FRIENDS of CANCER RESEARCH

A FRIENDS OF CANCER RESEARCH WHITE PAPER

Maximizing Data from Academic-Led Studies for Regulatory Decision-Making

Introduction

Clinical trials sponsored or conducted by academic investigators or through clinical trial network groups are an important component of the oncology clinical research landscape. These trials are integral to advancing our knowledge of cancer and improving patient care. Industry-sponsored trials are most often the primary data source for regulatory submissions to support new indications or other label updates (e.g., dose adjustments, safety updates). However, additional sources of data exist on the safety and effectiveness of a drug that may support regulatory submissions and approvals. One additional source that contributes to the scientific understanding around the benefits and risks of cancer therapies comes from trials conducted by academic investigators and clinical trial network groups, broadly referred to as "academic drug development trials" in this white paper.

Academic drug development trials offer a unique opportunity to address four critical aspects of cancer research and treatment:

1. They play an important role in generating additional data that can address key regulatory questions, including post-marketing commitments related to safety, alternative dose or administration schedules.
2. They may target rare cancers, underrepresented patient groups, or patients excluded in the pivotal trial (e.g., older adults or those with organ dysfunction), filling evidentiary gaps and expanding treatment options for additional patient populations.
3. They can provide access to clinical trials to more diverse patient populations through community networks, enhancing the representativeness of clinical findings.
4. They often focus on pressing scientific questions, such as exploring novel combination treatments, driving innovation in cancer therapy.

Collaborations between industry and academic drug development trial investigators can harness these opportunities, which can advance research, drug development, and patient care. These collaborations can take various forms, including funding or providing experimental agents for clinical trials, sharing expertise, providing access to patient populations, contributing resources to accelerate cancer research, and leveraging well-established infrastructures. For example, the

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This document reflects discussions that occurred among stakeholder groups on various topics. This document should not be construed to represent FDA's views or policies.

National Cancer Institute's National Clinical Trial Network (NCI NCTN) is one such infrastructure comprised of five US network groups (formerly known as cooperative groups), encompassing collaborative networks of researchers, clinicians, and institutions that conduct large-scale, multi-center clinical trials. The NCI NCTN serves as a valuable resource for coordinating and supporting cancer clinical trials by engaging in independent research initiatives and trials. By industry working directly with these network groups or even individual academic investigators with patient consultation, there can be greater alignment on shared research goals in specific therapeutic areas or patient populations to ultimately contribute to improving patient care and the development of new cancer treatments. Indeed, the U.S. Food and Drug Administration (FDA) Oncology Center of Excellence (OCE) has highlighted the NCI network as a potential opportunity to reach patients with clinical trials to obtain a patient population more representative of the U.S. population to support regulatory submissions, either alone or as a part of a larger multi-regional global clinical trial.[1]

Yet, challenges exist in leveraging data generated from academic studies for regulatory purposes. Not all academic studies are intended for regulatory use. For those that may potentially be used to support regulatory decision-making, industry partners and those conducting the trial should align on study designs and optimize data collection practices. For academic drug development trials where the industry partner indicates an interest in the potential use of the data to support registration or labeling updates, considerations should be given to enable proactive planning of the data collected and align with expectations of regulatory submissions. Submitting data to the FDA as well as other health-regulatory authorities for regulatory decision-making requires data to be comprehensive and formatted in well-defined and internationally recognized standardized ways.[2] This can be difficult to achieve if statistical designs, study conduct, data collection methodologies, and other processes do not meet the expectations of the FDA and other health-regulatory authorities.

Due to increased interest in leveraging data from academic drug development trials for regulatory submissions, Friends of Cancer Research (*Friends*) brought together key stakeholders from industry, academia, advocacy, and government to characterize challenges encountered in this space and propose ways to enhance the use of data from these studies. This white paper aims to address factors impacting the use of data from academic drug development trials, with a focus on streamlining processes to expedite results, ultimately advancing oncology drug development and care for patients.

Factors That Can Impact Use of Data from Academic Drug Development Trials

An industry partner's decision to engage in a collaboration with an academic group or investigator for a registrational trial can be influenced by various factors such as the study's prioritization within the overall clinical development plan, the study's design and complexity, intellectual property rights, as well as timeline-related considerations; however, the primary focus of this white paper is addressing issues that arise when industry partners pursue collaborations to use data produced from academic drug development trials for regulatory purposes. Several methodological, operational, and communication-related challenges have been identified as barriers affecting the use of data from academic drug development trials for regulatory decision-making, impacting both industry partners and health-regulatory authorities.

