NATIONAL CANCER INSTITUTE

CLINICAL TRIALS AND TRANSLATIONAL RESEARCH

ADVISORY COMMITTEE (CTAC)

STRATEGIC PLANNING WORKING GROUP

WORKING GROUP REPORT

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THE CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE

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EXECUTIVE SUMMARY

In October 2019, the Clinical Trials and Translational Research Advisory Committee (CTAC) of the National Cancer Institute (NCI) established an *ad hoc* Strategic Planning Working Group charged with assessing NCI's strategic vision for its clinical trials system for 2030 and beyond and making recommendations to achieve that vision. The Working Group focused on NCI treatment trials, with the understanding that many of the issues addressed may apply to other types of trials (e.g., prevention, symptom science) as well.

The Working Group membership represents a broad range of stakeholders in the cancer research enterprise, including experts from academic research institutions, community oncology practices, the pharmaceutical industry, the healthcare information technology industry, cancer patient advocacy groups, the Food and Drug Administration (FDA), the Centers for Medicare & Medicaid Services (CMS), and the Department of Veterans Affairs (VA). The membership of the Working Group is provided in Appendix A.

The Strategic Planning Working Group articulated a strategic vision of flexible, faster, simpler, less expensive, high-impact trials that seamlessly integrate with clinical practice. The Working Group identified eight aspects of the NCI clinical trials enterprise where improvements would facilitate achieving that vision. The first aspect is reducing the complexity of clinical trial procedures and the extent and frequency of data collection which impose burdens on clinicians, patients, and sites that may deter trial participation. The second aspect, largely inspired by the COVID-19 pandemic, is to evaluate the degree to which trial procedures can be performed locally or remotely without affecting trial validity. The third is improving accrual and access to NCI clinical trials, especially for minority and underserved patients. The fourth is improving the efficiency of data collection through electronic extraction from existing data sources or remotely from mobile devices instead of the current practice of *de novo* data collection at the participating clinical site, while the fifth is to make operational improvements in patient-reported outcome (PRO) data collection. The sixth aspect is reducing specific operational burdens that, if unaddressed, could limit trial participation and the seventh is improving the efficiency of statistical design and analysis. Finally, the eighth aspect is to enhance outreach to and training of the various workforce constituencies essential to the successful conduct of NCI clinical trials.

In addressing these opportunities for improvement, the Working Group proceeded through a three-stage consensus building process which began with an analysis of the challenges in each of these areas. The second stage focused on development of recommendations to address those challenges while the third stage defined key implementation actions for their practical realization.

The result of this broad-based, strategically driven effort, involving all the critical stakeholders in the cancer clinical trials community, is the set of 15 recommendations detailed in this report. The recommendations cover a wide range of components of the current system and their implementation will move the NCI clinical trials enterprise towards the vision of flexible, faster, simpler, less expensive, high-impact trials that seamlessly integrate with clinical practice. The 15 recommendations, which are described in detail in the report, are summarized below.

Trial Complexity and Cost

- Analyze the value and collection cost of various data elements and develop guidance for limiting data collection to those elements essential for the primary and secondary objectives of the trial *(Recommendation TCC1)*

Decentralized Trial Activities

- Determine whether adaptations due to the COVID-19 pandemic, such as conducting study procedures at a participant's local healthcare facility, shipping oral agents to patients, and performing audits remotely, can be accepted as standard clinical trial practice *(Recommendation DTA1)*
- Determine what actions are necessary to adopt telehealth use for recruitment, informed consent, and study visits as standard clinical trial practice *(Recommendation DTA2)*

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 *(Recommendation PA1)*
- Improve patient recruitment and retention in NCI trials, especially of minority and underserved populations *(Recommendation PA2)*
- 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 *(Recommendation PA3)*

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 *(Recommendation NDCA1)*
- 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 *(Recommendation NDCA2)*

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 *(Recommendation PRO1)*

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 *(Recommendation OB1)*
- 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 *(Recommendation OB2)*

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 *(Recommendation SI1)*
- 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 *(Recommendation SI2)*

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 *(Recommendation W1)*
- 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 *(Recommendation W2)*

In addition to these 15 strategic recommendations, the Working Group recommended three NCI Operational Initiatives that, although they do not rise to the level of strategic recommendations, were viewed as important improvements to be implemented.

NCI Operational Initiatives

- Develop a central Cancer Therapy Evaluation Program (CTEP) point of contact with expertise in international regulatory procedures from whom study managers and international site investigators can obtain information and assistance on the regulatory procedures required for international sites to participate in NCI-sponsored trials *(NCI Operational Initiative 1)*
- Provide NCI Central Institutional Review Board (CIRB) guidance on local context assessments and local noncompliance responses that would reduce delays and complexities for investigators and simplify the CIRB electronic infrastructure to facilitate the performance of tasks assigned to various study team members *(NCI Operational Initiative 2)*
- Assess the statistical consequences of patient-level data collection deviations and incremental morbidity and mortality due to COVID-19 *(NCI Operational Initiative 3)*

Implementing these recommendations and NCI operational initiatives will require considerable additional effort by the extramural clinical trials community, as well as an increased financial investment by NCI. But such new commitment and investment will result in a clinical trials system that better serves all Americans while advancing the vision of seamless integration of clinical research and oncology practice through flexible, faster, simpler, less expensive, high-impact trials.

SUMMARY VISION

The exponential growth in complexity and expense associated with cancer clinical trials threatens the entire enterprise. We must urgently strive for a new normal that dramatically decreases regulatory hurdles, streamlines processes for trial design and execution, focuses on essential endpoints, and increases the efficiency of data collection. The goal is flexible, faster, simpler, less expensive, high-impact trials that seamlessly integrate with clinical practice.

A great strength of the National Cancer Institute (NCI) clinical trials program has been its ability to adapt to evolving scientific opportunities and changes in the extramural clinical trials environment. In the years since the 2005 Clinical Trials Working Group report, the program has been transformed into a more integrated and coordinated enterprise that focuses on the most promising opportunities, enables implementation of novel trial designs evaluating treatments targeted at molecularly defined cohorts, and extends trial opportunities more broadly to sites and patients across the nation.

Yet even as scientific opportunities continue to expand, the resources available to support NCI clinical trials remain constrained. Moreover, because of trends in the overall healthcare system, academic and community institutions, investigators, and supporting staff face increasing pressure to prioritize clinical productivity at the expense of clinical research. These systemic challenges coupled with the growing complexity and logistical burden of cutting-edge trials threatens the sustainability and vitality of the enterprise. These challenges have been brought into even sharper focus by the COVID-19 pandemic, which has exacerbated the financial and resource pressures for healthcare institutions while simultaneously impeding the conduct of clinical trials.

But there is a positive side to the COVID-19 story as well. Regulatory authorities and NCI leadership have exercised the discretionary latitude put in place in anticipation of such emergencies, allowing for a blossoming of ingenuity at the ground level as clinical trial teams have adapted their procedures to allow recruitment, consenting, protocol treatment, and data collection to continue under these special circumstances. In turn, these deviations from usual practice have provided proof of concept for process changes that could be of long-term benefit even after the current crisis has passed.

The events of 2020 have also focused the spotlight on another critical aspect of NCI's mission: "NCI leads, conducts, and supports cancer research across the nation to advance scientific knowledge and help *all* people live longer, healthier lives" (emphasis added). NCI has long supported research that seeks to understand and address the greater burden of cancer on minority and underserved populations while also striving to extend opportunities for clinical trial participation to these populations that have historically been underrepresented. These efforts take on additional significance at this moment in our history.

Renewed debates about disparities and their societal context also have relevance in the clinical domain, including how the experience of cancer is shaped by a spectrum of comorbidities that disproportionally

afflict minority and underserved populations and how structural disparities in the cancer care delivery system affect both clinical trial and treatment opportunities. This renewed focus on disparities has highlighted the need for a research agenda that explicitly targets these challenges and seeks effective solutions.

The recommendations of the Strategic Planning Working Group address eight distinct but complementary domains: Trial Complexity and Cost, Decentralized Trial Activities, Promoting Accrual and Access, New Data Collection Approaches, Patient-Reported Outcome Data for Clinical Trials, Operational Burden, Statistical Issues, and Workforce Outreach and Training. Progress in each of these domains will reinforce efforts in the others. Moreover, the recommendations call not for minor technical adjustments but rather for more fundamental changes in how clinical trials are designed and conducted.

