



OPEN ACCESS



Approach for reporting master protocol study designs on ClinicalTrials.gov: qualitative analysis

Rebecca J Williams,¹ Heather D Dobbins,¹ Tony Tse,¹ Sandy D Chon,² David Loose,² Gisele A Sarosy,³ Sheila A Prindiville,³ Frank W Rockhold,⁴ Deborah A Zarin⁵

¹National Center for Biotechnology Information, National Library of Medicine, National Institutes of Health, Bethesda, MD, USA

²Essex Management, Coordinating Center for Clinical Trials, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

³Coordinating Center for Clinical Trials, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

⁴Duke Clinical Research Institute, Duke University Medical Center, Durham, NC, USA

⁵Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard, Cambridge, MA, USA

Correspondence to: T Tse
atse@mail.nih.gov
(ORCID 0000-0002-9906-6864)

Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2022;377:e067745
<http://dx.doi.org/10.1136/bmj-2021-067745>

Accepted: 09 May 2022

ABSTRACT

OBJECTIVE

To describe an approach for reporting master protocol research programs (MPRPs) that is consistent with existing good reporting practices and that uses structured information to convey the overall master protocol and design of each substudy.

DESIGN

Qualitative analysis.

DATA SOURCES

ClinicalTrials.gov trial registry.

MAIN OUTCOME MEASURES

Established goals and related practices of the trial reporting system were outlined, examples and key characteristics of MPRPs were reviewed, and specific challenges in registering and reporting summary results to databases designed for traditional clinical trial designs that rely on a model of one study per protocol were identified.

RESULTS

A reporting approach is proposed that accommodates the complex study design of MPRPs and their results. This approach involves the use of separate registration records for each substudy within one MPRP protocol (with potential exceptions noted).

CONCLUSIONS

How the proposed approach allows for clear, descriptive, structured information about each substudy's prespecified design and supports timely reporting of results after completion of each substudy is described and illustrated. Although the focus is on reporting to ClinicalTrials.gov, the approach supports broader application across trial registries and results databases. This paper is intended to stimulate further

discussion of this approach among stakeholders, build awareness about the need to improve reporting of MPRPs, and encourage harmonization across trial registries globally.

Introduction

In this paper, we describe novel issues specific to the registration and reporting of results for master protocols and propose an approach to support transparent, complete, and timely reporting to trial registries and results databases such as ClinicalTrials.gov.¹ Reporting issues relating to registration and disclosure of summary results for master protocol studies are largely unaddressed in the literature but are key to ensuring that researchers, journal editors, potential study participants, and other stakeholders have the information that they need to understand the overall master protocol, as well as each substudy. We summarize the goals and practices of the trial reporting system, define and describe the key characteristics of master protocols, provide an overview of the trial reporting system, and discuss the challenges that master protocol designs pose regarding trial reporting. We then present an approach to improving the reporting of master protocols and highlight additional issues for consideration. We do not directly look at the design and analytical aspects of master protocols, which have been discussed in other publications,²⁻⁴ but instead, we focus on how to ensure such designs and their results are accommodated and clearly reported by adapting existing good reporting practices. We aim to build awareness of the need to improve the reporting of master protocols, stimulate discussion among stakeholders about our proposed approach and issues that remain, and encourage harmonization across trial registries globally. Although our approach refers specifically to ClinicalTrials.gov, the process has the potential to be applied broadly to other trial registries and results databases.

Key characteristics of master protocol research programs (MPRPs)

Master protocols are being used more frequently across the clinical research enterprise, including in cancer research and in response to the covid-19 pandemic.⁵⁻⁸ These types of studies encompass various designs with different names based on specific design features⁹; however, all of these studies can generally be described as “one overarching protocol designed to answer multiple questions.”¹⁰ A master protocol is conducted with “a collection of trials or substudies that share key design components and operational aspects to achieve better coordination than can be achieved in single

WHAT IS ALREADY KNOWN ON THIS TOPIC

Master protocol research programs (MPRPs), which consist of a central protocol describing multiple substudies, challenge the established model for registration at trial initiation and reporting of summary results after completion

Condensing study design information specified in the protocol for multiple MPRP substudies into one registration record obscures important details, such as analysis population, primary outcome measures, and completion dates for each substudy

WHAT THIS STUDY ADDS

The approach proposes reporting each MPRP substudy in a separate study record to allow for meaningful descriptions of each substudy and to better support the transparency and accountability

Other factors that require further consideration include coordinating the registration and results reporting of MPRPs, supporting the identification of MPRP related records, and harmonizing trial registries worldwide

trials designed and conducted independently.”¹⁰ Thus, we use the term MPRP to highlight the use of an overarching research protocol for coordinating an evolving set of studies that constitute a program of research. We use the term substudy to refer to each individual trial within the MPRP to which participants can be assigned. MPRPs have been used to investigate many interventions for a specific disease with an umbrella or platform design, as well as various interventions that target a specific genetic subtype of tumor independent of cancer type with a basket design (box 1).¹¹⁻¹³ MPRPs can use bayesian or other adaptive techniques for assigning participants after screening to substudies or for determining when a substudy should end.

Generally, MPRPs can allow for greater efficiency than the traditional clinical trial model by coordinating within one shared centralized protocol and infrastructure for the investigation of multiple conditions, experimental interventions, or subgroups across multiple individual clinical trials (sometimes referred to as arms).^{8 14 15} For example, the RECOVERY MPRP (NCT04381936) efficiently identified eligible participants through a centralized process and assigned participants to substudies evaluating, over time, specific interventions for covid-19, as evidence and knowledge evolved. However, the multistudy nature of MPRPs challenges established reporting practices for trial registration and disclosure of summary results that are aimed at improving clinical research transparency and accountability as well as mitigating biases within the medical evidence base.^{1 16} Specifically, MPRPs, which can use a single protocol with multiple substudies, disrupt the current model of one protocol describing one trial in one trial registry record. The practice of referring to an entire MPRP as a single trial (eg, by acronym) might imply that a master protocol should be represented as one study record in a trial registry. Yet, many master protocols include plans for a series of substudies that might start, end, and be analyzed independently of each other (including designs with a shared control arm that is fully or partially used in analyses across substudies). Condensing this information into one study record can obscure details of the substudies, such as the end dates and primary outcome measures, thereby undermining key transparency and accountability goals of the trial reporting system. In particular, international trial registries have uniformly adopted