Lack of Early Engagement with FDA

One prominent issue is the lack of early engagement with the FDA by those conducting or supporting academic drug development trials, which can impact the ability to support registration. This is often an issue where trials are not clearly identified as potentially label-enabling at study inception due to ambiguity by the industry partner and can lead to skipping pre-study engagement with FDA resulting in downstream issues that may not be able to be mitigated mid- or post-study. Lack of early engagement can result in study designs that do not meet regulatory expectations or missing data points that impact the content and/or quality of data packages necessary to meet regulatory requirements and support regulatory decision-making.

Varying Data Capture and Monitoring Requirements

The way in which data are collected in an academic drug development trial as compared to an industry trial can vary. Industry sponsored trials follow the Clinical Data Interchange Standards Consortium (CDISC), a registrational-compliant format for data collection, programming, and analysis, which enables more streamlined regulatory submissions and more efficient FDA review of patient-level data. Academic drug development trials often employ varying data collection methods that do not always align with the intent of producing the required format for regulatory review including Study Data Tabulation Model (SDTM), which provide the raw data for FDA's review, and Analysis Data Model (ADaM) datasets, which facilitates the Agency's ability to replicate study results. Standardized medical terminology for safety data and approaches to safety data collection and reporting may also differ between industry-sponsored trials and academic institutions. Furthermore, data monitoring and quality aspects can vary. As such, these variations can result in a time and resource-intensive process of cleaning, reviewing, and programming of data generated from academic drug development trials to achieve regulatory-compliant SDTM source and ADaM datasets.

Limited Data Access During Trial Conduct

Trials conducted either within the NCI NCTN or with individual US network groups often have policies that only allow for limited interim data sharing between those conducting the trial and their industry partner. Data sharing policies are in place to maintain the integrity of the study but as a consequence restrict real-time access to data by the industry sponsor. Academic investigators, US network groups, and NCI have policies for data locks to protect the integrity of data, but these may be misaligned with steps to proactively identify potential issues and needs for data review. Resource-intensive tasks to clean and map data can delay primary analyses and interpretation and compilation of a submission-ready data package, thereby resulting in a time lag for getting important therapies to patients.

Together, several factors can lead to delays (up to 12+ months) in submitting data to the FDA for regulatory review (**Figure 1**). The timeline presented is one hypothetical scenario of event timing for preparing data from an academic drug development trial for regulatory use. The time from the study's last patient last visit to data sharing to submission to the FDA can be quick or delayed depending on a number of factors including 1) whether the study had registration-intent from the beginning or whether that determination was made after the data readout; 2) the level of planning, communication, and collaboration between those conducting the study, the industry partner, and the FDA; 3) the resource availability of the group conducting the trial; 4) the data

cleaning and reviewing process; and 5) whether additional data collection is required.

Addressing these challenges should involve both short-term measures and broader system-wide initiatives aimed at standardizing data management processes and enhancing collaboration between academic researchers, industry partners, and regulatory agencies. The strategies noted below are aimed at reducing the timeframe between the completion of an academic drug development trial and a regulatory submission to the FDA, ultimately speeding access of these therapies for patients.

