Using Real-World Evidence to Optimize Clinical Trials

Improving Trial Design, Patient Recruitment, and Data Analysis

- SHYFT ANALYTICS

Authors: Rayhnuma Ahmed, Emelly Rusli

Co-author: Aaron Stern

Senior Author: Josh Ransom, PhD*

* Please send all correspondence to jransom@SHYFTAnalytics.com | linkedin.com/in/joshuaransom

EXECUTIVE SUMMARY

This paper highlights how biopharmaceutical companies can better leverage existing real-world data (RWD) to improve the costs and efficiencies of reseach and development (R&D). This allows them to accelerate the timelines of clinical trials without compromising the quality of evidence development, while greatly enhancing trial feasibility, implementation, and data analysis.

Here, we explore and outline how RWE can be practically applied to pre-clinical research and subsequent trial design and implementation. After reading this whitepaper, you will have a better understanding of how to:

- Use RWE to generate feasible and clinically relevant hypotheses and refine your patient cohort
- Leverage genomic data to further tune your patient cohort
- Optimize clinical trial design
- Ensure patient availability
- Assess site feasibility
- Reduce control arm and recruitment burden
- And bolster data analysis using a patient-centric tool

> The current cost of developing a prescription drug that gained market approval has been estimated to be around $2.6 billion, which is a 145 percent increase from the early 2000s.

Background

For decades, the costs of biopharmaceutical R&D have been rising unsustainably and it has become glaringly clear that the current drug development model is broken. The current cost of developing a prescription drug that gained market approval has been estimated to be around $2.6 billion, which is a 145 percent increase from the early 2000s (DiMasi 2016). It has also been estimated that some top pharmaceutical companies have spent nearly $12 billion per approved drug (Sax 2012). Though costs have been climbing, the likelihood of a drug successfully getting from Phase 1 to approval has not budged significantly from around 10 percent (Thomas et al. 2016).

Because of the massive divide between the development costs and likelihood of approval, drug manufacturers have historically priced their drugs at prohibitive levels to recoup portions of their investment. For rare disease treatments in particular, these fixed developmental costs must be recovered from a limited patient population. Spinal muscular atrophy (SMA), for instance, is a genetic disorder that affects 1 in 11,000 newborns yearly for which there had been no effective treatment despite intensive research since the discovery of associated gene mutation in 1997 (Smith 2017). In 2016, the FDA approved an SMA

effective drug; Biogen, however, priced its treatment at $125,000 per dose for a regimen that requires SMA patients to receive six doses in the first year and three doses each year after that. This is one among many examples of prohibitively priced therapies for rare diseases. These rising costs for consumers have in turn resulted in healthcare payers placing growing pressure on biopharmaceutical companies to develop evidence of value to justify the costs, which reinforces a vicious feedback loop of increasing costs associated with evidence development. In 2015 alone, total US spending on pharmaceuticals was $325 billion and is projected to reach as high as $610 billion by 2021 (CMS 2015). Needless to say, the US economy cannot sustain this growth rate nor can it continue to support the industry's status quo, especially when solutions exist for transforming R&D methodology to reduce costs.

The healthcare industry has been experiencing rapid growth in data sources such as electronic health records, insurance claims data, patient registries, surveys, medical devices, imaging, genomics, and more that capture vast amounts of patient health and medical information. This RWD can provide valuable health information in the context of patients' day-to-day lives including real clinical practice. With this added clinical context, RWD becomes real-world evidence (RWE) that can be used to evaluate the epidemiology and burden of a disease, comorbidities, treatment patterns, adherence, and outcomes of different treatments. RWE can therefore be used to model clinical studies, inform hypotheses, and thus improve the likelihood of approval and successful treatment launch. Not only can these applications contribute to compressing clinical trial timelines and drive down treatment costs, RWE can also serve as a powerful complement to evidence gathered from randomized control trials (RCTs), which continue to be the trusted standard for assessing biopharmaceutical drug safety and efficacy.

> RWD can therefore be used to model clinical studies, inform hypotheses, and thus improve the likelihood of approval and successful treatment launch.