the World Health Organization Trial Registration Data Set, a standardized collection of structured data elements describing key study design components.¹⁷ Such structured information allows users to search for and retrieve registered trial records based on specific study characteristics, for needs ranging from patients seeking to enroll in trials to systematic reviewers identifying trials for a specified population, intervention, comparison, or outcome. However, each registry record contains only one set of structured data elements for describing the design characteristics of one trial. Designs for multiple trials or substudies can be reported in a free text field of a single record (eg, different start and end dates in the arms and interventions fields). Yet, such information will not be consistently described in the same place by study sponsors across trials and will not be readily identified by search tools that depend on structured information for high-precision data retrieval.

Overview of trial reporting system and challenges for reporting MPRPs

The trial reporting system was designed to track trials at each stage from registration at study initiation to results reporting after completion. Specifically, registration of key protocol information¹⁸ at trial initiation serves as a public record of the trial and provides public access to key information about its research plan, which was prespecified in the protocol. Timely updates to registered information throughout trial conduct help to keep the public informed. Public reporting of information on the summary results in a structured format after trial completion allows for documentation of basic scientific findings in a standardized format.¹⁹ This display thereby mitigates publication bias and selective outcome reporting, complements information on the results available from the biomedical literature, and facilitates evidence synthesis via systematic reviewers and other trial landscape analyses. The trial reporting system depends on timely and complete submission of information by study sponsors and investigators and supports important ethical and scientific goals. On trial initiation, registration on ClinicalTrials.gov involves extracting key information from the protocol for a single study and entering it into a set of structured data elements that support the display, search, and download of trial records.¹⁸ This model relies on each clinical trial having defined the study start and end dates based on key prespecified design and analytical features that uniquely identify and define the unit of an individual clinical trial. These features include the following:

- Population: a defined group of participants, as described in the conditions of interest and detailed in the eligibility criteria and target enrollment;
- Interventions: study arms and interventions to which participants are assigned; and
- Comparison and outcomes: primary and secondary outcome measures, including the specification of the arms and interventions being compared within

Box 1: Examples of MPRP study designs and substudies

- Umbrella design: Adjuvant Lung Cancer enricHmEnt Marker Identification and Sequencing Trials (ALCHEMIST) (eg, NCT02193282), erlotinib hydrochloride for early-stage non-small cell lung cancer¹¹
- Platform design: Randomised Evaluation of COVid-19 thErRapy (RECOVERY) (NCT04381936), which efficiently adds and removes specific interventions being studied for covid-19 based on decision algorithm¹²
- Basket design: US National Cancer Institute Molecular Analysis for Therapy Choice (NCI-MATCH) (eg, NCT04439279), MATCH-Subprotocol R involving trametinib for cancers with BRAF mutations and fusions¹³

the study to evaluate the effect of an intervention on a health outcome over a defined time frame.

Generally, these key features apply to each substudy in an MPRP but do not apply to the MPRP as a whole; that is, each substudy can have different protocol details. In a basket MPRP, such as NCI-MATCH, each substudy evaluates tumors with a specific genetic change (that is, a unique population) and an intervention intended to target that change (that is, a unique intervention). Unlike a traditional clinical trial, in which all the arms and interventions are prespecified in the protocol from the start, one or more substudies in an MPRP can be prespecified at the outset while other substudies are conceived of and added later. However, MPRPs maintain prespecified plans for the analysis of substudy results, whether pooled across substudies or, more commonly, analyzed independently. In this way, an MPRP can be distinguished from a multiarm study in which results from each arm are compared with other arms in the study.

After trial completion, information on the summary results is reported on ClinicalTrials.gov in a tabular format, by study arm, in four scientific modules (participant flow, baseline characteristics, outcome measures and statistical analyses, and adverse event information); the full study protocol and statistical analysis plan are also provided.¹⁹

Patient and public involvement

The approach described in this article for reporting MPRPs to trial registries and results databases such as ClinicalTrials.gov evolved over several years. Our proposal is based on the authors' direct experience with MPRPs, including reviewing submissions of registration and summary results and working with investigators, study sponsors, and other stakeholders, as well as from monitoring the medical literature. We did not involve patients or the public because the analysis focused on addressing largely scientific challenges in registering and reporting results information for MPRPs with complex designs.

MPRP trial registration and results reporting

Table 1 presents potential benefits and limitations of use of a single record to report the entire MPRP as compared with separate records for each component of the MPRP (screening and multiple substudies). This approach is based on the experiences of the National Cancer Institute in managing the reporting of its NCI-MATCH MPRP, which is also used for examples in table 1.²¹

Registration information for NCI-MATCH was initially posted on ClinicalTrials.gov on 19 June 2015 as one study listing four arms. Each reported arm was intended to represent a separate substudy with its own start and end dates and separate analysis plan (each substudy used the same primary and secondary outcomes). As NCI-MATCH expanded, the National Cancer Institute changed the way that the MPRP was registered to better support the scientific and administrative aspects of reporting.²² The single record

approach had two main limitations: end users could not easily search for and interpret key details of NCI-MATCH substudies, including recruiting status and summary results, and the sponsor (National Cancer Institute) found updating registration information for substudy specific protocol amendments burdensome (table 1). As of 1 April 2022, NCI-MATCH is represented on ClinicalTrials.gov by one screening record and 19 substudy records (with the possibility of more being added), with each substudy evaluating a specific intervention for patients with tumors containing particular genetic markers (supplemental material). This multirecord model has facilitated clear and transparent reporting of results for the six NCI-MATCH substudies to date and has been adopted for other National Cancer Institute's MPRPs, such as the basket MPRP Paediatric MATCH (NCT03155620 for the screening trial), the umbrella MPRPs ALCHEMIST (NCT02194738 for the screening trial), and the Lung Cancer Master Protocol or Lung-MAP (NCT03851445).

