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Incorporating Pragmatic Elements in Study Designs to Enhance Oncology Randomized Clinical Trials

Introduction

There has been a trend towards increased complexity in cancer clinical trials due to various factors resulting in burden to patients, research staff, and sponsors alike. While novel investigational therapies will require more frequent safety assessments and often a host of primary and secondary efficacy endpoints to characterize risks and benefits, other study contexts where more is known about the therapies under investigation may not necessitate this assessment intensity. Reducing the complexity of trials, where appropriate, may lead to reduced burden on patients, improved enrollment, reduced attrition, and expansion of the number of sites (e.g., site selection) that may be used to generate data on broader patient populations.

Efforts to streamline data collection and simplify clinical trial designs through introduction of pragmatic clinical trial (PCT) elements, where appropriate, are underway. Pragmatic elements range from recruitment, to broadening eligibility criteria and selection of routine clinical practice sites,[1] to flexibility in delivery and monitoring of therapy, to streamlined design, endpoints and data collection including follow-up. The Pragmatic-Explanatory Continuum Indicator Summary (PRECIS) 2[2] tool is one example of the types of pragmatic elements that can be considered to reduce complexity and make trials more reflective of routine clinical practice (See **Appendix 1** for examples). Appropriate integration of pragmatic elements into clinical trial designs will vary depending on the clinical context of the trial and how the results will be used (e.g., inform clinical practice, regulatory intent), and should be incorporated in a manner that ensures study data integrity and patient safety.

Incorporating pragmatic elements can reduce the burden of trial participation. Reduced patient burden holds promise to facilitate enrollment of potentially more diverse trial populations, enable quicker enrollment, and reduce attrition. The lower burden of participation can benefit patients and potential trial sites. Such sites may be in community settings interested in performing research integrated within clinical care and sharing valuable clinical insights, especially outside of academic medical centers in areas that may be enriched for patient populations typically underrepresented in clinical trials. Further, broadening eligibility criteria provides the opportunity to assess efficacy and safety of therapeutics in additional patient populations not usually included

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in clinical trials, such as those with significant organ dysfunction or reduced performance status. This ultimately enables an improved understanding of a treatment's effectiveness and safety in a population more representative of the heterogeneous populations that are affected by the disease.

Within the continuum of trial designs, trials can include various pragmatic elements and study objectives. The prospective nature of pragmatic trial designs is critical to address challenges typically seen in observational studies using real-world data which may include data quality, missingness, and heterogeneity of endpoints and outcomes when incorporating data collection more reflective of real-world practices and settings. While trials may be designed with pragmatic elements in various prospective settings, this white paper will focus on randomized interventional PCTs (**Figure 1**). Randomized PCTs can be categorized as "a type of clinical trial designed to compare an intervention and a comparator in participants who are more similar to those affected by the condition(s) under study in routine clinical practice settings."[3] While not the focus herein, non-randomized pragmatic studies may also be valuable for signal seeking in novel indications, such as the Targeted Agent and Profiling Utilization Registry (TAPUR) Study.[4]

