U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH (NIH)
NATIONAL LIBRARY OF MEDICINE (NLM)
BOARD OF REGENTS (BOR) PUBLIC SERVICE WORKING GROUP ON CLINICALTRIALS.GOV
MODERNIZATION MEETING
SEPTEMBER 2, 2022

MEMBERS PRESENT
Lourdes Baezconde-Garbanati, PhD, MPH, University of Southern California, Chair
Kent J. DeZee, MD, MPH, MACP, COL, MC, Defense Health Agency
Anna M. Fine, PharmD, MS, NLM, NIH, Executive Secretary
Jennifer (Jennie) S. Lucca, MSW, The Children's Inn at NIH
Omolola (Lola) Ogunyemi, PhD, FACMI, Charles R. Drew University of Medicine and Science

MEMBERS NOT PRESENT
Lauren A. Maggio, PhD, Uniformed Services University of the Health Sciences

EX OFFICIO NIH MEMBERS PRESENT
Lyric A. Jorgenson, PhD, Office of Science Policy

EX OFFICIO NIH MEMBERS NOT PRESENT
Pamela Reed Kearney, MD, Office of Extramural Research

EXTERNAL MEMBERS PRESENT
Carrie Dykes, PhD, University of Rochester Clinical and Translational Science Institute
Alissa T. Gentile, MSN, RN, Dana-Farber Cancer Institute
Sally A. Gore, MS, MS LIS, University of Massachusetts Medical School
Barbara Kress, BSN, RN, Merck
Seth A. Morgan, MD, National Multiple Sclerosis Society
Stephen J. Rosenfeld, MD, MBA, North Star Review Board and Freeport Research Systems
Joseph S. Ross, MD, MHS, Yale School of Medicine
Steven Woloshin, MD, The Dartmouth Institute for Health Policy and Clinical Practice

OTHERS PRESENT
Stacey Arnold, PhD, NLM, NIH, Protocol Registration and Results System (PRS) Subject Matter Expert
Annice Bergeris, AS, NLM, NIH, ClinicalTrials.gov Information Research Specialist, Acting Deputy Director, and Operations Team Product Owner
Nachiket Dharker, PhD, ICP-APO, ICP-LEA, ICF, PRS Beta Product Owner
Elisa Golfinopoulos, PhD, ICP-LEA, ICF, Automation Support Team Product Owner
Slava Gorelenkov, MS, ICP-LEA, NLM, NIH, ClinicalTrials.gov Technical Program Manager
Wendy Harman, JD, ICF Next, ClinicalTrials.gov Beta User Experience Lead
Hibah Nazir, MPH, CSPO, CSM, Computercraft, ClinicalTrials.gov Product Manager

Alison Powell, BA, ICF Next, Communications Specialist

Rupinder Randhawa, MASc, PMP, SAFe POPM, AWS CLF, ICF Next, ClinicalTrials.gov Modernization Project Manager

Christina Robinson, MA, ICP-LEA, NLM, NIH, ClinicalTrials.gov Beta Product Owner

Mary Sanders, MS, PMP, CSM, ICP-LEA, ICF, ClinicalTrials.gov Project Manager

Scott Smith, BA, CSPO, ICF Next, PRS Beta Product Manager

Tony Tse, PhD, NLM, NIH, ClinicalTrials.gov Analyst

Susan Wimmer, BA, ICF, ClinicalTrials.gov Editor

I. WELCOME AND INTRODUCTIONS

Lourdes Baezconde-Garbanati, PhD, MPH, Chair
Anna M. Fine, PharmD, MS, Executive Secretary

Dr. Fine welcomed the attendees, including BOR members, external members, and ClinicalTrials.gov staff. Meetings planned for the remainder of 2022 and throughout 2023 were mentioned. Dr. Fine noted the formation of the Working Group in 2019 and asked members to consider extending their participation for another year as the ClinicalTrials.gov modernization effort continues. Feedback on anticipated meetings and suggested approaches was encouraged.

II. RECAP OF PLAIN LANGUAGE IN THE PRS

Stacey Arnold, PhD, PRS Subject Matter Expert

Dr. Arnold highlighted the plain language checklist developed by Health Literacy Media, which was designed to promote the use of plain language by data providers when drafting the Brief Summary protocol registration data element. This checklist, along with a template, will be provided via just-in-time links on the PRS to assist users in real time during study registration.