This multirecord approach is generally consistent with other MPRP related recommendations that reinforce the concept of substudies as separate entities. For example, the addition of each substudy as a new appendix to the main protocol²³ and the use of separate electronic common technical document folders and separate investigational new drug applications¹⁴ or separate clinical trial authorisations²⁴ for substudies submitted to regulatory agencies. The National Cancer Institute's experience in using separate protocol documents and study records has helped limit the complexity of reporting over time, as closed substudies accumulate and new substudies continue to be added. Similarly, separate protocol documents and study records allow for improved tracking of the sites participating in each substudy and management of substudy-specific eligibility criteria. The multirecord approach for reporting MPRPs includes the use of an overall screening record, if applicable, and one record for each substudy (fig 1).

MPRP overall screening record

An MPRP screening record can provide information that is common to all substudies in the MPRP, allowing each substudy record to focus on that study's unique details. The record can include the procedures for assessing all eligible participants (and the eligibility criteria common to all substudies), the methods for allocating participants to substudies or a shared control group, and an overarching description of the research program. The screening record is updated over the conduct of the MPRP and should reflect the date on which the overall MPRP was opened to screen participants for eligibility (start date) and the date on which the eligibility screening ended for all substudies (completion date). Further attention is needed to optimize the reporting of other registration data elements. Particularly, whether the contents of the screening record should be limited to a description of the screening procedures (eg, listing only those interventions necessary for screening) or should the record also include specific key substudy

Table 1 | Comparison of single and multiple study record approaches for reporting master protocol research programs (MPRPs) to ClinicalTrials.gov, by trial reporting system goal

Goal	Issues to consider, by MPRP reporting approach	
	Single study record	Multiple study records (supplemental material)
Document trial existence Registration of key protocol details using required and optional structured data elements provides a publicly accessible record of a clinical trial with a unique identifier for reference; systematic registration also allows the identification of all trials with the study design characteristics of interest	Structured data elements are used to describe the overall MPRP but not for each substudy, potentially causing uncertainty about the participant groups and design of each substudy. Example: Key protocol details for the overall MPRP (NCT02465060v.1*), with selected details about the subprotocols described only in the narrative text. Brief title is "NCI-MATCH: Targeted Therapy Directed by Genetic Testing in Treating Patients With Advanced Refractory Solid Tumors or Lymphomas (NCI-MATCH)"; enrollment of 3000 participants (anticipated); four arms, each labelled as a unique subprotocol (F, G, H, and R) with the respective five interventions.	Structured data elements are used to describe each MPRP substudy, clearly reflecting the participant groups and design of each substudy. Example: Key protocol details provided in structured data elements for each substudy, such as for Subprotocol R (NCT04439279v.5). Brief title is "Testing Trametinib as a Potential Targeted Treatment in Cancers With BRAF Genetic Changes (MATCH-Subprotocol R)"; enrollment of 35 participants (actual); single arm labelled with the one assigned intervention.
Track trial progress Timely updates of key protocol details, such as recruitment status, changes to the protocol, and trial milestone dates, help locate the stage of each trial, from initiation to completion; potential participants can find ongoing trials for enrollment and a wide range of users can understand when summary results are expected	Updates to structured data elements can only document the progress of the overall MPRP, not for each substudy; progress of individual substudies can be described using free text data elements, such information would not be readily and consistently retrievable. Example: Substudy tracking information limited to a narrative format in free text data elements (eg, arm information), with structured data elements used only for tracking the overall MPRP. Overall recruitment status is "recruiting," if at least one subprotocol is "recruiting" (even if others are "completed"); primary completion date anticipated for June 2022, when the last substudy is completed.	Updates to structured data elements clearly document the progress of each substudy, thereby allowing the retrieval of key subprotocol details with precision. Example: Tracking information for the 19 subprotocols listed in the structured data elements available and updated individually in each study record. Overall recruitment status includes "active, not recruiting" (16 substudies), "completed" (two substudies), and "withdrawn" (one substudy). Eight substudies provide actual primary completion dates; 11 substudies provide estimated primary completion dates.
Verify current and historical record information Accessing required and optional information in all record versions allows users to review trial details for current and all previously reported protocol information; users can assess fidelity to the prespecified protocol when reviewing reported results for a primary outcome in a manuscript ²⁰	While the study record provides the most up-to-date information for the overall MPRP, the history of changes feature allows users to review all previously posted information as sequentially numbered versions and compare any two versions. However, the lack of structured details about substudies limits the usefulness of this function. Example: Increasing number of subprotocols listed in Overall MATCH MPRP record over time. NCT02465060v.1 had four subprotocols, using arm information, in June 2015; NCT02465060v.3 had 10 subprotocols in August 2015; NCT02465060v.104 had 17 subprotocols in March 2016; and NCT02465060v.318 had 30 subprotocols in March 2017.	MPRP subprotocol records provide the most up-to-date information for each substudy; the history of changes feature in each substudy record allows users to review all previously posted substudy information and compare any two versions. Example: Key changes in the subprotocol R record over time. NCT04439279v.1 had initial subrecord submitted in June 2020; NCT04439279v.2 had results information submitted in February 2021; and NCT04439279v.5 had additional updates submitted in February 2022.
Access trial results information Systematic submission and posting of structured results modules in a tabular format following trial completion provides timely access to summary trial results information independent of, or in complement to, journal publication; the use of structured data elements facilitates the enforcement of results reporting requirements and mitigates selective reporting	Structured results reporting modules in ClinicalTrials.gov have been designed to record findings from a single study, so reporting meaningful information is challenging for multiple substudies using a single record (see results section in table 2). Example: Baseline characteristics: reporting for 19 subprotocols requires 19 table columns; primary outcome measure: reporting for 19 subprotocols, which share one measure (that is, objective response rate up to three years), requires 19 table columns; secondary outcome measures: reporting for 19 subprotocols, which share two of the three secondary outcome measures (that is, progression-free survival, progression-free survival at six months, and time to progression), requires three tables with fewer than 19 columns per table.	Structured results reporting modules in ClinicalTrials.gov can be used to provide clear and meaningful information for each substudy in individual records, thereby facilitating understanding of the results of each substudy; reporting results analyses across substudies or with shared control groups is challenging without repeating participant information within records. Example: Of 19 separate substudy records, six have posted results and 13 have not. When results information is posted on each record: baseline characteristics were limited to participants enrolled in each subprotocol; primary and secondary outcome measures were limited to outcome measures prespecified in each subprotocol and information collected from participants enrolled in each substudy.

