Harvard MRCT Return of Results Initiative

Annual Meeting, December 3, 2014

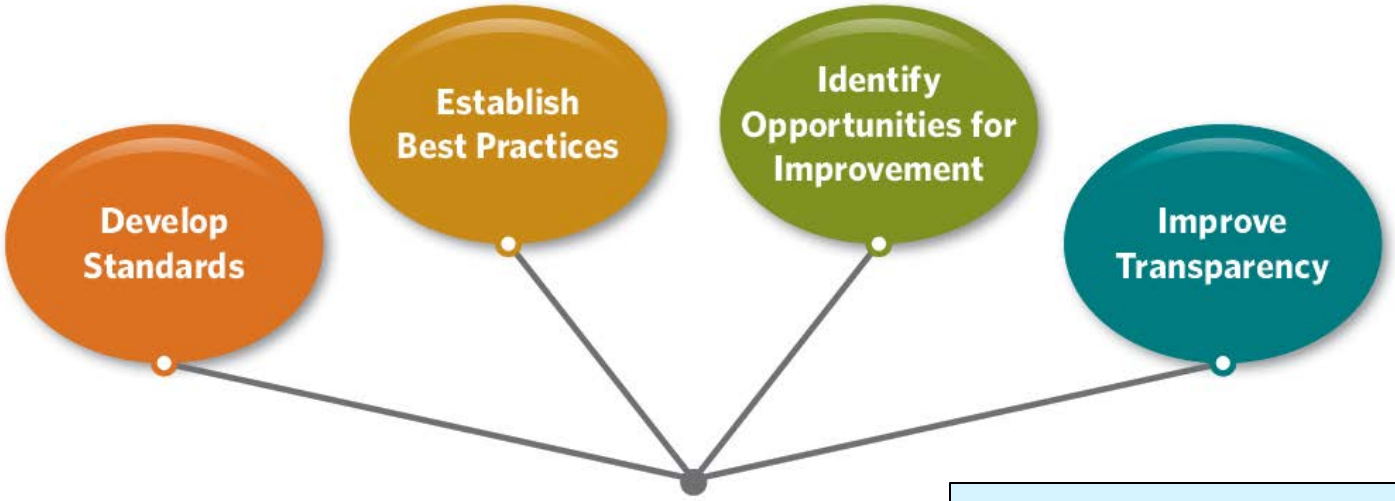
Barbara Bierer, MD

Today's Agenda

Harvard MRCT Center – Mission
Overview of Project Scope and Deliverables
Process for Returning Results
Incorporation of Health and Cultural Literacy Principles
Timing of Returning Results
Special Considerations
Regulatory Agency questions
Collaborations
Next Steps

Collaborating to Improve Multi-Regional Clinical Trials

The MRCT Center's Purpose is *to improve the design, conduct, and oversight of multi-regional clinical trials, especially trials sited in or involving the developing world; to simplify research through the use of best practices; and to foster respect for research participants, efficacy, safety and fairness in transnational, trans-cultural human subjects research.*



Return of general research results is one of many Harvard MRCT initiatives

Return of results: current Harvard MRCT workgroup

Salvatore Alesci – PhRMA
Mark Barnes - Ropes & Gray, LLP
Richard Bergstreom – EFPIA
Deborah Collyar – PAIR (COCHAIR)
Alla Digilova – MRCT
David Forster - WIRB Copernicus Group
Elizabeth Garofalo - Novartis Pharma AG
Barbara Godlew - The FAIRE Company, LLC
Laura Hagan - Merck Serano
Sandra Hayes-Licitra – Johnson & Johnson
Angelika Joos – Merck Sharp & Dohme
Paulo Lacativa - CCBR Clinical Research
Yann LeCam – EURODIS
Rebecca H Li – MRCT
Marcello Losso - HIV RAMOS
Laurie Myers – Merck (CO-CHAIR)
Pearl O'Rourke - Partners HealthCare
Nesri Padayatchi - Univ. of KwaZulu-Natal
Mary Ann Plummer – (prior CO-CHAIR)
Ben Rotz – Lilly
Jim Saunders - NE IRB
Amish Shah - MRCT / HLS
Patrick Taylor - Children's Hospital, Boston
Sarah White - Partners HealthCare
Sabune Winkler – HMS

Behtash Bahador - CISCRP
Nicola Bedlington – European Patients Forum
Barbara Bierer - Brigham & Women's Hospital/MRCT
Assunta De Rienzo - Brigham and Women's Hospital
Dimitrios Dogas – MRCT
Phyllis Frosst - Personalized Medicine Coalition
Pierre Gervais - QT Research
David Haerry – European AIDS Treatment Group
Zach Hallinan – CISCRP
Cheryl Jernigan - Susan G. Komen
Barbara Kress – Merck
Sarah Larson – Biogen Idec
David Leventhal – Pfizer
Craig Lipset – Pfizer
Holly Fernandez Lynch - Harvard Law School
Alex Nasr – AbbVie
Mary Oster – NEIRB
Jane Perlmutter – Gemini Group
Sandy Prucka – Lilly
Beth Roxland – Johnson & Johnson
Jessica Scott – GSK
Zachary Shapiro – MRCT/ HLS
David Walling – Collaborative NeuroScience
Marc Wilenzick
Elizabeth Witte - HMS

Returning Results and the MRCT Mission

Goals: Returning Clinical Trial Results to study participants

- **Develop standards and best practices.**
- **Create a guidance document,** including templates.
- **Address perceived barriers** to widespread implementation.

Returning results allows sponsors and investigators to recognize and honor the essential contributions and volunteerism of clinical trial participants.

Expectations of academic, industry, not-for-profit sponsors similar

Returning results is a key aspect of **Improving Transparency** of clinical trials and **Increasing Public Trust.**

Scope:
Communication and dissemination of summary research results to individual participants

Why Now?

EU Parliament: **Regulation (EU) No 536/2014 (2014):**

Sponsor of a clinical trial must submit **"**a summary of the results of the clinical trial together with a summary that is understandable to a layperson, and the clinical study report, where applicable, within the defined timelines."

Article 37:

4. Irrespective of the outcome of a clinical trial, within one year from the end of a clinical trial in all Member States concerned, the sponsor shall submit to the EU database a summary of the results of the clinical trial.

PhRMA/EFPIA
"…biopharmaceutical companies will work with regulators to adopt mechanisms for providing a factual summary of clinical trial results and make the summaries available to research participants."

Return of Results: Harvard MRCT Project

MRCT Multi-Regional Clinical Trials
The MRCT Center at Harvard

Potential audiences and scope:

1. **Communication and dissemination of *summary* research results:**
   - Through the scientific literature
   - To general public
   - To local community of the participants
   - **To individual participants**

2. Communication of ***individual*** results:
   - Specific results for each study participants (e.g. treatment arm assignment)
   - Incidental findings

Goal today: your feedback and discussion.
Perspectives from regulators, journal editors, pharma representatives, investigators and participants

Overview

Return of results should become the expectation and practice in clinical research. The practice demonstrates:

- Appreciation of the contributions and volunteerism of the individual participant and stewardship of the general public.
- The core principle that each participant has a right to know the outcome of his or her participation (and his or her own information) and understand the results.
- Participant has a right to choose whether to (and who can) have that information.

Standard methodologies and approaches should be developed so that roles and responsibilities are clear, expectations are set and met, and multinational requirements appreciated from the outset.

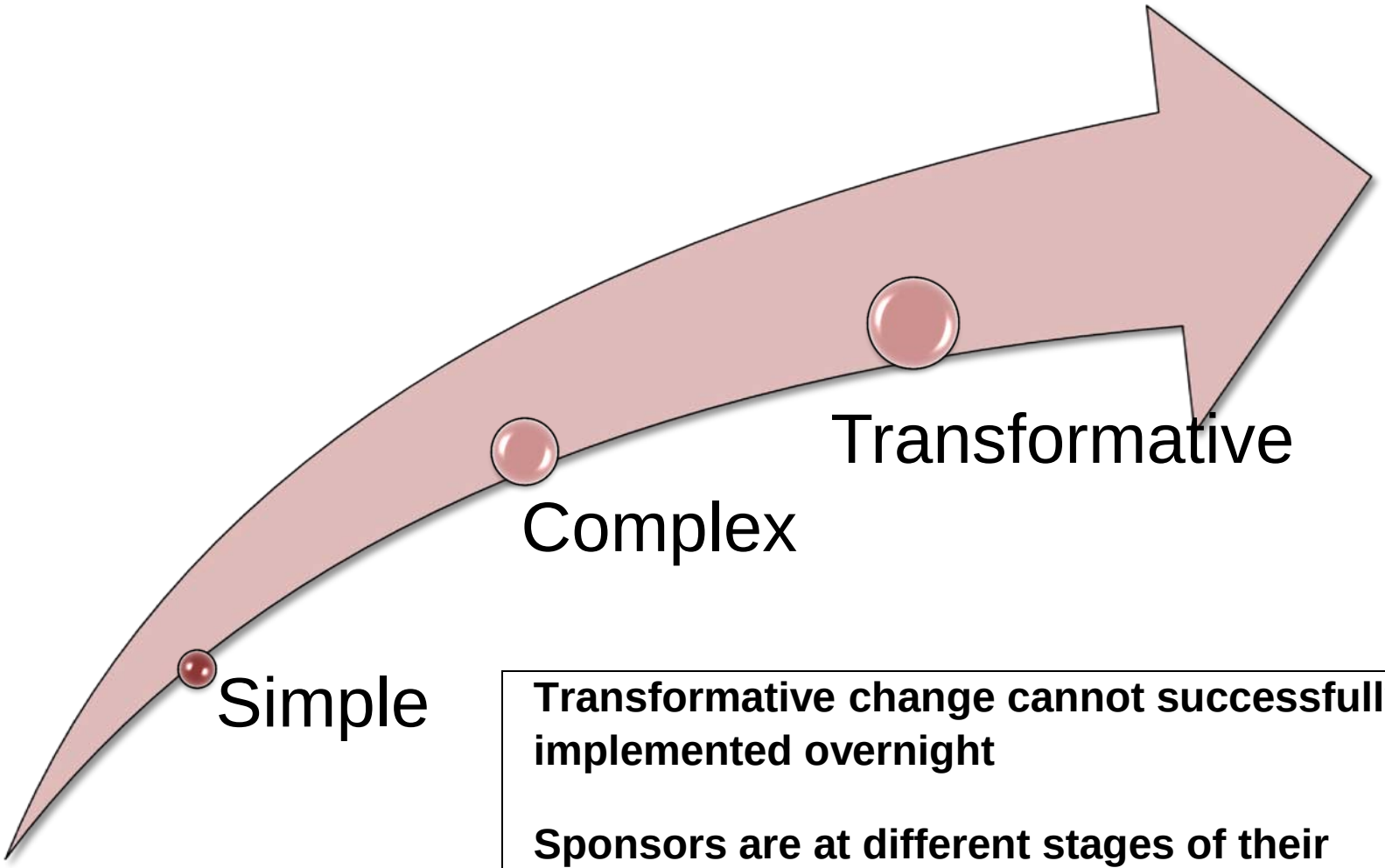
Funding for return of results should be provided as an anticipated component of human subjects research.

A Novel Approach to Returning Results

- **We have partnered with other working groups addressing returning results, including:**
    - Alliance for Clinical Trials in Oncology (Alliance)
    - CSCRIP Group
    - DIA Lay Summary Working Group
    - Pfizer Blue Button Project
    - NIH Alliance Working Group
    - Dana Farber Cancer Institute

- **Includes input from multiple stakeholder groups:**
    - Academics
    - Industry
    - Regulators
    - Patient-Advocates and patients
    - CROs
    - IRBs/ECs

Transforming the Participant Experience



Transformative change cannot successfully be implemented overnight

Sponsors are at different stages of their commitment to returning results – our pathway can assist sponsors regardless of the maturity of their program

The Harvard MRCT Deliverables

An **ROR Process Reference Guide** for groups wishing to return results including:

- Content (essential components, source documentation, cultural and health literacy considerations)
- Logistics and detailed processes for results sharing
- Timing
- Special considerations

An **ROR Users Toolkit** including:

- Templates for Phase1, Phase II/III, studies ending early
- Neutral language guide
- Endpoints language guide
- Useful Checklists

Returning Results: Perceived Barriers

Practical Considerations and Issues, including:

- Timing of release of study results
- Designating responsible party to deliver results (sponsor, study team, provider)
- Designated third party receipt of results (participant death, LAR, parent)
- Follow-on questions from and information required by participants
- Resource requirements for process

Logistics

- Cost implications of returning results (mail vs.web or online portal; IT vs other)
- How best to communicate? (online vs. in-person vs. paper-based delivery)
- Role of IRBs/Ethics Committee

Content and Comprehension

- Guidance on content should be made available and consistent with EMA
- What do patients/participants want to know? And do they understand implications?
- Language in letter should not be too scientific for non-scientists to understand

Misinterpreting intent

- FDA and other regulators might view returning results as a promotional activity

Process Flow for Returning Results

MRCT Multi-Regional Clinical Trials
The MRCT Center at Harvard

Pre-Study preparation

- Organizational preparation, policies, processes
- Establish level/timing/delivery
- Resource planning

Protocol Development

- Describes ROR as voluntary process, including who what where when how
- Include ICF section description

During study conduct

- Letter of appreciation
- Last study visit of participant content
- Intermittent engagement with participant thereafter

When study ends

- Content of summary document (and health literacy principles)
- Adherence to global regulatory framework

Aggregate Study Results: Suggestions

To Whom:

All participants that have been enrolled and, if appropriate, randomized

Method of Return:

- Interactive methods (e.g., face-to-face meeting(s), telephone call(s), two-way online meeting(s), dynamic email exchange, etc.,)
- One-way communications (video summary, automated phone message, printed materials)
- Internet based methods (flexible, cost-effective, current, security important)

Participant Clinical Trial Results Summaries

Creation of Summary

- To ensure that the summary is unbiased and not promotional, an independent and objective editor or editorial panel, and patient(s) or patient representative(s), should translate technical results into plain language (sixth-eight grade reading level) and apply health literacy principles. Content summary should be reviewed for accuracy.
- Translation into additional languages should be undertaken consistent with translations of informed consent
- An individual from either the study site (e.g. investigator, study team) or neutral informed third party should be available to answer questions for participants after receipt of study results
- Provisions should be made for vulnerable populations and other instances
- Consideration as to whether to, and whom to, inform in the event of a participants death

Content Annex V – EU Layperson Summary

http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2014.158.01.0001.01.ENG

1. Clinical trial identification
2. Name and contact details of the sponsor;
3. Main objectives
4. Population of subjects (include eligibility criteria);
5. Investigational medicinal products used;
6. Description of adverse reactions and frequency;
7. Overall results of the clinical trial;
8. Comments on the outcome of the clinical trial;
9. Whether follow up clinical trials are foreseen;
10. Where additional information could be found.

