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

# STREAMLINING CLINICAL TRIALS WORKING GROUP

# WORKING GROUP REPORT
# MARCH 13, 2024

**REPORT ACCEPTED ON MARCH 13, 2024**
**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-reported outcomes (PROs)
- Operational burden
- Statistical issues
- Workforce outreach and training

In July 2022, NCI convened the CTAC *ad hoc* Streamlining Clinical Trials Working Group (SCTWG, referred to hereinafter as the Working Group) to advise the NCI Director and CTAC on implementation of the SPWG recommended initiatives related to data collection and electronic health records. These initiatives include:

Limiting Clinical Trial Data Collection

1) Limit clinical trial data collection in late phase trials to data elements essential for the primary and secondary objectives of the trial

Utilizing Electronic Health Records (EHRs) to Support Clinical Trials

1) Resolve the logistical and data quality challenges of extracting clinical trial data from electronic health records
2) Engage EHR and Clinical Trial Management Systems (CTMS) vendors to create mechanisms for automatically integrating study-specific documents into local implementations of their products

The Working Group has been 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 at Flatiron Health. The full membership of the Working Group is provided in Appendix 1.

This Report summarizes the activities and conclusions of the Working Group with respect to each of the SPWG initiatives included in its charge.

## Limiting Clinical Trial Data Collection

### New Standard Practices for Data Collection

To inform the Working Group's deliberations on limiting clinical trial data collection, the NCI Coordinating Center for Clinical Trials (CCCT) reviewed study protocols and case report forms for recent NCI National Clinical Trials Network (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 experts, CCCT developed a list of potential opportunities for reducing data collection.

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, proposed Standard Practices for adult, late phase, IND-exempt, interventional treatment trial data collection were developed, reflecting the consensus of the Working Group. At its second and third plenary meetings, held on October 4 and October 25, 2022, respectively, the Working Group discussed and refined these proposed Standard Practices which address data collection in the following categories:

- Adverse events
- Medical history
- Concomitant medications
- Physical exam
- Laboratory tests
- Imaging and other assessment procedures
- Patient-reported data

These proposed Standard Practices were accepted by CTAC at its November 9, 2022 meeting as an Interim Report.

Subsequently, NCI convened an NCTN Implementation Committee to guide operational implementation of these Standard Practices across the network. The NCTN Implementation Committee included representatives of the Statistics and Data Management Center and the Operations Center of each of the NCTN Groups as well as the NCTN Imaging and Radiation Oncology Core (IROC). This committee is co-chaired by Dr. Mandrekar and Andrea Denicoff, Head of NCTN Clinical Trials Operations in the NCI Cancer Therapy Evaluation Program (CTEP) Clinical Operations Branch. The NCTN Implementation Committee reviewed the scope, meaning, and intent of each of the proposed Standard Practices from an operational perspective and identified refinements needed to provide clear operational guidance. The representatives from each NCTN Group have been asked to develop implementation plans for adoption of the Standard Practices by their respective Group.

Based on feedback from the NCTN Implementation Committee, the Streamlining Clinical Trials Working Group, at its meeting on November 8, 2023, recommended the following key refinements to the Standard Practices:

- Expanded scope of the Standard Practices to include pediatric trials
- Revised the Standard Practices to refer to data *submission* rather than data *collection*. This revision clarifies that the Standard Practices address submission of data to the clinical trial database and do not impact the recording of data in the medical record for site-level trial or non-trial purposes
- Added language to clarify that the purpose of data submission to the clinical trial database is to (a) enable pre-specified analyses or (b) document patient characteristics for publication or other reporting purposes
- Added language identifying two additional data submission purposes for which Group discretion can be exercised to continue current data submission practices deemed valuable for oversight of site-level trial processes

The resulting refined language for the Standard Practices for Data Submission to the Clinical Trials Database are presented in Appendix 2.

***RECOMMENDATION 1: The Working Group recommends implementation of the Standard Practices for Data Submission to the Clinical Trial Database defined in Appendix 2.***

**Additional Opportunities for Streamlining Data Collection**

***Imaging and Radiation Therapy Data*** The Working Group discussed challenges associated with submission of imaging and radiation therapy (RT) data and the potential to streamline submission of such data by (a) addressing institutional privacy/confidentiality regulations that make submission of imaging and RT data to IROC burdensome and (b) improving data flows to reduce duplication and source document submissions. Based on this discussion, the Working Group makes the following recommendation.

