitted procedure, regardless of whether that submission is accepted or denied (EMA Policy 0070).[5] To date, among other regulators, Health Canada has started the consultation process to implement a data-sharing regulation.

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[i] Approximate counts of the number of trials registered on the clinicaltrials.gov website are available at: https://trialstracker.ebmdatalab.net/#/. This is expected to be an undercount based on the exclusions that are implemented in the published methodology (e.g., Phase 1 trials).

[ii] For example, most requests to access clinical trial documents from the European Medicines Agency (EMA) have been from other sponsors[3]

2. **Via Freedom of Information requests.** Individuals or organizations can make Freedom of Information requests to a regulator such as the EMA, which would then release the documents to the requester (EMA Policy 0043).[6] This information is, for practical purposes, a public data release.
3. **Through the ICMJE policy on journal data.** The International Committee of Medical Journal Editors has issued a preliminary policy requiring publication of datasets from published clinical trials.[7] However, this is currently undergoing review based on stakeholder feedback (i.e., academics, industry and civic society). It is not clear where the final version will end in terms of sharing stipulations.
4. **On a voluntary basis.** Many companies (outside the scope of the EMA) are following industry principles around the voluntary sharing of clinical trial data,[8] typically to academic researchers under the terms of a data-sharing agreement.

Regardless of the data-sharing driver, data sharing can be public or non-public as follows

1. **Public data sharing.** Data is made available for anyone, with minimal requirements to access it. There are no constraints on who the users are or what they can do with the data.
2. **Non-public data sharing.** The data users will have constraints in that they must be identified, sign a data-sharing agreement and often must also provide a protocol for how the data will be analyzed.

These different data-sharing mechanisms are shown in Figure 2.

Figure 2: Characteristics of the different data-sharing mechanisms

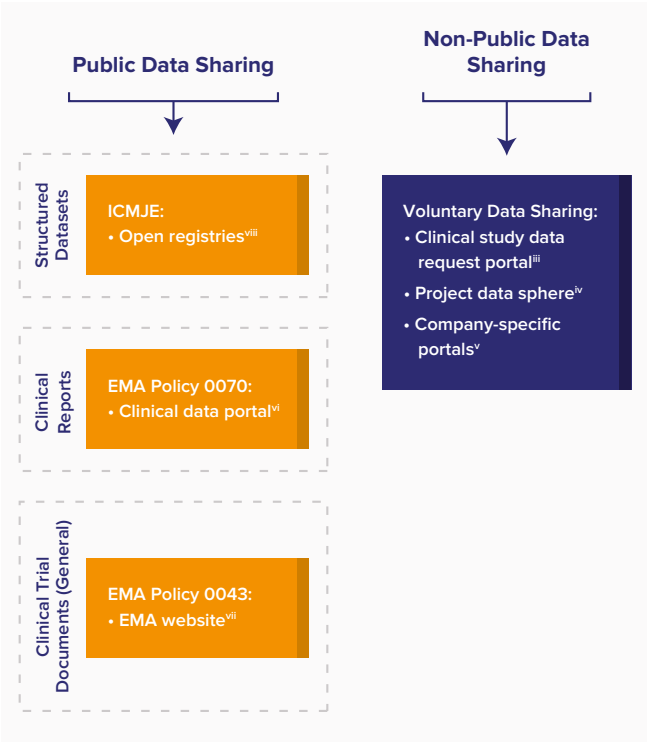
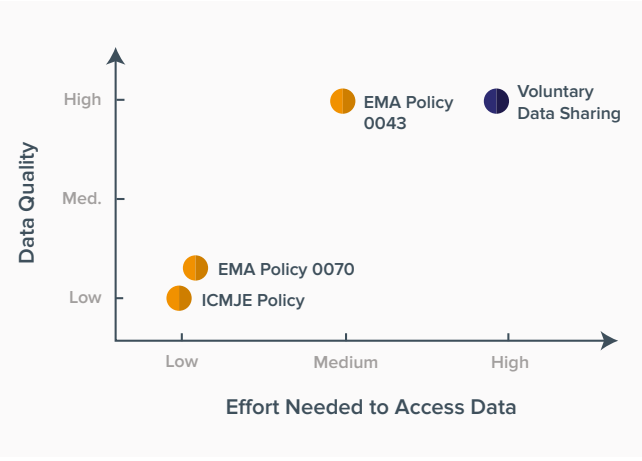


Figure 3: Effort and quality trade-offs under different data-sharing mechanisms



Pros and cons of data-sharing mechanisms

Collectively, these mechanisms address the needs of various stakeholders, from academic researchers to the media, citizen scientists, patients and companies working in the same therapeutic areas. Each has pros and cons in terms of the effort needed to gain access and the quality of the data that will be shared. For example, data for public consumption will have a lower quality due to the amount of anonymization required to protect patient privacy.

The trade-offs between patient privacy protection and data utility are illustrated in Figure 3. Data released under EMA Policy 0070, for instance, requires minimal effort to access (about five minutes to register online) but so far has been heavily anonymized. The information shared on the EMA Clinical Data Portal, therefore, has been subject to extensive redaction of narratives and other patient information.

EMA Policy 0043, on the other hand, requires more effort from the requester to clarify and discuss their request with the EMA, a process that may take many months.[9,10] However, once information is shared, only light anonymization is applied, yielding higher data quality. In this case, most of the narratives in the clinical reports are largely intact – the Agency is generally reluctant to redact information under the umbrella of confidentiality.

Both of these EMA mechanisms share documents only. Requesters wishing to access more detailed, structured datasets must go through one of the voluntary data-sharing portals. These provide extra information but require a commitment to a data-sharing agreement and preparation of an analysis protocol for review by an independent committee. Other restrictions on how the data can be accessed and used may also apply.

[iii] See https://clinicalstudydatarequest.com/
[iv] See https://www.projectdatasphere.org/projectdatasphere/html/home
[v] See http://transparency.efpia.eu/responsible-data-sharing/efpia-clinical-trial-data-portal-gateway
[vi] See https://clinicaldata.ema.europa.eu/web/cdp/home
[vii] Requesters must complete a form on the EMA web site to initiate the process, indicating which documents they require
[viii] For example, see http://datadryad.org/

Challenges in clinical trial data sharing

The pharmaceutical industry has made significant investments in the last two years to develop the infrastructure and expertise to operationalize data-sharing mechanisms. However, certain common challenges must be addressed to allow data sharing to scale. Some of these require active efforts by individual companies while others involve input from multiple stakeholders.

1. **Managing privacy risks.** Sharing clinical trial data raises patient privacy concerns. Any data shared has to be anonymized in a defensible manner to avoid litigation, minimize the chance of investigations by regulators (which may be prompted by patient complaints), and, of course, to respect the trial participants. Sophisticated anonymization capabilities are thus critical for companies to meet regulations globally and manage their liability.

   Privacy risks must be managed across all data release mechanisms. Information on the same trial may be shared publicly or with a researcher who has signed a data-sharing agreement, and can include datasets and/or clinical reports. The availability of trial information in one form should not increase the privacy risks for patients when it is also released in another form. Managing the risks across multiple data releases that may not occur at the same time adds further complexity. For example, the clinical reports may be shared publicly through EMA Policy 0070 today for a trial where the structured datasets were already shared through a portal a year ago. Could one be used to re-identify patients in the other? How should that risk be managed?

   There is a lack of generally accepted standards for what is sufficient anonymization. Multiple guidelines and white papers have been developed by different industry and academic organizations, but these do not always agree on what should be done. Nor are they always consistent with regulatory requirements, such as EMA anonymization guidance.[11] While anonymization is a discipline that has been around for at least four decades, it is new in the context of clinical trials, and stakeholders must learn how to apply known methods to this type of data and the sharing scenarios.

2. **Inconsistency among regulators**. It is not clear whether regulators other than the EMA (e.g., FDA) will require companies to share their clinical trial data. It is also uncertain whether authorities moving in that direction, such as Health Canada, will ensure their requirements are consistent with the EMA and prevailing practices or would necessitate a change in direction. As a practical matter, sponsors will face escalating costs if different agencies impose differing or conflicting anonymization requirements.

3. **Evolving business case for data sharing.** There is limited evidence that clinical trial data is in high demand by academic researchers or that they are able to conduct innovative research with secondary analyses. This makes it difficult to sustain investments in data-sharing mechanisms. However, examples of publications from secondary analyses are starting to emerge. Importantly, sponsors seem seriously committed to data sharing and it is unlikely that the clock will be turned back. Transparency is becoming an expectation and part of doing business.

4. **Reluctance to share academic clinical trial data** The sharing of *academic* clinical trials is still in its infancy, with clinical researchers having mixed views about the benefits of sharing their data. The effort and expertise needed to prepare, document and anonymize data, and the process of managing data-sharing efforts, are seen as an added burden with little return. Furthermore, researchers are concerned about being scooped using their own data if they are made to share it prematurely. Such a state of affairs excludes many trials from the data-sharing ecosystem.

The way forward

In just a short time, life sciences companies and their vendors, as well as academic and civic groups, have been implementing or initiating technology, process and governance changes to address some of these challenges. These changes will allow cost-effective data sharing to be the norm and sustainable in the longer term. Some are under the control of sponsors while others are evolutions in the general data-sharing ecosystem. Several examples are outlined below

- **Natural language processing (NLP) software.** NLP tools have been developed to identify and anonymize patient information in large clinical reports. In the medical domain these have typically been applied to short medical texts such as discharge notes. Scaling to large documents with only high-level standard formatting enables anonymization of full submissions consisting of tens of thousands of pages in a matter of weeks. Currently, many sponsors are manually redacting clinical trial documents for sharing, reading thousands of pages of clinical reports to identify information for removal – a process that is neither efficient nor scalable. The use of NLP software would automate detection, and more companies are starting to adopt this from either open or commercial sources as part of their anonymization practices.
- **Development of anonymization guidelines and standards.** Over the last three years, at least half a dozen guidelines and standards have been developed that are relevant for anonymizing clinical trial data. These are starting to converge in methodology, driven largely by the EMA's guidance and its implementation of Policy 0070. Although standardization takes time to have an impact, it is expected to accelerate adoption of more sophisticated anonymization techniques that balance the protection of patient privacy with ensuring high data utility. Consistent standards will make it easier to automate and scale more of the process of preparing clinical trial datasets and documents.
- **Training on anonymization.** Training and professional certification programs to develop skills in anonymizing clinical trial data are being discussed, and initiatives have recently been launched for health data in general.[ix]

[ix] See https://hitrustalliance.net/hitrust-academy/de-identification-methodology-course/

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These training initiatives will further support the ability to apply advanced methods of anonymization, allowing higher quality data to be shared and alleviating a key concern of many sponsors. Companies that are sharing large amounts of data have also started building the necessary internal expertise by registering their transparency teams for data anonymization courses. They can either apply this expertise to anonymize the data themselves or to manage external vendors providing that service.

- **Earlier anonymization.** Various efforts are underway to anonymize clinical reports during the authoring process rather than on completion. This entails embedding anonymization within the document management systems used in the authoring process, and the automated generation of safety narratives from structured individual patient data. Overall, this is likely a longer-term initiative, requiring significant infrastructure and technology changes as well as adjustments to the entire process of writing and submitting scientific clinical reports. Initial steps have been taken but whether this approach will materially impact the cost and effort to anonymize clinical trial data remains uncertain.