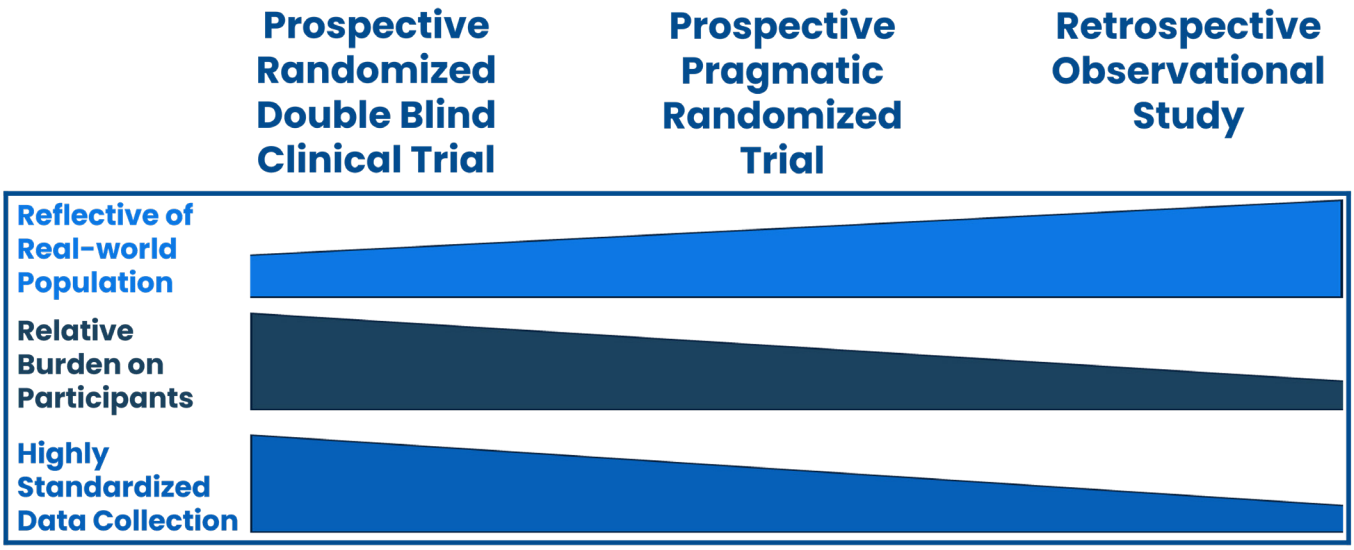

Figure 1. Spectrum of clinical trial designs and characteristics. *Prospectively designed randomized trials with pragmatic elements may include a broader patient population than in traditional clinical trials, with less overall burden and simplified data collection. However, these trials often require more structure and participant burden than traditional observational studies. Adapted from Bevan A, et al. Pragmatic randomized trials considerations for design and implementation, 2019 white paper.*

Outside of oncology, the pragmatic United Kingdom RECOVERY trial,[5] which randomized treatments for patients hospitalized with COVID-19, allowed for minimal patient eligibility criteria, and streamlined follow-up monitoring through a single online follow-up form recording when each patient was discharged, died, or at 28 days after randomization, whichever occurred first. To date, the trial has provided evidence supporting four treatments for severe COVID-19. These findings highlight the benefits of incorporating pragmatic elements into clinical trial designs to

reach a broader patient population1, which provides valuable translational lessons for oncology. The FDA Oncology Center of Excellence (OCE) is identifying opportunities to incorporate pragmatic elements into oncology randomized clinical trials as evidenced by the OCE's Project Pragmatica[3]. Incorporating pragmatic elements into clinical trials may not be appropriate for every drug, stage of development, disease setting, and clinical question. Friends of Cancer Research (*Friends*) convened a multi-stakeholder group of experts including members from the FDA and National Cancer Institute (NCI), drug developers (sponsors), patient advocates, and academic clinicians representing the NCI National Clinical Trial Network (NCTN) to lay out considerations for determining the appropriateness of incorporating pragmatic elements into randomized clinical trials and to outline potential innovative trial designs that can support a shift to streamlining the data collection plan for studies.

Opportunities to Leverage Clinical Trials with Pragmatic Elements

Randomized clinical trials with pragmatic elements could generate evidence to inform clinical practice and reimbursement (e.g., inform NCCN guidelines or payor decisions) as well as regulatory decision-making. Pragmatic trials may be conducted by a variety of entities. For example, pharmaceutical companies may be more likely to conduct trials with regulatory intent, while cooperative groups or academic centers may be more likely to conduct trials to generate evidence to support clinical practice. While trials may initially be designed as research focused only, evidence may ultimately support regulatory decision-making. Therefore, data should be collected in a manner amenable to regulatory submission where appropriate. For trials with regulatory intent, drug developers should meet with the FDA early to share the trial design and understand requirements for data collection, including methodological and evidentiary standards.

In certain circumstances, studies with pragmatic elements may be used to support a regulatory submission. Some examples include fulfilling a post-marketing commitment (e.g., additional safety information), supporting label updates to address evidence gaps, modifying treatment regimens (e.g., adding information on subpopulations not studied in the pivotal study, such as older patients or patients with worse performance status), or supporting a supplemental approval or expanded indication. As efficacy and safety evidence accumulate through the lifecycle of a drug, this expanded knowledge base may allow for the introduction of pragmatic elements to encourage continued evidence generation in an efficient manner through reduced data collection and expanded sources of data (e.g., EHR, registries, Digital Health Technologies) (**Figure 2**). Conversely, it is unlikely that a highly pragmatic trial design would support the registration of a new molecular entity, given the lack of previous safety and efficacy data.

