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

STREAMLINING CLINICAL TRIALS WORKING GROUP

INTERIM WORKING GROUP REPORT
NOVEMBER 9, 2022

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THE CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE

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Introduction

In November 2020, the Clinical Trials and Translational Research Advisory Committee (CTAC) *ad hoc* Strategic Planning Working Group (SPWG) released its report, which envisioned the development of flexible, faster, simpler, and less expensive high-impact clinical trials that seamlessly integrate with clinical practice. The SPWG developed 15 recommendations and 3 operational initiatives that span the following themes:

- Trial complexity and cost
- Decentralized trial activities
- Promoting accrual and access
- New data collection approaches
- Patient-report outcomes (PRO) data for clinical trials
- Operational burden
- Statistical issues
- Workforce outreach and training

Even as the SPWG's report was being brought to completion, the COVID pandemic was imposing extensive operational, workforce, and budgetary challenges on key partners in the NCI clinical trials program: the NCI-Designated Cancer Centers and their affiliates, which are central to NCI's National Clinical Trials Network (NCTN), the community hospitals and oncology practices that participate in NCTN trials through the NCI Community Oncology Research Program (NCORP), and other participants in NCTN studies. These challenges have persisted even as the acute phase of the pandemic has passed.

In July 2022, in response to the urgent need to mitigate the operational burden of NCI-sponsored clinical trials without compromising trial objectives or patient safety, NCI convened the CTAC *ad hoc* Streamlining Clinical Trials Working Group to advise the NCI Director and CTAC on the implementation of three of the SPWG recommendations:

- Limit clinical trial data collection in late phase trials to data elements essential for the primary and secondary objectives of the trial *(Recommendation TCC1)*
- Resolve the logistical and data quality challenges of extracting clinical trial data from electronic health records (EHR) *(Recommendation NDCA1)*
- Engage EHR and Clinical Trial Management Systems (CTMS) vendors to create mechanisms for automatically integrating study-specific documents into local implementations of their products *(Recommendation OB1)*

The Working Group is co-chaired by Dr. Sumithra J. Mandrekar, Professor of Biostatistics and Oncology, Group Statistician, Alliance for Clinical Trials in Oncology, Department of Quantitative Health Sciences at the Mayo Clinic and Dr. Neal Meropol, Vice President of Research Oncology, Scientific and Clinical Lead, Clinical Research at Flatiron Health. The full membership of the Working Group is provided in Appendix 1.

The Working Group's initial efforts have focused on the SPWG recommendation to limit data collection in late phase trials. In preparation for the Working Group's deliberations, the NCI Coordinating Center for Clinical Trials (CCCT) reviewed study protocols and case report forms for recent NCTN phase III adult treatment trials to characterize the scope and extent of data collection in relation to study objectives. Based on this analysis and in consultation with CTAC members and other expert informants, CCCT developed a list of potential opportunities for reduction of data collection supported by empirical findings and expert judgment.

At its first plenary meeting on July 13, 2022, the Working Group discussed these potential opportunities in light of the findings of the trial analysis and identified several to be pursued. During the summer of 2022, via an iterative process of comment and review, a draft recommended set of proposed standard practices for data collection for adult, late phase, IND-exempt trials was developed, reflecting the consensus of the Working Group. At its second and third plenary meetings, held on October 4 and October 25 respectively, the Working Group discussed and refined this draft resulting in a set of proposed standard practices for recommendation to NCI.

Given the urgent need addressed by this initiative, the recommended standard practices are presented to the NCI in this interim report rather than wait for a comprehensive report addressing all the tasks assigned to the Working Group. This strategy will allow NCI to consider the recommended standard practices and implementation strategies, including stakeholder consultations for further refinement as appropriate, identification of technical requirements for operationalization of the proposed standards, and revision of NCI guidance documents to reflect the standards. The recommended standard practices presented in this interim report do not represent the final set of Working Group recommendations. Once the Working Group completes deliberations for all assigned tasks, a final report will be issued.

The Working Group's initial recommendation and associated set of proposed standard practices is presented in the following section of the report.

Recommendation

A set of standard practices for data collected in NCI phase III and phase II/III adult, IND-exempt, treatment trials should be established.

To realize this recommendation, the Working Group proposes an initial set of standard practices for trials that meet the following criteria:

- Managed by the Clinical Investigations Branch of NCI's Cancer Therapy Evaluation Program (CTEP)
- Phase III or Phase II/III
- Interventional
- Focused on treatment
- Adult
- IND-exempt[1]

The proposed practices are intended to define a "new normal" for data collection that is less burdensome, more efficient, and more sustainable. It is important to note that the practices are not intended to be applied rigidly at the cost of compromising key study objectives. The intent is that investigators may depart from these standards, but for each proposed departure, justification specific to the clinical details and scientific objectives of the trial should be provided and undergo review according to established protocol review processes.