Taken as a whole, the recommendations move toward a clinical trial system that is more efficient, cost-effective, and focused on outcomes that matter as well as being more flexible, responsive, accessible, and equitable. Only in this way can NCI continue to take advantage of the most compelling new scientific opportunities while assuring that the benefits thereby achieved will be available to all.

INTRODUCTION

In October 2019, the Clinical Trials and Translational Research Advisory Committee (CTAC) of the National Cancer Institute (NCI) established an *ad hoc* Strategic Planning Working Group charged with assessing NCI's strategic vision for its clinical trials system for 2030 and beyond and making recommendations to achieve that vision. The Working Group focused on NCI treatment trials, with the understanding that many of the issues addressed may apply to other types of trials (e.g., prevention, symptom science) as well.

The Working Group membership represents a broad range of stakeholders in the cancer research enterprise, including experts from academic research institutions, community oncology practices, the pharmaceutical industry, the healthcare information technology (IT) industry, cancer patient advocacy groups, the Food and Drug Administration (FDA), the Centers for Medicare & Medicaid Services (CMS), and the Department of Veterans Affairs (VA). The membership of the Working Group is provided in Appendix A.

The Working Group recommendations presented in this report were developed through a sequential process, beginning with a face-to-face meeting in November 2019, during which priority areas of strategic concern were identified and topics were selected for more in-depth consideration within each of these areas. Following the November meeting, six thematic subgroups, addressing Operational Trial Design, Data Collection, Statistical Design, Regulatory Issues, Workforce, and Patient Access, were established and charged with developing recommendations within their topic areas and proposing actions that should be taken to implement each recommendation.

Each of the subgroups conducted at least three virtual webinar discussions during the spring and summer of 2020 to further develop and refine their recommendations and associated implementation actions. As subgroup deliberations proceeded, certain recommendations emerged in similar form from more than one subgroup. These cross-cutting recommendations were therefore consolidated into single recommendations representing the perspectives of both subgroups. In addition, the advent of the COVID-19 pandemic in 2020 both stimulated unique recommendations inspired by the effect of the pandemic on clinical trials and resulted in the modification of certain implementation actions. Two virtual plenary meetings were conducted via web conference in July and September 2020 to review the output of the subgroups and to develop consensus on definitive recommendations and recommended implementation actions.

Based on this iterative, consensus-building process, the Working Group developed 15 strategic recommendations organized under the following themes: Trial Complexity and Cost, Decentralized Trial Activities, Promoting Accrual and Access, New Data Collection Approaches, Patient-Reported Outcome (PRO) Data for Clinical Trials, Operational Burden, Statistical Issues, and Workforce Outreach and Training. The recommendations under each theme are presented in individual sections of this report and include the rationale underlying the recommendation as well as recommended implementation actions. In addition, the Working Group recommended three NCI Operational Initiatives that, although they do not rise to the level of strategic recommendations, were viewed as sufficiently important to be included in this report.

RECOMMENDATIONS

TRIAL COMPLEXITY AND COST

Trial complexity is a fundamental driver of cost at all stages of clinical trial development and conduct and can also be detrimental to accrual. The greatest impact, particularly for large, late phase trials, is on the extent and complexity of data collection, as each data element specified by the study protocol must be collected across all subjects according to the specified procedures.

Extensive, complex data collection imposes burdens on participants at all levels of a clinical trial:

- Clinicians who are responsible for collecting the required data elements according to the specified modalities, techniques, and timing
- Clinical research associates and supervisors who are responsible for managing data flows and ensuring their quality and integrity
- Data managers and statisticians who must manage, clean, and analyze the data
- Patients who must appear at a specified time and place, endure any discomfort and risk associated with the required medical procedures, and bear the associated time and out-of-pocket costs

At the site level, the increased time and cost required to collect large quantities of complex data elements can constitute a disincentive to trial participation.

Complex, data-intensive trials may also result in inequities in trial participation by minority and underserved patients because of limitations in their ability to meet the logistical and financial burdens of participation in these trials. Furthermore, safety net hospitals may be especially limited in their capacity to support extensive, complex data collection for their patient populations.

A range of factors has encouraged development of more complex, more data-intensive trials, including:

- Scientific benefits
  - Advance the understanding of biomarkers and mechanisms of action to inform further preclinical and clinical research
  - Obtain information for the design of future studies even if a clinical trial fails
  - Gain as much scientific insight as possible in return for the risks and burdens borne by the patients
- Regulatory considerations
  - Need to meet presumed regulatory requirements or provide for possible future use of the trial data for registration
  - Supply adverse event data to sponsors to meet regulatory requirements
- Principal Investigator career goals
  - Increase the number of publications from each trial because the opportunity to lead a late phase trial is so rare
  - Improve chances of trial approval and/or funding because of novelty resulting from trial complexity

In principle, automated data extraction from electronic health records (EHRs) could mitigate some of this data collection burden. However, such automation is in early stages of development and will take

some time before it has advanced to the point of having meaningful operational impact on NCI trials. Moreover, many of the data elements required for complex trials will likely remain beyond the data collected in routine care and hence will not be captured in the EHR.

Recommendation TCC1. Limit clinical trial data collection in late phase trials to data elements essential for the primary and secondary objectives of the trial

Rationale

The increasing complexity of NCI clinical trials and the resulting increased data collection burden warrant a focused analysis of the value of various data elements versus their collection cost with the goal of limiting data collection in late phase trials to those data elements essential for the primary and secondary objectives of the trial.

Recommended Implementation Actions

1. Gather information on any previous efforts to identify data elements that are not essential for a trial's primary or secondary objectives

2. Convene an expert group with the following responsibilities:
   - Analyze previous efforts to identify data elements that are not essential for a trial's primary or secondary objectives
   - Design and oversee analyses, including:
     - The values of various data elements relative to their collection burden
     - A comparison of clinical trial imaging and laboratory testing requirements with the imaging and laboratory testing conducted under the standard of care, taking into account whether standard-of-care assessments meet regulatory requirements
     - Data elements that were most valuable for recent FDA approvals
     - The impact of assessment frequency on clinical outcome measurements
   - Assess the balance between the advantages of limiting data collection and the factors that have led to more complex, more data-intensive trials
   - Build a consensus on data elements that should not be collected and develop guidance for minimizing nonessential data collection
   - Provide input on whether NCI should encourage use of late phase trial designs that collect more extensive data from early enrollees than from later enrollees

3. Ensure the expert group includes the perspectives from the following in addition to NCI clinical trial stakeholders:
   - Representatives from industry with responsibility for cancer clinical trials
   - Representatives of contract research organizations with experience in cancer clinical trials and knowledge of NCI programs
   - Representatives from the healthcare IT industry
   - Representatives of the FDA biomarker group
   - Patient advocates

4. Establish a dialogue with FDA and a separate dialogue with industry representatives to identify issues related to data collection that FDA or industry might not discuss in an open forum

The Working Group recommends that the expert group especially consider the following data elements as potentially unnecessary for the primary and secondary objectives of a trial:

- Adverse event attribution
- NCI Common Terminology Criteria for Adverse Events grade 1–2 nonserious adverse events
- Adverse events and their start and stop times for agents where the toxicity profile is already well-characterized, with the caveat that toxicity profiles may vary across populations
- Laboratory and imaging tests beyond standard of care
- Extensive physical examination data
- Patient-reported outcome data beyond that necessary for primary and secondary objectives
- Concomitant medications for agents where the toxicity profile is already well-characterized
- Data for correlative studies that do not address key trial objectives
- Long-term follow-up of data elements that do not address key trial objectives

In doing so, the expert group should refer to FDA guidance on collection of safety data.[1]

The Working Group further recommends that the expert group consider the following factors when judging the balance between data collection burden and value of the data:

- Pathophysiologic complexity of the study population
- Ability of study population to participate in extensive, complex data collection
- Cost and value of long-term follow-up for various data elements
- Impact of assessment frequency on clinical outcomes
- Whether a data element collected during routine care meets requirements for clinical trial use (e.g., appropriately structured, standardized)

[1] Determining the Extent of Safety Data Collection Needed in Late-Stage Premarket and Postapproval Clinical Investigations: Guidance for Industry. Food and Drug Administration, February 2016.

DECENTRALIZED TRIAL ACTIVITIES

The COVID-19 pandemic has understandably reduced the willingness and/or ability of NCI clinical trial participants to travel to a clinical trial site for study procedures. In response, NCI instituted a variety of changes to permit certain study procedures to be performed locally or remotely and thus keep clinical trial activities going. These modifications have now provided an unexpected opportunity to evaluate the advantages and disadvantages of moving certain clinical trial procedures away from study sites and into study participants' homes and local healthcare facilities even when the pandemic has passed.