Examples are drawn from archived versions of the NCI-MATCH study record and subrecords on ClinicalTrials.gov.²¹

*An NCT number followed by v.X denotes archived version X of the study record. To view archived versions of a record on ClinicalTrials.gov, click on the "History of Changes" link displayed on the study record.

information that provides an overview of the MPRP (eg, listing all interventions being evaluated as potential treatments in each MPRP substudy). Similarly, a screening record could focus on outcome measures related to the screening process, such as the number of participants whose tumor was sequenced, and the number of participants assigned to each substudy based on molecular sequencing.

After screening for all substudies ends, information on results specific to the centralized screening process can be added to the screening record. For example, in the participant flow module, the number started could include the number of participants screened, and the number completed could indicate the number of participants assigned to a substudy. In the adverse event information module, reporting would be limited

to events collected during screening and would not include adverse events collected after participants were assigned to a substudy; these events would be reported in the relevant substudy record.

MPRP substudy records

When separate study records are used to represent each substudy in an MPRP, registration and results reporting on ClinicalTrials.gov generally follow the established processes for traditional clinical trials. Each study registration record describes a substudy's design (eg, single arm or parallel design randomized multiarm study), specific eligibility criteria, prespecified outcome measures, arms and interventions, recruitment status, and facility locations. The substudy record should also include information connecting it to the overall MPRP.

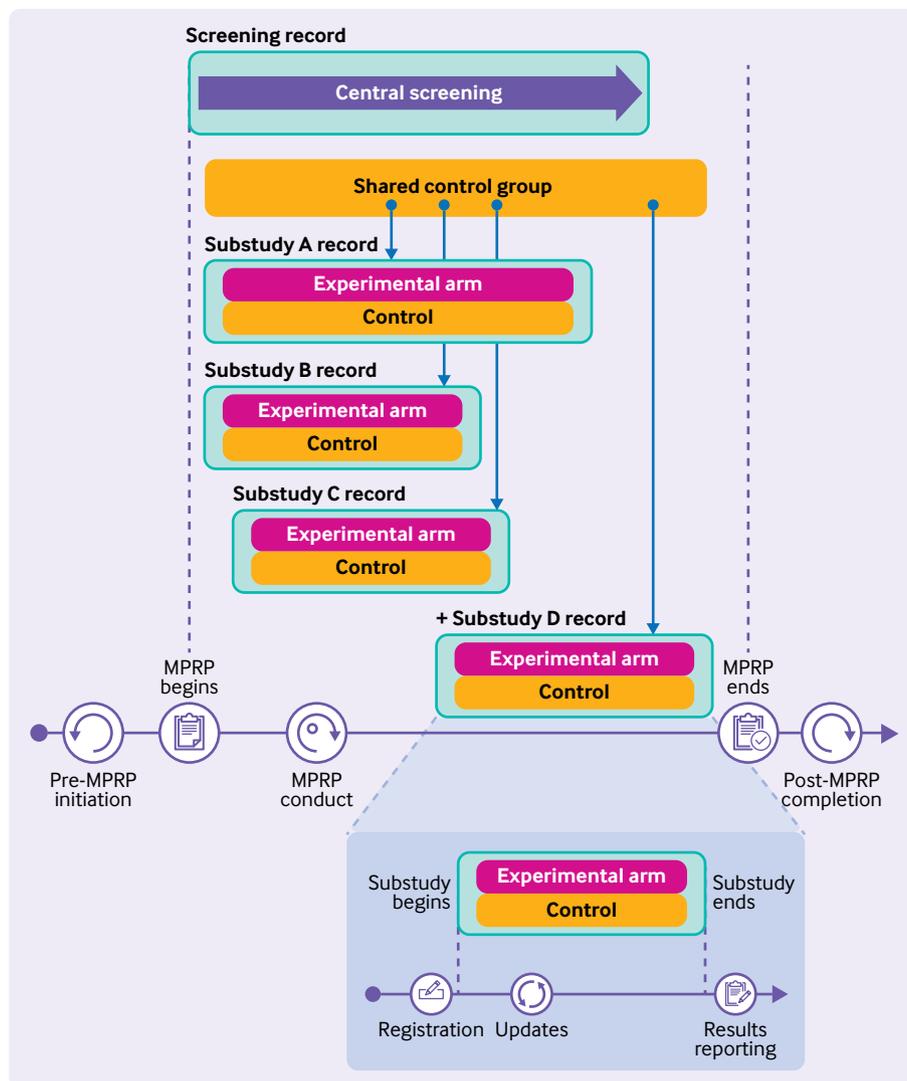


Fig 1 | Schematic of a fictional master protocol research program (MPRP) reported using multiple study records. This MPRP consists of a central screening process, three prespecified substudies (A-C), and a fourth substudy (D) added by protocol amendment. Five study records (green box enclosure with rounded corners) would be created on ClinicalTrials.gov: a screening record and one record each for substudies A-D. The control in each substudy includes appropriately selected participants from the shared control group (orange box below experimental arm). The shared control group is not reported as a separate record; the relevant control participants are reported as a separate arm in each substudy record. The inset shows key ClinicalTrials.gov reporting events for each study record

Summary results reported to ClinicalTrials.gov for each substudy describe findings related to data collected from the participants allocated to that particular substudy. In some cases, the prespecified analysis plan for summary results will include a comparison to a control, such as data collected from participants in a shared control group, whether as standard-of-care or other control (fig 1). Although the term “shared control group” is used to refer to one group to which participants are assigned, in practice, the actual set of control participants analyzed can differ across substudies because the participants and interventions change over time, especially if the control is standard of care. If detailed plans for applying data from the control group are prespecified in the MPRP protocol,²⁵ representing information about the specific participants analyzed in the control group in each substudy registration record (that is, as the analysis population for the control arm)

would be more informative than as a separate shared control registration record. This information allows the relevant analysis groups in the trial (eg, experimental and control) to be represented and the details of the shared control specific to that substudy (eg, specific interventions and attributes of the participants) to be reported. When reporting results in a substudy record, the relevant set (or subset) of shared control group data should be included. Results from participants (or subsets of participants) in the shared control group can be reported in the control data for more than one substudy record.