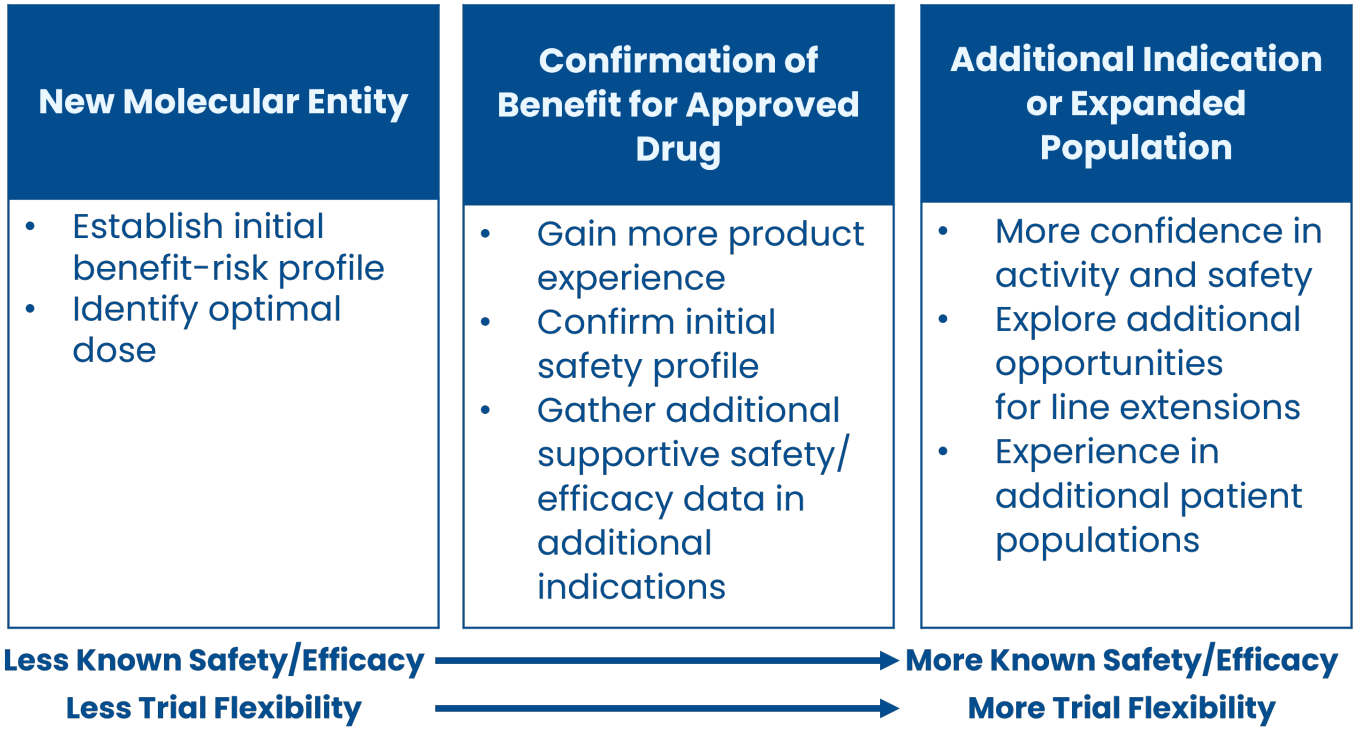

Figure 2. Key objectives across stages of evidence development

Considerations for Including Pragmatic Elements in Clinical Trial Designs

Including pragmatic elements may not be appropriate for every scenario. To aid in identifying characteristics of drug development scenarios that may be amenable to incorporating pragmatic elements, two ongoing oncology trials were assessed, Pragmatica Lung[6] and the Radiotherapy Comparative Effectiveness (RadComp) trial[7] (**Table 1**).

Table 1. Examples of pragmatic study designs and characteristics of scenarios amenable to pragmatic design

Trial Characteristics	Pragmatica Lung	Rad Comp	Characteristics Amenable to Pragmatic Designs
Purpose of Evidence Generation	Regulatory intent to support a supplemental approval for a new indication	Inform clinical practice and guidelines	Evidence generation from trials with pragmatic elements may inform both clinical and regulatory decision-making
Study Population	Patients with stage IV non-small cell lung cancer (NSCLC)	Patients with locally advanced breast cancer	Disease biology well understood with well understood treatments available