  On the other hand, it is important to keep in mind that as the technology improves for anonymizing clinical reports after they have been developed, there may be less need to perform this anonymization earlier in the process. Nevertheless, training medical writers to prepare clinical reports that are easier to anonymize later is going to be beneficial. This includes, for example, reducing the amount of scanned content in clinical reports and not embedding patient information in graphs.

- **Enhanced data searching functionality.** Meta-search engines are being developed that would allow clinical trial data to be identified across multiple portals and repositories such as Open Trials[x] and Vivli.[xi] This will make it easier for researchers to identify where clinical trial data resides – an important advancement given the multiple data-sharing platforms now being developed which are unlikely to be consolidated into a single platform any time soon. The availability of meta-search engines is expected to aid increased analysis of shared trial data, strengthening the business case for sustaining such sharing efforts.

- **Better consent.** More companies are revising their consent forms to explicitly notify patients about the anonymization and sharing of their data for secondary analysis. While this will not affect current data releases, it will at least ensure that patients are informed in the future. Doing so, and highlighting the benefits of data sharing, supports the social license to use this data for secondary purposes.

- **Increased promotion of data sharing for secondary analysis.** Academic research funders and journals are increasingly active in supporting and promoting clinical trial data-sharing efforts, particularly via funding and creating the career incentives to share academic trials.

Preparing for data sharing

While individual sponsors have roles to play in the above, there are some shorter-term actions that can put them on the path to better, easier data sharing

- **Assess readiness for technology to automate and scale data-sharing practices.** Many technology solutions are making their way into the marketplace and are starting to impact the ability to share data. It is critical to understand how well the organization is prepared for these practices and where the role of new technologies fits in.

- **Participate in cross-industry initiatives.** In order to develop consistent standards and community tools that add value to all stakeholders, sponsors should seek out opportunities to be part of the standards that are being set.

- **Develop internal expertise.** Building internal capabilities in the various areas supporting data sharing, such as anonymization and privacy regulations, will help guide effective investments and actions.

We are entering a new era where access to clinical trial data is becoming the expected norm. This will bring significant benefits to scientists, researchers, sponsors and patients by enhancing public trust in the pharmaceutical industry and contributing to accelerated innovation in the discovery of new medicines.

[x]See http://opentrials.net/, [xi] See http://mrctcenter.org/projects/vivli/

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How real-world insights revived clinical trial recruiting

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For years, clinical researchers have sought to use real-world data (RWD) to help improve trial operations. Significant new innovations are finally turning aspiration into application globally. A recent case study provides an early example of the next generation of RWD-driven research for a rare disease trial in Europe.

Pharmaceutical companies have long searched for ways to improve efficiency as clinical development continues to grow in complexity. Protocol amendments, enrollment delays, shortfalls in recruitment targets and high patient dropouts remain particular challenges in this process. In the past, the data was limited (i.e., mostly US-focused) and cumbersome to interrogate. Now, innovative approaches leveraging integrated datasets, including RWD and advanced analytics alongside deep therapeutic and operational expertise, are creating an exciting opportunity to fuel a new generation of clinical research. The example that follows demonstrates the power of these new approaches to significantly improve patient enrollment in an especially demanding indication.

A better approach to site selection globally

Increasing the precision in trial site selection and optimizing enrollment can drive substantial efficiencies. This is especially true in the case of rare diseases and orphan drugs, where patients can be particularly hard to find. A key challenge is that individuals are not quickly or clearly diagnosed, especially when their condition lacks approved therapies. One sponsor, conducting a study on a rare disease in Europe, encountered a number of factors that were impeding successful recruitment, including

- Limited patient pool
- Challenging inclusion criteria
- Placebo arm in the study design, making participation less attractive for patients and potential investigators

Having reached a point where sites located in three key countries had started to plateau in enrollment, far before reaching their targets, QuintilesIMS began to investigate a data- and analytics-driven approach to identify target patient pools and help accelerate recruitment.

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Methodology

The QuintilesIMS team brought together expertise in advanced data analytics, clinical knowledge of the indication, and clinical operations. Their first step was to evaluate the available data sources and assets, including

- Real-world, anonymous patient reimbursement claims data
- Reference data on relevant specialists and institutional (hospital) affiliation
- Prior performance and quality data
- Information on status and outreach to date

Individually, each available asset offers a slice of insight. Many options exist to integrate and analyze these disparate and disconnected sources of information, often combining different methodologies. Among them is the use of machine learning techniques and predictive modeling, such as QuintilesIMS proprietary dynamic investigator tiering and visualization tools.

In this case, the team chose a mapping visualization tool that combined integrated data with deep local site knowledge and operational experience to visualize comprehensive site potential. Local medical insight was key to structuring the analysis; the team's in-country expertise enabled understanding of local physician coding behaviors, helping them 'see' patient pools by better interpreting reimbursement claims (or payment) data.

As illustrated in Figure 1, QuintilesIMS applied the analytic platform to an approach which was designed to

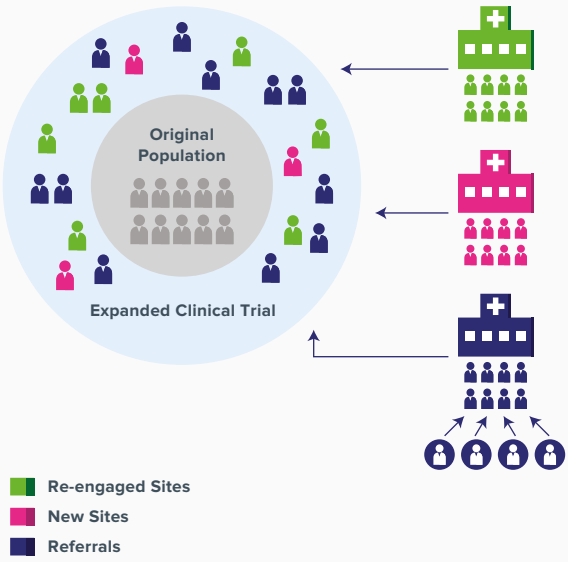
1. Identify additional investigators and sites with target patient pools that could be engaged for participation. This included
   - Finding new, high-quality investigators
   - Clarifying high-potential sites where training and support would mitigate risk around minor quality concerns
   - Re-engaging known sites that were previously unable to participate
2. Evaluate referral opportunities by engaging investigators, using insights from the data on patient pools in the surrounding community

1. Identifying additional investigators and sites

In the case of rare disease populations, patients will often gravitate to treatment centers of excellence. Historically, site selection has relied primarily on investigator performance data, key opinion leader (KOL) perspective, investigator reputation, and site experience. In this instance, a close review of investigator sites that had been excluded, despite strong recruiting potential, revealed the importance of a more robust RWD-driven approach.

Specifically, initial analysis of the country-specific data showed that some of the centers treating the largest population of these patients were not active sites in the study. In certain cases, this was due to lack of interest in the study among individual investigators at the site. In others, it related to prior experience with the sites.

Figure 1: The study identified additional sites and investigators, including referral opportunities



> "This is the next generation of clinical development, where data, advanced analytics, therapeutic expertise and a fresh mindset provide new, innovative solutions to longstanding challenges"

In both cases, RWI validated the imperative to find the right investigator at the site treating these patients and to prioritize selected hospitals for further review and planning.

- **Finding new, high-quality investigators.** One site had been rejected because the known investigator there was deemed unreliable and did not meet quality standards. However, further research showed the site had both a large number of target patients and another expert in this field with a history of high-quality research. The expert in question was, in fact, completely independent with a dedicated study coordinator and infrastructure to support quality clinical research. This new insight transformed the value proposition of working with the site.
- **Clarifying high-potential sites where training and support would mitigate risk.** For other high-potential sites with minor quality concerns, the team recommended additional monitoring, refresher training and staff support to improve the quality of their processes. This mitigated the risk of including those sites in the study, while opening up access to target patients. Such support would also help them improve their clinical research process and infrastructure, and make them viable candidates for future trials.
- **Re-engaging known sites.** Several high-density centers with known investigators were previously unable to participate in the study due to challenges such as limited resources or competing studies. QuintilesIMS data insights reinforced the potential of the site location, and by leveraging its expert team of local site relationship managers it was able to re-gain the interest of investigators who had previously foregone the study.

2. Evaluating referral opportunities to existing sites

Referrals from a treating physician to an investigative site can be a powerful way to increase enrollment. While referrals have great promise, historically they have not been used due to knowledge gaps and financial barriers. Rare diseases are often more conducive to referrals, particularly in cases where patients are actively searching for new treatment options or there are no approved drugs for the specific indication.

The mapping analysis identified several sites that had patient pools at nearby community hospitals, which were not research centers and not part of traditional investigator databases. These presented opportunities to explore referrals as a targeted recruitment tactic with the investigator at the existing sites. One such discussion revealed that the investigator had a relationship with treating specialists at the nearby hospital, whom he agreed to approach about referring patients into the study.

For sites considered unlikely to meet the required quality criteria even with additional support, RWI enabled the development of referral networks to connect physicians with large, eligible patient populations to a nearby study investigator.

Expanded reach and collaborative commitment

Having identified and prioritized optimal sites for the trial, QuintilesIMS worked with the sponsor, global clinical team and local site management staff to ensure the full commitment of the investigators. This included the development of an engagement plan and discussion points to underscore the trial opportunity for the site and guide conversations around its participation.

Ultimately, by analyzing broader datasets, the team was able to expand the reach of the trial to a wider network of investigative sites as well as research-naïve community hospitals, thereby mitigating the challenges that might otherwise have derailed recruiting goals. Further, the approach opened up the opportunity for the sponsor to work with more experts in the field and to access a significant population of patients needing treatment.

While respecting previous relationships and data inputs, QuintilesIMS also leveraged advanced analytics to validate operational decisions and question conventional wisdom, enabling the pharma company to focus on areas that would generate the strongest results. The sponsor team is now confident in meeting the enrollment milestones set through the end of 2017 and has already set its sights on a stretch goal targeted for early 2018.

Paving the way for insights-based clinical development

The trial will continue to be an early case study for implementing a more analytical, data-driven approach to clinical development. As the site expands to the US, the QuintilesIMS team will implement this approach – proactively applying similar strategies and leveraging data analytics for recruiting from the start.

By leveraging the relationships and expertise within its project team and applying advanced data analytics to local market data, QuintilesIMS was able to create an operational strategy that identified and engaged sites with the greatest potential to accelerate recruitment and deliver a higher rate of success.

Taking time to analyze targeted data and combine it with qualitative insights from clinical experts enabled the sponsor to achieve better results and improve the experience for patients and site staff alike.

Similar approaches can enhance studies from their early clinical development days to prospective observational stages and enable greater predictability and speed to evidence. This is the next generation of clinical development, where data, advanced analytics, therapeutic expertise and a fresh mindset provide new, innovative solutions to longstanding challenges.

Market tracking for commercial success using multi-faceted real-world data (RWD)

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Market tracking is a core requirement for understanding product performance. Done well, however, it can go far beyond enlightening the past. With the range of data, analytics and technology now available, it has the power to reveal untapped opportunities for future growth and value creation. These advances are particularly important for oncology, where the surge of recent novel agents and the need to analyze rapidly changing market dynamics make accurate insight all the more important.

Commercial teams face a dizzying array of variables when it comes to market tracking, as they seek to define the unique reports and metrics for monitoring performance ahead of every product launch. Such reports are not static and are ultimately refined on a regular basis in response to changing stakeholder requirements or a new market entrant. The growing dimensions of product performance are a complicating factor that adds to the daunting nature of these tasks. At the same time, the data resources underpinning such reports have become deeper and richer as real-world data (RWD) evolves with greater coverage, flexibility and granularity. While this data evolution can now enable more challenging analyses, the difficulty lies in determining which analyses to prioritize.