***RECOMMENDATION 2: The Working Group recommends that NCI, IROC and the NCTN Groups work together to address the institutional privacy/confidentiality and data flow issues hampering submission of imaging and RT data.***

***Data on Pharmacologic Therapy Administration*** The Working Group discussed the wide range of data elements currently submitted to document pharmacologic therapy administration in clinical trials and whether a Standard Practice to reduce such treatment data submission could be developed. Following the Working Group meeting, consultations were conducted with Working Group and NCTN Implementation Committee members concerning potential wording for such a standard.

Working Group and Implementation Committee members shared several observations about current scientific and administrative uses of treatment data, including the following:

- Data elements collected vary with the nature of the agent and the regimen
- Data on dose modifications are used to make necessary corrections or adjustments in efficacy and safety analyses
- Data on the frequency of and reasons for dose modifications are especially important for safety analyses
- Data are used to monitor each subject's treatment status and to trigger deployment of Medidata Rave forms based on the subject's status

The variety and complexity of these uses make development of a Standard Practice complicated. Moreover, the Standard Practice would need to balance reduced data submission burden against the disruption in current operating practices caused by any recommended changes. As finding the optimal approach will require substantial additional discussion, the Working Group recommends that the NCTN should proceed with implementation of the agreed Standard Practices for other data categories while NCI and the NCTN work together to develop guidance for submission of data on pharmacologic therapy administration that aligns with the Standard Practice principles.

***RECOMMENDATION 3: The Working Group recommends that NCI and the NCTN work together in a timely manner to develop guidance for submission of treatment data that aligns with the Standard Practice principles.***

***IND Trials*** While the Standard Practices for data collection outlined in this report focus on IND-exempt trials, the Working Group noted that many of the principles could be extended, in certain clinical and regulatory contexts, to studies being conducted under an IND. For example, NCI and the FDA Oncology Center of Excellence collaboration which the led to the March 2023 launch of the Pragmatica-Lung Study (SWOG S2302), demonstrates that, in the appropriate setting, a highly-streamlined, pragmatic approach to data collection can be incorporated into trials testing IND agents under FDA purview. The Working Group recommends that NCI work with FDA to identify the clinical and regulatory contexts for which the Standard Practices for Data Submission described in Appendix 2 could be extended to trials conducted under an IND/IDE.

***RECOMMENDATION 4: The Working Group recommends that NCI work with FDA to identify the clinical and regulatory contexts in which the Standard Practices for Data Submission could be extended to studies conducted under an IND/IDE.***

## Optimizing Use of Electronic Health Records to Support Clinical Trials

### Extracting Clinical Trial Data from Electronic Health Records

To inform the Working Group's deliberations on the SPWG recommendation to resolve the logistical and data quality challenges of extracting clinical trial data from electronic health

records (EHRs), NCI's Coordinating Center for Clinical Trials (CCCT) conducted a landscape analysis identifying and characterizing the status of several academic and commercial initiatives seeking to develop, pilot test and disseminate software tools for automated or semi-automated extraction of oncology clinical trial data from EHRs. Two of these initiatives, the ICAREdata project of the Alliance for Clinical Trials in Oncology and a collaboration between SWOG and nCoup Inc., have begun pilot testing of EHR data extraction tools in association with specific NCTN trials. At its July 2022 meeting, the Working Group discussed the findings of this analysis and noted the challenges posed to both tool development and implementation by the wide variety of EHR implementations across institutions serving as clinical trial sites.

After the July meeting, CCCT staff provided briefings for key staff in the NCI Center for Biomedical Informatics and Information Technology (CBIIT) and the NCI Childhood Cancer Data Initiative (CCDI) covering the SPWG recommendation on data extraction from EHRs and the findings of the landscape analysis. In November 2022, CCDI held a workshop addressing various aspects of the use of EHR data in childhood cancer research. The workshop included a session on EHR uses in support of clinical trials including data extraction with presentations from representatives of the academic, industrial, and not-for-profit sectors. In December 2023, CCDI issued a request for information, NOT-CA-24-021, seeking further information on current capabilities in automated data entry and extraction from EHRs. The associated questionnaire specified a range of technical questions on which NCI seeks input, including the use of tools to automatically populate clinical trial case report forms with data sourced from EHRs.

