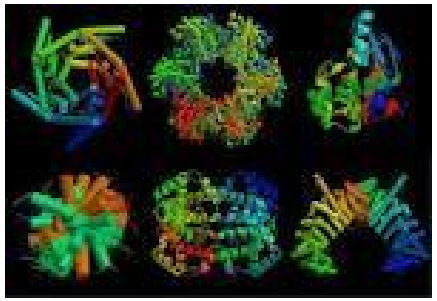
Lost in translation?

-Opportunities & Risks of Increased Research and Clinical Trials Data Transparency



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AGENDA

- Introduction
- General policy considerations on transparency
- Transparency rules under the new CTR
- EMA's transparency policy & new guidance
- Conclusions

Introduction I- General trend & US

- Tremendous movement towards more clinical trial data transparency (CTDT).
- CTDT initiatives under various frameworks & for different reasons
- Pathbreaking new disclosure requirements by medical journals

- Initiative moved into industry & government.
- US: new FDA rules on disclosure of masked & de-identified patient-level data.
- Drug industry responded with own transparency projects

Introduction II – EU developments

- EP & Council adopted "Regulation on clinical trials on medicinal products for human use" (CTR) (April 2014).

- Pharma companies & academic researchers must disclose end-results of clinical trials AND comprehensive clinical study reports.
- Within 30 days after +/- MA decision failure to comply = fines.
- Data in EU database shall be *prima facie* publicly accessible unless documents are demonstrated to be confidential;
- CTRs & other "main characteristics" of trial generally not confidential.

Introduction III – EU developments

- New EMA transparency policy (Oct. 2014- effect. Jan. 2015)
- *New Guidelines March 2016*
- Consensus that disclosure is on balance worthwhile.

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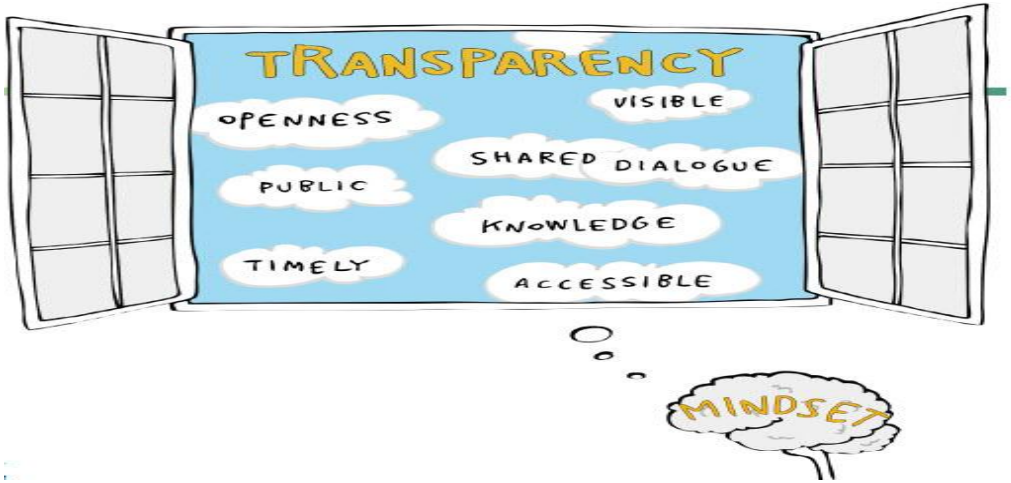
Potential benefits of more transparency & *independent verification of drug data*



- *better framework for international collaboration & open innovation*
- *facilitating large cross-border clinical trials*
- *More accountability and safety (pre and post MA grant)*
- *greater public trust in research results, drugs and industry*
- *finding new uses and applications for known drugs*
- *more possibilities in for big data analysis and precision medicine*

