

FDA REQUEST FOR COMMENTS: CLINICAL TRIALS DATA SHARING

SACHRP – JULY 10, 2013



BACKGROUND: FROM REGISTRIES TO RESULTS REPORTING

- Late 1990s:
 - Food & Drug Modernization Act of 1997 establishes ClinicalTrials.gov, which went live in February 2000
 - Required registration of clinical trials for drugs treating “serious or life-threatening conditions”
 - Registration was voluntary for other trials

BACKGROUND: FROM REGISTRIES TO RESULTS REPORTING

- 2004: The World Health Organization (WHO) creates the International Clinical Trials Registry Platform (ICTRP)
 - “The registration of all interventional trials is a scientific, ethical and moral responsibility.” *WHO Statement on Clinical Trial Registries*
- 2005: International Committee of Medical Journal Editors (ICMJE) requires clinical trials registration as a condition of publication

BACKGROUND: FROM REGISTRIES TO RESULTS REPORTING

- 2007: Food and Drug Administration Amendments Act (FDAAA)
 - Mandates registration on ClinicalTrials.gov of most interventional trials of drugs, devices and biologics under FDA jurisdiction, excluding Phase I drug trials
 - Requires summary results reporting from trials “that form the primary basis of an efficacy claim” or are conducted after the drug or device is approved or cleared
 - Must certify compliance with FDAAA when filing certain submissions with FDA

BACKGROUND: FROM REGISTRIES TO RESULTS REPORTING

- 2012: *BMJ* policy
 - *BMJ* announces that starting January 2013, it will only publish drug or device trials for which authors disclose anonymized, participant-level data upon “reasonable request”
- 2012-2013: Industry initiatives
 - GlaxoSmithKline (GSK) announces that it will make anonymized participant-level data available to researchers through an application process
 - Roche announces a similar policy

EMA POLICY DEVELOPMENT

- 2004: EMA establishes its own clinical trials database, eudraCT, to enable data sharing between member states
- 2010: EMA begins releasing clinical study reports on request as part of its access-to-documents policy
- 2011: EMA launches clinicaltrialsregister.eu, making clinical trials information publicly available and searchable
- November 2012: EMA announces that as of January 2014, it will require that participant-level clinical trials data used to support the authorization of a medicine be made publicly available

EMA POLICY DEVELOPMENT

- EMA has outlined general goals
 - “We are committed to proactive publication of clinical trial data, once a marketing authorisation decision has been taken. We will deliver this project in dialogue with our stakeholders.” *Introductory Presentation - November 2012*
EMA Workshop on Access to Clinical Trial Data
 - “We are not here to decide *if* we will publish clinical-trial data, only *how*. We need to do this in order to rebuild trust and confidence in the whole system.” Guido Rasi, EMA Executive Director

EMA POLICY DEVELOPMENT

- EMA rationales for data sharing
 - Decrease possibility of selective reporting
 - Allow for study replication
 - Give clinical trials participants greater confidence that their contribution will be used to further medical knowledge
 - Increase efficiency of research by allowing secondary analyses of data sets
 - Provide patients and their advocates a greater ability to analyze relevant data

MAJOR CONCERNS WITH EMA PROPOSALS

- De-identification is false promise, esp. for small studies, pediatric studies, studies of rare conditions
- Informed consent objections
- Commercial interest objections
- Loss of “learned intermediary” status of a regulatory agency

EMA POLICY DEVELOPMENT

- Timeline
 - January-April 2013 – Advisory groups meet
 - June 24, 2013 – Draft policy released
 - July 1-September 30, 2013– Comment period
 - November 2013 – Final policy published
 - January 2014 – Policy takes effect

PROCESS OF DATA RELEASE IN DRAFT EMA POLICY - JUNE 24, 2013

- How are data released?
 - Some data are “open access” and will be downloadable from the EMA website, whereas others are subject to a “controlled access” policy
 - Method of access depends on type of data
 - EMA policy places data into three categories:
 - Category 1: Data containing commercial confidential information (CCI)
 - Category 2: Data without protection of personal data (PPD) concerns
 - Category 3: Data with PPD concerns; essentially “raw CT data”

PROCESS OF DATA RELEASE IN DRAFT EMA POLICY – JUNE 24, 2013

- Category 1 – Data Containing CCI
 - Documents containing CCI will not be made available (may be available under the Policy on Access to Documents)
 - Draft policy affords EMA a great deal of flexibility in determining whether a document contains CCI
 - EMA position is that only a “small number of CT data/documents” contain CCI
 - Examples of CCI include details of the investigational medicinal product itself, some in vitro studies, and bioanalytical data characterizing the product
 - Such information “will only be deemed CCI in duly justified cases”