The following is a guide to best practice approaches for both defining and refining a market tracking report using RWD. It is particularly helpful when the product in question

- Has **more than one indication** and/or is expected to receive additional indications in the short term, and/or if other therapies in the competitive set have multiple indications
- Has both **oral and infused/injected therapies** within its competitive market basket
- Has **multiple combination regimen therapies** within its competitive market basket
- Makes extensive use of **specialty pharmacies for dispensing** and/or competitive therapies do so
- Is **approved for later lines** of therapy

Foundational data for market tracking

Within oncology, a high degree of specificity is crucial given the complexities associated with multiple lines of therapy. This is especially challenging in less common tumor types with a smaller volume of patients and treatment data compared to larger cancers such as breast, lung and prostate. The following longitudinal patient-level data is of particular value for market tracking in oncology

- **Medical claims data.** Typically pre-adjudicated claims, sourced from CMS-1500/837p professional claims and 837i institutional claims. Key data fields include patient (de-identified), physician, service date, diagnosis code and procedure code.
- **Pharmacy claims.** Typically adjudicated claims, sourced from retail, mail order and specialty pharmacies. Key data fields include patient (de-identified), physician, fill date, pills/days supply and NDC 11 code. Companies can enhance this dataset by providing their own 'raw data', be it from retail, mail order or specialty pharmacy (SP). Data from the SP channel can be especially impactful to supplement any concerns over coverage in this channel.

Significantly, medical and pharmacy claims can be integrated at the patient level, enabling the creation of a full market picture that includes both oral products (typically captured in prescription data) and infused/injected treatments (typically captured in medical claims due to in-office administration requirements). The most advanced pharma companies are also integrating lab, EMR and other sources of data to enrich their level of insight. Patient metrics can be derived from all of these datasets due to the use of patient IDs created during the data encryption process.

Supplementary manufacturer data

Tracking a market also implies the need for metrics based on national volumes, requiring projection of raw sample data to the national level. While not essential, the integration of internal data with external RWD can enhance the national view in a number of ways

- Increase coverage across geographies
- Help refine the projection calculations
- Address 'thin' areas of the dataset depending on the granularity of the data views

Volume trends in the internal data can also help validate those seen in the RWD.

Utilizing the appropriate projection methodology is key to accurately reflecting dynamics in the overall marketplace.

A gold-standard approach is to use sell-in data in terms of units (such as '867' data) and let this data indicate the national 'universe' to which the raw data is projected. While methodologies differ, the approach should reflect current trends in the raw data.

Figure 1 illustrates the value of tracking both raw and projected data. The vertical scales in both charts have been edited to allow for easier visual comparison between the two. The trend lines in each chart show patient volume for diagnosed and treated populations. Those in the left chart are based on raw/unprojected data and show that both patient populations have gradually increased over time and trended similarly.

The chart on the right shows the patient volumes projected to the national population. Here, the diagnosed and treated populations have also gradually increased over time and are significantly larger than the raw volumes in the left chart.

Typically, raw and projected volumes should trend together; a divergence of these lines would be cause for deeper inquiry. Prospectively, these volumes (diagnosed and treated, unprojected and projected) should be tracked to ensure that the trend lines are moving consistently. For further validation, internal raw data can be compared to the unprojected treatment data.

Tracking and analyzing market dynamics

There are a variety of dimensions to track in national-level market reports. Two key components are described below.

1. **Product performance.** Successful market tracking requires analysis of numerous aspects of product performance. However, the following attributes are the most essential to gain insight
   - Patient volumes and share, overall and within indication
   - Share within line of therapy
   - Duration of therapy
   - Inclusion of combination therapy regimens as well as monotherapies

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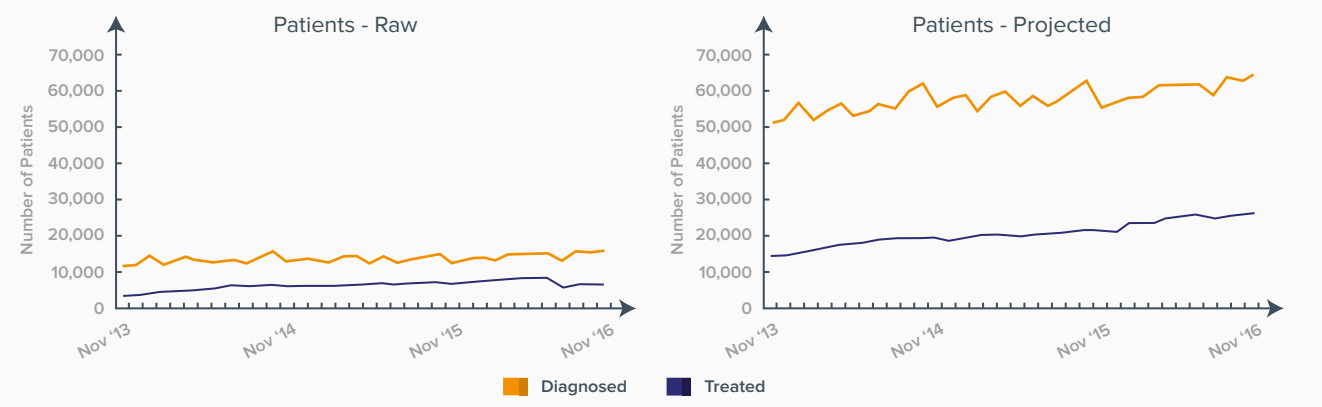
Figure 1: Comparing patient trends in raw vs. projected data



While these attributes may be straightforward, in reality they are frequently in flux and require continual attention. As new studies of new regimens are presented in the medical literature, the business rules used to extract metrics from the datasets need to be updated and refined to generate this new RWE. New FDA approvals may also necessitate changes to the rules as can new drug formulations to appropriately break out these volumes.

2. **Market dynamics.** The essential measures for understanding market dynamics are
   - **Regimen use over time.** Provides insights into patient counts and regimen market share for each reporting time period by indication, line of therapy levels and patient status (new to line or continuing on line)
   - **Product-based use over time.** Provides insights into patient counts and market share at the product, indication and line of therapy levels, and for patient status (new to line or continuing on line)
   - **Demographics.** Provides insights into product usage by line of therapy and indication for physician specialty, patient age and gender, and pay-type metrics
   - **Length of therapy.** Tracks total duration of therapy for patients who have completed each regimen, with insights into duration of therapy during the reporting period based on regimens and line of therapy

   For each of the data views above, trends can be examined in greater detail through the inclusion of key attributes, namely
   - **Tumor type.** Indication A, Indication B, etc.
   - **Line of therapy.** Line 1, Line 2, Line 3+
   - **Patient status.** New, Continuing, Total
   - **Time period.** Monthly, Quarterly, Annual, Rolling 3-month average, etc

Market share analysis by regimen (combination therapy) is frequently the view referenced for tracking market performance as it includes both volume and share for all the key regimens in a market basket. Given the extensive use of combination therapy in many oncology markets, regimen volume and share can be more informative than product volume and share combinations alone.

Best practice pharma clients are extending these analytics from retrospective to projected to predictive. They are not only using reporting to understand their current performance, but also predictive modeling to understand where they need to target their commercial resources to unlock underserved patient populations.

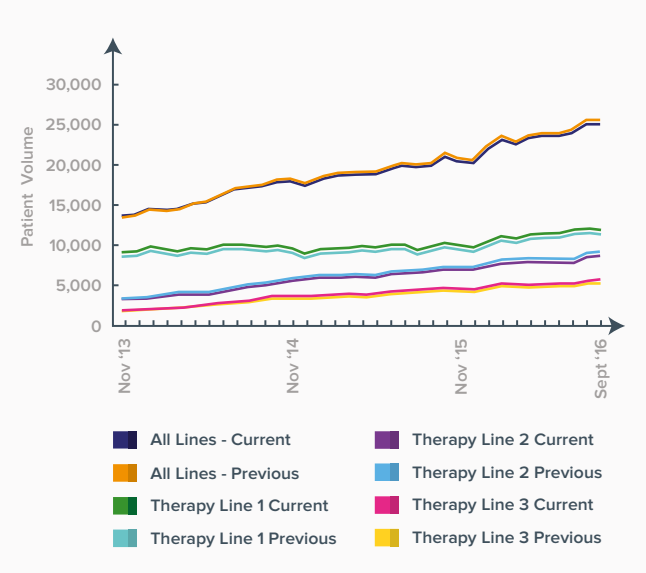
Formatting the output

The resulting output can be viewed in Excel or a business intelligence (BI) software application such as Tableau, allowing the ability to drill down into the data to analyze various market scenarios. These scenarios may be related to time, key competitors and indication and/or line of therapy, based on the projected data.

Ideally, especially when three or more foundational datasets are being integrated to reflect a market (such as breast, lung or prostate), these can be loaded to a BI and analytics platform for ease of use and to reduce the processing time to generate reports. In addition to using patient-level ID tokens to protect anonymous patient-level data (APLD), heterogeneous datasets can be combined using a Common Data Model such as OMOP (Observational Medical Outcomes Partnership) and designed to use software such as SAS to minimize investment.

Figure 2 illustrates a report that is often used by commercial teams, where patient volume is tracked over time and within line of therapy. Multiple lines show the trend curve for the current month along with that of the previous month to easily identify where data has been refreshed.

Figure 2: Reports offer ability to track patient volume over time within line of therapy



Ad hoc questions

A report platform or BI software also enables ad hoc questions to be quickly researched. The illustrative report in Figure 3, for example, shows regional, integrated delivery network (IDN) and provider market share in Tableau over time.

The future of market tracking

When setting out to generate market tracking reports, commercial teams need to understand which datasets are most relevant to their needs and the ways in which their stakeholders will wish to analyze that data. Extensive experience in market tracking analysis reveals the value of a comprehensive approach focused on

1. Selecting the appropriate foundational RWD to capture all key metrics
2. Defining the right data views
3. Formatting the file layout to enhance ease of use and aid ad hoc enquiries

For complex markets where more than two datasets might be used, combining them may require more than patient IDs from encryption, such as the conversion of the datasets to a common environment (e.g., OMOP) and then use of an evidence platform leveraging SAS or other language.

With the strategic use of multiple datasets and thoughtful investment reflecting the needs of multiple stakeholders, companies can accurately monitor product performance, gain rapid insights into product use by physicans and patients in relevant populations, and identify areas of competitive opportunity for their product. Such an approach is particularly beneficial in complex disease areas such as oncology (see case study below) where the multiple dimensions of product performance involve many layers of treatment across multiple indications that must be fully understood.

However, with integration of newly available datasets, such as lab data and patient-reported outcomes (PROs), and the application of advanced analytics such as predictive modeling, tracking can go beyond performance insight to provide targeted market insight for competitive advantage.

Figure 3: Illustration of Tableau report showing market share by region, IDN and provider over time

Case study

Challenge. A start-up company launching its first oral oncolytic into the US market with multiple indications faced the challenge of sourcing and generating various market reports to track post-launch performance. The drug had received breakthrough status and the commercial team, in a rush to prepare for launch, had numerous decisions to make around sourcing and analyzing the required data.

Novel approach. Leveraging multiple patient-level datasets, including medical claims, pharmacy claims and longitudinal patient tracking (LRx), QuintilesIMS Oncology Real-World Insights supported the commercial team with both pre-launch market sizing and post-launch tracking in several indications.