***RECOMMENDATION 5: The Working Group recommends that NCI support the timely further testing and implementation within NCI clinical trial networks of tools for extracting clinical trial data from electronic health records and report periodically to CTAC on progress.***

**Facilitating EHR Study Builds**

At its November 2022 meeting, the Working Group was briefed on NCI's current activities aimed at enabling efficient implementation of clinical trial order sets and investigational drug medication data in the EHR systems of clinical trial sites.

In 2016, the Cancer Trials Support Unit (CTSU) launched a Site Study Setup Initiative (SSSI) to facilitate setup of NCI clinical trials at participating sites. The SSSI provides two services: National Coverage Analysis to assist with clinical trial billing, and extraction of key study information into a structured template to facilitate study builds within site EHRs. The template was pilot tested on both NCTN and Experimental Therapeutics Clinical Trials Network (ETCTN) studies. At present, completed templates are being routinely provided for all CTEP NCTN trials (NCTN trials sponsored by the NCI Division of Cancer Prevention are currently not included) as well as ETCTN trials for which protocols have been drafted by the Central Protocol Writing Service of the NCI Division of Cancer Treatment and Diagnosis.

In 2020, NCI awarded administrative supplements to the Cancer Center Support Grants of 10 NCI-Designated Cancer Centers organized into two consortia to support development of

standardized treatment plan builds for NCI-supported clinical trials. Following completion of the supplement award periods, the projects have been integrated into a single Clinical Trials Rapid Activation (CTRAC) consortium to continue work under a subcontract via Leidos Biomedical Research Inc. The project lead, Dr. James Yao of the University of Texas MD Anderson Cancer Center, briefed the Working Group in January 2023 on the project's progress in developing standard representations of protocol-specified investigational drug data, treatment plans, and assessment procedures, as well as an approach to packaging the standard representations in a form that can either be imported directly into a site's EHR or used to substantially facilitate manual study build activities at sites where direct import is not feasible.

***RECOMMENDATION 6: The Working Group recommends that NCI continue the CTSU SSSI, continue to support the CTRAC consortium, and report periodically to CTAC on CTRAC progress.***

## Conclusion

The Streamlining Clinical Trials Working Group has developed six recommendations designed to improve the operational efficiency of NCI late phase clinical trials. These recommendations define new Standard Practices designed to reduce data submission, identify imaging/RT and treatment data as two additional opportunities for streamlining that NCI should pursue, encourage NCI to work with FDA to extend the Standard Practice principles to IND trials, endorse further testing and implementation of tools for extraction of clinical trial data from EHRs, and endorse continued support for tools designed to facilitate EHR study builds. Implementation of these recommendations is anticipated to materially reduce the operational burden of participating in NCTN trials, which is critical to sustaining a publicly-supported late-phase cancer clinical trial enterprise.

## Appendix 1 – Working Group Roster

**NATIONAL INSTITUTES OF HEALTH**
**National Cancer Institute**

**Clinical Trials and Translational Research Advisory Committee**
***Ad hoc* Working Group on Streamlining Clinical Trials**

**CO-CHAIRS**

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# Appendix 2 – Standard Practices for Data Submission to the Clinical Trial Database

## I. Scope

1. Standard practices apply to trials meeting the following criteria:
    a. Managed by CTEP
    b. Phase III or Phase II/III
    c. Interventional
    d. Primary Purpose is Treatment
    e. Adult or pediatric
    f. IND-exempt
2. Standard practices apply to data submitted for purposes of the clinical trial. These practices do not replace or override requirements to record data in the local electronic medical record that are associated with recognized standards of care or imposed by local institutions (e.g. local clinical practice guidelines) nor do they replace or override data submission requirements imposed by regulatory authorities (e.g. requirements for the content and timing of adverse event reporting).
3. Standard practices are not intended to require submission of data elements that a Group does not currently submit.

