FRIENDS of CANCER RESEARCH

Pragmatism in Postmarket Trials

Friends of Cancer Research White Paper | 2024

Executive Summary

Incorporating pragmatic clinical trial elements (i.e., pragmatic elements) into trial designs provides an opportunity to reduce patient, site, and investigator burden, while increasing the generalizability and applicability of trial results to the intended use population by more closely reflecting routine clinical practice. Considerations for incorporation of pragmatic elements include the specific research question, trial objectives and clinical setting, available safety and efficacy data on the treatment of interest, and intended use of the trial results, including whether the data will be submitted for regulatory review. These factors will influence the appropriateness and operationalization of incorporating selected pragmatic elements and the level of risk assumed regarding trial integrity, data quality and missing data, and the rigor of endpoint assessment.

Friends of Cancer Research assembled a working group of experts, including members from the U.S. Food and Drug Administration (FDA) and National Cancer Institute (NCI), drug developers, patient advocates, health technology data experts, and academic clinicians, to identify specific trial objectives in the postmarketing setting to frame a discussion on the benefits and risks of incorporating pragmatic elements into future trials. Introduction of pragmatic elements may be most feasible initially in the postmarketing setting, where more is known about the safety of the product, and additional questions remain about its optimal use in practice. Objectives in the postmarketing setting include postmarketing requirements or commitments issued by the FDA following initial approval, or new interventional studies initiated by sponsors seeking expansion of a product's indication to additional patient populations.

The working group evaluated the following scenarios as example research objectives to guide discussion of incorporating pragmatic elements in postmarket clinical trials. For each, we provide specific considerations for increasing pragmatism:

- Conduct a clinical trial that enrolls racially and ethnically underrepresented patients in proportion to their representation in the U.S. population of patients within the disease indication, in sufficient numbers to characterize the safety and efficacy of the approved drug in the patient population.
- Conduct a clinical trial to further characterize the risk of a cumulative toxicity and potential mitigation measures in patients receiving the drug.
- Conduct a clinical trial to characterize the safety and efficacy of the drug in a biomarker-selected population expanded from the biomarker cutoff used for the initial indication.

As is true for any trial objective, for each of these three scenarios, not all pragmatic elements may be appropriate. The scenarios illustrate opportunities to introduce pragmatism into a clinical trial and provide considerations applicable to additional trial objectives. While incorporating pragmatic elements may decrease burden, there may be an increase in risk for the data to be used for regulatory decision-making. Therefore, thoughtful consideration should be given to the potential benefits and risks and early interactions with FDA on trial design will be essential.

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Introduction

Traditional randomized controlled trials (RCTs) have generally included standardized patient selection, specific assessment and monitoring intervals, and substantial follow-up to generate robust data to inform regulatory decision-making. However, clinic visits and data collection requirements that are required beyond routine clinical care can be burdensome to trial participants, investigators, and trial sites, and can limit the participation of some patients and trial sites.[1] Overly strict eligibility criteria can further reduce both participation and the generalizability of clinical trial results to the intended use population.[2] Furthermore, unnecessary data collection and frequent monitoring can be resource intensive (e.g., time and cost) for sponsors.

Incorporating pragmatic clinical trial elements (henceforth pragmatic elements) into trial designs, where appropriate, can introduce operational efficiencies in a less burdensome framework, and generate data that are more reflective of intended use populations.[3,4] The U.S. Food and Drug Administration (FDA) has signaled interest in incorporating pragmatic elements into clinical trials through the Center for Drug Evaluation and Research (CDER) Center for Clinical Trial Innovation (C3TI) Streamlined Trials Embedded in clinical Practice (STEP) demonstration project[5], launch of the Oncology Center of Excellence (OCE) Project Pragmatica[6], and more recently Project 5 in 5[7], focusing on pragmatic clinical trials in oncology. Friends of Cancer Research (*Friends*) assembled a collaborative working group in 2023 to draft a white paper, "Incorporating Pragmatic Elements in Study Designs to Enhance Oncology Randomized Clinical Trials[8]," which laid out considerations to inform the appropriateness of incorporating pragmatic elements into RCTs for evidence generation across the lifecycle of a drug.

Considerations for incorporating pragmatic elements into a clinical trial include the specific research question, trial objectives and clinical setting, the available safety and efficacy data on the treatment of interest, and the intended use of the trial results, specifically whether or not the data will be submitted for regulatory review. These factors will influence the appropriateness and operationalization of incorporating pragmatic elements as well as the level of risk assumed by trial sponsors regarding trial integrity, data quality and missing data, and the rigor of endpoint assessment. *Friends* assembled a new working group of experts, including members from the FDA and National Cancer Institute (NCI), drug developers, patient advocates, health technology data experts, and academic clinicians, to build on the foundation and operationalize concepts from the 2023 white paper. To better discuss the opportunities to incorporate pragmatic elements into future clinical trials, the group focused on the postmarket setting, a specific phase of drug development with high potential value for incorporating pragmatism.