Trial Design	Prospectively designed randomized Phase 3 trial with registrational intent to evaluate overall survival	Prospectively designed randomized trial to evaluate major cardiovascular events	Prospective design, randomized trials, objective endpoint that is meaningful to patients, clearly defined and able to be ascertained in the clinical setting
Previous Supporting Data- Safety and Efficacy	Phase 2 randomized controlled trial reported positive efficacy results for the combination therapy with novel safety concerns not expected, individual agents have known safety profiles	Both therapies are considered standard of care with known efficacy for the intent to treat population with known safety profiles	Previous clinical trials/SOC clinical practice in disease setting support efficacy and safety
Intervention	Combination of two previously FDA approved agents (ramucirumab and pembrolizumab) in NSCLC, albeit not FDA approved in combination or for the specific treatment setting under investigation	Standard of care proton therapy	Agents are FDA approved in relevant cancer type
Control	Standard of care chemotherapy, physician and patient choice	Standard of care photon therapy	Standard of care treatment available for control
Pragmatic Study Design Elements	• Overall survival efficacy endpoint • Minimal adverse event (AE) reporting- only severe (Grade 3 or higher) AEs • Broader Eligibility: Enrollment of patients with lower performance status	• Patient-centric health-related quality of life (HRQOL) measurements • Eligibility is minimally restricted (not excluding pre-existing comorbidities) • Treatment is flexible in dosing and techniques • Treatment decisions are at the discretion of the local providers and patients	Validated clinically meaningful endpoints that are not overly burdensome for data collection (e.g., focused, minimal, and amenable to real-world data collection) and patient centric

A few key characteristics emerged from the two trials. As seen in **Table 1**, the therapies under investigation were FDA approved agents. For Pragmatica Lung however, the drug approvals were for a different patient population/indication than the one investigated, but the novel combination of agents had been studied in a Phase 2 trial in the specific patient population. In each case, there were previous data supporting the safety and efficacy profile of the interventions, such that it was reasonable for data collection to be streamlined. Additionally, the endpoints used in the trials are clinically meaningful, important to patients, validated for the disease setting, and amenable to capture in a routine clinical practice setting. Such trials may need to be larger to accommodate for the potential heterogeneity that can occur in a more flexible trial design. A large effect size can support the use of pragmatic elements as it increases confidence that there would be sufficient statistical power to be able to delineate outcomes, even if there is more heterogeneity in the data due to pragmatic elements, such as a broader patient population and flexibility in design based on routine clinical practice.

Considerations for Incorporating Pragmatic Elements into Study Designs

Trials incorporating pragmatic elements may have a more streamlined design, endpoints, and/or targeted data collection. In all cases, the acceptability of pragmatic elements should be justified by the clinical and regulatory context. The specific scientific question, intent (e.g., inform regulatory decision or treatment guidelines), indication, and drug(s), as well as the totality of evidence previously generated from clinical trials and observational studies, will dictate the elements that may be simplified or streamlined. PCTs may include specific pragmatic elements, though incorporation of all elements may not be feasible. For example, a trial may broaden eligibility criteria and streamline safety evaluation, while maintaining the rigor of primary efficacy endpoints such as radiographic progression endpoints. These elements should be prospectively defined, and patient consultation can add value to the design and planning of the trial. A standardized data collection template for use across all clinical sites to support streamlined data collection and for ease of analysis should be used. Highlighted below are a few pragmatic dimensions to consider for incorporation into a pragmatic trial.

Eligibility Criteria

One pragmatic element that should be considered across most cancer clinical trial contexts is eligibility criteria. Eligibility criteria may be broadened to enable the enrollment of a patient population that is more reflective of the real-world population affected by the disease. There is a sustained effort1 to encourage broadening eligibility criteria in all oncology clinical trials and pragmatic designs[1] offer the opportunity to study patient populations that may have been excluded from prior trials. Prior evidence will be important in determining the appropriate degree of pragmatism. Broadening the patient population can be nuanced and only specific criteria may be broadened instead of multiple criteria. For example, the performance status may be broadened, but patients with chronic kidney disease may still be excluded if the drug is renally cleared. The totality of available clinical data, including historical trial data, should support the rationale for broadening specific eligibility criteria. Another important consideration is the safety profile of the investigational therapy; there should be enough evidence that there is no safety concern overall in the additional patient population (i.e., known toxicities associated with the therapy are not expected to worsen or be exacerbated by pre-existing conditions included in the broader patient population). If there are concerns with the safety of the agent in the broader patient population that is planned to be included in the pragmatic trial, then additional safety data should be collected and approaches to ameliorate adverse events should be prospectively identified.