Dr. Arnold then reviewed related legal and other information, including Section 801 of the Food and Drug Administration Amendments Act of 2007 and the 2017 Final Rule for Clinical Trials Registration and Results Information Submission (42 CFR Part 11). Although the Final Rule declined to require submission of plain language summaries (PLS) to ClinicalTrials.gov because of a lack of evidence that it could be done systematically without being misleading or promotional, several responses to the 2020 modernization request for information (RFI) supported the posting of summaries, either directly or via linking, on the ClinicalTrials.gov website. Dr. Arnold noted that a European Union (EU) regulation that recently went into effect requires the inclusion of PLS with EU registry submissions and that the EU has developed a Good Lay Summary Practice guidance document. She also noted that PLS guidance has been provided by other groups and in publications.

Although the Working Group will not be reconsidering the Final Rule decision regarding PLS, the group may consider ways to leverage other PLS initiatives on ClinicalTrials.gov in response to the RFI comments. Possible approaches include the inclusion of helpful information within the PRS and the optional linking from the study record to PLS posted on external websites, which could be limited to sites operated by the U.S. government and the EU.

III. LIGHTNING TALKS AND DISCUSSION
Barbara Kress, BSN, RN, Merck
Sally A. Gore, MS, MS LIS, University of Massachusetts Medical School
All Working Group Members

Ms. Kress reviewed the importance of health literacy, both for patients and caregivers and for health organizations, and presented the PLS process from the perspective of a pharmaceutical study sponsor. Industry organizations have a responsibility to equitably enable patients and caregivers to find and understand the available information in order to make informed health decisions.

The EU Clinical Trial Regulation and Requirements for PLS, which went into effect earlier this year, require sponsors to submit both protocol PLS (primarily for regulators) and results PLS (for the public), and the EU has provided guidance to help sponsors draft protocol and results PLS. Ms. Kress noted that because sponsors are already developing PLS for their submissions to the EU Clinical Trials Information System, there is the potential for voluntary posting of results PLS on ClinicalTrials.gov, thereby increasing harmonization between these EU and U.S. trial registries. She also suggested that sponsors should be responsible for the review and accuracy of PLS content, instead of quality-control (QC) reviews by ClinicalTrials.gov staff.

Ms. Gore observed that ClinicalTrials.gov is a single platform serving multiple stakeholders with diverse needs, and this challenge includes providing trustworthy resources that are accessible to the lay public. She noted that public acceptance of non-peer-reviewed scientific information is increasing, as demonstrated by the extensive sharing of initial data and results via preprints and on social media during the COVID-19 pandemic. Ms. Gore then presented several ideas for improving ClinicalTrials.gov to better support the lay public, such as rewriting in plain language the How to Read a Study Record webpage, better utilizing links to NLM-vetted resources (e.g., MedlinePlus) and sponsor-provided information, adding more prominent links than those available at present, and embedding relevant plain language resources directly in the study record.

Working Group members discussed possible ways for study sponsors to embed additional resources in their study records.

IV. MODERNIZATION UPDATES
Anna M. Fine, PharmD, MS, Executive Secretary
Nachiket Dharker, PhD, ICP-APO, ICP-LEA, PRS Beta Product Owner
Elisa Golfinopoulos, PhD, ICP-LEA, Automation Support Team Product Owner
Christina Robinson, MA, ICP-LEA, ClinicalTrials.gov Beta Product Owner

The modernization effort is nearing the end of its third year, with, most recently, the successful release of a ClinicalTrials.gov Beta update on August 22. A draft report summarizing the modernization effort during the past year, which describes the launch of

ClinicalTrials.gov Beta and PRS Beta, Working Group and stakeholder input, and future modernization activities, will be provided to Working Group members for review and input prior to publication this fall. The ClinicalTrials.gov team will continue to conduct usability research to inform updates and further improvements to both ClinicalTrials.gov Beta and PRS Beta.

Dr. Dharker reviewed the features included in recent and upcoming PRS Beta releases. Recently released features include:

- an updated Record List that provides a customizable display and additional content (study dates with date type)
- Record List enhancements that provide additional functionality to allow for multiple filter selections and the addition of a Documents column to allow filtering by document type
- an About drop-down menu that includes an About PRS Beta page with added navigation tips and a new Release Notes page that is accessible outside of the PRS login
- a Planning View and a Public Site View for administrators who manage records for multiple users as well as a Group column that allows administrators with multiple groups within an organization to search records by group

User feedback on recent beta releases was mostly directed at the Record List View, including design-related issues, with additional comments focusing on webpage access errors and requests to add features and filters. In response to this feedback, the team is continuing to make updates and provide further clarification as needed. Dr. Dharker also shared positive feedback received from users on various beta features.