Additional Considerations: Health Literacy

Emphasis on health literacy

- Health Literacy is not the same as literacy level or ability to read.
  - Health Literacy: “the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions.”[1]

- Even those with adequate health literacy can struggle at times to understand health information, and appreciate clear communication.

- The guidance template applies principles of health literacy.

- The appendix provides additional information on how to integrate health literacy into clinical trial processes to assure understanding, including information on numeracy; testing for readability; visuals; and writing style.

1. U.S. Department of Health and Human Services (HHS). Healthy People 2010. Washington, DC: U.S. Government Printing Office. 2000.

Equally important: Numeracy and Cultural Literacy

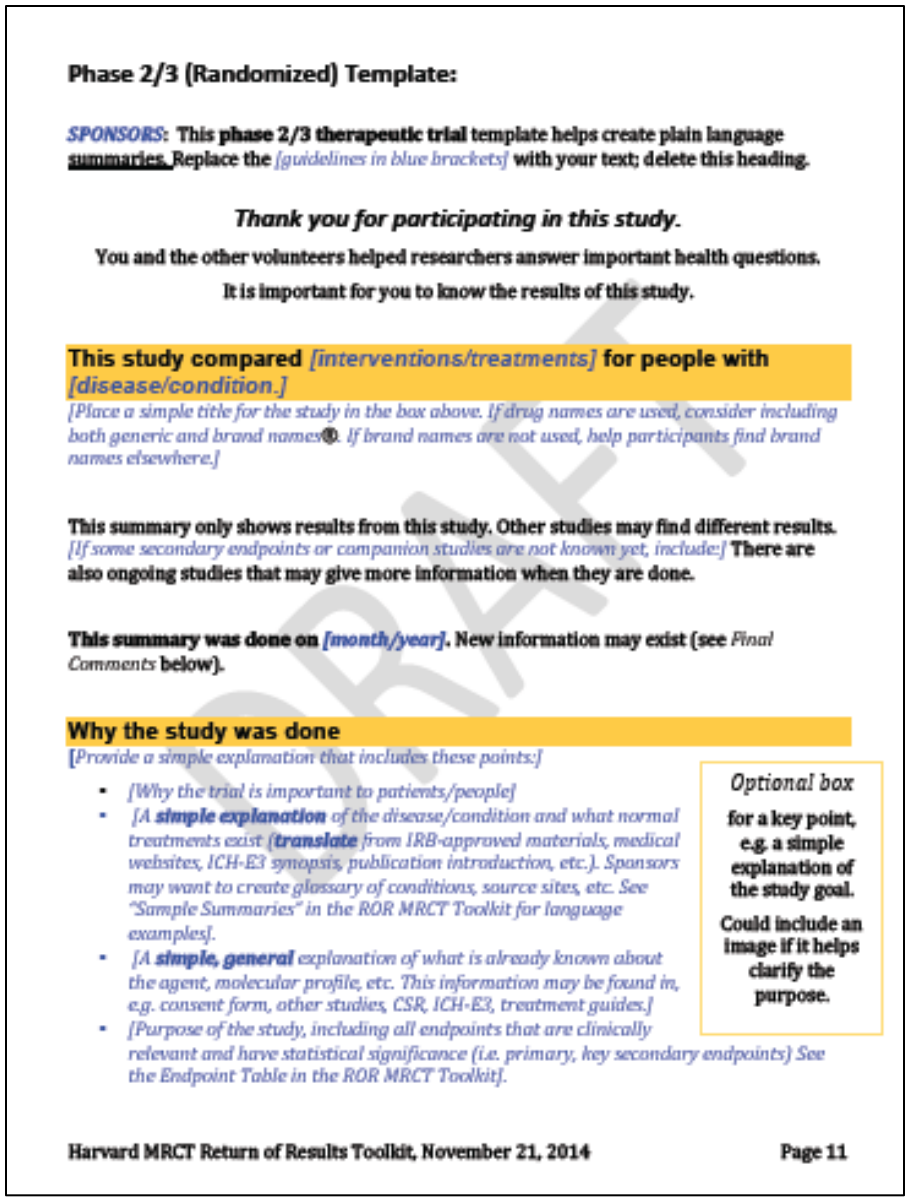
Numeracy is the ability to use probability and basic mathematical concepts, necessary to function effectively in the health care environment and act appropriately on health care information (whole numbers, important information only, do the math, use visuals, explain concepts of risk and probability)

Cultural literacy: To avoid informational disparities among underrepresented populations sponsors should ensure processes for ROR reflect cultural literacy principles (translation, back translation, medical terms in native language, cultural norms and appropriateness.

Neutral Language

Language to avoid	Language to consider
This study proved…	This study found that... This does not mean everyone in that group had these results.
This study proved that using <*Drug A*> to prevent <*disease*> is effective.	This study found that people with <*disease*> who got <*Drug A*> had <*primary endpoint*>.
The combination treatment of <*Drug A and B*> may also help alleviate <*a different disease/condition than what was studied*>	When <*Drug A and B*> are used together, people in this study had <*study endpoint*> .
This means that <*Drug A*> is better than <*Drug B*>.	In this study, people who got <*Drug A*> had more <*study endpoint*> than some people who got <*Drug B*> if they had the same health conditions.
<*Drug A*> works better than <*Drug B*>, but some people didn't tolerate it as well.	In this study, more people got <*study endpoint*> with <*Drug A*>. They also had more adverse events that interfered with their daily lives, like <*specific adverse events*>.
<*Drug A*> is better tolerated than Drug B	In this study, fewer patients who took <*Drug A*> had <*list adverse events*> than patients who took

Harvard MRCT Templates



Phase 2/3 (Randomized) Template:

***SPONSORS*: This phase 2/3 therapeutic trial template helps create plain language summaries. Replace the** *[guidelines in blue brackets]* **with your text; delete this heading.**

Thank you for participating in this study.

You and the other volunteers helped researchers answer important health questions.

It is important for you to know the results of this study.

This study compared *[interventions/treatments]* **for people with** *[disease/condition.]*

[Place a simple title for the study in the box above. If drug names are used, consider including both generic and brand names®. If brand names are not used, help participants find brand names elsewhere.]

This summary only shows results from this study. Other studies may find different results. *[If some secondary endpoints or companion studies are not known yet, include:]* **There are also ongoing studies that may give more information when they are done.**

This summary was done on ***[month/year]*****. New information may exist (see** *Final Comments* **below).**

Why the study was done

[Provide a simple explanation that includes these points:]

- *[Why the trial is important to patients/people]*
- *[A* ***simple explanation*** *of the disease/condition and what normal treatments exist (****translate*** *from IRB-approved materials, medical websites, ICH-E3 synopsis, publication introduction, etc.). Sponsors may want to create glossary of conditions, source sites, etc. See "Sample Summaries" in the ROR MRCT Toolkit for language examples].*
- *[A* ***simple, general*** *explanation of what is already known about the agent, molecular profile, etc. This information may be found in, e.g. consent form, other studies, CSR, ICH-E3, treatment guides.]*
- *[Purpose of the study, including all endpoints that are clinically relevant and have statistical significance (i.e. primary, key secondary endpoints) See the Endpoint Table in the ROR MRCT Toolkit].*

Optional box

for a key point, e.g. a simple explanation of the study goal.

Could include an image if it helps clarify the purpose.

Harvard MRCT Return of Results Toolkit, November 21, 2014 **Page 11**

DRAFT

- Located in ROR Toolkit
- Includes EMA required elements
- Examples
- Incorporates principles of Health Literacy and Numeracy
- Templates created for Phase I, Phase II/III, Trials ending early and Observational studies

Endpoint Descriptions and Examples

Endpoint
Composite
Surrogate
Mortality
Morbidity
Progression-free survival (or disease-free survival)
Patient-Reported Outcome on symptoms or functions (e.g., pain)
Exploratory Biomarker / Pharmacogenomics
Prevention or incidence endpoint
Non-inferiority endpoints

Timing of Return of Results: Suggestions

Trial Type	Timing	Source Document	Action
Regulated trials (typically industry sponsored interventional studies) Consistent with EMA regulation	Within 1 year of completion or 'end of study' defined as 1 year after LSLV	Clinical study report (CSR) or ICHE3 synopsis (CSR synopsis)	• Return RRS to trial participants • Post non-technical summary on CT.gov, EudraCT (not required or supported to-date) • Harmonization across sites
Academic / non-regulated trials	Within 1 year of the study close by the IRB or final data analysis or concurrent with the release of the first study publication	Publication	• Return RRS to trial participants including unpublished trials
Longitudinal / observational studies	Concurrent with the release of each major study publication	Publication	• Return RRS to trial participants and after each update

Special Considerations

Trials that close early

- Futility
- Efficacy
- Safety
- Low accrual

Observational, long-term follow-up, and extension studies

Notification of results to a 3rd party designated by the participant

Vulnerable populations

Legally Authorized Representatives and other designated parties

Return of Results in the event of participant death

Assent for Return of Results to Children

Complexities of the Global Context

Role of the IRB/RECs: Special Considerations

- If return of results is planned, the ICF should include that statement and the plan, and the IRB/REC should review.
- If returning results occurs when the study is still open, the IRB/REC should review the materials (ICH E6).
- When a study is closed, the IRB/REC does not have jurisdiction and will likely not wish to review materials; patients/participants are not considered “human subjects”. Note that definition of “end of study” may vary by sponsor and regulatory authority.
- Many investigators think it would be helpful for the IRB/REC to know plan for communicating the results, and the content of that communication, at the same time the subjects are provided the results but not as a mandatory process. In this situation, the role of the IRB/REC should be decided beforehand
- IRB/RECs vary significantly. Sponsors and investigators should ask the IRB/REC of record early in the process. Guidance for IRB provided

Studies that *may* not warrant return of results

- Results indeterminate or not powered to deliver “results:”
  - Exploratory tissue and blood studies
  - Pilot proof of concept studies
  - Some minimal risk studies may be of insufficient scientific rigor to justify the return of results, such as research required of students in order to graduate.
- Tissue banking and bio banking activities
- Research conducted under a waiver of consent
- Exempt studies
- Cluster randomized studies
- Pragmatic clinical trials.
- Studies of illegal or socially unacceptable behavior such as illegal drug use or prostitution, where providing results may create the potential for a breach of confidentiality and subsequent harm.
  - Studies with certificates of confidentiality
  - Small studies with limited numbers of subjects may compromise privacy

Promotional activity and Agency concerns

- Regulatory requirements prohibit any type of promotional communication prior to FDA (and other regulatory agencies) marketing approval
- What constitutes “promotional language” in describing results?
- Will the FDA (and other regulatory agencies) provide guidance on what the agency considers “promotional” in a timely fashion?
- If not, does the FDA (and other regulatory agencies) plan to review –or require review of – each participant summary prior to release?
  - Will the review be timely?
  - Will the review differ for different phases of drug development (Phase1 vs Phase III, etc)?

Collaborations

- Our current Guide and Toolkit are designed for all sponsors (PI-initiated, industry, NIH) to use in all trial types (all phases, FDA- and EMA-regulated, comparative effectiveness, biobanking, etc)
- Harmonization and consistency is critically important.
- We have discussed with TransCelerate and EFPIA potential collaboration to disseminate our work further through their efforts. We have approached NIH to partner in this transparency effort.

Next Steps

- Disseminate draft for further comment and revision
- Regulatory input
- Finalize draft
- Encourage pilot implementation
- Iterative improvement of guidance
- Enhance and refine toolkit as needs arise
- Global harmonization in approach and expectations

Thank you

Barbara E. Bierer
bbierer@partners.org
mrct@harvard.edu

Laurie Myers
laurie_myers@merck.com

Rebecca Li
Rebecca_Li@harvard.edu

Mark Barnes
mrct@harvard.edu

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Clinical Trial Transparency
The European Perspective

Harvard MRCT 3rd Annual Meeting (3rd December 2014)

Presented by Anabela Marçal
Head of Compliance and Inspections Department

An agency of the European Union

Clinical Trial Transparency – Why?

- Public record
- Contribution to global registration of all clinical trials (WHO ICTRP)
- Public reference information
- Public scrutiny and critique – establishing trust and confidence in the system
- Inform and enable participation in discussion, in clinical trials…
- Increasing knowledge contributing to innovation, research and healthcare

Clinical Trial Transparency – Why?

