EMORY
UNIVERSITY

February 12, 2015

Docket No. NIH-2011-0003
RIN 0925-AA52
Jerry Moore, NIH Regulations Officer
Office of Management Assessment
6011 Executive Boulevard, Suite 601 MSC 7669
Rockville, MD 20852-7669

RE: Comment on Draft Notice of Proposed Rulemaking for Clinical Trials Registration and Results Submission

We write on behalf of Emory University in order to provide comments in response to the proposed regulatory changes set forth in the *Notice of Proposed Rulemaking for Clinical Trials Registration and Results Submission* as published at 79 Federal Register 225 (November 21, 2014).

As a leading institution of higher education, clinical research conducted at Emory University is responsible for important scientific advances in a number of fields, and it includes a large number of clinical trials that are conducted to evaluate new drugs and agents, new devices, new regimens, and new strategies for the treatment and prevention of disease.

Scope of the Proposed Amendments – Dissemination of Clinical Trial information funded by the NIH through registration and submission of summary results on ClinicalTrials.gov

Emory University agrees with the intent of the proposed regulatory changes to promote data sharing and enhance transparency in clinical trials, and ultimately to mitigate publication bias in scientific research. Unfortunately, the NPRM is drafted in a broad manner that makes adherence to it difficult in academic medical centers wherein investigator-initiated research is not conducted in a centralized manner as it is in the pharmaceutical industry. Specifically, compliance with the NPRM, as currently set forth, is particularly difficult to ensure as an academic institution with the application of the expanding scope of results requirements under 42 Code of Federal Regulations (CFR) Part 11, Subpart C and in the stringent timing of updates and corrections delineated under 42 CFR Part 11, Subpart D.

Investigators conducting independent research at academic medical centers will be severely impacted by the policy as currently proposed, and investigator-initiated clinical trials will be discouraged by the onerous requirements without any corresponding gain. Emory's general concerns and comments on the NPRM are enumerated below:

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1. The NPRM as proposed does not recognize the time and effort required to register and report results for clinical trials in ClinicalTrials.gov. Furthermore, there is a lack of recognition of the ongoing time commitments involved in maintaining compliance with FDAAA Section 801 and the NPRM as currently written. The proposed policy for requiring registration and results information for all applicable clinical trials and the additional delineation that all clinical trials would be subject to the forthcoming proposed rule-making under FDAAA, does not account for the significant impact and the financial and time obligations required by investigators and institutions with this unfunded mandate. ***Recommendation:*** *Emory requests that the FDA further recognize the time and effort required for both updating current study records and the ongoing updates that will be required under the proposed regulatory changes.*

2. Compliance with the suggested NPRM timeline constraints for updating study records (on both applicable clinical trials and the newly proposed NIH-funded clinical trials obligations) is virtually impossible to maintain. Many of the proposed data element timelines require updates within 15 to 30 calendar days; these timeframes do not consider the time necessary to communicate pertinent data and to update the study record. Furthermore, information as proposed by the NPRM does not properly consider the widening scope of the data element expansion that will be required of investigators at academic medical centers (e.g., U.S. FDA approval clearance or licensing status within 15 days after a change in status). Such time-consuming requirements unnecessarily detract from the available time emphasis on subjects and the intent of the research. ***Recommendation:*** *Emory University requests that updates required under the NPRM be consistent with those currently mandated by the FDA and OHRP for continuing review of active clinical trials within ClinicalTrials.gov – at least annually or more frequently, depending upon IRB continuing review requirements dictated for the study. For active and enrolling clinical trials, it is suggested that updates continue to be required 180 days from the time a change occurs similar to current FDAAA Section 801 update requirements.*