Trial Feasibility: Generate a feasible and clinically relevant hypothesis and tune your patient cohort

Designing an effective trial begins with generating a hypothesis and defining the patient cohort. This process is one that requires extensive research and testing and is thus a lengthy and iterative one, requiring many sequences of refinement. RWE can be leveraged to rapidly explore and test hypotheses across diverse datasets. With the use of multiple and broad datasets, one can gain insights specific to an indication and severity of interest (e.g. rheumatoid arthritis, stage 4 chronic kidney disease, lymphoma, etc.) to identify clinical phenotypes,

indication and severity of interest (e.g. rheumatoid arthritis, stage 4 chronic kidney disease, lymphoma, etc.) to identify clinical phenotypes, outcomes, unmet needs, and more. *What are the treatment journeys of patients with the disease of interest? How rapidly do symptoms progress?* These are questions one can ask of RWE to assess clinical gaps, and the subsequent findings can be used to bolster a hypothesis and to design and tune the RCT to all possible unmet needs.

> Use RWE to rapidly leverage insights on your patient population of interest to generate a data-driven hypothesis.

A desired outcome of using RWE at this stage of R&D is to be able to develop a hypothesis regarding a specific patient cohort in a way that is data-driven and comprehensive. Conventionally, the primary tools used to generate a hypothesis have been limited to 1) published findings from previous studies and trials conducted in the patient population of interest or 2) costly and time-consuming primary chart studies. These methods do not provide extensive breadth or depth, especially when it comes to rare diseases and less common disease subsets. A new model has emerged that allows researchers to look at actual populations and their behavior and outcomes in near real-time. Advances in RWE technologies can provide researchers the ability to test hypotheses rapidly to determine clinical relevance along with care and treatment pathways of the desired cohort.

The longer-term impact of this use of RWE would be to fully model the clinical trial itself by applying predictive analytics. Using machine learning technology, researchers will be able to feed patient data into artificial neural networks trained to mine data and gather hypothesis-specific insights to design a trial tailored to the desired patient cohort and optimized for the highest likelihood of success. Machine learning systems can remove the need for researchers to manually test hypotheses and shorten the time from generating a hypothesis to optimizing the trial design.

Leverage Genomic Data to Tune Patient Cohorts

RWE is rich in phenotypic data that is optimal for exploring and testing hypotheses. However, one historic limitation of RWE has been a deficiency in genotypic information to link to the phenotypes. To address this limitation and to boost the predictive power of hypotheses and further tune and microsegment patient cohorts, RWE can be coupled with molecular and traditional biomarker data.

LEVERAGE GENOMIC DATA TO TUNE PATIENT COHORTS

Because biomarkers are measurable characteristics indicative of biological conditions, they can be mapped to diseases and outcomes. Examples of relevant biomarkers include levels of a particular protein in body fluids, patterns of gene expression, or genetic polymorphisms. As such, biomarkers can be used as inclusion or exclusion criteria for determining which patients to enroll into clinical trials. This use of selection biomarkers has increased since the human genome project (BIO, Biomedtracker, Amplion 2016). A study of clinical drug development success rates from 2006 to 2015 performed by BIO across 9,985 phase transitions, shows that selection biomarker use increases a trial's likelihood of approval from Phase I by 17.5% across all disease areas (BIO, Biomedtracker, Amplion 2016). The probability of success with selection biomarkers across indications is 46% from Phase II to Phase III (compared to 28% without), 76% from Phase III to New Drug Application (NDA)/Biologic License Application (BLA) (compared to 55% without), and 94% from NDA/BLA to approval (compared to 83% without). However, only 512 phase transitions out of the 9,985 used biomarker data for patient stratification. This illustrates how underutilized biomarker data is and its power when leveraged.

> Leveraging genomic data in clinical trials improves the likelihood of success across indications to 46% from Phase II to Phase III, 76% from Phase III to NDA/BLA, and 94% from NDA/BLA to approval.

Optimize Trial Design

Once a hypothesis has been formulated for the patient cohort of interest, RWE can be further leveraged to inform the design of the trial. This step is critical for ensuring that the study is optimized for feasibility and set up for the highest likelihood of success. Using information such as real-world treatment lengths and adherence data, researchers can determine a viable study length and frequency of study events. A leading cause of clinical trial failures is the inability to retain participants due to burdensome and poorly designed trials (Gul et al 2010). A near-term impact of using RWE is the ability to design participant-centric trials by mining RWE for measures of adherence, for example, to project and minimize the burden for a trial participant when thinking about number of study events, frequency of visits, treatments, or procedures. Often, when designing a trial, participants are regarded as interchangeable resources as researchers optimize for the best way to answer a scientific question without realistically accounting for participant retention. Many protocols therefore disregard participants' full lives outside the trial, which results in trial protocols with invasive and painful procedures, exorbitant numbers of procedures per visit, and/or a high frequency of visits throughout the duration of the trial.