The datasets were combined using patient-level identification tokens generated during the encryption process to ensure HIPAA compliance. The analytical reports were then generated in Excel and Tableau to enable various stakeholders to conduct ad hoc queries in the data. Pre-launch, working in close collaboration with the client, QuintilesIMS developed a comprehensive set of market sizing analyses to address key questions regarding product performance. These included overall market size of the projected patient population, volume of new and continuing patients, distribution of patients by line and length of therapy, as well as various persistence and compliance metrics such as percent of patients compliant over time, and dosing measurement such as pills per day. Post-launch, QuintilesIMS provided ongoing market and client product tracking for all the indications of interest. The report set comprised

- Monthly market reports (Excel and PowerPoint summaries)
- Patient-level data files (monthly)
- Ad hoc analysis support to address key launch and ongoing business questions

Impact. The product has been in the market for over a year and has already received follow-on indications. With the variety and depth of the data views and reports provided, the company can accurately track monthly performance by indication, line of therapy and patient type (both new and continuing). It can respond swiftly to shifting market dynamics relayed in these monthly reports, the frequency of which allows the various teams to quickly and efficiently share insights, track performance against annual goals and explore new areas of potential growth.

QuintilesIMS joins Cardiac Safety Research Consortium/FDA Think Tank to share knowledge and best practice for assessing drug cardiovascular safety using RWD

Experts demonstrate valuable potential for RWD to accelerate drug safety insights

Heightened focus on the safety of medical products, and increasing requirements for evidence, are driving an urgent need to find better and more efficient ways of understanding the risks and potential adverse events of new therapies. Here, cardiovascular (CV) safety is often in the spotlight, being a common consideration even when assessing non-CV drugs. As a key step towards establishing a consistent approach, a recent stakeholder meeting hosted at the US Food and Drug Administration (FDA) explored the use of real-world data (RWD) to inform and improve research and evaluation.

In some therapeutic areas, manufacturers must rule out a certain degree of CV risk to receive marketing approval, and meet even more stringent requirements in the post-marketing space. To date, the most common method of assessing CV safety has been classical interventional studies, conducted both pre- and post-marketing. However, because of a low occurrence of adverse events, these studies must often involve tens of thousands of patients and hundreds of investigational sites over a 5–8 year period. Unsurprisingly, the cost can be staggering, sometimes hundreds of millions of dollars. Manufacturers are eager to find an alternative approach.

The Cardiac Safety Research Consortium (CSRC)

The CSRC is a transparent, public-private partnership coordinated under a 2006 Memorandum of Understanding between the US FDA and Duke University. Its goal is to enhance new medical product development and advance the practice of medicine via a specific focus on CV safety. Virtually housed at Duke University's Clinical Research Institute, the CSRC brings together stakeholders from industry, academia and government (including regulatory agencies) in a neutral, pre-competitive environment to share data and expertise and to support research into issues related to CV safety.

Exploring a role for RWD

On 19 October 2016, the CSRC and FDA co-sponsored a Think Tank, held at the FDA's White Oak headquarters, to discuss the use of RWD to assess CV safety.

Two QuintilesIMS experts were invited to present at the meeting and participate in moderated discussions throughout the day. Dr. Nancy Dreyer, Chief of Scientific Affairs and Head of the Center for Advanced Evidence Generation, addressed pragmatic trials and the use of enriched databases for follow-up, including linkages between electronic health records (EHRs), observational registries and insurance claims. Dr. Christina Mack, Director of Epidemiology and Health Outcomes, considered the attainment of CV events within EHRs as well as practical solutions to working with this data.

Understanding CV outcomes through pragmatic trials

Dr. Dreyer spoke about the value of pragmatic randomized clinical trials (pRCTs) to study CV outcomes. This approach randomizes patients to treatments compared to standard of care, with naturalistic follow-up through the regular course of medical care. Follow-up may also be performed through existing data, including EHRs and insurance claims. (For a more detailed look at pragmatic trials, see Dr. Dreyer's article on page 26).

Dr. Dreyer presented examples of recent work showing a strong positive predictive value of EHRs and claims to match the more labor intensive (and expensive) results achieved via classical randomized clinical trials. Illustrating the impact on the economics of conducting such trials, the budget for a classical CV outcomes trial is roughly *thirty times* more than the budget for a pragmatic trial with a light-touch follow-up using secondary data.

Addressing potential validity issues

Dr. Mack honed in on clinical records, discussing practical solutions to attaining data and potential issues of using EHRs alone in assessing the validity of CV outcomes. She discussed the inner workings of the medical record system, including the varied locations where CV events may be found, and the likelihood of providers recording these outcomes with high quality and completeness. In cases where the EHRs are expected to lack adequate event reporting (especially in mortality, as death is typically not noted in an EHR unless the event took place at the facility), Dr. Mack suggested alternate approaches, including external linkages and direct-to-provider data collection.

Moving the science forward

The CSRC will capture discussions from the Think Tank in a white paper for publication by special arrangement in the American Heart Journal. The goal of these papers (the CSRC has published 30 other such reports in the last decade) is to assess the current state-of-the-science in a given field, consider where it would ideally be in the next three to five years, and present consensus approaches to move it forward. An update on the paper publication will be reported in a future issue of AccessPoint.

For further information or to discuss the presentation topics outlined above, please email Rick Turner at rick.turner@quintilesims.com

Voices from across healthcare join QuintilesIMS at the 2017 US Market Access Conference in New York

Market access event reveals fast-changing landscape with new imperatives for RWE

QuintilesIMS Consulting Services hosted its 14th annual Market Access Conference in March, with industry experts discussing trends and new insights into the market access landscape over two days. This year, evidence requirements was a dominant theme and the role of real-world evidence (RWE) in data, pricing and therapy areas led many of the conversations.

Scientific advancements, social and public policy pressures, and an intensifying demand for both cost control and innovation are reshaping the market access environment. Even in previously favored areas such as orphan drugs, payers are exerting greater demands on pharma companies to demonstrate long-term value and leverage RWE. At the same time, dramatic shifts in the political landscape are encouraging, if not demanding, a new discussion about the role that RWE can – and should – play in improving patients' experiences and outcomes in the healthcare system.

Gaining perspective

A hallmark of the Market Access Conference is the presence of industry experts to fuel conversation and debate around some of the most critical market access issues. This year, participants enjoyed impassioned discussions from the payer, policy, clinical and financial sectors about the current situation and what can be expected in the months and years to come.

- **The view from Wall Street.** Without doubt, the industry is facing strong headwinds. Public- and policy-driven pricing pressures and an increased scrutiny on pharma operating and pricing models are defining the investor perspective. These headwinds highlight the potential impact of certain 'wow' events in therapeutic areas and game-changing innovations in drug development. RWE is also poised to provide a crucial counter-balance to the dependence on clinical data as these trends take hold, especially if it can provide 'proof of concept' in early stages.
- **Repeal and replace, and then what?** The evolution of US healthcare policy and specifically the implications of the American Health Care Act were standout concerns for everyone in the room. This debate ultimately takes shape around two core themes: the need to increase patient choice while maximizing affordable access; and the challenge of lowering drug costs while promoting innovation. But critical questions remain unanswered: What is the most sustainable model to incorporate all patients, sick and healthy? What role can, and should, state innovation play in healthcare delivery? How can the market stimulate competition and drive innovation, not just in access and coverage but in promoting better health overall? These questions and many more are spurring a lively debate among policy leaders and payer groups – a debate that thrives on RWE and insight.
- **The past, present and future of cancer treatment.** We are fighting a multi-front battle against cancer. In this confrontation, RWE is playing an increasingly critical role. Patient- and data-driven approaches to clinical trials are essential in getting the right drug to the right patient population, bridging the gap between treatment innovation and clinical outcomes.

The Conrad Hotel in New York hosted more than 220 invited guests at the 2017 Market Access Conference

Getting hands on with trends, new tools and RWE

Over the course of two days, QuintilesIMS experts shared a wide range of insights, including the relevance of the European environment in understanding biosimilar competition; the outlook for the orphan drug market, given past opportunity and early indications of future challenges; and the competing forces that need to be addressed in order to succeed in emerging markets.

Indeed, navigating the 'new normal' was a recurring theme across conversations. To address this landscape, technology-enabled analytics and platforms were center stage at the tech forum and poster session.

RWE emerged as a core issue throughout the event, particularly as all stakeholders become more fluent with the intersection of cost, value and outcomes. Indeed, as the use of RWE to articulate 'what you know' and 'what you say' becomes more commonplace, there is a greater focus on 'how you engage'. Ultimately, RWE is not a one-size-fits-all solution for market access challenges. Instead, it is a disciplined combination of tools, data and mechanisms that facilitates a more valuable connection between pharma and customers.

For further information or to discuss the presentation topics outlined above, please email Amber Frasketi at amber.frasketi@quintilesims.com or contact.us@imscg.com

21st Century Cures Act elevates real-world evidence (RWE) as a facilitator of accelerated drug development and approval

RWE a focus in US healthcare legislation with important implications for pharma

On 13 December 2016, the 21st Century Cures Act was signed into law in the United States, signaling a new era for the value of real-world evidence (RWE).[1] Within provisions to accelerate drug development and approval is a mandate for the US Food and Drug Administration (FDA) to regulate the application, interpretation and communication of RWE. Such emphasis on where and how RWE should be used increases its importance for pharma but also strengthens the imperative to make RWE a strategic priority across all healthcare organizations.

Over the course of more than 300 pages, the 21st Century Cures Act proposes to "accelerate the discovery, development and delivery of 21st century cures".[1] Born of a recognized need to bridge the widening gap between biomedical innovation and the US regulatory process, the "game-changing" Cures Act has been hailed as "the most transformational biomedical legislation in the past 40 years."[2]

Research funding and expedited R&D

The Cures Act recognizes the need for two levers in achieving its transformative vision. First, ensuring adequate funding for research and treatment innovations; and second, the expanded (and expedited) role of evidence in proactively meeting unmet need and reducing the time and cost of R&D.

Investment in innovation

Of the total $6.3B authorized by the Cures Act, $4.8B is appropriated to the National Institutes of Health (NIH) to increase funding for innovative research over the next 10 years.[1] This comprises

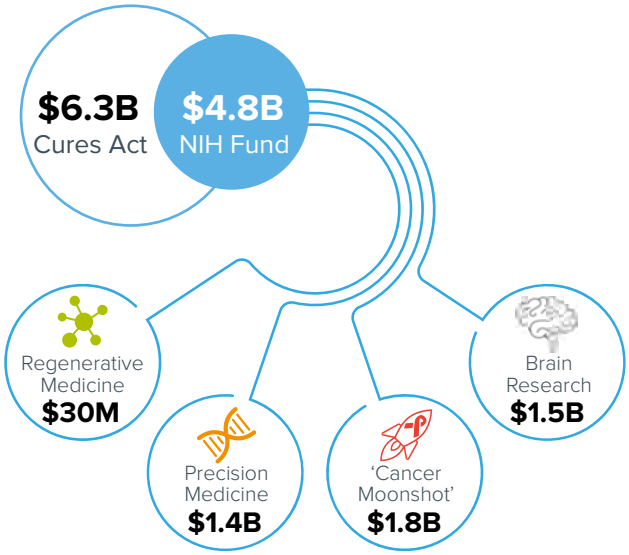
- $1.5B for Brain Research through Advancing Innovative Neurotechnologies (BRAIN)
- $1.8B for the 'Beau Biden Cancer Moonshot' program
- $1.4B for precision medicine, collecting genetic data from US volunteers to help develop new treatments
- $30M for regenerative medicine using adult stem cells

Evidence takes center stage

In seeking to accelerate drug review and approval, the Cures Act underscores the need for a patient-centric approach with the consideration of patient experience data in the risk-benefit assessment. This includes the disease and treatment impact on patient lives as well as treatment preferences.