3. The expansion of registration and results reporting in ClinicalTrials.gov ultimately impacts both the institution and the investigator without increasing the availability of public knowledge overall. The results reporting requirements for ClinicalTrials.gov are currently overly burdensome without contributing to a lay person's understanding of the results of a clinical trial under FDAAA Section 801 regulations. ***Recommendation:*** *If a study is currently published in a peer-reviewed journal, it could be suggested that formal submission of results to ClinicalTrials.gov not be required. Inclusion of a web link (e.g., PubMed ID link) to the publication(s) and a lay summary of results could be provided for the study record; this mechanism would be sufficient for the purpose of data sharing and transparency.*

4. The expanding scope of ClinicalTrials.gov and the proposed requirements under the NPRM increases the burden on investigators at academic institutions. As such, the requirements discourage investigator-initiated clinical trials and may further limit research to only large pharmaceutical companies that can afford to implement programs to ensure

compliance to the proposed policy and regulations. Academic medical centers and investigators conducting research independently may have to deal with a lack of uniformity and decentralization of information in regards to meeting the proposed regulations as well. Furthermore, there is generally greater mobility within these entities in regards to young investigators conducting independent research as fellows or Responsible Parties transferring between institutions. Without consideration of these factors in the proposed requirements for ClinicalTrials.gov, investigator-initiated research at academic medical centers may be hindered, and investigators may be discouraged overall by the difficulties in ensuring compliance to the stringent regulations as currently proposed. ***Recommendation:*** *Please see requests made by Emory in numbers two and three as referenced above.*

5. Further, under the NPRM, the adherence stipulated by the NIH policy elicits additional concerns regarding ensuring compliance by investigators and academic medical centers conducting research with physician investigators as Responsible Parties. Many of the newly proposed requirements and timelines are especially burdensome in an academic environment where data elements required to be entered are not maintained in a centralized manner and the onus is on both the Investigator under FDAAA Section 801 and also the institution as the NIH Awardee. ***Recommendation:*** *Emory suggests that the scope of penalties under the NIH Policy for registration and results summary reporting be limited to the Responsible Party, both under the NPRM and in regards to individualized NIH funding – the NIH Awardee delineation currently drafted encompasses Emory University NIH funding as a whole.*

6. Emory University is also concerned that the ClinicalTrials.gov website is unnecessarily confusing. The proposed regulatory changes may promote misunderstanding by individuals using the website for interest and availability of a clinical trial for enrollment purposes. If analysis information continues to be displayed for the public solely in a technical manner, this could hamper recruitment efforts and foster the potential for confusion on the behalf of research participants. Because the public website utilizes both lay language for dissemination to the general public and also technical and scientific information, this information could potentially be misinterpreted. ***Recommendation:*** *As the results summary reporting is the most technical and scientifically data-driven part of the study record, Emory suggests a lay summary results paragraph for the general public, and a link to any pertinent publications as referenced above in number four.*

7. Additional concerns and comments by Emory University regarding mandatory compliance with the NPRM are outlined below:

   A.) III.C.7, (FR 69582): **Submission of the Full Protocol**

   > Requirements for the submission of the full protocol or such information on the protocol for the trials as may be necessary to help evaluate the results of the trial.

While the current recommendation is that the additional proposed registration and results information are sufficient to meet the statutory requirements under the PHS Act, comments are requested. Per this request, if the full protocol were eventually required, full protocol submissions would be a concern in terms of proprietary and intellectual property interests. In addition, this would potentially place an extensive burden on investigators conducting research if, upon review, NLM reviewers required certain formatting standards. Further, standards for submitting amended protocols and revisions would need to be established creating an even greater burden on investigators conducting clinical trials as Responsible Parties. ***Recommendation:*** *Emory University supports the view that the current information detailed by registration and results summary submission of data elements for clinical trials is sufficient to meet compliance standards and for public dissemination.*

B.) III.C.12-13, (FR 69584, FR 69587): **Quality Control Procedures & Updating Submitted Clinical Trial Information**

The NPRM changes seek to require the Responsible Party to correct errors within 15 calendar days of notification to NIH or becoming aware of the errors. An additional 11 data element fields (§11.64) are proposed to require updates between 15 to 30 calendar days after a change in information.