Defining Opportunity in Postmarket Clinical Trials

Incorporating pragmatic elements into prospective studies offers the opportunity to support evidence generation across the life cycle of a drug. The introduction of pragmatic elements may be most feasible in the postmarket setting, where more is known about the safety of the product, but

additional questions remain about its optimal use in practice. Such questions might include a better understanding of the safety and/or efficacy of an agent in populations underrepresented in the registrational trial(s) or information about potential new uses of the treatment. Additional research questions may be driven by the interests of the drug sponsor, regulatory authorities (i.e., through postmarketing requirements or commitments), or clinical investigators, and evidence generated may be used to support regulatory decision-making, such as updating a label or approving a new indication. Importantly, results from pragmatic studies can also inform decisions outside of regulatory agencies. Examples include informing clinical practice, supporting updates to clinical practice guidelines, or providing evidence for coverage decisions by payers. Given the level of safety and efficacy data already available from the pivotal trial(s), introducing pragmatic elements in the postmarket setting may be viewed as a lower risk for sponsors regarding trial integrity than in the premarket setting.

Data Considerations to Inform Pragmatic Trial Designs

Data regarding safety and efficacy from prior, completed registrational trials should inform the appropriateness of implementing specific pragmatic elements in a postmarket trial. Sponsors could consider which data elements from the pivotal trial were or were not critical for determining safety and efficacy. Through formal discussions with regulatory agencies, trial protocols may be revised to improve efficiency. This could involve reducing the collection of unnecessary data elements or allowing for greater heterogeneity in data collection, when appropriate. For trials intended for regulatory approval, early engagement with the relevant FDA review division is essential to discuss currently available data and clarify the evidentiary requirements for demonstrating safety and/or efficacy needed to support a new regulatory submission.

For instance, available safety data from a pivotal trial may demonstrate no discernible difference in toxicity in patients with mild versus moderate renal dysfunction, suggesting that broadening eligibility criteria to include patients with higher levels of renal dysfunction may be appropriate if also supported by non-clinical data and knowledge of the drug's pharmacokinetics. Alternatively, existing safety data may show that an adverse event occurs commonly in relation to the administration of a therapeutic agent, suggesting that additional trials should continue to include frequent assessment and mitigation strategies for the event.

Phase II trials, often investigator-initiated or led by NCI cooperative groups, or real-world data (RWD), may suggest areas of additional efficacy or effectiveness, respectively, and/or novel safety findings, which could be used to support and identify potential patient populations for further study in a prospective clinical trial and inform the degree and type of pragmatism to incorporate into the design. The use of RWD can improve understanding of the potential impact of broadening eligibility criteria on representativeness and on outcomes[9], as well as inform flexibility in follow-up approaches and frequency of assessments. For example, a recent study found that heterogeneity in real-world visit frequency for patients with newly diagnosed multiple myeloma contributed to surveillance bias but that bias could be quantified in evaluating endpoint measurements.[10] Information such as this

example and others[11] could inform a trial design with pragmatic elements where flexibility could be introduced in the assessment interval for patients, and the study could be more tolerant of shifts in visit schedule. This could allow for reduced patient burden without substantively compromising efficacy insights.

For trials incorporating multiple pragmatic elements, the cumulative impact on the sensitivity to detect treatment effect must be carefully considered. For example, pragmatic elements such as introduction of broader eligibility criteria or allowing flexibility in assessment intervals, may increase variability and decrease statistical sensitivity to detect small treatment effects, thus requiring a larger sample size. Larger clinical trial populations typically result in trial delays and additional costs, but this concern could be mitigated if the cumulative effect of all pragmatic elements incorporated ultimately result in more rapid accrual and/or reduced attrition. Products or treatment sequences that are expected to have a large effect size may be more appropriate for higher degrees of pragmatism. Conversely, a highly pragmatic design may not be appropriate for a non-inferiority trial design.

Introducing Pragmatic Elements into Postmarket Trial Designs

The pragmatic-explanatory continuum indicator summary (PRECIS)-2[12] is a conceptual framework that provides nine domains to consider for determining the degree of pragmatism in a given trial design, including eligibility, recruitment, setting, organization, delivery, adherence, follow-up, primary outcome, and primary analysis. The level of pragmatism is graded on a scale within each domain, and within each domain the amount of pragmatism that is appropriate or necessary may vary depending on the context in which the study is conducted. Use of pragmatic elements should aim to create the highest generalizability and reduction in burden while maintaining appropriate rigor to answer the prespecified research objectives in the population of interest. Many applications of pragmatic approaches and their considerations are relevant across research questions in the postmarket setting. Table 1 outlines these considerations by the PRECIS-2 domains. Below are further insights into how pragmatic elements may be incorporated across research questions.

Operational Efficiencies through Technology

To facilitate research participation in routine care settings, digital health and data technologies can enhance operational efficiencies. These tools and technologies include the use of telemedicine, electronic health record (EHR) to electronic data capture (EDC) data transfer software, and automated patient clinical trial matching based on EHR documentation. Telemedicine can support remote consenting, clinical assessments, monitoring, and follow-up, and data collection. EHR-to-EDC software leverages routine clinical workflows, automating transfer of clinical data quickly and accurately to the research database, helping to avoid time-consuming, error-prone, and duplicative data entry tasks. Patient trial matching software can aid in recruitment by helping sites evaluate the suitability of a particular study by identifying trial-eligible patients at the point of care. This approach can reduce site burden and also mitigate potential unconscious biases associated with patient

ascertainment, ultimately supporting more equitable and representative study participation. These technologies can enable operational efficiencies that allow sites to identify, recruit, enroll, and evaluate trial participants more effectively, introducing pragmatic elements across PRECIS-2 domains.

