Registering and Reporting Results to ClinicalTrials.gov

>> Stacey Arnold: Hello, my name is Stacey Arnold, and I am a contractor with ICF working as a Results Team Subject-Matter Expert for clinicaltrials.gov. Clinicaltrials.gov is a part of the National Center for Biotechnology Information in the National Library of Medicine at the National Institutes of Health. Today, I will be discussing registering and reporting results to clinicaltrials.gov. During this presentation, I will cover the following topics. First, I will provide a rationale for registering clinical tries and reporting summary level results to clinicaltrials.gov. Next, I will give an overview of registration and results reporting. Then, I will review an online training platform that has been developed to facilitate the registration and reporting processes, the PRS Guided Tutorials. And finally, I will describe an effort that is underway to modernize the clinicaltrials.gov website and PRS database. Why register clinical trials and report summary level results? One of the most compelling reasons for registering clinical trials is the International Committee of Medical Journal Editors, or ICMJE, publication policy that requires that all clinical trials for all interventions be registered at the time the first participant is enrolled. More information about the policy can be obtained by accessing the link provided. In addition to this policy, Section 801 of the Food and Drug Administration Amendments Act of 2007, or FDAAA 801, requires the submission of summary results, including adverse events. The final rule, or 42 CFR Part 11, was issued in 2016 and has been in effect since January of 2017. It clarifies and expands the regulatory requirements and procedures established by FDAAA 801 for submitting registration and results information at clinicaltrials.gov. It is intended to make clear which trials must be submitted and when by, clarifying, for example, the definition of an applicable clinical trial, or ACT. Review the noted resources more information about what classifies a record as an ACT. In conjunction with the release of a final rule in 2016, the NIH issued a policy to promote broad and responsible dissemination of information from NIH-funded clinical trials. This policy requires that every clinical trial funded in whole or in part by NIH be registered on clinicaltrials.gov and have summary results information posted in a timely manner whether subject to FDAAA 801 and the final rule or not. The policy has been in effect for applications submitted for funding in January of 2017 or later as well as trials initiated from that time onward. Finally, there are local institutional and organizational policies that require registration and results reporting. Such is the requirement by the Department of Veterans Affairs that trials be reported to clinicaltrials.gov as a condition of funding. More information about these policies can be found by accessing the links provided. The general requirements of the final rules stipulate that the responsible party for an ACT must register the ACT on clinicaltrials.gov no later than 21 days after enrollment of the first participant. It further requires that the ACT be updated at least once a year, with some information requiring more timely updates. For example, the study start date should be revised from anticipated to actual within 30 days of enrollment of the first participant, and the primary and study completion dates should be revised from anticipated to actual within 30 days of meeting completion criteria for those fields. Finally, the final rule stipulates that summary results, including adverse events, be submitted no later than 1 year after the trial's primary completion date, but delays are allowed in some circumstances. Access the noted link for more information about how to determine the responsible party for a trial. Apart from the noted requirements for reporting to clinicaltrials.gov, there are practical reasons for sharing information through this mechanism. For example, there are a number of issues with relying upon publications alone to convey the results of clinical trials. Not all clinical trials are published in the literature, so studies that fail to produce significant results or worse that are terminated due to safety concerns can be unknown to other researchers, potentially resulting in the duplication of efforts that are doomed to meet the same end. In other cases, publications might include only partial results, again failing to share results that are not deemed significant, or results might be reconfigured to address a different question than was the original focus, leading to a different interpretation of the study than was originally intended. As a consequence, the incomplete disclosure of research results can impede the scientific process. Further, the implications for incomplete reporting extend beyond the science to potentially affecting the patient population. Trial results, whether significant or not significant, inform medical decisions and determine which research opportunities will be further explored. Since clinical trials depend on volunteers, it is important to honor their time and effort to encourage continued participation in the future. In summary, there are many public benefits to access to clinical trial information on clinicaltrials.gov. Primarily, transparent reporting meets an ethical obligation to human subjects. Trial registration promotes patient access to enrollment in clinical trials. The report of trial results informs future research and funding decisions, mitigates the information bias that can stem from nonpublication or altered representation of study results, allows the research community to evaluate adherence to the prespecified study protocol, and by extension, the integrity of the research in hopes to prevent duplication of