SACHRP comment regarding the June 4, 2013 FDA Request for Comment relating to the availability of masked and de-identified non-summary safety and efficacy data

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SACHRP has followed closely the development of various clinical trials data sharing and data transparency initiatives, including those of the European Medicines Agency (EMA), Roche and GSK, the British Medical Journal (BMJ), and now the proposal of the FDA. SACHRP fully supports the spirit and intent regarding these and other efforts to facilitate analysis of aggregated data, which promises to improve information relating to diagnostic and treatment measures. In SACHRP's view, the FDA proposal is quite different, and more well considered, than measures discussed by the EMA and required by BMJ for studies whose results are submitted to that journal for possible publication. This narrower scope proposed by the FDA – specifically, the limitation of data sharing to information that does not involve an identified or identifiable product, which the FDA proposal terms "masked" data – is entirely salutary in regard to subject privacy and welfare, as excluding the product identity lessens risk to subjects of their re-identification from data derived from clinical trials in which they participated.

The instances of beneficial use of aggregated clinical trials data reported in the FDA Request for Comments, as well as common sense, suggest that knowledge valuable to science and to industry may be gained through careful aggregation of clinical trials and post-marketing data. This is a decided good, which SACHRP enthusiastically supports, as long as the effort is tempered by appropriate safeguards, given the various interests involved, including those of research subjects.

SACHRP observes that the more restricted the data released, the less valuable those data likely would be to serious researchers, and inversely, the more inclusive the data set released, the more useful those data will be to those seeking to discern disease and treatment indicators. FDA should therefore foresee that once the door has been opened to the availability of these data, demands likely will inexorably increase and become more aggressive in regard to the number and detail of data fields sought. This is neither good nor bad in effect, but should be foreseen as FDA plans implementation of any more robust data sharing initiative.

Based upon its charge relating to the protection of human subjects in research, SACHRP is particularly mindful of the possible effects of clinical trials data sharing proposals, including that of the FDA, on this population. With the increasing availability of public databases of all kinds, and future and unpredictable development of yet more public databases, it is not certain that any subject-level or patient-level data, even if de-identified by today's most rigorous standards, will remain de-identified in the future. In trials with small enrollments and/or of products to treat rare diseases, it is more likely that subjects could be re-identified. Similarly, data "masked" to hide product identity may be deciphered, in increasingly sophisticated ways. For example, if there has been only one product or a few products for which approval was sought for a medical condition and a request is made for data related to that condition, then any data released will be presumed to be – and likely will be – related to some identifiable product(s). In responding to

data requests, the FDA or its designee therefore should consider, among other factors, the likely identifiability of subjects and of products.

In designing a system by which the FDA may respond to external requests for "masked" and de-identified data, or under which the FDA may choose, on its own accord, to offer such data sets to researchers, it will be essential that standards for access and oversight of access be robust. The FDA could choose to perform these tasks directly, or it could work through an external entity contracted to the FDA to act as a neutral and independent arbiter of external data requests and as a distributor of data that the FDA itself wishes to make available to researchers. Regardless of whether the FDA performs this function directly, or through a "learned intermediary" contractor, some office or entity must be able to perform screening, management, oversight and enforcement functions, the purpose of which will be to protect the privacy of research subjects and to safeguard private commercial interests in product development, while at the same time maximizing the scientific opportunities made possible by data aggregation.

SACHRP recommends, as a primary method of protecting research subjects, as well as patients in post-marketing studies, that FDA screen and monitor with a high degree of care those who are requesting these data from the FDA. Only responsible researchers with some defined and meritorious research plan should be allowed access, and only under conditions that would protect subject and product identities. For example, under SACHRP's recommended approach, data recipients should be compelled, as a precondition for the receipt of data, to enter into data use agreements with FDA (or with an external party contracted to FDA for this purpose) under which the recipient would pledge only to use the data for the purposes specified; not to disclose the data to others (except insofar as needed to assure research integrity and except under specific publication conditions); and not to try at any point to re-identify subjects. The data users should be subject to monitoring and auditing of their use of shared data, to assure compliance with data conditions.

Without active oversight to identify any attempted re-identification, and without meaningful penalties for violation of the pledge not to re-identify subjects, access to individual subject-level data risks violation of a fundamental ethical principle, and the attendant risks would have a chilling effect on willingness of subjects to enroll in studies and thus on clinical research itself. Further protection to subjects therefore must be offered through a system of civil and criminal penalties, including those applicable to corporate and not-for-profit entities, that would attach to researchers' efforts to re-identify subjects, or otherwise to violate terms and conditions of data sharing.