To that end, the FDA is charged with evaluating the broader use of "evidence from clinical experience" to

Funding distribution from the Cures Act authorization[1]



1. Support approval of new indications for previously approved drugs
2. Support or satisfy post-approval study requirements

Such evidence encompasses "data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than randomized clinical trials, including from observational studies, registries and therapeutic use."

This expansion in the mandate for RWE requires swift collaboration with a wide range of stakeholders. The end goal? To establish and implement an RWE framework within two years that articulates

- Current sources of data developed through clinical experience, including ongoing safety surveillance, registry, claims and patient-centered outcomes research activities
- Gaps in current data collection activities
- Current standards/methodologies for the collection and analysis of data generated through clinical experience
- Priority areas, challenges and potential pilot opportunities that the program will address[1]

Within five years, draft guidance from the FDA will set out the circumstances under which drug sponsors may rely on RWE, and the standards and methodologies for collecting and analyzing such evidence. In addition, the FDA must also finalize guidance no later than 18 months after the public comment period closes.

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Says Andrea Spannheimer, Global Head, Real-World Evidence Solutions at QuintilesIMS: *"Combined with the imperatives for an increased focus on patient experience data, this guidance creates opportunity for the expanded application of RWE across the development continuum and will move RWE to the forefront of thinking for all clinical development professionals."*

Implications and imperatives for pharma

Dr. Kenneth Park, Vice President, Real-World Insights at QuintilesIMS notes that *"the anticipated changes arising from implementation of the Cures Act make RWE more important than ever for the success of the pharmaceutical industry."* Through its use, manufacturers can seek new indications for their label, meet post-approval regulatory requirements and communicate the economic value of their products to relevant customers. Further, the additional establishment of a regulatory pathway for patient-reported outcomes (PROs) and adaptive trials allows for ever increasing application of RWD into enriched trials.

The implication, notes Dr. Park, is that *"to be successful, pharmacos must move from thinking of RWE as primarily relevant in HEOR and epidemiology to being a foundational capability that is integral to the enterprise, from R&D through to commercial."*

Certainly, the provisions of the Cures Act create new incentives – and imperatives – for manufacturers to invest in real-world data (RWD) and RWE, and to build competence around associated strategies. In particular, armed with innovative approaches that combine secondary and primary data collection, RWE can support multiple stakeholder needs and inform decision making at a range of organizational levels.

As Andrea Spannheimer emphasizes, *"this intensifies the need for well-designed, high-quality RWE strategy and execution, both alongside the drug development process and beyond. It will require integrated and early development of a comprehensive approach, taking advantage of new methods, new technologies and data sources for RWE."*

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[1] https://www.congress.gov/bill/114th-congress/house-bill/34/text
[2] https://globalgenes.org/raredaily/chairman-fred-upton-kicks-off-debate-on-curesnow-with-powerful-speech/

For further information or to discuss the implications of the 21st Century Cures Act for RWE strategies, email Dr. Kenneth Park at kenneth.park@quintilesims.com or Andrea Spannheimer at andrea.spannheimer@quintilesims.com

ISPOR Vienna harnesses 30 years of learnings from HEOR to address key challenges for managing access to innovation

Exploring exciting opportunities for enhanced research leveraging RWE

Given growing pressure on cost and performance and the widening use of HTAs worldwide, how can three decades of HEOR experience be best employed to support regulatory decision making, the funding of medical technologies, and patient preferences for new innovations?

This was the question underpinning topics for debate at the ISPOR 19th Annual European Congress in Vienna in October 2016. More than 4,700 experts from 89 countries gathered to explore issues related to **"Managing Access to Medical Innovation: Strengthening the Methodology-Policy Nexus",** sharing research and building knowledge from nearly 2,500 presentations to advance the application of health economics and outcomes research (HEOR) for the benefit of healthcare globally.

QuintilesIMS shared insights and offerings at its exhibition stand during ISPOR in Vienna

Improving the efficiency and effectiveness of HEOR

The Congress showcased for the first time QuintilesIMS newly combined scientific and disease area expertise, technology and operational capabilities in a range of presentations.

Within the theme of improving methodology in research, the QuintilesIMS symposium considered **"Novel approaches to evidence-driven design and study sample-frame validation"**. Senior pharma and QuintilesIMS experts shared insights with more than 400 participants into the way that real-world evidence (RWE) can help HEOR become more effective and efficient throughout the development lifecycle.

R&D challenges and RWD applications

Specifically, the panelists considered how evidence-driven design can improve clinical development and late phase studies. Shortening time to market has long been a mantra for pharma in the interests of both consumers and manufacturers. Natalia Balko, Director, Analytics Center of Excellence, R&D Solutions at QuintilesIMS acknowledged

The expert panel discussed novel approaches to using real-world data at the QuintilesIMS Symposium in Vienna

the achievements to date but also the need to go beyond: *"The industry has made significant progress in improving development timelines and managing pipeline value attrition through organizational change programs, substantial regulatory realignment and fundamentally different approaches to research. However, there is still more that can be done."*

Classical methods for clinical development and late phase research revolve around understanding clinical outcomes from published studies and KOL insights to inform study design. Today, as Natalia underscored, the answer may lie in RWE: *"Applying new techniques, the analysis of real-world data can help to improve efficiency directly, for example by enabling understanding of competing recruitment pressure or to ensure that the right sites are selected. It can also drive improvements indirectly, such as helping to determine protocol endpoint feasibility."* Demonstrating these capabilities through practical cases, she also illustrated how the use of this data can improve the effectiveness of studies by increasing their external validity.

RWE can also inform endpoint strategy in clinical trials. Guest speaker Dr. Solomon Iyasu, VP, Pharmacoepidemiology, Center for Observational Real-World Evidence at Merck & Co, focused particularly on its role in target product profile definition. Finally, Dr. Andrew Bate, Senior Director, Epidemiology Group Lead at Pfizer Ltd, detailed how new approaches to post-authorization safety studies (PASS) and post-authorization efficacy studies (PAES) leveraging real-world data (RWD) can help address concerns over their timeliness and quality. Both thought-provoking and insightful, the presentations stimulated a lively participant Q&A finale, moderated by Chair Dr. Jacco Keja, Senior Principal, Real-World Insights at QuintilesIMS.

Managing the winds of change

QuintilesIMS also held a workshop on managing change in RWE studies. Intriguingly entitled **"Let's go fly a kite,"** this engaging and interactive session explored the significant impact that changes to data models, tools, data elements and even the healthcare environment, as well as common

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International Society for Pharmacoepidemiology (ISPE) membership elects new President from QuintilesIMS for term commencing August 2018

QuintilesIMS Scientific Director embraces opportunity to serve ISPE

Alison Bourke, Scientific Director at the Center for Advanced Evidence Generation at QuintilesIMS and Fellow of the International Society for Pharmacoepidemiology (ISPE), has been elected President of ISPE by the society's membership. She will be recognized as the incoming President Elect at ISPE's Annual Conference in Montreal in August 2017 and will formally transition to President in August 2018.

ISPE is a non-profit international professional membership organization committed to providing an unbiased forum for sharing knowledge and scientific approaches to foster the science of pharmacoepidemiology. This includes its annual and Asian conferences, proactive communities, regional and national chapters, and official journal "Pharmacoepidemiology and Drug Safety." Members span a variety of scientific disciplines involved in studying drugs, from pharma, academia, government agencies, and non-profit and for-profit private organizations in 53 countries. Since its inception in 1989, ISPE has become a highly respected and influential driver in developing, informing and advancing best practice in this increasingly important field.

In her new role, Alison will serve as the principal executive officer at ISPE, reporting directly to the Board of Directors. She will chair Board and Executive Committee meetings as well as work with the Board, members and community to support the organization's goal of "advancing the health of the public by providing a forum for the open exchange of scientific information and for the development of policy; education; and advocacy for the field of pharmacoepidemiology, including pharmacovigilance, drug utilization research, outcomes research, comparative effectiveness research and therapeutic risk management."

Alison is a database researcher with over 30 years of experience working with primary care patient data resources in the UK. She has been a member of ISPE for more than 20 years.

Commenting on her appointment, Alison says: *"I feel extremely honored to have been elected by ISPE members to serve as their President. The Society has been my second career home for many years, helping me to learn so much and providing opportunities to meet many bright and enthusiastic people. I hope I can maintain our tradition of openness by welcoming and integrating all members, especially those in geographies where drug safety is underrepresented. We are entering a world of not just big but also massively varied health data, and I look forward to seeing ISPE meet the challenges and to further developing as an expert in this arena."*

For further information on the work of ISPE, visit www.pharmacoepi.org/ and to find out more about Alison's extensive experience, see page 57.

QuintilesIMS at ISPOR Vienna

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developments such as the addition of recent data, can have on research. The importance of addressing this was stressed by presenter Alison Bourke, Scientific Director at QuintilesIMS: *"Change is inevitable in our continually evolving real-world data research environment. Sustainable design is key in both retrospective and prospective database research, and it is vital to the validity, clarity and reproducibility of database studies."*

Questioning how well such change is currently anticipated and managed, the workshop demonstrated a tool to help and account for factors that can vary over time, as reported in a paper co-authored by Alison and presenters Dr. Gillian Hall, an independent consultant in pharmacoepidemiology and Dr. Andrew Bate of Pfizer, among others.[1] Participants were assigned to working groups where they used the tool to identify and consider changes across a simulated HEOR study, before entering a discussion on anticipating such events.

Offering RWE insights from original research

QuintilesIMS experts also contributed to an ISPOR Forum on **"New issues and emerging trends in HEOR"** as well as more than 100 posters and a podium presentation, showcasing research completed in a broad range of therapy areas and geographies, in many cases employing creative and innovative methodologies. They also provided practical demonstrations of QuintilesIMS technology solutions including HTA Accelerator, which delivers instant insights into payer decision making in more than 30 countries, and E360™, a powerful suite of RWI applications that can help answer even challenging questions in a standardized, intuitive way.