This proposal adversely impacts physician investigators conducting research independently at academic medical centers such as Emory University, and is particularly burdensome in attempts to ensure compliance within the suggested timeframes with no tangible benefit. These requirements would mandate ongoing monitoring and updates within a timeframe to which it would be difficult to adhere. This would especially be true in cases where amendment changes to a protocol are complex or when a physician investigator is not explicitly aware of a nonproprietary name change of an intervention or expanded access availability. Industry Sponsors of clinical research would be at an advantage due to the more centralized ability to access the needed information for updating ClincalTrials.gov with the proposed requirements for data elements. However, correction of errors and a response to Quality Assurance Review within a 15 day window would create a significant burden to investigators and academic institutions, as there is a definitive distinction between their ability to access the necessary data and information to update the study records. Further, the data elements and timelines proposed for required updates would also be very difficult to maintain, review, and revise within the rigid 30-day window on both a centralized and site investigator level. Moreover, within the current requirements, no information has been provided that demonstrates that study records are not being updated within a timely manner. As currently written, the updates proposed in the NPRM are significantly more stringent than the requirements for updating the Human Subjects Review Board and do not correspond with the current requirements for updates (in the majority of human subjects research) at least annually for continuing review and approval of human research studies. ***Recommendation:*** *Emory requests that the*

timeframe for correction of errors and response to Quality Assurance reviews be required within a 30-day timeframe. Additionally, as stated above, Emory University proposes that the timeframes for any data element updates required be consistent with those currently mandated by the FDA and OHRP for continuing review of active clinical trials within ClinicalTrials.gov – at least annually or more frequently, depending upon IRB continuing review requirements dictated for the study. For active and enrolling clinical trials, it is suggested that updates be required 180 days from the time a change occurs similar to current FDAAA Section 801 update requirements.

C.) IV.A.2, §11.4, (FR 69595): (1) **Determination of Sponsor &** (3) **Withdrawal of the Designation of a Principal Investigator as Responsible Party**

The NPRM confirms that each clinical trial must have one Sponsor, confirming that a trial conducted under an IND or IDE, the IND/IDE holder is considered the Sponsor; for those trials not conducted under an IND/IDE, the individual/entity initiating and holding authority over the study is the Sponsor.

Further clarification is requested regarding the definition of Sponsor under extenuating circumstances. If an individual investigator is the IND or IDE holder for a clinical trial and the investigator transfers to a new institution, it is unclear how the study record should be maintained in terms of designated responsibility if the original institution remains the sole site where the research was conducted. Confirmation is requested as to whether or not the responsibility lies with the original institution as the Sponsor or the investigator (IND/IDE holder) as the Responsible Party. ***Recommendation:*** *Emory requests clarification if an IND/IDE holder transfers to a new institution or corporation, as to whether or not the responsibility is bound with the study site where the research was conducted if the data is not transferred to the new institution. Additional language could be provided for guidance in these types of extenuating circumstances.*

Additional requests are made for guidance regarding circumstances in which there is an issue between the investigator at an institution initially deemed as Responsible Party and the Sponsor as an institution or corporation. Under certain circumstances, issues may arise (e.g., death of Responsible Party, inability of Sponsor to obtain data) that may inhibit results summary reporting. At present, there is no formal process addressing these types of circumstances and liability falls both on the Sponsor (e.g., the institution) under NIH policy as the Awardee and the Responsible Party (e.g., physician investigator conducting research at the institution as an IND/IDE holder) under FDAAA, Section 801. ***Recommendation:*** *In these extenuating and rare circumstances, it is requested that a waiver of results requirements may be deemed acceptable and provisions made for these exceptions. Additionally, Emory University expresses the need for a method of removing trials from the Problems list in ClinicalTrials.gov, wherein the Responsible Party has left the institution and the clinical trial has been abandoned by the investigator. Emory also requests guidance regarding extenuating circumstances and that direct contact phone*

numbers for ClinicalTrials.gov Quality Assurance reviewers be made available for questions and concerns.