Adaptations allowed by NCI and regulatory authorities to enable continuation of trial activities during the COVID-19 pandemic include:

- Performing recruitment, consent, and enrollment procedures remotely
- Performing study visits via telehealth
- Performing study visits with a local provider who is not a formal study investigator
- Conducting study procedures such as imaging, electrocardiography, and laboratory testing at a participant's local healthcare facility rather than at the clinical trial site
- Shipping oral agents directly to patients
- Conducting site audits remotely

Some of these adaptations have been facilitated by technology advances that allow study participants to interact with physicians and other clinical trial staff through desktop computers, mobile phones, and other electronic devices without being physically present.

A key benefit of these modified procedures is greater flexibility for both prospective and enrolled study participants. Remote trial recruitment, consent, and enrollment procedures; remote study visits through telehealth; and data collection at local sites facilitate patient participation by eliminating the time and cost of travel to a study site. As the requirement to travel is likely especially burdensome for minority, rural, low–socioeconomic status, and other underserved populations, expanding the use of remote procedures may also serve to increase participation by these populations.

However, these modified procedures also pose certain challenges, including data consistency and reliability, verification of local provider expertise in performing study procedures, and differences in methods and standards for data reporting.

Because of the potential long-term benefits but also the challenges of performing NCI clinical trial procedures locally or remotely, the Strategic Planning Working Group has developed two recommendations focused on assessing whether use of such procedures should be expanded and perhaps become standard practice.

Recommendation DTA1. 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

Rationale

Systematic analysis by clinical trial and regulatory experts, as well as feedback from patients, will be required to assess the advantages and disadvantages of conducting NCI clinical trial procedures locally or remotely and determine what actions are necessary to implement these modified procedures as standard clinical trial practice.

Recommended Implementation Actions

1. Conduct surveys of National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) investigators, Cancer Centers, sites performing local procedures and patients with regard to the impact of local/remote procedures on:
   - Data accuracy and completeness
   - Ease of patient participation
   - Roles/responsibilities of Principal Investigators and local providers
   - Additional workload placed on local healthcare staff

2. For a representative sample of trials, collect information on recruitment, adherence, data quality, and data loss for patients interacting with the study team in the usual way via clinic/hospital visits versus patients that have remote study visits and local performance of imaging, laboratory, and other tests

3. Convene an expert group with the following responsibilities:
   - Analyze the stakeholder survey results and the comparative data on patients participating remotely versus those participating through clinic/hospital visits
   - Based on those analyses, identify procedures where the benefits of local or remote performance justify adoption as standard clinical trial practice despite the challenges
   - Determine whether the additional effort required of local healthcare staff to perform study procedures is sufficient to warrant reimbursement from NCI clinical trial funds
   - Determine actions necessary (e.g., regulatory changes, standardized procedures, local expertise verification) to implement these local/remote procedures as standard practice

4. Ensure the expert group includes the perspectives from the following in addition to NCI clinical trials stakeholders:
   - Statisticians
   - Data management specialists
   - Representatives of FDA and the Department of Health and Human Services Office for Human Research Protections (OHRP)
   - Clinical trial auditors
   - Industry representatives with responsibility for cancer clinical trials

- Representatives of contract research organizations with experience in cancer clinical trials and knowledge of NCI programs

5. Establish separate dialogues with FDA, OHRP, CMS, and industry representatives to identify issues related to local/remote procedures that might not be discussed in an open forum

Because the local/remote procedures due to COVID-19 are very recent and undoubtedly have been implemented differently across institutions, the stakeholder surveys must be carefully designed including attention to the following factors:

- Clear and consistent specification of the procedural changes being assessed, including any variation across different care settings
- Choice of process and outcome measures for characterizing impact and benefit for various stakeholders
- Survey design, including definition of target populations, range of respondents and venues sampled, and framing of questions

Recommendation DTA2. Expand the use of telehealth in clinical trials including for enrollment, consent, and study visits

Rationale

With the support of regulatory agencies and payors, the use of telehealth in NCI clinical trials has greatly expanded during the COVID-19 pandemic. This provides an opportunity to demonstrate the value of telehealth for NCI clinical trials and determine what actions are necessary to maintain expanded use of telehealth as standard clinical trial practice.

Recommended Implementation Actions

1. Gather information on use of telehealth in NCI clinical trials before and during COVID-19

2. Convene an expert group with the following responsibilities:
   - Review information on use of telehealth in clinical trials before and during COVID-19, including documented successes and failures
   - Identify procedures conducted via telehealth during the COVID-19 pandemic that are sufficiently beneficial to recommend adopting as standard clinical trial practice
   - Assess impact of local institutional review board (IRB) policies on use of telehealth in clinical trials
   - Determine what actions are necessary to expand telehealth usage in clinical trials and address technology and cost barriers as well as audit, regulatory, and legal obstacles
   - Design a pilot trial to determine whether using telehealth for consent, enrollment, and study visits increases rural and underserved enrollment

3. Ensure the expert group includes the perspectives from the following in addition to NCI clinical trials stakeholders:

- Representatives of FDA, OHRP, and state medical licensure authorities
- Legal experts in telehealth
- Industry representatives with responsibility for cancer clinical trials
- Representatives of contract research organizations with experience in cancer clinical trials and knowledge of NCI programs
- Patient advocates

4. Establish separate dialogues with FDA, OHRP, CMS, state medical licensure authority, and industry representatives to identify issues related to telehealth use in clinical trials that might not be discussed in an open forum

5. Engage telecommunications companies concerning a waiver or reduction of data charges for use of telehealth in NCI clinical trials to ensure that cost is not a barrier to patient participation

When making recommendations with regard to expanding use of telehealth in NCI trials, the expert group will need to consider impact of the following factors:

- Medical licensure laws, as cross-state recognition of licensure will be required when telehealth procedures are conducted across state lines
- Extension of malpractice insurance to cover telehealth
- Coverage by CMS or private insurance for use of telehealth for trial procedures that are otherwise eligible for reimbursement

One factor working in favor of special consideration for clinical trials in these areas is that it is a clearly defined and much smaller domain than clinical practice, and thus the potential fiscal, regulatory, and competitive implications of allowing telehealth procedures are more limited.

Another factor the expert group will need to consider is that differential access to and facility in using electronic communication tools may lead to disparities in the ability to take advantage of the benefits of telehealth procedures in NCI clinical trials. It will be important to identify approaches for addressing such obstacles, especially for minority and underserved populations.

Finally, it may be useful for the expert group to review submissions received by NCI in response to its recent request for information (RFI), "Seeking Stakeholder Input on Scientific Gaps and Research Needs Related to Delivery of Cancer-related Care via Telehealth" (NOT-CA-20-080). Although the RFI is focused on understanding issues surrounding use of telehealth in cancer-related care rather than clinical trials, the information may also clarify issues with regard to use of telehealth in trials.

PROMOTING ACCRUAL AND ACCESS

Expanded patient participation in NCI clinical trials serves the dual goals of equity and scientific progress. From an equity perspective, it provides clinical trial access to a broader range of patients, including patients who are underserved due to race, ethnicity, native language, culture, insurance status, socioeconomic status, geographic residence, access to care, and other factors (referred to in this report as minority and underserved patients). From a scientific perspective, it allows inclusion of patients with a broader range of molecular and socioeconomic characteristics, which may prove to be valuable correlates if not drivers of outcomes. This, in turn, increases the likelihood that clinical trial results will be more applicable to the entire cancer population.

With the goal of expanding NCI clinical trial participation, the Working Group offers three recommendations. The first addresses the distinctive medical problems that may complicate clinical trial participation by minority and underserved patients. The second focuses on developing new tactics for improving both recruitment and retention, especially for minority and underserved populations. The third has the goal of modernizing the informed consent process to better tailor it to the risks and benefits of the trial, make it more user-friendly for patients, and lead to a consent that is genuinely informed. Since the complexity of the informed consent form and process is viewed as a potential obstacle to accrual, this should also lead to expanded patient participation.

Recommendation PA1. Address the distinctive medical problems experienced by minority and underserved patients during cancer clinical trials and treatment

Rationale

Higher rates of chronic comorbidities such as diabetes, obesity, hypertension, and cardiovascular disease in minority and underserved populations limit eligibility for trials and increase treatment complexity. The Working Group concluded that two strategies are necessary to address this problem.