## II. Standard Practices for Submitting Data to the Trial Database

1. Adverse Events (AEs)
    a. Submit to the trial database only the following AE data
        i. AEs of grade 3 or higher, unless there is a stated objective for the use of lower grade AEs in analyses pre-specified in the statistical plan[1]
        ii. CTCAE term and CTCAE grade for each AE
        iii. At Group discretion, the verbatim term[2] for submitted AEs
        iv. Solicited AEs if needed for analyses pre-specified in the statistical plan
    b. Do not submit AE attribution or AE start/stop times
2. Medical History[3]
    a. Submit to the trial database only the following medical history data:
        i. Data needed for analyses pre-specified in the statistical plan (endpoint data, stratification factors, etc.)
        ii. Data needed to document patient characteristics for publication or other reporting purposes

[1] For example, planned analyses of AE data, including PRO-CTCAE and other patient-reported data, to better characterize tolerability and inform care decisions, or planned analyses of AEs associated with treatment discontinuation.

[2] The exception is included to allow Groups to adhere to CDISC standards where this is deemed necessary. "Verbatim AE term" refers to the content of the variable AETERM specified in the CDISC Study Data Tabulation Model Implementation Guide: Human Clinical Trials, Version 3.4. The guide defines AETERM as "verbatim name of the event". The NIH Common Data Element Repository defines "adverse event verbatim text" as "text that describes the adverse event word for word as described by the participant/subject."

[3] "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.

iii. At Group discretion, data needed to determine eligibility for enrolled patients
iv. At Group discretion, data needed to determine treatment assignment or dosing

3. Concomitant Medications
    a. Submit to the trial database only the following concomitant medication data:
        i. Data needed for analyses pre-specified in the statistical plan (endpoint data, stratification factors, etc.)
        ii. Data needed to document patient characteristics for publication or other reporting purposes
        iii. At Group discretion, data needed to determine eligibility for enrolled patients
        iv. At Group discretion, data needed to determine treatment assignment or dosing
4. Physical Exam
    a. Submit to the trial database only the following physical exam findings[4]:
        i. Findings needed for analyses pre-specified in the statistical plan (endpoint data, stratification factors, etc.)
        ii. Findings needed to document patient characteristics for publication or other reporting purposes
        iii. At Group discretion, findings needed to determine eligibility for enrolled patients
        iv. At Group discretion, findings needed to determine treatment assignment or dosing
5. Laboratory Tests
    a. Submit to the trial database only the following laboratory test results:
        i. Test results needed for analyses pre-specified in the statistical plan (endpoint data, stratification factors, etc.)
        ii. Test results needed to document patient characteristics for publication or other reporting purposes
        iii. At Group discretion, test results needed to determine eligibility for enrolled patients
        iv. At Group discretion, test results needed to determine treatment assignment or dosing
6. Imaging and Other Assessment Procedures[5]
    a. Submit to the trial database only the following results from imaging and other disease or safety assessment procedures:
        i. Assessment results needed for analyses pre-specified in the statistical plan (endpoint data, stratification factors, etc.)
        ii. Assessment results needed to document patient characteristics for publication or other reporting purposes
        iii. At Group discretion, assessment results needed to determine eligibility for enrolled patients
        iv. At Group discretion, assessment results needed to determine treatment assignment or dosing

[4] Performance status assessed during the trial is considered a physical exam finding and should be submitted if it meets the specified criteria.
[5] E.g., bone marrow biopsies.

7. Patient-Reported Data
    a. Submit to the trial database only those patient-reported data needed for analyses pre-specified in the statistical plan (endpoint data, stratification factors, etc.)

**III. Additional Guidance to Investigators Writing Protocols**

1. Departures from these standards require justification specific to the clinical details and scientific objectives of the trial and must be approved in the course of the established Group and CTEP review processes
2. When specifying data collection requirements, limit the frequency and duration of data collection procedures to those required to meet specified trial objectives
3. Data collection plans for patient-reported data must justify the collection instruments, items and/or rating scales chosen as well as how this data collection will be coordinated with other data collection activities so as to achieve specified trial objectives while minimizing patient burden

**IV. Guidance to Physicians and Clinical Staff at Trial Sites**

1. These standard practices for submission of data to the clinical trial database do not override or otherwise affect participating sites' practice guidelines for collecting clinical information and recording it in the local medical record.