Streamlined Safety Data Collection

If the data suggest a similar adverse event profile for a drug in the new trial population of interest compared with the patient population included in the registrational trial, selective safety data collection may be appropriate. The International Council for Harmonization (ICH) draft guidelines for Optimization of Safety Data Collection- E19[13] note data collection may be limited or stopped for non-serious adverse events, routine laboratory tests, concomitant medications, or physical examinations, as appropriate. In these scenarios, capturing serious adverse events and grade 3 or higher adverse events and reducing collection of low-grade events may be appropriate. These recommendations are similar to those recently proposed by the NCI Streamlining Clinical Trials Working Group[14]. However, collection of only high-grade events may diminish the ability to assess treatment tolerance and chronicity of low-grade adverse events. Therefore, strong existing evidence to support the safety profile and a rationale for why the expanded patient population will likely have a similar safety profile should be provided.

Table 1. Select Considerations for Incorporating Pragmatic Elements into Postmarket Trials by PRECIS-2 Domains.

PRECIS-2 Domain	Pragmatic Element to Introduce	General Considerations	Potential Impacts on Patients, Sites, and Sponsors
Eligibility	• Less restrictive eligibility criteria (e.g., expanding lab values, organ function) • Reduced number of eligibility criteria (e.g., not requiring certain lab values) or requirements for extra tests to confirm eligibility	• Eligibility criteria should be based on the known preclinical and early clinical safety data. A rationale for exclusion criteria focused on patients' safety should be provided	• Patient- Potentially lower burden, increased accessibility; fewer screening procedures • Site- Reduced screening simplifies workflow, less pre-study documentation needed • Sponsor- Faster accrual; more diverse population
Recruitment	• Tech/AI enabled trial matching for screening patients using existing EHR data • Integration of research fields into the EHR • Simplify informed consent document • Permit electronic consent	• Enables rapid identification of potentially eligible patients • Infrastructure needed to support enabling technology • Training of site staff to engage potentially eligible patients and support informed consent • Improved patient understanding of study designs, risks, benefits and alternatives • Facilitates consenting process	• Patient- Less burden and reduced complexity in informed consent • Site- Reduced site burden with technology enabled features but may require more upfront resources and infrastructure investments. Facilitates better communication between physicians and patients • Sponsor- Faster accrual
Setting	• Multi-site trial conducted in community setting, including community-based clinical practices	• Meeting patients where they receive care increases the likelihood of accrual and retention • Community sites serve a more representative patient population	• Patient- Reduces travel/cost, maintains provider relationship • Site- Allows site to retain patients, provide continuity of care • Sponsor- Increased complexity of trial management*

PRECIS-2 Domain	Pragmatic Element to Introduce	General Considerations	Potential Impacts on Patients, Sites, and Sponsors
Organization	• Care given by community and local providers • Technology-enabled trial management	• Leverage technology for operational efficiency- i.e., EHR to EDC integration to reduce duplicative data entry • Invest in robust technology infrastructure	• Patient- Less burden by allowing local care • Site- Burden associated with maintenance of site research infrastructure, training, but could be alleviated with EHR to EDC • Sponsor- Increased monitoring burden (e.g., CRO may be needed) with decentralization or decreased with EHR to EDC; Increased training cost for less experienced research sites*
Delivery	• Embedded in routine care, with treatment and assessment cadence aligned with routine care • Site-based treatment visits would be scheduled per approved dosing schedule, but other visits may be remote and flexible on timing, potentially using technology-enabled delivery • Shipping of oral medications as appropriate	• Invest in robust technology infrastructure • Develop and implement effective patient engagement strategies • Potentially widens the pool of participating sites as trials embedded in practice are not as resource intensive • Adequate training and support to enable remote and flexible visits	• Patient- Reduced burden with fewer visits/ assessments • Site- Does not require significant additional data capture • Sponsor- May increase burden to provide more resources/ infrastructure but technology has the potential of reduced cost and increased efficiency
Adherence	• Patient-centered adherence strategies that prioritize patient autonomy, engagement and self-management	• Treatment at local site or at home promotes adherence, treatment and assessment compliance, as well as retention	• Patient- Reduced burden • Site- Does not require additional work

PRECIS-2 Domain	Pragmatic Element to Introduce	General Considerations	Potential Impacts on Patients, Sites, and Sponsors
	• Technology-enabled adherence support to enhance patient adherence and engagement		• Sponsor- May require more resources and infrastructure investment*
Follow-up	• Follow-up visits reflective of standard of care, in routine care location • Flexibility in monitoring cadence, and intervals, including remote patient monitoring • Selective safety monitoring- as per NCI Streamlining Clinical Trials Working Group (and ICH E6 and E19) recommendations • Use of DHTs to prompt patients, inclusion of PROs	• Flexibility in monitoring cadence may be dependent on the drug's mechanism of action, PK, and the natural history of disease. • Patients may not be amenable/adherent to rigorous schedule of assessments • The appropriateness of PROs inclusion will depend on the research question. This may introduce additional patient burden, but may offer insights into low grade AEs, Quality of Life.	• Patient- Reduce burden of follow-up (frequency, duration) visits • Site- Reduce burden of follow-up visits • Sponsor- May require more resources on trial management and logistics, and infrastructure investment*
Primary Outcome	• Outcome should not require specialized or central review (rw-RECIST, OS) • Efficacy endpoints based on data routinely collected in clinical practice (e.g., rwPFS, time to subsequent therapy, OS) • AEs: Might collect G3-5 or those that result in treatment change • Flexible outcome assessment schedules	• Need statistical analyses to understand what magnitude of effect would be acceptable because of heterogeneity in patient population and/or assessments at trial design stage.	• Patient- Minimizes extra visits/tests beyond routine care • Site- Minimizes data collection as is in routine clinical care, reduce workload • Sponsor- May require more resources and infrastructure investments to ensure relevant clinical data are being collected*