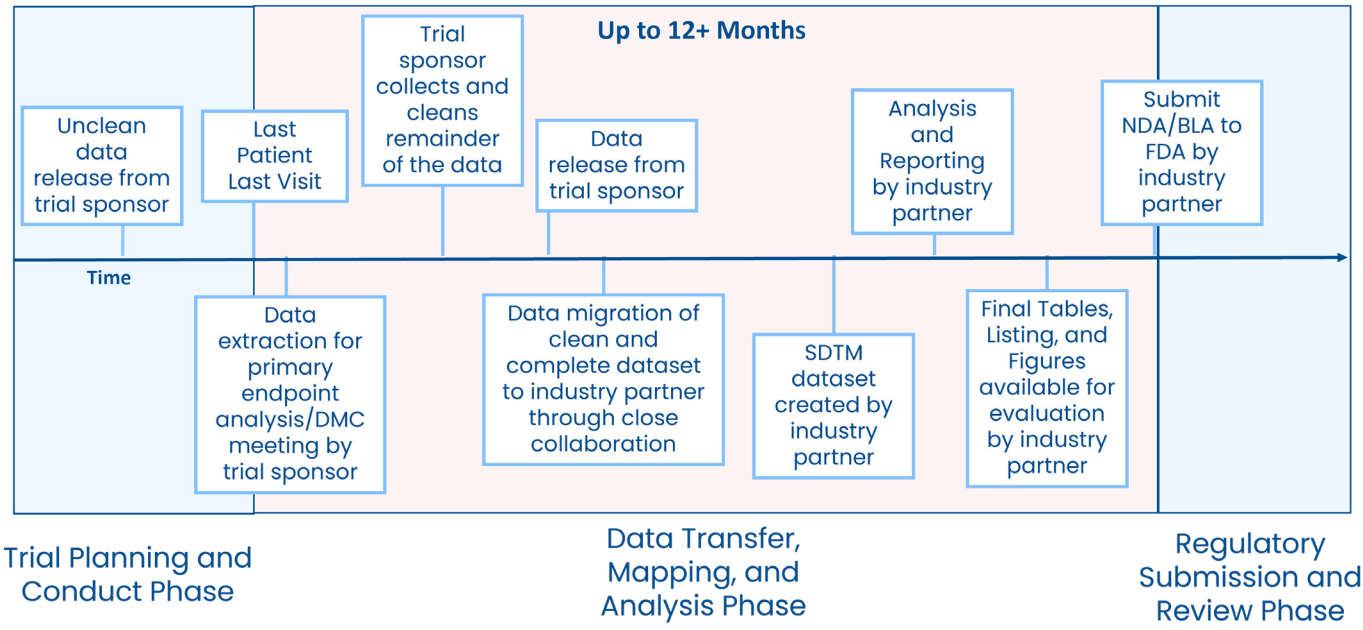

Figure 1. Example of a timeline of typical events associated with preparing data from an academic drug development trial for regulatory use.

Strategies to Reduce Time Between Completion of Academic Drug Development Trials and FDA Submission

Initiate Early Commitment and Communicate Registrational Intent

Industry partners should establish internal processes for identifying the inclusion of academic drug development trials within their development plans. This process could lead to or support potential registrational intent thereby facilitating proactive planning versus waiting until the study reads out to determine registrational potential and enabling industry partners to be more systematic and intentional with those conducting the academic drug development trial, including prioritizing initial planning conversations. Early commitment can help trigger discussions around requirements and expectations of all parties engaged, including availability of required systems, data collection requirements, data sharing needs and platforms, and regulatory engagement strategies. This proactive approach will increase the likelihood that the data from the trial will

meet regulatory standards and allow the industry partner to better plan for timely data transfers to support critical regulatory submission activities.

Initiate Discussions Early with FDA

When an academic drug development trial is identified as having the potential for registrational intent after review by the industry partner, joint meetings should be requested between the appropriate FDA review division and those conducting the trial (e.g., the academic investigator/network group, industry partner, NCI) with patient consultation to discuss the scientific rational and strategy of the proposed trial design, clinical endpoints, and statistical analysis plan. This will also provide an opportunity for discussion and feedback on operational elements (e.g., data collection and cleaning) that may not align completely with standard industry practices and are not routinely discussed with FDA. Subsequently, those conducting the trial can align study designs, methodologies, and data collection strategies with regulatory requirements. Discussions can focus on key phases of the study:

- Study concept development: Conduct joint meetings to discuss the protocol, study design, endpoints, safety reporting considerations, and statistical analysis plan for potential registration studies; Discuss case report forms, collection of data (e.g., blinded independent central review, adverse event terminology)
- Study ongoing: Conduct joint meetings to discuss data cleaning, data transfer and mapping, database lock planning
- Study conclusion: Conduct joint meeting to discuss the results and dossier preparation, final data transfer, dataset, and tables, listings, and figure generation

These interactions can be achieved through Prescription Drug User Fee Act (PDUFA) meetings, and content and format meetings. Overarching feedback can also be received through workshops and collaborative forums where academic researchers, industry partners, and FDA can have informational exchanges to share learnings, expectations, and best practices for success. These interactions should ideally introduce opportunities to discuss and gain early agreement on the optimal type/amount of data needed to address the specific scientific question, leading to more compliant downstream regulatory submissions and reducing submission delays. By involving the FDA prior to study initiation, potential regulatory concerns that may impact the readiness of the data for regulatory submission can be identified and mitigation strategies discussed. In addition, there are numerous FDA/OCE guidance documents aimed at providing insight to potential applicants on topics, such as endpoint selection, typical analyses expected in specific disease areas, and other considerations when planning a trial for submission.[3]

In instances where a trial starts as a non-registrational trial and later intends to support regulatory decisions, it will be necessary to identify mechanisms for mid-study check-ins. Potential future FDA guidance documents specific to academic drug development trials could further clarify expectations and types of meetings that can be leveraged for these interactions.