Strategy 1: Broaden eligibility criteria for late phase NCI clinical trials as much as possible, especially with regard to comorbidities, while still achieving the trials' primary and secondary objectives

The comorbidities characteristic of minority and underserved populations can result in individuals from these populations being ineligible for clinical trials. The resulting underrepresentation may, in turn, lead to clinical trial results that are less applicable for these populations. A major step in addressing this problem was the publication in 2017 of a joint statement on broadened clinical trial eligibility criteria, based on a collaborative effort of the American Society of Clinical Oncology (ASCO), the Friends of Cancer Research (Friends), and FDA.[2] In 2018, NCI issued guidance on inclusion/exclusion criteria for NCTN and NCI Experimental Therapeutics Clinical Trials Network (ETCTN) trials, reflecting the

[2] Kim ES, Bruinooge SS, Roberts S, et al. Broadening eligibility criteria to make clinical trials more representative: American Society of Clinical Oncology and Friends of Cancer Research joint research statement. *J Clin Oncol*. 2017 November 20;35(33):3737–3744.

ASCO/Friends findings as informed by further internal review and expert input.[3] Building on its initial activity, the ASCO/Friends collaboration is continuing to work on further broadening of recommended eligibility criteria.[4]

Because of this extensive ongoing effort, the Working Group decided that until the effect of these activities was assessed, it was premature to recommend a new independent initiative in this arena. Therefore, the Working Group recommends the following implementation actions:

Recommended Implementation Actions

1. Brief CTAC concerning:
   - CTEP's assessment of the implementation of the 2017 ASCO/Friends broadened eligibility criteria recommendations for NCTN/ETCTN trials
   - ASCO/Friends ongoing efforts to further broaden eligibility criteria

2. Based on the assessment results and ongoing ASCO/Friends activities, have CTAC decide whether NCI should undertake a new initiative in this arena or continue to monitor the status of ongoing initiatives by ASCO/Friends and any other organizations and annually brief CTAC on status

3. If results of the CTEP assessment are positive, encourage implementation of the ASCO/Friends recommendations for NCI trials beyond NCTN/ETCTN (e.g., investigator-initiated trials, grant-funded trials)

The Working Group noted the importance of cultivating a consensus that broad eligibility criteria should be the default for late phase trials and criteria should be narrowed only when a specific need arises. If investigators are concerned about utilizing the broad criteria in situations where the toxicity of a drug is unknown, they should consider trial designs that use narrow criteria for an initial group of patients and then move to broader criteria as the trial progresses or have a separate cohort with broader eligibility criteria, with appropriate prespecified criteria for early stopping for toxicity.

Strategy 2: Conduct trials investigating areas of specific concern for minority and underserved patients during cancer treatment

The comorbidities often observed in minority and underserved populations can impede optimal cancer treatment and clinical trial eligibility. For example, poor control of comorbidities due to inadequate primary care may result in patients having poor performance status and thereby being ineligible for trial participation. Even when comorbidities are well-managed, patients may be at higher risk of adverse events making it difficult or impossible to tolerate an otherwise preferred cancer treatment regimen. A

[3] National Cancer Institute. Inclusion/exclusion criteria for National Cancer Institute (NCI) sponsored clinical trials: NCI recommended protocol text and guidance based on joint recommendations of the American Society of Clinical Oncology (ASCO) and Friends of Cancer Research (Friends). https://ctep.cancer.gov/protocolDevelopment/docs/NCI_ASCO_Friends_Eligibility_Criteria.pdf. Accessed October 5, 2020.

[4] Rahman NA, Ison G, Beaver JA. Broadening eligibility criteria for oncology clinical trials: current advances and future directions. *Clin Pharmacol Ther*. 2020 July 8. doi:10.1002/cpt.1919.

second area of concern is that the resources available in safety net hospitals and other treatment settings serving these populations may limit the range of feasible treatments. In order to address these concerns, clinical trials and cancer care delivery research studies should be conducted to specifically address these issues in cancer treatment. The Working Group therefore recommends the following implementation actions.

Recommended Implementation Actions

1. Convene an expert group to identify trial questions that address the special concerns of minority and underserved patients, including comorbidities and toxicities; examples include:
    - Approaches for managing, during cancer treatment, chronic comorbidities especially prevalent in minority and underserved patients
    - Alternative or modified treatments for patients with significant chronic comorbidities who cannot tolerate standard therapies
    - Examining cancer care differences at safety net hospitals versus academic and other cancer care settings

2. Ensure the expert group includes the perspectives from the following in addition to NCI clinical trial stakeholders:
    - Clinical directors of Cancer Centers that serve large minority and underserved populations
    - Researchers with expertise in cancer care delivery
    - Primary care physicians
    - Staff at safety net hospitals and other care providers that serve large minority and underserved populations
    - Minority and underserved patient advocates

3. Design and implement trials addressing these questions through either NCTN or NCORP

4. Identify initiatives, including support for infrastructure and mentorship, that would enhance the ability of safety net hospitals and care sites to participate in NCI clinical trials

The Working Group further recommends that NCI partner with industry, FDA, and other clinical research organizations in developing this research agenda and identify any lessons learned from other clinical domains for addressing the distinctive medical problems experienced by minority and underserved patients during clinical trials and treatment. In addition, design of these trials should be informed by advances in the characterization of comorbidity status, including an ongoing NCI initiative on this topic.[5]

[5] https://healthcaredelivery.cancer.gov/seermedicare/considerations/comorbidity.html. Accessed October 5, 2020.

Recommendation PA2. Identify and pilot tactics that have high potential to improve patient recruitment and retention, including for minority and underserved patients

Rationale

Despite many past and ongoing initiatives for improving patient recruitment to and retention in NCI clinical trials, recruitment and retention remain a challenge, especially for minority and underserved patients. However, before launching any new initiatives, the Working Group considered it essential that these past and ongoing initiatives be analyzed to identify the reasons for their success or failure and their potential for wider dissemination. It was also recommended that strategies used outside of cancer for improving trial recruitment and retention be included in this analysis. It was further emphasized that new forms of communication and social media may provide new possibilities that should be explored.

Recommended Implementation Actions

1. Gather information on completed or ongoing initiatives for enhancing patient recruitment and retention for trials in cancer and other clinical domains, especially for minority and underserved patients

2. Convene an expert group with the following responsibilities:
    - Analyze completed and ongoing initiatives for enhancing patient recruitment and retention, especially for minority and underserved patients
    - Determine which tactics have been most successful
    - Identify ways in which successful tactics might be more widely and/or more effectively disseminated
    - Assess the potential value of new tactics that could be tested in pilot trials, including the following:
        - Using simple language to describe trials and potential results
        - Assuring patients they will have access to their data
        - Incorporating outcomes highly valued by patients (e.g., quality of life)
        - Communicating the importance of randomization more effectively
        - Expanding the number and training of navigators
        - Ensuring that investigators and navigators of various ethnic and racial groups are available
    - Prioritize the tactics that should be piloted based on their potential to improve patient recruitment and/or retention and the feasibility of piloting
    - Identify approaches for addressing cultural sensitivities and mistrust of research in minority and underserved populations
    - Determine whether a more detailed understanding of characteristics that may limit participation (e.g., race/ethnicity, native language, cultural distinctions, insurance status, socioeconomic status, travel distance, availability of technology and other infrastructure) is needed to inform efforts to improve recruitment and retention

3. Pilot use of the prioritized tactics in a selected group of NCI trials to see whether they improve recruitment and/or retention

4. If pilots demonstrate that recruitment and/or retention is improved, develop approaches for implementing these tactics broadly across NCI trials

Recommendation PA3. Modernize the informed consent process by moving toward risk-based, modularized, dynamic consent forms and procedures

Rationale

Current informed consent processes are logistically burdensome for both patients and investigators while often failing to convey a clear understanding of the clinical trial and its risks. To address these issues, new approaches are needed that tailor the informed consent process both to the risk and complexity of the trial and to the concerns and health literacy of patients.

Working Group deliberations highlighted several issues with the current informed consent process. The first is that consent language is often not specifically tailored to the nature of the study protocol and its associated risks. In addition, the use of a standard consent form makes it difficult to communicate effectively with prospective trial participants whose life circumstances, cognitive capacity, and health and research literacy may differ widely. Finally, consent documents have become more complex over time to meet institutional requirements for legal protection and documentation.

