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Examining the Feasibility of Real World Evidence Through Pilot Studies

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Summary

Technological advances in data capture are raising the potential that information collected as part of broad care delivery can be used to support the observed clinical benefit of a new drug and supplement post-marketing commitments or label claims for additional indications in rare cancers, where few treatment options exist.

Introduction

Traditional evidence generation for the development of new treatments follows well-established pathways beginning with defining safety profiles, establishing initial efficacy, and expanding to pivotal trials to support regulatory approval. Often pivotal trials rely on randomized controlled clinical trials (RCTs) that provide the most reliable information, through comprehensive designs to control for most sources of bias, regarding the effects of therapeutic interventions. In recent years, biomedical advances have facilitated broader use of alternative evidence collection models, including non-randomized approaches, where RCTs may not be feasible or ethical.[1]

While providing mechanisms to comprehensively address the safety and efficacy of novel therapies, these traditional approaches to evidence generation only provide information of relatively homogeneous populations found in clinical trials and needed for regulatory approval, yet, leave many questions unanswered regarding drug effectiveness, tolerability, and treatment heterogeneity in real-world populations. While many new drugs continue to be monitored through systemic post-market evaluation to address certain practical aspects of drug applications, the systemic monitoring of clinical practice has yet to be more broadly applied to other stages of drug development, particularly in oncology.

Additionally, new scientific advancements in drug development have led to the increase in molecularly targeted therapies, which target "subgroups of patients (within the larger population with a given disease) who are predicted to benefit from them."[2] The increased specificity and potential for substantially greater benefits over other therapies provide great promise, but also may lead to tension between the regulatory requirements and development resources, including ethics, time, costs, and patients. The Breakthrough Therapy Designation (BTD) program, for example, seek to mitigate some of these tensions by expediting the clinical development of drugs that are intended to treat serious and life-threatening diseases and for which preliminary clinical data indicate that the drug may provide a substantial benefit over available therapies, while minimizing valuable resources. While BTD and Accelerated Approval programs have contributed to the expedited development of many novel therapies, they rely on the need to expand the safety profile and confirm clinical benefit of the drug in other disease settings and/or in the post-market setting.

Real-World Evidence

The growing use of electronic health records (EHRs) have facilitated collection of patient data outside of clinical trial settings, and hold potential to further inform patient care, supplement current clinical trial methodologies, and speed drug development; in general, EHR-derived clinical data, which is a comprehensive collection of a patient's medical and clinical history, is referred to as "real world data" (RWD). EHRs, along with numerous other data sources including, randomized trial supplements, pragmatic trials, patient registries, administrative claims, surveys, pre-approval access programs, and mobile health-generated data (e.g., smartphones, wearables, social media)

[1] The role of Non-Randomized Trials for the Evaluation of Oncology Drugs. November 2014. http://www.focr.org/sites/default/files/pdf/Non-Randomized%2BTrials.pdf 2

[2] Sherman RE, Li J, Shapley S, Robb M, and Janet Woodcock. Expediting Drug Development—The FDA's New "Breakthrough Therapy" Designation, NEJM. 2013. 369:1877–1880.

all contribute to the broader concept of Real-World Evidence (RWE), referring to evidence generated from data collected outside the traditional clinical trial setting including use of data that is routinely collected in the daily practice of medicine, and thus reflective of the heterogeneous patients seen in real world practice. RWE may better reflect the general population and the care they receive, given that enrollment in clinical trials is often limited to patients with specific baseline characteristics. Therefore, high quality RWE can potentially enable a more generalizable estimate of the safety and effectiveness of therapies than well-controlled clinical trials with narrow eligibility criteria.

RWE may be particularly useful in the case of a drug with a large effect size, such as a BTD, where confidence in the original efficacy data is relatively high. While concerns regarding data quality, owing to factors such as missing information and non-systematic data collection, are substantial, information gathered from EHRs holds the promise of allowing data to be collected on more patients and more rapidly than traditional phase 4 trials, or phase 2/3 trials designed to provide evidence for new indications. Thus, in cases of transformative treatments, the question under what conditions would it be feasible to confirm clinical benefit in new indications in the real world setting and use this evidence to support new label claim, warrants serious consideration.

Real-World Evidence Applications

There are numerous uses and advantages to collecting RWD and applying it as a source of RWE to extend our understanding of the safety and effectiveness of a therapeutic.[3] The challenge for studies utilizing RWE, will be to balance the need to ease access to new promising therapies and at the same time provide strong convincing evidence of clinical benefit.