D.) IV.A.5, §11.10, (FR 69598): **Definitions Applied – *Adverse Event*** means any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

The required terminology for *Adverse Event* is vague and unclear, and the scope of the definition utilized is unnecessarily loosely defined. Further, the HHS regulations at 45 CFR Part 46 do not define or use the term *Adverse Event*; the definitions applied by IRB reporting requirements and the FDA definition differ. Furthermore, confirmation is requested by Emory that the definition does not intend that every Adverse Event be reported, considering the following indication by the NPRM (69587): "Proposed §11.64(a) (2) specifies that a Responsible Party must submit updates until the final clinical trial results information has been submitted for all primary and secondary outcome measures and all adverse events collected in accordance with the protocol".
Recommendation: *Emory suggests that "adverse event" be explicitly defined and in a manner consistent with current requirements stipulated by IRB reporting at continuing review. Emory requests clarification regarding the requirement that every adverse event must be reported in accordance with the protocol as stated in the proposed language in §11.64(a)(2).*

E.) IV.A.5, §11.10(32) (FR 69670): **Facility Information** means, for each participating facility in a clinical trial, the following information: (i) Facility Name, (ii) Facility Location and (iii) Either: (A) For each facility participating in a clinical trial, Facility Contact, including the name or title, telephone number, and email address of a person to whom questions concerning the trial and enrollment at that site can be addressed or (B) Central Contact Person, including the name or title, toll-free phone number and email address of a person to whom questions concerning enrollment at any location of the trial can be addressed.

Emory University understands the importance of providing contact information to interested research participants for the purpose of public interests. However, the information proposed above is especially burdensome in regards to operationalizing the contact and providing central information in an academic medical center. Furthermore, contact directly to an investigator or central phone line could be difficult to manage if a study elicits a higher volume of interest from the research community. Requirement of this information and in the stipulated format does not recognize the efforts and time that would be required of the contact listed to respond and manage inquires in a timely manner. Furthermore, requiring the availability of a toll-free number is an added cost to investigators conducting research independently at academic institutions.

Recommendation: *Emory requests consideration of the time and effort required for managing potential research participant interest, as well as confirmation that a toll-free number not be required for the site contact.*

F.) IV.A.5, §11.10(38) (FR 69670): **Responsible Party Contact Information** defined as administrative information to identify and allow communication with the Responsible Party by telephone, email, and regular mail or delivery service – includes the name, official title, organizational affiliation, physical address, mailing address, phone number, and email address of the individual who is the Responsible Party or a designated employee of the organization that is the Responsible Party.

It is the understanding of Emory University that the level of detail proposed for requiring contact information is for agency use only. ***Recommendation:*** *Emory requests that the additional administrative information at this detailed level not be required, as this information should already be available and on file with the NIH and FDA. If required, however, Emory requests confirmation that the contact information is not publicly available.*

G.) IV.B. §11.28(c) (FR 69671): **Expanded Access Record.** If expanded access is available under Section 561 of the Federal Food, Drug, and Cosmetic Act to a drug studied in an applicable drug clinical trial and specified data elements have not been submitted for a previously-registered applicable clinical trial of the drug, the Responsible Party must submit the clinical trial information in the form of an expanded access record.

The requirement of the inclusion of an expanded access record is of concern for investigators conducting research at academic medical centers in which they are the IND holders. ***Recommendation:*** *Emory University requests confirmation as to how this would be handled for expanded access availability when the Responsible Party is an independent investigator. Further clarification is also requested regarding whether one expanded access study record would be considered sufficient per drug, per indication and also be under the purview of the company that manufactures or provides the drug for the purpose of ClinicalTrials.gov registration.*

H.) IV.C.1, §11.40, §11.42 (FR 69632): **Submission of Clinical Trial Results Information** by the Responsible Party as identified in § 11.42 must be submitted for the applicable clinical trial.