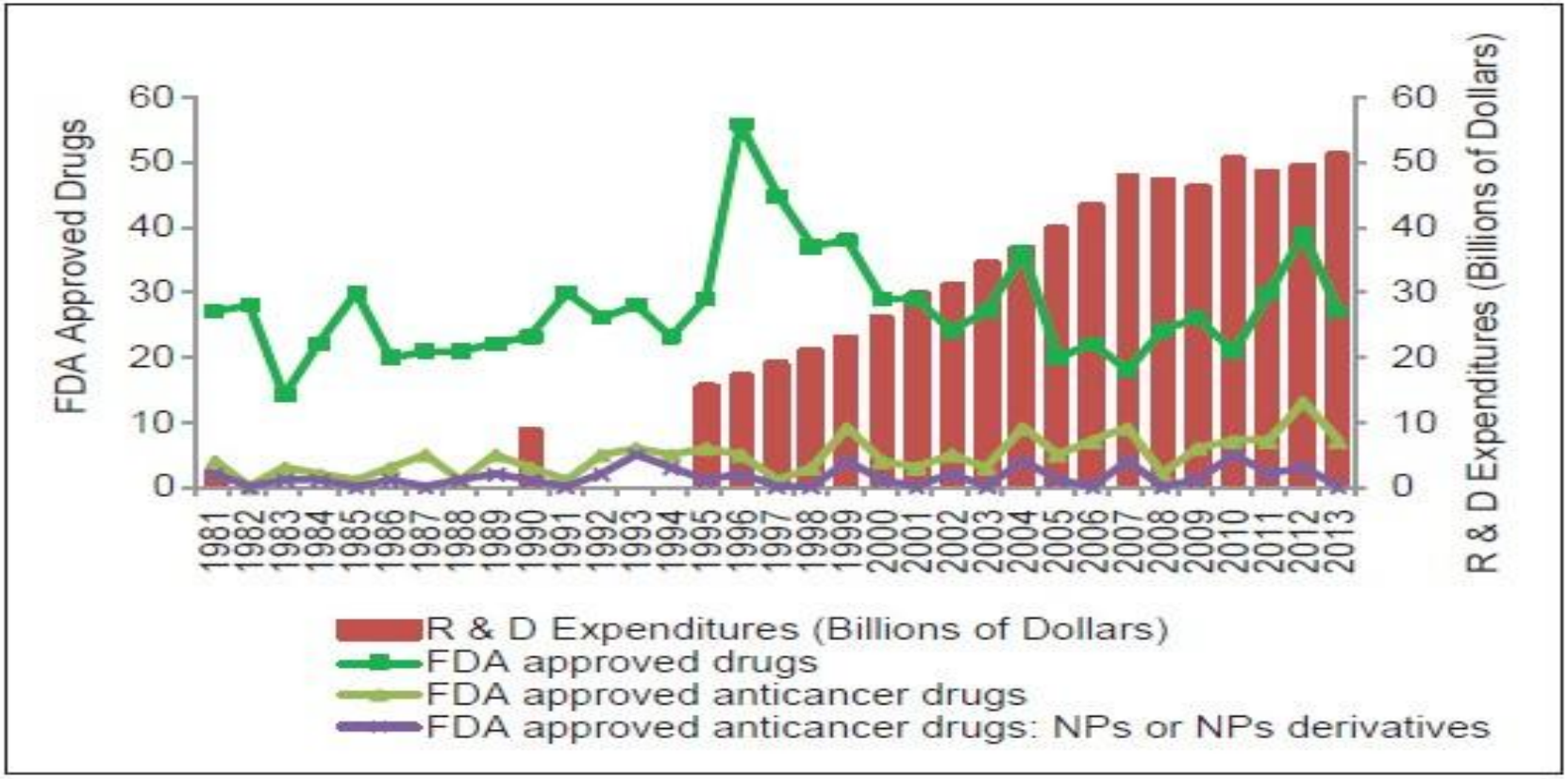
Who are the beneficiaries?

Mello et al.,Preparing for responsible sharing of clinical trial data. NEJM 2013;369:1651-1658

Table 1. Potential Benefits of Sharing Clinical Trial Data.

Benefit	Primary Beneficiaries				
	Public or Patients	Research Participants	Scientific Community	Regulators	Trial Sponsors
Encourage accurate characterization of the benefits and risks of drugs in research reports, improving public confidence in clinical research and pharmaceuticals	X		X	X	X
Improve surveillance of drug safety and effectiveness	X		X	X	
Facilitate secondary analyses of clinical trial data to explore new scientific questions	X		X		X
Speed innovation	X		X		X
Enable patients and advocacy groups to learn more about their specific medical problem	X				
Ensure that research participants are not exposed to unnecessary risk		X	X		
Ensure that research subjects' participation advances science		X	X		
Achieve operational efficiencies in conducting clinical trials			X		X
Inform strategic decisions about potential avenues of research and development			X		X

Pharma Innovation Gap



Better numbers in 2014- just an exception?

Dangers and pitfalls

- *for patients*
  (protection of personal data and patient privacy),
- *for research and patients*
  (misuse of clinical trial data)
- *for authorities and administration*
  (costs and complexity of the system)
- *for technology transfer & commercialization*
  (obstacles to IP protection, competitive harm & increased litigation).

