NATIONAL CANCER INSTITUTE
CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE (CTAC)

STRATEGIC PLANNING WORKING GROUP

IMPLEMENTATION REPORT
JULY 17, 2024

REPORT ACCEPTED ON NOVEMBER 6, 2024
THE CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE

Introduction

In November 2020, the Clinical Trials and Translational Research Advisory Committee (CTAC) *ad hoc* Strategic Planning Working Group (SPWG) released its report, which envisioned the development of flexible, faster, simpler, and less expensive high-impact clinical trials that seamlessly integrate with clinical practice. The report included 15 recommendations for achieving this vision spanning eight themes: trial complexity and cost, decentralized trial activities, promoting accrual and access, new data collection approaches, patient-reported outcomes (PRO) data for clinical trials, operational burden, statistical issues, and workforce outreach and training.

NCI reconstituted the SPWG in June 2024 to accomplish the following:

1. Review the implementation status of the 2020 strategic planning initiatives
2. Determine whether SPWG recommendations not yet implemented should be pursued at this time
3. Identify any new initiatives that should be considered

The Working Group is chaired by Dr. Julie Vose, Neumann M. and Mildred E. Harris Professor, Chief, Division of Hematology and Oncology, Department of Internal Medicine at the University of Nebraska Medical Center. The full membership of the Working Group is provided in Appendix 1. This report summarizes the deliberations of the Working Group's virtual meeting held on July 17, 2024.

The implementation status of the 15 recommendations outlined in the 2020 SPWG report was reviewed by the Working Group and is provided in Appendix 2. Implementation activities underway for eight recommendations have been discussed previously by CTAC and were not discussed further by the Working Group. At the July virtual meeting, 3 of the 7 recommendations that were deferred for initial implementation were reassessed. The Working Group discussed the continued relevance of these recommendations and whether they should be pursued at this time. Additionally, a potential new initiative was proposed.

Assessment of Select SPWG 2020 Recommendations Not Yet Pursued

1. Statistical Issues – Use of External Control Arms

2020 SPWG Recommendation: Investigate whether and in what situations data from previously completed clinical trials or contemporaneous clinical practice sources could be used as "synthetic" control arms without jeopardizing trial validity.

2024 Assessment

An external control arm is a patient cohort created from contemporaneous and/or historical clinical trial data, medical records, or registries that is matched or statistically comparable to the characteristics of patients recruited to the investigational arm of a trial in every characteristic that affects eligibility for and outcomes of treatment. The first consideration for use of external control arms is accessibility and availability of data sets that contain the required variables. If such data sets are available, a second consideration is whether a statistical model can be developed for selecting an adequately matched control arm from those data sets. Past attempts to construct external control arms have been met with varying degrees of success, yet investigators continue to express interest in determining whether reliable external controls could be developed for drug development trials in certain disease settings, particularly rare diseases for which randomization may be difficult.

The Working Group noted the potential value of external control arms in certain clinical situations, while recognizing the technical challenges. The Working Group's assessment is that this initiative is still timely in 2024 and that NCI should proceed with this SPWG recommendation by convening an expert group to rigorously assess the feasibility of external control arms and to identify clinical trial scenarios for which use of external control arms would be appropriate.

2. Promoting Accrual and Access – Modernizing the Informed Consent Process

2020 SPWG Recommendation: Modernize the informed consent process by moving toward risk-based, modularized, dynamic consent forms and procedures.

2024 Assessment

The Working Group discussed the regulatory requirements for informed consent to which NCI trials must adhere and acknowledged the regulatory constraints which limit CTEP's freedom to change the process. These regulations include International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice, 21 Code of Federal Regulations (CFR) 50 (covering FDA-regulated trials), and 45 CFR 46.116 (Common Rule).

Efforts undertaken by NCI's Cancer Therapy Evaluation Program (CTEP) to improve the informed consent process were reviewed as well as draft FDA guidance on "Key Information and Facilitating Understanding in Informed Consent Guidance for Sponsors, Investigators, and Institutional Review Boards."

The Working Group's recommendation is that CTEP should continue its ongoing efforts as well as monitor external efforts to improve communication with trial participants (e.g.,

videos, artificial intelligence-based tools to improve consent materials) to identify approaches appropriate for adoption by CTEP and/or the National Clinical Trials Network (NCTN) Groups.

3. Operational Burden – Refinement of the NCI Audit Process

2020 SPWG Recommendation: Redesign the audit process to audit only data elements that are essential for determining safety, efficacy, and regulatory compliance.

2024 Assessment

The Working Group's assessment is that audit burden continues to be a concern, and that this recommendation remains a priority. A retrospective analysis of past audit results should be conducted as a first step towards implementing this recommendation. Findings from the analysis will be helpful in identifying specific areas where changes to the audit process could most effectively reduce burden.

