MULTI-REGIONAL CLINICAL TRIALS

THE MRCT CENTER of BRIGHAM AND WOMEN'S HOSPITAL and HARVARD

Responsible Clinical Trial Data Sharing

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CBI Conference: Clinical Trial Data Disclosure and Transparency

January 28, 2016 Philadelphia, PA

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- The opinions contained herein are those of the author and are not intended to represent the position of Harvard or Brigham and Women's Hospital.
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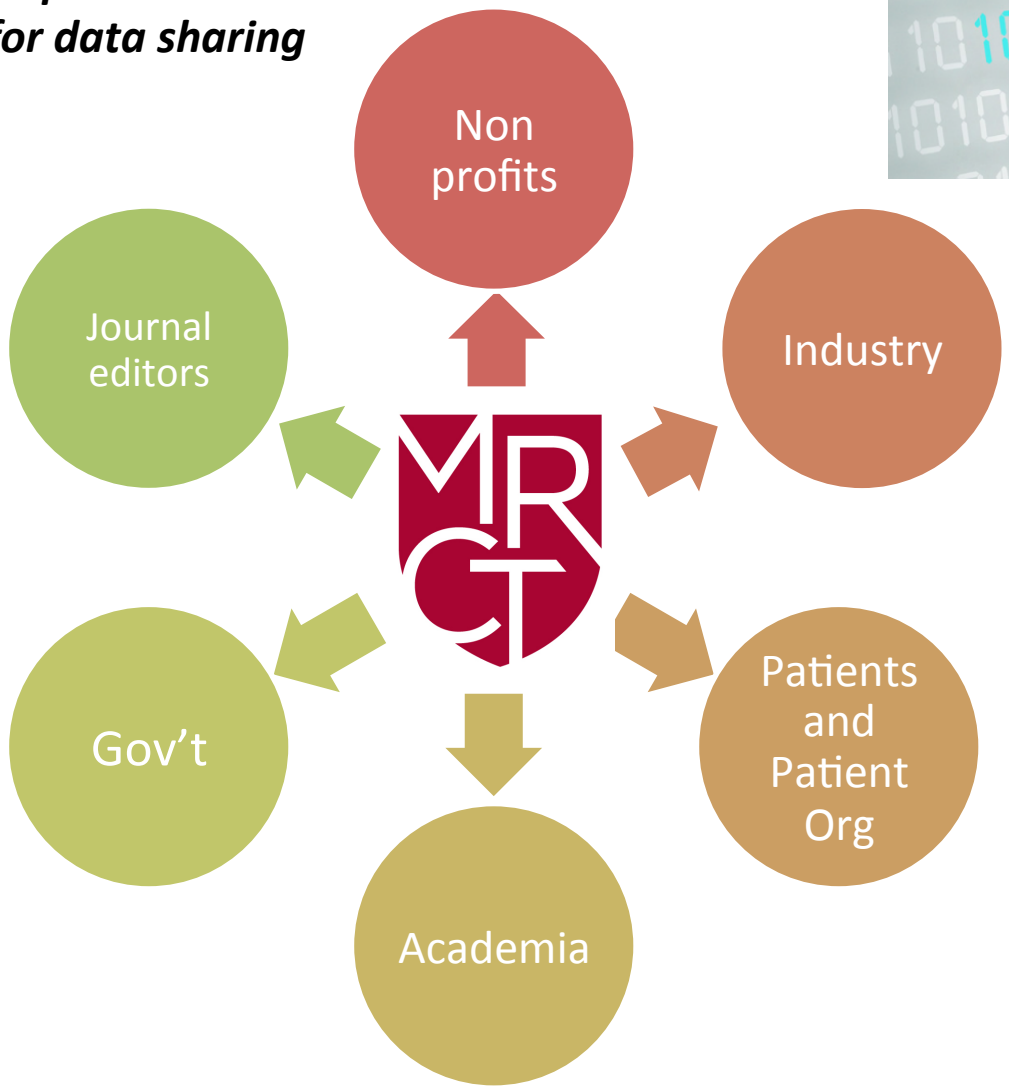
Our Mission

Engage diverse stakeholders to define emerging issues in global clinical trials and to create and implement ethical, actionable, and practical solutions.

MRCT Center as a Neutral Convener

To create implementable solutions for data sharing

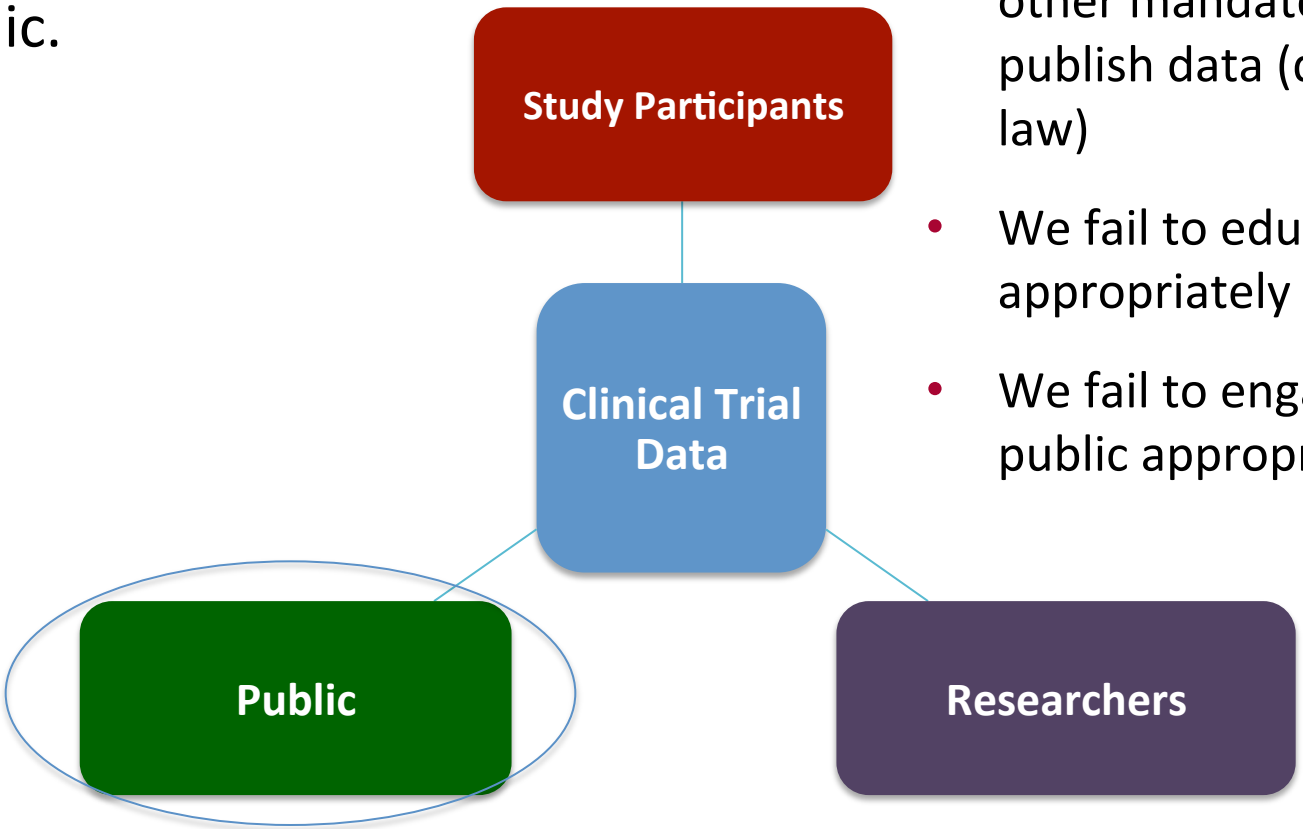


Agenda

- MRCT Center involvement in data sharing
- Data sharing with the public
- Data sharing with participants
  - Responsible return of aggregate research results to participants
  - In flight: return of individual research results to participants
- Data sharing with the research community
  - History and launch of current project
  - Current data sharing efforts
  - A look to the future