We exemplify such reporting of a shared control arm using the trial STAMPEDE (Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy MPRP; NCT00268476), an MPRP that is evaluating treatment strategies for prostate cancer.²⁶ STAMPEDE was initiated with one standard-of-care

Table 2 | Key considerations for selected data elements in reporting master protocol research programs (MPRPs) to ClinicalTrials.gov using multiple substudy records

Selected data element	Brief description	Notes for substudy records
Registration (summary of key protocol items)¹⁸		
Brief title and acronym	A short title for the clinical study written in language intended for the lay public and including information on the condition, participants, and interventions	For each substudy, provide information specific to that substudy and indicate that the substudy is part of an MPRP: include any acronym or other identifying title for both the MPRP and the substudy. Example (NCT02193282): Erlotinib Hydrochloride in Treating Patients With Stage IB-IIIa Non-small Cell Lung Cancer That Has Been Completely Removed by Surgery (ALCHEMIST treatment trial) Identify a central screening study, indicate that it is part of an MPRP, and include any acronym or other identifying title for the MPRP. Example (NCT02194738): Genetic Testing in Screening Patients With Stage IB-IIIa Non-small Cell Lung Cancer That Has Been or Will Be Removed by Surgery (ALCHEMIST screening trial)
Overall recruitment status	Select one: not yet recruiting; recruiting; enrolling by invitation; active, not recruiting; completed; suspended; terminated; withdrawn	Indicate the status for each substudy, updating it within 30 days of a change Select "recruiting" only while the specific substudy is seeking new participants. Example (ALCHEMIST): of four MPRP related records, the screening study has a status of "recruiting" (NCT02194738), two substudies are "active, not recruiting" (NCT02595944 and NCT02193282), and one substudy is "recruiting" (NCT02201992)
Study start date	Estimated date when the clinical study opens for recruitment of participants or the actual date when the first participant enrolled	For each substudy, enter the estimated date or the actual date
Primary completion date and study completion date	Date when the final participant was examined or received an intervention for the purposes of final collection of data for the primary outcome, and the date when data collection was completed for all of the primary outcomes, respectively	For each substudy, enter the date when final collection of data for the final participant occurred for that substudy. Example (ALCHEMIST): screening study record (NCT02194738) estimates a primary completion date of 28 September 2026; three substudies list estimated primary completion dates of 1 July 2024 (NCT02595944), 10 October 2026 (NCT02193282), and 1 May 2022 (NCT02201992)
Brief summary	A short description of the clinical study, including a brief statement of the hypothesis, written in language intended for the lay public	For each substudy, provide a non-technical description, including the aim of the substudy; identification as a substudy in an MPRP; explanation of enrollment through a centralized eligibility screening process and the NCT number of the MPRP screening record, if applicable
Enrollment	Estimated or actual total number of participants enrolled; the term "enrolled" indicates an individual's agreement to participate after completing the informed consent process	For each substudy, initially provide the total estimated number of participants to be enrolled, then update the record with the actual number after enrollment ends. Include the estimated and actual number of participants from the shared control group used for comparison as a control arm, as specified in the protocol or analysis plan
Arms, groups, and interventions	Prespecified group or subgroup of participants and the specific interventions (including no intervention or standard of care) that they are assigned to receive, according to the protocol	For each substudy, specify the arms to which participants will be allocated and provide a name for and description of the interventions associated with each arm. List the control arm, including any shared control arm, for each substudy if it is prespecified to be included as a comparator in the analysis of results
Outcome measures	Planned measures that are important to evaluating the effects of the intervention	For each substudy, include all prespecified primary and secondary outcome measures. Example (NCT03213665): The primary outcome for National Cancer Institute's Paediatric MATCH is the objective response rate (time frame up to two years) Primary and secondary outcomes for each substudy should be included in the substudy record, even if they are the same for multiple substudies in the MPRP
Eligibility	Limited list of key inclusion and exclusion criteria for the selection of participants in the clinical study	For each substudy, describe the key criteria for participants to be assigned to that substudy (eg, specific biomarker, disease characteristics) If participants must go through a centralized screening process, list the NCT number and brief title or acronym of the screening record as the first inclusion criterion in each substudy Example (NCT04439279): MATCH-Subprotocol R's first inclusion criterion is that patients must have met applicable eligibility criteria in the Master MATCH Protocol (NCT02465060) before registration to treatment subprotocol.
Central contact person (or facility contact)	A person who can answer questions about enrollment at any study location	For each substudy provide appropriate contact information If a central screening process is used, ensure that the person whose contact information is provided can answer questions about centralized screening
References	Citations and links to publications and websites that are relevant to the protocol	For each substudy, include any references that help users to understand the relation between the substudy and the overall MPRP design
Uploaded study documents (full study protocol document and statistical analysis plan)¹⁹		
Document upload information	Full study protocol, statistical analysis plan, and informed consent forms	For each substudy, we recommend that the protocol document and appendices for that substudy be uploaded during study registration to assist users in understanding the substudy's design, plans for data collection and analysis, and relation to the overall MPRP For each substudy, the final protocol and statistical analysis plan are submitted at the time of results submission
Results (summary results information)¹⁹		
General	Results information, provided in modules as tables with study arms as columns and summary results as rows, is generally expected to be submitted by one year after the primary completion date	For each substudy, provide results information after the primary completion date is reached Include control arm data in each substudy record as prespecified in the analysis plan. Data reported for the control arm derived from the shared control group will likely vary across substudies based on when a substudy took place and when the data were analyzed. Creating separate records for each substudy facilitates clear reporting of the relevant participants from the control group included in each substudy analysis
Participant flow	A summary table of participants' progress, by assignment group, including the number of participants who started and completed the study; analogous to a CONSORT flow diagram	For each substudy specify the arms to which participants in that substudy were assigned. If relevant, include the control arm with participants from the shared control group Identify the total number of participants that started and completed each arm of the substudy