The Working Group concluded that with the advent of digital tools, it may be possible to address these issues by designing an electronic consent process that is more flexible, more dynamic, and better tailored to the needs of each patient. In principle, it should be possible to convey the necessary information incrementally, beginning with information on trial procedures. Once patients understand what they will experience during the trial and wish to proceed, they can be provided information on the risks distinctive to the trial. After they understand and accept those trial-specific risks, patients can be given the institutional caveats that are common to all trials. Such a dynamic process could also provide the option for patients to obtain more detailed information about the trial if desired.

The Working Group noted that moving to this type of dynamic electronic consent would allow tailoring of the consent process to the risks posed by each trial. Consent for low-risk trials could be performed remotely, even from a patient's home. Without the pressure of a clinical visit, the patient might be able to gain a thorough understanding of the trial and its risks and benefits more easily. In contrast, trials posing especially high and complex risks could be flagged for more intensive, direct interaction with the study team. Electronic consent processes could also be embedded in broader informational resources providing prospective trial participants with opportunities to learn more about the clinical research process in general as well as about members of the study team.

Recommended Implementation Actions

1. Convene an expert group with the following responsibilities:
    - Define informed consent content modules that
        - Describe the trial in a stepwise fashion so patients can understand sequentially the trial procedures, the trial-specific risks, and the institutional caveats
        - Provide more detailed information about the trial for those patients who are interested

- Identify other ways in which consent forms and procedures can be simplified

2. Ensure the expert group includes perspectives from the following in addition to NCI clinical trial stakeholders:
   - NCI Central Institutional Review Board (CIRB) representatives
   - Representatives of FDA and OHRP
   - Legal and IRB representatives from institutions active in NCI clinical trials
   - Patient advocates

3. Based on input from the expert group, design proposed new consent forms and procedures

4. Pilot use of the proposed new forms and procedures in a selected group of NCI trials

5. Reconvene the expert group to review results of the pilot studies and determine whether the ease and quality of the consent process was improved by the new forms and procedures

6. If pilots demonstrate that the ease and quality of consent was improved, develop guidance for implementing the new forms and procedures

NEW DATA COLLECTION APPROACHES

Data collection is a major contributor to the cost of conducting clinical trials. This is due at least in part to the fact that most clinical trial data are collected *de novo* or manually extracted rather than being drawn directly from existing data sources. Moreover, with few exceptions (e.g., some PRO survey instruments), measurements of required data elements are conducted only at the participating clinical trial site. Advances in digital technology now offer the potential to address these inefficiencies through automated collection of clinical trial data either by extraction from existing data sources, such as EHRs, or by remote data collection directly from patients using mobile devices. In addition, such automation would facilitate centralized oversight and quality control.

With the goal of capitalizing on these innovative new approaches to clinical trial data collection, the Working Group developed two recommendations.

Recommendation NDCA1. Resolve the logistical and data quality challenges of extracting clinical trial data from electronic health records

Rationale

Although extraction of clinical trial data directly from EHRs would simplify trial operations and reduce burden, there are substantial challenges due to lack of EHR data element standardization and of interoperability with clinical trial systems, as well as mismatches in data collection consistency and schedule between trial requirements and routine practice.

After decades of effort to make standardized, interoperable EHRs a reality, the electronic health data landscape remains fragmented. Data element definitions and clinical event coding practices are tailored primarily to facilitate reimbursement rather than provide the data robustness required for clinical research. In fact, while certain structured EHR data elements may be of sufficient quality to be used for clinical trials (e.g., vital signs, laboratory test results, drug administration), other critical information (e.g., history, physical exams, biomarkers, imaging, pathology) are not yet adequately structured and standardized and thus may not be as useful for clinical trials. Moreover, primary and secondary cancer endpoints such as disease response and adverse events are generally not well-represented in EHRs today. Another challenge is the extensive effort required to build data transfer interfaces between EHRs and Clinical Trial Management Systems (CTMS) and to validate and map data elements for utility in clinical research. Based on present standards, even a successful effort to automate clinical trial data collection from EHRs would collect only a fraction of required data elements, and these may be of variable quality.

Pilot efforts are underway to develop data standards for use of EHR data for cancer clinical trials[6] and

[6] See, for example: Bertagnolli MM, Anderson B, Quina A, Piantadosi S. The electronic health record as a clinical trials tool: Opportunities and challenges. *Clin Trials*. 2020 June;17(3):237-242. https://mcodeinitiative.org/. Accessed October 6, 2020.

demonstrate scalable processes for extraction of unstructured data elements from EHRs for research and regulatory purposes.[7] Although promising, these approaches have not yet reached the stage where they can be applied broadly to NCI-sponsored clinical research.

Given the many ongoing efforts to address this problem, the Working Group concluded that before recommending a new independent initiative in this arena, it was essential to fully understand the status of major ongoing efforts to extract clinical trial data from EHRs. Therefore, the Working Group recommends the following implementation actions.

Recommended Implementation Actions

1. Gather and analyze information on initiatives to collect clinical trial data from EHRs completed and ongoing at Cancer Centers, in the NCTN, and through NCI grant-funded activities, advocacy groups, EHR vendors, industry, and more
    - Brief CTAC on the results and current status of these initiatives
    - Based on the results and current status, have CTAC decide whether NCI should undertake a new initiative in this arena or continue to monitor the status of ongoing initiatives and annually brief CTAC

2. Encourage advocacy efforts to:
    - Establish an interface standard and common data model with which all proprietary EHR formats would interoperate
    - Convince institutions providing cancer care as well as oncology professional organizations to support software and clinical practice standards for recording data in EHRs that achieve clinical trial standards for data completeness and quality
    - Convince vendors of the importance of supporting clinical research as well as clinical care by incorporating into their EHRs a defined interface standard and common data model as well as new data standards for completeness and quality, recognizing that these must align with emerging healthcare informatics standards (including legislative requirements and regulatory standards) that vendors are obliged to meet[8]

[7] See, for example: Griffith SD, Tucker M, Bowser B, et al. Generating real-world tumor burden endpoints from electronic health record data: comparison of RECIST, radiology-anchored, and clinician-anchored approaches for abstracting real-world progression in Non-Small Cell Lung Cancer. *Adv Ther*. 2019 Aug;36(8):2122–2136; Bertagnolli et al., op. cit. http://icaredata.org/. Accessed Oct 6, 2020.

[8] Examples include the Office of the National Coordinator for Health Information Technology (ONC) 2015 Edition Cures Update, Interoperability and Patient Access, United States Core Data for Interoperability (USCDI), and Fast Healthcare Interoperability Resources (FHIR).

Recommendation NDCA2. Resolve the logistical and data quality challenges of collecting clinical trial data from mobile and other remote technology devices

Rationale

Although hardware and software advances in mobile technology devices (handheld and wearable) offer the possibility of passive data collection and remote patient monitoring of physiologic measures for clinical trials, there are substantial challenges both in evaluating under what circumstances it would be possible and beneficial to use such devices and in their effective implementation.

The widespread use of mobile communication technologies, together with advances in sensor technology embodied in compact, affordable devices, has opened new possibilities for remote collection of physiologic measures such as heart rate, activity level, and glucose level directly from patients for clinical trials. However, effective use of such devices in clinical trials requires standards for data definitions, calibration (including accuracy, precision, and consistency across devices and over time), and usability by study participants.

As remote data collection is a relatively new field, these challenges may be somewhat easier to surmount than those encountered with EHRs, because there are no entrenched standards and practices to overcome. Furthermore, it is not necessary to develop a universal solution that addresses all or even a majority of available devices. Substantial benefit can be achieved by defining standards that vendors can incorporate, thus providing investigators with commercial device options that can be used without additional standardization and/or validation. When appropriate, such standards should also be concordant with regulatory standards necessary for device approvals.

The Working Group noted that by enabling data collection away from the clinic and eliminating constraints on the times that data can be collected, automated remote data collection offers the potential for expansion of patient monitoring in clinical trials, particularly with respect to adverse events and impact on general physiologic and performance status. However, it was also noted that remote data collection may pose new challenges with respect to participant adherence to study protocols.

Because this is such a new approach for clinical trial data collection, there is a pressing need on the part of investigators for assistance in understanding and evaluating the available technologies and choosing those that are best suited to a given trial. Therefore, the recommended implementation actions focus on assessing the current status of mobile technology devices for collecting physiologic data and determining whether a centralized service and/or platform protocols would facilitate use of these devices in clinical trials.