PRECIS-2 Domain	Pragmatic Element to Introduce	General Considerations	Potential Impacts on Patients, Sites, and Sponsors
	• Technology enabled outcome monitoring		
Primary Analysis	• Intention to treat principle • Clinically relevant primary outcome • Minimize secondary objectives	• Define statistical endpoints, and a statistical model to guide interpretation of routinely collected data	• Patient- Patient-centric • Site- Reduces burden of collection • Sponsor- Likely no impact on burden

* It is acknowledged by the working group that the initial burden in logistics, infrastructure and trial management that may be associated with pragmatic or decentralized elements are likely to improve over time and with experience.

Postmarket Trial Objectives

To frame the working group's discussion on incorporating pragmatic elements in postmarket clinical trials, the following trial objectives were selected by the working group to explore as examples of where pragmatism would be feasible and impactful. For each, we provide specific considerations for increasing pragmatism in the PRECIS-2 domains, specifically focusing on unique considerations related to eligibility, setting, delivery, follow-up, and primary outcome.

Trial Objective 1: Conduct a clinical trial in a specific patient population to further characterize the safety and efficacy of the treatment.

Evaluating the safety and/or efficacy of a drug in a specific population underrepresented in the trial is a common research question in many postmarketing studies and may be appropriate for incorporating a more pragmatic approach to evidence generation for a variety of reasons.[15] There may be an initial signal in a registrational trial that demonstrated differential safety or efficacy in a subgroup of the patient population, or there may have been too few patients in this subgroup to make robust conclusions. Additionally, some specific patient populations may have been excluded from the registrational trial due to strict eligibility criteria, prompting interest to characterize product safety and/or efficacy in this population. In such cases, a postmarketing trial further studying the population may lead to important FDA label updates. Evidence from the registrational trial(s) will influence the extent to which pragmatic elements are appropriate to incorporate into a postmarket study. For example, differential safety identified in subgroups within the registrational trial may impact the types and frequency of safety data collected in the postmarket trial, making safety assessment not amenable to a highly pragmatic approach.

Examples of specific patient populations for Trial Objective 1:

- Underrepresented Racial and Ethnic Group
    - Study including a racial and/or ethnic population underrepresented in the registrational trial.
- Underrepresented Age Group
    - Study including older adult populations underrepresented in the registrational trial.
- Patients with Organ Dysfunction
    - Study including patients excluded from the registrational trial due to organ dysfunction.
- Patients from a Specific Geographic Location
    - Study including patients underrepresented in the registrational trial from a specific geographic location.

Case Study #1: Conduct a clinical trial that enrolls racially and ethnically underrepresented patients in proportion to their representation in the U.S.

population of patients within the disease indication, in sufficient numbers to characterize the safety and efficacy of the approved drug in this patient population.

A common objective of postmarketing requirements or commitments is postmarket investigation with sufficient numbers of patients in an underrepresented racial or ethnic group[16]. Considerations for incorporating pragmatic elements by PRECIS-2 domains, specific to the case study:

Eligibility- Understanding the factors associated with underrepresentation of the patient population of interest will be informative. Patients may not be eligible as restrictive inclusion/exclusion criteria may disproportionately exclude underrepresented populations. Less restrictive eligibility criteria (e.g., expanding laboratory value requirements, comorbidities, performance status) could increase eligibility. This approach may come with potential risks, not unique to studying minority populations, but due to the broadening of eligibility criteria resulting in trial participants with different risk/benefit profiles compared to the initial trial. For patients, there may potentially be differential outcomes (both adverse events and clinical outcomes) than in the registrational clinical trial that may be attributable to other factors (e.g., organ dysfunction) given the more heterogeneous patient population. For sponsors, the increased heterogeneity of the trial population may obscure modest clinical benefits, raising the risk of trial failure and possibly making results interpretation more challenging.

Setting- Another factor contributing to the underrepresentation of the patient population of interest may be the trial sites selected for patient enrollment. Patient populations historically underrepresented in oncology clinical trials, including racial and ethnic marginalized groups, are more likely to be treated at community sites with limited access to clinical trials or that are relatively inactive (e.g., sites that do not have clinical trial programs or are have programs with low enrollment).[17] Expanding access to clinical trials at these community sites by designing studies better suited to routine care settings could increase the ability to recruit more representative patient populations. Meeting patients where they receive routine care in the community also increases the likelihood of accrual and retention, reducing costs and burden for patients while maintaining the patient-provider relationship and continuity of care.[18] However, some community sites may lack the infrastructure to effectively conduct clinical trials, and there may be increased complexities of trial management for sponsors. The diversity of sites may lead to increased regulatory risks such as non-compliance or trial failure due to difficulties in maintaining protocol adherence.

