International Clinical Trials Data Sharing: Principles and Mandates

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Agenda

- Preliminary Thoughts
- Background
- European Medicines Agency (EMA) Policy Development
- Current Industry Initiatives

Preliminary Thoughts

- The Promise of Clinical Trials Data Sharing
  - Acts as a check on failure to report adverse effects of a drug or device
  - Acts as a check on positive conclusions regarding effectiveness
  - May lead to discoveries from new analyses of existing raw data
  - Allows for the combining of data sets from multiple sources to facilitate better science

Preliminary Thoughts

- The Risks of Clinical Trials Data Sharing
  - Re-identification of research subjects
  - Consistency with original informed consent
  - Proliferation of low-quality studies that would not advance scientific knowledge, or worse, may spread misinformation
  - Potential of competitive harm to sponsors whose data have been made public
  - Possible effects on regulatory agency behavior and regulatory climate

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Background

- Clinical trials data sharing movement has its roots in clinical trials registration requirements
  - Food & Drug Modernization Act of 1997 established ClinicalTrials.gov, which went live in February 2000 and required registration of:
    - Trials of drugs treating “serious or life-threatening conditions”
    - Expanded use protocols
    - Group C cancer drug protocols
  - Registration was voluntary for other trials

Background

- 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

- 2007: Food and Drug Administration Amendments Act (FDAAA) § 801
  - Required registration on ClinicalTrials.gov of most drug and device clinical trials (excluding Phase I trials), including trials conducted outside the United States that are “on products with or seeking FDA approval”
  - Introduced a **summary results reporting** requirement for all registered clinical trials studying drugs, biologics, and devices that are “approved, licensed, or cleared by FDA”

Background

- FDAAA compliance challenges
  - Motivating investigators to report results to ClinicalTrials.gov has been difficult
    - 2012 *BMJ* article found that only 22% of completed clinical trials subject to mandatory reporting had delivered results to ClinicalTrials.gov within one year of study completion. *See* Andrew P. Prayle et al., *Compliance With Mandatory Reporting of Clinical Trial Results on ClinicalTrials.gov: Cross Sectional Study*, 344 BMJ (2012).
    - 2013 *Journal of Clinical Oncology* article found that only 9% of cancer trials had reported results to ClinicalTrials.gov within one year of study completion. *See* Thi-Anh-Hoa Nguyen et al., *Public Availability of Results of Trials Assessing Cancer Drugs in the United States*, 31 J. Clinical Oncology 2998 (2013).

Background

- 2012: *BMJ* policy
  - *BMJ* announces that as of January 2013, it will only publish drug or device trials for which authors disclose anonymized, participant-level data upon “reasonable request”

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EMA Policy Development

- EMA was historically opposed to sharing of clinical trials data and clinical study reports
- In 2007 a researcher requested access to clinical trials data held by EMA regarding anti-obesity drugs
- EMA denied access on the grounds that granting such access would harm the commercial interests of drug manufacturers
- The European Union Ombudsman reviewed the situation and ruled that the EMA should release data from the studies
- In late 2010, EMA began to release clinical study reports on request as part of its **access-to-documents policy**

EMA Policy Development

- Access-to-Documents Policy Litigation
  - AbbVie and Intermune sued EMA in early 2013 to prevent the release of clinical study reports held by EMA
  - AbbVie sought to “protect [its] confidential and commercially-sensitive information” by opposing disclosure that “does not meaningfully contribute to the scientific review or evaluation of our products”
  - Interestingly, the clinical study reports in the AbbVie case were not requested by an academic researcher, but rather were requested by a rival pharmaceutical manufacturer (UCB)
  - AbbVie withdrew its suit in April 2014 after EMA agreed to accept redacted documents from AbbVie and agreed to the company’s rationale for removing certain commercially confidential information from released clinical study reports
  - Intermune dropped its lawsuit in the summer of 2014

EMA Policy Development

- November 2012: EMA announced that it would institute a new policy requiring that **participant-level clinical trials data** used to support a marketing authorization of a medicine be made publicly available
- EMA made clear its commitment to **proactive release** of data
  - "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

- June 2013: EMA released a draft policy entitled “Publication and access to clinical-trial data” (Policy/0070)
  - Proposed **open access** to data contained in Clinical Study Reports that do not have any “protection of personal data (PPD)” concerns (*e.g.* summary tables presenting aggregate data)
  - Proposed **access upon request** to individual patient line-listings that have been “adequately de-identified”
- Over 1,000 comments submitted during summer/autumn of 2013

EMA Policy Development

- EMA issued mix signals on its policy during 2014, showing the tension between transparency and privacy
  - In May 2014 it was reported that those wishing to access data would have only “on-screen” access
  - In June 2014, EMA indicated that its final policy would permit the downloading and printing of released data

EMA Policy Development

- EMA released its final policy, entitled "Publication of Clinical Data for Medicinal Products for Human Use," on October 2, 2014
  - Makes "clinical reports" submitted in support of a marketing authorization publicly available once the decision on the marketing authorization has been finalized
  - Indicates that the release of "individual patient data" will be addressed in a future phase of the policy (though the expected timeline for the future phase has yet to be announced)

