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WHITE PAPER

When Clinical Trials Meet the Real World

Bridging the experimental and post-launch divide with data integration

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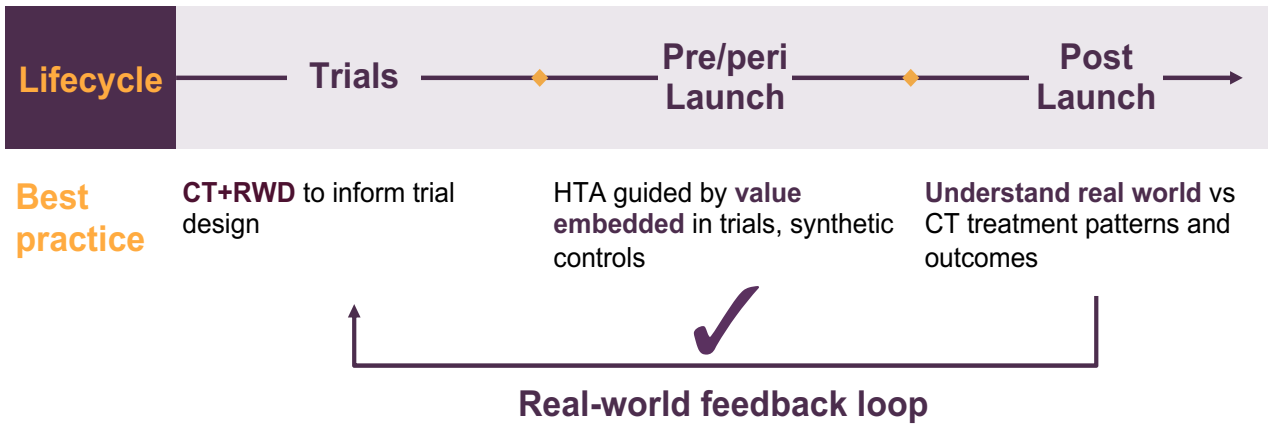
Unlocking Value with Data

The biopharma industry faces a troubling problem: Trial design is foundering on multiple fronts. About 64 percent of phase three trials fail, and about two thirds of these failures occur due to flawed design, inappropriate endpoints or under-enrollment. Even when trials don't fail, they incur on average 1.5 institutional review board (IRB) amendments per trial, costing roughly $500,000 each and potentially delaying trials for months. Many biopharma companies do not fully embed value in their clinical development programs, and struggle with achieving uptake or demonstrating the value of the new therapies they've worked so hard to develop. That's because real world patients often look very different from trial patients, or because the clinical guidelines don't match up with the new therapies. When drugs work in the lab, but not out in the real world, doctors don't want to prescribe them and patients don't want to take them.

And yet, it doesn't have to be this way. The industry possesses a wealth of data from both clinical trials and real world clinical settings that could address these gaps. Today, the feedback loop is broken. Valuable data is slipping through the cracks where it is most needed because companies don't have the tools or the experience to put it to work. The answer lies in pooling and integrating disparate datasets to form a complete picture of the patient experience. These insights can then be used to inform decision-making across the product life cycle, from R&D to prelaunch to post launch, letting it inform truly adaptive trial design and tailored medical engagement.



Biopharma companies already use real world data today to inform clinical development and rare disease research. For example, electronic medical record data is used to find patient pools for trial recruitment and to benchmark real world outcomes for new therapies. Real world data is also used to identify unmet needs in real world patient populations that could justify label expansion for existing therapies or the exploration of new therapies. Pfizer's Ibrance expanded its label from female to male breast cancer patients, a population with a high unmet medical need, using real world data. Real world treatment patterns are also often harnessed to inform novel therapy development and adoption. In addition, real world data is used to support the regulatory approval process. For instance, last year, the FDA took steps to encourage the use of natural history studies to support rare disease research with two new grants as well as guidance issued for the design of such studies.