(Continued)

Selected data element	Brief description	Notes for substudy records
Baseline characteristics	A summary table of demographic and baseline measures, by arm and for the overall study, including all relevant measures (eg, age, sex, race, and ethnicity)	For each substudy, specify the number of participants analyzed at baseline and the baseline characteristics, by arm. If relevant, include the control arm with collected baseline measures from the shared control group
Outcome measures	A summary table with descriptive information for each primary and secondary outcome measure, by arm, including any scientifically appropriate statistical analyses	For each substudy, specify the number of participants analyzed, by arm, and report the results of outcome measures evaluating the effect of an intervention on participants An MPRP can use the same or different outcome measures across substudies. If relevant, include the control arm with collected data from the shared control group
Adverse event information	Three summary tables of anticipated and unanticipated adverse events for all cause mortality (all deaths); serious adverse events; and other (not including serious) adverse events	For each substudy, specify the overall percentage of participants (number affected or number at risk) with adverse events in each arm and identify each adverse event by system organ class. If relevant, include the control arm with collected data from the shared control group
Other		
Study record updates ³³	Made at least once a year, with some data elements required sooner after a change	Update each substudy record regularly and with any important changes to the study protocol
External to the study record—publications and other sources ³⁴	Include NCT numbers in abstracts of publications and other communications	For the substudy, include the NCT numbers of both the screening record and the specific substudy record

shared control arm and five experimental intervention arms (NCT00268476v.1). Note, an NCT number followed by “v.X” (when X is a number) denotes archived version X of the study record; to view archived versions of a record on ClinicalTrials.gov, click on the “History of Changes” link displayed on the study record. Results of STAMPEDE were then published in two articles, one presenting findings from three of the arms (zoledronic acid, docetaxel, and zoledronic acid plus docetaxel)²⁷ compared with the shared control group, and the other presenting findings for the two other arms (celecoxib and celecoxib plus zoledronic acid)²⁸ also compared with the shared control group. More experimental intervention arms have been added and analyzed independently of the others, including abiraterone with prednisolone²⁹ and radiotherapy,³⁰ each compared with data collected from patients assigned to the standard-of-care shared control group contemporaneously to the experimental arms (NCT00268476v.50). This pattern of adding new arms and reporting their results independently indicates that an MPRP study design is well suited for the proposed multirecord approach, with each registration record identifying the prespecified interventions and analytical comparisons for each substudy. By contrast, a less common MPRP design plan that prespecifies the pooling of data across substudies for analysis might not be appropriate for multirecord registration of an MPRP.³¹ For example, a biomarker strategy design, which was implemented in the TCA Ovarian Cancer Trial, compared pooled results from assay-directed assignment of participants to one of 12 biomarker-targeted chemotherapy interventions (biomarker-strategy arm) to participants assigned by physician’s choice (control arm).³² Table 2 displays key considerations for reporting MPRPs to ClinicalTrials.gov using multiple substudy records.

Additional factors to consider

Although the use of multiple study records greatly facilitates registration and results reporting for an MPRP, some challenges remain.

Coordinating registration and results reporting of MPRPs

MPRPs generally require, and have resulted in, unprecedented cooperation among public and private organizations, such as in the ACTIV (Accelerating covid-19 Therapeutic Interventions and Vaccines) partnership.⁶ However, one study sponsor or principal investigator must take responsibility for each study record. Maintaining and updating information for the overall screening record and multiple substudy records for an MPRP, including uploading study protocol and statistical analysis plan documents,³³ require careful coordination among partners regarding roles and responsibilities for reporting.²⁴ An advantage of reporting MPRPs using multiple substudy records is flexibility in identifying the most appropriate sponsor or investigator to be responsible for each study record. Our experience has been that what might be perceived as extra burden of managing multiple substudy records is counterbalanced by the ability to focus the work of research partners and investigators to their specific substudies and to facilitate clear and timely communication about the research design and better support results reporting for each substudy.

Identification of MPRP related records

Trial registries provide search features to help researchers, journal editors, potential study participants, and other stakeholders identify relevant studies of interest. Researchers, in particular, rely on such features to understand the landscape for a condition or intervention. ClinicalTrials.gov does not include a specialized structured method for systematically and automatically identifying study records that are related, including the multiple substudies that make up an MPRP; however, study sponsors and investigators can support the identification of related MPRP study records by ensuring a brief title and acronym is standardized for each substudy if a multiple record approach to reporting MPRPs is used (table 2).²⁴ Registries could evaluate methods for further facilitating identification

in a structured way, for example, by adding a data element that would allow sponsors and investigators to identify the NCT numbers of all ClinicalTrials.gov study records related to a single MPRP or by using other methods for sharing unique identifiers to identify study records as part of a related research program.

Based on current ClinicalTrials.gov functionality and the fact that some researchers use one record for an entire MPRP, users should be aware of potential challenges related to the multistudy nature of MPRPs and key data elements.^{4,21} For example, separate study records for the overall screening process and for each substudy could lead to the double counting of studies related to a specific disease, condition, or intervention and, similarly, of the number of participants enrolled and for which results are reported. However, single record MPRPs could lead to similar (and potentially worse) problems with overcounting, resulting from the inability to disaggregate the number of participants enrolled in specific substudies.

These challenges are not unique to ClinicalTrials.gov and also apply to other types of trial reporting, such as in journal publications. Some of the challenges can be managed, in part, if sponsors and investigators clearly title MPRP screening and substudy records and if users use these and other data elements to help identify potential overlap in MPRP records. Additionally, inclusion of the relevant NCT numbers (or other identifiers) for the screening and substudy records in all communications, such as at the end of abstracts for published articles as recommended by the International Committee of Medical Journal Editors,³⁴ can help bolster clear identification of related MPRP components.

