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

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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. 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, 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. These types of studies encompass various designs with different names based on specific design features; however, all of these studies can generally be described as “one overarching protocol designed to answer multiple questions.” 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...
trials designed and conducted independently.\textsuperscript{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).\textsuperscript{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).\textsuperscript{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 MPRP's 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.\textsuperscript{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.\textsuperscript{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 information\textsuperscript{18} 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.\textsuperscript{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.\textsuperscript{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 cancer\textsuperscript{11}
- **Platform design**: Randomised Evaluation of COVID-19 thErApY (RECOVERY) (NCT04381936), which efficiently adds and removes specific interventions being studied for covid-19 based on decision algorithm\textsuperscript{12}
- **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 fusions\textsuperscript{13}
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 applications15 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 all MPRPs to trial registries and results databases such as ClinicalTrials.gov evolved. Updates to the overall screening record can happen over the lifetime of the MPRP and should be made when the overall screening record is updated to reflect changes in substudy records. The screening record should be updated with the date on which the first substudy was opened to screen participants for eligibility (start date) and the date on which the MPRP overall was opened to screen participants for eligibility (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
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.
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

<table>
<thead>
<tr>
<th>Selected data element</th>
<th>Brief description</th>
<th>Notes for substudy records</th>
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</thead>
<tbody>
<tr>
<td><strong>Registration (summary of key protocol items)</strong></td>
<td></td>
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</tr>
<tr>
<td>Brief title and acronym</td>
<td>A short title for the clinical study written in language intended for the lay public and including information on the condition, participants, and interventions</td>
<td>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)</td>
</tr>
<tr>
<td>Overall recruitment status</td>
<td>Select one: not yet recruiting; recruiting; enrolled; enrolled and randomized; completed; terminated; withdrawn</td>
<td>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-IIA Non-small Cell Lung Cancer That Has Been or Will Be Removed by Surgery (ALCHEMIST screening trial)</td>
</tr>
<tr>
<td>Study start date</td>
<td>Estimated date when the clinical study opens for recruitment of participants or the actual date when the first participant enrolled</td>
<td>Indicate the status for each substudy, updating it within 30 days of a change</td>
</tr>
<tr>
<td><strong>Primary completion date and study completion date</strong></td>
<td>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</td>
<td>Identify a central screening study, indicate that it is part of an MPRP, and include any acronym or other identifying title for both the MPRP and the 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)</td>
</tr>
<tr>
<td><strong>Brief summary</strong></td>
<td>A short description of the clinical study, including a brief statement of the hypothesis, written in language intended for the lay public</td>
<td>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</td>
</tr>
<tr>
<td><strong>Enrollment</strong></td>
<td>Estimated or actual total number of participants enrolled; the term “enrolled” indicates an individual’s agreement to participate after completing the informed consent process</td>
<td>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</td>
</tr>
<tr>
<td><strong>Arms, groups, and interventions</strong></td>
<td>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</td>
<td>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 arms, including any shared control arm, for each substudy if it is prespecified to be included as a comparator in the analysis of results</td>
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<tr>
<td><strong>Outcome measures</strong></td>
<td>Planned measures that are important to evaluating the effects of the intervention</td>
<td>For each substudy, include all prespecified primary and secondary outcome measures. Example (NCT03211665): The primary outcome for National Cancer Institute's Paediatric MATCH is the objective response rate (time frame up to two years)</td>
</tr>
<tr>
<td><strong>Eligibility</strong></td>
<td>Limited list of key inclusion and exclusion criteria for the selection of participants in the clinical study</td>
<td>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</td>
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<tr>
<td><strong>Central contact person (or facility contact)</strong></td>
<td>A person who can answer questions about enrollment at any study location</td>
<td>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</td>
</tr>
<tr>
<td><strong>Uploaded study documents (full study protocol document and statistical analysis plan)</strong></td>
<td>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.</td>
<td>For each substudy, the final protocol and statistical analysis plan are submitted at the time of results submission</td>
</tr>
<tr>
<td><strong>Results (summary results information)</strong></td>
<td>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</td>
<td>For each substudy, provide results information after the primary completion date is reached</td>
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Table 2 | Continued

<table>
<thead>
<tr>
<th>Selected data element</th>
<th>Brief description</th>
<th>Notes for substudy records</th>
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<tbody>
<tr>
<td>Baseline characteristics</td>
<td>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)</td>
<td>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.</td>
</tr>
<tr>
<td>Outcome measures</td>
<td>A summary table with descriptive information for each primary and secondary outcome measure, by arm, including any scientifically appropriate statistical analyses</td>
<td>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.</td>
</tr>
<tr>
<td>Adverse event information</td>
<td>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</td>
<td>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.</td>
</tr>
<tr>
<td>Other</td>
<td>Study record updates</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>External to the study record—publications and other sources</td>
<td>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.</td>
</tr>
</tbody>
</table>

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 prednisolone\(^{29}\) 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 multicorecord 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 multicorecord 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.\(^{4}\) 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.\(^4\)\(^-\)\(^2\) 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,\(^3\)^\(^4\)\(^\) 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.

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**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).

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Web appendix: Online appendix