OPTIMIZE TRIAL DESIGN

Leveraging RWE allows trial planners to assess and model the burden of protocols during the design stage to then minimize potential pain points for participants prior to executing the trial. Treatment and adherence data can be used to assess the threshold for number of study events to build into the study to minimize activity burden and maximize subject retention throughout the duration of the study. This step of optimizing the RCT design can reduce IRB amendments, which have been estimated to cost $450,000 on average with approximately 1.5 IRB amendments per trial (Covance Inc. 2014). These costs incurred during RCTs in turn slow development. Review of IRB amendments can often take between five to ten business days, and when accounting for local IRB timelines, review can take upwards of a month (Fuller 2014). This delays the timeline for when trial research can be resumed and can therefore impact the prices of the treatments that are subsequently launched into the market.

> Optimize a trial design using insights from RWE to minimize the burden for a trial participant and prevent exorbitant costs of and delays from IRB amendments.

So far we've covered how RWE empowers biopharmaceutical companies to:

- Generate feasible and clinically relevant study hypotheses
- Tune patient cohorts using RWE coupled with genomic data, *and*
- Optimize trial design

This next section of the white paper will explore how RWE can help overcome the challenges of patient recruitment. We will do this by first exploring how insights from RWE can be used to ensure patient availability and site feasibility prior to the start of recruitment. Second, we will introduce the revolutionary concept of crafting Synthetic Control Arms (SCA) from RWE to reduce control arm and recruitment burden. Finally, all these efforts can be more impactful with the use of a patient-centric tool to bolster data analysis.

Ensure Patient Availability

Finding the appropriate population is one of the biggest challenges in patient recruitment. Study criteria have now become more specific and selecting patients who meet these stringent criteria requires extensive screening and a higher likelihood of identifying inappropriate patients. This process is time consuming, as demonstrated by the fact that only 10-17% of studies complete patient enrollment on time (Suso 2017). Furthermore, about 11% of clinical trials are not able to enroll more than a single patient (Suso 2017).

ENSURE PATIENT AVAILABILITY

The burden is more apparent in less common disease subsets and rare diseases, such as oncology. About 60% of oncology studies are not able to enroll even a single patient (Covance Inc. 2014). All these statistics perfectly illustrate the challenge that patient recruitment and enrollment pose in a clinical trial.

RWE can help mitigate these hurdles by enabling early validation of whether there are sufficient patients with an indication in a given region, and whether these types of patients can be recruited based on known visits to candidate trial sites. This information can then be used to assess whether it is feasible to conduct the study. If a study does not pass this assessment, it allows researchers to quickly mine for other alternatives by identifying where available patients are located and going for care. In other words, RWE empowers researchers to microsegment patients based on their clinical profiles and geographical locations. Such an approach can alleviate the recruitment burden of trial implementation and make the process more efficient compared to current recruitment methodology of using information gathered from feasibility surveys.

> About 60% of oncology studies are not able to enroll even a single patient (Covance Inc. 2014).
>
> Perform early validation on patient availability with RWE to proactively avoid designing a non-recruitable trial and prevent delays due to extended recruitment phases.