Harmonizing trial registries

We have described an approach to registering a single MPRP using multiple study records in the context of the ClinicalTrials.gov registration and results reporting model. Study sponsors might also have an obligation to report MPRPs to other trial registries; therefore, consideration of coordinating MPRP reporting approaches across registries is important. A harmonized approach would entail efficient and reliable registration and results reporting processes that support sponsors and investigators and minimize confusion among end users when information about the same trial is found in multiple places. Because registries support trial reporting policies and legal requirements, broad global collaboration and harmonization across requirements to support this approach for reporting MPRPs would be welcomed.

Conclusion

The clinical research enterprise is highly dynamic, with a continuous evolution of study designs to meet new challenges. The trial reporting system must adapt as new study designs emerge to ensure that the system can continue to satisfy the goals of reporting. MPRPs and their substudies challenge the traditional trial reporting model, whether via submission to a trial registry and

results database or via dissemination in biomedical publications. We cannot allow the complexity of these research designs to undermine the gains that the research enterprise has made towards ensuring careful, accurate, complete, and timely reporting. The approach that we describe here is intended to ensure that MPRPs are reported in a manner consistent with the goals of the trial reporting system. MPRP substudy records could help potential participants to identify studies of interest, aid researchers and journal editors in the evaluation of reporting integrity, and mitigate the impact of publication bias. Overall, we anticipate that carefully structured reporting of MPRPs and their substudies across the clinical research enterprise would enhance understanding of this important research design and improve communication of the results in publications and in trial registries and databases such as ClinicalTrials.gov.

Contributors: All authors conceived the idea, drafted the manuscript, or critically revised the manuscript for important intellectual content, gave final approval of the version to be published, and are accountable for all aspects of the work. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. RJW acts as the guarantor.

Funding: Supported, in part, by the National Center for Biotechnology Information of the National Library of Medicine and the Intramural Research Program of the National Cancer Institute, National Institutes of Health. The funders had no role in considering the study design or in the collection, analysis, interpretation of data, writing of the report, or decision to submit the article for publication. Dr Williams worked on this article mostly while employed by the National Library of Medicine, National Institutes of Health. The views expressed in this article are those of the authors and do not necessarily reflect the views or policies of the National Institutes of Health. Neither patients nor the public were involved in any way.

Competing interests: All authors have completed the ICMJE uniform disclosure form at <https://www.icmje.org/disclosure-of-interest/> and declare: supported, in part, by the National Center for Biotechnology Information and the Intramural Research Program of the National Cancer Institute for the submitted work; RJW, HDD, and TT received support from the National Center for Biotechnology Information of the National Library of Medicine, National Institutes of Health; SDC, DL, GAS, and SAP received support from the Intramural Research Program of the National Cancer Institute, National Institutes of Health; and DAZ received personal fees from ClinicalTrials.gov (and provided technical consultation to ClinicalTrials.gov outside the submitted work); no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Neither patients nor the public were involved in any way.

Data sharing: No additional data are available.

The lead authors affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: We plan to share this work through an accompanying opinion piece describing the context and relevance of this approach to increasing transparency and accountability. We also plan to share it on social media, post a link on ClinicalTrials.gov, and ensure that the article is publicly accessible on PubMed Central (as required by the NIH Public Access Policy).

Provenance and peer review: Not commissioned; externally peer reviewed.