Follow-Up and Primary Outcome- Design of a trial better suited to routine care settings will be driven by the degree of protocol specified safety assessment and primary outcome measures. If the existing safety data and mechanism of action do not suggest a differential safety in the patient population of interest, selective safety data monitoring, as per the NCI Streamlining Clinical Trials Working Group[14] and ICH E19[13] guidelines, may be appropriate, such as assessing only grade 3 or higher adverse events or those that result in a treatment change. The inclusion and frequency of collection of patient-reported outcomes (PROs) could also be streamlined, if appropriate. The efficacy endpoints may also be more pragmatic, assessing outcomes that do not require specialized

or central review, such as overall survival, or real-world (rw) assessment of tumor response that employ RECIST criteria based on tumor measurements, but permit more flexibility than standard RECIST criteria (e.g. scan cadence as per routine practice rather than prespecified)[19]. Assessment of rw-response based on the clinician assessment of response may also be used to gauge efficacy in place of RECIST measurements. This measure could be further supported by a retrospective review of imaging data where available, acknowledging that imaging type and frequency would not be prespecified. This can minimize the extra visits, paperwork, and tests for patients beyond what is expected in routine care, also minimizing the data collection and workload for sites.

It is acknowledged that there may be areas of potential variability associated with reduced data collection. For instance, there may be delayed identification of imaging progression and treatment change, due to non-standardized assessment schedules. For sponsors, there may be a risk that outcomes are not directly comparable to registration-directed clinical trials given the potential increase in heterogeneity. Reduced safety data collection may diminish the ability to assess treatment tolerance and chronicity of low-grade adverse events, although expected symptomatic toxicities may be characterized with electronic PRO data. For this reason, reduced safety collection may be best suited for mature products (e.g., later in lifecycle management) with a well-characterized safety profile. An a priori statistical analysis plan with strong clinical rationale will be important to understand what magnitude of effect would be acceptable because of the potentially less fit population and heterogeneity in assessments.

Trial Objective 2: Conduct a clinical trial to further characterize a specific adverse event/toxicity and its management.

Conducting additional studies focused on a specific toxicity or adverse event seen in the registrational trial to better characterize its frequency and management is also a common postmarketing study objective. Given that the impetus for the study often comes from a signal from the registrational trial, leveraging the existing data on the temporality (frequency, onset, reversibility, chronicity) and mitigation strategies of the toxicity can inform the appropriate pragmatic elements to include in a study design. This study may be in a specific patient subpopulation found to have differential toxicity, such as those with organ dysfunction, or be more broadly studied in the intended use population. Evidence generation may result in a label modification for management of the adverse event and/or could inform clinical management and/or practice guidelines. The type of adverse event under study will dictate the ability to incorporate flexibility in trial design.

Examples of specific adverse event categories for Trial Objective 2:

- Long-term Toxicities
    - Specific adverse events that may be late or cumulative.
- Short-term Toxicities

- Specific adverse events that occur while on treatment (acute) within a fairly reproducible timeframe but were rarely seen or incompletely characterized in the registrational trial(s).

Case Study #2: Conduct a clinical trial to further characterize the risk of a cumulative toxicity and potential mitigation measures in patients receiving the drug.

This case study focuses on long-term, significant chronic toxicities, and may be applicable to toxicities or adverse events that require long-term follow-up, such as neurological toxicities. Considerations for incorporating pragmatic elements by PRECIS-2 domains, specific to the case study:

Eligibility– There would likely be minimal expansion of eligibility, as the risk of chronic toxicity needs to be better understood in the patient population studied in the registrational trial. The significant expansion of eligibility may run the risk of coming to an erroneous conclusion about the presence, absence, or quantitative parameters (e.g., frequency, severity) of a safety risk. There may be an opportunity to broaden eligibility to allow for the assessment of the relationship of risk to the severity and chronicity of the toxicity and to better understand potential confounding factors. If patients with an increased risk were allowed to enroll, this may require more careful and frequent monitoring to better assess the nature and severity of the toxicity and predefined design and statistical plans. This may also increase the risk to these patients, as high-risk patients may experience worse or more prolonged toxicity. By including high-risk patients, sponsors may also risk higher toxicity findings in the product label. However, this could be offset by comfort in the prescribing community to expand treatment outside of the strict eligibility criteria of the trial if safety is felt to be similar or marginally higher. Nonclinical pharmacology and toxicology data will inform the rationale for a more narrow or broad eligibility criteria.

Setting and Delivery– Robust data from the registrational trial(s) on the toxicity, including the time to onset, management, mitigation strategies, and outcomes, will dictate the level of flexibility and pragmatism appropriate for the postmarket trial design. A prospectively designed highly pragmatic trial may approach the simplicity of a disease registry, with prespecified evaluations capturing the relevant safety data while reducing the level of burden associated with an explanatory trial. However, more specialized testing may be required to assess causation or functional impact, especially when there is a desire to characterize the frequency of the event in a representative population. Specialized testing may also be required to adequately assess the severity and potential cause of an individual toxicity (e.g., for neurological toxicity, referrals to the neurologist, nerve conduction velocity studies, nerve biopsies, EEG, circulating neurotoxin levels) and therefore certain community settings with lesser access to specialists may not be appropriate.