At the same time, the use of pooled clinical trial data is on the rise. These richer datasets can support a greater range of insights, such as baseline risk stratification of patient subgroups, in-depth characterizations of adverse events or the validation of primary and secondary endpoints. Pooled clinical trial data is also increasingly being used to design synthetic control arms, and even to power algorithms that can predict things like patient drop out or patient identification. For example, Friends of Cancer Research has used pooled data to do some concept work on synthetic control arms for lung cancer and multiple myeloma. Celsion Corporation recently announced that Medidata developed regulatory grade synthetic control arms to support a Phase IB study in ovarian cancer. Acorn AI's synthetic control arm was able to provide near perfect matches for patient characteristics and showed strong progression-free survival treatment effect. Based on the potential demonstrated by synthetic controls, certain clients are incorporating them into breakthrough turnkey submission or designing partial synthetic control arms to increase the safety of their studies.

Closing the Feedback Loop

One way to integrate all this data into trial design is to examine real world and pooled clinical trial datasets side by side, to identify differences between your clinical trial and real world populations. Medidata showcased one example of how this might work last year at the ASCO conference in Chicago. We looked at acute myelogenous leukemia (AML) and explored real world data from an oncology electronic medical record source compared with pooled clinical trial data. Bringing these datasets side-by-side allowed us to better understand and contextualize real world patient characteristics and explore safety events.

We wanted to know, for example, whether the trial population adequately reflected real world population diversity in terms of age, ethnic breakdown and gender balance. In the case of AML, we found that there was actually a lot of similarity between the two populations with respect to demographics. Then we looked at how quickly treatment guidelines were being adopted or modified and whether there were significant differences in how patients were treated in recent trials versus in the real world. We found that in real world settings, patients used more demethylation agents and fewer cytotoxics than in the historical clinical trials. This insight helped to inform both patient recruitment, medical engagement, payor discussions, and provider messaging.

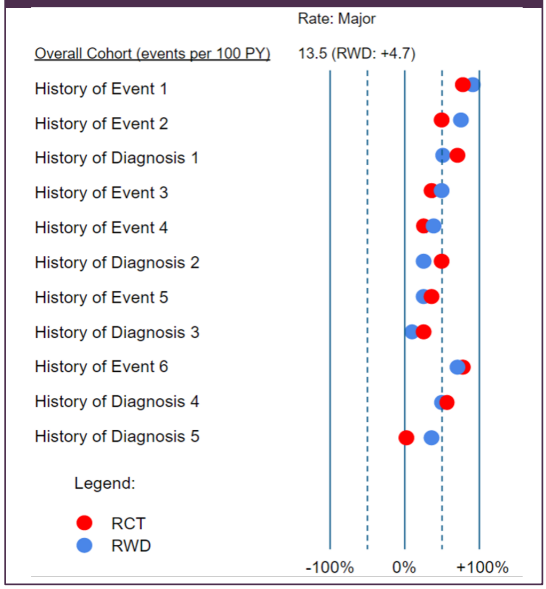
Exploring Gaps in an Existing Market

Integrated datasets can also help explore gaps in an existing market. For example, Medidata recently partnered with a company interested in designing a trial to explore new therapies for cardiometabolic disease, a market with a lot of well-established therapies. In this case, the company needed a robust estimate of competitor treatment effect, in a trial context, to inform trial enrollment assumptions. Using pooled trial data allowed us to do a comprehensive job of stratifying patient populations and matching them with envisioned trial criteria. Also, because of changing treatment guidelines in this disease space, we needed to understand if real world event rates had changed with the introduction of new therapeutic options over the past few years. Because the company was interested in exploring a broader patient inclusion criteria than what competitors had pursued in the past, they needed insights into event rates in populations that were either not available or not widely available in historical trials. Getting good answers demanded the pairing of real world and clinical trial data.