trials of unsafe or ineffective interventions and provide access to data that can be used to support evidence-based medicine. All of these benefits of transparency contribute to an increased public trust in clinical research. In the next section, I'll provide a brief overview of registration and results reporting to clinicaltrials.gov. The clinicaltrials.gov website was designed to not only satisfy the legal requirements described in the first part of this presentation but to promote objective, standardized reporting. The database is intended to facilitate good reporting practices including adherence to publishing and regulatory guidelines. It provides structured data entry to ensure complete reporting and to make the review of submissions more efficient. The consistent display of data elements across records also allows for ready comparison of published trials and the database structure supports detailed searches of record content. With the structured presentation and adherence to legal requirements in mind, it is important to note that these requirements do not prescribe how a study should be conducted. Further, the database is intended to capture summary-level results when the primary completion date is met or at the end of the trial. It is not intended for participant-level reporting, nor should interim results be reported. The database is structured to capture information in tables and to be understandable to readers of the medical literature. Conclusive language or discussion of results is not permitted. The intent is to provide the results of investigations in statistical analyses without interpretation. Finally, submission of results is not required for registered studies that are not subject to the final rule to NIH policy or to other funding policies. For the purposes of adhering to the requirements of the law, the deadline for submitting results to clinicaltrials.gov is independent of publication status. Submitting results to clinicaltrials.gov is not considered prior publication, and will not interfere with publication of results in a journal. However, failure to register the trial will interfere with publication, as it is in direct conflict with the policy outlined by the ICMJE. Clinicaltrials.gov records are linked via their assigned NCT number to publications either via the references module and the protocol section of the record or by automatic indexing on the clinicaltrials.gov website. Therefore, reported results to clinicaltrials.gov is complimentary to publication and can be considered a way to fully represent the results of the trial. Registration of the clinicaltrials.gov record captures the following types of information. Details transferred over from the study protocol help to populate the Study Description, Conditions and Keywords, Study Design, Arms, groups and Interventions and Outcome Measures modules in the Protocol section. Recruitment information is represented in the Eligibility and Contacts and the Locations modules. And additional information about the trial is captured in the Sponsor/Collaborators, Oversight, Study Identification, Study Status, IPD Sharing Statement and References modules. For example, the Study Identification module is the place to report the study title and type. That ism whether it is interventional, observational or expanded access as well as the associated grant number. The Study Status module is the place to indicate the anticipated or actual dates for starting and completing the study. The Results section of the record captures two types of information: scientific and administrative. The scientific modules of the results section include Participant Flow, Baseline and Demographic Characteristics, Outcome Measures, including prespecified primary and secondary outcomes and scientifically appropriate tests of statistical significance, Adverse Event Information and Limitations and Caveats. The administrative modules capture the results' point of contact for the study as well as any restrictions on the principle investigator that impact his or her ability to discuss or publish study results. For studies with a primary completion date on or after January 18th, 2017, a protocol and statistical analysis plan are required to be reported by the time results are submitted. The Informed Consent Form is optional except for those trials subject to report in accordance with the revised Common Rule. The Protocol and Statistical Analysis Plan can be provided in a single document or as separate components and should include all amendments to the protocol approved by the Human Subjects Review Board before the time of submission that apply to all of the study locations. Each document should include a cover page with the official title of the study as entered on clinicaltrials.gov, the NCT number and the date on which that version of the document was completed. The submission may redact sensitive details, including personally identifiable information and trade secret or confidential commercial information. The documents must be in PDF/A format to prohibit any issues accessing the information in future, and they must be in English since they will be posted to the clinicaltrials.gov website. The revised Common Rule requires that one consent form be posted on a publicly available federal website within a specific time frame for any trial conducted or supported by a Common Rule department or agency. The federal agencies that satisfy this requirement include clinicaltrials.gov as well as regulations.gov, and the compliance date for this provision went into effect in January of 2019. In the next part of the presentation, I'll provide a brief overview of the content and features of an online training designed to help users become familiar with the process for submitting information to clinicaltrials.gov: the PRS Guided Tutorials. The PRS Guided Tutorials