Emory University requests guidance regarding requirements and the designation of the Responsible Party for situations in which the IND or IDE holder, as the Responsible Party, transfers to another academic institution, while the original academic institution continues to conduct the clinical trial under the IND. ***Recommendation:*** *Emory suggests that the Responsible Party, as the IND or IDE holder and the designated Principal*

Investigator, be held accountable for utmost compliance of the study record, even upon departure from the academic institution in which the clinical trial may have been conducted. In such circumstances, Emory requests guidance or a formal mechanism for changing the Sponsor from the initially designated academic institution or removing the Sponsor if the Responsible Party has left the institution.

I.) IV.C.4, §11.48(3)(v) (FR 69638): **Statistical Analyses.** Results of scientifically appropriate statistical analyses will be required for (A) pre-specified in the protocol and/or statistical analysis plan that was performed on the outcome measure data (B) made public by the Sponsor or Responsible Party prior to the date on which results information is submitted for all primary and secondary outcome measures in the clinical trial, or (C) conducted in response to a request made by the U.S. Food and Drug Administration prior to the date on which complete clinical trial results information is submitted for all of the primary outcome measures studied in the clinical trial.

As the NPRM states that reporting of summary results would be required as stated above, it is unclear as to whether this will entail the reporting of all statistical analyses done for a clinical trial. If all statistical analyses that are completed are required to be reported, this would be excessively burdensome to the Responsible Party, without an added benefit to the lay public or in the interest of data sharing. Further, NPRM (69608) states that secondary outcome measures are considered "to be those outcome measures (other than primary outcome measures) that are not considered exploratory and for which there is a specific analysis plan". Based on the information in IV.C.4, §11.48(3)(v) (FR 69638) for Statistical Analyses, results summary reporting would be required for secondary outcome measures if they are pre-specified in the protocol. The NPRM further states the view that "outcome measures that are not part of an analysis plan or are indicated to be exploratory as tertiary or lower level outcome measures that do not need to be submitted to ClinicalTrials.gov, but for which information may be submitted voluntarily". The language regarding the secondary outcome measures and the statistical analyses results reporting requirements is vague and open-ended. Exploratory outcome measures and a planned statistical analysis may be outlined in a protocol; however, it is unclear if an exploratory or lower level outcome measure would require results with the current verbiage. ***Recommendation:*** *Emory requests limitations to primary outcome measures for statistical analyses required for results summary reporting. Clarification regarding the proposed requirements for results reporting for all levels of outcome measures is further requested.*

J.) IV.C. §11.48(4)(i) (FR 69638): **Adverse Event Information.** Information for completing two tables summarizing adverse events collected during an applicable clinical trial.

Per the updated requirements for adverse event reporting within the scope of the NPRM, the assessment type (systematic versus non-systematic) will be required.
Recommendation: *Emory requests clarification on the classification of routine investigator assessment of adverse events (when an investigator asks if the subject has had an adverse event) as a Systematic Assessment. Emory further suggests that the Protocol Registration System embed a mechanism to generate an Adverse Event summary table formatted to the required specifications to capture data for direct upload into ClinicalTrials.gov at the time of required reporting.*

K.) IV.D. §11.64 (FR 69679): **Updates to Clinical Trial Information Submitted to ClinicalTrials.gov.** Updates for data fields requiring changes within 15 to 30 calendar days.

While Emory University understands the need for updated information and ensuring the accuracy of the study information within ClinicalTrials.gov in a timely manner, the requirements outlined by the NPRM for updates, specifically 15 calendar days for updates to the U.S. FDA Approval, Licensure, or Clearance Status data element (§ 11.64(3)(b)), these constraints for turnaround will be very challenging for investigators acting as Responsible Parties at academic institutions. Because some of the data elements requiring these updates may not be disseminated in a centralized fashion (e.g., (§ 11.64(2)) U.S. FDA Approval, (§11.64(3)(b)(1)(iii)) Intervention name change and establishment of non-proprietary name), it is of significant concern to Emory that it would be extremely difficult to ensure compliance within the 30-day window proposed in the NPRM.
Recommendation: *As mentioned previously, Emory respectfully requests timeframes that updates required be consistent with those currently mandated by the FDA and OHRP for continuing review of active clinical trials within ClinicalTrials.gov; updates would be at least annually or more frequently, depending upon IRB continuing review requirements dictated for the study. For active and enrolling clinical trials, it is suggested that updates be required 180 days from the time a change occurs similar to current FDAAA Section 801 update requirements.*