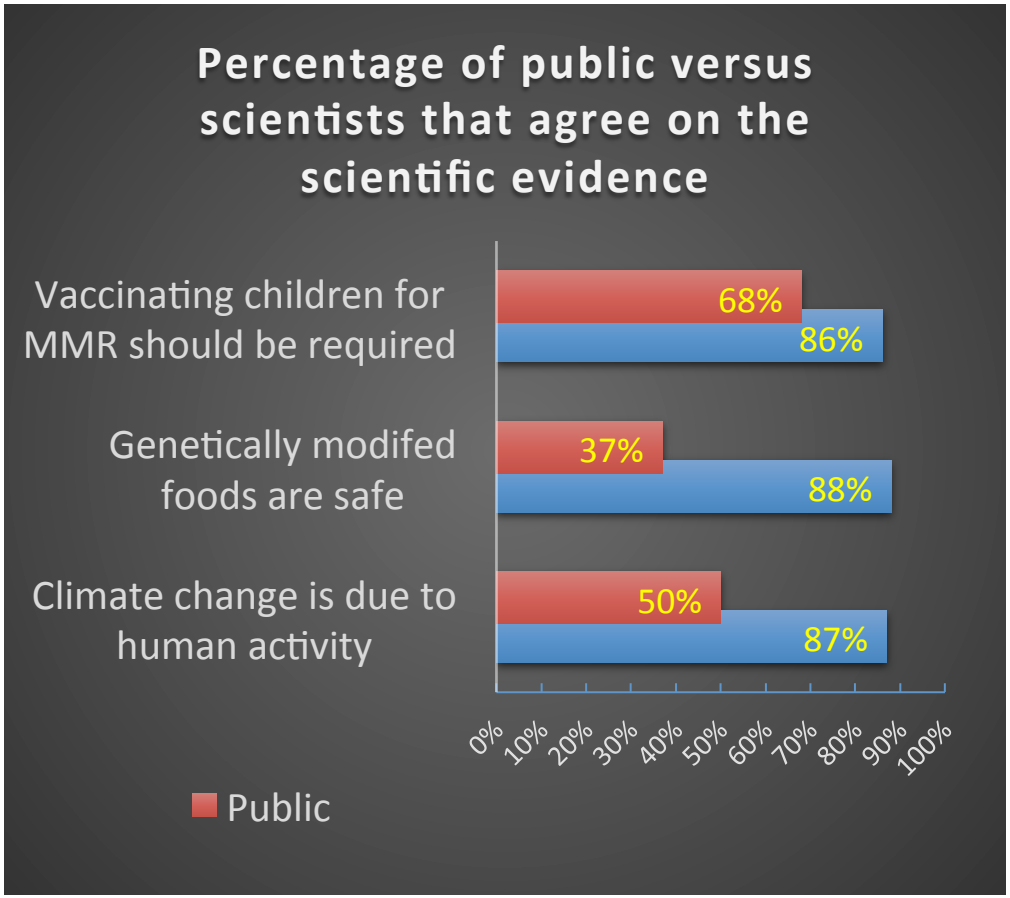
The various audiences of clinical trials data sharing

To date, we have failed in our responsibility to the public.



- We fail to comply with Clinicaltrials.gov and other mandates to publish data (despite the law)
- We fail to educate appropriately
- We fail to engage the public appropriately

Public versus scientists perceptions of science



The gap in understanding and mistrust of science affects personal and health decisions as well as public policy

Source: Pew Research Center, 2015

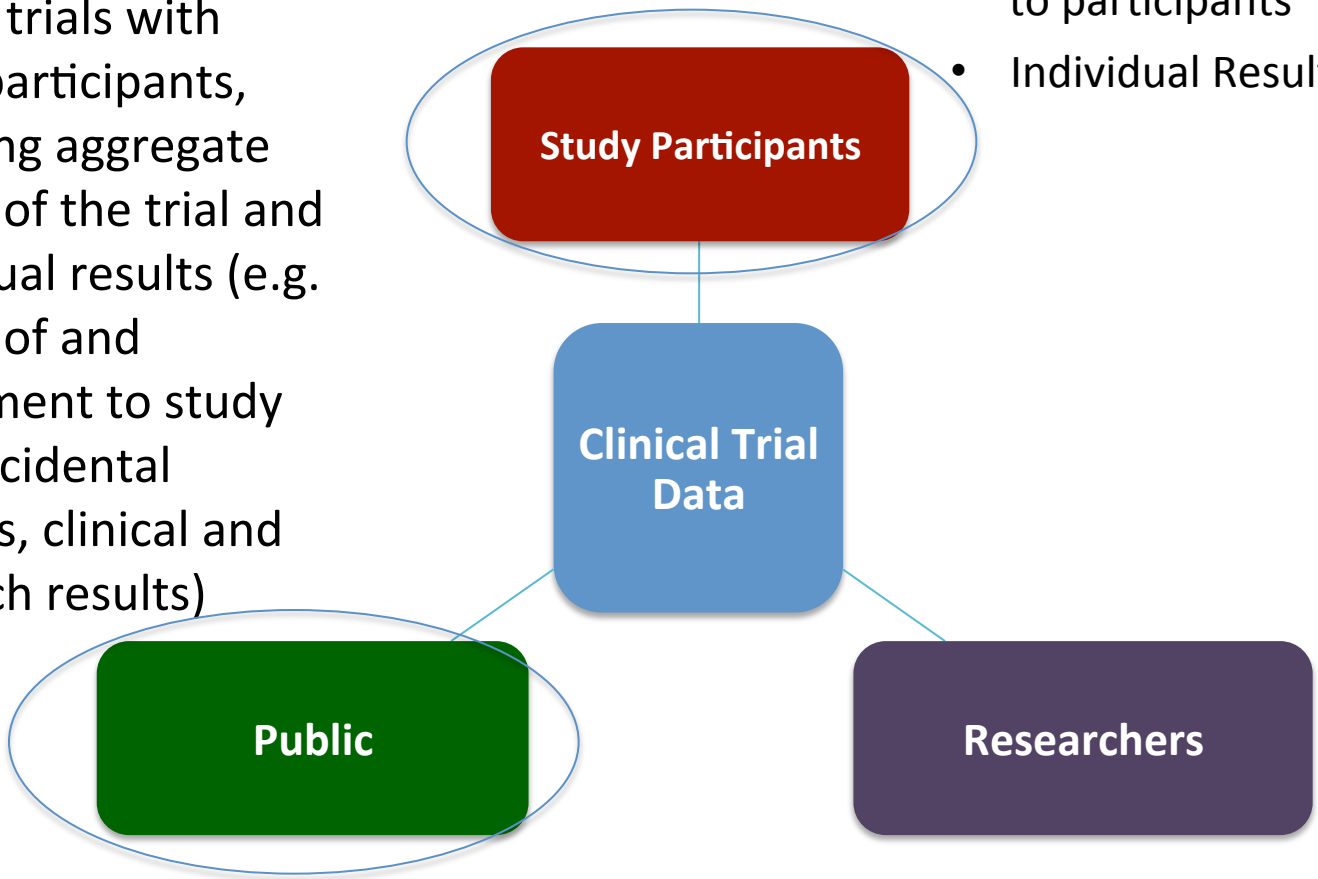
We must attend to our responsibilities and respond to the public.