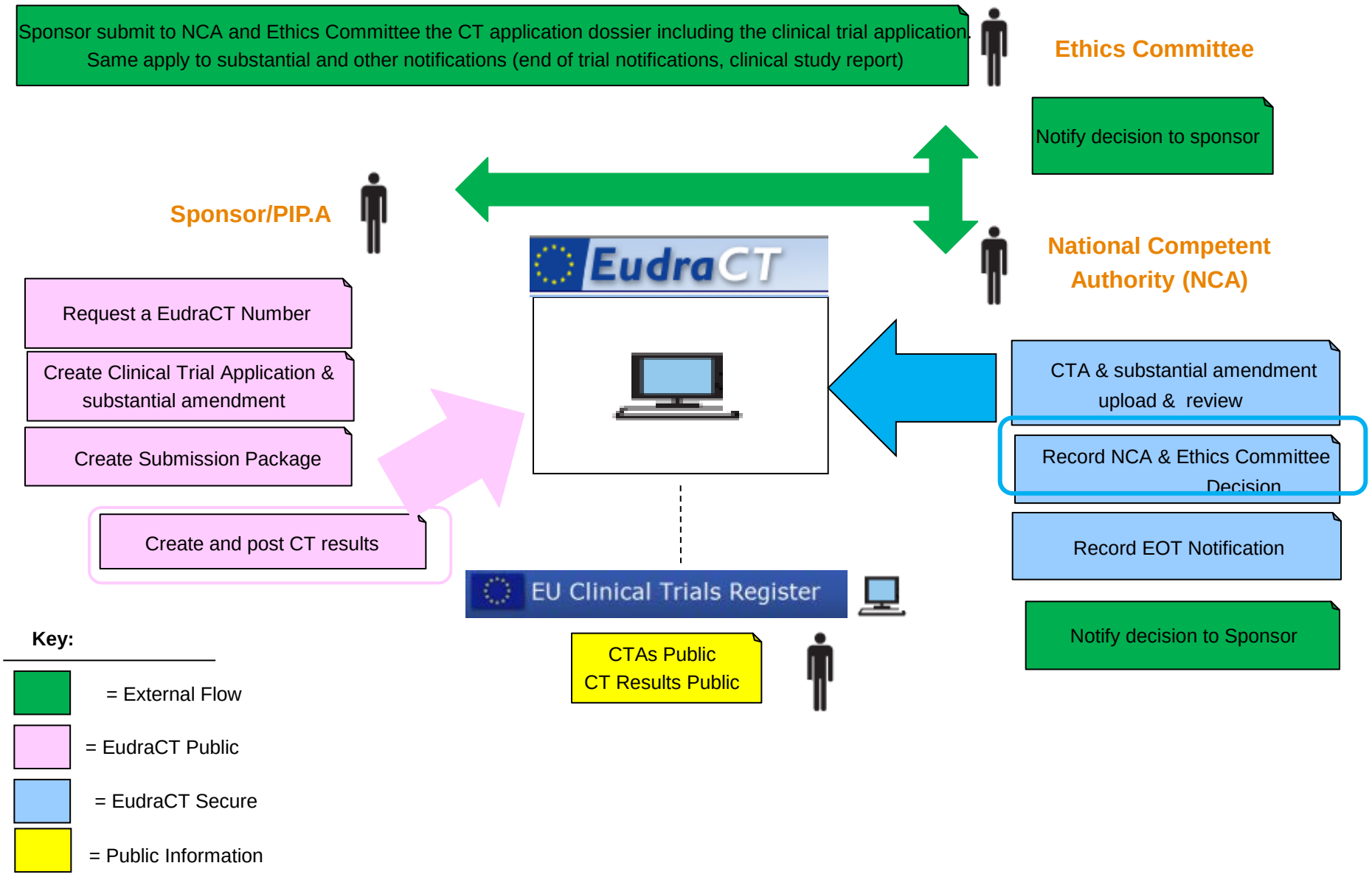
- Have all clinical trials been publicly registered?
- Is there a trial in which I could participate?
- What was the outcome of the trial I did participate in?
- What trials were the basis of the marketing authorisation, what were their results?
- What is known about the medicine I am taking/prescribing?
- Can we analyse the data used to support the marketing authorisation?
- Has the trial we are designing already been conducted? Were there problems with similar trials?

Clinical Trial Transparency: an overview

- **EudraCT and EUCTR**
- **The EU Portal and EU Database**
  - Clinical Trial Regulation (Regulation (EU) No 536/2014)
- **Other initiatives: EMA Policy on Clinical Data Publication**
  - Policy 0070 “European Medicines Agency policy on publication of clinical data for medicinal products for human use”

EudraCT

- Legal Framework: Article 11 of Directive 2001/20/EC (current legal framework)
- One trial consists of a clinical trial application dossier per MS (for interventional trials)
- A clinical trial application dossier consists of several documents but only the clinical trial application (CTA) is uploaded in the database (EudraCT)
- The database (secure) is only accessible by the Competent Authorities, European Commission and EMA
- Since October 2013, **sponsors can log on (EudraCT public) to prepare and post the summary results of CT**
- **Source of data for EU CTR** and WHO ICTRP


Sponsor submit to NCA and Ethics Committee the CT application dossier including the clinical trial application.
Same apply to substantial and other notifications (end of trial notifications, clinical study report)
Ethics Committee
Notify decision to sponsor
Sponsor/PIP.A
National Competent Authority (NCA)
EudraCT
Request a EudraCT Number
Create Clinical Trial Application & substantial amendment
Create Submission Package
Create and post CT results
CTA & substantial amendment upload & review
Record NCA & Ethics Committee Decision
Record EOT Notification
Notify decision to Sponsor
EU Clinical Trials Register
CTAs Public
CT Results Public
Key:
= External Flow
= EudraCT Public
= EudraCT Secure
= Public Information

Results in EudraCT V10

- Official date of the end of the programming of EudraCT = 21 July 2014.
  The posting of summaries of clinical study results in the European Clinical Trials Database (EudraCT) is mandatory for Sponsors as of 21 July 2014.
- This date corresponds to the finalisation of the programming of the database as referred to in a European Commission guideline on results related information (2012/C 302/03).

Press release:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/06/news_detail_002127.jsp&mid=WC0b01ac058004d5c1

Results in EudraCT V10

- Results are provided for the trial and not per CTA

- Results can be presented as follows:
  - ✓ With an attachment only (PDF…): option reserved for old trials that have ended in the past and before 21 July 2013
  - ✓ With structured data (full data set - with or without attachment):
    - Trials that have ended on or after 21 July 2013 (less than a year before the finalisation of EudraCT)
    - Trials that have ended before 21 July 2013 and include paediatric population

- Delay of 14 days between the posting date and the publication date

EU Clinical Trials Register

Clinical trials

The European Union Clinical Trials Register allows you to search for protocol and results information on:

- interventional clinical trials that are conducted in the European Union (EU) and the European Economic Area (EEA);
- clinical trials conducted outside the EU / EEA that are linked to European paediatric-medicine development.

Learn more about the EU Clinical Trials Register including the source of the information and the legal basis.

The EU Clinical Trials Register currently displays **23940** clinical trials with a EudraCT protocol, of which **3184** are clinical trials conducted with subjects less than 18 years old.

The register also displays information on **17724** older paediatric trials (in scope of Article 45 of the Paediatric Regulation (EC) No 1901/2006).

EU Clinical Trials Register

- Launched in March 2011
- Contains **protocol and results** related data for interventional CT started after May 2004
  - Phase II-III-IV trials conducted in adults in the EEA
  - Phase I-II-III-IV paediatric trials in the EEA
  - Phase I trials conducted in adults & part of a Paediatric Investigation Plan (PIP) are made public (small %)
  - NCA decision positive and IEC opinion positive recorded in EudraCT for adult trials – for paediatric trials IEC opinion positive or negative
  - Paediatric CT outside of the EEA if they are part of an agreed PIP

EU CTR and summary results of trials

42 result(s) found. Displaying page 1 of 3.

1 2 3 Next»

EudraCT Number: 2010-019524-31	**Sponsor Protocol Number:** REC15/2375–IT–CL 0332			**Start Date*:** 2010-06-08	
Sponsor Name: RECORDATI					
Full Title: Safety of an ACE-I/CCB fixed combination (Lercanidipine/Enalapril) in elderly hypertensive patients not adequately controlled by CCB monotherapy					
Medical condition: Essential Hypetension					
Disease:	**Version**	**SOC Term**	**Classification Code**	**Term**	**Level**
	12.1		10015488	Essential hypertension	LLT
Population Age: Elderly				**Gender:** Male, Female	
Trial protocol: IT *(Completed)*					
Trial results: View results					

Summary results

Clinical Trial Results:

Safety of an ACE-I/CCB fixed combination (Lercanidipine/Enalapril) in e adequately controlled by CCB monotherapy

Summary	
EudraCT number	2010-019524-31
Trial protocol	IT
Global completion date	29 Sep 2011
Paediatric regulatory details	
Is the trial part of an agreed EMA paediatric investigation plan?	No
Is the trial in scope of article 45 of Regulation (EC) No 1901/2006?	No
Is the trial in scope of article 46 of Regulation (EC) No 1901/2006?	No
Results information	
Results version number	v1(current)
This version publication date	05 May 2014
First version publication date	27 Apr 2014
Other versions	
Summary report(s)	SUMMARY

Document title	**Clinical Study Report Synopsis**
Study title	**Efficacy and safety of agomelatine (25 mg/day with potential adjustment to 50 mg) given orally for 8 weeks in out-patients with severe Major Depressive Disorder.** **A randomised double-blind, parallel groups, international study *versus* fluoxetine (20 mg/day with potential adjustment to 40 mg) with a double-blind extension period of 16 weeks.**
Study drug	**Agomelatine (S-20098)**
Indication	**Major Depressive disorder**
Development phase	**III**
Protocol code	**CL3-20098-045**
Study initiation date	**06 October 2005**
Study completion date	**14 March 2008**
Main coordinator	[redacted] **UNITED KINGDOM**
Sponsor	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 rue Carnot** **92284 Suresnes Cedex – France**
Responsible medical officer	[redacted] **(I.R.I.S.)**
GCP	**This study was performed in accordance with the principles of Good Clinical Practice including the archiving of essential documents.**
Date of the report	**Final version of 10 March 2009**
	~~CONFIDENTIAL~~

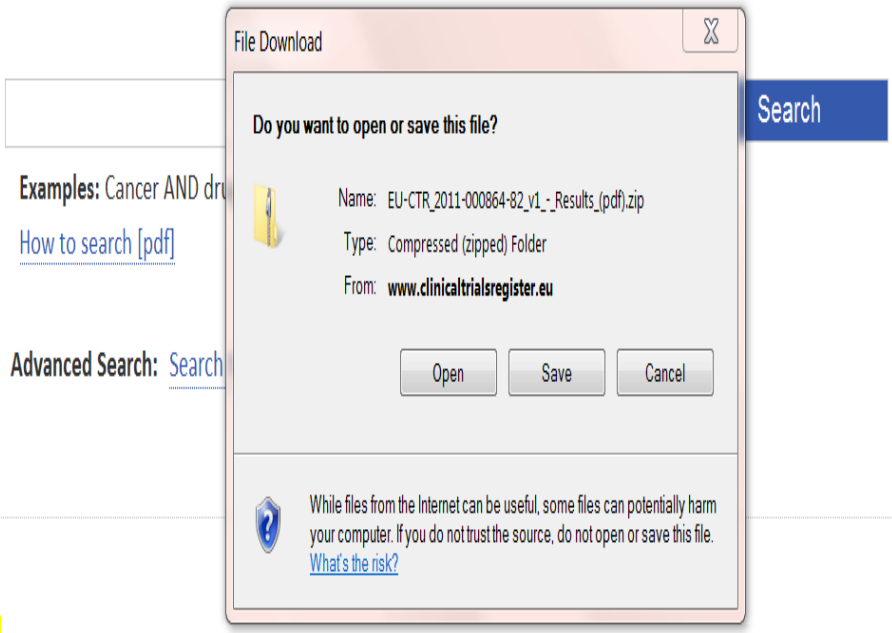
Note: The legislation allows summary attachments to be posted instead of the full dataset for this trial. Refer to Commission Guideline 2012/C 302/03 for further information.

Summary	
EudraCT number	2011-000864-82
Trial protocol	NL
Global end of trial date	12 Jun 2013
Results information	
Results version number	v1(current)
This version publication date	26 Jun 2014
First version publication date	26
Other versions	

Trial Information
Subject Disposition
Baseline Characteristics
End Points
Adverse Events
More Information

Primary: RBMT - immediate memory		Top of page
End point title	RBMT - immediate memory	
End point description		
End point type	Primary	
End point timeframe	Cognitive performance was measured after each treatment period.	
End point values	Subjects receiving a low dose of hydrocortisone	Subject receiving a high dose of hydrocortisone
Number of subjects analysed	47	47
Units: Zscore	-0.41 ± 0.95	-0.42 ± 1.33
arithmetic mean (standard deviation)		

Nervous system disorders		
Sciatica		
subjects affected / exposed	0 / 58 (0.00%)	1 / 55 (1.82%)
occurrences all number	0	1
Eye disorders		
Diplopia with surgical correction		
subjects affected / exposed	0 / 58 (0.00%)	1 / 55 (1.82%)
occurrences all number	0	1
General disorders and administration site conditions		
Tiredness		
subjects affected / exposed	3 / 58 (5.17%)	1 / 55 (1.82%)
occurrences all number	3	1
Dizziness		
subjects affected / exposed	1 / 58 (1.72%)	1 / 55 (1.82%)
occurrences all number	1	1



Clinical Trial Results:

A randomized double blind cross-over study of the effects of low dose and high dose hydrocortisone replacement therapy on cognition, quality of life, metabolic profile and somatosensation in patients with secondary adrenal insufficiency

THE EU PORTAL AND EU DATABASE
REGULATION (EU) No 536/2014

Legal basis

Art 80 – EU Portal

"*The Agency shall, in collaboration with the Member States and the Commission, set up and maintain a* ***portal at Union level*** *as a single entry point for the submission of data and information relating to clinical trials in accordance with this Regulation. The EU Portal shall be technically advanced and user friendly so as to avoid unnecessary work.*

Data and information submitted through the EU portal shall be stored in the EU Database."