Some examples of eligibility criteria that may be relaxed include:

- **Performance Status:** Enroll patients with varying performance statuses, such as patients with an Eastern Cooperative Oncology Group (ECOG) score of 2 in addition to 0-1 scores. Evidence generated from this expanded patient population may inform clinical practice.
- **Organ Dysfunction:** Include patients with pre-specified organ dysfunction, particularly if there is not significant concern from prior clinical data, and the drug's mechanism of action and side effects are known and pose minimal risk. Evidence generated from this expanded patient population may support labeling changes to modification of treatment regimens or optimization of dosing for specific patient subpopulations or inform clinical practice guidelines. Additional safety and clinical pharmacology data may be necessary to support label modifications.
- **Comorbidities:** Include patients with comorbidities such as those diagnosed with HIV, Hepatitis B and/or C, or those that may be immunocompromised if there is no concern for additional patient risk or side effects. Evidence generated from this patient population may inform clinical practice or labeling changes.

Some examples of eligibility criteria that may be specified to ensure adequate representation[8] include:

- **Age:** Enroll older patients than may have been underrepresented in the pivotal trial but are known to be impacted by the disease. Evidence generated from this expanded patient population may inform clinical practice.
- **Race and Ethnicity:** Enroll patients who may have been underrepresented in the pivotal trial (e.g., non-white and/or Hispanic patients). Evidence generated from this expanded patient population may inform clinical practice or may satisfy a post-marketing commitment or requirement.
- **Gender:** Enroll patients who may have been underrepresented in the pivotal trial (e.g., females) but are known to be impacted by the disease. Evidence generated from this expanded patient population may inform clinical practice.

Efficacy Outcomes

Efficacy data collection may be simplified to reduce patient and site burden by decreasing the number of patient visits/assessments while still providing meaningful information to inform patient treatment. Efficacy endpoints suitable for a pragmatic approach should be clinically meaningful, patient-centric (i.e., meaningful to patients), and amenable to measurement in routine clinical practice, such as overall survival (OS).

The choice of endpoint will depend on the clinical context and trial intent (i.e., how the trial results will be used). When considering efficacy endpoints, it is important to determine if the endpoint measurement would be influenced if the trial design is not double-blinded (both patients and/or investigators are blinded to the treatment the patient receives on the trial). For example, Pragmatica Lung allows investigator's choice of standard of care therapy as the control agent. While objective endpoints such as OS would not be affected by unblinding, endpoints such as disease progression and time to treatment discontinuation (TTD) may be impacted by a patient's or investigator's knowledge of being assigned to control or investigational therapy.
Some examples of specific efficacy endpoints that may be amenable to incorporate in pragmatic trials include:

- **Overall Survival (OS):** OS is a validated clinically meaningful endpoint that is not overly

burdensome for data collection, is patient centric, not subject to bias, and encompasses an understanding of both safety and efficacy. While the trial protocol may only specify collection of survival status, disease assessment will likely also occur based on standard of care. Trials may require the collection of additional efficacy endpoints depending on the disease setting and indication and the intent to support regulatory submission, especially since OS is influenced by subsequent lines of treatment. Further, collecting the cause of death (e.g., disease-related or not) may provide additional context.

- **Response Endpoints:** Response endpoints, such as objective response rate and progression-free survival (PFS), that require strict adherence to assessment criteria (e.g., Response Evaluation Criteria in Solid Tumors- RECIST and the International Myeloma Working Group response criteria for multiple myeloma), central review and evaluation, and a strict schedule of assessment may not be amenable to a simplified approach. Without this strict adherence, heterogeneity and bias in evaluation may be introduced due to variability in the timing of scans, non-biased objective review of scans, or lack of adherence to the strict assessment criteria. Endpoints that rely on tumor assessments may lead to surveillance bias, and consideration should be given to the schedule of data collection to reduce biases. While the criteria for assessment may be more rigid and reflective of a traditional clinical trial, there may be opportunity to relax the schedule of assessments. For example, less frequent assessments with a wider window (e.g., an assessment every 12 weeks +/- 7 days versus a traditional 4 weeks +/- 3 days) may allow a more pragmatic approach to response assessment.
- **Time to Treatment Discontinuation (TTD) and Time to Next Treatment (TTNT):** The inclusion of endpoints that may be captured more easily in clinical settings, such as TTD and TTNT may be considered. However, these endpoints are not routinely used in clinical trials, and therefore may be challenging to standardize and establish thresholds for success/failure. Further, there is difficulty discerning the cause for treatment discontinuation, which may be due to AEs or tolerability, a lack of efficacy, or may be due to a therapy shortage, insurance lapse, or other interruption due to circumstances unrelated to the disease. Past studies have shown patient-level association between TTD and PFS in clinical trials of NSCLC patients across therapeutic classes, and further work is needed to strengthen the evidence of association, including the association with OS. These endpoints are subject to bias of the investigator and patient's clinical circumstance. Thus, the need for randomization of the trial minimizes potential biases. While such endpoints may be appropriate for trials intended to inform clinical practice, at this time they would not be appropriate for trials intended to support regulatory decision-making.