The various audiences of clinical trials data sharing

The sharing of research results from clinical trials with study participants, including aggregate results of the trial and individual results (e.g. results of and assignment to study arm, incidental findings, clinical and research results)

Return of

- Aggregate Research Results to participants
- Individual Results



Sharing clinical trial results on a website enables public transparency and trust

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.
- Reflects 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.
- Expectations of academic, industry, not-for-profit sponsors similar
- Funding for return of results should be provided as an anticipated component of human subjects research.
- Returning results is a key aspect of **Improving Transparency** of clinical trials and **Increasing Public Trust.**

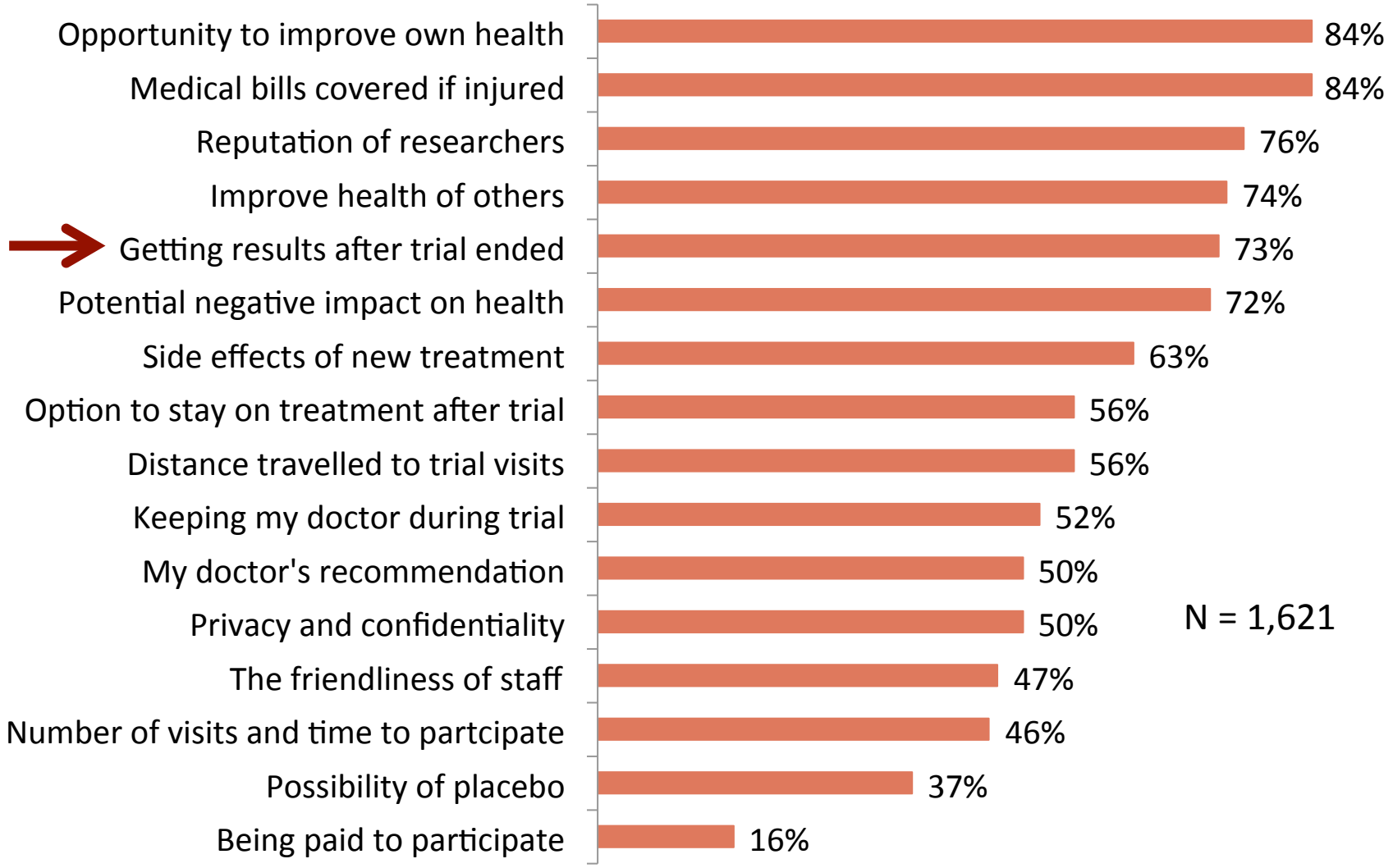
Why now?

- **Declaration of Helsinki**: Paragraph 26:
  - "All medical research subjects should be given the option of being informed about the general outcome and results of the study."

    http://www.wma.net/en/30publications/10policies/b3/
- **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 Principles for Responsible Clinical Trial Data Sharing**
  - In order to help inform and educate patients about the clinical trials in which they participate, 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.

    http://www.phrma.org/sites/default/files/pdf/PhRMAPrinciplesForResponsibleClinicalTrialDataSharing.pdf

Factors important when considering research



patientslikeme®

MRCT Center 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
  - http://mrctcenter.org/resources/2015-03-19-training-materials-mrct-return-of-results-guidance-document/

An **ROR Users Toolkit** including:

•Templates for Phase1, Phase II/III, studies ending early

•Neutral language guide

•Endpoints language guide

•Useful Checklists

- http://mrctcenter.org/resources/2015-10-02-template-mrct-ror-toolkit-version-2-0/

Process Flow for Returning Results

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

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.

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.
  - Guidance: testing for readability; visuals; and writing style.
- Emphasis on **numeracy**
- Emphasis on **cultural literacy**

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

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/condition*> is effective.	This study found that people with <*disease/condition*> who got <*drug A*> had <*primary endpoint*>.
The combination treatment of <*drug A and B*> may also help <*a different disease/condition than what was/was not studied elsewhere*> as observed in new small studies.	When <*Drug A and B*> are used together, people in this study had <*study endpoint*>. The drugs may be helpful in other diseases/conditions, but this was not studied here. Further studies in <*disease/condition*>will be necessary.
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*> with 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 received or were treated with <*study endpoint*> with <*Drug A*>. They also had more side effects that interfered with their daily lives, like <*list specific adverse events*>.