Various mechanisms to enhance transparency

Mello et al.,Preparing for responsible sharing of clinical trial data. NEJM 2013;369:1651-1658

Table 2. Four Possible Models for Expanded Access to Participant-Level Data.

Variable	Open Access	Database Query	Sponsor Review	Learned Intermediary
Decision maker	None	Independent review board or trial sponsor	Trial sponsor	Independent review board
Process	Trial sponsor routinely posts data and supporting documentation when trial results are publicly reported or submitted to regulatory agency; researchers download the material	Requester submits a research query to the data holder, who then runs the query and returns results, not data	Trial sponsor reviews request, decides, and publicly documents rationale for the decision, which may be appealed to an independent board, whose decision is final	Board reviews request, collects input from trial sponsor, decides, and publicly documents rationale for decision
Criteria for releasing data	*Responsible-use attestation:* Full access as long as requester attests that data will not be used inappropriately (e.g., to reidentify research participants)	*Sound science*: Is there a reasonable scientific hypothesis, sound analytical plan, and adequate plan to disseminate findings? *Benefit–risk balancing*: Do the potential public health benefits of answering the proposed questions outweigh the probable adverse effects on the trial sponsor (e.g., intellectual-property interests, competitive concerns, technical-support burden) and the potential risks to research participants?	Same criteria for sound science and benefit–risk balancing as in database-query model *Expertise*: Does the research team have expertise sufficient to carry out the proposed analyses?	Same criteria as in sponsor-review model

Mitigating tools

- Misuse of data:

  - Special computer programs could hold data requesters accountable in their re-use of the data.

  Arg: If scientists can make progress in ensuring the replicability of studies that include the use of genetically modified mice, surely the far easier task of ensuring replicable re-analyses can be achieved.

  Cf. Friedman, N Engl J Med 370;5 nejm.org january 30, 2014

- Technology transfer & commercialization:

  - alternative forms of protection and new concepts for incentives
  - more flexibility regarding regul. exclusivities on global scale
  - alignment of CTDT with approaching new TS Directive

  Cf. WN Price II, T Minssen, Will clinical trial data disclosure reduce incentives to develop new uses of drugs? Nature biotechnology 33 (7), 685-686

Transparency under the new clinical trial legislation 536/2014 (CTR)

Transparency under the new clinical trial legislation

- EU portal and EU database in Article 81: (May 2016?)
- Functional specifications for the EU portal and EU database to be audited went through public consultation
- Rules on transparency have been finalised following discussion with MSs, EC, patients, HCPs' organisations and academic researchers

Requirements of the new CT regulation

- EU database publically accessible by default, the only exceptions being possible on the following grounds:
  - Protection of personal data
  - Protection of CCI (MA status of the medicinal product, overriding public interest in disclosure)
  - Protection of confidential communication between MSs (preparation of assessment report)
  - Ensuring effective supervision of the conduct of a clinical trial by MSs

Summary of rules (1/5)

- apply irrespective of if sponsor is a pharma company or academic research group or other type of organisation
- depend on Investigational Medicinal Products (IMPs) used in a trial and how they are used
- Trials defined as belonging to one of three categories, based on the IMPs and protocol, at the time of initial assessment of the clinical trial application:

Summary of rules (2/5)

- Category One: Pharmaceutical development clinical trials – essentially Phase I trials in healthy or patient volunteers, bio-equivalence and bio-similarity trials

- Category Two: Therapeutic exploratory and confirmatory clinical trials - essentially Phase II and III trials of novel products or new indications or formulations of existing products

- Category Three: Therapeutic use clinical trials – essentially Phase IV and low-intervention trials

Summary of rules (3/5)

- Depending on the category of trial the sponsor will have the possibility to defer publication of certain data and
- Defer publication of documents up to a maximum time limit, if needed, to protect commercially confidential information
- The use of deferrals will be monitored and should not exceed what is really needed

Summary of rules (4/5)

- The default is to make public at the first opportunity
- All data and documents in the system will be made public except for
  - manufacturing/quality information,
  - details of financial agreements between sponsors and
  - investigators, and specified personal data
- Public registration of trials at their start including all information needed for patients who may wish to participate in trials with therapeutic, diagnostic or preventive objectives

Summary of rules (5/5)