The following data collection practices are recommended:

1. **Adverse Events (AEs)**
    a. Collect only AEs of grade 3 or higher, unless assessment of tolerability related to lower-grade AEs is a stated objective with a prespecified analysis plan
    b. For each AE, collect only CTCAE[2] term and CTCAE grade
    c. Do not collect AE attribution or AE start/stop times
    d. Solicited AEs[3], regardless of grade, should be limited to those that would result in dose modification, treatment discontinuation, or non-adherence

[1] IND-exempt studies are those that meet criteria defined by the Food and Drug Administration for exemption from the requirement to submit an Investigational New Drug application to the FDA. In general, studies that are IND-exempt involve agents that have received marketing approval in the United States and that are not intended to be reported to the FDA in support of a new indication or other significant change in the labeling of the agent. Approximately 40% of NCI's NCTN phase II/III and phase III trials are IND-exempt.
[2] Common Terminology Criteria for Adverse Events.
[3] "Solicited AEs" are defined as protocol-specified AEs that are required to be assessed and reported on a regular schedule (e.g., with each treatment cycle) as present or absent.

2. **Medical History**[4]
    a. Collect only those medical history items that are relevant to trial inclusion/exclusion criteria

3. **Concomitant Medications**
    a. At baseline, collect concomitant medications only if their use requires modification of the study treatment
    b. During the trial, collect only changes in concomitant medications that cause modification or discontinuation of the study treatment

4. **Physical Exam**
    a. Physical exams should be conducted according to standard of care, augmented by any trial-specific requirements
    b. Only the following physical exam findings[5] are collected:
        i. Findings that are protocol-specified endpoints or are required to assess protocol-specified endpoints
        ii. Findings that represent AEs (per section 1 above)
        iii. Findings that result in dose modification or treatment discontinuation

5. **Laboratory Tests**
    a. Laboratory tests should be conducted according to standard of care, augmented by any trial-specific requirements
    b. Only the following laboratory test results are collected:
        i. Test results that are protocol-specified endpoints or are required to assess protocol-specified endpoints
        ii. Test results that represent AEs (per section 1 above)
        iii. Test results that result in dose modification or treatment discontinuation

6. **Imaging and Other Assessment Procedures (e.g., bone marrow biopsies)**
    a. Limit imaging and other assessment procedures to those required to meet specified trial objectives (e.g., determining treatment assignment or modification, assessment of clinical outcomes)
    b. The cost of any imaging or other assessment procedures not covered by insurance must be covered by the research study

[4] "Medical history" is defined as medical events or ongoing conditions identified at trial baseline either via patient report or via review of the patient's medical record.

[5] Performance status assessed during the trial is considered a physical exam finding and should be collected if it meets criteria specified in 4b.

7. **Patient-Reported Data**
    a. Patient-medication diaries should not be required unless the protocol defines how the data will be analyzed to address specified trial objectives
    b. Data collection plans for patient-reported outcomes (PRO) must address how PRO instruments[6] will be chosen and data collection scheduled[7] to achieve specified trial objectives while minimizing patient burden

Although the Working Group has not focused on the operational mechanics of data collection, one aspect did emerge during its deliberations: the need to assure that data collection requirements are specified consistently across study protocols, case report forms, and data collection calendars/schedules, and that this consistency is maintained when protocols are amended.

Conclusion

Timely implementation of a set of standard practices for data collected in NCI phase III and phase II/III, adult, IND-exempt, treatment trials is expected to have a material impact on the operational burden of these trials and will provide important insights that will inform future Working Group discussions addressing the development of data collection standards appropriate to the requirements of late phase IND trials and of pediatric trials, respectively. These subsequent discussions will draw on lessons learned in advancing to implementation the proposed practices outlined in this report for IND-exempt trials. The Working Group notes that early phase trials have distinctive scientific and clinical objectives that will require careful reconsideration of each of the topics covered in the current set of proposed practices.

Implementation of these standards is also synergistic with ongoing efforts to assess and address operational frictions and inefficiencies in data collection processes experienced by clinical research associates and other front-line operations staff working on NCI-sponsored clinical trials. Changes in standard operating procedures at NCI and the NCTN Groups should address required changes in data collection scope and improvement in data collection procedures in an integrated, transparent, and efficient manner.

[6] "PRO instruments" may include complete instruments, selected questions and/or rating scales, as appropriate to the trial's scientific objectives.

[7] "Scheduling" includes timing, frequency, duration of follow-up, and coordination with other data collection activities.

Appendix 1 – Working Group Roster

NATIONAL INSTITUTES OF HEALTH
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