MULTI-REGIONAL CLINICAL TRIALS

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

MRCT Center 2016 Annual Meeting

December 7, 2016

Our Mission

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

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MULTI-REGIONAL CLINICAL TRIALS

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

Overview of ICH E17

Laurie Letvak, Novartis Pharmaceuticals Corporation
William Wang, Merck & Co., Inc.

December 7, 2016

Disclaimer

- The views expressed in this presentation are those of the presenters and do not necessarily reflected the view of their employers, BWH MRCT, or any other organization.

Objectives & Scope of ICH E17

- The purpose of this guideline is to describe general principles for the planning and design of MRCTs with the aim of increasing the acceptability of MRCTs in global regulatory submissions.
- The primary focus of this guideline is on MRCTs designed to provide data that will be submitted to multiple regulatory authorities for drug approval (including approval of additional indications, new formulations and new dosing regimens) and for studies conducted to satisfy post-marketing requirements.

Impact of E17 guideline in drug development

- Avoid duplication
  - Reduce the need to conduct standalone regional or national studies including bridging studies.
- Promote international harmonization
  - A globally harmonized approach to drug development should be considered first.
- Provide better evidence for drug approval in each region
  - Encourage better planning and design of MRCTs based on the latest scientific knowledge and experiences
- Deliver innovative therapy to patients sooner

From ICH E5 to ICH E17: A 20+ Year Journey

- Bridging with local data (ICH E5)
- From bridging to simultaneous confirming
- From sequential to parallel
- From a local mindset to a global mindset

ICH E17 Guideline

ICH E17: Proposal, Expert Working Group, Status

ICH
harmonisation for better health

Final Concept Paper
E17: General principle on planning/designing Multi-Regional Clinical Trials
dated 21 May 2014
Endorsed by the ICH Steering Committee on 5 June 2014

Type of Harmonisation Action Proposed

This Concept Paper supports a proposal for a new harmonised tripartite guideline on general principles on planning/designing Multi-Regional Clinical Trial (MRCT).

Statement of the Perceived Problem

Drug development has rapidly been globalized recently and MRCT for regulatory submission has widely been conducted in non-ICH regions as well as ICH regions. Regulatory agencies currently face challenges in evaluating data from MRCTs for drug approval. However, there is currently no harmonised ICH Guideline on MRCTs, especially focusing on scientific issues in planning/designing MRCTs, although Q&A of ICH E5 Guideline partly covers issue relating to MRCTs. An international guideline will be needed to promote conducting MRCT appropriately. A lack of harmonisation on this topic may cause additional burden for sponsor and difficult situation for conducting MRCTs.

Issues to be Resolved

The new guideline will describe practical issues in planning/designing MRCT. Issues on data interpretation may be discussed in a process of discussion for establishing this guideline, but are out of scope in this guideline. Main objective of this guideline is to provide common points to consider in planning/desingning MRCTs and minimize conflicting opinions from regulatory bodies. The below may be examples of topics covered in this guideline, but more details will be determined by discussion among experts of the group.