Art 81- EU Database

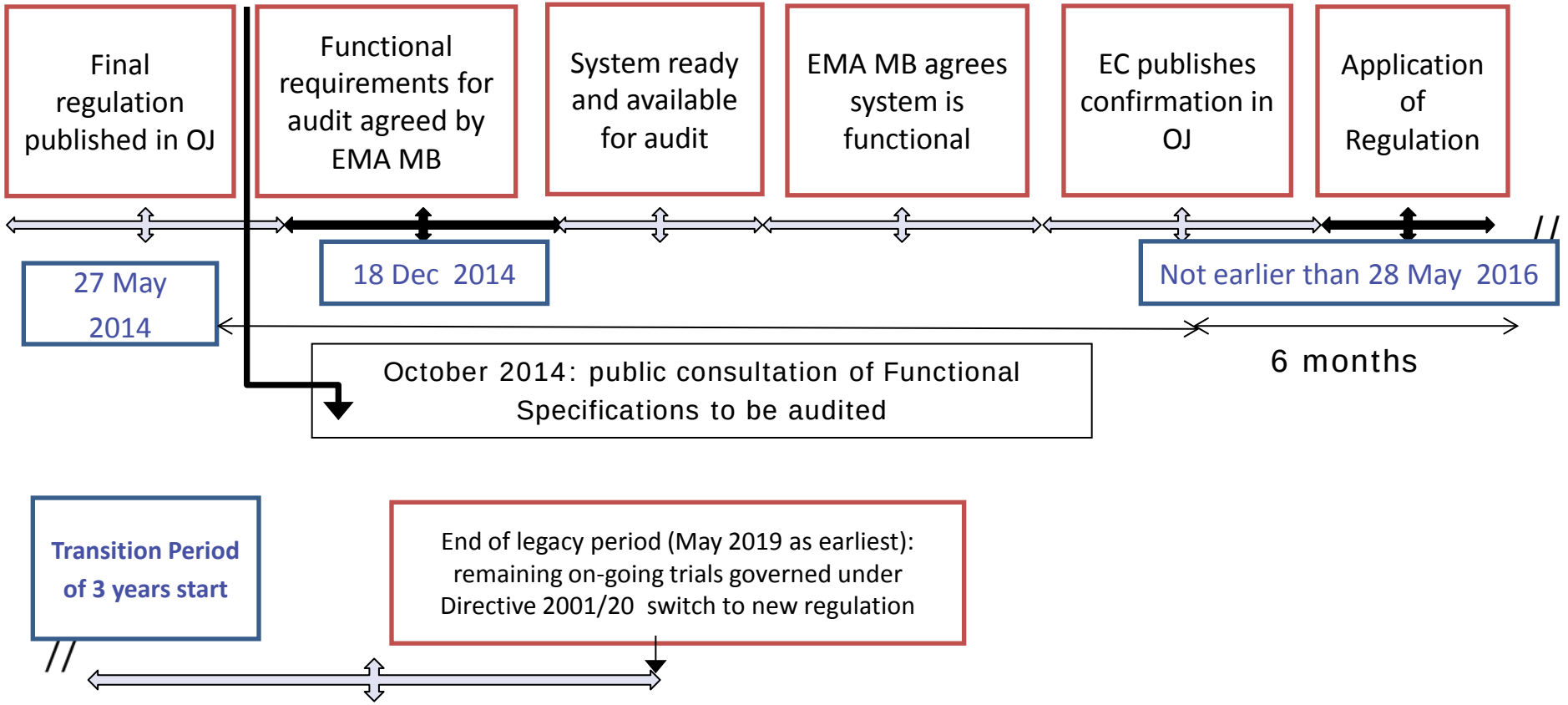
"*The Agency shall, in collaboration with the Member States and the Commission,* ***set up and maintain a EU database*** *at Union level. The Agency shall be considered to be the controller of the EU database and shall be responsible for avoiding unnecessary duplication between the EU database and the EudraCT and Eudravigilance databases."*

Single EU Portal and Database

Single EU portal and database to support:

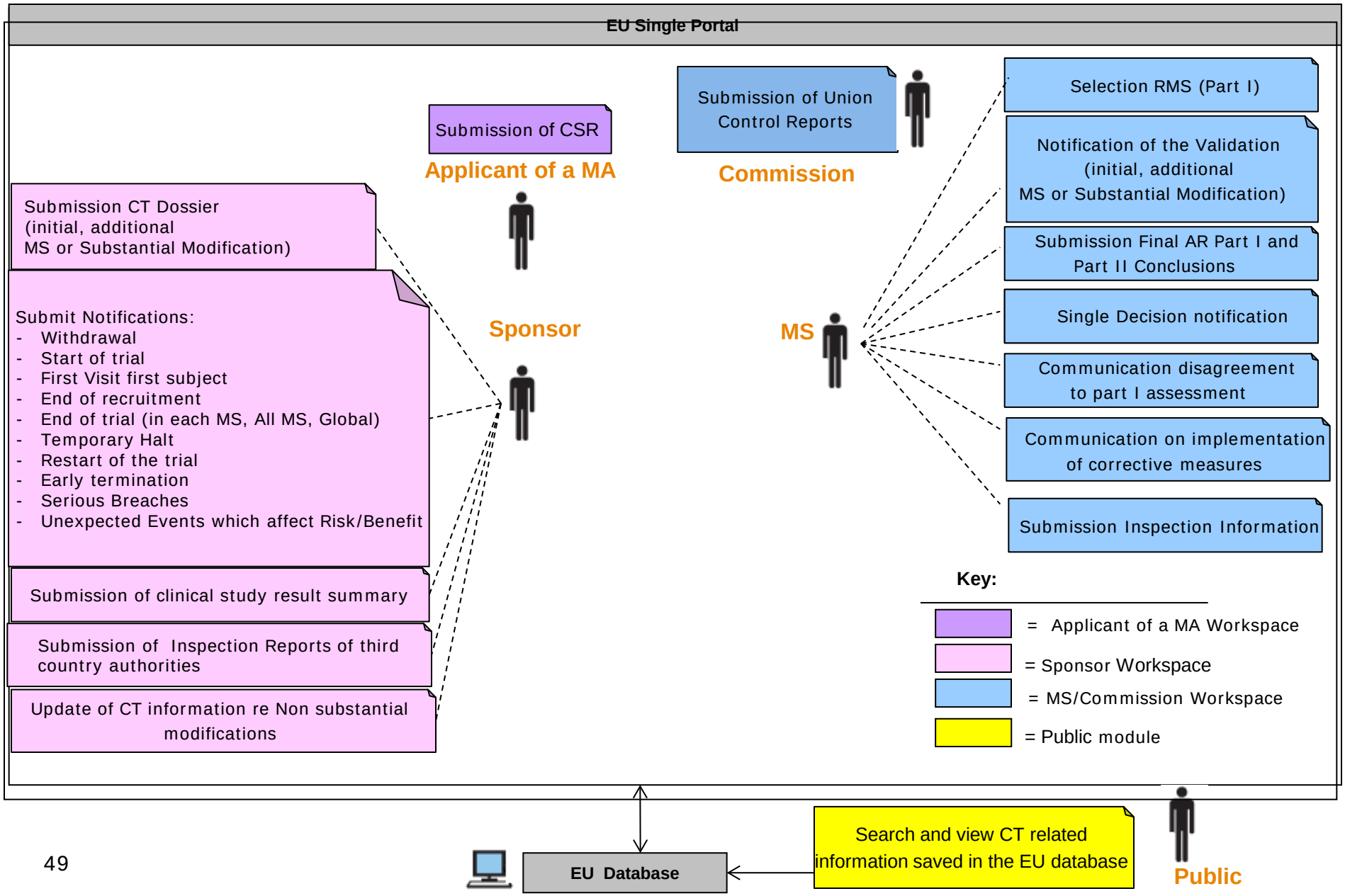
- One application dossier for each clinical trial or modification to it
- Coordinated approach to clinical trial authorisation and supervision
- **Transparency of clinical trial authorisation, conduct and results**

CT regulation timelines/key milestones



Regulation applies 6 months after the publication of the confirmation note in the OJ and not earlier than 2 years after the publication of the Regulation (Not earlier than 28th May 2016)

EU Portal and Database



Draft functional specifications for the EU Portal and EU Database to be audited

Public consultation: 10 October – 31 October 2014

http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2014/10/WC500175227.pdf

Functional specifications – EU Database

4- EU DATABASE			
No	**Functional specification**	**Details**	**Link to the legal requirements presented in Table 1**
4.1	Document store and database	The EU database should enable the storage and retrieval of documents and data specified by the legislation as being saved in the EU database. The document and data store should allow: • Metadata elements associated with all documents and data to be captured. • Support multiple aggregations without duplication. • Every record and associated aggregation must have a unique identifier persistently linked to it. This allows to the user to locate records and helps them to distinguish between versions. • Establish a classification scheme that can facilitate the capture, titling, retrieval, maintenance and disposal of records by defining the way in which individual electronic records are grouped together (aggregated). • Records may be altered or deleted by system administrators.	Req. 1 to 17
4.2	Document and data retention	Retention period to be unlimited.	Req. 1-17
4.3	Publication of CT data and information	The clinical trial data and information is to be made publicly available through a publication module according to detailed rules to be defined. The rules are to be automated and implemented through the publication module taking into consideration the workflow of the trial.	Req. 18
4.4	Search functionality	The public user interface to allow querying the clinical trial information by use of metadata based on fields present in the application dossier, MSC notification and decision and to have download functionalities.	Req. 18

Functional specifications – EU Database

4 - EU DATABASE					
No	**Functional specification**	**Sponsor/ Applicant**	**MS/EC**	**Details**	**Link to the legal requirements presented in Table 1**
4.5	Presentation of the information	Allow related information to be grouped together by way of the EU trial number with links or display of data and document of relevance.			Req. 18
4.6	Download option	The public user interface to enable the download of document and data as XML and other document format (e.g. pdf, word, excel etc).			Req. 18
4.7	Public interface	The public interface to support all Union official languages.			Req.18
4.8	Help and training features	Allow for online help and tooltips to be made available to the public to assist in the understanding of the information published.			Req.18
4.9	Dependencies with other systems	The data terms in the EU database to use the master data list. Enable the transitions from using current Master data system (e.g. EUTCT) to future Master data management (e.g. Substance and Product management systems, organisation management system and referential management system). To be able to use master data in such a way that it can be linked to future versions of those terms.			Req. 1 to 17

Transparency

EU database publically accessible by default, with exceptions justified on any of the following grounds - Art 81 (4):

- Protection of personal data
- Protection of commercially confidential information in particular taking into account the MA status of the medicinal product, unless there is an overriding public interest in disclosure
- Protecting confidential communication between MS in relation to the preparation of the assessment report
- Ensuring effective supervision of the conduct of a clinical trial MSs

Transparency

Recital 67 – EU Database

- Ensure a sufficient level of transparency … the EU Database should contain all relevant information as regards the clinical trial submitted through the EU Portal
- Publicly accessible
- Data should be presented in an **easily searchable format**
- **Related documents and data linked together** by the EU trial number: e.g. linking together the summary, the layperson's summary, the protocol and the clinical study report
- Start and end dates of recruitment of subjects should also be published
- **No personal data** of data subjects participating in a clinical trial should be recorded
- Publicly available information should contribute to protecting public and fostering the capacity of European medical research, while recognising the legitimate economic interest of sponsors

Transparency

Recital 68

- CSR should not be considered commercial confidential once MA is granted or application withdrawn
- In general should not be considered confidential:
  - Main characteristics of a trial
  - Conclusion on Part I of the assessment report for authorisation of a clinical trial
  - Decision on the authorisation of a clinical trial
  - Substantial modification of a clinical trial
  - Clinical trial results including reasons for temporary halt and early termination

Transparency – Results of clinical trials

- **Specific obligations on sponsor to submit summary of results and lay person summary one year after the end of the trial**
  - this applies to all clinical trials authorised under the new regulation or transitioned to it
- **MAH required to submit the CSR once the MA procedure is complete (positive or negative) or withdrawn by the applicant**
  - this applies to trials in a MA with EU sites and authorised under the new regulation – hence not to non-EU trials or trials in EU authorised under current legislation
- **MS introduce the penalties for breach of transparency provisions**

Transparency – Results of clinical trials

Annex IV – Content of the Summary of the Results of the Clinical Trial

- Clinical Trial Information
- Subject Disposition
- Baseline Characteristics
- End points
- Adverse Events
- Additional Information

Transparency – Results of clinical trials

Annex V–Content of the Summary of the Results of the CT for Laypersons

- Clinical Trial Identification
- Name and contact details of the sponsor
- General information (where and when conducted, main objectives, reasons for conducting it)
- Population of subjects (number of subjects, age group breakdown, gender breakdown, inclusion and exclusion criteria)
- Investigational medicinal products used
- Description of adverse reactions and their frequency
- Overall results
- Comments on the outcome of the clinical trial
- Indication if follow up clinical trials are foreseen
- Indication where additional information could be found

Functional specifications of the EU Portal and Database and transparency

Functional specifications and underlying principles to support the transparency requirements of the Regulation currently being prepared:

- Will become integral part of the Functional Specifications
- **Public consultation** planned for early 2015
- To be completed at the latest by March 2015

Clinical Trial Transparency: Other Initiatives

EMA Policy on Clinical Data Publication (Policy 0070)

- **Scope**
  - Clinical data: **clinical reports** (i.e. clinical overviews (module 2.5), **clinical summaries** (module 2.7) and **CSRs** (module 5), together with appendices (16.1.1, 16.1.2 and 16.1.9) and individual patient data (IPD)
  - Submitted under the **centralised procedure**: initial **Marketing Authorisation Application**, post-authorisation procedures, **after the effective date**