Thus, an opportunity exists to outline approaches and considerations for developing and testing pilot studies that aid in determining the feasibility of collecting and using RWE to provide strong clinical evidence to support regulatory decisions. Pilot projects have opportunities to 1) test data collection systems and identify reliable sources of RWD, 2) assess the feasibility and utility of real-world data, 3) identify novel endpoints that correlate with clinical benefit and reflect correlations between clinical practice and trial settings, and 4) determine other study criterion, such as biomarkers and study size, important for meeting study objectives. Ultimately, such studies can inform regulatory practices, including identifying criterion for label expansion, and improving our understanding of drug performance and clinical trial generalizability.

Exploring RWE Collection: Hypothetical Case Studies

We explore three potential uses for RWE using a hypothetical scenario. In this scenario, the original approval of "Therapy A" was based on a single arm study, which displayed activity similar to a Breakthrough-like product. The drug received either full approval in an indication with a small overall patient population or accelerated approval that was later converted to full approval based on a randomized study in a less sick population. The drug has been available on the market for 1+ years and additional data, including phase 4, investigator initiated studies and RWD, confirms the positive risk/benefit in the approved indication.

Based on this scenario, three case studies are considered below for using RWD could be used to support and expand the safety and efficacy dataset for hypothetical Therapy A. The goal of these approaches is to learn about the utility of collecting real-world data in the specific cases described and determine if the generated evidence that meets a pre-specified data quality

[3] Blueprint for Breakthrough: Exploring the Utility of Real World Evidence (RWE). June 2016. http://www.focr.org/sites/default/files/pdf/RWE%20-%20Project%20PRE-MEETING%20DRAFT.pdf

standard, could support a label claim for an additional indication or an update to the label considering dosage and/or schedule of approved treatment regimen. Thus, each approach requires a discussion, between the sponsor/investigator and the FDA around determining the appropriate standard for collecting real-world data, which may include observational data, as well as best approaches for combining data from multiple sources, determining the appropriate study sample size, analysis approaches, and data quality expectations.

1. Prospectively-defined collection and review of patient experiences on off-label use (i.e., observational data) for approved agents.

   Application: *Early phase 1 trials and evidence from a "basket" phase 4 trials, based on 10-15 treated patients, indicates the Therapy A maybe very active in a rare cancer, where no other treatment options are available. To gain access to this drug (off-label), the sponsor requests a meeting with the FDA to review and discuss existing evidence and the ability to collect observational data to supplement the existing limited data obtained in clinical trials.*

   Determining the feasibility of using observational data as the basis to update the label of Therapy A, will depend on an agreement around the assurance of data quality and necessary documentation, the necessity of conducting an observational study over a traditional single-arm approach, and the ability to define and meet study objectives.

   Based on the feedback received, the sponsor conducts analyses using the most relevant endpoints (e.g., physician defined response, time on current therapy, compared to time on previous therapy and/or decrease of pain medication use on current therapy, compared to previous 6 months). If significant activity is observed, sponsors may consider requesting a FDA meeting to discuss the submission of reports and data.

2. Phase 2 randomized trial approach to assess or confirm a robust response rate and continue long-term follow-up in the real-world setting.

   Application: *In a narrow disease setting, patients have limited treatment options once they exhaust the 3-4 available therapies resulting in unfavorable outcomes. A strong scientific rational exists that Therapy A could be active in a specific indication (e.g., biomarker defined). A detailed assessment of the activity of Therapy A could be done using a relatively small, approximately 60-80 patients, randomized (2:1) phase 2 study of Therapy A vs. physician's choice. If the patients on Therapy A experience significant response compared to patients on the control arm, who are progressing rapidly, then crossover at the time of progression would be allowed.*

   Concurrent to the phase 2 study, an observational data collection strategy for the same indication, matching patients on a set of pre-specified baseline characteristics and number of prior therapies, could be employed. The collection of observational data could also be used as a control arm to the phase 2 trial to assess and compare longer-term outcomes (e.g., time on the most current therapy, and even overall survival). The feasibility of this approach would depend on sponsor/FDA agreed upon criteria for collecting, analyzing, and assuring appropriateness of data quality and study design.

3. Pragmatic randomized trial approach leveraging existing clinical infrastructure to test interventions in everyday clinical settings.

   Application: *Following initial approval of Therapy A, additional clinical experience suggests*

that a lower dose given more frequently could be just as efficacious and possibly safer than the original dose studied and included in the product label.

Efficacy and safety of the new dose could be assessed by conducting a non-inferiority pragmatic randomized study comparing the two treatment regimens. Following randomization, the data for the study (including patient characteristics, treatment, and outcomes) could be obtained from electronic health records. The feasibility of this approach would depend on sponsor/FDA agreed upon criteria for collecting, analyzing, and assuring appropriateness of data quality and study design. This approach would allow for assessment of feasibility of both obtaining consent and randomizing patients at sites beyond those typically conducting randomized controlled trials. Given the pre-specified criteria are met, the generated evidence could be used to update the label with information on the new regimen.