Recommended Implementation Actions

1. Gather information on the status of collection of physiologic data from mobile technology devices

2. Convene an expert group with the following responsibilities:
    - Review the status of physiologic data collection from mobile technology devices

- Identify data elements that could be collected using mobile technology devices without adversely affecting data quality/integrity, including any novel data elements made possible through the use of remote devices (e.g., level of physical activity)
- Determine whether an NCI centralized service should be established to support clinical trial data collection from mobile technology devices by providing the following services:
    - Assessment of readiness of candidate devices for collection of clinical trial data
    - Advice on when mobile technology devices should be used for data collection
    - Implementation and analytic support for use of the devices
    - Centralized, standardized data cleaning, analysis, and interpretation services
- Determine whether it would be valuable and feasible to develop "platform protocols" to:
    - Resolve technical and regulatory issues for specific devices
    - Facilitate use of these devices in clinical trials whenever desired

2. Ensure the expert group includes the perspectives from the following in addition to NCI clinical trials stakeholders:
    - Representatives from FDA
    - Representatives from remote monitoring device vendors
    - Cancer Center specialists with relevant engineering and technology expertise
    - Representatives from the healthcare informatics industry with expertise in real-world data capture and curation

3. Based on the expert group deliberations, determine whether a funding announcement should be issued for standards-compliant devices for use in NCI clinical trials

PRO DATA FOR CLINICAL TRIALS

For decades, academic researchers have developed and refined methods for assessing a patient's perception of his or her health status and the impact of disease and treatment. At the same time, patient advocates have sought to raise awareness of the patient's experience as critical to the provision of health care and that treatments should be tailored to improve the patient's quality of life as well improve their clinical outcomes.

A key challenge has been to advance assessment of these patient-reported outcomes (PROs) beyond a largely academic exercise to become an integral part of routine patient care and new drug and medical device development. The 21st Century Cures Act,[9] enacted in 2016, was a landmark in addressing this challenge. Title III, Subtitle A of the Act, entitled "Patient-Focused Drug Development," directs FDA to issue guidance on "the collection of patient experience data and the use of such data and related information in drug development." FDA guidance on the use of PROs in oncology product development, which predates the Cures legislation,[10] is now organized and documented under the Patient-Focused Drug Development Program in the agency's Oncology Center of Excellence.[11]

In addition to funding extramural research on PROs, NCI has made important technical contributions in this area, notably the development of a PRO version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™)[12] as well as NCI's involvement in the NIH-wide Patient-Reported Outcomes Measurement Information System (PROMIS) initiative.[13] The NCTN Groups and NCORP Research Bases have developed a substantial base of PRO expertise, facilitating the incorporation of PRO measures into NCTN and NCORP studies. About half of NCTN treatment trials now incorporate secondary PRO endpoints, as do the vast majority of symptom management trials. Some ETCTN trials have incorporated PRO data as well, in some cases reflecting increased interest on the part of industry in using PRO endpoints.

Recommendation PRO1. Improve the operational efficiency and utility of PRO data collected for NCI clinical trials

Rationale

Despite progress in integrating PRO measures into NCI trials, there remain operational barriers to efficient PRO data collection. One important barrier is the wide range of software products for PRO data collection currently in use at Cancer Centers and other institutions active in NCI clinical trials, as well as the cost of these products. This brings implementation burdens that may discourage site participation in trials that collect PRO data. In addition, there is a desire to share PRO data collected in clinical trials with

[9] 21st Century Cures Act, Pub. L. No. 114-255, 130 Stat. 1033 (December 13, 2016)
[10] Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. Guidance for Industry. Food and Drug Administration, December 2009.
[11] https://www.fda.gov/about-fda/oncology-center-excellence/patient-focused-drug-development. Accessed October 7, 2020.
[12] https://healthcaredelivery.cancer.gov/pro-ctcae/. Accessed October 7, 2020.
[13] https://www.healthmeasures.net/explore-measurement-systems/promis. Accessed October 12, 2020.

the patient's treatment team so that it can shape the patient's overall care and not simply be used for analysis at the trial level. Sharing of these patient-centered clinical trial parameters with the clinical team may also enhance patient engagement, retention, and adherence. The Working Group recommendation therefore focuses on these operational issues.

Recommended Implementation Actions

1. Inventory PRO collection software products currently in use at Cancer Centers and other institutions active in NCTN and/or NCORP clinical trials

2. Convene an expert group to provide input to NCI on whether to:
   - Recommend/endorse one or more PRO collection software products for use in NCI trials
   - Establish standards and required features for PRO collection software used in NCI trials
   - Establish a downstream PRO data model for NCI trials with which institutional or commercial PRO collection software products must be interoperable
   - Establish a centralized service to provide operational support for PRO collection and analysis in NCI trials and to facilitate a standard approach to the analysis of PRO endpoints

3. Investigate approaches for providing PRO clinical trial data to patient care teams

4. Determine whether a request for proposal should be issued for PRO collection technologies meeting the following criteria:
   - Easy for patients and clinical staff to use
   - Compatible with or built with the suite of NCI-preferred PRO measures
   - Interfaces smoothly with the Medidata Rave CDMS
   - Compatible with existing and new institutionally implemented PRO data collection software that meets specified data interchange standards
   - Providing a mechanism for sending trial-collected PRO data to patient care teams

5. Engage telecommunications companies concerning waiver or reduction of data charges for PRO data collection in clinical trials to ensure that cost is not a barrier to patient participation

OPERATIONAL BURDEN

Institutions that participate in NCI clinical trials generally must devote substantial institutional resources to support that participation, because current per-case reimbursements and other funding do not cover the total cost of enrolling and managing patients on those trials. Therefore, any factors that place additional operational burdens on those institutions above and beyond the costs of interacting with patients and collecting and reporting data have the potential to further limit trial participation. The Working Group identified two areas where it would be beneficial to reduce such operational burdens: integration of study documents into local EHR/CTMS systems and overly extensive audits.

Recommendation OB1. Engage EHR and CTMS vendors to create mechanisms for automatically integrating study-specific documents into local implementations of their products

Rationale

The need to manually build and validate study-specific documents such as calendars, order sets, and data collection forms in local EHR and CTMS systems results in duplicative, burdensome, expensive, and nonproductive activity.

This local implementation is necessary for several reasons: The markets for EHR and CTMS systems are divided among incompatible proprietary products, local installations of a given EHR or CTMS product can vary across institutions, and EHRs were generally not designed to meet the needs of clinical trials. Therefore, study documents must be integrated from scratch at each participating institution for each clinical trial. The cost of this activity in required staff time is substantial for a participating institution. This consumes scarce institutional resources and is a substantial disincentive to participation in NCI clinical trials, particularly trials where an organization expects to accrue only a few patients.

Recommended Implementation Actions

1. Assemble information on efforts to automatically integrate centrally developed study documents into local EHR and CTMS systems:
    - Initiatives underway at Cancer Centers[14]
    - Initiatives being pursued by EHR and CTMS vendors
    - Initiatives being pursued by other commercial vendors
    - Initiatives being pursued by research foundations and patient advocacy groups
    - Initiatives being pursued by industry
    - The Veterans Health Administration (VHA)/Department of Defense (DOD) standard chemotherapy order set system

[14] NCI has recently launched a pilot study involving two groups of Cancer Centers and affiliated sites as well as two major EHR vendors addressing EHR integration of order templates.

2. Convene a Working Group jointly with an oncology professional organization(s) that includes Cancer Center representatives and major EHR and CTMS vendors to:
   - Review information assembled by NCI
   - Identify barriers to developing automated integration of study documents into local EHR and CTMS systems and possible solutions to those barriers

3. Based on input from the Working Group, design, develop, and pilot-test an approach for automated integration of study documents into local EHR and CTMS systems

4. Encourage advocacy efforts by users to convince and incentivize EHR and CTMS vendors to develop technologies for the automated integration of study-specific documents

Recommendation OB2. Redesign the audit process to audit only data elements that are essential for determining safety, efficacy, and regulatory compliance

Rationale

Clinical trial audits that include data elements not essential for evaluating patient safety, efficacy, or regulatory compliance add unnecessary expense and complexity for sites and may deter participation in NCI clinical trials, particularly when an organization expects to accrue only a few patients.