Clinical Trial Transparency: Other Initiatives

EMA Policy on Clinical Data Publication (Policy 0070)

- Stepwise implementation:
  - First phase: publication of clinical reports only
  - Second phase: review of various aspects in relation to IPD
- Effective date:
  - 1 January 2015 for any new MAA submitted as of that date
  - 1 July 2015 for extensions of indication/line extension applications for CAPs submitted as of that date
  - Other post-authorisation procedures: effective date TBD

Conclusion

Europe is paving the way on further increasing transparency on clinical trials to:

- Support public scrutiny and critique – establishing trust and confidence in the system
- Inform and enable participation in discussion in clinical trials
- Foster innovation

Thank you for your attention

Further information

Anabela Marcal
anabela.marcal@ema.europa.eu

European Medicines Agency
30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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Regulatory Perspective, FDA

Richard Moscicki, MD

Jerry Menikoff, MD, JD

OHRP

NEJM Perspective

Jeffrey Drazen, MD

Return of Results to Participants

Harvard MRCT Panel

December 3, 2014

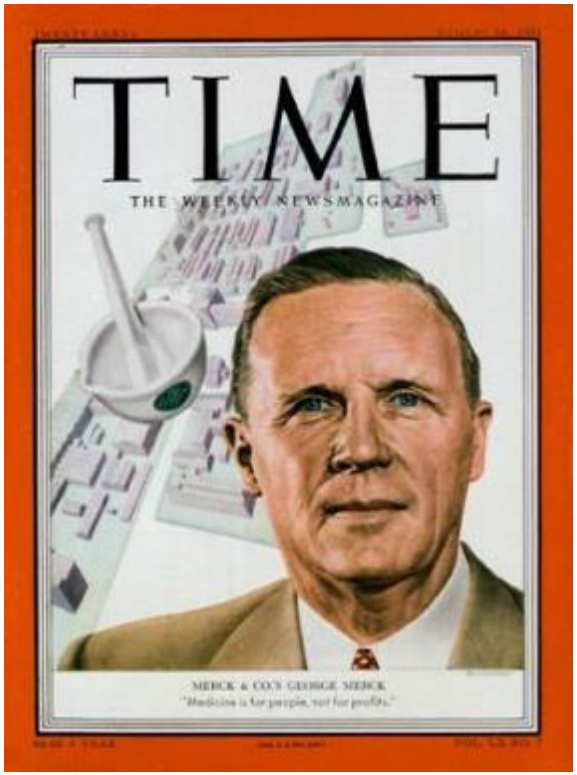
Dr. Michael Rosenblatt

Chief Medical Officer, Merck & Co., Inc.

MERCK

Be well

A Responsibility Beyond Our Products



"We try never to forget that medicine is for the people. It is not for the profits.

The profits follow, and if we have remembered that, they have never failed to appear."

- George W. Merck, 1950

MERCK
Be well

Key Issues for Discussion

Focus on the perspective of the patient/research participant
Rationale for global harmonization of return of results policies
FDA guidance to industry on promotional questions
Transparency – clear link between data and conclusions
Interest in bi-directional exchange with patients (not one-way street); learn their perspective on benefit:risk
Critical importance of health literacy and clear communication

Example of collaboration - Patient labeling

Partnership with Merck and academia (Northwestern/Emory), engagement with FDA

Demonstrate increased patient understanding and use by optimizing development and testing of PPI (Patient Package Insert)

High comprehension in qualitative research by respondents with both low and adequate health literacy (>90%)

Recommendations

Transparent, timely disclosure of return of results to participants
Continued partnership to model health literate return of results – focus on the patient
Alignment of global requirements for return of results
Engagement with Regulators to address promotion issues

Principles for Communicating Clinical Trial Result Summaries with Study Volunteers

Jocelyn Ulrich, PhRMA

PhRMA
RESEARCH • PROGRESS • HOPE

Background

- Research has shown that volunteers want to be informed about the results of the clinical trial[1]
- Many sponsors of clinical research have indicated interest in making summaries of results available to participants and/or the public[2]
- Section 801 of FDAAA requires study sponsors to make results of "applicable trials" publicly available on the clinicaltrials.gov database
  - Volunteers must be made aware they have access to it as part of the informed consent form.
    - Participants may not have access to the internet
    - Tabular format difficult to understand

PhRMA RESEARCH • PROGRESS • HOPE

Background (cont.)

- Section 801 of FDAAA provides for the possible dissemination of a "summary of the clinical trial and its results that is written in non-technical, understandable language for patients ("lay summaries")
- Lay summaries can only be **required** through formal rulemaking **and** *only* if the Secretary of HHS determines that such summaries can be drafted "without being misleading or promotional"
- EFPIA – PhRMA Principles for Responsible Clinical Trial Data Sharing (2013) include a commitment for pharmaceutical companies to work with regulators to adopt mechanisms for providing a factual summary of clinical trial results and make the summaries available to research participants

PhRMA
RESEARCH · PROGRESS · HOPE

Purpose

- FDA regulations prohibiting sponsors from representing that an investigational new drug is safe of effective are "not intended to restrict the full exchange of scientific information"[3]
- FDAA provisions also recognize the importance of disseminating clinical trial results whether positive, negative, or inconclusive
- Public health and policy justifications designed to foster full and open scientific exchange apply to the communication of clinical trial results to study volunteers
- Fostering open communication about results may strengthen the clinical research enterprise

PhRMA
RESEARCH · PROGRESS · HOPE

Principles for Communicating Clinical Trial Result Summaries with Study Volunteers

- Clinical trial summaries should:
  - Accurately describe the results of a clinical trial in a format that provides the most important information
  - Avoid as much as possible technical or scientific jargon
  - Provide a basic description of the results for the efficacy and safety endpoints in the trial that the volunteer participated
  - Make clear that the product may not be approved by the FDA for which it was studied
  - Make clear that the results studied for the product are current as of the issue date and for the specific study, may not be consistent with how product was approved by FDA, and should not be viewed as certain or final
  - Encourage patients to discuss the relevance of the results on their health with their doctor

PhRMA
RESEARCH · PROGRESS · HOPE

Principles for Communicating Clinical Trial Result Summaries with Study Volunteers (cont.)

- Information communicated should:
  - Not be false of misleading
    - But this does not require the sponsor to include information from any source other than the clinical trial described in the lay summary.
  - Provide a factual description of the study results

Source of Study Summary

- Study summaries intended for dissemination to clinical study volunteers should be prepared with input by individuals with appropriate scientific and/or medical training

Manner in which to Disseminate Clinical Trial Information

- Because participants have different preferences to access clinical trial information, it is important to maintain flexibility in how it is disseminated
- Study sponsors may provide information to volunteers through any of the following forms:
  - Hard-copy, written document (e.g. given by sponsor or investigator)
  - Password-protected website
  - Password-protected telephone line
  - Posting on ClinicalTirals.gov (when regulations are implemented)
  - Electronic transmission
  - Public posting on company or other web site

PhRMA RESEARCH · PROGRESS · HOPE

Summary

- Public health can be served when study participants receive truthful and non-misleading scientific and medical information regarding the results of the clinical investigations in which they participated

MRCT Annual Meeting
December 3, 2014

Elizabeth Frank
Patient Advocate
Dana Farber Cancer Institute/Harvard Cancer Center

In conversation with advocates…

- "As a social worker who works with hundreds of patients yearly, I continually hear from participants in clinical trials how much they would like to see results. There is an overall feeling of being dismissed or invisible when one never hears the results."
- "Personally, I have participated in several trials and never heard results. I think that any participant would want to know the results of their efforts."
- "If we are able to explain the importance of a trial, then we also have to believe that those patients can understand the results."
- "I think there is much mistrust of clinical trials and that having the opportunity to review the results would provide some validity."
- "Patients are, through participating, working with researchers to find answers and want to know the results of their work."

Patients as Partners in Research

- Patients are a critical part of our clinical trials system
- They deserve the opportunity to learn about the results of studies in which they participate
- They should be thanked and feel appreciated for their participation in research
- They should have a sense of how their participation contributes to future knowledge
- Sharing results increases the transparency of medical research
- Can lead to increased motivation to participate in and support research

What do clinical trial participants want know?

- What were the results of the trial in which I participated?
- How are these results being used to help patients?
- How did my experience on the clinical trial compare to the experience of other patients?
- Did my participation make a difference?
- What do the clinical trial results mean for me?

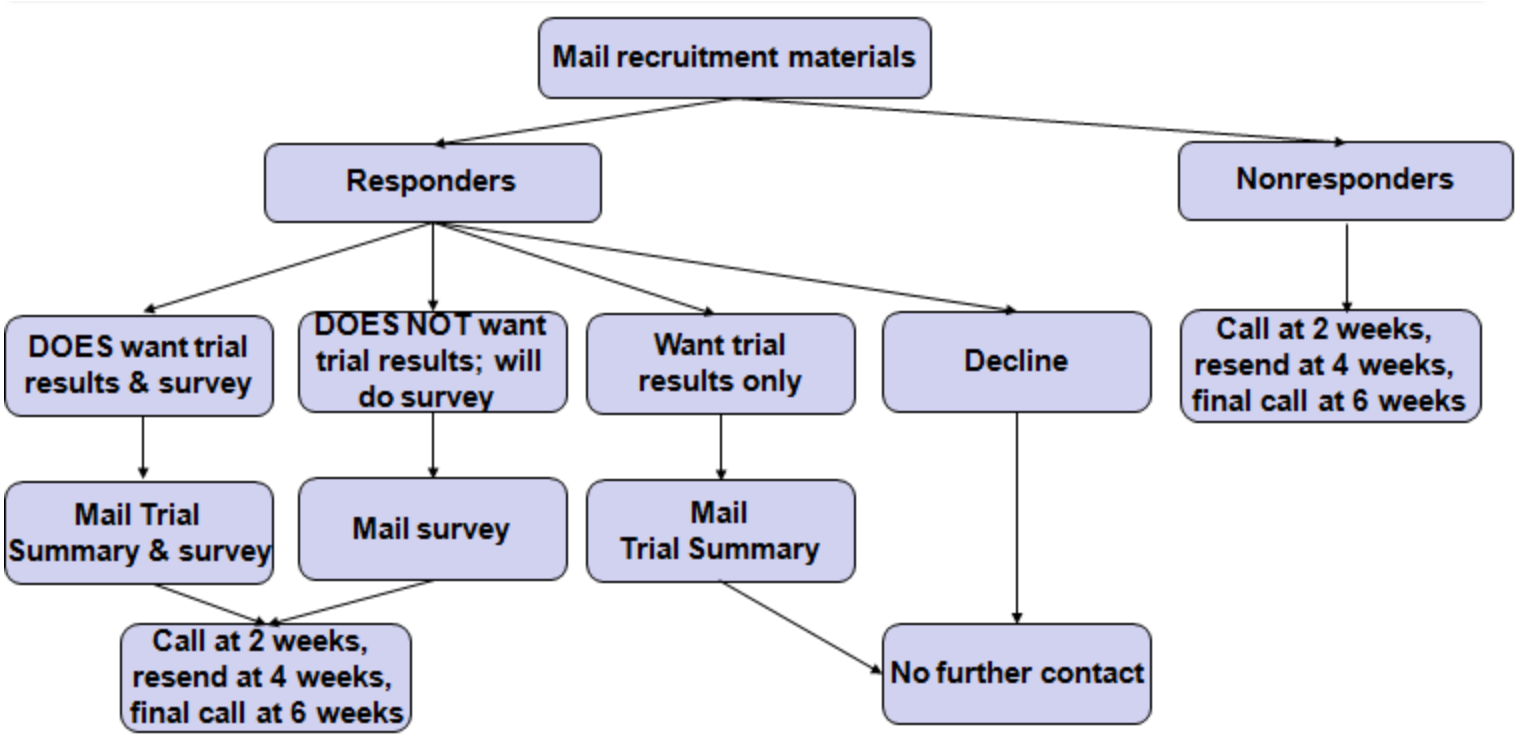
Patient Advocate Collaborations

- The CALGB/Alliance and ECOG Cooperative Groups
- Translational Breast Cancer Research Consortium (TBCRC)
- ISPY-2 Clinical Trial
- Dana Farber Cancer Institute /Harvard Cancer Center Breast Cancer Advocates (DFCI/HCC)

DF/HCC Breast Cancer Advocates

- 14 breast cancer patients/survivors interested in research related issues
- Created 8 years ago for NCI funded breast cancer SPORE
- Mission is to support and enhance the work of the DF/HCC investigators by providing an informed patient perspective
- Led a project in collaboration with Dr. Ann Partridge to develop tools and procedures for sharing the results of an investigator initiated trial to patient participants

Research Study Design



Lessons about returning results: Process

- 94% of the respondents believe clinical trial results should be offered to participants
- 88% were happy to receive the summary in the mail.
- 55% felt that the clinical trial results summary included the material they wanted. Most who felt differently wanted more detail.
- Most all reported reading the entire results summary

Lessons about returning results: Impact

- Being offered the results summary resulted in 56% of the participants feeling more appreciated for their participation
- 88% reported that reading the RSS did not have an effort on how often they felt anxious
- 24% were somewhat concerned about what they might learn when reading the results
- 97% were glad to have been offered the results summary

Conclusions

- All stakeholders benefit from offering to return research results
- Patients choosing to receive results are not likely to experience increased anxiety or concern.
- The level of detail and the type of information expected in a RRS varies among participants
- Protocols for clinical trial protocols should routinely include a plan to offer RSS to interested participants.