Upcoming releases will include updates to the protocol registration section, single-screen data entry, and other changes based on user feedback. A Help Drawer feature is also being developed to provide just-in-time brief guidance, additional information, and data element definitions, which will help facilitate data entry. Working Group members recommended that the minimum help drawer content (the brief guidance only) be visible by default, which would allow users to immediately view basic information and then expand the rest of the content as needed.

Dr. Golfinopoulos presented research focused on potential applications of artificial intelligence (AI), specifically machine learning, to help streamline the ClinicalTrials.gov QC review process. Using a sample of 21,266 unique records, the Automation Support Team explored different classification algorithms to determine which model could best identify a frequently occurring issue that results in the record being reset during QC review, namely, the reporting of more than one measure with different units in a single outcome measure (the Multiple Measures major issue). Two models were examined, and Dr. Golfinopoulos noted that the DistilBERT model outperformed the logistic regression model, when favoring sensitivity over specificity. Although it is feasible for AI to detect specific issues, reviewer

judgment is still necessary, so reviewers will need to learn when to accept and when to reject the model's suggestions. Next steps include the examination of machine-learning models for detecting other issues, including the Vague Time Frame major issue in the Protocol Section and the Missing Scale Information and the Invalid/Mismatched Unit of Measure major issues in the Results Section.

Working Group members discussed additional approaches to reducing errors before and during QC review, including applying machine learning during data entry to provide real-time feedback to users. Currently, most data elements are structured (e.g., options selected from a drop-down menu); however, some have free-text fields that require manual review, and this project targets problems found in entries for those unstructured fields. All AI-generated models will first be assessed by the QC review staff before being released to data providers.

Ms. Robinson reviewed the features included in recent and upcoming ClinicalTrials.gov Beta releases and provided a brief overview of the most recent release. Recently released features include:

- an enhanced search, which provides rapid access to additional search fields without complicating a basic search
- additional filters to help users refine their search results
- a tabular view of search results to facilitate the comparison of multiple trial attributes across search results
- the pilot Fast Healthcare Interoperability Resources (FHIR) application programming interface (API), a new feature supporting interoperability between ClinicalTrials.gov and other platforms

A tabular view of the study record and of the study record history are under development. Future features include an updated ClinicalTrials.gov API, an XML download option, links to trusted health information, and new ways to orient and support users who are new to ClinicalTrials.gov.

Working Group members confirmed that the key features that the team plans to develop are ones that Working Group members would like included in the next releases of ClinicalTrials.gov Beta, namely, links to trusted health resources, guidance on next steps for joining a study, an XML download option, API access, and more educational resources about clinical trials. Ms. Robinson noted that the banner on the classic site was updated, as discussed during the April Working Group meeting, and after only a few weeks, beta site traffic had increased nearly threefold. Working Group members emphasized the goal of increasing the clarity and accessibility of study records for the lay public.

Dr. Fine shared several mentions of the ClinicalTrials.gov Beta website in the literature and by stakeholders on social media. Regarding timelines, the next PRS Beta release is anticipated for early 2023 and will include protocol registration submission tools. It is anticipated that ClinicalTrials.gov Beta will become the primary website by mid-2023.

Communications about upcoming releases and other changes will continue to be shared using multiple modalities, including social media. Stakeholder engagement via public webinars is anticipated for fall 2022 and spring 2023. Working Group members expressed concerns about access to the classic site after ClinicalTrials.gov Beta becomes the primary site and the interoperability of PRS Beta and third-party vendor systems used by sponsors to submit trial information to the PRS.

V. NEXT STEPS
Anna M. Fine, PharmD, MS, Executive Secretary

Dr. Fine said that the discussion and decisions from this Working Group meeting will be included in a report presented at the September 13 NLM BOR meeting. A draft high-level meeting summary will be provided to the Working Group for review and feedback, and the final, Section 508-compliant PDF version will be posted on the NLM BOR webpage. A draft of the modernization summary report will also be provided to Working Group members for their review.