were created to serve as an online version of our Train the Trainer workshop: an in-person training for PRS administrators. The online tutorials are designed to provide step by step instructions for entry of information into the PRS with an overview of the registration document upload and results modules and explanations of the data elements contained therein. They also include tips for how to avoid issues when submitting records for quality-control review. The PRS Guided Tutorials include three sets of tutorials representative of the three sections of a record: the protocol section, the documents section and the results section. The registration and results tutorials sets each include an introductory tutorial, a series of module-specific tutorials and a record-review tutorial. The list of results tutorials is shown here as an example. The tutorials in each set are designed to be used in order but can be accessed independently as needed. The PRS Guided Tutorials are accessible on multiple platforms to facilitate their use alongside entry of information into the PRS. The tutorials are resizable as well so that they can be pulled up alongside the PRS database in a second window on the same screen. The PRS Guided Tutorials can be accessed from several pages on the public site, including the support materials and training materials pages. They can also be accessed from within the PRS via help menus throughout the user interface. The form of means of access takes the user to the landing page for the tutorials, while the latter takes the user to content that is specific for the module of the PRS within which they are working. In addition to resizing the tutorials by adjusting the size of the browser window within which they are viewed, a user can use the hamburger icon at the top of each page to collapse the menu if more space is needed to visualize the page or to expand the menu if the user would like to navigate to a different page. Each set or section of tutorials can be independently expanded or collapsed within the menu as well to narrow the focus to specific content. The tutorials can be searched for terms that describe specific content. The search is initiated by clicking on the magnifying-glass icon shown to the left then typing the search term in the pop-up window as shown in the middle of this slide. The search returns a list of pages wherein the requested content can be found, and as shown on the right, all instances of the selected search term are highlighted in yellow on the page. The content on each page is available in a PDF. Each PDF file can be accessed at the top of the page and downloaded for various purposes such as printing or saving a copy or sharing a copy with colleagues. All tutorial pages include an overview of the content that will be discussed for the given module or page. In this example, the purpose of the participant flow module is defined, and the translation of information from a study's consort diagram to a structured participant flow table is depicted. Most tutorial pages also include links to relevant resources. For example, in the participant flow information tutorial, links to the participant flow data preparation checklist and to our participant flow template are provided to inform the user about ways in which to prepare for the entry of information into the module. The results data element definitions link takes the users directly to the section of the document that defines the data elements pertinent to the module. Finally, a link is provided for the user to access the results-review criteria to help guide successful completion of information entry. Audio narration of the text that proceeds stepwise instruction is provided for the uploading study documents and results tutorials. The narration is intended to allow a user to listen to explanations of the data elements as they navigate through the stepwise entry process. The stepwise instruction for each tutorial is provided using the the parallel study design as an example, but the walkthroughs can be used to enter information for any type of study. Figures can be enlarged by hovering in the cursor over top and clicking to expand. The expanded figure will fill the tutorial's window. So to return to the previous page, users can click on the figure once more to collapse it. Questions that address content not described in the stepwise entry process are provided in a collapsed accordion view, and answers to those questions can be revealed by clicking on the accordions. Figures within an accordion can be expanded or collapsed using the method already described, and the according content can be collapsed by clicking once more no the question. Annotated tables for additional study examples, including those for crossover, factorial, dose escalation, multiple period and units other than participants designs are provided in the same type of accordion view and can also be expanded and collapsed, as can the figures contained within. Each example provides links to the fictional manuscript and full-example clinicaltrials.gov record for the study design so that the table can be visualized in the context of the entire record entry. At the conclusion of the information-entry process, the user should distribute the record as needed to obtain feedback from colleagues about the accuracy and completeness of the submission. The PRS generates system validation messages, including errors, warnings and notes which should be evaluated and addressed before the record is submitted. However, other apparent errors, deficiencies and inconsistencies might exist that should be rectified before the record is submitted for quality-control review. Issues frequently identified in the QC process that prevent publication of a record to the public site are termed Common Major Issues and should be addressed as well. Five common major issues are