

A view from outside industry

Matthew Sydes

MRC Clinical Trials Unit at UCL

Aug-2013

**European Statistical Workshop (EFSPI/PSI):
EMA Clinical Trial Data Transparency**

V1.00, 21-Aug-2013

MRC Clinical Trials Unit at UCL


- Many years of experience in providing data for collaborations and secondary uses
 - Well-versed in these data-sharing processes
 - Defined approach to data sharing
- Holds hundreds of IPD datasets
 - From clinical trials performed over several decades
 - Some including patient identifiers
- Extensive experience in requesting & receiving data
 - Holds many IPD datasets for meta-analysis
- Follows MRC policy on data storage

Firefox

All Trials | All Trials Registered. All Result... +

www.alltrials.net

Google



All Trials Registered | All Results Reported

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It's time all clinical trial results are reported.

Patients, researchers, pharmacists, doctors and regulators everywhere will benefit from publication of clinical trial results. Wherever you are in the world please sign the petition:


Thousands of clinical trials have not reported their results; some have not even been registered.

Information on what was done and what was found in these trials could be lost forever to doctors and researchers, leading to bad treatment decisions, missed opportunities for good medicine, and trials being repeated.

All trials past and present should be registered, and the full methods and the results reported.

We call on governments, regulators and research bodies to implement measures to achieve this.

The petition has also been translated into [many different languages](#). If you would like to sign the petition on behalf of an organisation then please [contact us](#). Data will be held by Sense About Science. Read our [privacy policy](#) here.

LATEST NEWS: 

Sign the petition

| | |
|---|--------------|
| First Name ** | Last Name ** |
| Email ** | |
| Country | Occupation |
| I signed this because... (add your comment for the wall here) | |

x

★★★★★

EMA Initial Position

- “The Agency has committed to publishing the full data sets from clinical trials”
 - EMA Transparency statement
- Our understanding:
 - Release all sets of IPD
 - Including for multiple imputation, bootstrapping, etc
 - + computer programs and output
 - Enables cross-checking & reproduction
- Applies to **all** trials **ever submitted** to EMA for licensing purposes

EMA Consultation Process

- Five Advisory Groups
 - Jan-April 2013
 - Teleconferences
 - < ~50 participants
- MRC CTU rep on 4 groups
 - 1) Protecting patient confidentiality – MRC CTU present
 - 2) Clinical trial data formats – MRC CTU present
 - 3) Rules of engagement – MRC CTU present
 - 4) Good analysis practice – MRC CTU present
 - 5) Legal aspects – Not present

EMA Draft Policy

- EMA committed to
 - Proactive publication of data
 - From clinical trials
 - Supporting marketing-authorisation application
 - After decision-making process ended

EMA Draft Policy: 3 data categories

1. **CCI**: Commercially confidential information

2. **O**: Open access information

3. **C**: Controlled access

EMA Draft Policy: 3 data categories

1. **CCI**: Commercially confidential information
 - IMP details
2. **O**: Open access information
 - Any trial data, information or documents that do not contain patients' personal data
3. **C**: Controlled access
 - Clinical trial data, information or documents containing patients' personal data (incl IPD sets)

EMA Draft Policy: 3 data categories

- 1. CCI:** Commercially confidential information
 - IMP details
 - Will not be disclosed by EMA
- 2. O:** Open access information
 - Any trial data, information or documents that do not contain patients' personal data
 - Freely downloadable from EMA website
- 3. C:** Controlled access
 - Clinical trial data, information or documents containing patients' personal data (incl IPD sets)
 - Available with conditions and agreements

EMA Draft Policy: Scope

- "...concerns only those CT data that will be submitted to the Agency..."
 - Teleconferences anticipate EMA standards would apply to all trials
- Important implications for academic trials

MRC CTU approach – Principles

- Data release must not compromise an ongoing trial
- Investigators invested time + effort in trial
 - Deserve reasonable period of exclusivity with data
 - Before available to others
- Never under-estimate effort required in processing requests
 - Particularly successful requests
 - Adequate resources must be available for processing

MRC CTU Approach – Discoverability

- Trials should be discoverable
 - Achieved through clinical trial registration
- Transparency of data collection
 - May facilitate secondary uses
 - May discourage inappropriate applications
- Timelines for access