EMA Policy Development

- “Clinical reports” include the following ICH Common Technical Documents:
  - Clinical Overview (Module 2.5)
  - Clinical Summaries (Module 2.7)
  - Clinical Study Reports (Module 5), including only the following appendices:
    - 16.1.1 (protocol)
    - 16.1.2 (sample case report form)
    - 16.1.9 (documentation of statistical methods)

EMA Policy Development

- Clinical reports will be available through two methods of access
  - "View-on-screen-only" access available through a limited registration process
    - Persons seeking access must obtain a user name/ password, but do not need to provide identifying information
  - Downloadable access will be provided to users who identify themselves in the registration process
    - Identifying information includes name, date of birth, passport or ID card number, and professional affiliation

EMA Policy Development

- Both methods of accessing clinical reports require that the user agree to standard “terms of use,” which include the following:
  - Intended use is for general information purposes or non-commercial research purposes
  - No attempt may be made to re-identify the trial subjects or other individuals through use of the information
  - A watermark is applied to published information to emphasize that it may not be used for commercial purposes
  - EMA accepts no responsibility for user’s compliance with the terms of use

EMA Policy Development

- Final policy provides for redaction of commercially confidential information ("CCI")
  - The policy provides that information contained in clinical reports generally will not be considered CCI
  - An annex to the policy lists the sections of the clinical reports that may contain CCI (*e.g.*, product development rationale and overview of clinical pharmacology)
  - The company seeking redaction must provide a justification for why certain information is considered CCI before the EMA will permit redaction

EMA Policy Development

- EMA's policy regarding data seems contrary (at least in spirit) to the direction of EU privacy law
  - EU's Proposed General Data Protection Regulation ("GDPR") requires that consent for processing of "personal data" be "**specific, informed and explicit**"
  - EU guidance on the term "specific" suggests that it does not permit "**broad consent**" to future data sharing
  - The proposed GDPR also contains a "**right to erasure**" or "**right to be forgotten**"

EMA Policy Development

- The requirements for “specific consent” and of a “right-to-be forgotten” seem inconsistent with broad data sharing for secondary research purposes
- Anonymization of data may help to diminish, but will not completely eliminate, the tension between privacy and broad data sharing
- Future litigation will likely test the boundaries of these two policies

EMA Policy Development

- EMA's actions have global significance because data from a clinical trial conducted anywhere in the world may be used in support of a marketing application submitted to EMA, and thus such data may become subject to the policy
- Investigator-initiated research may also be subject to the EMA data sharing requirements, if results/data are used in support of an EMA marketing authorization

EMA Policy Development

- Also in Europe, the new European Union Clinical Trials Regulation enacted in 2014 has as one of its goals an increase in transparency
- The Regulation creates a database containing:
  - Information submitted as part of the clinical trials application process
  - Summary results of clinical trials
  - Clinical study reports for trials used to support a marketing authorization
- The regulation is expected to take effect in 2016

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Industry Initiatives

- Late 2012: GlaxoSmithKline (GSK)
  - Announced that it will make anonymized participant-level data available to researchers through an application process

Industry Initiatives

- GSK Initiative
  - Makes available to researchers:
    - Raw data set
    - Analysis-ready data
    - Protocols with any amendments
    - Annotated case report forms
    - Reporting and analysis plan
    - Data set specifications
    - Clinical-study reports
  - Data will be released through a controlled access process requiring:
    - Submission of a brief research proposal
    - Presence of a statistician on the research team

Industry Initiatives

- (GSK Continued)
  - Evaluation of research proposal
    - Panel of GSK-appointed experts will evaluate the analysis plan
    - Unlike the EMA proposal, the panel will evaluate the qualifications of the investigators and the relevance of the research proposal to patient care
    - Reasons for acceptance/rejection of research proposal will be shared with investigator
  - For more information on GSK initiative, *see* Perry Nisen & Frank Rockhold, *Access to Patient-Level Data from GlaxoSmithKline Clinical Trials*, 369 N. Eng. J. Med. 475 (2013)

Industry Initiatives

- Bayer, Boehringer Ingelheim, Lilly, Novartis, Roche, Sanofi,Takeda, UCB, Viiv Healthcare and Pfizer have announced policies similar to those of GSK
  - GSK and some of its competitors have together established a common portal website through which researchers can submit data requests
  - https://www.clinicalstudydatarequest.com/Default.aspx

Industry Initiatives

ClinicalStudy DataRequest.com

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Future of Data Sharing

- EMA has set forth a broad data sharing requirement, which is likely to expand when the next phase of its policy is announced
- Controversy will attend the types of data determined to be commercially confidential information
- Company-specific initiatives will likely proliferate
- Journal policies not yet defined
- Mechanisms of adjudication of requests must be defined, along with enforcement of sanctions
- Secondary, unintended effects are unknown