- Publication of all results (summary, layperson summary and in case of MA application the clinical study report)
- Possibility of justified deferral only for summaries in case of category I trials up to a maximum of 30 months post trial
- Option to defer publication of the IMP-Dossier, Investigator Brochure (IB), protocol and subject information sheet, after end of trial up to
    - 7 years for category one, &
    - 5 years for category two, or,
    - if earlier, the time of MA using that trial

The new clinical trial regulation 536/2014 (CTR) vis-à-vis EMA's transparency policy and new guidance

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3 aspects the EMA had to consider

- Response to access requests under the EU transparency rules (Regulation 1049/2001) for information to an EU institution
- The European Medicines Agency's (EMA) policy on proactive release of clinical study reports (CSRs)
- Related: The transparency rules under the new Clinical Trial Regulation

New EMA transparency policy (Oct. 2014- effective January 2015)

EMA:

"the public will be able to access extensive details of each trial including the major characteristics of the trial, the start and end of recruitment, end date of the trial and substantial modifications to the trial. These details will be made public as they occur starting with the decision on the trial. A summary of results and lay summary will be published 12 months after the end of the trial".

- EMA launched public consultation on how the transparency rules of the EU CT Regulation will be applied in CT database.

- Stakeholders were invited to comment before 18 February 2015.

New EMA transparency policy: Controversies at the EMA

- EMA lays out the following exceptions:
  - Protection of personal data
  - Protection of commercially confidential information
  - Protection of confidential communication between MS in the preparation of their assessment
  - Protection of the supervision of clinical trials by Member States
- Yet, EMA criticized for its interpretation and redaction of CCI (Ex. AbbVie's biologics data requested by biosimilar producers).
- Health Care Institutes stress that non-disclosure of information must remain absolute exception, and that
- …manufacturers who black-out records, must in each case justify their reasons & EMA must examine justifications precisely
- For industry TS and their definition increasingly crucial
- Discussions with EMA on policy & EU reg. TS Directive

The EMA's new March 2016 Guidelines

- The guidance has 4 Chapters:

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1. Scope and definition
2. Details on procedural aspects of CR submission
3. Guidance on how to anonymize CRs for publication.
4. Identification and redaction of CCI

Conclusions

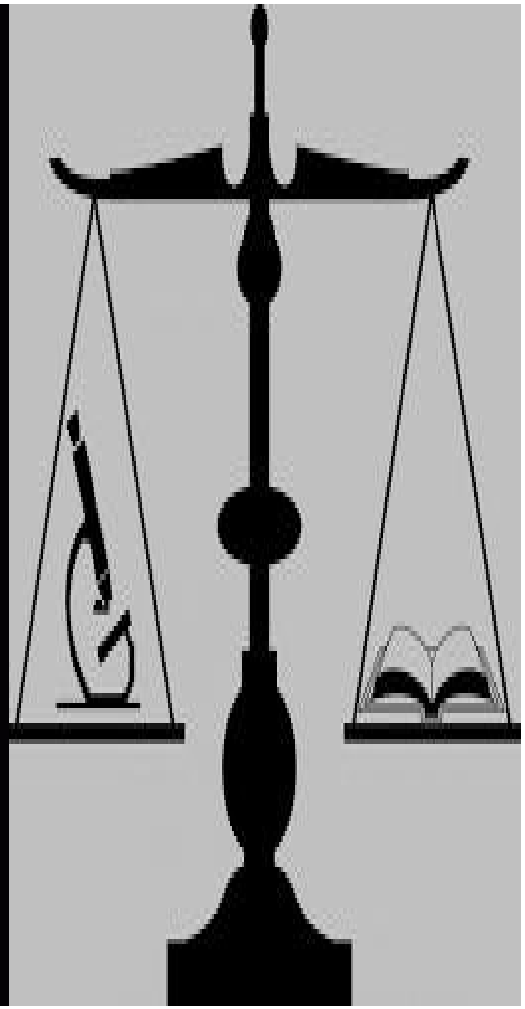
- Transparency is important because of ...

  - Trust
  - Confidence: I understand what is happening
  - Empowerment: knowledge to support pers. decision-making
  - Support of science (precision medicine) & open innovation
  - Safety

- But to realize full benefits and not get lost in translation unwanted side-effects must be tackled, such as

  - *obstacles to IP protection & tech transfer*
  - *increased litigation*
  - *misuse of personal data and breach of patient privacy,*
  - *misuse and misinterpretation of CTD*

Careful consideration & evaluation of full impact of more transparency necessary, including IPRs



Thanks you for attention!

Any questions or comments?

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