Follow-up and Primary Outcome– If the toxicity onset window is well characterized with a fairly standard cadence across patients and easily captured through standard of care assessments, it may be appropriate to conduct follow-up visits focusing on more rigid assessment windows within the predicted onset window and less stringent assessments outside of onset based on the biology and

pharmacology of the medical product. This approach will be more easily implemented if the drug label characterizes the toxicity and its management, which will likely lead to a more standardized approach to assessment in routine care as clinicians use the label as guidance. The use of digital health technologies (DHTs) can aid in prompting patients to provide PROs and other assessments of treatment-related symptom and functional outcomes to capture low grade adverse events and their impacts that persist. Overall, this will reduce the patient and site burden of follow-up by reducing the frequency or duration of in-person follow-up visits. However, if the toxicity onset is variable and not well captured in standard of care assessments, assessment windows will likely need to be prespecified throughout, thus necessitating less pragmatism. As data generation is focused on safety, efficacy data capture can be reduced, further minimizing data collection and trial complexity. Capturing toxicities in routine practice settings allows for a more generalizable understanding of the safety of a therapeutic agent, and the opportunity to characterize exacerbating and mitigating factors. However, variability in routine practice and local assessment could impact the interpretability of the study.

Trial Objective 3: Conduct a clinical trial intended to expand the indication to characterize the safety and efficacy of the treatment in a similar disease setting.

Another common objective for post-approval clinical trials is to generate safety and efficacy data to provide evidence supporting an approved drug in a new patient population. This trial objective facilitates identification of patients that are responsive to the drug beyond the label indication, meaning that more patients that could benefit from a safe and effective therapy are identified. Expanding a drug indication requires strong scientific and clinical justification with an adequate and well controlled investigation(s) that provide substantial evidence of drug efficacy with an acceptable safety profile to provide meaningful clinical benefit. The specific populations of interest may be identified in RWD or sponsor-supported expanded access programs, where retrospective analysis of efficacy and safety data may be feasible. A trial design to support this objective will likely be a randomized, prospective study. The appropriate level of pragmatism for such a trial would depend on the primary efficacy endpoint, as well as what is already known about the adverse event profile of the drug(s) and how or whether it would be expected to differ in the new population of interest.

Examples of new uses for Trial Objective 3:

- Changing the Biomarker Cut Point for a Biomarker-Selected Population
    - Study medical product in a biomarker-selected population outside of the biomarker cutoff for the initial indication or defined by a new biomarker.
- New Therapeutic Combination
    - Study two medical products already approved in the indication of interest in a novel combination.

- New Drug Formulations
    - Study medical product already approved in the indication of interest, with a new formulation (e.g., intravenous to subcutaneous).

Case Study #3: Conduct a clinical trial to characterize the safety and efficacy of the drug in a biomarker-selected population expanded from the biomarker cutoff used for the initial indication.

To conduct a trial expanding the biomarker cutoff of the initial indication to a larger biomarker-selected population, there must be strong scientific and clinical rationale to support the new cutoff. This objective requires precision around both the biomarker status of the patients and intermediate tumor-based endpoints, if used (typically RECIST based ORR and/or PFS), to evaluate smaller but important differences in efficacy between the new biomarker subgroup and the approved biomarker-selected population. Considerations for incorporating pragmatic elements by PRECIS-2 domains, specific to the case study:

Eligibility– Select eligibility could be expanded from lessons learned in the accumulated clinical experience, but would likely be kept more similar to the registrational trial, except for the expansion of the biomarker selected population. There is a risk to patients in the new biomarker population, that they do not achieve adequate efficacy to overcome the known toxicity of the treatment. As such, the subgroup of patients that would be expanded by the new cut point would need to be analyzed separately to assure that the overall efficacy is not predominately attributed to the previously approved population that used a higher threshold. While local testing may lower patient and site burden with fewer screening procedures, the precision of the biomarker is critical for this research objective and tests with variable performance could negatively impact the reliability of trial results. If the study has regulatory intent, early discussion with FDA would be important to obtain advice on companion diagnostic development.

Follow-up and Primary Outcome– Safety data collection may be streamlined if the expanded biomarker selected population is expected to have similar safety signals. In this case, grade 3 or higher adverse events, serious adverse events, and those leading to dose changes or discontinuation should be collected. If the trial is intended to support a label update, the extent of safety data collection should be discussed with regulators prior to the start of the study. Efficacy outcomes will likely necessitate a more explanatory approach given the importance of the precision around the efficacy outcome to assess the risks and benefits in the new biomarker-selected population.

Balancing Risk with Opportunity

The workgroup discussion highlighted the context-dependent nature of integrating pragmatic elements into prospective clinical trials. Pragmatic elements can help to reduce burden for patients and sites while answering critical research questions, but may come with uncertainty and potential risks. When determining the appropriateness of incorporating pragmatic elements, balancing the

potential risks of increased data variability with the benefits in reduced complexity and burden is important. Uncertainties inherent in new approaches to trial conduct naturally create perceived risks to incorporating pragmatic elements, however these risks may not be founded or supported by data. It is expected that perceived risks and uncertainties as well as operational complexity will be reduced with experience as more trials integrate pragmatic and decentralized elements.