This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different

terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

- 1 Zarin DA, Tse T, Williams RJ, Rajakannan T. Update on trial registration 11 years after the ICMJE policy was established. *N Engl J Med* 2017;376:383-91. doi:10.1056/NEJMSr1601330
- 2 Cecchini M, Rubin EH, Blumenthal GM, et al. Challenges with novel clinical trial designs: Master protocols. *Clin Cancer Res* 2019;25:2049-57. doi:10.1158/1078-0432.CCR-18-3544
- 3 Janiaud P, Serghiou S, Ioannidis JPA. New clinical trial designs in the era of precision medicine: An overview of definitions, strengths, weaknesses, and current use in oncology. *Cancer Treat Rev* 2019;73:20-30. doi:10.1016/j.ctrv.2018.12.003
- 4 Meyer EL, Mesenbrink P, Dunger-Baldauf C, et al. The evolution of master protocol clinical trial designs: A systematic literature review. *Clin Ther* 2020;42:1330-60. doi:10.1016/j.clinthera.2020.05.010
- 5 US Food and Drug Administration. COVID-19: Master protocols evaluating drugs and biological products for treatment or prevention: Guidance for industry [final guidance for industry]. 2021 May. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/covid-19-master-protocols-evaluating-drugs-and-biological-products-treatment-or-prevention>.
- 6 Collins FS, Stoffels P. Accelerating COVID-19 therapeutic interventions and vaccines (ACTIV): An unprecedented partnership for unprecedented times. *JAMA* 2020;323:2455-7. doi:10.1001/jama.2020.8920
- 7 Park JH, Hsu G, Siden EG, Thorlund K, Mills EJ. An overview of precision oncology basket and umbrella trials for clinicians. *CA Cancer J Clin* 2020;70:125-37. doi:10.3332/caac.21600
- 8 Yee LM, McShane LM, Freidlin B, Mooney MM, Korn EL. Biostatistical and logistical considerations in the development of basket and umbrella clinical trials. *Cancer J* 2019;25:254-63. doi:10.1097/PPO.0000000000000384
- 9 Siden EG, Park JJ, Zoratti MJ, et al. Reporting of master protocols towards a standardized approach: a systematic review. *Contemp Clin Trials Commun* 2019;15:100406. doi:10.1016/j.conctc.2019.100406
- 10 Woodcock J, LaVange LM. Master protocols to study multiple therapies, multiple diseases, or both. *N Engl J Med* 2017;377:62-70. doi:10.1056/NEJMra1510062
- 11 Govindan R, Mandrekar SJ, Gerber DE, et al. ALCHEMIST Trials: A Golden Opportunity to Transform Outcomes in Early-Stage Non-Small Cell Lung Cancer. *Clin Cancer Res* 2015;21:5439-44. doi:10.1158/1078-0432.CCR-15-0354
- 12 RECOVERY Collaborative Group. Horby P, Lim WS, Emberson JR, Mafham M et al. Dexamethasone in hospitalized patients with covid-19. *N Engl J Med* 2021;384:693-704. doi:10.1056/NEJMoa2021436.
- 13 Johnson DB, Zhao F, Noel M, et al. Trametinib Activity in Patients with Solid Tumors and Lymphomas Harboring BRAF Non-V600 Mutations or Fusions: Results from NCI-MATCH (EAY131). *Clin Cancer Res* 2020;26:1812-9. doi:10.1158/1078-0432.CCR-19-3443
- 14 U.S. Food and Drug Administration. Master protocols: efficient clinical trial design strategies to expedite development of oncology drugs and biologics: Guidance for industry [final guidance for industry]. 2022 Mar. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/master-protocols-efficient-clinical-trial-design-strategies-expedite-development-oncology-drugs-and-biologics>.
- 15 Park JH, Siden E, Zoratti MJ, et al. Systematic review of basket trials, umbrella trials, and platform trials: a landscape analysis of master protocols. *Trials* 2019;20:572. doi:10.1186/s13063-019-3664-1
- 16 Zarin DA, Fain KM, Dobbins HD, Tse T, Williams RJ. 10-year update on study results submitted to ClinicalTrials.gov. *N Engl J Med* 2019;381:1966-74. doi:10.1056/NEJMSr1907644
- 17 World Health Organization. WHO trial registration data set (version 1.3.1). <https://www.who.int/clinical-trials-registry-platform/network/who-data-set>.
- 18 National Institutes of Health. National Library of Medicine. ClinicalTrials.gov protocol registration data element definitions for interventional and observational studies. 2020 Oct. <https://prsinfo.clinicaltrials.gov/definitions.html>.
- 19 National Institutes of Health. National Library of Medicine. ClinicalTrials.gov results data element definitions for interventional and observational studies. 2021 Feb. https://prsinfo.clinicaltrials.gov/results_definitions.html.
- 20 Zarin DA, Tse T. Trust but verify: trial registration and determining fidelity to the protocol. *Ann Intern Med* 2013;159:65-7. doi:10.7326/0003-4819-159-1-201307020-00011
- 21 Conley BA, Doroshow JH. Molecular analysis for therapy choice: NCI MATCH. *Semin Oncol* 2014;41:297-9. doi:10.1053/j.seminoncol.2014.05.002
- 22 Yee LM, McShane LM, Freidlin B, Mooney MM, Korn EL. Biostatistical and logistical considerations in the development of basket and umbrella clinical trials. *Cancer J* 2019;25:254-63. doi:10.1097/PPO.0000000000000384
- 23 Adaptive Platform Trials Coalition. Adaptive platform trials: definition, design, conduct and reporting considerations. *Nat Rev Drug Discov* 2019;18:797-807. doi:10.1038/s41573-019-0034-3
- 24 European Medicines Agency. Complex clinical trials—Questions and answers. 23 May 2022. EMA/298712/2022. https://ec.europa.eu/health/system/files/2022-06/medicinal_qa_complex_clinical-trials_en.pdf.
- 25 Dodd LE, Freidlin B, Korn EL. Platform trials - Beware the noncomparable control group. *N Engl J Med* 2021;384:1572-3. doi:10.1056/NEJMc2102446
- 26 James ND, Sydes MR, Clarke NW, et al. Systemic therapy for advancing or metastatic prostate cancer (STAMPEDE): a multi-arm, multistage randomized controlled trial. *BJU Int* 2009;103:464-9. doi:10.1111/j.1464-410X.2008.08034.x
- 27 James ND, Sydes MR, Clarke NW, et al, STAMPEDE investigators. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. *Lancet* 2016;387:1163-77. doi:10.1016/S0140-6736(15)01037-5
- 28 James ND, Sydes MR, Mason MD, et al, STAMPEDE investigators. Celecoxib plus hormone therapy versus hormone therapy alone for hormone-sensitive prostate cancer: first results from the STAMPEDE multiarm, multistage, randomised controlled trial. *Lancet Oncol* 2012;13:549-58. doi:10.1016/S1470-2045(12)70088-8
- 29 James ND, de Bono JS, Spears MR, et al. STAMPEDE Investigators. Abiraterone for prostate cancer not previously treated with hormone therapy. *N Engl J Med* 2017;377:338-51. doi:10.1056/NEJMoa1702900
- 30 Parker CC, James ND, Brawley CD, et al. Systemic Therapy for Advanced or Metastatic Prostate cancer: Evaluation of Drug Efficacy (STAMPEDE) investigators. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. *Lancet* 2018;392:2353-66. doi:10.1016/S0140-6736(18)32486-3
- 31 Yee LM, McShane LM, Freidlin B, Mooney MM, Korn EL. Biostatistical and logistical considerations in the development of basket and umbrella clinical trials. *Cancer J* 2019;25:254-63. doi:10.1097/PPO.0000000000000384.1097/PPO.0000000000000384
- 32 Cree IA, Kurbacher CM, Lamont A, Hindley AC, Love S, TCA Ovarian Cancer Trial Group. A prospective randomized controlled trial of tumour chemosensitivity assay directed chemotherapy versus physician's choice in patients with recurrent platinum-resistant ovarian cancer. *Anticancer Drugs* 2007;18:1093-101. doi:10.1097/CAD.0b013e3281de727e
- 33 National Institutes of Health, Department of Health and Human Services. Clinical Trials Registration and Results Information Submission. Final rule. *Fed Regist* 2016;81:64981-5157. <https://www.federalregister.gov/documents/2016/09/21/2016-22129/clinical-trials-registration-and-results-information-submission>.
- 34 International Committee of Medical Journal Editors. "Publishing & editorial issues: Clinical trials – Registration." Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals. <http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html#one>.

Web appendix: Online appendix