FDAs points to consider:

No FDA regulation or guidance directly on this issue

- Truthful accurate and non-misleading information about trial results that may benefit participants
- More specifically
  - The language should be simple and factual, neutral in tis description
  - The information should not be selective
  - The information cannot make pre-approval claims of safety or effectiveness in a promotional context

Adapted from R Moscicki, 5 Feb 2015; 28 Feb 2016

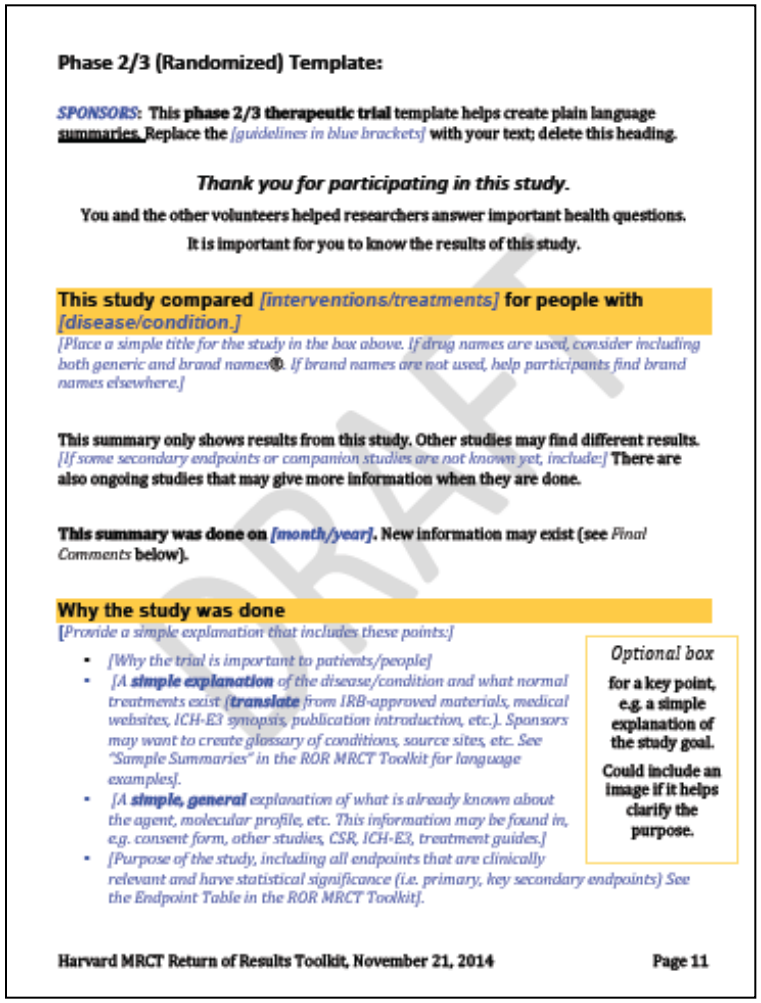
TransCelerate Recommendations:

Non-Promotional Language in Lay Summaries

- Tone and content should be factual, accurate and objective, without inferences or assessments of outcome, avoiding superlatives. (see MRCT Return of Results Toolkit)
- Materials should be fair and balanced (e.g. including safety and efficacy in content and format), without commercial or marketing appearance
- Plain language summary is made available in a non-promotional context
- A statement should be added:
  - Where further information can be found (e.g. ClinicalTrials.gov)
  - Results are from a single trial and other results may be available
  - therapeutic changes should be made based only by consulting a healthcare professional.
- Approval status should not be provided in the lay summary
- If translations provided, translated text should not be promotional

http://www.transceleratebiopharmainc.com/wp-content/uploads/2015/04/TransCelerate-Non-Promotional-Language-Guidelines-v10.pdf

MRCT Center 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**

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
Dose Escalation
Exploratory Biomarker / Genomics Markers
Mortality (Overall survival)
Morbidity
Non-inferiority Endpoints
Patient Reported Outcomes
Prevention or Incidence Endpoints
Progression-Free Survival (PFS)
Surrogate Endpoints

http://mrctcenter.org/wp-content/uploads/2015/11/2015-10-02-MRCT-ROR-Toolkit-Version-2.0-2.pdf

Endpoint Descriptions and Examples

Endpoint Table with Simple Language

The following table lists common clinical trial endpoints. Terms are defined with general descriptions, followed by examples of simple, plain language that can be used in Research Result Summaries (RRS).

Endpoint	Description of the type of endpoint	Example in simple, plain language
Composite	A **composite endpoint,** as the primary endpoint, combines multiple outcomes (e.g. death, getting sick again (relapse), serious event) and test results into one measure of how well the drug/therapy/device works. This is useful when there are many different outcomes that can happen during a trial. This can also be called a **combined** or **multi-part endpoint**.	"The XXX study measured *[patients/people]* to see if those in Group A (ABC treatment) or Group B (XYZ treatment) lived longer, had fewer heart attacks, or fewer hospital visits for heart failure. These events were measured together (combined) because each one is quite rare. Researchers also wanted to see if the drug worked in patients who had all 3 conditions. The study found that there was no change in the number of events for [*patients/people*] in Group A or Group B."
Dose Escalation	Dose escalation is used in phase 1 studies to measure safety. People in the study start with a low dose of the medicine (drug). If that dose does not cause safety problems, then more people are given a	"This study was done to find the highest *[dose/amount]* of treatment that people could take without having too many side effects."

Special Considerations

- Role of the IRB/REC
- 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
- Assent for Return of Results to Children
- Complexities of the Global Context
- Studies that may not warrant return of results

Collaborations and the future

- Research participants clearly want to receive information about the clinical trial to which they participated. There is no reason not to do so. Return of results should become the expectation and practice in clinical research. It is the right thing to do.

- Logistics, Content, Process and Standard methodologies and approaches have been delineated and are designed for all sponsors and for all trials. Methods are efficient, roles and responsibilities are clear, expectations are outlined, and multinational requirements have been incorporated.

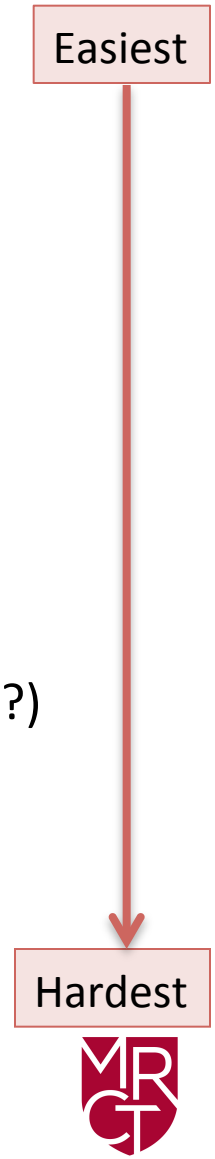
- Funding for return of results should be provided as an anticipated component of human subjects research.

- We have collaborated with TransCelerate BioPharma, HRA, EU, EFPIA and PhRMA. We invite additional collaborators and partners.

