March 23, 2015

Francis S. Collins, M.D., Ph.D
Director, National Institutes of Health
9000 Rockville Pike
Bethesda, Maryland 20892

Re: Clinical Trials Registration and Results Submission [NIH-2011-0003-0003]

Dear Dr. Collins:

The American Society for Gastrointestinal Endoscopy (ASGE) and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) offer comments on proposed requirements published on November 21, 2014 in the *Federal Register* for submitting registration and summary results information for specified clinical trials of drugs and devices and for pediatric post-market surveillances of devices to ClinicalTrials.gov.

Since its founding in 1941, ASGE has been dedicated to advancing patient care and digestive health by promoting excellence and innovation in gastrointestinal endoscopy. ASGE, with more than 13,000 members worldwide, fosters endoscopic research, promotes the highest standards for endoscopic training and practice, and is the foremost resource for endoscopic education.

NASPGHAN is an organization comprised of more than 2,000 members who have specialized training and clinical expertise in caring for infants, children, and adolescents with disorders of the digestive system, liver and nutrition. As experts in these fields, NASPGHAN recognizes the importance of extending gastroenterology, hepatology, and nutrition education throughout all health care professions, the importance of providing outstanding patient care, and the importance of advancing science through research, including through pediatric clinical trials.

We support the goal of ClinicalTrials.gov to improve public access to clinical trials. Additionally, we acknowledge the proposed requirements are intended to fulfill compliance with the Food and Drug Administration Amendments Act of 2007 (FDAAA) which broadens the scope of trials required to be registered at ClinicalTrials.gov to include controlled trials (other than phase 1trials) of any Food and Drug Administration (FDA)-regulated drug or biologic for any disease or condition, and certain studies of FDA-regulated medical devices, excluding small feasibility studies, but including FDA-required pediatric

post-market surveillance studies of a device. The broadened scope will allow for more informed patient decisions and will give clinicians and researchers access to important information about efficacy, safety, and adverse effects and will provide researchers with information for future study designs.

Our societies offer the following comments to support the purpose of FDAAA to enhance patient enrollment in clinical trials, provide a mechanism to track subsequent progress of clinical trials, provide more complete results information, and enhance patient access to and understanding of the results of clinical trials.

General Provisions – Subpart A

As articulated in the proposed rule, requirements for submitting registration and summary results information to ClinicalTrials.gov would primarily apply to those trials that meet the definition of an applicable clinical trial, including: (I) controlled, interventional studies of drugs, biological products, and devices that are regulated by the FDA, but exclude phase 1 studies of drugs and biological products and feasibility studies of devices; and (2) pediatric post market surveillance of a device that is required by FDA. In general, clinical trials of products regulated by FDA will meet one or more of the following criteria: include one or more sites in the United States; study a drug, biologic, or device that is manufactured in the United States or its territories and is exported for use in a clinical trial outside the United States; or be conducted under an FDA investigational new drug application (IND) or investigational device exemption (IDE).

In the proposed rule, "interventional" is defined as a clinical study or investigation in which participants are randomly assigned prospectively to evaluate the effect of the intervention(s). The NIH states in the proposed rule that it considers a "prospective" clinical study to be "any study that is not retrospective or, in other words, one in which subjects are followed forward in time from a well-defined point (i.e., the baseline of the study) or are assessed at the time the study intervention is provided." A 'prospective clinical study' also may have non-concurrent (e.g., historical) control groups." As an example, the proposed rule explains that a retrospective study, and therefore not an applicable device clinical trial, is a study in which subjects are selected based on the presence or absence of a particular event or outcome of interest (e.g., from hospital records or other data sources) and their past exposure to a device is then studied. **Our organizations support NIH's interpretation of "prospective" clinical study.** We do understand, however, per the proposed rule that an applicable clinical trial that is a pediatric post-market surveillance of a device or intervention can have a study type designation of "interventional'' or ''observational," which could include retrospective studies.

Registration – Subpart B

This subpart sets forth the requirements for ClinicalTrials.gov registration. It identifies, among other things, which applicable clinical trials must be registered.

Which applicable clinical trials must be registered? - § 11.22

The NIH is proposing to use specified data elements to determine whether a clinical trial or study meets the definition of an applicable clinical trial. This approach would replace the current approach which asks potential registrants to indicate whether their trial is an applicable clinical trial.

The proposed rule states that algorithms following the registration approach outlined in the proposed rule could be developed to allow potential registrants to determine before going through the registration process whether their clinical trial or study meets the definition of an applicable clinical trial. **We support the development and accessibility of algorithms on ClinicalTrials.gov prior to the registration system.**

Results Submission – Subpart C

Our societies agree with the intent of FDAAA and this proposed rule to make more information about clinical trials and studies available to the public. We believe appropriate safeguards are necessary to ensure submitted data are accurate, correctly obtained, and properly and explicitly explained in terms of limitations and caveats. There is great benefit to researchers to have access to study details and the results, even when the study results do not have positive findings and/or are never published. While we acknowledge that some of the proposed requirements will be more time-intensive, especially for a study that is not published in a peer-reviewed journal, they are necessary steps for broader dissemination of information for federally funded and private research.