For further information or to discuss the presentation topics outlined above, please email Angelika Boucsein at angelika.boucsein@quintilesims.com

[1] Bourke A, Bate A, Sauer BC, Brown JS, Hall GC. Evidence generation from healthcare databases: recommendations for managing change. Pharmacoepidemiol Drug Saf, 2016; 25 (7): 749–754. doi: 10.1002/pds.4004

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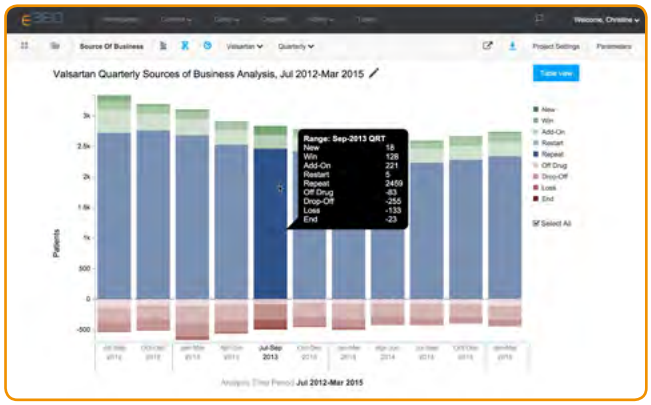

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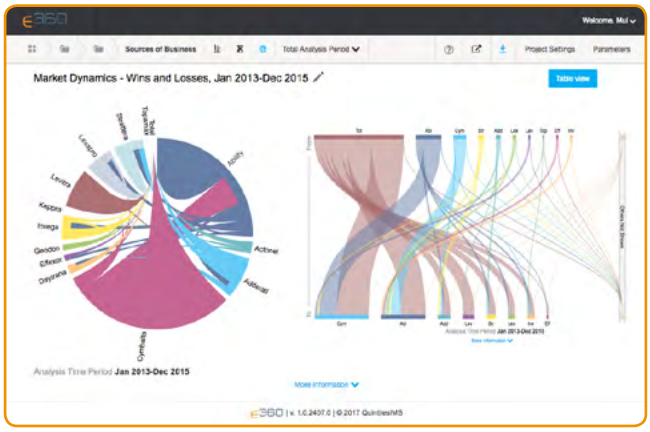

From RWD to actionable insights

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The QuintilesIMS Real-World Insights team is supporting events around the world

20-24 May 2017
ISPOR
Boston MA, USA
International Society for Pharmacoeconomics and Outcomes Research, 22nd Annual International Meeting

26-30 August 2017
ICPE
Montréal, Canada
33rd International Conference on Pharmacoepidemiology & Therapeutic Risk Management

18-22 June 2017
DIA
Chicago IL, USA
Drug Information Association Annual Meeting

8-12 September 2017
ESMO
Madrid, Spain
European Society for Medical Oncology Congress

15-17 September 2017
ISPOR
São Paulo, Brazil
International Society for Pharmacoeconomics and Outcomes Research, 6th Latin America Conference

2-6 June 2017
ASCO
Chicago IL, USA
American Society of Clinical Oncology 53rd Annual Meeting

19-22 June 2017
BIO
San Diego CA, USA
Biotechnology Innovation Organization International Convention

17-18 October 2017
NORD
Rare Summit
Arlington VA, USA
National Organization for Rare Disorders (NORD), Rare Diseases and Orphan Products Breakthrough Summit

4-8 November 2017
ISPOR
Glasgow, UK
International Society for Pharmacoeconomics and Outcomes Research, 20th Annual European Congress

15-17 November 2017
EuroDURG
Glasgow, UK
European Drug Utilisation Research Group Conference

17-18 November 2017
CMSS
Arlington VA, USA
Council of Medical Speciality Societies Fall Meeting

17-21 June 2017
HTAi
Rome, Italy
Health Technology Assessment international 14th Annual Meeting

26-27 June 2017
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Philadelphia PA USA
Real-World Data & Analytics Centers of Excellence Best Practices Forum

31 Oct-1 Nov 2017
World Biosimilar
Basel, Switzerland
World Biosimilar Congress, Europe

13-15 November 2017
World Orphan Drug Congress
Barcelona, Spain
8th Annual World Orphan Drug Congress

For more details or to

Meet us at these events

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Global scope, local expertise

QuintilesIMS Real-World Insights experts are located in over 20 countries worldwide and they have published on projects completed in more than 50 countries on all continents.

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Expertise in depth

The QuintilesIMS Real-World Insights (RWI) team brings together unrivaled experience and therapy area expertise from life sciences, consulting, government and academia. With a proven track record in all key therapy areas, as well as a range of global markets, we have helped clients capture opportunity and embrace innovation in an increasingly complex pharmaceutical landscape.

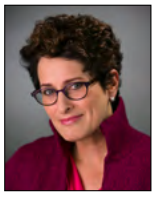
Our senior team

Adam Collier, MCHEM *adam.collier@quintilesims.com*

- Adam Collier is Senior Principal, North Europe, Middle East & Africa, RWI and is responsible for the 150-person Medical/Scientific RWE team across the NEMEA region.
- Adam has 20 years of commercial analysis experience in the UK and European healthcare industry, spanning work in pharmaceuticals, consulting, and healthcare provision. This includes three years at QuintilesIMS. Previously, he spent nine years at GlaxoSmithKline in roles within customer and trading strategy, commercial analysis and European marketing. He also worked at Accenture, where he completed a secondment in the Medicines and Healthcare Products Regulatory Agency (MHRA) to work on its patient data asset GPRD (now CPRD). Adam has also spent several years with a private healthcare provider.
- Adam holds a Master's degree in Chemistry from the University of Oxford in the UK.

John J. Doyle, Dr.PH, MPH *john.doyle@quintilesims.com*

- Dr. John J. Doyle is Senior Vice President and Managing Director of the RWI Enterprise Solutions team, which provides innovative, technology-enabled evidence platforms and research networks to help transform clinical, commercial and medical operations.
- John previously co-founded and served as President of Analytica International, which provided market access, HEOR and RWE services to the global pharmaceutical industry. He also led the health economics team for the Center for Health Outcomes and Economics at Bristol Myers Squibb. John has facilitated workshops internationally on topics including health technology assessment, value frameworks and outcomes-based contracting. Over the past two decades, he has authored over 70 peer-reviewed publications in a variety of therapeutic areas, with a special concentration in oncology.
- John holds a Doctor of Public Health degree and a Master of Public Health degree in Epidemiology from the Mailman School of Public Health at Columbia University, and a Bachelor of Science degree in Business Management and Applied Economics with a concentration in Life Sciences, from Cornell University in the US. He maintains a faculty position at Columbia University, where he serves as an Adjunct Assistant Professor of Pharmacoepidemiology.



Nancy Dreyer, PHD, MPH, FISPE, FDIA *nancy.dreyer@quintilesims.com*

- Dr. Nancy Dreyer is Global Chief of Scientific Affairs, RWI and heads the Center for Advanced Evidence Generation. She is responsible for developing and executing innovative methods for real-world research on the safety, effectiveness and value of medical treatments using secondary and/or primary data collected through pragmatic, minimally interventional and non-interventional studies. Nancy also leads programs on sports injury surveillance and analytics for the National Football League and for the National Basketball Association.
- Well-known internationally, Nancy is a senior editor of "Registries for Evaluating Patient Outcomes: A User's Guide," published by the US Agency for Research on Healthcare and Quality, now in its third edition with translations in Chinese and Korean. She also led the GRACE Initiative for Good Research Practices for Observational Studies of Comparative Effectiveness.
- Nancy is a Fellow of both the International Society for Pharmacoepidemiology (ISPE) and the Drug Information Association (DIA). She holds a doctorate in Epidemiology and a Master's degree in Public Health from the University of North Carolina at Chapel Hill in the US.

Ben Hughes, PHD, MBA, MRES, MSC *ben.hughes@quintilesims.com*

- Dr. Ben Hughes is Vice President, RWI, responsible for the company's global technology strategy and development across the RWE and Payer and Provider businesses. He has helped many pharmaceutical industry clients to articulate and implement their RWI strategies through RWE vision, business cases for RWE investments, capability roadmaps, partnerships, brand evidence reviews, HEOR function design, RWE training programs and related clinical IT strategies.
- Ben was previously a junior partner at McKinsey & Company where he co-led their Health Informatics practice in Europe, advising life-sciences clients on RWE strategy, and various health systems on IT strategy and EHR adoption. Prior to this, he worked as the development lead at Accenture on large-scale IT systems implementations across different sectors.
- A widely-published author on health informatics, Ben holds a Doctorate in Medical Informatics from ESADE Barcelona, a Master of Business Administration degree from HEC Paris, a Master's degree in Research from ESADE Barcelona, and a Master's degree in Physics from University College, London.

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QUINTILESIMS RWI EXPERTISE

Brian Kelly, MD, MBA, MS

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- Dr. Brian J. Kelly is President, Payer and Provider Solutions. He is responsible for leading the company's strategy to leverage its extensive therapeutic, scientific and analytics expertise to grow its presence in promising hospitals and health plan markets.
- Brian was previously the head of Informatics at Aetna. He also led Accenture's global electronic health record practice, where he consulted for numerous health plans, hospitals and governments with a primary focus on using information technology to improve healthcare. Brian is a former Navy neurologist and intensive care medicine specialist, retiring with the rank of Captain in 2003. During his 20-year military career, he was recognized internationally for his expertise in the emerging field of neurocritical care and served as chairperson of the neurocritical care section of the American Academy of Neurology.
- Brian holds a Doctor of Medicine degree from New York Medical College; a Master of Business Adminstration degree from George Washington University; a Master's degree in Bioengineering from Clemson University; and a Bachelor's degree in Russian, Premed, from the College of Holy Cross in Worcester MA, USA.

Rob Kotchie, M.CHEM, MSC

rob.kotchie@quintilesims.com

- Rob Kotchie is Vice President and Global Head of Operations, RWI, responsible for the worldwide delivery of client solutions.
- Previously with ZS Associates, Rob has more than 15 years of consulting experience specializing in the synthesis and application of RWI to facilitate market access, drug uptake and the responsible use of medicines. In his former role as Chief of Staff to Ari Bousbib, QuintilesIMS Chairman and CEO, he supported all operational and management activities related to execution of the company's strategy. He also played an integral role in its 2013 dividend recapitalizations, initial public offering in 2014, and more recently the merger and integration of IMS Health with Quintiles.
- Rob has expertise in the areas of oncology, respiratory, cardiovascular and CNS and he has published more than 30 peer-reviewed journal articles and poster presentations. He holds a first-class honors degree in Chemistry from the University of Oxford and a Master's degree in International Health Policy from the London School of Economics in the UK.

Jonathan A. Morris, MD

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- Dr. Jonathan A. Morris is Vice President, Provider Solutions, and Chief Medical Informatics Officer, RWI, working with the company's portfolio of businesses at the convergence of RWI and connected health. Jon's specific areas of focus include RWI design, generation and dissemination, as well as the intersection of quality and outcomes measurement for providers, payers and patients.
- Previously, Jon was Senior Vice President and Chief Scientific Officer for United BioSource Corporation (UBC). In this role, he had global responsibility for building and managing operational and service functions for data and information used to generate evidence for pharmaceutical product effectiveness, safety and value. Prior to joining UBC, Jon was Chairman, President and Chief Executive Officer at ProSanos, a patient safety and health outcomes-focused informatics company that he co-founded and sold to Medco in 2010.
- Jon holds a Doctor of Medicine degree from Washington University in St. Louis and a Bachelor's degree in Economics from the University of Michigan. He completed his surgical internship, residency and pediatric surgical research fellowship at Stanford University in the USA. He is a well-regarded international speaker and has authored over 100 peer-reviewed publications and presentations.

Kenneth Park, MD

kenneth.park@quintilesims.com

- Dr. Kenneth Park is Vice President and Head of Offering Development, RWI. He has extensive experience in launching and building new business lines, and innovative capabilities in the healthcare data, analytics and technology arena.
- A medical physician, Kenneth previously led clinical data strategy at Anthem, including the creation of the California Integrated Data Exchange (Cal INDEX). He also managed the data environment for Anthem's research subsidiary, HealthCore. Prior to this, Kenneth was a leader of Big Data in Healthcare and RWE activities at McKinsey & Company, helping clients across the stakeholder landscape develop Big Data capabilities and enter new business adjacencies.
- Kenneth holds a Doctor of Medicine degree from the University of Southern California, Keck School of Medicine and a Bachelor's degree in Psychology from Harvard College.

