August 5, 2013

Via electronic submission
http://www.regulations.gov

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: *Comments to Docket No. FDA–2013–N–0271: Availability of Masked and De-identified Non-Summary Safety and Efficacy Data;*

Dear Sir or Madam:

Harvard University's *Multi-Regional Clinical Trials Center* (MRCT) respectfully submits the following comments on FDA's proposal, 78 Fed. Reg. 33421 (June 4, 2013), to make de-identified and masked clinical and preclinical data, from marketing applications submitted to FDA, available to external experts and others, as part of the Agency's transparency initiative. FDA proposes to make pooled data available to the public that have been sufficiently de-identified and masked (as to the drugs involved in the trial) in order to protect confidential commercial information, for analysis by the broader community. [1]

MRCT, a public-private partnership, convenes working groups to study ways to facilitate greater access to subject-level clinical trials data. One recent MRCT working group has explored models for sharing access to patient level data, ultimately presenting these models for feedback to a large multi-stakeholder group including experts from academia, industry, government and patient groups at MRCT's May 2013 Conference in Cambridge, MA.[2] The conference materials, including slides and a summary of the discussions from the conference are available on our website, http://mrct.globalhealth.harvard.edu.

[1] We note that confidential commercial information is not restricted to pharmaceutical or device company-sponsored information, but can include information provided by academic and not-for-profit entities.

[2] The models reviewed in May included mechanisms by which (1) queries of patient-level data from a trial could be submitted to a third-party data holder for analysis, (2) patient-level data could be obtained directly from the trial sponsor, (3) patient-level data could be obtained through submission of a request to a learned intermediary (independent of the trial sponsor) which would review and approve individual requests, and (4) researchers would have direct access to patient-level clinical trial data sets which would be publicly available. As described in the conference minutes, the vast majority of the participants favored the use of an independent, learned intermediary to ensure access by qualified researchers.

An MRCT work group is currently developing a practical and workable framework for research subject-level data sharing. The goal is to allow researchers to reproduce scientific findings while continuing to protect research participant privacy and maintain commercial incentives for medical innovation. MRCT would be happy to share the results of that work with the Agency when completed. [3]

As a general principle, MRCT endorses enhanced data sharing in support of improved development paradigms and acceleration of strategies for precision medicine. We believe that facilitating greater access to trial data for secondary research has the potential to enhance development of drugs, biologics and medical devices. Further, access to data from discontinued programs, including early, exploratory trials, could inform future research and potentially reduce the risk to subjects in new clinical trials. Access to all clinical trial data should balance the need to maintain confidentiality of commercially-sensitive information (e.g., exploratory biomarker studies) and to assure privacy of research participants' personal information, against the benefits of using those data to inform science, including the planning of new studies.

A promising approach to achieve these goals involves the use of an intermediate party or entity, independent of the data generator, to assess and make determinations on data access requests from third party researchers. The independent party could help to ensure that the data would be provided only under controlled conditions that protect research subject privacy and confidentiality, take account of commercial sensitivity of data, and help ensure that the data would only be used in accordance with a sound scientific plan. Such an independent party could also be used to review initial decisions of data generators, when they have declined to provide data requesters with access to data. A "learned intermediary" approach could bolster public confidence in the objectivity of decisions about access to patient-level data for secondary research.

The Agency's proposed approach to sharing of clinical trials data varies significantly, however, from other approaches now being considered, not only by MRCT, but also by, for example, the EMA. Unlike proposals for the sharing of research participant-level data, the Agency proposal would seek to "mask" the identity of the product(s) tested. The challenges of pooling confidential, participant-level data for use by researchers external to the Agency, as currently proposed by the Agency, are substantial. "Masking" the data will entail significant effort, while at the same time, decreasing the utility of data by the very process of masking it. Releasing pooled data publicly may also have significant unintended consequences, despite best efforts by the Agency to mask and de-identify the data — not the least of which is the likelihood that the data

[3] The Agency should also note the work of the CEO's Roundtable on Cancer, which has developed a promising framework for pooling data across cancer trials, with plans to provide third-party access to data from comparator arms from up to 60 datasets by the end of 2013. See http://ceo-lsc.org/projectdatasphere (accessed July 28, 2013), as well as the GSK approach to providing access to patient-level data; NEJM, 369;5: 475-478 August 1, 2013.

will be increasingly susceptible to re-identification and to 'un-masking'. The consequences of even rare, but widely publicized, instances of study participant re-identification may result in decreased study enrollment for fear of potential loss of anonymity. Further, the sole use of pooled or aggregated data will not allow for validation of results, a process necessary and inherent to furthering scientific discovery.