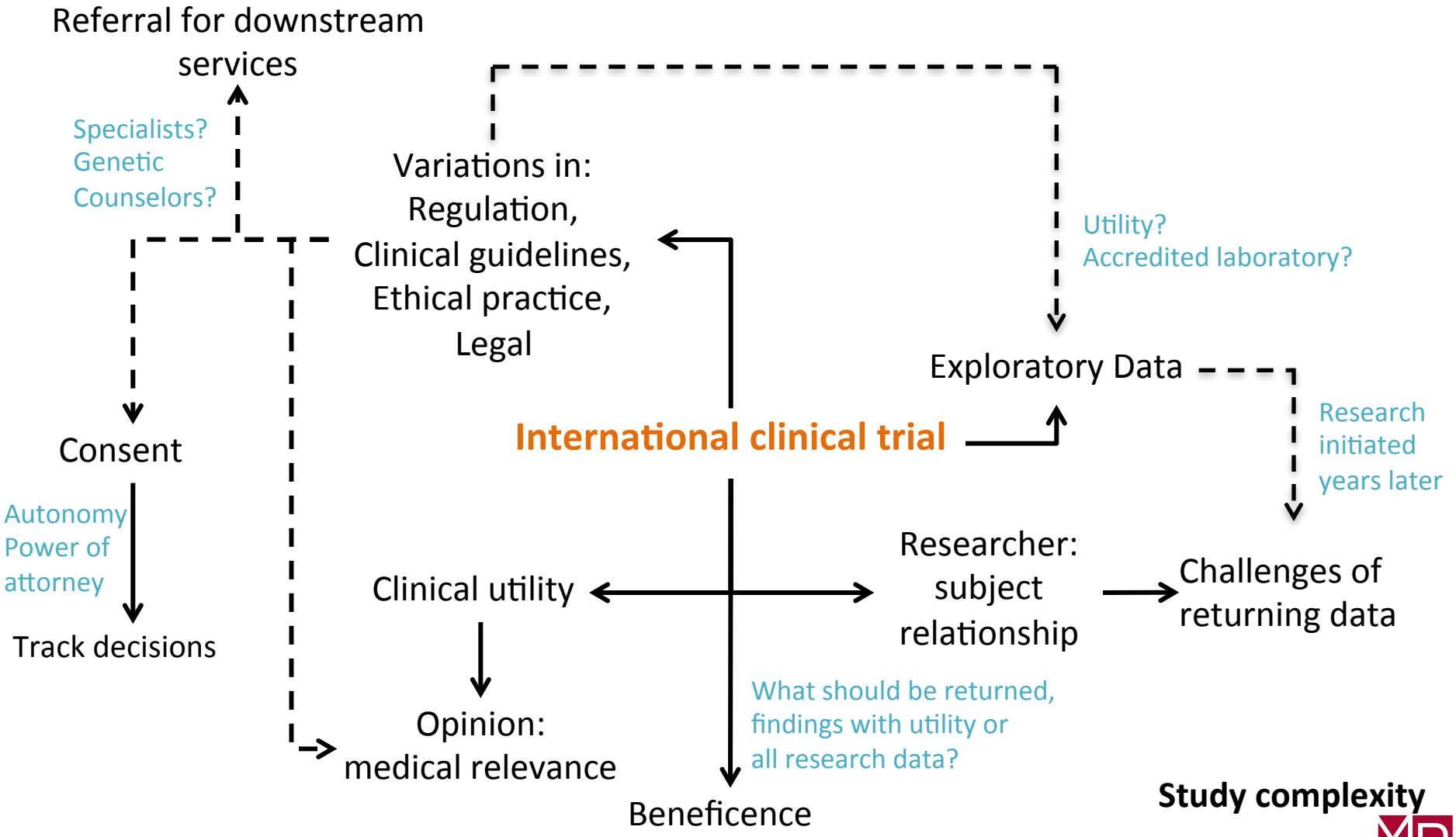
- *Harmonization and consistency is critically important.*

Spectrum of results to return to participants:

- Aggregate research results
- Assignment to and results of study arm
- Routine clinical results performed in the course of research
  - USA: CLIA –approved or –unapproved laboratories and processes
  - What is global standard for trustworthiness and does it matter?
- Incidental findings discovered in the course of a clinical trial
  (e.g. mass on an MRI done for research purposes)
  - Of potential clinical significance or actionable
  - Of uncertain significance (and does the patient have a right to know?)
- Research results
  - Of likely or uncertain significance
  - Of potential proprietary importance
  - Genetic/genomic results
- Other results