PROCESS OF DATA RELEASE IN DRAFT EMA POLICY – JUNE 24, 2013

- Category 2 – Data Without Protection of Personal Data (PPD) Concerns
 - Classified as “open access” data
 - Data will be available as downloads from the EMA website
 - “Personal data” are defined as “any information relating to an identified or identifiable natural person”

PROCESS OF DATA RELEASE IN DRAFT EMA POLICY – JUNE 24, 2013

- Category 2 Data – Subcategories
 - Documents that lack personal data (e.g., summary tables presenting only aggregate data)
 - Documents in which any personal data have been “adequately de-identified”
 - Instances in which public health needs override considerations of PPD
 - This subcategory is used to justify open access to personal data of CT personnel, including investigators and others who carry out observations or analysis of primary or other efficacy variables (e.g., a nurse or biostatistician)

PROCESS OF DATA RELEASE IN DRAFT EMA POLICY – JUNE 24, 2013

- Category 3 – Data with PPD Concerns
 - Such data are available only through a “controlled access” policy
 - Includes documents containing “raw CT data,” defined as individual patient data sets, individual patient line-listings, individual Case Report Forms, and documentation explaining the structure and content of data sets
 - Appendices to CSRs will often fall into this category (e.g., lists of discontinued patients, protocol deviations, and demographic data)

PROCESS OF DATA RELEASE IN DRAFT EMA POLICY – JUNE 24, 2013

- Category 3 Data – Data Protections
 - Two “complementing” levels of protection are employed to prevent re-identification of participants
 - Data must undergo “appropriate de-identification”
 - EMA does not explain how the level of de-identification required here differs from the level of de-identification that can qualify data as Category 2 data
 - Controlled access

PROCESS OF DATA RELEASE IN DRAFT EMA POLICY – JUNE 24, 2013

- Category 3 Data - Controlled Access Requirements
 - Requesters must identify themselves; EMA will verify their identity
 - Requesters must be “established” in the EU
 - Requesters must enter a legally binding data sharing agreement
 - Requesters have the “opportunity” to upload a statistical analysis plan
 - EMA will not take into account a requester’s failure to upload an analysis plan when evaluating a request for data

PROCESS OF DATA RELEASE IN DRAFT EMA POLICY – JUNE 24, 2013

- Category 3 Data – Data-Sharing Agreement Requirements
 - Data requesters must:
 - Access data for the sole purpose of addressing a question or conducting analyses in the interest of public health
 - Refrain from any attempt to retroactively identify participants
 - Refrain from using data for *any purposes* outside the boundaries of the patients' informed consent
 - Refrain from using data to gain a marketing authorization in a non-EU jurisdiction

PROCESS OF DATA RELEASE IN DRAFT EMA POLICY – JUNE 24, 2013

- (Continuation of previous slide)
 - Refrain from sharing in any way or format data with anyone else
 - Have already obtained ethics-committee approval
 - Be aware of standards for good analysis practice
 - Agree to the EMA publishing requesters' identities, aims of accessing the data, and statistical analysis-plan status
 - Make all results of their analyses public within a reasonable period of time (usually one year after accessing the data)
 - Destroy all accessed data once analysis is complete

PROCESS OF DATA RELEASE IN DRAFT EMA POLICY – JUNE 24, 2013

- Category 3 – EMA Data Request Review Process
 - When evaluating requests for Category 3 data, EMA will not judge the requester's professional competence to conduct analyses or the quality of the requester's statistical analysis plan, if one has been provided
 - ***Category 3 data will not be made available until January 1, 2015, due to need to create data request processes; additional guidance expected by October 31, 2014***

PROCESS OF DATA RELEASE IN DRAFT EMA POLICY – JUNE 24, 2013

- Summary of data sharing by data type

	Examples	Release Mechanism
Category 1 - CCI	<ul style="list-style-type: none">• Details of investigational products• In vitro studies	<ul style="list-style-type: none">• None; these data are not released
Category 2 – Data without PPD concerns	<ul style="list-style-type: none">• Summary statistics• Aggregate data	<ul style="list-style-type: none">• Open access via EMA website
Category 3 – Data with PPD concerns	<ul style="list-style-type: none">• Lists of protocol deviations• Adverse event listings	<ul style="list-style-type: none">• De-identification• Controlled access

