DCRI **THINK TANKS**

FROM INSIGHT TO ACTION

The Power and Potential of Real-World Data in Randomized Clinical Trials

BACKGROUND AND CONTEXT

The DCRI Think Tank is an interactive meeting that engages diverse perspectives and leadership expertise from academia, industry, government agencies, and payer groups to address key issues in clinical research, policy, and practice to improve health.

On May 29-30, 2024, a DCRI think tank session investigated the potential applications of real-world data (RWD) in randomized clinical trials by sharing prior experiences, identifying barriers, and proposing solutions acceptable to clinical researchers, healthcare communities, and regulators in both the United States (US) and Europe with the intention of identifying efficient and appropriate approaches to integrate RWD in randomized clinical trials.

KEY TAKEAWAYS AND THEMES

Real World Data (RWD) are useful for clinical trials, but infrastructure is still lacking

The use of RWD has the potential to enhance the conduct of randomized clinical trials. Real world data can be used across different steps of trial conduct, e.g., protocol design, data acquisition and safety monitoring. Notably, one of the key benefits of RWD is its application in study planning. Researchers can inform power calculations through use of RWD and by leveraging RWD they can efficiently identify eligible patients and the trial sites that have access to those patients, facilitating site selection practices that take trials to where the patients are.

The highlighted potential of RWD allows for larger trials of more inclusive study populations, alignment with the execution of point-of-care trials, longer follow-up durations, reduced loss-to-follow-up, decreased "per-study" burden on sites, and has the potential for reduced costs for sponsors. However, challenges must be overcome to realize the full potential of RWD. To begin, infrastructure gaps pose significant hurdles. Particularly in the US, the fragmented healthcare- and payer systems create difficulties in tracking patients who receive care from multiple organizations or switch health insurance providers. Secondly, challenges in standardizing healthcare data complicates the use of RWD. While subsets of organizations have implemented and adopted standard data structures (e.g., OHDSI/OMOP, FDA Sentinel, PCORnet), these are not universal and standardizing differences in the standard of care and coding practices across providers, healthcare systems, and countries remains complex.

Furthermore, the various RWD sources that exist may not always be well aligned with the needs of clinical research (i.e., relevance can be an issue). Mitigating infrastructure gaps across countries in international trials may involve prioritizing validity over representativeness, recognizing the value in having a large number of patients from a few countries rather than a few patients from many countries.

The clinical research ecosystem can and must be simplified

Simplifying the landscape of clinical research would encourage and enable researchers to perform more trials and potentially larger trials. Simplifying study design in terms of eligibility criteria, data collection, and endpoint assessments has the potential to reduce burden on sites and physicians, thereby improving clinical trial recruitment and facilitating broader site engagement. Examples of simplification include leveraging validated algorithms applied to claims or electronic health record (EHR) data to ascertain endpoints as well as fact of hospitalization and death rather than central adjudication or "change from baseline" assessments. However, when implementing such simplifications, it remains essential to maintain randomization and blinding (when possible) to reduce biased trial results.

The notion that inclusion of patients should be easy ("two clicks") and sites should not have to enter data that already exists electronically in health care systems is key. Data collection, such as detailed accounts of commonly occurring safety events via serious adverse event (SAE) narratives, are very labor intensive for sites due to extensive research-specific data entry and the value-add is minimal for understanding safety profiles.

Streamlined safety considerations are addressed by ICH E19 guidelines which suggest collection of study-specific safety data may be reduced or offset by RWD in certain scenarios; however, site and data monitoring efforts (and regulatory inspections) must be adjusted to better align with how data are captured from RWD sources and RWD sources may need to be adjusted to enable reliability and access for monitoring.

Use of RWD requires careful consideration of fitness for purpose

The use of RWD may require accepting less detailed data in exchange for higher volumes of data. In the right context, this premise is reasonable; studies such as TASTE (DOI: 10.1056/NEJMoa1308789) and TOTAL (DOI: 10.1056/NEJMoa1415098) or DAPAMI (DOI: 10.1056/EVIDoa2300286) and EMPACT (DOI: 10.1056/NEJMoa2314051) have shown that traditional randomized trials and trials including data from RWD sources can yield comparable results.

However, the issue of timeliness should be considered when using RWD. While research data is collected in "real-time", RWD from sources such as healthcare claims and registries may be significantly delayed, depending on the elements of interest. Various European registries such as Swedeheart have succeeded in obtaining timely complete national data and existing standardized data models in the US such as OHDSI/OMOP, PCORnet, and FDA Sentinel have also been successful, albeit with subsets of healthcare systems in the US.

ACTIONABLE ITEMS

1. Identify challenges in acceptability of RWD use and develop an educational process to overcome these challenges

Accepting the tradeoff of challenges and benefits associated with leveraging RWD sources in randomized clinical trials is crucial for success. This starts with a cross-sector collaboration on a consensus of barriers to use RWD in clinical development. Beyond just barriers to use, challenges in the acceptability by patients, regulators, payers, sponsors, and the broader healthcare community must be understood. With this understanding, a strategy for improved acceptability through better education and training could result in increased use of clinical trials that leverage RWD.

2. Simplify study design

Simplification of clinical trial design and data collection, as well as use of RWD to inform design has the potential to improve recruitment, increase site engagement, and reduce trial design modifications. Specifically, streamlining eligibility criteria will decrease burden for sites/physicians, but also create more generalizable populations. Moreover, study design such as cluster randomized trials and the ability of patients to self-identify for trials are different ways to reduce burden on physicians and could be considered more broadly. Enhancing self-identification could be managed through work with patient advocacy groups or implementation of a "data donator card" as a way for patients to volunteer for their data to be linked/leveraged for research and to indicate their willingness to participate in research. Extensive safety collection has presented a hurdle for leveraging RWD for safety assessments, however regulatory guidance such as ICH E19 supports streamlining of these activities. Early dialogues with regulatory authorities can result in implementation of more efficient data collection.

3. Support collaboration, cooperation, and partnership between sponsors and regulatory authorities

There is a vital need to partner and collaborate across the clinical trial ecosystem to advance the use of RWD. This includes leveraging existing infrastructure by partnering across healthcare communities, systems, the EHR, claims databases, Health Economic Outcomes Research databases, sponsors and regulatory authorities both in the US and Europe and building infrastructure which supports multiple trials. This will allow researchers to leverage existing data and frameworks, thereby reducing redundancy and accelerating the pace of clinical research. For instance, implementing platform trials and hybrid trials within patient registries can streamline the clinical trial process, making it more efficient and less resource heavy. Particularly for the US, the use of less fragmented systems, such as the Veterans Administration, Medicare/Medicaid, and other insurance claim systems linked to registries could have the potential to alleviate infrastructure issues.

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