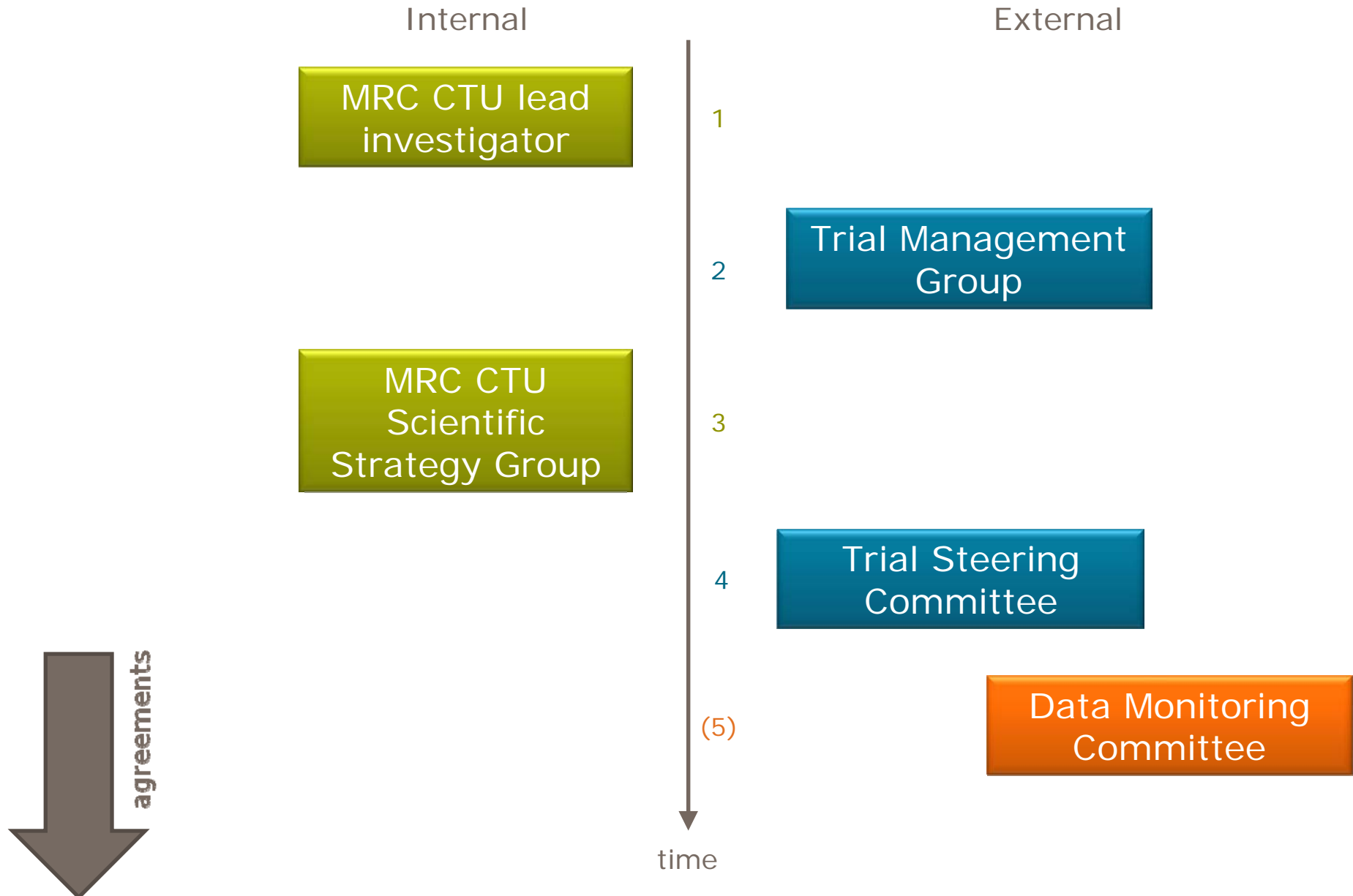
MRC CTU Approach – Data Management

- Data Management Plan (DMP) describes:
 - Data to be collected
 - Method by which data are collected
 - How data will be managed, stored and curated
 - Methods of data preservation
 - Security risks
 - Data sharing principles and methods
- Standardisation
 - C-DISC
 - COMET Initiative www.comet-initiative.org

MRC CTU Approach – Assessment

- Applicants specify:
 - Objectives
 - Study design
 - Data and/or samples required
 - Ethical approval and consent requirements
 - Planned outputs
 - Authorship, publication policy, implications for CTU
 - Funding and resources needed and support available
 - Timelines