The Working Group also noted the need for improved standardization and coordination of timing and frequency of audits across the NCTN Groups as well as the increased use of remote and virtual auditing. Additionally, the Working Group discussed exploring the use of centralized audits. Finally, the Working Group urged that any audit process revisions be implemented in a way that preserves and enhances the role of audits as collaborative efforts in education and process improvement.

Proposed New Initiative: Clinical Trial Activation Timelines

New 2024 SPWG Recommendation: The Working Group recommends that an analysis of NCTN clinical trial activation timelines be conducted.

Based on recommendations of the 2010 CTAC Operational Efficiency Working Group, standard timelines were established that reduced both median and outlier durations for trial activation steps. However, trial activation timelines are perceived to have deteriorated in recent years due to the effects of COVID, staffing challenges, the complexity of precision medicine trials, institutional practice and payment issues, and industry delays in supplying agents.

The SPWG recommends that a new analysis of NCTN trial activation timeline performance be conducted. The analysis should: (a) document which timeline components and milestones are under control of NCI, the NCTN Groups, Cancer Centers, other NCI clinical trial network participants, and pharmaceutical companies; (b) assess outliers as well as median values; and (c) investigate the causes of any observed bottlenecks. The SPWG further

recommends that, provided data are available, the analysis be extended to the activation of NCI Community Oncology Research Program and non-NCTN Cancer Center trials.

Conclusion

The Strategic Planning Working Group met in July 2024 and reaffirmed the importance and timeliness of three 2020 recommendations that proposed assessing the feasibility of external controls for clinical trials, modernizing the informed consent process, and reducing the burden of audits. Four additional SPWG recommendations not yet implemented will be assessed and discussed at a future CTAC meeting. A new recommendation to analyze NCTN clinicals trials activation timelines was offered with the goal of identifying where activation timelines could be further reduced.

Appendix 1 – Working Group Roster

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute
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***Ad hoc* Strategic Planning Working Group**

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Appendix 2 – Implementation Status of 2020 SPWG Recommendations

Trial Complexity and Cost

- Limit clinical trial data collection in late phase trials to data elements essential for the primary and secondary objectives of the trial ***(Implementation Underway)***

Decentralized Trials

- Identify study procedures, including informed consent and auditing, modified due to COVID-19 to be performed locally or remotely that are sufficiently beneficial to be adopted as standard clinical trial practice ***(Implementation Underway)***
- Expand the use of telehealth in clinical trials including for enrollment, consent, and study visits ***(Implementation Underway)***

Promoting Accrual and Access

- Improve access of minority and underserved patients to NCI clinical trials through broadened eligibility criteria and conduct clinical trials that investigate areas of specific concern for these populations during cancer treatment ***(Implementation Underway)***
- Improve patient recruitment and retention in NCI trials, especially of minority and underserved populations ***(Implementation Underway)***
- Develop a modernized informed consent process that is tailored to the risk and complexity of the trial and to the concerns and health literacy of patients ***(Currently Deferred)***

New Data Collection Approaches

- Analyze and monitor ongoing initiatives to extract clinical trial data from electronic health records (EHRs) and determine whether NCI should launch a new independent initiative in this arena ***(Implementation Underway)***
- Provide investigators with assistance in understanding and evaluating mobile device technologies for collecting physiologic clinical trial data in order to facilitate use of these devices in NCI clinical trials ***(Currently Deferred)***

PRO Data for Clinical Trials

- Facilitate the collection of PRO data for NCI clinical trials by establishing desired standards and features for collection software products, a standard downstream data model, and operational support for PRO data collection and analysis ***(Implementation Underway)***

Operational Burden

- Coordinate efforts to automatically integrate study-specific documents into local EHRs and Clinical Trial Management Systems in order to avoid the duplicative and expensive

effort to manually build and validate these documents at each participating institution, for each clinical trial ***(Implementation Underway)***

- Determine whether current NCI audits focus on data elements essential for determining safety, efficacy, and regulatory compliance and, if not, develop a new audit process that does focus on these data elements and reduces the auditing burden on sites ***(Currently Deferred)***

Statistical Issues

- Enact policy and operational changes to encourage the early involvement of statisticians in correlative, early phase, and Cancer Center led studies to improve protocol design, reduce data collection requirements, and ensure that statistically robust approaches are utilized ***(Currently Deferred)***
- Investigate whether and in what situations data from previously completed clinical trials or contemporaneous clinical practice sources could be used as "synthetic" control arms in order to improve efficiency and conserve clinical trial resources and accrual without jeopardizing trial validity ***(Currently Deferred)***

Workforce Outreach and Training

- Analyze current outreach activities designed to increase the interest of community oncologists and leaders of healthcare institutions in NCI clinical trial participation and determine whether additional efforts are warranted ***(Currently Deferred)***
- Analyze current activities designed to provide clinical trials training for community oncologists interested in becoming NCI clinical trial investigators, oncology residents, and fellows and allied health/IT staff providing ancillary support for NCI clinical trials and determine whether additional activities are warranted ***(Currently Deferred)***