L.) **Additional Comments and Limitations of ClinicalTrials.gov Website and Protocol Registration System Communication.**

The structure of the ClinicalTrials.gov database and the tiered mechanism for entry of data elements (in categories and sub-categories) is currently difficult to navigate for Responsible Parties conducting independent research at academic medical centers. The lack of intuitiveness of the design of the website and the complicated manner in which it is organized is also a concern in regards to compliance. Furthermore, study records undergoing the Quality Assurance Review process are still included in the list of Problems

and this can lead to confusion. The status of a clinical trial (e.g., Completed) in the system is also difficult to readily decipher and greater visibility of the status of a study record within the Administrator's view of the website would assist with compliance. ***Recommendation:*** *Emory University suggests that study records pending Quality Assurance Review be temporarily removed from the list of Problems into a separate designation within ClinicalTrials.gov, as this can be confusing to users. Moreover, additional mechanisms to decipher clinical trial status and greater visibility within the website regarding the status of a clinical trial in the system are recommended.*

Additionally, automated email communication from the Protocol Registration System requesting updates to study records is often not helpful in managing update requests since communication is not sent to the Administrator account for the institution; the manner in which requests are sent often depends on the user account utilized to last update the study record as well. The inconsistency of the Protocol Registration System for relaying communication and reminders is of concern and potentially hinders compliance if a Responsible Party or other account holder is not available or an email address is no longer valid. ***Recommendation:*** *Emory requests an improved and discernible method for Protocol Registration System communication to institutional user accounts for reminders and study record notices.*

At present, the Protocol Registration System Administrator at a Sponsoring institution is very limited in the information that can be obtained from the database. This impedes the ability of a Sponsoring institution to track study records and facilitate requests to Responsible Parties to ensure the information is accurate and verified. ***Recommendation:*** *Emory requests a method to sort, filter, and generate usable reports utilizing an extended set of data element fields from ClinicalTrials.gov for institutional management of study records and requests for updates.*

Conclusion and Recommendations

In summary, the revisions recommended by the NPRM are unnecessarily overbroad in requiring changes that significantly impact investigator-initiated research at academic institutions such as Emory University. This comes without full recognition of the time and effort required on an ongoing basis to ensure compliance under these unfunded mandates. As outlined above, many of these changes and the requested timelines stipulated are overly stringent and may serve as deterrents for investigator-initiated clinical trials in settings other than large pharmaceutical companies. The shortcomings of these proposals adversely impact important scientific research activities and discourage investigator-initiated research being conducted at academic institutions. This occurs without significantly advancing public knowledge.

Emory respectfully suggests that, if the NPRM is adopted, the expansion of scope and the time and effort of investigators be considered as addressed above. Furthermore, a phased approach to implementation, with regards to the effective and compliance dates of the NPRM and then the

subsequent NIH policy, would assist with facilitating adaptation of processes at academic medical centers with the proposed regulations.

While Emory endorses and supports the increase in data sharing and transparency, and while publication bias is of great concern, some consideration should be given to the onerous regulations proposed and its effects on physician investigators conducting clinical trials. It remains Emory's concern that the expanding scope of ClinicalTrials.gov under the proposed NIH policy and the proposed regulatory changes outlined in the NPRM as a compliance requirement may impede clinical trials and serve as a detriment to independent research at academic medical centers.

Emory University appreciates the opportunity to provide comments on the NPRM and appreciates consideration of this submission.

Sincerely,

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