MRC CTU Approach – Assessment



MRC CTU Approach – Agreements

- Successful researchers expected to publish
 - According to their initial plans
 - MRC CTU to receive regular updates
- Agreements to specify boundaries data use
 - e.g. used only for purposes for which released
- Which dataset?
 - Data used for a specific prior publication
 - Updated dataset?
- Support for dataset preparation

EMA Draft Policy: Concerns

1a. Consent: vs assent

- No mention of CT where pt cannot consent to entry

i.e. where investigators rely on 3rd party assent:

- children
- unconscious patients
- patients with cognitive impairment
- patients with some mental illnesses

EMA Draft Policy: Concerns

1b. Consent: process

- Release of IPD requires consent prior to entry but:
 - Added burden: complex issues at trial entry
→ Where is my data going?
 - Increased likelihood of pt refusal to join?
 - Selective consent damaging: must be all pt
 - Increased unwillingness to provide assent?

EMA Draft Policy: Concerns

2. Secondary analyses

- Those conducting secondary analysis allowed reasonable period of time
- What is a reasonable amount of time?

EMA Draft Policy: Concerns

3a. Consequences of release -- 1

- Self-identification possible by pt despite “blinding”
 - Aware in a trial
 - Easier with rare conditions
- Pt may learn:
 - Tests performed of which previously unaware
→ worry
 - Results of tests outside doctor-patient relationship
→ more worry

EMA Draft Policy: Concerns

3b. Consequences of release -- 2

- Distortion of data to avoid self-identification may
 - Cause distress
- Some pt may demand correction
 - e.g. under Data Protection Act
- Concern addressed by controlled access?

EMA Draft Policy: Concerns

4. Disputes

- Secondary analyses may lead to serious disputes with already published results
 - Damage reputation of research
 - Who is right now?
 - Why is anyone wrong?
 - Worry pt they have been misused
 - Duty of care to counsel pt
- Plan for reconciliation or honest broker
 - Secondary use should be discussed with or checked by original group or EMA prior to dissemination

EMA Draft Policy: Concerns

5. Access process

- Who should data requests go to?
 - EMA
 - Original company

EMA Draft Policy: Concerns

6. Costs of release

- Preparation of shareable IPD add to trial costs
- Requires retention of trial staff
 - Prepare data files for release in an acceptable format
 - Plus documentation e.g. coding of data
 - Extension of staff contracts
- Requires funding
- Who will do prepare datasets?
 - Reluctance if not seen as career-enhancing?

Summary

- Support principles
- Broadly in line with attitudes
- Some specific concerns remain

Acknowledgements

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MRC CTU approach – references

MRC APPROACHES

- www.mrc.ac.uk/Ourresearch/Ethicsresearchguidance/datasharing/Policy/PHSPolicy/index.htm
- www.mrc.ac.uk/Ourresearch/Ethicsresearchguidance/Datasharing/Policy/index.htm

CALDICOTT REVIEW: INFORMATION GOVERNANCE IN THE HEALTH AND CARE SYSTEM

- <https://www.gov.uk/government/publications/the-information-governance-review>

MHRA CORPORATE PLAN

- <http://www.mhra.gov.uk/home/groups/comms-ic/documents/publication/con261796.pdf>

NIHR ANNUAL REPORT

- <http://www.nihr.ac.uk/files/Publications/NIHR%20Annual%20Report%202011-12%20final.pdf>

COMMONS SCIENCE AND TECHNOLOGY SELECT COMMITTEE

- <http://www.parliament.uk/business/committees/committees-a-z/commons-select/science-and-technology-committee/inquiries/parliament-2010/clinical-trials/>

EUROPEAN MEDICINES AGENCY (draft)

- http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/06/WC500144730.pdf

Why am I here?

- Senior Scientist & Statistician at MRC CTU, London
- Lead teams designing, running, analysing and publishing independent clinical trials
- 18 years experience with RCTs
- Ethics Committee for 7 years
- Involved in various external discussions about data access and data sharing
- Author of Data Sharing SOP

EMA Public Consultation following advice

- After advice from Advisory Groups...
- Release of Draft policy: 24-Jun-2013
- Comments by: 30-Sep-2013
- Policy in effect from: 01-Jan-2014

EMA Draft Policy: Concerns

1c. Consent: sufficiency

- Any other use of IPD oversteps boundaries of patients' informed consent
 - Shall not be enabled by the policy
- Pt motivation for trial participation varies e.g.
 - Altruism: hope to help future patients
 - Personal hope: access to trt that might help me
 - Duty: current treatment options from predecessors
- Are all of these inconsistent with further uses?
- What are the implications of non-sharing?