PRIVACY PROTECTION AND INFORMED CONSENT IN DRAFT EMA POLICY

- EMA definitions of de-identification
 - Policy has no guidance on what constitutes “adequate de-identification” rendering data Category 2 data
 - EMA includes a minimum de-identification standard from the following article:
 - Iain Hrynaszkiewicz et al., “Preparing Raw Clinical Data for Publication: Guidance for Journal Editors, Authors, and Peer Reviewers,” *BMJ* (2010)
 - Advocates removal of all “direct identifiers” (essentially the 18 HIPAA identifiers)
 - EMA notes that in some cases additional de-identification methods (e.g., statistical) may be needed

PRIVACY PROTECTION AND INFORMED CONSENT IN DRAFT EMA POLICY

- EMA references to informed consent are vague
 - Draft policy states generally that uses of released data for purposes other than advancing science or public health would “overstep” the boundaries of informed consent
 - Draft policy requires that requesters of Category 3 data address only questions that are in line with the “spirit” of informed consent; data requesters also may not perform analyses that are “outside the boundaries of patients’ informed consent”

PRIVACY PROTECTION AND INFORMED CONSENT IN DRAFT EMA POLICY

- Unclear what will be deemed outside boundaries of informed consent
 - Will all uses related to public health be deemed to fall within informed consent boundaries?
 - What if the clinical trial consent form did not contemplate secondary uses, or specifically forbade them?

SCOPE OF FDA REQUEST FOR COMMENTS

- FDA issued a request for comments on June 4, 2013 (78 FR 33421) regarding a proposal to make available for research de-identified and masked data from medical product applications
 - FDA recognizes a “potential to further advance regulatory science” by allowing non-FDA experts to analyze data submitted to FDA
 - CCI and trade secret information will be excluded from any data release
 - Comments due August 5, 2013

SCOPE OF FDA REQUEST FOR COMMENTS

- Data under consideration will be both masked and de-identified
 - “Masked data” = data with information removed that could link it to a specific product or application
 - “De-identified data” = data that does not identify an individual nor provide reasonable basis to believe that individual could be identified

SCOPE OF FDA REQUEST FOR COMMENTS

- FDA seeks comments on five questions
 - What factors should be considered in “masking” study data?
 - What limitations should be placed on FDA’s ability to make available “masked” data?
 - Are there any additional factors FDA should consider in de-identifying information beyond direct identifiers?
 - Would regulatory changes facilitate implementation of this proposal?
 - In which situations would disclosing “masked” data be most useful to the advancement of public health?

COMPARISON OF DRAFT EMA POLICY AND FDA REQUEST FOR COMMENTS

- EMA proposal is more advanced in the development process
- EMA proposal is broader because it links data to a given product application and proposes to make some data available via open access on the web
- FDA process better protects participant privacy by “masking” and de-identifying data; without knowledge of the trials at issue, it will be harder to re-identify participants

COMPARISON OF DRAFT EMA POLICY AND FDA REQUEST FOR COMMENTS

- FDA process is more protective of commercial interests; both EMA and FDA claim to limit access to CCI, but FDA also discusses trade secret information and does not start from the premise that CCI is extremely limited
- Details of FDA “masking” process must be worked out; how will researchers know which data are useful without knowledge of the product for which they were generated?
- Unclear if FDA will be able to resist calls for greater data release once the door to partial release has been opened

SACHRP DRAFT LETTER TO FDA

- ...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 trials with small enrollments or of products to treat rare diseases, subjects could be re-identified.

SACHRP DRAFT LETTER TO FDA

- 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.

SACHRP DRAFT LETTER TO FDA

- FDA or “learned intermediary” must screen requests
- Authenticity of requester
- Defined research plan
- Data use agreement
- No re-identification
- No handing on of data to other parties
- Transparency about research and results

SACHRP DRAFT LETTER TO FDA

- Perform data de-identification and “masking”
- Weigh privacy and commercial concerns vs. usefulness of data for additional research
- Institute penalties for non-compliance with data use agreement provisions
- Notification to research subjects of these future uses

SACHRP DRAFT LETTER TO FDA

- FDA should follow closely the EMA process and consult with EMA
- U.S. clinical site subjects' records will be used in EMA data releases
- This is not presently recognized by most U.S. research sites and IRBs