ASH TOOLKIT FOR CLINICAL TRIAL SPONSORS

Principles for Strengthening Research Throughout the Clinical Trial Life Cycle

This guide is designed to help trial sponsors take practical steps throughout the trial life cycle, to enhance access and overall representation in clinical trials with the ultimate goal of yielding results that are generally applicable to patients impacted by the disease or therapy. It includes actionable recommendations, reference articles, and additional resources from both national and international regulatory bodies and research organizations.

ACTIONABLE STEPS TO STRENGTHEN RESEARCH

THE CLINICAL TRIAL PROCESS

FORMULATING YOUR RESEARCH QUESTION

- Understand the patient population/epidemiology of the disease you are studying, set goals for the trial that capture the disease epidemiology and track your results.
- Based on the epidemiology of the disease and demographics of the site catchment area, select clinical trial sites (and the site leads) with the goal of achieving a representative patient population.
- Review existing resources aimed at improving enrollment of underrepresented participants in clinical trials (e.g., FDA diversity plan, ICH guidelines, MRCT diversity clinical research tool kit, Just Ask, NIH All of Us Research Program, etc.).
- Engage with relevant patient advocacy groups and lived experience experts (LEEs)* early and often as:
    - You craft your research question.
    - Outline your enrollment goals by population demographics; and
    - Strive to build trust with the patient community that will be participating in the study.
- Seek meaningful contribution from health care providers (HCPs) on study concept/design.

**Lived Experience Experts (LEEs) are individuals, their caregivers, and family members directly impacted by hematologic diseases. Their personal knowledge of the disease gives them the unique ability to translate lived experiences into meaningful system change. Collaborating with patient advocacy groups may be a good source for identifying appropriate LEEs.*

TRIAL DESIGN

- Carefully consider and assess your trial's eligibility criteria.
    - Specifically examine how each criterion may impact the target patient population's ability to participate. For example, avoid unnecessarily strict organ function in eligibility criteria, or unnecessary/irrelevant eligibility tests. For exclusion criteria, avoid nonspecific and potentially biased terms like "unacceptable" or "uncontrolled" where specific definitions can be used.
    - Government agencies like the FDA, NIH, Health Canada, Medicines and Healthcare products Regulatory Agency (MHRA), and European Medicines Agency (EMA) are supportive of broadening inclusion criteria, so develop a protocol that represents patients in the real world.
- Solicit the guidance of a statistician to help with the selection of an appropriate sample size and heterogeneous population.
- Consider opportunities for de-centralizing of clinical trial with study activities closer to home (e.g., mobile nursing or phlebotomy for safety monitoring).

TRIAL DESIGN (continued)

- Consult with LEEs to understand how much effort may be required for the enrollment objectives.
- Leverage the expertise of LEEs, patient advocacy groups, and/or community advisory boards (CABs) to:
  - Create a plain language version of the protocol for patients. This version should describe the purpose of the study, key inclusion and exclusion criteria, major efficacy outcomes, potential adverse events, and why the study will benefit the patient population. This document should be translated into different languages as appropriate.
  - Develop culturally and linguistically appropriate educational resources for HCPs and patients to build their understanding around why a trial is designed the way it is, e.g., a 1-page information guide on describing the trial that can complement a more in-depth informed consent form (ICF).
  - Review your protocol to provide patient-centric feedback.
- Incorporate strategies to effectively engage HCPs or community physicians who will likely be offering your trial to their patients. Your strategies should consider the following:
  - Return of the patient to the HCP after the trial is complete.
  - Communication of trial results with the HCP during and at the end of the trial.
  - Acknowledgement of the HCPs participation in the study.
- Clearly articulate recruitment goals to the trial site(s). Note: These recruitment goals should bebased on the demographics of the population impacted by the disease.
- Design consent forms that are easy to read and translated into different languages especially for trial sites with significant proportions of patients for whom English is not their primary language.
- Avoid the inclusion of unnecessary study visits in the trial design (e.g., excessive PK/PD visits).
- Ensure that patients understand that they can stop participating at any time without risk or repercussions.

TRIAL BUDGET

- Include funding for patient assistance in your budget for community engagement efforts, appropriate participant compensation (e.g., travel, housing or childcare assistance, or debit card that can be used at patient discretion for trial related activities like gas, food, etc.), and for unique geographic or societal challenges that may present as barriers for trial participants.
- Consider adding LEEs to key personnel in your research grant and compensate them for their time.

THE CLINICAL TRIAL PROCESS

ETHICS & OTHER REVIEWS

- Develop a protocol that ensures the institutional review board (IRB) or research ethics committee (REC) is reviewing the trial not just for safety and ethics principles, but also for its justice principle. The latter takes into consideration fairness in distribution of benefits realized from the research study as well as its burdens.
- Include information on how the drug, device, or other therapy being studied could work in different subgroups and any prior data on heterogeneity of treatment effect. This will further justify your rationale for the selected inclusion and exclusion criteria, and will facilitate the review of your protocol.
- Initiate early and regular conversations with regulators to establish changes to the protocol, including eligibility criteria, that will broaden enrollment. See the FDA Support for Clinical Trials Advancing Rare Disease Therapeutics (START) Pilot Program for more information.