Establish a Regulatory Track for Studies with Potential Registrational Intent

In instances where academic drug development trials are identified as having potential for registrational intent, a "regulatory track" could be established within the network group or NCI NCTN.

The regulatory track would trigger certain expectations for data lock procedures, study protocols, interactions with the FDA, and outline data requirements to meet regulatory submission needs. Additional needs for the study may also be agreed upon by those conducting the study and the industry partner. The primary objective is to ensure uniformity in data collection methodologies, encompassing crucial aspects such as demographic information, patient outcomes, disease characteristics, treatment specifics, and adverse event documentation. Minimum expectations around what and how data is collected and the types of questions that need to be addressed should be outlined. Moreover, these guidelines should include standardized definitions, particularly for adverse event categorization and the criteria for defining treatment response and endpoints. Notably, the level of safety data collection and the use of verbatim terms in academic trials often differ from what is required for FDA regulatory submissions. Harmonizing these practices will help to ensure that data can be appropriately mapped to meet the stringent regulatory requirements which are in place to ensure the safety of these agents, thereby expediting the evaluation and approval of promising therapies.

Evaluate Data Sharing Policies for Studies with Potential for Regulatory Intent

Earlier evaluation of data quality and formatting could enable more proactive efforts to clean and map data, but current policies can limit access to data during trial conduct. Appropriate data transfers between trial collaborators while the trial is ongoing can enable an iterative data review process that accelerates the identification of potential issues to enable programming for SDTM-compliant mapping to occur and would increase the overall data quality and scientific rigor of the trial. This could be accomplished by establishing secure blinded data-sharing policies that allow for the exchange of relevant data throughout the trial's lifecycle while also maintaining appropriate trial oversight, patient and trial confidentiality, and data and statistical integrity. Alternatively, the use of third-party organizations that can engage with those conducting the academic drug development trials for access to blinded data for the purposes of data cleaning and/or SDTM mapping could be explored if current policies or concerns around data integrity are encountered when sharing directly with an industry partner.

Establish a Streamlined Process for Submitting Data to the FDA

Traditionally, complete datasets from academic drug development trials are submitted to the FDA, which can be time-consuming and resource-intensive to evaluate if the data are not captured with the intent of conforming to regulatory standards. In these instances, one approach for more efficient data submissions could involve providing an abbreviated or summary data package to the FDA earlier for review with full datasets to follow. With FDA agreement, initial submissions could prioritize the mapping and transfer of key subsets of data, including initial submissions with primary/secondary endpoints and select safety data. This approach aims to improve efficiency, reduce redundant efforts, and accelerate the review process while maintaining data integrity and regulatory compliance. The Real-Time Oncology Review (RTOR) program at the FDA provides some general principles and practices that can be adapted to help structure submission of data from academic drug development trials. Specifically, this framework could include several necessary components:

1. Pre-submission activities to discuss the data that will be included in the application,
2. Submission of initial abbreviated data that includes the clinical study report and datasets,

3. Review of the initial data including the study design, efficacy data, and safety data, and
4. Submission of the final data that includes any additional data that was not included in the initial submission.

Conclusions

Leveraging academic drug development trials presents significant opportunities for enhancing evidence generation and bringing innovative therapies to patients faster. While efforts to implement standardized practices across all academic drug development trials are important, near-term opportunities center around improving collaboration and coordination of academic drug development trials intended for regulatory decision-making to reduce the delays from study readout to FDA submission, which can slow access to potentially practice-changing trial results. Given resource limitations for many academic drug development trials and significant efforts to streamline data collection and workflows for site staff, it is important to recognize that it may not be feasible for those conducting academic drug development trials to program every study to meet regulatory requirements (e.g., SDTM/CDISC format) due to limited resources and differing objectives. As such, industry partners should consider long-term partnerships with academic investigators or US network groups that allow for more sustained support for these efforts and help develop the infrastructure for these types of studies.

Addressing challenges through near-term and longer-term solutions will enable a more efficient and impactful process for leveraging academic drug development trials for regulatory use. In the future, it is important to establish early collaboration with the FDA to synchronize data collection and analysis approaches, evaluate data sharing guidelines, and specify preferred data formats for academic drug development trials.

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