A commonly stated perceived risk for sponsors is conducting trials outside of specialized centers in community-based clinical practices that may not be well versed in clinical trial conduct. Concerns include protocol deviations due to a site's inexperience with clinical trials, regulatory non-compliance or trial failure due to difficulties in maintaining protocol adherence, or data quality and integrity concerns. These risks are not inherent to conducting a trial at a community site, but rather whether the site has established infrastructure and appropriate resources to conduct the trial. Importantly, highly pragmatic designs require less protocol-directed conduct which can facilitate community site participation that is closer to routine clinical care. While there may initially be a cost to the sponsor to stand up the required infrastructure at a community site, introducing operational efficiencies and technology enablement can reduce costs over time and provide long-term benefit to support enrollment and retention at these sites. Sponsors should support inclusion of community sites and balance perceived risks with the opportunity to enhance accrual and enrollment of more diverse patient populations.

Conclusions and Future Directions

Prospective trial designs that incorporate pragmatic elements provide the opportunity to reduce patient, site, and investigator burden and increase the generalizability of trial results by more closely reflecting routine clinical practice. By aligning research more with routine clinical care, pragmatic study designs hold promise to reduce complexity and burden of trial conduct and participation and expand access in community settings where most patients receive their care. However, not all pragmatic elements will be appropriate for every clinical trial context and design selection depends on the research questions, available data, and intended use of the trial results. While incorporating pragmatic elements may decrease burden, there may be an increase in potential risk and uncertainty regarding consistency and quality of data collected and interpretability of trial results. Uncertainty and sponsor burden may decrease as more experience is gained conducting trials with pragmatic and decentralized elements. In the near-term, consideration should be given to the potential benefits and risks of introducing pragmatic elements, and discussion with regulatory agencies regarding trial design is essential.

Trials conducted in the postmarket setting to answer additional questions are likely to be most amenable to the initial introduction of more pragmatic elements, as the safety and efficacy of the product have been established. The postmarket research questions and case studies provided herein are not exhaustive or representative of all scenarios in which introduction of pragmatic elements may be considered. The case studies described illustrate factors to consider when introducing pragmatism into a clinical trial and will likely apply to additional postmarket scenarios. Additional

statistical aspects should be considered, including sample size and power calculations that may mitigate some of the uncertainty around potential variability in outcomes that may be instilled by more pragmatic approaches.

We focused our discussion on post-marketing settings, but lessons learned from pragmatic approaches to post-marketing trials can inform premarketing trial designs conducted prior to regulatory approval. While limited knowledge of safety and efficacy data in the premarket setting may make certain pragmatic elements inappropriate, opportunities to decentralize trial conduct or expand eligibility criteria can be considered in most contexts and may lead to more rapid accrual and more representative patient populations. The working group also discussed the opportunity to conduct a more pragmatic premarket trial in parallel to an explanatory registrational trial to provide complementary data on a broader patient population. Data from such a parallel pragmatic study could obviate the need to conduct some postmarket studies if acceptable data on underrepresented populations can be generated.

Recent FDA guidance documents, including Conducting Clinical Trials with Decentralized Elements[20] and Integrating RCTs for Drug and Biological Products Into Routine Clinical Practice[18], provide helpful guidance that can be applied to many of the considerations discussed. As these trials move into the community setting, there should be a focus on infrastructure to allow such sites to participate in the trials more feasibly, as there are significant constraints on staffing and resources. Investment in site education and infrastructure are steps toward accomplishing the objective of embedding research into routine care.

As more trials incorporate pragmatic elements, evidence-based insights on which elements have the greatest impact on reducing burden and complexity can lead to prioritizing best practices for introducing pragmatism. Trials with pragmatic and decentralized elements led by the European Organisation for Research and Treatment of Cancer (EORTC)[21,22] and the Alliance and NCTN[4,23] will provide additional lessons learned. Uncertainties and regulatory risks highlighted by sponsors are acknowledged, and continued discussions with sponsors and FDA on acceptability of trial designs is encouraged.