Indeed, the multiplicity of tasks required by such a system would suggest that a "learned intermediary" is the best currently recognized alternative to screen applications for research data; assure authenticity of requests and requestors; oversee the drafting and execution of data use agreements; assure that before release, data have been de-identified as to subjects and as to identity of product; and monitor data use to assure compliance with conditions of use of those data. Such a body should be generally charged with weighing subject privacy and any industry/academia proprietary interests against the benefit of making specific aggregate data sets available to secondary researchers. A set of case precedents would soon be amassed through formal responses to specific data requests.

Although the FDA is now proposing only that "masked" and de-identified data be made available, SACHRP is mindful that the vast majority of subjects now and previously enrolled in clinical trials has no particular awareness that their individual-level data, though de-identified, might be released by, or under the jurisdiction of, a government agency to private parties for secondary research. Subjects are also generally unaware of the risk, which will likely grow over time, that even their de-identified data may allow them to be re-identified. Therefore, to preserve values related to subject autonomy, SACHRP recommends that the FDA consider the value of inserting into clinical trial informed consent documents some acknowledgement of these data practices and their possible effects. An "opt-out," by which subjects might decline to have their de-identified data so used, appears not feasible, but notification of the practice would seem indicated.

SACHRP also recommends that FDA clarify that the access and use of "masked" and de-identified data for these research purposes do not constitute a clinical investigation and do not require IRB review and oversight. FDA may also wish to obtain confirmation from OHRP that such use is not human subjects research under 45 CFR 46, so that this issue could be clarified as well.

Although, as described above, aggregation of data for meta-analysis offers great prospect for new discoveries, release of data, commensurate with detail of data released, could lead to robust debate about, criticism of, or support for FDA determinations about specific products or groups of products. This in turn could lead to potentially far-reaching changes in the functioning of the agency itself, even though this potential will be mitigated to the extent that data released have been effectively de-identified as to subjects and products.

SACHRP would urge FDA to be mindful of the regulatory proposals that continue to emerge from the EMA. Under the current EMA proposal, clinical trials performed in the U.S., if used to support applications to the EMA, would be subject to all EMA requirements for data sharing, including subject-level data. Therefore, subjects in U.S. clinical trial sites, as well as researchers at those sites and industry sponsors, will be affected directly by the EMA's final regulations in this area. To avoid compromise to the interests of subjects and the clinical trials enterprise here in the U.S., it would seem essential that FDA consult in detail with the EMA during the EMA's current rule-making process, and impress upon EMA the subject privacy and industry proprietary interests that FDA has noted in introducing its own proposal.

In summary, when considering implementation of data sharing, even in the restricted form described by the FDA, the FDA should consider carefully the mechanisms through which requests and requestors are screened, data are "scrubbed," and appropriate conditions on use are imposed, overseen, monitored, and enforced. SACHRP therefore recommends the following:

- FDA should proceed with its plans to share aggregated data more robustly, to fulfill the scientific promise of data amassed in clinical trials, which SACHRP recognizes and fully supports.

- A “learned intermediary” or similar entity should be charged with responsibility and authority to screen data requests and data requesters, using criteria that include meritorious research design and expertise to undertake the proposed research.
- That intermediary entity should weigh the privacy interests of subjects and any recognized commercial interests against the scientific value of the proposed research, and should make determinations and impose conditions in order, optimally, to allow research to proceed while protecting other interests.
- The process of careful, case-by-case determinations of data requests and of data sets that FDA may proactively wish to offer can and should calibrate conditions of use to the recognized interests of all parties to the clinical trials enterprise – especially, in SACHRP’s view, those of subjects.
- FDA’s “de-identified” data approach should be pursued, and “masking” should be explored for circumstances in which additional protection for the privacy of human subjects is warranted.
- Data use agreements with standardized terms (such as pledges not to re-identify subjects and not to hand data over to other users) should be imposed on data recipients/users, with additional terms inserted at the direction of the intermediary entity, as needed to protect subject and sponsor interests.
- The intermediary entity should be empowered to monitor, audit and enforce the terms and conditions of access granted to data. Having criminal and civil penalties available and used appropriately would bolster public, subject and industry confidence in the data sharing process.
- Subjects should be informed as to the downstream research uses of their de-identified or anonymized data and risks of re-identification, and should be told that those data may be used and shared according to FDA and other programs, such as that of the EMA.
- FDA should engage in close consultation with EMA, whose data sharing proposal would directly affect subjects in U.S.-based trials, and in that dialogue should seek to protect the interests of those subjects.

We thank you for your attention to these comments. SACHRP would be happy to assist FDA in this matter, to the extent FDA may request.