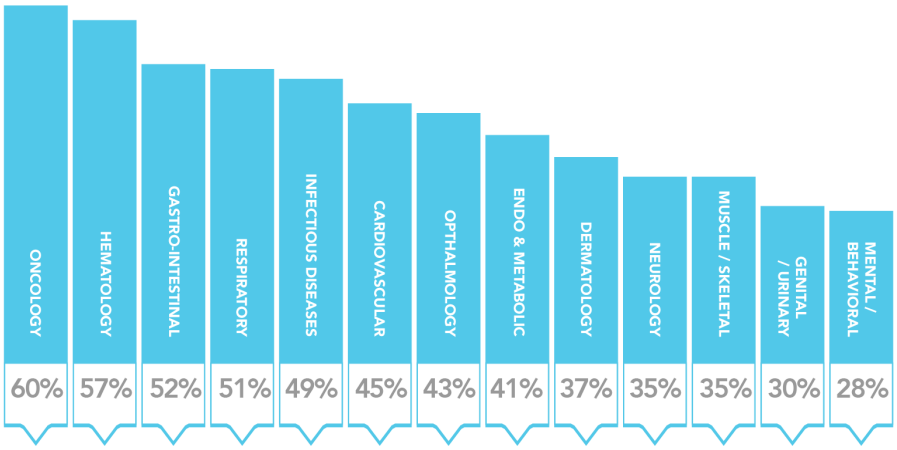
Assess Site Feasibility

Biopharmaceutical organizations on average conduct about 40 clinical trials per year at 86 sites per trial, according to our analysis. Of these trials, the non-recruitable sites contributed to a $2 billion loss between 2006 and 2010 (Covance Inc. 2014). Given this large scale of investment, ensuring that sites have sufficient number of patients is just a starting point. The traditional site survey administration is deemed inefficient. There is a glaring need for a more holistic approach to conducting site assessments by incorporating real-world practice data to gather information on non-clinical factors that contribute to fruitful site selection, such as patient engagement, researchers' skill sets, and their passion for the research and advancing treatment technology.

RWE can boost site feasibility assessments by allowing researchers to utilize best practices from previous site-specific clinical trials that were successful. Examples of areas within which best practices could better inform assessment include research methodology, trial administration, and investigator's experience with specific research topics. In addition, specific real-world data like Patient Reported Outcomes (PROs) can be used to measure patient engagement by predicting follow-up patterns and adherence trends projected for patients who get recruited into the trial. Combining these insights with patients' clinical profiles will improve likelihood of trial implementation success.

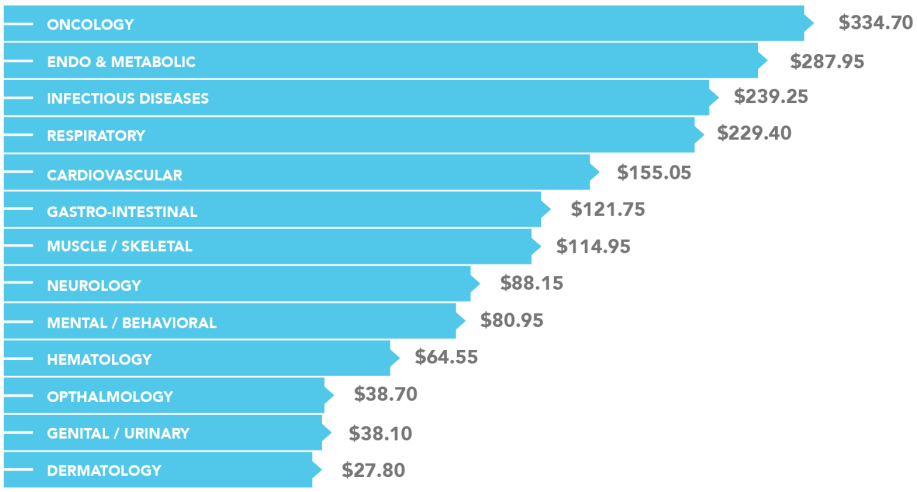
ASSESS SITE FEASIBILITY

1



PERCENTAGE OF NON-PERFORMING SITES BY THERAPEUTIC AREA

2



$1,917,550,000 WASTED ON NON-PERFORMING SITES

> Assess site feasibility using data regarding patient engagement, previous research methodology, and trial administration, etc. in RWE to allow for more fruitful prospective patient recruitment.

[1, 2] *"Addressing Ever-Rising Cost in Conducting Clinical Trials" Covance.com, Covance, 2015*

REDUCE CONTROL ARM AND RECRUITMENT BURDEN

RWE thus far has served as a passive source of information that provides insights on patients, care sites, etc. In this section, we will introduce RWE as an active source of information – specifically, we will discuss using RWE to create Synthetic Control Arms (SCA).

In a double-arm randomized trial, biopharmaceutical sponsors often deal with ethical concerns or challenges of assigning patients to a placebo treatment.