Safety Evaluation

Safety data collection may also be streamlined to reduce patient and trial site burden.[9] Data collection should focus on signals that may cause physicians to modify or discontinue treatment or pose significant concerns.[10] Fewer patient assessments may be used, such as only evaluating a patient's vital signs and completing study AE forms once per cycle, to streamline safety collection. In addition, attribution has been shown to have minimal value and thus collection of attribution should be minimized or eliminated.[11,12]

Some examples of specific safety data collection that may be amenable to incorporate in pragmatic trials include:

- **Grade 3 or Higher AEs:** If there is a well-established safety profile and expectation that an expanded population would tolerate the treatment in a similar fashion, the trial may only need to report AEs that are serious and unexpected. Currently, most NCTN Phase 3 trials do not collect these Grade 1 and 2 AEs.
- **Targeted Safety Event Collection:** If a trial incorporates a reduced safety data collection method, the mechanism of action of the drug and prior clinical data will be critical to determine if additional targeted safety data is needed. For example, in study of a novel combination, if there is overlapping toxicity or concerns for specific safety events with the combination, additional data may be needed. Further, if there is a concern for a specific adverse event in a specific patient population included in the pragmatic trial due to previous data, additional data collection for the specific AE may be warranted. This additional data collection may be imperative to support regulatory decision-making.
- **Patient Reported Outcomes (PROs):** PROs could be considered to capture the safety and tolerability events relevant to patients, for more patient-centric data. The Patient Reported Outcome Common Terminology Criteria for Adverse Events (PRO-CTCAE) item library evaluates the symptom attributes of frequency, severity, interference, amount, and presence/absence for patients. Additionally, digital health technologies (DHTs) may be used to collect long-term longitudinal data on patients' symptoms. With all patient assessments of symptoms, consideration should be given to the items and frequency of data collection to reduce patient burden, and patient advocates should be included in the decision-making process for PRO inclusion. PRO data must be well designed, adequately collected, and carefully measured such that data integrity is maintained. Additionally, the intent of PRO inclusion for the overall trial objective is important. A primary endpoint using PROs may be used to inform clinical practice, however incorporation of PROs into a trial intended for regulatory decision-making with other primary endpoints may add additional data collection burden and not support a streamlined approach.

Operational Aspects of Implementing Trial Designs

While this white paper does not go into depth regarding operational aspects to consider when designing trials incorporating pragmatic elements, including simplified informed consent, considerations related to site selection and data sources, these elements are critical to successful implementation of the trial design. Work by the Clinical Trials Transformation Initiative[13] on embedding clinical trial elements into clinical practice highlights operational aspects to consider, as well as the white paper on point of care trials by Duke Margolis Center for Health Policy.[14] Careful consideration is needed to determine the appropriate research infrastructure and clinical setting in which to conduct these trials; this will have a large impact on data collection and quality, patient population, and overall evidence generation.

Innovative Study Designs to Incorporate Pragmatic Elements

There are numerous approaches to incorporating pragmatic elements into clinical trial design, depending on the specific scenario. To encourage consideration for innovative study designs, a few case studies highlight pragmatic trial design considerations amenable to each scenario. These considerations may inform the inclusion of pragmatic elements into a development program. However, each development program is unique, and the trial design, data collection, evidentiary needs will be different for each scenario. Sponsors should meet early and often with FDA to discuss possible trial designs for their specific indication and therapy.

Case Study 1: Evaluating two well-characterized, FDA approved drugs in a novel combination

Pragmatica Lung is a pragmatic clinical trial including multiple pragmatic elements and is an example of targeted data collection that was acceptable for regulatory decision-making given the prior data available.

Trial Design: Randomized trial comparing a novel combination therapy to control arm of physician's choice of standard of care (following NCCN guidelines).