Jon Resnick, MBA

jon.resnick@quintilesims.com

- Jon Resnick is President, RWI. This includes overseeing patient-level data asset strategies, RWI-related technologies, and offering development and collaborations, to meet the RWI needs of healthcare stakeholders.
- Jon has more than 20 years of healthcare experience. A former Professional Health and Social Security staffer for the United States Senate Committee on Finance in Washington DC, Jon has led the global RWI team since 2012. Prior to that, he led the European management consulting team and global HEOR businesses.
- Jon holds a Master of Business Administration degree from the Kellogg School of Management, Northwestern University in the USA, with majors in Management and Strategy, Finance and Health Industry Management.

Emile Schokker, MBA, MSC *emile.schokker@quintilesims.com*

- Emile Schokker is Vice President, RWI and leads the regional RWI team in Central, East and South Europe. He has nearly 20 years of international pharmaceutical and consulting experience and expertise in launch, brand and portfolio strategy and the application of RWE.
- Previously, Emile was Senior Expert and Associate Principal at McKinsey & Company, leading strategic engagements in the Pharmaceutical and Medical Products Practice, based in Copenhagen and Brussels. He has also worked in leadership roles at Unaxis/Oerlikon in Switzerland, Arthur D. Little in the Netherlands, and Unilever in various international locations.
- Emile holds a Master of Business Administration degree from IMD in Lausanne in Switzerland and a Master of Science degree in Applied Physics from the Delft University of Technology in the Netherlands.

Dana Sellers, BSC *dsellers@encorehealthresources.com*

- Dana Sellers is Chief Executive Officer of Encore Health Resources, a QuintilesIMS company, named one of Modern Healthcare's 'Best Places to Work in Healthcare'. Dana works with healthcare providers across the US, helping them bring about positive change by improving processes, enabling technology and providing insights that come from business intelligence and health analytics.
- Dana has more than 25 years of experience in healthcare, technology and consulting. Prior to founding Encore in January 2009, she was President and Chief Operating Officer at Healthlink. Following the acquisition of Healthlink by IBM, Dana served as Partner in IBM's Global Business Services organization and leader for the US Healthcare Provider team. Dana's career has also included leadership roles in DuPont Healthcare Products and Trinity Computing Systems.
- Dana earned a Bachelor of Science degree in Chemical Engineering from The University of Texas at Austin. She has served on the Board of the College of Healthcare Information Management Executives (CHIME), the CHIME Foundation and the CHIME Education Foundation, and she is a past Chair of the Board of Healthcare for the Homeless in Houston. Dana is also an Ernst and Young Entrepreneur of the Year in the Gulf Coast Region, a UT Distinguished Engineering Alum, and she has recently been inducted into the UT Academy of Distinguished Chemical Engineers.

Andrea Spannheimer, MS *andrea.spannheimer@quintilesims.com*

- Andrea Spannheimer is Global Head, RWE Solutions. In this capacity, she is responsible for the design and execution of RWE studies. These span from observational studies to Phase 4 interventional studies, using either primary data collection, secondary data or a combination of both. Andrea also oversees the global offering in Health Economics and Health Technology Assessment.
- Andrea has more than 22 years of experience in late phase research, RWE and HEOR in the Clinical Research Organization (CRO) industry. Prior to joining Quintiles in 2014 and latterly becoming the Global Head of Real-World Late Phase Research, Andrea served as President for Global Real-World Evidence, Late Phase Research and Health Economics at Optum Lifescience (a division of UnitedHealth Group). She previously built and led i3's Late Phase group in EMEA as well as Kendle's Late Phase and HEOR group in EMEA and APAC.
- Andrea holds a Master's degree in Biology from the Friedrich-Alexander-Universität Erlangen-Nürnberg in Germany.

Jamie Thompson, BA *jamie.thompson@quintilesims.com*

- Jaime Thompson is Vice President, RWE Solutions in the US. This includes responsibility for HEOR, oncology, commercial patient, enterprise technology (evidence platforms) and informed media business.
- Jaime's background spans consulting and sales roles, including Answerthink and Andersen. She has extensive experience in pharmaceutical marketing sciences, market research, sales operations and brand management, and strong expertise assisting companies with strategic analytical planning. She serves as an advisor in several specialty markets based on her skills leveraging secondary data. Jamie has worked with clients to design and implement a data warehouse environment to capture the full patient treatment paradigm, build an EMR repository for monitoring treatment progression, and re-engineer and roll out a use-by-indication algorithm used for incentive compensation.
- Jaime holds a Bachelor's degree in Government and Economics from Franklin & Marshall College in Lancaster PA and the London School of Economics.

Ashley Woolmore, D.CLIN PSYCH, MBA *ashley.woolmore@quintilesims.com*

- Dr. Ashley Woolmore is Vice President, RWE Solutions, with a focus on developing innovative approaches to RWD, infrastructure development and evidence generation to encourage the integration of RWD into strategic decision making. He has 20 years of experience in the life sciences and healthcare sector.
- Ashley leverages a uniquely diverse background in clinical, healthcare system management and life sciences strategy consulting in senior advisory roles to work with a broad range of clients and stakeholders on healthcare system issues. His expertise includes strategy development, healthcare analytics, RWE for strategic insight, population health management applications and differentiated market access approaches.
- A thought leader with a particular interest in opportunities arising from the convergence between the life sciences industry and the broader healthcare system, Ashley holds a doctorate in Clinical Psychology from the University of Oxford in the UK, an MBA in Strategy from HEC in Paris, and a Bachelor of Science (Hons) degree in Natural Sciences and Psychology.

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Our therapeutic experts

Ali Ashrafzadeh, MD

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- Dr. Ali Ashrafzadeh is Head of the Rheumatology Center of Excellence, responsible for bringing together the accumulated experience in rheumatology and immunology and applying this to study design, strategy and innovation. Previously he has led a number of global programs, successfully delivering studies, clinical development plans and clinical study reports in various rheumatologic indications. He has also been a leader in the development strategies for stem cell therapeutics, rheumatologic rare disease indications and biosimilars.
- Prior to joining QuintilesIMS, Ali worked at Genentech where his role included Phase 2–4 study design, program oversight, analysis and presentation of complex results to senior management. He was also involved in interacting and managing CROs as partners, as well as cross-functional, cross-departmental partnering with key function stakeholders in Basic Research, Medical Affairs, Marketing and Regulatory Affairs.
- A rheumatologist/internist by training, Ali has 14 years of private practice experience running a variety of Phase 1–4 clinical studies prior to joining pharma. He holds a Masters in Medical Sciences from Boston University School of Medicine and a Doctor of Medicine degree from Ross University School of Medicine. He completed his fellowship at the University of Arizona and his residency at the New York Methodist Hospital.

Erica Caveney, MD

erica.caveney@quintilesims.com

- Dr. Erica Caveney is Head of the Cardiovascular, Metabolic and Renal Center of Excellence, responsible for the strategy, innovation, design and implementation of the company's work in these therapeutic areas. She previously served as medical advisor for Phase 2-4 endocrinology and diabetes clinical trials and led the Cardiovascular Outcome Center of Excellence at QuintilesIMS.
- Prior to joining QuintilesIMS, Erica served on the faculty of the Duke University Medical Center in the Endocrinology, Metabolism and Nutrition division where she specialized in Type 1 and Type 2 diabetes management. She has authored many peer-reviewed articles on diabetes and obesity, including diabetes biomarkers, cardiovascular outcomes studies in anti-diabetes drugs and a review of obesity drugs.
- Erica trained at the West Virginia University School of Medicine and completed her internship and residency in Internal Medicine at West Virginia University Hospitals. She completed her fellowship in Endocrine, Diabetes and Metabolism at the University of North Carolina Hospitals and Nutrition division.

Joan L. Drucker, MD

joan.drucker@quintilesims.com

- Dr. Joan Drucker is Vice President and Global Head of the Infectious Diseases and Vaccines Center of Excellence. This is a cross-functional team charged with overall strategic guidance for clinical trials of infectious diseases or vaccines.
- Joan began her career in the pharmaceutical industry at GlaxoSmithKline, holding senior leadership positions in both US and international clinical research and medical affairs. Subsequently, she was Chief Medical Officer at Trimeris, Radiant Development and Accelovance. She has broad therapeutic area experience, with a focus on infectious diseases and vaccines, and has directed successful regulatory submissions for INDs and NDAs in multiple indications.
- Joan graduated from Harvard University and from the University of Virginia School of Medicine. After completing a residency in Internal Medicine at Faulkner Hospital (Tufts), she completed a Fellowship in Infectious Diseases at Duke University Medical Center. She was a consulting faculty member in the Division of Infectious Diseases at Duke for 10 years. Joan holds an active medical license in North Carolina and maintains Board Certification in Internal Medicine.

Fez Hussein, MBChB, MRCP

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- Dr. Fez Hussein is Head of the Gastroenterology and Rheumatology Center of Excellence, leading global drug development strategy and innovation for these therapeutic areas.
- Prior to joining QuintilesIMS, Fez worked in Medical Affairs at GlaxoSmithKline for a number of years. He also has more than 10 years of clinical experience in UK National Health Service hospitals, including positions as a Consultant Gastroenterologist and Team Leader.
- Fez has Board Accreditation in both Gastroenterology and Internal Medicine. He has published in peer-reviewed journals in the gastroenterology field and presented at meetings of the British Society of Gastroenterology and the American Gastroenterology Association.

Cynthia Jackson, DO, FAAP

cynthia.jackson@quintilesims.com

- Dr. Cynthia Jackson is Head of the Pediatric and Rare Diseases Centers of Excellence, responsible for the enterprise-wide strategy for pediatrics and rare diseases. This encompasses drug development as well as other healthcare services. She is also a consulting Assistant Professor in the Division of Pediatric Infectious Diseases at Duke University, Durham NC.
- Throughout her career, Cynthia has served as a medical advisor for clinical trials in therapeutic areas related to pediatric patients, including asthma, allergies, migraines, nutrition, a variety of rare diseases and vaccines. In addition, she has experience with infectious diseases indications such as antivirals, anti-HIV compounds, tuberculosis, antifungals and antibacterials. Prior to joining QuintilesIMS, Cynthia was the Chief of Pediatric Infectious Diseases at the University of Illinois-Chicago College of Medicine in Peoria, IL. As a clinical investigator, she has worked on antiretroviral, antifungal, antiviral and vaccine studies.
- Cynthia earned her doctorate from Des Moines University College of Osteopathic Medicine in Iowa. She completed a pediatric residency at Western Reserve Care System in Ohio and a fellowship in Pediatric Infectious Diseases at Duke University, as well as a research fellowship in Retrovirology at Glaxo Wellcome.

Laurence H. Keller, MD, FACC

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- Dr. Laurence (Larry) H. Keller is Vice President and Head of the Cardiovascular Center of Excellence, leading global drug development strategy and innovation for the cardiovascular therapeutic area.
- Prior to joining QuintilesIMS, Larry held clinical R&D leadership positions at Pfizer and Kos Pharmaceuticals and was Chief Medical Officer at Aldagen. He also held medical affairs leadership positions at Pfizer and GlaxoSmithKline. Larry has experience across the spectrum of drug development and in addition to working in the cardiovascular space he has worked in rare diseases, regenerative medicine, diabetes and respiratory among other therapeutic areas.
- Larry earned his Doctor of Medicine degree at The George Washington University School of Medicine, completed his internship and residency in pediatrics at The New York Hospital-Cornell Medical Center, and completed his Fellowship in Pediatric Cardiology at the Children's Hospital of Michigan. He is a Fellow of the American College of Cardiology.