Such cases act as a barrier to patient recruitment and retention, especially when it comes to treatments for terminal illnesses and rare diseases. In a review of supportive care and palliative oncology trials by Hui et al., it was assessed that the attrition rate in 18 trials between 1999 and 2011 was about 44% by the end of the study (Hui et al., 2013). This can be partly explained by symptom burden where patients quickly realize that they didn't receive the active treatment and hence perceive their lives are on the line causing them to drop out of the study.

Creating an SCA mitigates this issue by providing a comparable control arm and allowing all recruited patients to be in the active arm. Such approach will improve retention and ease the patient recruitment process. For sponsors, this would not only improve study validity but also lower costs associated with patient recruitment and negate the need to outsource to third parties to handle the job.

Conventionally, SCAs are built using historical or previous trial information. This is hugely problematic due to the lack of breadth or depth of the patient's clinical profile, particularly for rare disease or less common conditions. This SCA methodology does not quite account for real-world practice that demonstrates standard of care for a disease. RWE is therefore the long-awaited answer for better designed SCAs. Not only does RWE capture standard of care in real-world settings, but it also contains large sample sizes that can further give power to trial data analysis.

Creating SCAs from RWE is however not without its challenges. The nature of real-world data is that it is unorganized and not collected in a controlled environment. Albeit difficult, it is not without resolution. A technique like propensity score matching can be leveraged to match patients' demographics, as well as their clinical profiles and treatment patterns to those of the participants enrolled in the trial.

> Design Synthetic Control Arms using RWE to cut costs associated with patient recruitment and provide a comparable control arm based on the real-world practices with a more significant sample size to enhance the power of the data analysis.

BOLSTER DATA ANALYSIS USING A PATIENT-CENTRIC TOOL

The next section of this paper will introduce how technology may accelerate the data analysis process, including a propensity score analysis.

Adopting RWE to create SCAs is perhaps still further off in the future; however, there's growing interest in this approach across biopharma, payers, and even regulatory agencies. In the interim, the insights provided by RWE are still valuable for market access strategy and clinical trial operations as mentioned in the previous sections.

Bolster Data Analysis Using a Patient-Centric Tool

In the six areas discussed above, we've seen the power of RWE in clinical trial design and execution. However, this power cannot be fully optimized without a technological tool that advances the data analysis process itself.

Of the numerous technologies being offered in the market these days, it is important to focus on tools that can consume real-world data and provide insights from this data in a way that's centered on the user's research needs. We've learned so far that RWE is unorganized and collected in uncontrolled environments. It is therefore essential to invest in a technological tool that can improve data quality and enable researchers to gather information on patient populations of interest with more granularity.

One feature to look for should be the adoption of machine learning to rapidly capture errors in the data and thereby improve its quality. Another important feature of the tool should be the ability to allow researchers to build ad-hoc patient cohorts, plan, and execute analyses. In other words, the tool must bolster researchers' ability to describe and learn about the patient population (i.e., a patient-centric tool): who are they and where they are located, how and when do their symptoms progress, what do their treatment patterns look like, etc. To maximize utility, the tool must also empower researchers to rapidly perform a matching technique, such as calculating propensity scores. This is particularly important at the hypothesis generation stage of designing a clinical trial. Using technology that can rapidly produce insights from RWE at the patient level within an indication of interest is extremely valuable. Capturing insights on a patient population within the therapeutic area early and accurately empowers researchers to be smarter in designing a trial, iterate quickly, and recruit the right study participants, which will result in an accelerated drug submission process.

> Bolster your trial data analysis by iteratively gathering insights on your patient cohort using a patient-centric tool that can ingest RWE. Building and running analyses on an ad-hoc patient cohort, rapid propensity analysis, and machine learning capability are important features to consider when deciding on a tool.