Trial Design Aspects	Prior Data Available to Support Pragmatic Elements	Pragmatic Element(s)	Operationalizing Pragmatic Elements in Trial Design	Considerations for Including Pragmatic Elements
Patient Eligibility	• Phase II randomized study of combination in patients with ECOG 0-1 • Two standard of care (SOC) agents with known safety/efficacy profile	• Expanded eligibility	• Lower performance status (ECOG 0-2) ○ Stratification factor (ECOG 0-1 vs. 2) • All patients with the ability to safely receive the regimens, per FDA label and investigator's discretion (e.g., includes reduced organ function, etc.)	• The totality of evidence in higher performance status patients and early FDA input led to acceptable probability of technical and regulatory success
Efficacy Evaluation	• Phase II randomized study of combination versus SOC with a signal for improved OS	• Reduced efficacy data collection • Patient-centric endpoint	• Overall survival as primary endpoint • No protocol required disease assessment (e.g., CT, imaging) • No protocol required lab tests, specimen collection • Collect primary cause of death, but not contributor causes or source of information	• The disease setting/ indication (e.g., disease stage, existing therapies, etc.) may require the need to collect additional efficacy endpoints
Safety Evaluation	• Well-known safety profile of individual agents (both FDA approved) • Safety profile in combination (Phase II randomized study of combination) showed no new events	• Reduced safety data collection	• Serious Grade 3 or higher AEs (Grade 5 or unexpected Grade 3/4 treatment related AE) • Fewer patient assessments ○ Only vital status and AE form (once per cycle)	• If there has not been extensive study of the combination (e.g., not yet studied or in a small number of patients that may not be representative of the broader patient population), additional safety data will be needed • If there is overlapping toxicity, or concerns for specific safety events with the combination, additional data may be needed

Case Study 2: Evaluating an FDA approved drug to optimize dosing in a specific patient population

The ASCO PCORI grant[15] is studying dosing strategies of oral CDk4/6 inhibitors in older patients with metastatic breast cancer. This trial aims to collect more evidence on optimal dose for a patient population not well represented in registrational trials. The study design may be best suited to generate evidence to support changing clinical practice/guidelines to inform practitioners of dose modifications in a specific patient population. If there is regulatory intent (e.g., label modification for specific patient population, or to satisfy a post-marketing requirement for dose optimization), additional data will need to be collected.

Trial Design: Randomized trial comparing FDA approved dosing in the patient population to a titrated dosing approach using the same dose schedule but starting at a lower dose and escalating if tolerated.

Trial Design Aspects	Prior Data Available to Support Pragmatic Elements	Pragmatic Element(s)	Operationalizing Pragmatic Elements in Trial Design	Considerations for Including Pragmatic Elements
Patient Eligibility	• FDA approvals for patients in the study indication	• Expanded eligibility (focused on specific patient population)	• Enroll a specific population not included, or minimally included, in registrational trial (e.g., older adults >65)	• Initial evidence in the specific patient population to drive exploration of alternate dosing
Efficacy Evaluation	• FDA approvals in study indication proving efficacy	• Patient-centric endpoint	• TTD as primary endpoint • EFS, PFS, OS as secondary endpoints	• FDA does not commonly use TTD as a primary endpoint for regulatory decision-making, and would likely need additional data (e.g., response and durability of response, PFS) to support a label modification • It may be valuable to collect the reason for treatment discontinuation
Safety Evaluation	• Registrational trial data, albeit limited in the specific patient population, supports the safety of the therapy; well known safety profile	• Patient-centric endpoints • Reduced safety collection	• Tolerability (Grade 3-4 AEs) • PRO-CTCAEs • Quality of life (PROMIS-29) and FACT-G single item GP5 • Healthcare utilization	• To support a label modification, additional safety and PK data collection will likely be required • Consideration for the frequency of patient assessment for PROs and surveys to limit patient burden

Case Study 3: Streamlined safety data collection for a pivotal trial investigating a new indication for a previously approved drug

This case study is theoretical and provides considerations for how one may incorporate pragmatic trial elements as part of the pivotal trial in the clinical development program for a targeted agent not yet approved in a new indication (e.g., new cancer type). In this case study there is strong early scientific evidence (e.g., strong scientific rationale for the mechanism of action and prior Phase I/II data that showed a large effect size with the safety profile expected from the approved indication) to support investigation in the new indication. The Phase III trial might be conducted with reduced safety data collection based on the supportive evidence of the earlier phase trial(s). This trial design could provide evidence to support regulatory decision-making by collecting the appropriate efficacy data while streamlining safety data. This reduction in safety data collection could ease burden enabling additional trial sites to participate and to reach additional patient populations.