STUDY CONDUCT & DATA COLLECTION

- Engage a workforce with a variety of perspectives, talents and experiences (including trial leaders) to inform the execution of the trial.
- Offer cultural competency and patient-centered clinical research training for all research staff.
- Discuss with the trial site(s) the importance of representative enrollment and make sure the site(s) are aware of your diversity goals as the sponsor.
- Recruit participants/sites from regions that are historically under-represented in trials.
- Engage patient advocacy groups and HCPs in the recruitment of patients. Enable availability of trial participation in community practices that resemble the desired trial population.
- Use social media to promote awareness, education, and to build trust with patients, caregivers, and advocates.
- Meet the patients where they are, if possible, and leverage telemedicine and other decentralized approaches for data collection.
- Ensure a robust informed consent discussion and process, and allow time for questions for patients, caregivers, and allies. Avoid same day consent if possible (especially if the provider hasn't established a relationship and/or trust with the patient).
- Use clear language and definitions around what compensation is available. Intentionally and proactively discuss opportunities for compensation and respect the time and effort the patients are committing.

DATA ANALYSIS AND RESULTS REPORTING

Both to the Scientific & Patient Communities

- Disseminate the results to patients in language that they can read and understand (e.g., plain language/multilingual summaries, photovoices) – Leverage relevant patient-centric organizations, and/or cultural and linguistic community experts.
- Leverage any existing patient facing technology used during the trial to deliver key findings to participants.
- Ensure standardization of demographic data reporting for studies, such as required by clinicaltrials.gov.
- Collaborate with patient groups with experience/expertise in developing patient friendly graphics and social media posts that can help translate the results of the study to the relevant patient population in an engaging way.
- Seek post-study feedback and overall takeaways/impressions from the study population and their supporting communities. This will help guide future and follow up studies relating to the same topic.
- Recognize HCPs who participated in the study through acknowledgement (with permission) in publications and seek their input on the interpretation of findings, review, and revisions of manuscripts thereby giving them an opportunity to meet ICMJE criteria for authorship.
- Acknowledge the contributions of patients, their families, and supporting communities.

RELEVANT RESOURCES TO EXPAND INCLUSIVITY IN CLINICAL TRIALS

FDA Guidance: Diversity Action Plans to Improve Enrollment of Participants From Underrepresented Populations in Clinical Studies

This draft guidance describes the form, content, and manner of these action plans, the applicable medical products, and clinical studies for which an action plan is required, the timing and process for submitting one, and the criteria and process by which FDA will evaluate sponsors' requests for waivers from the requirement to submit and action plan.

FDA Guidance: Collection of Race and Ethnicity Data in Clinical Trials, Guidance for Industry and Food and Drug Administration Staff

This guidance is to provide FDA expectations for and recommendations on use of a standardized approach for collecting and reporting race and ethnicity data in submissions for clinical trials for FDA regulated medical products conducted in the United States and abroad.

FDA Guidance: Evaluation and Reporting of Age, Race and Ethnicity-Specific Data in Medical Device Clinical Studies, Guidance for Industry and Food and Drug Administration Staff

The primary intent of the recommendations in this guidance is to improve the quality, consistency, and transparency of data regarding the performance of medical devices within specific age, racial, and ethnic groups.

FDA Strategies To Increase Clinical Trial Participation Webinar

A webinar from the FDA addressing ways to enhance trial participation.

FDA Support for Clinical Trials Advancing Rare Disease Therapeutics Pilot Program

The agency is announcing the opportunity for a limited number of sponsors to participate in a pilot program allowing for more frequent communication with FDA staff to provide a mechanism for addressing clinical development issues.

NASEM Report to Congress: Improving Representation in Clinical Trials and Research

This report models the potential economic benefits of full inclusion of a broad demographic group in clinical research and highlights new programs and interventions in medical centers and other clinical settings designed to increase participation.

RELEVANT RESOURCES

NIH All of Us Research Program

All of Us is a database that can inform thousands of studies on a variety of health conditions. It is meant to create opportunities to: a) know the risk factors for certain diseases; b) figure out which treatments work best for people of different backgrounds; c) connect people with the right clinical studies for their needs; d) learn how technologies can help us take steps to be healthier.

National Institute of Minority Health & Disparities (NIMHD) – Diversity In Clinical Trials

Outlines the institute's strategic goals on enhancing representation in clinical trials

MRCT Guidance Document on Achieving Diversity, Inclusion, and Equity in Clinical Research

This guidance document aims to clarify the importance of, advance the goals of, and provide practical and actionable ways to improve representation of participants in clinical research.

Just Ask – Equity and Diversity in Clinical Research

This program provides support to research teams and clinical staff to improve enrollment in research.

PCORI: Guide for Researchers: How to Assist Community Partners to Use Digital Technology

This guide can be used broadly by research teams wanting to engage community members and patients who are not familiar with digital technology.

ICH - Guideline on General Considerations for Clinical Trials

Includes guidance that is both appropriate and flexible enough to address the increasing diversity of clinical trial designs and data sources being employed to support regulatory and other health policy decisions, while retaining the underlying principles of human subject protection and data quality.

ICMJE – Authorship Guidelines

The International Committee of Medical Journal Editors (ICMJE) recommendations are a set of guidelines produced by the International Committee of Medical Journal Editors for standardizing the ethics, preparation and formatting of manuscripts submitted to biomedical journals for publication. Authorship Guidelines outline specific criteria to be met to qualify for authorship of a medical journal manuscript.

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QUESTIONS?

For more information about this resource, contact the ASH Director, Scientific Affairs, Alice Kuaban, MS, at akuaban@hematology.org