SUMMARY

The costs of biopharmaceutical research and development (R&D) has been rising unsustainably, and the US economy cannot continue to feed our industry's gambling addiction of increasing costs associated with evidence development. The rapid growth of real-world data (RWD) in the healthcare field provides valuable data regarding patients' care. The richness of the data captured by sources of real-world evidence (RWE) can be used to evaluate various aspects of therapeutic areas: epidemiology, comorbidities, treatment patterns, costs, etc. This paper highlights 7 actionable strategies for leveraging RWE to transform the traditional R&D process:

1. Generate feasible and clinically relevant study hypotheses
2. Tune patient cohorts using RWE paired with genomic data, *and*
3. Optimize trial design
4. Ensure patient availability
5. Assess site feasibility
6. Reduce control arm and recruitment burden
7. Bolster data analysis using a patient-centric tool

These 7 strategies demonstrate the patient-centric benefits of RWE in areas of trial feasibility, implementation, and data analysis. Conducting a clinical trial with comprehensive and rapid insights on the patient population of interest allows researchers to be smarter in designing a trial, iterate quickly, and recruit the right study participants, which will result in an accelerated drug submission process. As such, these 7 approaches to using RWE in clinical trials will tremendously compress trial timelines, drive down treatment costs, and set up biopharmaceutical organizations for the highest likelihood of success in their R&D pathways.

REFERENCES

Bio, Biomedtracker, and Amplion. "Clinical Development Success Rates 2006-2015." BIO Industry Analysis Published Reports (2016): https://www.bio.org/sites/default/files/Clinical%20Development%20Success%20Rates%202006-2015%20-%20BIO,%20Biomedtracker,%20Amplion%202016.pdf

Centers for Medicare & Medicaid Services. "National Health Expenditures 2015 Highlights." Statistics Trends and Reports (2015): https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/downloads/highlights.pdf

Covance Inc. "Addressing Ever-rising Cost in Conducting Clinical Trials." Xcellerate Challenger Infographic. Last modified 2014. https://www.covance.com/content/dam/covance/assetLibrary/infographics/Xcellerate%20Challenger%20Infographic-2014.pdf

DiMasi JA, Grabowski HG, Hansen RA. Innovation in the pharmaceutical industry: new estimates of R&D costs. Journal of Health Economics 2016;47:20-33.

Fuller, Felicia. "Minimizing IRB Resubmissions to Maximize Clinical Trial Enrollment." Imperial A Clinical Research Support Organization (2014): http://www.imperialcrs.com/files/CRS_White_Paper_Minimizing_IRB_Resubmissions_Aug_2014.pdf

Gul, Raisa B., and Parveen A. Ali. "Clinical trials: the challenge of recruitment and retention of participants." Journal of clinical nursing 19, no. 1&2 (2010): 227-233.

Hanstedt, Paul. "This is Your Brain on Writing: The Implications of James Zull's The Art of Changing the Brain for the Writing Classroom." Presentation at the Annual Convention of the Conference on College Composition and Communication, San Francisco, CA, March 11-14, 2009.

Hui, David, Isabella Glitza, Gary Chisholm, Sriram Yennu, and Eduardo Bruera. "Attrition rates, reasons, and predictive factors in supportive care and palliative oncology clinical trials." Cancer 119, no. 5 (2012): 1098-105. doi:10.1002/cncr.27854.

REFERENCES

Platero, Suso PhD. "Optimizing CDx Clinical trial Design, Recruitment/ Enrollment & Execution." Covance Inc. (March, 2017).

Sax F. Clinical Trial Planning & Design: Can Better Design Save Biopharma?. Quintiles 2012: http://www.quintiles.com/library/white-papers/can-better-planning-save-biopharma-clinical-trial-planning--design

Smith, Gordon A. "The Cost of Drugs for Rare Diseases Is Threatening the U.S. Health Care System." Harvard Business Review (2017): https://hbr.org/2017/04/the-cost-of-drugs-for-rare-diseases-is-threatening-the-u-s-health-care-system

Thomas DW, Burns J, Audette J, Carroll A, Dow-Hygelund C, Hay M. Clinical Development Success Rates 2006 – 2015. 2016 https://www.bio.org/sites/default/files/Clinical%20Development%20Success%20Rates%202006-2015%20-%20BIO,%20Biomedtracker,%20Amplion%202016.pdf

About SHYFT

SHYFT is the leading analytics platform for life sciences with products designed specifiically for the unique needs of the pharmaceutical, biotech, and medical device industries. SHYFT's Data Analytics Platform is the most efficient and scalable way to transform massive amounts of complex healthcare data into on-demand clinical and commercial insight.

CONTACT US

- Phone – 781-547-7500
- Email – infos@shyftanalytics.com