Overly extensive audits can arise for a variety of reasons. For example, trial designs that include data elements beyond those necessary for the primary and secondary objectives of the trial result in the collection of excessive amounts of data. Moreover, trial protocols may not clearly identify data elements critical to quality and to meeting regulatory requirements. In addition, clinical trial auditors may not yet have taken sufficient advantage of current FDA guidance on adaptive, risk-tailored monitoring.[15] The Working Group concluded that overly extensive audits are a serious enough concern to warrant a systematic assessment of whether the current auditing approach for NCI trials goes beyond data elements required for determining safety, efficacy, and regulatory compliance and, if so, to redesign the audit process.

Recommended Implementation Actions

1. Conduct a retrospective analysis of audit results (including industry trials if possible) to determine whether audits are focused on data elements essential for determining safety, efficacy, and regulatory compliance[16]

2. Convene an expert group with the following responsibilities:
   - Based on the audit results analysis, identify data elements that could be eliminated from

[15] Guidance for Industry: Oversight of Clinical Investigations—A Risk-Based Approach to Monitoring, Food and Drug Administration, August 2013; A Risk-Based Approach to Monitoring of Clinical Investigations, Questions and Answers, Draft Guidance, Food and Drug Administration, March 2019

[16] NCI should engage with FDA and trial auditors to ensure that the retrospective analysis is well designed and can generate robust evidence.

auditing because they are not essential for evaluating patient safety, efficacy, or regulatory compliance
    - Propose an updated approach to auditing that is limited to data elements essential for evaluating patient safety, efficacy, or regulatory compliance and will reduce the auditing burden on local sites

3. Ensure the expert group includes the perspectives from the following in addition to NCI clinical trials stakeholders:
    - Data managers from sites participating in NCI clinical trials
    - Auditors, representing experience with NCI trials and industry trials
    - FDA representatives
    - Patient advocates

STATISTICAL ISSUES

The statistical design and analysis plan are fundamental to the scientific conception of a clinical trial. Statistical expertise plays a key role not only for power calculations and determination of sample sizes but also in clarification of study objectives; assessment of the feasibility, efficiency, and appropriateness of alternative study designs; choice of data elements to be collected; design of the analytic approach; development, where needed, of innovative study designs and analytic methods; and, finally, the interpretation of analysis results and framing of scientific conclusions in a way that is consistent with the study design, data collected, and statistical analyses performed.

The two Working Group recommendations reflect this critical role, with one of them addressing effective engagement of statisticians with the trial development process and the other drawing on statistical expertise to evaluate the appropriateness of and best practices for a proposed alternative approach to study controls.

Recommendation SI1. Revise procedures and standards to ensure early involvement of statisticians in protocol design for correlative, early phase, and Cancer Center–led studies

Rationale

Greater statistician involvement is needed in the initial stages of protocol design for correlative, early phase, and Cancer Center–led studies to optimize protocol design and data collection requirements and assure that statistically robust approaches are used, especially for model-based studies of treatment/biomarker combinations.

This recommendation emerged from Working Group deliberations for two reasons. The first was the observation that while early statistician involvement in the design of late phase NCTN and NCORP clinical trials is now standard with clear benefits in both the quality and efficiency of trial design and approval, correlative studies that use data from these trials and are driven by collaborations with external investigators often suffer from inadequate statistical plans developed without the input of NCTN or NCORP statisticians. Addressing the resulting statistical design issues often delays study approval.

The second motivation was NCI's experience in reviewing not only correlative studies but early phase and Cancer Center–led trials as well. Many initial submissions have fundamental defects in clarity and consistency due to inadequate explanations of the empirical foundation for the concept, exactly what the study is seeking to accomplish, and how the study design, data collection approach, and proposed analysis plan are tailored to achieve the stated objectives. The consequence is delay and extra effort on the part of both investigators and reviewers as concepts go through multiple cycles of revision.

The Working Group noted that obtaining greater statistical involvement early in the design of these studies is likely to require additional resources to cover statisticians' time as well as an investment in the training of additional statisticians especially with regard to design and analysis of correlative studies using biomarkers and early phase treatment/biomarker-focused designs. However, investment of these

resources up front will avoid the significant but hard-to-quantify costs of multiple rounds of concept and protocol revision that occur today.

Recommended Implementation Actions

1. Issue formal NCI guidance that NCTN/NCORP statistical review processes should include correlative studies in association with NCTN/NCORP trials as well as the trials themselves

2. Conduct a retrospective analysis of biomarker studies, including those not completed or published, to gain a systematic understanding of any design deficiencies characteristic of these studies

3. Issue formal NCI guidance encouraging improved communication among clinical investigators, correlative study specialists and statisticians across institutions for correlative, early phase, and Cancer Center–led studies

4. Encourage Cancer Center biostatistics cores to have statistical expertise in the design and analysis of biomarker studies that may be embedded in a trial or performed later as a correlative study

5. Convene regular meetings of the heads of the Cancer Center biostatistics cores, NCTN/NCORP statisticians and NCI statistical staff to share statistical ideas and experiences related to clinical trial and correlative studies and develop approaches for increasing early involvement of statisticians in protocol design for early phase, correlative, and Cancer Center–led studies

Recommendation SI2. 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

Rationale

Conducting prospective clinical trials using control data from previously completed clinical trials or contemporaneous clinical practice sources to replace or supplement concurrent, study-specific control arms has the potential to improve efficiency and conserve clinical trial resources and accrual. However, there are substantial concerns about the validity of trial results obtained using such synthetic control arms as well as the ability to locate adequately matched synthetic control patients.

The prospective, randomized, double-blind, controlled clinical trial has been the "gold standard" for clinical evidence for decades. The robustness of these gold-standard trials arises not only from use of control groups but also from the randomization of study subjects to investigational and control arms. Randomization eliminates the possibility of investigator bias in subject allocation, tends to limit the extent to which the two groups can differ in characteristics that might affect treatment outcomes, and provides the basis for statistical inference procedures that assume random sampling. When trial arms differ in unknown factors, conclusions may be distorted by unrecognized bias that cannot be corrected by stratification for known factors. With synthetic control data, no such randomization is possible. Moreover, use of synthetic controls is complicated by the ongoing evolution in standards of care, which

changes expected outcomes, as well as the increasing selection and stratification of patients using biomarkers, because biomarker data will often not be available for the synthetic population.

However, the cost of gold standard studies, in both money and other scarce resources, including patients, limits the number of clinical questions that can be addressed. Thus, there is an urgent need to investigate whether it may be possible to use synthetic control arms in certain situations. Although there are pilot efforts already underway in this area,[17] the Working Group recommends additional analyses focused on NCI's clinical trial portfolio.

Recommended Implementation Action

1. Convene an expert group to:
    - Review results from previous studies that utilized control data from completed clinical trials or contemporaneous clinical practice sources rather than concurrent control arms
    - Oversee design, conduct, and analysis of prospective, methodologically rigorous proof-of-principle studies comparing results of completed trials to the results that would have been obtained from use of one or both of these synthetic control arms:
        - Historical clinical trial control data from patients as carefully matched as possible to the actual control group
        - Clinical practice data from patients as carefully matched as possible to the actual control group
    - Oversee an analysis of how broadly feasible the use of matched historical clinical trial control patients would be across the NCI trial portfolio
    - Oversee an analysis of how broadly feasible the use of matched clinical practice patients as controls would be across the NCI trial portfolio
    - Based on the results of these studies and analyses, define criteria for determining:
        - Whether and in what situations particular clinical research questions and study designs can make effective use of synthetic control arms
        - For those studies where a synthetic control arm is appropriate, which historical and/or contemporaneous alternative data sources should be used
        - Quality standards for data to be collected from alternative data sources for use in synthetic control arms

[17] See, for example: Characterizing the use of external controls for augmenting randomized control arms and confirming benefit. White paper. Friends of Cancer Research, 2019. https://friendsofcancerresearch.org/sites/default/files/Panel-1_External_Control_Arms2019AM_2.pdf. Accessed October 11, 2020; Carrigan G, Whipple S, Capra WB, et al. Using electronic health records to derive control arms for early-phase single-arm lung cancer trials: proof-of-concept in randomized controlled trials. *Clin Pharmacol Ther*. 2020 February;107(2):369–377; Stewart M, Norden AD, Dreyer N, et al. An exploratory analysis of real-world end points for assessing outcomes among immunotherapy-treated patients with advanced non–small-cell lung cancer. *JCO Clin Cancer Inform*. 2019 July;3:1–15.