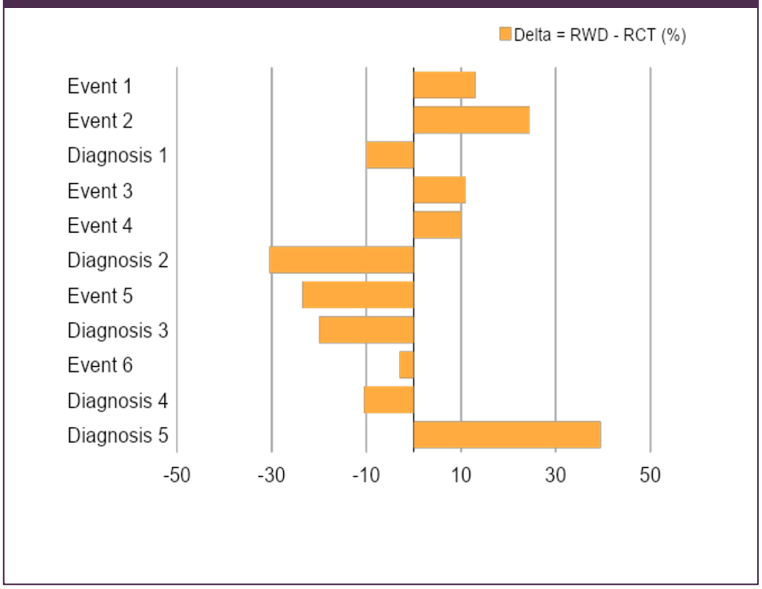
To gather our pooled clinical trial data sample, we started with our Medidata archive of 22,000 studies of 6 million patients and collected studies with the appropriate indication and therapeutic agents against which there was a desire to benchmark. Then we extracted and standardized the necessary data fields. Next we stratified the pooled data cohort to examine target indication populations for other relevant subgroups of interest, which gave us a robust starting point for more advanced analysis like propensity matching.

Finally, we pulled real world claims data and conducted a comprehensive side-by-side analysis of the datasets. What we found was that the clinical trial population was younger, with fewer comorbidities and less overall morbidity than the real population, all factors we were able to quantify. We also looked at subpopulations, people with certain comorbidities that were less well represented in clinical trial populations. For some diagnoses, the event rates were much lower in the real world and for others they were much higher.

Comparison of clinical event rates



Delta between RWD vs. RCT



Our insights yielded several key takeaways for clinical trial design. First, the historical clinical trial population was not representative of the real world disease population, which was justification to use broader inclusion criteria in an upcoming trial. Because of differential event rates, broadening of inclusion populations would not only make the clinical trial population more representative, it might make it possible to reduce the sample size needed to power an event-driven trial. This could reduce costs significantly, given that the cost per patient can range from $10,000 to well over $150,000 in oncology. For serious conditions, higher event rates can also translate into shorter trial durations, and that means faster time to get new treatments to patients who need them. We were also able to quantify differences between various patient populations in ways that could be communicated to health insurance payers. We were also able to improve assumptions about effect size and population variability. The findings were robust.

Conclusions

These are just two examples that illustrate some of the benefits of bridging the experimental and post launch worlds of clinical data. As we evolve into this new era of data integration, biopharma companies should extend the linked approach into the entire product lifecycle, from R&D to pre launch and post launch. Drug companies stand to benefit enormously from making data-driven decisions about how to design their clinical trials and how to engage providers and patients post launch. Real world evidence and pooled clinical trial data are increasingly available, linkable and minable to find valuable insights quickly. To date, we've helped our customers run shorter, smaller trials, strengthen FDA submissions and better articulate the value of the therapy before and after launch to support the entire product lifecycle. We look forward to sharing more impact stories with you in the future. Together, we can fortify clinical trial design by closing the feedback loop, making all of the data we work so hard to collect work for us in return.

About AcornAI

Acorn AI™ is a Medidata company that represents the next horizon of the industry leader's 20-year mission of powering smarter treatments and healthier people. Acorn AI is designed to make data liquid across the entire lifecycle and to answer the most important questions in R&D and commercialization for customers. Built upon the Medidata platform comprising more than 20,000 trials and 5 million patients, Acorn AI products feature one of the industry's largest structured, standardized clinical trial data repository connected with real world, translational and other datasets. For more information:

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