Terry L. Murdock, MSC, BSC

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- Terry L. Murdock is Head of the Oncology Center of Excellence. He focuses on creating innovative solutions to continually enhance the company's oncology development projects and programs. Working with his team, he provides customers with alternative and novel designs to help improve the efficient development of their oncology assets.
- Terry has 20 years of experience as a successful senior executive in the medical research industry, specializing in oncology, multiple sclerosis and other autoimmune diseases. He is skilled in establishing operational excellence within culturally diverse environments, with a track record of executing operational, clinical and commercial plans. Prior to joining QuintilesIMS, Terry held senior positions focused on clinical drug development at Ergomed, Genzyme/Sanofi, ILEX Oncology and US Oncology.
- Terry earned his Master's of Science degree in Biology and Batchelor of Science degree in microbiology from the University of Texas at Arlington. He is a registered microbiologist for the American Society of Clinical Pathology and a registered medical technologist for American Medical Technologists.

Edward E. Philpot, MD, MBA

edward.philpot@quintilesims.com

- Dr. Edward Philpot is Head of the Respiratory Center of Excellence. He has over 30 years of experience encompassing all aspects of medical and clinical research. This includes 18 years in the pharmaceutical and medical device industry working in R&D, Medical, and Clinical Affairs.
- Prior to joining QuintilesIMS in 2017, Edward acted as a pharmaceutical and medical device industry consultant and held positions at several pharmaceutical companies. He was Chief Medical Officer, Biologics Division, at Smith & Nephew; Global Executive Director, Respiratory and Immuno-inflammation at GlaxoSmithKline; and Director, Medical Therapeutics – Respiratory and Anti-infectives, at Hoechst Marion Roussel/Aventis Pharmaceuticals.
- Board Certified in Internal Medicine and Allergy/Immunology, Edward earned his Doctor of Medicine degree at the University of New Mexico School of Medicine. He completed a Residency in General Internal Medicine and a Fellowship in Allergy/Immunology at Wilford Hall USAF Medical Center in San Antonio TX. He also holds a Master of Business Administration degree from Duke University's Fuqua School of Medicine in Durham NC.

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Penny Randall, MD *penny.randall@quintilesims.com*

- Dr. Penny Randall is Head of the Central Nervous System Center of Excellence. Since joining QuintilesIMS in 2003, she has provided medical and scientific leadership on numerous development programs, many of which have resulted in successful CNS drug approvals. She has more than 20 years of CNS clinical drug development experience.
- Penny has a background in academic medicine, previously holding faculty positions at Yale University and the University of California, Irvine. She has also worked for the large health plan, Optum, where she focused on implementing quality initiatives to improve health outcomes of the membership.
- Board Certified in Psychiatry and Addiction Medicine, Penny completed her psychiatry residency at Georgetown University School of Medicine and a research fellowship in Psychopharmacology at Yale University School of Medicine. She received her medical degree from the University of Louisville School of Medicine. Penny also holds a graduate business degree from the Merage School of Business at the University of California, Irvine, concentrating on Healthcare Management.

Nigel Rulewski, MD *nigel.rulewski@quintilesims.com*

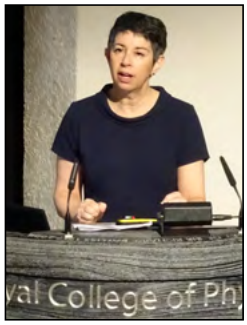
- Dr. Nigel Rulewski is Head of the Biosimilars Center of Excellence. In this role, he works with companies around the world advising on drug development strategies, with an active focus on biosimilars. His experience spans multiple therapeutic areas, particularly oncology, respiratory medicine and biosimilars, and he has led development planning activities for EPO, GCSF, peg-GCSF, Remicade, Enbrel, Rituximab and Herceptin biosimilars.
- Prior to joining QuintilesIMS in 2008, Nigel held numerous senior management positions, including Vice President of Drug Development for AstraZeneca for 10 years. In this role, he managed a department that expanded to more than 200 employees and achieved approval of multiple NDAs in the areas of pain control, respiratory, cardiovascular and AIDS indications. Nigel has worked in venture capital in New York, establishing funding for multiple early stage start-up companies predominantly focused on oncology. He has also served as Chief Medical Officer for two oncology-focused biotechnology companies, Procept and Arqule.
- Nigel earned his medical degree from St. Bartholomew's Medical School, University of London. After completing his training in Pediatrics and Obstetrics and Gynecology, he practiced in the UK in London and Guildford.

Susan Tansey, MD *susan.tansey@quintilesims.com*

- Dr. Susan Tansey is Head of the Infectious Disease/Vaccines and Women's Health Center of Excellence. She trained in pediatrics in the UK's National Health Service, with a specialty in respiratory pediatrics and neonatology, before joining the pharmaceutical industry in 1998. She has since worked in clinical development in several therapeutic areas, including cardiovascular, vaccine research and oncology. She is an expert in pediatric clinical trials and is currently Chair for a working party at the European Network for Paediatric Research at the EMA. She also chairs the Children's Research Industry Group for the Clinical Research Network of the National Institute for Health Research.
- Susan's industry experience includes a role as Clinical Research Manager in the UK R&D department at Servier, covering the cardiovascular therapeutic area, and more than six years heading up global vaccine trials for Wyeth/Pfizer. As a member of the global submission team for Prevenar 13, she provided medical leadership for studies in Europe, India, the USA and China. Susan then joined TMC Pharma as Director of Medical Services for 18 months after which she moved to Premier Research as Senior Director in Pediatrics.
- Susan obtained her medical degree from Manchester University, UK. She also holds an MRCP (UK). She is a Consultant Pharmaceutical Physician (CCST 2011), a member of the Royal College of Paediatrics and Child Health, and a Fellow of the Faculty of Pharmaceutical Medicine. She was a member of the Nuffield Council of Bioethics Working Party on Children and Clinical Research whose work was published in May 2015.

Focusing on science

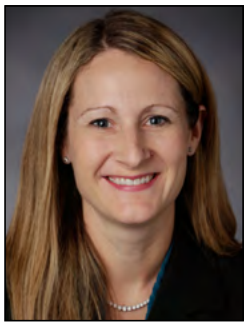
QuintilesIMS is proud to recognize two key leaders of our scientific community. These individuals represent the forefront of our thinking on evidence generation and demonstrate our deep commitment to pushing boundaries and driving innovation.



Alison Bourke, MSC, MRPHARM.S, FISPE *alison.bourke@quintilesims.com*

> My main focus is on preparing for the next frontier of real-world patient-generated data. The unprecedented volume, variety and velocity of new datastreams emanating from social media, wearables and mobile apps will present many challenges, not least relating to privacy and analytics. However, the medical insights from patient-generated data are huge and their role in helping citizens manage their own health has the potential to reduce costs and prevent suffering in the globally aging population.

- Alison Bourke is Scientific Director at the Center for Advanced Evidence Generation (CAEG). She is a database researcher with over 30 years of experience working with primary care patient data resources in the UK.
- Previously, Alison was Managing Director of CSD Medical Research UK (formerly known as EPIC), where she headed the research team providing primary care data and support for a wide range of studies, including pharmacoepidemiology and health outcomes research. Alison also worked in both the hospital and pharmaceutical industries before helping to establish the General Practice Research Database GPRD (known then as the Vamp Research Bank), a database of electronic medical records. In this role, she was responsible for defining a quality standard for the data, leading a team to provide feedback to general practice contributors, and extracting information from the database for the needs of external drug safety and outcomes researchers.
- In 2002, Alison was instrumental in setting up the Health Improvement Network (THIN) database, which currently provides access to 12 million de-identified patient records. She is particularly interested in using such databases, as well as novel data sources, to explore innovative scientific methodologies. Both GPRD and THIN have become valuable contributions to all stages of the drug development cycle.
- Alison is a Fellow of the International Society for Pharmacoepidemiology (ISPE), and has been elected as the Society's President for a term beginning August 2018 (see News, page 47). She is also Vice Chair of the PRIMM (Prescribing and Research in Medicines Management) organization. She has degrees in both pharmacy and computing.



Jennifer Christian, PHARM.D, MPH, PHD, FISPE *jennifer.christian@quintilesims.com*

> Globally, there is a dearth of clinical information readily available for physicians and patients to make informed decisions. I am deeply motivated to advance a learning system that enables rapid, informed decision making through RWE generation and technology to improve health. We are helping to move the field forward in generating timely and meaningful evidence that impacts important health decisions. That said, there are still many advancements to come and I look forward to contributing to these.

- Dr. Jennifer Christian is Vice President, Clinical Evidence at the Center for Advanced Evidence Generation (CAEG), providing scientific oversight to the design and conduct of real-world studies. The CAEG team is dedicated to developing and conducting innovative and rigorous study designs, such as pragmatic trials, enriched studies, single-armed studies and roll-over safety studies. Previously, Jennifer held a senior position within the Chief Medical Office at GlaxoSmithKline that focused on strengthening clinical effectiveness and safety evaluations.
- Jennifer has worked on numerous real-world and clinical trials in the areas of diabetes, severe hypertriglyceridemia, skin cancer, lupus, rheumatoid arthritis, chronic kidney disease and others. Her research has focused on strengthening clinical effectiveness and safety evaluations of newly approved treatments through advanced epidemiology methods, examining treatment effect heterogeneity and conducting patient-centered analyses. Her latest efforts have focused on using RWD to optimize study design, inform site selection strategy and improve adherence and healthcare resource utilization.
- An accomplished author, Jennifer has published numerous articles and served as an editor of the e-book "Increasing Focus on the Patient in Patient Registries" to be published by the US Agency for Research on Healthcare and Quality. Other notable works include a perspective in Science, a paper for the National Academy of Medicine and a lead authorship position on the FDA's Cardiac Safety Research Consortium.
- Jennifer is a graduate of the UNC-Chapel Hill School of Pharmacy, UNC School of Public Health and Brown University School of Public Health in the USA. She is an Anniversary Fellow at the National Academy of Medicine and an adjunct faculty member at Weill Cornell Medical College in New York NY. She is also a Fellow and former board member of ISPE and has served on various editorial boards.

About QuintilesIMS

QuintilesIMS is a leading integrated information and technology-enabled healthcare service provider worldwide, dedicated to helping its clients improve their clinical, scientific and commercial results. Formed through the merger of Quintiles and IMS Health, QuintilesIMS's approximately 50,000 employees conduct operations in more than 100 countries. Companies seeking to improve real-world patient outcomes and enhanced clinical trial outsourcing through treatment innovations, care provision and access can leverage QuintilesIMS's broad range of healthcare information, technology and service solutions to drive new insights and approaches. QuintilesIMS provides solutions that span clinical to commercial bringing clients a unique opportunity to realize the full potential of innovations and advance healthcare outcomes.

As a global leader in protecting individual patient privacy, QuintilesIMS uses healthcare data to deliver critical, real-world disease and treatment insights. Through a wide variety of privacy-enhancing technologies and safeguards, QuintilesIMS protects individual privacy while managing information to drive healthcare forward. These insights and execution capabilities help biotech, medical device, and pharmaceutical companies, medical researchers, government agencies, payers and other healthcare stakeholders in the development and approval of new therapies, identify unmet treatment needs and understand the safety, effectiveness and value of pharmaceutical products in improving overall health outcomes.

To learn more, visit www.quintilesims.com

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www.twitter.com/QuintilesIMSRWI

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