WORKFORCE OUTREACH AND TRAINING

Cultivation of community support and a robust training pipeline are critical to sustaining the existing NCI clinical trials enterprise, as well as extending participation to previously underserved populations. Several stakeholder groups are important in this respect. The leaders of cancer care organizations need to be willing to allow investigators and staff to devote resources to NCI trials. Oncologists must be willing to participate as investigators, provide ancillary clinical trial support, and/or refer patients for participation in NCI trials. Other clinical, allied health, and IT staff need to be trained for a variety of ancillary roles in trial conduct. All of these needs must be met in an environment of increasing financial pressure and competing demands on organizations and clinicians.

To address these issues, the Working Group developed two recommendations, one focused on outreach and the other on training. When implementing these recommendations, the Working Group highlighted the importance of understanding the reasons why these issues exist today by asking questions such as the following:

- Why do clinicians and organizations not participate in NCI clinical trials?
- What economic and other pressures make participation difficult?
- What steps can be taken to mitigate those pressures?
- What guidance can be provided by leaders of healthcare organizations where clinical trials are understood as an integral component of high-quality cancer care?

The Working Group also noted that the impact on NCI clinical trial participation due to the acquisition of independent community oncology practices by large healthcare systems should be considered. In this regard, it may be instructive to determine whether and, if so, how Cancer Centers have integrated acquired community practices into their NCI clinical trial activities and how this trend has affected community practice participation in NCORP.

Recommendation W1. Increase interest in and support for NCI clinical trials participation through outreach efforts to community oncologists and their staff as well as leaders of healthcare institutions

Rationale

In order to increase participation in NCI clinical trials, community outreach is needed for two audiences. The first audience is community oncologists and their staff (e.g., nurses, physician assistants [PAs]) for whom it would be valuable to provide increased awareness of NCI clinical trials as an option for their patients and also encouragement to provide local support for their patients on NCI trials. The second audience is the leaders of healthcare institutions without whose support it will be difficult for community oncologists to participate in NCI trials. Focused outreach to these leaders is needed to reinforce the importance of NCI clinical trials as a key element of high-quality cancer care despite the financial pressures under which their institutions operate.

Recommended Implementation Action

1. Convene an expert group to:
    - Assess current outreach activities by professional societies and other organizations, including industry that:
        - Increase the interest of physician practices in supporting clinical trials participation
        - Increase support of clinical trials participation by leaders of healthcare organizations
    - Determine whether additional approaches, content, and/or incentives are needed to:
        - Increase awareness by community oncologists and their staff of NCI clinical trials as an option for their patients
        - Increase willingness of community oncologists and their staff to provide local ancillary support for their patients on NCI clinical trials
        - Increase willingness of leaders of healthcare organizations to support participation of their patients and staff in NCI clinical trials
        - Better demonstrate to community oncologists and leaders of healthcare organizations the personal, professional, and societal impacts of clinical trials as the standard of care for individuals with cancer
    - Assess whether and in what ways outreach efforts should be modified to reflect the post–COVID-19 environment
    - Advise on the outreach approaches that have the greatest potential to increase interest in NCI clinical trials participation, including those informed by behavioral economics and social norms marketing
    - Guide and oversee development and implementation of communication methods, materials, and platforms for the recommended approaches

Recommendation W2. Develop clinical trials participation training programs for (1) community oncologists interested in becoming research investigators for NCI trials, (2) oncology residents and fellows, and (3) physicians and allied health/IT personnel providing ancillary support for NCI clinical trials

Rationale

Enhanced training programs offer the potential to strengthen two key aspects of the NCI clinical trials enterprise. The first is to ensure a pipeline of investigators for NCI clinical trials by developing a formal training program for community oncologists and their staff (e.g., nurses, PAs) who would like to become research investigators and determining whether expanded clinical trials training is needed as part of oncology education. A second is to ensure that physicians, allied health practitioners, and IT personnel who, although not serving as investigators, conduct ancillary procedures in support of NCI clinical trials receive training in the proper conduct of these activities.

Recommended Implementation Action

1. Convene an expert group, including representatives of the relevant professional specialty societies, to:
    - Develop operational definitions for each of the target audiences

- Assess current training standards and activities for each of these audiences, including, as applicable, any industry-sponsored efforts and any professional society guidelines and initiatives
- Determine whether additional approaches and/or content or additional capacity in existing programs is needed for each target audience and, if so, in what areas
- Assess whether and in what ways training should be modified to reflect the post–COVID-19 environment
- Guide and oversee the selection and/or development of core and specialized content modules to meet the identified training needs of each of these audiences
- Guide and oversee pilot testing of these training modules
- Identify incentives for participating in such training and recommend tactics for improving those incentives

NCI OPERATIONAL INITIATIVES

NCI OPERATIONAL INITIATIVES

In the course of deliberations, the Working Group identified certain operational improvements in the NCI clinical trials enterprise that did not rise to the level of strategic recommendations and did not require fundamental policy changes or substantial non-NCI input. However, the Working Group considered these improvements important enough that they are included in this report as recommended NCI Operational Initiatives, the progress of which should be reported periodically to CTAC.

NCI Operational Initiative 1. Develop a single CTEP point of contact from whom study managers and international site investigators can obtain information and assistance on the regulatory procedures required for international sites to participate in NCI-sponsored trials

The Working Group expressed its consensus that globalization of clinical trials is of strategic importance, especially as trials seek to recruit subjects who are more finely stratified with respect to genomic or other criteria. However, international sites that are interested in participating in NCI-sponsored trials, as well as NCI investigators who seek to include international sites in their trials, have long faced barriers because of the complexity of regulatory procedures involved. Navigating those regulatory complexities would be greatly facilitated if there were a central NCI resource with expertise in international regulatory procedures. This would save time for investigators and reduce the barriers to accrual from international sites.

NCI Operational Initiative 2. Provide CIRB guidance on local context assessments/local noncompliance responses and simplify the CIRB electronic infrastructure

The NCI CIRB conducts local context reviews for all CIRB approved protocols. Unfortunately, during local context review at sites, some institutions and local IRBs continue to perform reviews that are at least partially duplicative of the NCI CIRB review. A second problem is that responses from the CIRB and the local IRB to a given noncompliance report may be different. This creates complexities for investigators, who must take actions to address both responses. Both of these issues add complications for investigators rather than simplifying the IRB process, which was the goal of creating the CIRB. Clearer guidance and educational outreach on these matters from the CIRB would be very valuable. A third issue is that the CIRB electronic infrastructure needs to be simplified to facilitate performance of tasks assigned to various study team members, including the Principal Investigator.

NCI Operational Initiative 3. Assess the statistical consequences of patient-level data collection deviations and incremental morbidity and mortality due to COVID-19

The COVID-19 pandemic has affected both NCI clinical trial procedures and the participating patients in ways that were not anticipated in trial design. As the impact of these changes on the statistical analysis

of trial results is unknown, once a number of trials with accrual materially affected by COVID-19 are completed, it will be important to analyze clinical trial operational logs and data sets in order to characterize practice deviations and assess any impacts of these deviations on trial endpoints.

CONCLUSION

The COVID-19 pandemic has exacerbated the resource pressures on the NCI clinical trial enterprise while simultaneously impeding the conduct of clinical trials. However, successful implementation of operational changes to deal with the immediate effects of the COVID-19 crisis has pointed the way to solutions for long-standing challenges. The events of 2020 have also focused renewed attention on a critical aspect of NCI's mission: the need to extend the benefits of cancer clinical research to all, including minority and underserved populations. Building on the resourcefulness and adaptability demonstrated during this difficult time, NCI must make its approach to clinical trials more sustainable and responsive.

This report outlines 15 strategic recommendations and three NCI operational initiatives that will collectively accelerate progress toward an NCI clinical trials system that is faster, simpler, less expensive, and focused on outcomes that matter as well as more flexible, responsive, accessible, and equitable. Eight distinct but complementary domains are addressed such that progress in each will reinforce efforts in the others. Moreover, the recommendations call not for minor technical adjustments but rather for more fundamental changes in how clinical trials are designed and conducted.

These recommendations and NCI operational initiatives lay the foundation for integrating clinical trials more seamlessly with clinical practice and a clinical trials system that better serves all Americans. Expeditious implementation of the actions proposed in this report is of utmost urgency so that NCI can continue to take advantage of the most compelling new scientific opportunities while ensuring that the benefits achieved will be available to all.

APPENDIX A: STRATEGIC PLANNING WORKING GROUP ROSTER

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute
Clinical Trials and Translational Research Advisory Committee

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