Thank you

- Dana Farber/Harvard Cancer Center Breast Cancer Advocates
- Dr. Ann Partridge, DFCI
- Deborah Collier, The Alliance
- TBCRC Patient Advocacy Group

Publication of NHLBI Cardiovascular Trials

David Gordon, MD, PhD
Division of Cardiovascular Sciences,
NHLBI/NIH

Harvard MRCT 3 -- December 3, 2014

Financial Disclosures: None.

Timeliness of publication of NIH Trials?

"Conclusions: Despite recent improvement in timely publication, fewer than half of trials funded by NIH are published in a peer reviewed biomedical journal indexed by Medline within 30 months of trial completion. Moreover, after a median of 51 months after trial completion, a third of trials remained unpublished."

BMJ 2011;344:d7292 doi: 10.1136/bmj.d7292 (Published 3 January 2012)

What's wrong with this picture?

Failure to publish complete trial results

- Reneges on the investigator's implicit promise to trial participants undertaking the burden and risk of participation to use the results to help others.
- Wastes taxpayer funds – opportunity cost.
- May foster promulgation of ineffective treatments.

➢ **Sharing data – at least at the study level – is not merely desirable; it is an ethical mandate.**

Analysis of 244 NHLBI Cardiovascular Trials (2000-2011)

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

Publication of Trials Funded by the National Heart, Lung, and Blood Institute

David Gordon, M.D., Ph.D., Wendy Taddei-Peters, Ph.D., Alice Mascette, M.D., Melissa Antman, Ph.D., Peter G. Kaufmann, Ph.D., and Michael S. Lauer, M.D.

ABSTRACT

BACKGROUND

Rapid publication of clinical trials is essential in order for the findings to yield maximal benefits for public health and scientific progress.

METHODS

We analyzed 244 extramural, randomized, clinical trials of cardiovascular interventions that were supported by the National Heart, Lung, and Blood Institute (NHLBI). We selected trials for which data collection had been completed between January 1, 2000, and December 31, 2011. Our primary outcome measure was the time between completion of the trial and publication of the main results in a peer-reviewed journal.

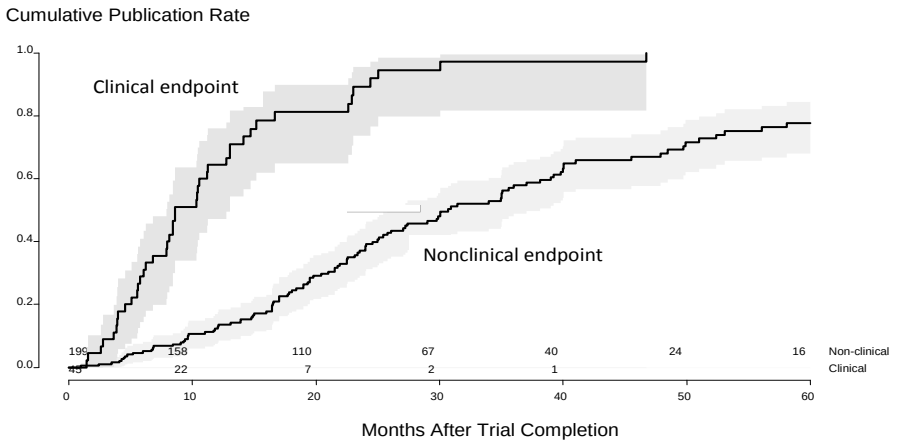
RESULTS

As of March 31, 2012, the main results of 156 trials (64%) had been published (Kaplan–Meier median time to publication, 25 months, with 57% published within 30 months). Trials that focused on clinical events were published more rapidly than

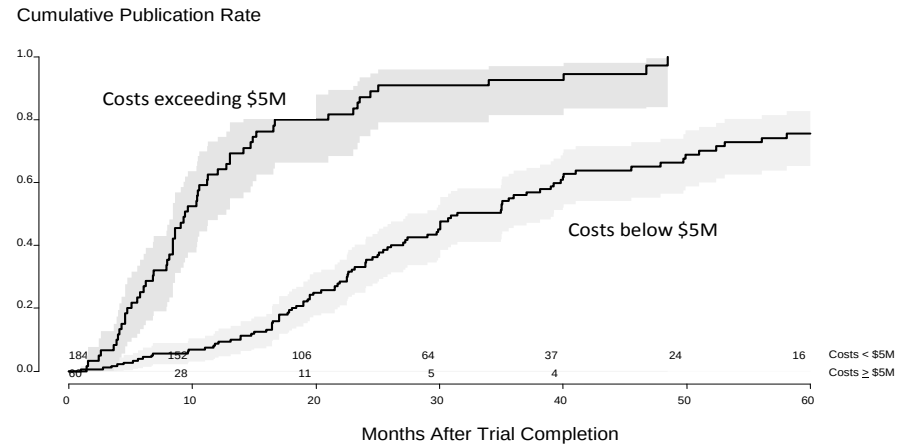
From the Office of Special Projects of the Division of Cardiovascular Sciences (D.G., W.T.-P., A.M.), Office of Science and Technology (M.A.), the Clinical Applications and Prevention Branch of the Division of Cardiovascular Sciences (P.G.K.), and Office of the Director of the Division of Cardiovascular Sciences (M.S.L.) — all at the National Heart, Lung, and Blood Institute, Bethesda, MD. Address reprint requests to Dr. Lauer at 6701 Rockledge Dr., Rm. 8128, Bethesda, MD 20892, or at lauerm@nhlbi.nih.gov.

N Engl J Med 2013;369:1926-34.
DOI: 10.1056/NEJMoa1300237

Kaplan Meier Publication Plots



Endpoint Type	# of Trials	% Published	
		12 mo	30 mo
Clinical	45	64%	95%
Other	199	12%	48%

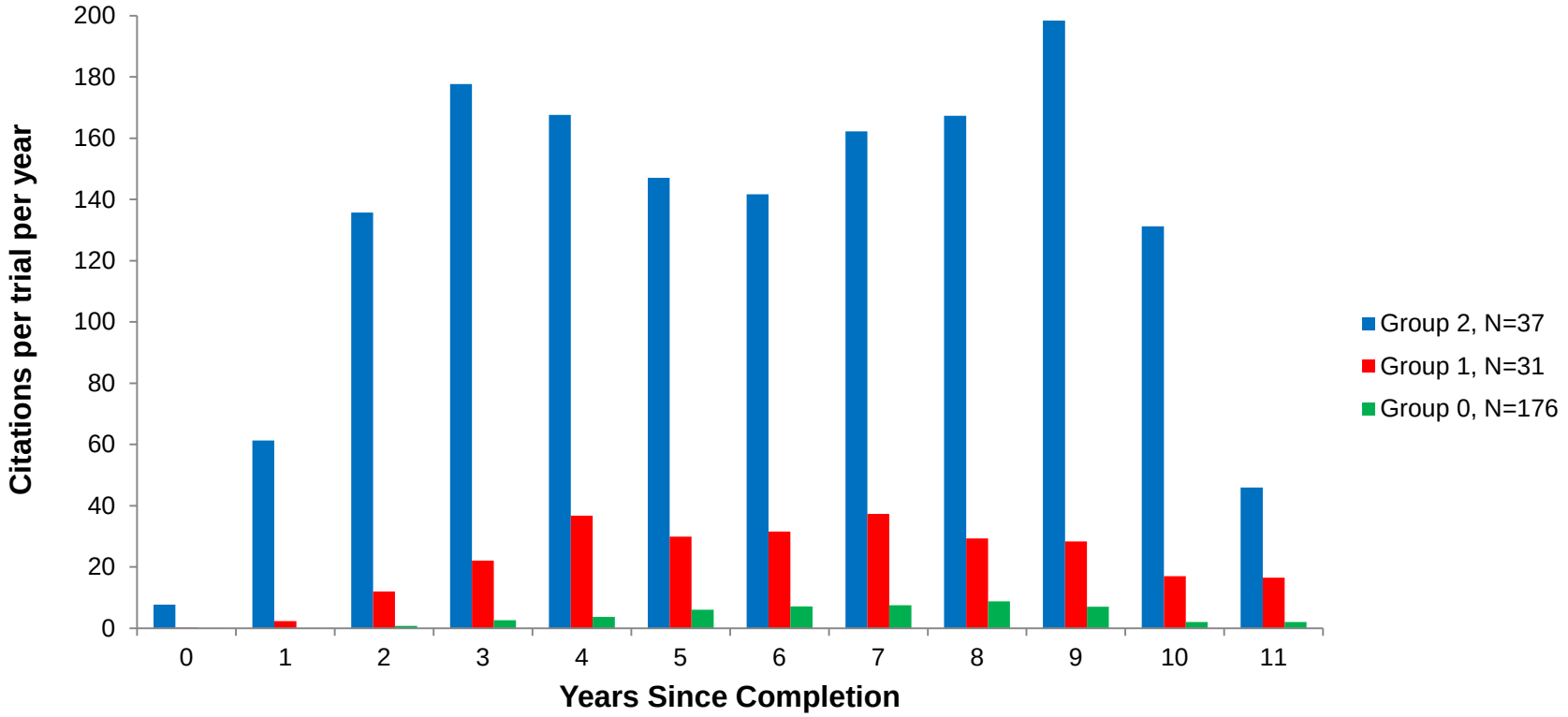


Cost	# of Trials	% Published	
		12 mo	30 mo
≥ $5 M	60	63%	91%
< $5 M	184	9%	45%

NIH National Heart, Lung, and Blood Institute

Annual Citation Rates for 3 Trial Categories

Group 2: Trials used clinical event as primary endpoint and cost ≥ $5 M.
Group 1: Trials used clinical event as primary endpoint or cost ≥ $5 M, but not both.
Group 0: Trials did not use clinical event as primary endpoint and cost < $5 M.



NIH National Heart, Lung, and Blood Institute

Preferential Publication of Positive Results

Clin. Ev. & Cost ≥ $5M	Number of Trials	Median Mo. to Publication	% Published at		
			12 mo.	30 mo.	48 mo.
Both (37 trials)					
Positive	6	7	83	97	100
Negative	31	9	68	100	100
One (31 trials)					
Positive	15	9	53	76	84
Negative	16	23	39	82	100
Neither (176 trials)					
Positive	80	31	10	49	73
Negative	84	36	5	41	61

Summary

- Large trials with clinical event endpoints and budgets ≥ $5 M publish quickly and are widely cited.
- Relatively inexpensive surrogate endpoint trials (which comprise >70% of NHLBI trials and consume 20% of the clinical trial budget) are slow to publish and make little impact.
  - 2 WHI HRT trial results papers have >10,000 citations – nearly 4 times as many as the 176 smaller trials combined.
- Modest bias toward more rapid publication of positive trials.

Why don’t investigators publish primary results?

- Flaws in design or execution. Examples:
  - Multiple outcomes; none designated as primary
  - Poor retention or compliance
  - Failure to observe intent-to-treat principle
  - Selective publication
- Lack of PI follow-up: Examples:
  - New projects
  - Career change
- Journal disinterest and/or delay

NIH Response

- All NIH-funded trials (not just those subject to FDAAA) will be required to register in ClinicalTrials.gov within 21 days of initiating enrollment and post summary results within 1 year of completing primary data collection.
- Failure to comply will negatively affect future NIH funding of grantee (i.e., institution) and principal investigator.

NHLBI Trials with ≥ 50 Citations per Year

	Trial Acronym	Completed	Published	Journal	Citations /Yr
1	WHI-EP	31-May-02	17-Jul-02	JAMA	828.5
2	ACCORD Diabetes	06-Feb-08	06-Jun-08*	N Engl J Med	314.7
3	ALLHAT-BP	31-Mar-02	18-Dec-02	JAMA	292.2
4	WHI-E	29-Feb-04	14-Apr-04	JAMA	252.7
5	SCD-HeFT	31-Oct-03	20-Jan-05	N Engl J Med	209.3
6	AFFIRM	01-Oct-01	05-Dec-02	N Engl J Med	177.7
7	REMATCH	27-Jul-01	15-Nov-01	N Engl J Med	123.2
8	WHS ASA	31-Mar-04	07-Mar-05*	N Engl J Med	109.1
9	ALLHAT-Dox	31-Jan-00	19-Apr-00	JAMA	83.7
10	PEACE	01-Dec-03	07-Nov-04*	N Engl J Med	72.1
11	WHI CD	31-Mar-05	16-Feb-06	N Engl J Med	71.5
12	ALLHAT-LLT	31-Mar-02	18-Dec-02	JAMA	67.6
13	ENRICHD	30-Apr-01	01-Jun-03	JAMA	63.3
14	BARI 2D	30-Nov-08	07-Jun-09*	N Engl J Med	52.9
15	PREVENT	01-Dec-02	24-Feb-03*	N Engl J Med	50.9
16	WHS E	31-Mar-04	06-Jul-05	JAMA	50.8

Publication Bias: Are negative trials slower to publish than positive trials?

- One person (Mike Lauer) reviewed all 156 published primary outcome papers and all available final reports of the 88 unpublished trials from NHLBI files.
- Scored positive if active treatment was significantly superior to control for the primary endpoint and negative otherwise. Did they prove what they set out to prove?
- Approximately 50 PIs with no available outcome reports were contacted on 24-Dec-2012. After responses were collected, the primary outcomes of only 12/244 trials– only 3/172 trials that were completed before 1-Jan-2010 -- remained unknown .