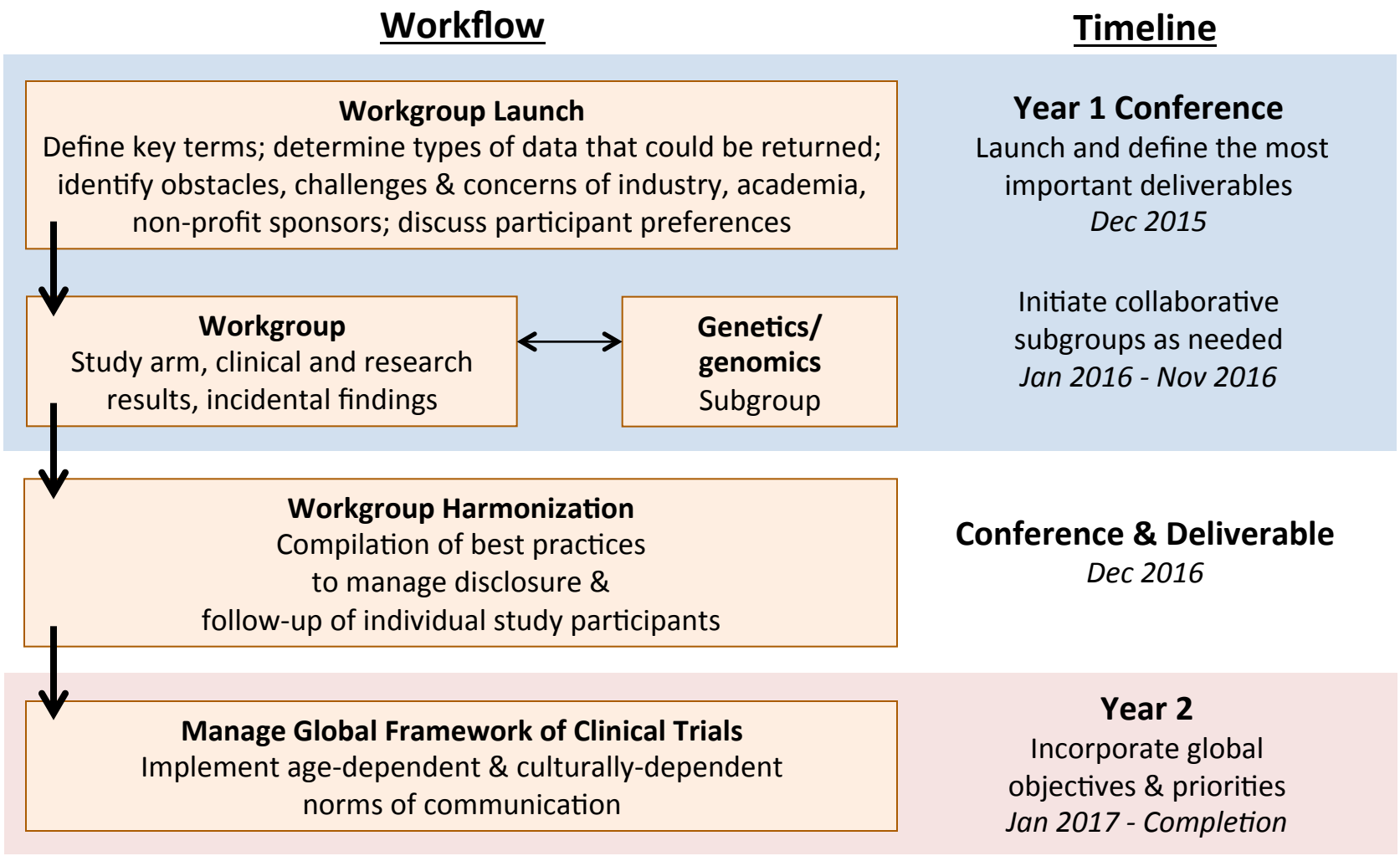
One-size-does-not-fit-all



Questions to address

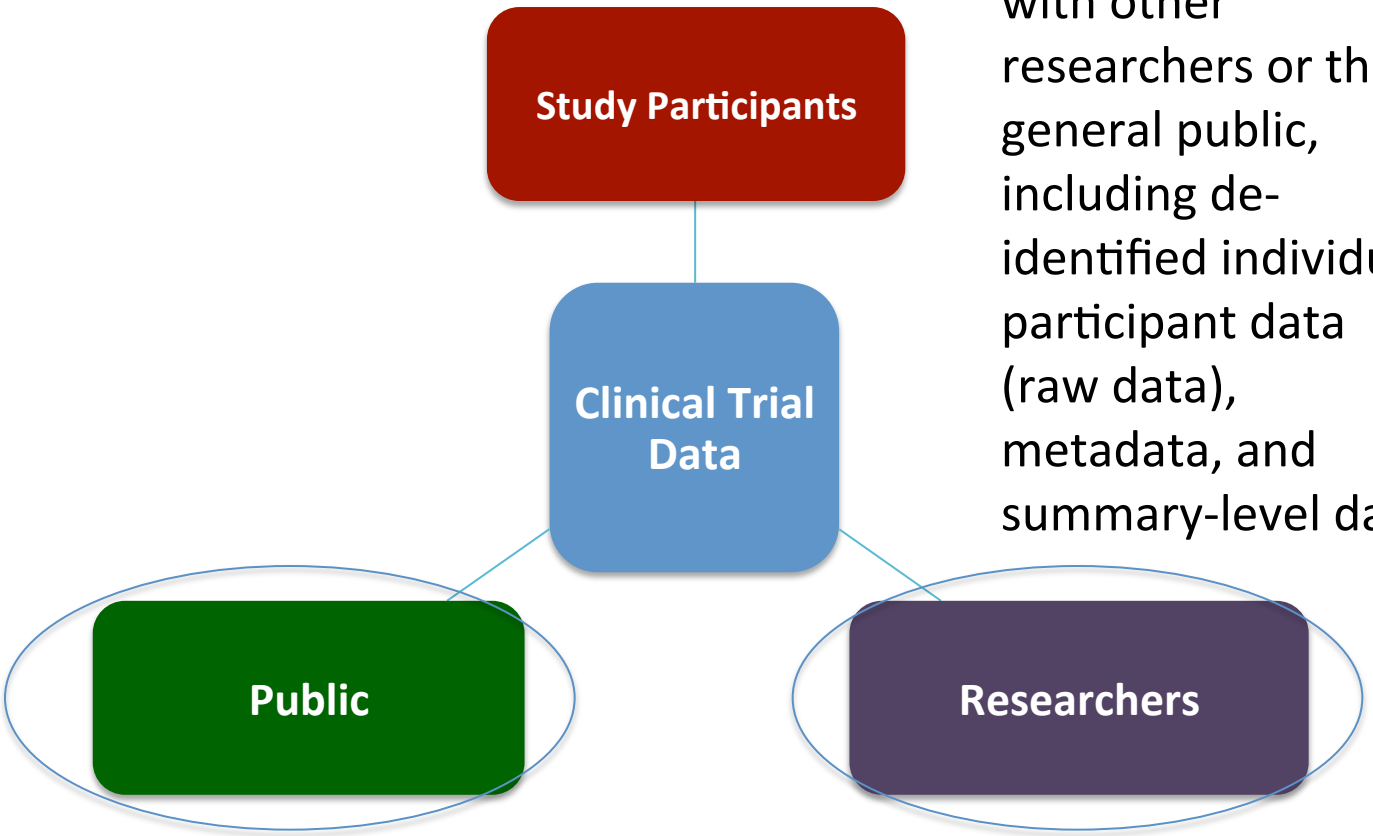
- Is “actionable” or “potential health or reproductive importance” the appropriate threshold for consideration of return?
- Is there *any* threshold requirement for return of individual results to participants? What types of results should be returned, and what are the characteristics of those that should not be? If certain results are not returned, does time-dependent understanding impart a continuing obligation to reconsider whether to return? That is, do we have a continuing obligation to search for actionable results?
- If results are returned, who should do so (and how) and who is responsible and accountable for ensuring its execution?
- If results are returned, are participants availed of or entitled to follow up medical care or counseling?

Return of individual results to clinical study participants



We invite participation to the MRCT work group (mrct@bwh.harvard.edu)

The various audiences of clinical trials data sharing



The sharing of data from clinical trials with other researchers or the general public, including de-identified individual participant data (raw data), metadata, and summary-level data

2012-2015 Major Milestones in Clinical Trial Data Sharing: Platforms

- **GSK** and the Clinical Study Data Request (CSDR) platform, a multi-sponsor request site where data are used in a secure environment
- **J&J** - YODA project through which Yale partners with J&J and Medtronic
- **Pfizer's** Integrated System for Pfizer PI Initiated Research (INSPIIRE) Portal
- **Duke** Clinical Research Institute – Bristol Myers Squibb Strategic Initiative (SOAR), which supports open access to clinical trials data
- **NIH** BioLINCC data repository and others
- **FDA** -Project Data Sphere (cancer comparative data) and High-Performance Integrated Virtual Environment (HIVE), a private, cloud-based environment that comprises data storage library, algorithms for analysis, and computational capacity

However these are not interoperable nor are these systems integrated

ICJME data sharing proposal, 26 Jan 2016

- The ICMJE defines a *clinical trial* as any research project that prospectively assigns people or a group of people to an intervention, with or without concurrent comparison or control groups, to study the cause-and-effect relationship between a health-related intervention and a health outcome.
- "As a condition of consideration for publication of a clinical trial report in our member journals, the ICMJE proposes to require authors to share with others the deidentified individual-patient data (IPD) underlying the results presented in the article (including tables, figures, and appendices or supplementary material) no later than 6 months after publication. The data under-lying the results are defined as the IPD required to re- produce the article's findings, including necessary metadata. This requirement will go into effect for clinical trials that begin to enroll participants beginning 1 year after the ICMJE adopts its data-sharing requirements."*
- Anyone can provide feed-back at www.icmje.org by 18 April 2016.

http://www.icmje.org/news-and-editorials/M15-2928-PAP.pdf

And the call for action is growing

- British Pharmacological Society (BPS) has called for greater transparency in the testing of new medicines, following the phase I catastrophe in France, and following the 2006 trial in Great Britain, recommending “release of the study design and protocol, the full Investigational Medicinal Product Dossier and the batch release for such studies, at the earliest possible stage.”

https://www.bps.ac.uk/news-events/news/society-news/articles/improve-early-access-to-data-from-catastrophic-cli

Purpose-driven data sharing will enhance scientific discovery (….and public trust)

- Benefits are substantial (e.g.):
  - Eliminate duplicative trials
  - Evaluate common AEs by compound class or subpopulation
  - Identify surrogate endpoints
  - Enhance correlative and explanatory science
- But benefits only realized if:
  - Risks are minimized, with attention to participant privacy
    - Attention to informed consent and respect for consent
    - Data de-identification and/or anonymization
  - Data are interoperable, data sets can be pooled
    - Data standards are available, or alternative methodology
    - Metadata is shared
    - Real-time analytics are available
  - State-of-the-art security is in place

The MRCT Center's Focus in Data Sharing: A Brief Timeline

Timeline	Milestones
February 2013	Working Group launched with 18 stakeholder organizations
March 2013	Convened 4 sub-groups on key issues: -Rationales for clinical trial data sharing -Safeguarding patient privacy, consent principles -Balancing intellectual property interests -Implications of patient-level data shared in public domain
May 2013	Co-hosted a conference "**Issues and Case Studies in Clinical Trial Data Sharing: Lessons and Solutions**"
March 2015	Hosted a conference, "**Promoting Clinical Trial Data Transparency**"at Harvard University in Cambridge, MA

Data Sharing: Common ICF and DUA

TEMPLATE ICF LANGUAGE FOR DATA SHARING*

INFORMED CONSENT LANGUAGE FOR CONFIDENTIALITY AND DATA SHARING

What information about me will be used in the study?