We ask NIH to consider adding disclaimers on ClinicalTrials.gov that since studies and their results are not subject to peer review as a prerequisite for posting on ClinicalTrials.gov, the database serves simply as a repository for information and should not be used to make treatment or coverage decisions and should be cautiously interpreted. For example, consider a situation in which a clinical trial compares two devices and finds positive results for one of the devices compared to the other and submits a paper for peer review and publication. If the journal refuses to accept the paper on the grounds that the study is poorly designed or the analysis is wrong, how is this outcome reconciled with what is made publicly available on ClinicalTrials.gov? The public will have access via ClinicalTrials.gov to information that one device is better than the other but will be unaware that it was rejected for publication due to study design or analysis flaws. We are very concerned with the potential for the occurrence of this type of situation and how study information and results that are not peer-reviewed and published will be interpreted and used. **Furthermore, because information submitted to ClinicalTrials.gov is only verifiable by the study author, we strongly encourage NIH's use of disclaimers stating that data obtained from ClinicalTrials.gov should not be cited as evidence in peer-reviewed literature.**

What constitutes results information? - § 11.48

The proposed rule describes a situation in which outcome measures for a clinical trial are collected but the actual enrollment falls well below the target enrollment. The proposed rule states that even in such situations collected results information must be submitted to ClinicalTrials.gov as specified in the proposed rule. The proposed rule further states that if the clinical trial was terminated because of safety concerns or efficacy, the results information would be of considerable interest to human health and safety. The proposed rule continues by stating, "In order to reduce the chance that users of ClinicalTrials.gov might misinterpret submitted results information, we would encourage the responsible party to voluntarily submit additional information about the clinical trial in the Analysis Population Description data element and/or in the Limitations and Caveats module of ClinicalTrials.gov." We believe it is very important that in these types of instances limitations of the data be well understood by the public. **We are therefore concerned that NIH is only requiring voluntary submission of additional information in instances where submitted results could be easily misinterpreted due to situations such as low study**

enrollment or study termination. We request that submission of additional information be required rather than voluntary.

Submission of Non-Technical and Technical Summaries of Trial Results

Based on NIH's interpretation of the law, proposed regulations are to require the submission of non-technical and technical narrative summaries if such summaries can be produced in such a way that they will not be misleading or promotional to potential users of the data bank. We believe the submission requirement of non-technical summaries could be useful, to the general public and clinicians outside the field of study in particular, but we agree with NIH's assessment that it is necessary to demonstrate that narrative summaries of applicable clinical trials can be consistently produced in a way that will not be misleading or promotional. **We support the NIH's plans to undertake an evaluation to assess the value to the public of such summaries and whether they can be provided in a manner that is objective and not misleading.** We also suggest that NIH consider establishing guidelines for writing non-technical summaries and that the summaries be required to follow a specified format.

Submission of the Full Protocol

The law requires that the regulations shall require submission of ''[t]he full protocol or such information on the protocol for the trial as may be necessary to help to evaluate the results of the trial.'' The proposed rule seeks comment on whether the registration and results information that is proposed for submission to ClinicalTrials.gov is sufficient to meet the statutory requirement to provide ''information on the protocol'' as may be necessary to help evaluate the results of the clinical trial or whether submission of additional information, including submission of the full protocol, should be required.

Our organizations support the NIH's decision to not propose requiring submission of the full protocol or other ''information on the protocol'' at this time. Because the information on ClinicalTrials.gov is available to the general public, we are concerned that including all the technical details that would be required with submission of the full protocol would not be understandable to the general public and could have a detrimental effect on improving clinical trial recruitment.

Additional Submissions of Clinical Trial Information – Subpart D

What are the requirements of clinical trial information? - § 11.66

The proposed rule states that it expects that responsible parties that become aware of needed corrections to ClinicalTrials.gov data must submit corrected information as soon as possible, but not later than 15 calendar days after the data that they become aware of the need for correction or that NIH informs them of the needed correction. **To ensure that data in ClinicalTrials.gov are not false or misleading, we support requirements for correcting information, but strongly believe that disclaimers on ClinicalTrials.gov, per our comments above, are needed to inform the public that ClinicalTrials.gov is not responsible for the accuracy of the study results.**

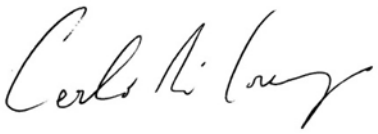
Conclusion

While we understand there are complexities regarding the vast data necessary for the web-based repository, the data input process is perceived as unnecessarily cumbersome by our members. Our

organizations are hopeful that ClinicalTrials.gov can become more user-friendly through further design efforts, perhaps with feedback from end-users or focus groups. Compliance with the site may be hampered owing to the difficulties perceived by researchers in navigating what can be a non-intuitive data entry system. Our societies appreciate your consideration of our comments. Should you require any additional information or have any questions, please contact Camille Bonta at cbonta@summithealthconsulting.com or (202) 320-3658.

Sincerely,

Colleen M. Schmitt, MD, MHS, FASGE
President
American Society for Gastrointestinal Endoscopy



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