described for the protocol section of the record at the end of the Registration Tutorials in the "Addressing Common Major Issues and Submitting Protocol Registration" tutorial. Similarly, five major common major issues are described for the results section of the record at the end of the Results Tutorials in the "Addressing Common Major Issues and Submitting Results" tutorial. For each example of a major issue, introductory text is provided to discuss related review criteria and to describe how to resolve the issue. The general clinicaltrials.gov review criteria state that information in the protocol and result sections of the record must be clear and informative, logical and internally consistent, valid and meaningful and exemplify appropriate use of the PRS database structure. The quality-control review process is not equivalent to peer review in that no judgments are made regarding the scientific value of the reported information. In addition, information provided in the record is not verified against external sources or the attached documentation. The onus is on the data provider to fully and faithfully represent the study as conducted. The five major issues covered for registration and for results are listed here. Major issues commonly identified in the registration review include missing interventions, unclear or multiple outcome measures and vague or multiple time frames. Major issues commonly identified during results review include insufficient scale information, invalid or inconsistent unit of measure, written results or conclusions, unclear measures or internal inconsistencies between different parts of a record. The tutorials provide examples of each major issue as well as possible solutions to resolve the issues. In this example of a major issue that might be detected during review of the protocol section, the Removeral intervention is described in the arm description for the placebo arm, but it hasn't been listed as an intervention or assigned to a study arm. The issue is resolved in this case by adding an arm to represent participants who received the Removeral intervention and adding a Removeral intervention to assign to the arm. In this example of a major issue that might be detected during a review of the result section of a record, the information provided in the measure description is insufficient to interpret the data reported in the data table. The issue is resolved in this case by revising the measure description to include the minimum and maximum values on the scale and by indicating how to interpret those values. We are currently in the process of utilizing user feedback about the tutorials to make updates to the tutorials. We are developing quick overview guides to help users navigate the processes of submitting a new registration, posting initial results, uploading study documents and updating a record. We are including a PDF library for easy access to all of the PDFs included throughout the tutorial pages. We are revising the introduction page to include more information about navigating the tutorials and utilizing the features contained within. We are also providing annotated tables and links to fictional manuscripts and example clinicaltrials.gov records for additional study examples, and we are clarifying some of the tutorial content. These updates are planned to be introduced this fall. In the final portion of the presentation, I will give a quick overview of modernization efforts that are currently underway at clinicaltrials.gov. The goal of clinicaltrials.gov modernization is to ensure that clinicaltrials.gov continues to be a trusted and valued public-health resource that provides maximum value to the public while serving its mission well into the future. The modernization process involves close scrutiny of the clinical-research life cycle to identify pain points and opportunities for making registration and results reporting a less stressful part of the process. In the current year of the modernization effort, we have been engaging with stakeholders to determine approaches to take to achieve this goal. We issued a request for information in December of 2019, gathered and summarized feedback and discussed the feedback in a public meeting in April of this year. We have been working with an NLM Board of Regents Working Group to validate our approach and specifications. We have also been working to develop a modernization roadmap and to enhance our internal business processes. In the coming period of implementation, we will conduct user testing and evaluation and continue to engage with users. We will initiate improvements to support the compatibility of clinicaltrials.gov with steps along the clinical trial life cycle in hopes of promoting a seamless end-to-end process. Finally, we will institute an upgrade of system infrastructure components. Before I conclude my presentation, I wanted to point out some resources related to the topics covered. To get more information about the Final Rule, you can access the Final Rule information page at the given web address. It includes links to the Final Rule Webinar Series, the ACT Checklist, frequently asked questions, data element definitions and the PRS User's Guide. In addition, result submission one-on-one assistance is available. Contact register@clinicaltrials.gov to schedule a teleconference. Access the links on this page to review the ICMJE Policy, the NIH Policy and to take a look at the Final Rule. Additional information about conducting trials and reporting trial information can be found via the links on this page. Finally, a selects list of relevant publications is shown here, and additional publications are available on clinicaltrials.gov at the given web address. With that, I will conclude my presentation and ask that any questions be directed to register@clinicaltrials.gov. Thank you for listening.