Relation of Outcome to Publication (unadjusted)

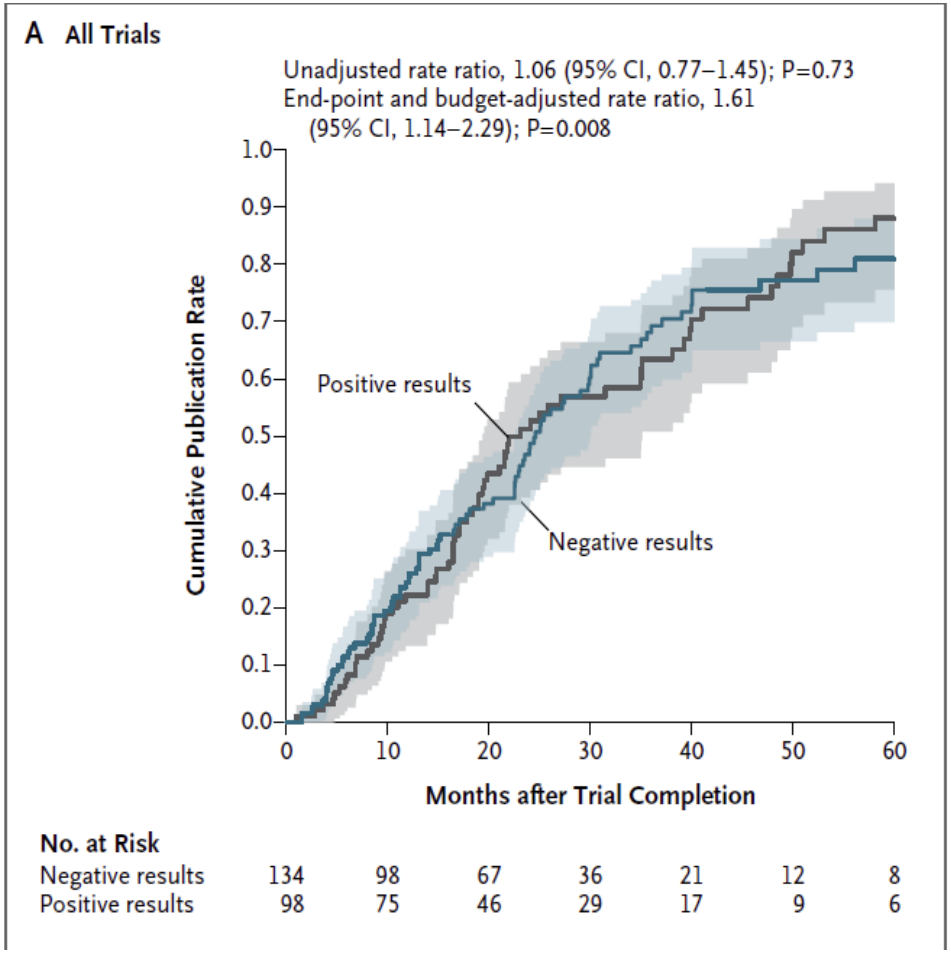
Completion Date	Number of Trials	Median Mo. to Publication	% Published at		
			12 mo.	30 mo.	48 mo.
All					
Positive	98	23	22	57	76
Negative	134	25	24	60	77
< 1/1/10					
Positive	71	22	21	58	76
Negative	97	25	23	59	77

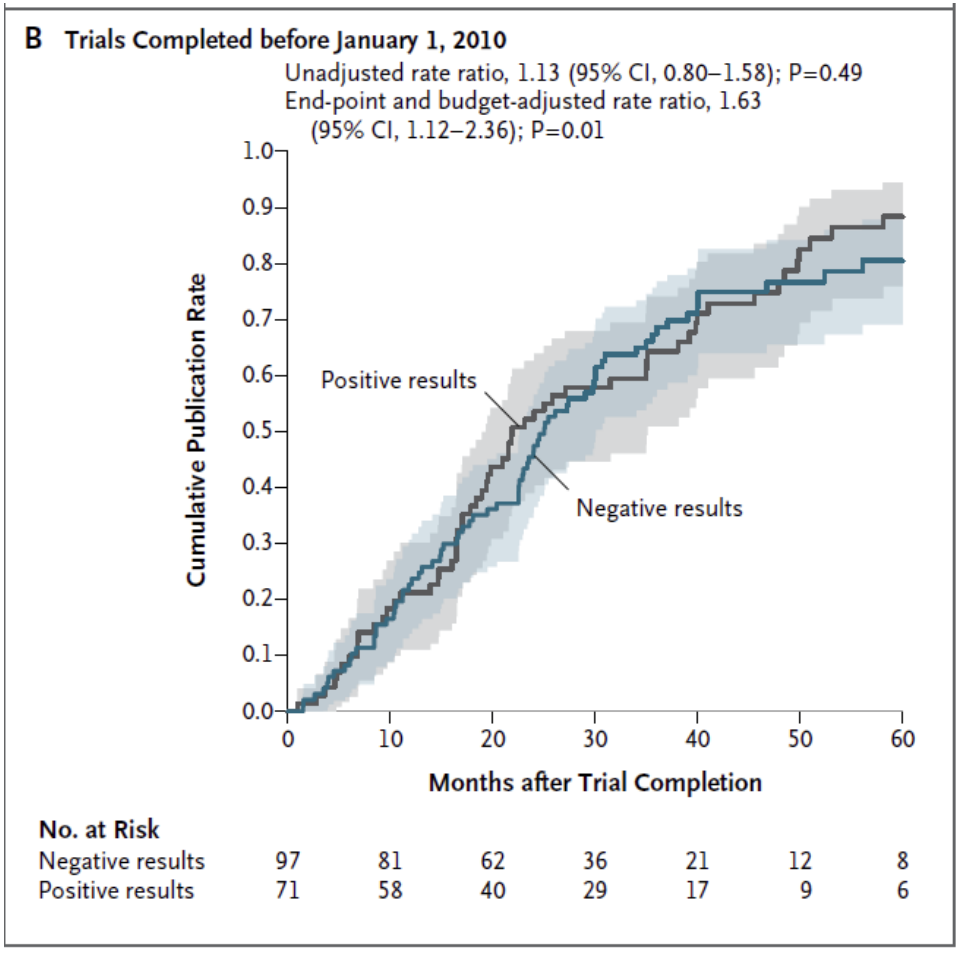
Primary Outcomes by Study Type

Primary end-point results	Clinical-Event EP & Cost ≥ $5M (N = 37)	Clinical-Event EP or Cost ≥ $5M, but not both (N = 31)	Neither Clinical-Event EP nor Cost ≥ $5 M (N = 176)
Positive	16%	48%	45%
Negative	84%	52%	48%
Uncertain	0	0	7%

- All results known for trials with clinical-event EP and/or cost ≥ $5M.
- 84% of trials with both clinical-events EP and cost > $5M were negative
- Just over 50% of other trials were negative

Publication of Positive and Negative Trials Kaplan Meier Plots





Harvard MRCT Return of Results Panel Discussion

Moderator: Mark Barnes, JD, LLM

Panel Discussion

- Are there tria/s or situations where return of results would be inappropriate/
- What is the role of IRB or other administrative review?
- Is there a centralized role for the sponsor in coordinating the communication, one that protects participant privacy but permits common information transfer?
- Given that utilization of the internet for communication is simple and cost effective, how should we approach the participants that do not have access to the internet?
- What are the implications for a global approach to return of aggregate results?
- Since return of results will be communicated often long after the trial is closed, how should questions from participants be managed?
- How can academic sponsors be motivated to participate?

Panel Discussion

- Next steps for the FDA, EMA, PhRMA, NEJM, NIH and OHRP to harmonize their efforts / guidelines on Returning Results? Timing?

- What role can Harvard MRCT play in facilitating this effort?

- Where can Harvard MRCT leverage its efforts moving forward?

    - *Pilot studies with sponsors using our guidance? (US vs ex-US)*
    - *Patient focus group testing of templates ?*
    - *Dissemination of the current materials?*
    - *Broaden our focus to individualized results return or genomics data?*

- Feedback on the Harvard MRCT effort?

- Questions from the audience

MRCT Multi-Regional Clinical Trials

The MRCT Center at Harvard

MRCT Center at Harvard: India Regulatory Update, Causality and Compensation

Building A Learning Community Among Key Stakeholders

Parlimentary Review

In 2011, Indian Parliament formed a committee to report on functioning of CDSCO, following the deaths of seven girls who had died while on an HPV vaccine observational study.

- *The Committee concluded that subjects who died were not adequately compensated and that compensation should be paid to the next of kin.*
- *The Committee also concluded that DCGI lacked clinical/scientific expertise and not able to judge exact scientific rationale as well as the appropriateness of conducting specific trials.*

In 2012, a public interest litigation (PIL) was filed before the Supreme Court of India against the MoHFW alleging several flaws in regulatory framework surrounding clinical trials in India.

In early 2013, the Supreme Court suspended the power of CDSCO/DCGI to approve clinical trials

New regulations followed

In Jan and Feb, 2013, the government issued new rulings, that essentially curtailed or inhibited the introduction of new trials in India.

These rulings mandated:

- Compensation in the case of injury or death during a clinical trial, to be provided by sponsor (not investigator or site)
- Sponsor to provide subject free medical management for injury during trial, for as long as required
- If injury related to the clinical trial, subject also entitled to financial compensation from sponsor
- If subject dies during trial, his/her nominee is entitled to financial compensation "over and above any expenses incurred on the medical management of the subject."

“Trial-related injury or death”

Defined very broadly as any injury during a trial due to:

- Adverse effect of investigational product(s) – even if anticipated
- Violation of the approved protocol, scientific misconduct or negligence by sponsor, sponsor representative, or investigator
- Failure of investigational product to provide the intended therapeutic effect
- Use of placebo in a placebo-controlled trial
- Adverse effects due to concomitant medication, excluding standard care, necessitated as part of approved protocol
- Injury to child in-utero due to participation of parent in trial
- Any clinical trial procedures involved in the study

Compensation

Formula:

$$\text{Compensation} = \frac{B * F \times R}{99.37}$$

Base amount is 800,000 rupees.

F is a multiplier based on age and corresponding working years lost.

R is the Risk Factor (factors seriousness and severity of the disease, presence of co-morbidity and duration of disease of the subject at the time of the enrollment in the clinical trial. Multiplier 0.5-4)

Range of formula is from 400000 rupees ($6667) to 73600000 rupees ($122666)

For death: **Expert** Committee recommendation, Licensing Authority determines

For serious adverse events other than death: **Ethics** Committee recommends, Licensing Authority determines

Relationship of causality to compensation

Compensation definition extremely broad (at this time). AEs thought to be “related to” the trial are, for example:

(1) the failure of the experimental agent to have the desired effect

(2) any harmful effect of a clinical trial procedure, even if the procedure was part of the standard of care for the condition

(3) the worsening of a condition that could have been expected due to the natural history of the disease condition.

Compensation

The amendment clarifying expectations for compensation of clinical trial related injury or death states that compensation will be made for:

(a) Adverse effect of investigational product(s)

(b) Violation of the approved protocol, scientific misconduct or negligence by sponsor or its representative or the investigator

(c) Failure of investigational product to provide intended therapeutic effect

(d) Use of placebo in placebo-controlled trial

(e) Adverse effect due to concomitant medication excluding standard care, necessitated as part of approved protocol

(f) For injury to child in utero because of the participation of parent in clinical trial

(g) Any clinical trial procedures involved in the study

See Ministry of Health and Family Welfare. GSR 53(E). Central Drugs Standard Control Organization, India. 2013 Jan 30. Available from: http://cdsco.nic.in/writereaddata/ GSR%2053(E)%20dated%2030.01.2013.pdf.

And other regulations and/or office orders:

- Ancillary care for any other illness afflicting patients in a clinical trial
- Clinical trials must be conducted in accredited site after review by accredited (and registered) IRB/REC, and only involving certified (accredited) investigators
- Clinical investigators may participate in no more than three clinical trials at any one time
- 50% of clinical trials must be performed in public hospitals with over 50 beds

Every informed consent must be video-recorded by a videographer and preserved

Structural issues

- Reorganization of CDSCO, and review of trial applications by CDSCO to be done within 3 months
- Drugs to be marketed in India must involve trials in India; BA and BE studies should not be allowed for drugs to be exported and not sold within India.
- Drugs marketed for more than 4 years outside India, may apply for a license for sale in India with ‘bridging’ studies or 4 year monitoring studies
- No regulations for devices

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MRCT has partnered with AIIMS, AHERF, ISCR, FERCI and others to assist with clinical trials reform implementation

AHERF

From left to right: Barbara Bierer (MRCT/HMS); GN Singh (Drug Controller General of India), YK Gupta (AIIMS), Ranjit Roy Chaudhury (Apollo), Shri RK Jain (Additional Secretary, Ministry of Health and Family Welfare)

Global Regulatory Engagement – India

MRCT Center in the last year has focused on India regulatory issues including:

- Proposed India regulatory reforms relating to required certification for investigators, and accreditation for research sites and or IRBs/RECs
    - Introduction of AAHRPP, ACRP, and PRIM&R
- Compensation for injury standards – global comparative research project
- Understanding of causality assessment for determination of relatedness
- Videotaping of informed consent process – confidentiality and ethics
- Limitation of involvement of most competent investigators to 3 trieals

Developments

Prime Minister Narendra Modi elected in May 2014 with majority vote and mandate for change, and clear appreciation for importance of business and innovation. Bharatiya Janata Party (BJP) in control of Parliament.

Appointment of Dr. Harsh Vardan as Minister of Health and Family Welfare on 26 May 2014.

Removal of Dr. Harsh Vardan in early November, 2014 – to Ministry of Science and Technology

Appointment of Shri Jagat Prakash Nadda as the Union Minister for Health and Family Welfare on November 10, 2014.

Many believe that little will be finalized before resolution of the pending Supreme Court PIL case

Certification and Accreditation

- Quality Council of India chosen as central agency in charge of standards and accreditation, including defining process and inspections

- QCI published draft standards, posted on National Accreditation Board for Hospitals & Healthcare Providers (NABH) this week:

  http://nabh.co/Notice_draft_accreditation_standards.aspx#sthash.ZFPCfUxD.dpuf

  Comments due by December 15, 2014

AV Recording

Audiovisual recording should be mandated only for a subset of clinical trials:

- Required when the subject is willing to participate but is not willing to provide written consent.
- Required for vulnerable populations
  - Mentally Incapacitated
  - Institutionalized Individuals
  - Children
  - Prisoners
  - Terminally-Ill Patients
  - Students
  - Subordinate Staff

General concerns and recommendations regarding Phase I enrollment.