The success of these three approaches depends on a rigorous assessment of outcomes within the RWD setting. The assessment process needs to assure reliability, consistency and validity of the outcomes. It maybe also be required that real world data outcomes in the original indication are consistent with the results from the clinical trials in the original indication.

While not captured in the above approaches, RWD collection for Therapy A post-approval may additionally provide information on the safety profile of the drug including: dose interruptions, dose modifications, concomitant medications, additional toxicity and other adverse events, therapy duration, and may contribute to the enhanced evaluation of an appropriate dose of the drug in the post-market setting. Thus, data around patient characteristics, safety, and mortality in patients receiving treatment with Therapy A, in any treatment setting using even a limited patient pool that meet the criteria of the study population, may facilitate determination of appropriate treatment safety, dosing, and sequencing.

Real-World Evidence Considerations

Each approach will require additional considerations and questions to be addressed to determine the appropriate study mechanism. These are summarized in the below table.

Considerations	Questions
Disease setting	■ Is randomization feasible? ■ Should rarity be a factor? ■ Could study enrollment and completion be effected (i.e., inability to accrue patients)?
Efficacy experience	■ What efficacy data is available? ■ Is it consistent with a BTD? ■ Does preliminary information on the activity of the BTD in this specific indication exist?
Safety profile	■ Is there a well-described safety profile on this therapy? ■ Are adverse events well described? ■ Has appropriate dosing and sequencing been determined?
Existing treatment options	■ Could these serve as a control? ■ Could alternative treatment options effect study accrual or analysis?

Study outcomes	■ Which outcomes are appropriate for the study? • Physician assessed response rate • Duration of physician assessed response • Decrease in pain medication use as compared to patients previous 6 – 8 months • Decrease in medication use to control other disease specific symptoms • Duration on previous anti-tumor therapy as compared to duration on the most recent breakthrough therapy • Time to switch in therapy (versus control) • Overall Survival (versus control) • Physician assessed PFS (versus control)
Sample size	■ What data is already available? ■ What is the expected sample size, based on factors such as response rate?
Feasibility	■ Given the above, is the study feasible? • Can it be enrolled considering disease rarity? • What will it take to complete the study (time and resources)? • Will control patients agree to be part of this study, or will they look for other treatment options? • Where appropriate, is crossover possible? How will the point of cross-over be determined?
Data collection and use	■ What approaches can be used to minimize bias? • Data is collected from multiple medical institutions with varying standard practice • Gather data for same indication for patients treated with any other therapy as a control arm ■ Can patient level data be submitted to FDA? ■ What documentation is available for these data and can any of the source documents be audited?
Benefit/Risk	■ What are the benefits of this approach compared to other approaches? ■ Under what conditions would it be preferable to other approaches for labeling claims, i.e., additional indications for BTD? ■ Are there any legal ethical concerns with the approach? i.e., off-label promotion? ■ How can the risks for sponsors and the FDA be mitigated? ■ Can a clinical trial, or pragmatic trial be initiated in the same indication, but in earlier lines of therapy? ■ Are there conditions under which this approach would be able to support label claim for an additional indication for BTD? • Outside BTD? • Under-represented groups? (e.g. patients with brain metastases, leptomeningeal carcinomatosis) • Biomarker selected studies (e.g. selection based on liquid biopsy rather than tissue testing)?

Conclusions

As real-world evidence is increasingly used to support drug development, more research, collaboration, and transparency is needed to improve data capture, quality, and analytics. Already advancements in data capture have expanded opportunities to better incorporate patient experiences and outcomes from routine clinical care into a range of drug development processes that can improve evidence quality used to support decision making. Additional efforts, including legislative proposals and Prescription Drug User Fee Act VI (PDUFA)[4] negotiations have highlighted these issues as a priority.

The first step in realizing the numerous opportunities offered by real-world data, will be to begin testing the ability of such data to address outstanding questions in drug development. This work group considered possible approaches for designing prospective pilot studies to assess the ability of using RWE to support regulatory decisions. The three approaches outlined above for developing pilot studies are intended guide developers in considering broader data collection to inform the totality of evidence during drug development; however, careful consideration and discussions between sponsors and regulatory agencies will be needed including an agreed upon pre-specified approach, data standards, and considerations that account for any observed outcomes, such as loss of efficacy, within the real-world.

[4] PDUFA VI Commitment Letter http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM511438.pdf