Leaving these complications aside, MRCT appreciates the Agency's stated effort to obscure private, identifiable information prior to making the data accessible more widely. From a practical perspective, this respects HIPAA de-identification standards but also is far more complex, especially as data sets may be combined with and triangulated against other publicly available data. The more that data are obscured, such as would be necessary if data were shared publicly, the greater the compromise as to their utility. Yet pooling of genomic information, for instance, to identify genetic markers of subpopulations of 'responders' and 'non-responders', would actually be quite useful for scientific discovery. Thus, a 'controlled access' model may provide the balance needed such that highly useful data can be shared while participant privacy can simultaneously be adequately protected. In developing solutions, consideration must be given to the resources required to create and operate any system; efficiency must be assured, and burdens on data generators minimized, to the greatest extent possible.

MRCT supports a model that incorporates the principles described above relating to an intermediate entity and a 'controlled access' model. A potential addition for consideration could include a system under which data generators could directly provide clinical trials data to researchers, with referral or appeal to an intermediate entity only in instances in which the data generator had determined to deny access. This 'learned intermediary' model, with access carefully controlled, substantially embodies core principles of data sharing considered and endorsed by MRCT. These principles, in brief, include:

- The need for adequate protection for the privacy of research participants.
- Provision of sufficient data (and access to those data) to achieve the broader objective and benefits for scientific innovation and public health.
- Assurance as to accountability on both data generators and data requesters for responsible use of data and analyses.

- Equal treatment of all sponsors of data, including industry, academia and government.
- Minimizing the cost and burden to data generators and requestors, including adopting standards for data sharing that are uniform across national jurisdictions.

The integrity of any process to be used to share and disseminate data is of paramount importance. The Agency may further its objectives by helping to build confidence in a data sharing framework that incorporates the key principles described above and involves an independent and trusted intermediate entity to assess the adequacy of the requests, and monitor and enforce adherence to the principles. This approach would empower an intermediate entity with appropriate expertise to review and approve requests submitted by external researchers. Among the standards applied would be the need to confirm that the research proposal is bona fide, and includes robust scientific and statistical analysis. An independent intermediate entity could provide the valuable service of monitoring and enforcing conditions of use for data provided. A standardized data sharing agreement could help ensure that the data recipient is transparent as to the analysis that it will undertake, its publication plans, collaborators with whom the data would be shared, and a pledge not to attempt to re-identify any of the research participants whose date have been provided.

This approach appears to balance the public health purposes of secondary research with protection of the privacy interests of study participants – interests that may differ depending on the disease being studied. Indeed, in the case of research involving participants with genetic diseases, or chronic, debilitating diseases or those having potential social stigmas attached (e.g. Huntington's disease, amyotrophic lateral sclerosis, HIV, mental illness), the potential for uncontrolled access to pooled trial data (even if masked and de-identified) may be concerning to participants, particularly if data are made widely available. Using a competent and accountable independent intermediary entity, with appropriate safeguards, to review requests for secondary research would help address these varying concerns and may also provide reassurance to data owners/generators, and the public, as to how responsible use would be ensured.

In summary, MRCT Center strongly supports the Agency's interests and objectives in increasing the sharing of participant-level clinical trials data to further regulatory science and to benefit more patients, more rapidly. Models now being developed in conjunction with data generators (academic, industry and government) for sharing data with external researchers will assure transparency, promote public health and trust, increase efficiency of drug development, and build experience and confidence. Ideally, any Agency action would recognize and respect these collaborations currently underway involving not just industry but multi-stakeholder groups, all of which are seeking, with their different approaches, to achieve greater clinical trials data transparency. At this time, based upon our deliberations to date and as set forth above, MRCT favors a model that incorporates the key principles described above; respects voluntary efforts of data generators to promote data access; incorporates the use of an independent intermediate party to assess data requests (or hear appeals of denials of access); and also uses that independent intermediary party to monitor and enforce conditions of data use agreements, including proposed research plans.

MRCT thanks the Agency for the opportunity to comment on this proposal, and stands ready to work the Agency on these important issues.

Sincerely,

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