3 Trials per Investigator

General agreement that three trials per investigator is arbitrary, not based on quality, quantity, stage or complexity of trail nor investigator capacity to conduct trials in consideration of other responsibilities.

Explicit responsibility of trial sponsors to select appropriate investigators

3 proposals pending:

1. Eliminate numerical cap and transfer responsibility to IRB/REC to review
2. “Count” only actively enrolling trials
3. Raise the ‘count’ to 6.

Compensation

- Injury must be caused by clinical trial, not just occurring while enrolled in a trial
- Eliminate liability for therapeutic failure of experimental agent
- Liability for injury in placebo arm only if standard of care has been denied
- Causality determination important

Note: even with these modifications, many questions remain

Causality Determination

Project Deliverables:

A “how to” primer detailing points to consider in determining causality of an adverse event and the likelihood it is caused by the treatment.

PI – Professor Prem Pais

Guidance can be used to:

- assure causality assessments are conducted consistently across jurisdictions
- deliver training in various international settings
- delineate when unblinding is justified
- develop case studies

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Causality Assessment Workshop for Clinical Trial Investigators

Delhi, India November 22, 2014
~35 principal investigators attended
Guidance draft document circulated

Agenda:

- Background
- Important definitions
- Distinction between cause & correlation
- Steps Involved in ADR diagnosis
- Causality Assessment by different stakeholders
- Common methodologies to assess causality
- WHO-UMC system and modification thereof
- Case studies

Table 1: Recommended Data

No.	Information to be Collated	Suggested Source
1.	Adverse event description: symptoms, signs, laboratory test results, pathological findings, etc.	Adverse Event Report and Follow-Up Reports
2.	Adverse event term or phrase that fits the event described under item #1.	Adverse Event Report and Follow Up Reports
3.	List of known adverse effects of the drug.*	Safety and Tolerability Section of the Investigator's Brochure
4.	Approved labels of other drugs of the same class.	Regulatory authority database.
5.	Description of mechanism of action and pharmacological actions of the drug.	Pharmacology Section of the Investigator's Brochure
6.	Date and time of last dose of drug before onset of event.	Patient history or hospital/clinic notes
7.	Pharmacokinetic parameters of the drug: time to peak plasma concentration; half-life.	Pharmacology Section of the Investigator's Brochure
8.	Date and time of onset of event.	Adverse Event Report and Follow-Up Reports
9.	Dose of drug, frequency, duration of continuous use till last dose before onset of event.	Prescription, hospital notes and patient history
10.	Name/description of underlying disease for which the patient was receiving the drug.	Hospital/clinic notes
11.	Any complications of underlying disease present at onset of event.	Hospital/clinic notes
12.	Concomitant illnesses the patient was suffering from at onset of event.	Hospital/clinic notes
13.	Duration of pregnancy at onset of event and EDD or actual delivery date, if applicable.	Hospital/clinic notes
14.	Cause of underlying physical/mental stress or injury, if any.	Patient history, hospital/clinic notes
15.	Surgeries in the past 3 months	Hospital/clinic notes
16.	Literature linking disease and background conditions to the event, if any.	Literature search through the Internet or other sources
17.	Concomitant medicines consumed by the patient within 7 days prior to onset of event.	Patient history, hospital/clinic notes
18.	Approved labels of concomitant medicines being taken by the patient.	Regulatory authority database
19.	Action and toxicity of traditional and alternative medicines being taken by the patient.	Literature search through the Internet or other sources
20.	Addiction history and use of recreational substances by the patient prior to onset of event.	Patient history, hospital/clinic notes
21.	Action, toxicity, and interactions of recreational substances used by the patient, if any.	Literature search through the Internet or other sources
22.	Post event history: evolution of event; changes in therapy; treatment of event, with precise details.	Hospital/clinic notes

***"Drug" refers to the investigational product**

Table 2: Revised WHO-UPC system for clinical tri

Q#	Question	T1 Ref*
1	Is the drug or other drugs of the same class known to have this adverse effect? Guidance*: Consult the Investigator's Brochure, approved labeling or prescribing information, and other reliable information available on the drug.*	1-4
2	If the answer to question 1 is "No", is the event consistent with the known pharmacological, toxicological or immunological action of the drug? Guidance: *Consult the Investigator's Brochure, approved labeling or prescribing information, and other reliable pharmacological information available on the drug.*	5
3	Did the onset of the event occur within a reasonable time after the last dose of the drug to justify an association between the drug and the event? Guidance: *Consider the half-life of the drug and whether the drug persists within the body. Drugs are generally washed out of the body within 5-6 half-lives, but some drugs are known to persist in isolated compartments even after they are washed out from the blood. Sometimes, some drugs can trigger a pathological process that manifests itself long after the drug has been eliminated from the body - although this is extremely rare.*	6-8
4	Was the event of acute nature that would be expected to correlate with circulating concentrations of the drug within the body? Guidance: *E.g., drug induced cardiac arrhythmia or convulsions are concentration dependent acute events while liver damage or pulmonary fibrosis are generally dose dependent.*	1-2
5	If the answer to question 4 is "Yes", does the time of onset of the event correspond to a period when the plasma concentration of the drug is expected to be high? Guidance: *Consider the time to peak plasma concentration of the drug and its plasma half-life.*	6-8
6	Does the event fit the description of a known pharmacological phenomenon (such as grey baby syndrome, tardive dyskinesia, or anaphylaxis)?	1-2
7	If the answer to question 6 is "Yes", is the dose, duration of therapy, and lag time prior to onset of event consistent with a causal relationship between the drug and the phenomenon? Guidance: *Base your judgment on descriptions of the phenomenon available in the literature.*	6-9
8	Did the patient have an active disease or complication at the time of onset of the adverse event? Guidance: *Some clinical trial subjects, such as healthy volunteers in Phase 1 studies, and those participating trials of prophylactic agents such as vaccines, may not have an active disease at the time of onset of adverse event. In some patients the adverse event may be the first sign of an active disease.*	10-12
9	Did the patient have an underlying physiological condition at the time of onset of the adverse event? Guidance: *E.g., pregnancy or puerperium.*	13
10	Was the patient suffering from the effect of an underlying physical or mental stress or injury at the time of onset of the adverse event?	14
11	Was the patient recovering from a surgical procedure at the time of onset of the adverse event? Guidance*: Consider the duration of the healing process after surgery. Do not consider the effects of anesthesia for this point.*	15
12	If the answer to questions 8, 9, 10, or 11 is "Yes", is the disease, complication, condition, injury, stress or surgical procedure known to cause this adverse event? Guidance: *Textbook references or any other credible reports of association between underlying state and event would be valid for a "Yes" response.*	16
13	If the answer to question 12 is "Yes", does it seem possible that the disease, complication, condition, injury or surgical procedure caused this adverse event? Guidance: *Consider whether the severity of underlying disease/injury, temporal sequence, and evolution of the event are consistent with a causal association. If your response to this question is "No", document the reason for ruling out the underlying state of the patient as cause for the event.*	16
14	Was the patient known to be taking any concomitant medicines at the time of onset of the adverse event? Guidance: *Consider regular as well as intermittent or one-time use of concomitant medication. Include use of traditional and herbal medicine as well as other forms of alternative medicine and the effect of anesthetics in postoperative patients.*	17
15	If the answer to question 14 is "Yes", are any of the concomitant medicines known to cause this adverse event? Guidance: *Refer approved prescribing information and any other literature available, for each of the concomitant medicines being taken by the patient.*	18-19
16	If the answer to question 15 is "Yes", does it seem possible that one of the concomitant medicines known to cause this adverse event actually caused it? Guidance: *Consider whether the dose, duration of therapy, temporal sequence and half-life of the concomitant medicine was consistent with the time-course and severity of the event.*	18-19

Continued on next page….

Table 2: Revised WHO-UPC system (con't)

17	Was the patient known to be taking any recreational substances at the time of onset of the adverse event? Guidance: *Include use of tobacco, alcohol, and abuse of prescription medicines as recreational use.*	20
18	If the answer to question 17 is "Yes", are any of the recreational substances known to cause this adverse event?	21
19	If the answer to question 18 is "Yes", does it seem possible that any one of the recreational substances known to cause this adverse event actually caused it? Guidance: *Consider whether the extent of abuse and time sequence is consistent with a causal relationship of abuse to event.*	21
20	Was the drug dose reduced or the drug withdrawn at any time after the onset of the adverse event? Guidance: *Enter "No" if, after the onset of the adverse event, the patient continued to receive the same dose of the drug at the same frequency as before onset of the event. Enter "Not Applicable" if the patient was expected to receive only one dose, or if the event occurred after the last scheduled dose of the drug, or if the patient died before the next dose could be given or before any effect of drug discontinuation can be expected (keeping drug half-life and reversal time of drug effects in mind).*	22
21	Was the dose of any of the concomitant medicines reduced or withdrawn at any time after the onset of the adverse event? Guidance: *Enter "Not Applicable" if the patient was not receiving any concomitant medicines at the time of onset of the adverse event.*	22
22	Was the nature of the event such that withdrawal of the causative agent would be expected to lead to reduction/disappearance of manifestations in the days after withdrawal? Guidance: *Adverse events resulting from the direct pharmacological action of a drug are generally rapidly reversible, while recovery from effects of drug-induced injury to cells depends on the pace of regenerative processes in the affected tissue. Drug-induced degenerative changes and fibrosis may not be reversible. Choose your response based on the nature of the event and the withdrawal period that was available to observe the effect of drug withdrawal. You may choose "Not Applicable" if withdrawal was not possible.*	22
23	If the answers to questions 20 and 21 are both "Yes", were the dose reductions/withdrawals of drug and concomitant medicines sequential? Guidance: *Enter "No" if one or more concomitant medicines were withdrawn (or their dose reduced) at the same time as withdrawal or dose reduction of the drug. Enter "Yes" only if there was sufficient gap between withdrawal of drug and the concomitant medicines to allow for a de-challenge effect to be observed for the drug and the concomitant medicine/s separately.*	22
24	If the answers to question 20, 22 and 23 (if applicable) are all "Yes", did severity of the event reduce or did manifestations of the event disappear on drug dose reduction/withdrawal? Guidance: *Confine your response to the effect of withdrawal or dose reduction of the drug, irrespective of the effect of withdrawal or dose reduction of concomitant medicines, and irrespective of whether withdrawals and dose reductions happened simultaneously or sequentially.*	22
25	If the answers to question 21, 22 and 23 (if applicable) are all "Yes", did severity of the event reduce or did manifestations of the event disappear on concomitant medicine dose reduction/withdrawal? Guidance: *You need to respond to this question only if withdrawal or dose reduction of one or more concomitant medicines occurred sequential to withdrawal or dose reduction of the drug.*	22
26	If the answer to question 24 or 25 is "Yes", are there any confounding factors that make the de-challenge results ambiguous? Guidance: *Specific treatment of a drug-related adverse event may confound the de-challenge results as both will reduce severity of the event.*	22
27	If the answer to question 20 is "Yes", was the drug restarted after a period of withdrawal?	22
28	If the answers to questions 24 and 27 are both "Yes", did the manifestations of the event reappear after the drug was restarted?	22
29	If the answer to question 28 is "Yes", are there any confounding factors that make the re-challenge results ambiguous? Guidance: *A positive re-challenge result would be ambiguous if drug and concomitant medicines were restarted at the same time.*	22

***Corresponding Table 1 row numbers for reference**

Table 3

Q#	Response Options			CERTAIN		PROBABLE		POSSIBLE		UNLIKELY	
				(+)	(-)	(+)	(-)	(+)	(-)	(+)	(+)
1	Y	N	-	Y							N
2	Y	N	-								N
3	Y	N	-	Y	N	Y	N	Y	N	N	Y
4	Y	N	-								
5	Y	N	B			Y/B	N				
6	Y	N	-	Y	N						
7	Y	N	B	Y	N						
8	Y	N	-								
9	Y	N	-								
10	Y	N	-								
11	Y	N	-								
12	Y	N	B	N/B	Y						
13	Y	N	B			N/B	Y	Y			Y
14	Y	N	-								
15	Y	N	B	N/B	Y						
16	Y	N	B			N/B	Y	Y			Y
17	Y	N	-								
18	Y	N	B	N/B	Y						
19	Y	N	B			N/B	Y	Y			Y
20	Y	N	NA								
21	Y	N	NA								
22	Y	N	NA								
23	Y	N	B								
24	Y	N	B	Y/B	N	Y/B	N				
25	Y	N	B	N/B	Y						
26	Y	N	B	N/B	Y	N/B	Y				
27	Y	N	B								
28	Y	N	B	Y/B	N						
29	Y	N	B	N/B							

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Causality Assessment for Clinical Trial Investigators

Open workshop in February 2015
Revised training and guidance

Pilot of WHO-UHS revision
- Test inter-rater reliability
- Test understanding and applicability

Broaden implementation

Develop on-line training module for dissemination

India: still pending

- Requirement for placement of trials in 50-bed hospital
- Compensation revisions for situations not modified (e.g. Phase 4 trials, post-marketing surveillance, noncompliance)
- Compensation formula for injury
- Definition of “ancillary care” expectation for intercurrent illness during clinical trial
- Structure, education and training of regulatory authorities
  - Elevation of CDSCO/DCGI to higher authority and status in government
  - Increased investment in regulatory offices and competence of officials
  - Transparency of regulatory processes and decisions

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Questions and Discussion