Citations

1. Ford I, Norrie J. Pragmatic Trials. New England Journal of Medicine. 2016;375(5):454-463. https://pubmed.ncbi.nlm.nih.gov/27518663/
2. Denicoff AM, Ivy SP, Tamashiro TT, et al. Implementing Modernized Eligibility Criteria in US National Cancer Institute Clinical Trials. JNCI: Journal of the National Cancer Institute. 2022;114(11):1437-1440. https://pubmed.ncbi.nlm.nih.gov/36047830/
3. Cannon TL, Rothe M, Mangat PK, et al. Pertuzumab Plus Trastuzumab in Patients With Biliary Tract Cancer With ERBB2/3 Alterations: Results From the Targeted Agent and Profiling Utilization Registry Study. J Clin Oncol. 2024;42(27). https://pubmed.ncbi.nlm.nih.gov/38748939/
4. Reckamp KL, Redman MW, Dragnev KH, et al. SWOG S2302, PRAGMATICA-LUNG: A prospective randomized study of ramucirumab plus pembrolizumab (PR) versus standard of care (SOC) for participants previously treated with immunotherapy for stage IV or recurrent non-small cell lung cancer. Journal of Clinical Oncology. 2024;42(16_suppl):TPS8657-TPS8657. https://ascopubs.org/doi/10.1200/JCO.2024.42.16_suppl.3008
5. Streamlined Trials Embedded in clinical Practice (STEP) Demonstration Project | FDA. Accessed October 29, 2024. https://www.fda.gov/about-fda/cder-center-clinical-trial-innovation-c3ti/streamlined-trials-embedded-clinical-practice-step-demonstration-project
6. Project Pragmatica | FDA. Accessed October 29, 2024. https://www.fda.gov/about-fda/oncology-center-excellence/project-pragmatica
7. Project 5 in 5 | FDA. Accessed October 29, 2024. https://www.fda.gov/about-fda/oncology-center-excellence/project-5-5
8. Friends of Cancer Research. Incorporating Pragmatic Elements in Study Designs to Enhance Oncology Randomized Clinical Trials; 2023. Incorporating_Pragmatic_Trial_Elements_Study_Designs_Oncology.pdf
9. Kaur M, Frahm F, Lu Y, et al. Broadening Eligibility Criteria and Diversity among Patients for Cancer Clinical Trials. NEJM evidence. 2024;3(4). https://pubmed.ncbi.nlm.nih.gov/38771994/
10. Ackerman B, Gan RW, Meyer CS, et al. Measurement error and bias in real-world oncology endpoints when constructing external control arms. Frontiers in Drug Safety and Regulation. 2024;4:1423493. https://www.frontiersin.org/journals/drug-safety-and-regulation/articles/10.3389/fdsfr.2024.1423493/full
11. Adamson BJS, Ma X, Griffith SD, Sweeney EM, Sarkar S, Bourla AB. Differential frequency in imaging-based outcome measurement: Bias in real-world oncology comparative-effectiveness studies. Pharmacoepidemiol Drug Saf. 2022;31(1):46-54. https://pubmed.ncbi.nlm.nih.gov/34227170/
12. Loudon K, Zwarenstein M, Sullivan F, Donnan P, Treweek S. Making clinical trials more relevant: improving and validating the PRECIS tool for matching trial design decisions to trial purpose. Trials. 2013;14. https://pubmed.ncbi.nlm.nih.gov/23782862/

13. E19 A Selective Approach to Safety Data Collection in Specific Late-Stage Pre-Approval or Post-Approval Clinical Trials | FDA. Accessed October 29, 2024. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e19-selective-approach-safety-data-collection-specific-late-stage-pre-approval-or-post-approval
14. NIH. NATIONAL CANCER INSTITUTE CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE (CTAC) STREAMLINING CLINICAL TRIALS WORKING GROUP WORKING GROUP REPORT. Published online 2024. https://deainfo.nci.nih.gov/advisory/ctac/0324/Mandrekar2.pdf
15. PMR/Cs for Novel Oncology Therapies - Friends of Cancer Research. Accessed October 29, 2024. https://friendsofcancerresearch.org/pmr-cs-for-novel-oncology-therapies/
16. Collins G, Andrews HS, McKelvey B, Rice C, Allen JD, Stewart MD. An Evaluation of Novel Oncology Approvals with a PMR/C for Assessing Data in Racial and Ethnic Populations Underrepresented in Premarket Clinical Trials. Clin Cancer Res. 2024;30(16):3388-3394. https://pubmed.ncbi.nlm.nih.gov/38884580/
17. Altomare I, Wang X, Kaur M, et al. Are community oncology practices with or without clinical research programs different? A comparison of patient and practice characteristics. JNCI Cancer Spectr. 2024;8(4):pkae060. https://pubmed.ncbi.nlm.nih.gov/39041606/
18. Integrating Randomized Controlled Trials for Drug and Biological Products Into Routine Clinical Practice | FDA. Accessed October 29, 2024. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/integrating-randomized-controlled-trials-drug-and-biological-products-routine-clinical-practice
19. Izano MA, Tran N, Fu A, et al. Implementing Real-World RECIST-based Tumor Response Assessment in Patients With Metastatic Non-small Cell Lung Cancer. Clin Lung Cancer. 2022;23(3):191-194. https://pubmed.ncbi.nlm.nih.gov/35283071/
20. Conducting Clinical Trials With Decentralized Elements | FDA. Accessed October 29, 2024. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/conducting-clinical-trials-decentralized-elements
21. Preusser M, Kazda T, Le Rhun E, et al. Lomustine with or without reirradiation for first progression of glioblastoma, LEGATO, EORTC-2227-BTG: study protocol for a randomized phase III study. Trials. 2024;25(1). https://pubmed.ncbi.nlm.nih.gov/38849943/
22. Grisay G, Turco F, Patrikidou A, et al. EORTC GUCG 2238 De-escalate: A pragmatic trial to revisit intermittent androgen-deprivation therapy in metastatic hormone-naïve prostate cancer in the era of new AR pathway inhibitors. Journal of Clinical Oncology. 2024;42(4_suppl):TPS232-TPS232. https://pubmed.ncbi.nlm.nih.gov/38779087/
23. Miller ED, Hitchcock K, Shi Q, et al. Alliance A022101/NRG-GI009: A pragmatic randomized phase III trial evaluating total ablative therapy for patients with limited metastatic colorectal cancer—Evaluating radiation, ablation, and surgery (ERASur). Journal of Clinical Oncology. 2024;42(16_suppl):TPS3633-TPS3633. https://pubmed.ncbi.nlm.nih.gov/38350888/