Trial Design: The pivotal registrational clinical trial is conducted for an agent in a novel indication. The pivotal trial streamlines safety data collection while maintaining efficacy data collection reflective of a traditional explanatory trial.

Trial Design Aspects	Prior Data Available to Support Pragmatic Elements	Pragmatic Element(s)	Operationalizing Pragmatic Elements in Trial Design	Considerations for Including Pragmatic Elements
Safety Evaluation	• Prior pre-clinical and Phase I/II trial data in the new indication showing no new or concerning safety data • Well known safety profile in other approved indications	• Reduced safety data collection	• Serious Grade 3 or higher AEs only	• Given the pre-clinical and Phase I/II data, targeted data collection may be needed to address any safety concerns

Conclusions and Future Directions

Clinical trials with pragmatic elements have the potential to bridge clinical research and clinical practice by reducing the burden of trial participation. Potential advantages to a more pragmatic clinical trial include enrollment of a more diverse trial population, more rapid enrollment, and reduced attrition. The clinical and regulatory context will determine which scenarios are more appropriate for incorporating pragmatic elements. Approved drugs with established safety and efficacy data are amenable to a more highly pragmatic approach, but all trial contexts can benefit from evaluating how or if increased pragmatism is possible. Thoughtful consideration should be taken regarding whether including pragmatic elements is feasible early in the trial design process. Engagement with FDA will be crucial to determine the data collection, study design, and statistical analysis strategy, should those trials be intended to serve a regulatory purpose.

While the idea of pragmatic clinical trials has existed for decades,[16] there are not many examples used in regulatory decision-making, particularly in oncology. Additional work is needed to encourage and enable the uptake of trials incorporating pragmatic elements with robust evidence generation. Beyond the study design elements discussed in this paper, additional considerations to enable the conduct of pragmatic trials include elements related to data sources and data quality and building local infrastructure at the point of care. Even with conduct in the routine practice setting, there are standards for acceptable data quality to generate evidence. All data may not exist in the electronic health record (EHR) in a structured or standardized way across sites, and data missingness is also of concern; prospectively defined data standards and templates may be needed. Sites that may not routinely conduct clinical trials who have interest in participating in these trials may be inexperienced or lack support staff or the infrastructure necessary to capture needed data to accurately assess endpoints. Therefore, initially there is likely to be some burden on these trial sites while they build their infrastructure and not all sites may be feasible for a trial. Efforts to increase the standardization and level of structured data in the EHR, such as mCODE,[17] may eventually support data collection. Alignment between clinical care and clinical research on data collection standards is needed. In addition, resources and best practices are needed for engaging sites that are not large academic centers and may not regularly conduct clinical trials.

As the field gains more experience identifying ideal scenarios for incorporating pragmatic elements and conducting these trials, it will be important to evaluate whether the predicted benefits are realized and to develop best practices to encourage future use of trials with pragmatic elements to generate robust evidence to support regulatory decision-making.

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Abbreviations of Terms

AEs	Adverse Events
DHT	Digital Health Technologies
ECOG	Eastern Cooperative Oncology Group
FACT-G	Functional Assessment of Cancer Therapy- General
FDA	Food and Drug Administration
HRQOL	Health-Related Quality of Life
mCODE	minimal Common Oncology Data Elements
NCCN	National Comprehensive Cancer Network
NCTN	NCI National Clinical Trials Network
OCE	Oncology Center of Excellence
OS	Overall Survival
PCT	Pragmatic Clinical Trial
PFS	Progression-Free Survival
PRECIS	Pragmatic Explanator Continuum Indicator Summary
PRO-CTCAE	Patient-Reported Outcome Common Terminology Criteria for Adverse Events
PROMIS-29	Patient-Reported Outcomes Measurement Information System
TTD	Time to Treatment Discontinuation
TTNT	Time to Next Treatment

Appendix 1

The PRECIS 2 tool highlights the spectrum of elements that may be more or less pragmatic for a specific study, dependent on the regulatory and clinical context of the trial. A trial incorporating pragmatic elements (see Pragmatic Randomized Trial) may not utilize each element in the most pragmatic manner, or utilize every element.[18]