If you join the study, information about you will be used for the study. This information will be called "your data". Your data includes personal information that can be used to identify you, such as your name or address. It also includes your birth date and information from your medical record. As part of the study we will get new information about you such as heart rate, blood pressure and results of tests on your blood and other samples. By signing this consent form you agree that 'Your Data' can be used as described here.

At any time, you may ask the study doctor to see your personal information and ask to correct it if necessary. In some circumstances, you may not be able to see your study information while the study is ongoing. This is to ensure the reliability of the study. However, the study doctor will share any important medical information if it is relevant to your health during the course of the study.

Who will have access to my information?

The researchers at the study site (the "Site Study Team") will give Your Data a unique study code number (such as, 123321). This number will be u

sed in place of your name and other information that directly or easily identifies you (for instance, your address or national identification number.) We will call this new data "Your Coded Data". The Site Study Team will keep the link between "Your Data" and "Your Coded Data". They will not send the link to SPONSOR. Your Data that identifies you will remain at the study site. It may be checked by the sponsor, the ethic committee or government agencies that approve medicines to check how the study was run. The Site Study Team will send only Your Coded Data to the sponsor.

How will my information be used?

SPONSOR will take steps to ensure that your coded data stays confidential and secure. SPONSOR will protect Your Coded Data in accordance with current law. SPONSOR and those working with SPONSOR will use Your Coded Data for research only. They may:

DATA USE AGREEMENT TEMPLATE

Data Sharing Agreement

This DATA SHARING AGREEMENT (this "Agreement") is effective as of _____, 20 (the "Effective Date") between _____ ("Researcher") located at _____ and [INSTITUTION NAME] ("[ABBREVIATED NAME]") located at [INSTITUTION ADDRESS].

1) **Definitions**

a) "[ABBREVIATED NAME] Confidential Information" means all information (including, without limitation, participant-level data, research specifications or Protocols, reports, specifications, computer programs, or models and related documentation, know how, trade secretes, or business or research plans) of [ABBREVIATED NAME] or [ABBREVIATED NAME]'s affiliates that are provided to researcher in connection with this Agreement.

b) "New Intellectual Property" means all discoveries, developments, inventions (whether patentable or not), improvements, methods of use or delivery, know-how or trade secrets that are made by Researcher in connection with the use of [ABBREVIATED NAME] Confidential Information under this Agreement.

c) "Analytical Tools" includes but is not limited to any methodology, statistical methods, formulae or other methods or tools used by Researcher in conducting the Analysis.

2) **Data Sharing**

a) [ABBREVIATED NAME] and Researcher intend to establish this Agreement with respect to Researcher's access to [ABBREVIATED NAME]'s data.

b) Researcher desires access to certain data collected by [ABBREVIATED NAME] for the sole purpose of analysis according to the Researcher's approved research plan (the "Analysis"). This plan is detailed in EXHIBIT A, which provides a detailed description of the Analysis and the information required (e.g., diagnosis, gender, age, and other information specified immediately below) to achieve its purpose. In addition to restricting its use of any data shared under this Agreement to the Analysis, Researcher agrees to comply with any additional requirements that have been imposed by applicable law or regulation or that were identified by the independent review panel that approved the Analysis. Requirements identified by the independent review panel, if any, are set forth in EXHIBIT B.

*Panel at 2:30 today will discuss issues in informed consent

Data Sharing Conference: Consensus of Future Vision March 30-31, 2015

- 70 representatives of pharma, biotech, patient/patient advocates, foundations, academics, journal editors and others:
- **Consensus on future strategic vision:**

1. Expectations and practices of registration and results reporting of all clinical trials would be regularized among industry and academia;
2. Greater access to participant-level clinical trial data could be facilitated;
3. Researchers would be able to access and combine data across various platforms and sponsors, to multiply opportunities for data analysis; and
4. Research participant privacy must be safeguarded, through IT design as well as conditions imposed on data users.

Sponsored by the MRCT Center, Laura and John Arnold Foundation and Wellcome Trust

March 2015 Data Sharing Conference: Future Vision

- **Organizational structure and Governance** - A coordinating, centralized, international, not-for-profit organization with accountability;
- **A centralized and single portal** - A central user interface with a robust search engine functionality, including information on trials around the world;
- **Data requirements** – Data standards, definition, data ontology and metadata to allow for and enable the integration of differing datasets for analysis;
- **Shared or common services** – Efficient shared or common services across data generators/sponsors (e.g. policy setting, data de-identification, criteria for independent review panel decisions or reliance, and statistical services); and
- **Flexibility** – Data platform accommodating differing expectations and needs: ability to host data, access data from third party hosts, or download data if freely available. Ability to utilize middleware to perform analyses.

Data Sharing: An international non-profit entity to promote, coordinate, and facilitate clinical research data sharing

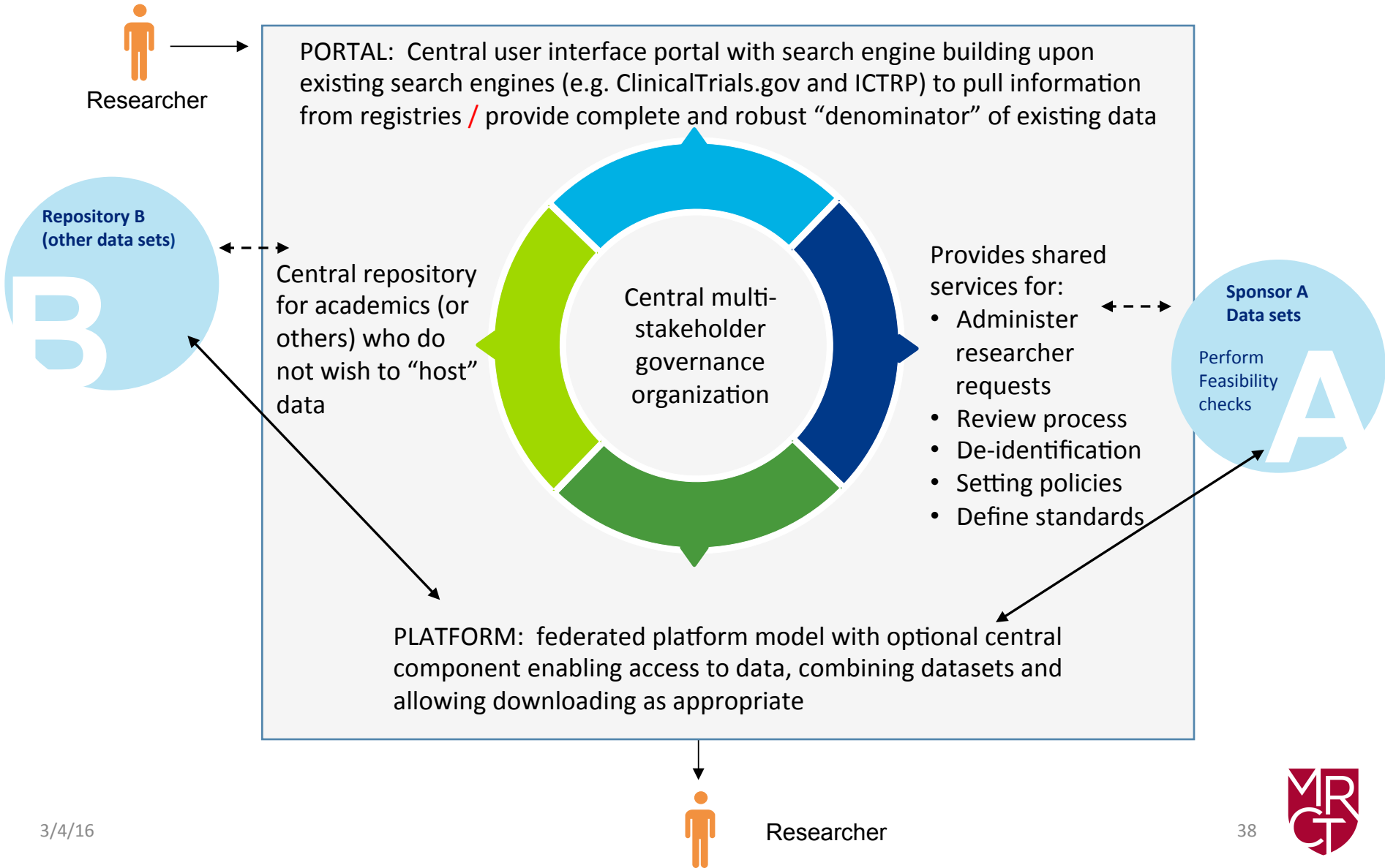
Vision:

- **To maximize the contribution of clinical trial participants to advance science and patient care through the sharing of participant data for further research.**

Principles:

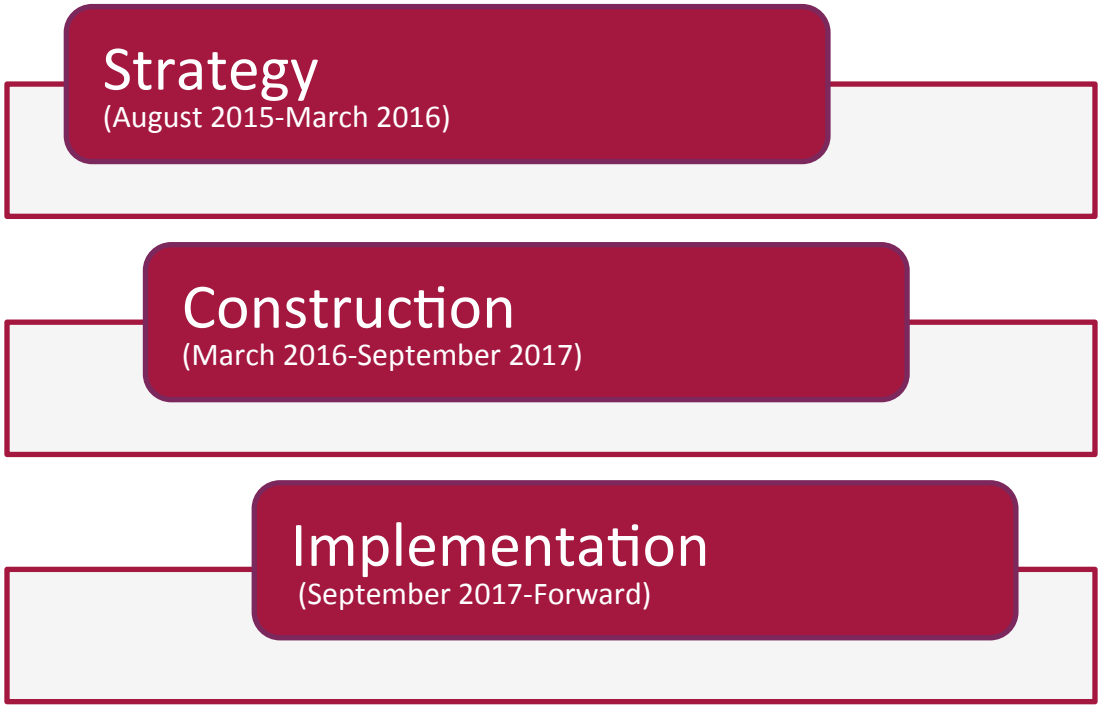
- Protection of study participants' privacy and confidentiality
- Functionality to search and interact with existing data platforms
- Ability to host and analyze data (metadata, SAP, code, etc.), as well as to provide access to data elsewhere
- Complement and interdigitate with regulatory initiatives and registries
- Harmonize and promote good data sharing practices

Data Sharing: Proposed Model Platform - Draft



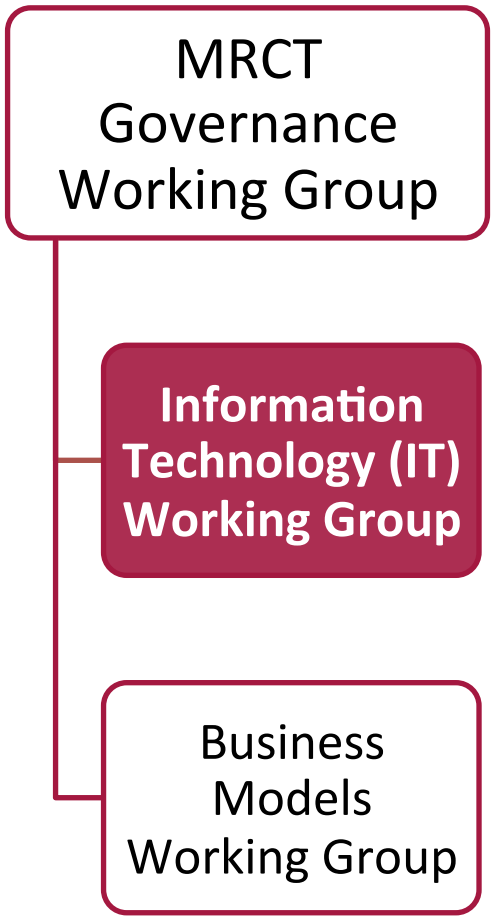
Data Sharing: Next Steps

- We are now developing the blueprint for a new not-for-profit organization whose goal is to create, direct, implement and oversee a sustainable data-sharing platform
  - 3 Phases of Realization:



Data Sharing Strategy Phase: IT Workgroup

- Progress:



Use Case Documents –Define scope, utility and feature set of IT platform including:

- **Data Analysis Use Cases**
  - Outline how data users will interact with the platform to request and analyze data
  - Analyzing published and unpublished data from studies
- **Data Submission Use Cases**
  - Outlines how data generators will deposit and format data in the platform
  - Submitting a data package to be hosted by the platform

Entity to establish resources and expertise to promote transparency, standards and equity

- Common templates and resources:
  - Public education and tools
  - Informed consents, optimized for country and purpose
  - Data contributor agreements
  - Enforceable data use agreements, specific for purpose, that prohibit re-identification
- Independent review panels (or reliance agreements) for data that are subject to intermediary review
- Data standards (pre-hoc or post-hoc)
- Risk-based data de-identification and anonymization
- Develop standards and frameworks to integrate data platforms
- Ability to host data, aggregate data, and create datamarts
- Dynamic analytic tools
- State-of-the-art security provisions to minimize risk

Data-driven learning system

- Engage with global regulators
- Centralize efforts to ensure global equity
- Integrate positions of stakeholders and adapt to change
- Monitor data uses and secondary publications
- Collect and publish outcomes data
- Prepare for integration of electronic health information, mHealth, genomic and omic data, etc.

Data Sharing: Next steps

- March 21-22, 2016, the Wellcome Trust and MRCT will host a Data Sharing Conference at which the MRCT Center and collaborators will present, review, seek endorsement of and feedback on plans to date
- Following the March 2016 Data Sharing Conference, MRCT Center and partners will move to establish and empower the new entity in the next phases of construction and implementation.

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Questions and Discussion
and
Thank you

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