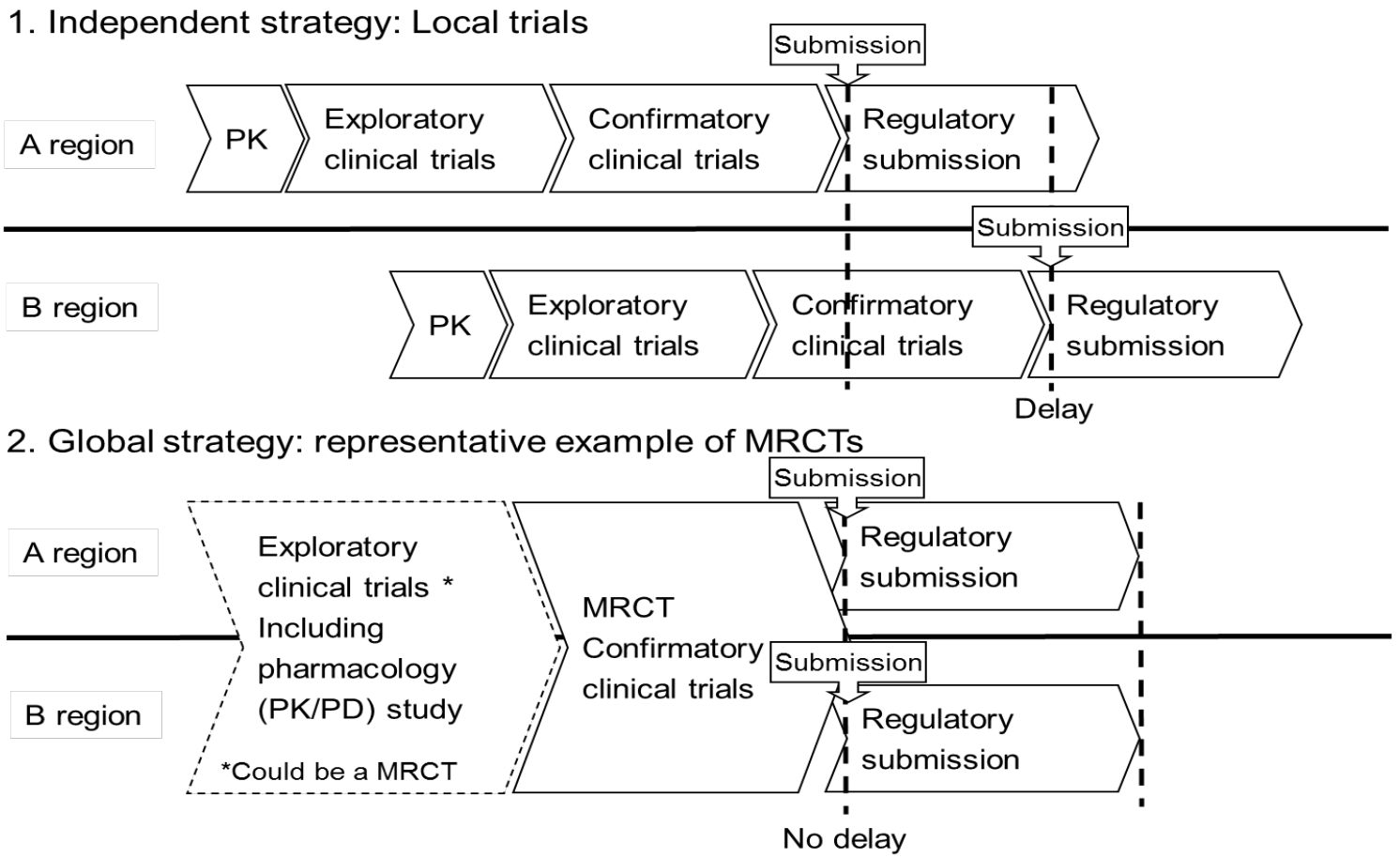
- Issues in planning MRCTs
  - Usefulness of MRCTs in drug developments
  - Essential points for conducting MRCTs (GCP etc)
  - Importance of ethnic factors evaluation on drug efficacy/safety in MRCTs etc.
- Issues in designing MRCTs
  - Points to consider in dose determination for MRCT (exploratory and confirmatory)
  - How to control various concomitant medications in each country
  - Consideration on definition of a population and methods of sample size estimation for a population/region etc.
- Others
  - Encouraging a parallel scientific consultation with multiple regulatory agencies in advance

- E17 EWG: established in June 2014
- Rapporteur: PMDA
- Regulatory/Industry membership from EU, Japan, US,
- Regulatory members/observers from Health Canada, Brazil, Sandi, Korea, Singapore, Taiwan, and WHO

- Status:
  - Step 2b: ICH draft signed off 6/16
  - Step 3: public comments Jul16 –Jan 17)
  - EWG met in Osaka to begin review of comments

  Finalization anticipated 4Q 2017

Encouraging simultaneous global drug development



MRCTs in an exploratory stage

- Encourage to conduct MRCTs in an exploratory stage as well as a confirmatory stage
  - MRCTs can play an important role in drug development programmes beyond their contribution at the confirmatory stage.
  - For example, exploratory MRCTs can gather scientific data regarding the impact of extrinsic and intrinsic factors on pharmacokinetics and/or pharmacodynamics (PK/PD) and other drug properties, facilitating the planning of confirmatory MRCTs.
  - MRCTs may also serve as the basis for approval in regions not studied at the confirmatory stage through the extrapolation of study results.

Promoting conduct of MRCTs

- MRCTs are generally the preferred option for investigating a new drug for which regulatory submission is planned in multiple regions. The underlying assumption of the conduct of MRCTs is that the treatment effect is clinically meaningful and relevant to all regions being studied.
  - This assumption should be based on knowledge of the disease, the mechanism of action of the drug, on a priori knowledge about ethnic factors and their potential impact on drug response in each region, as well as any data available from early exploratory trials with the new drug.
  - The study is intended to describe and evaluate this treatment effect, acknowledging that some sensitivity of the drug with respect to intrinsic and/or extrinsic factors may be expected in different regions and this should not preclude consideration of MRCTs.

Quality of MRCT

- Ensuring trial quality is of paramount importance for MRCTs.
- This will not only ensure the scientific validity of the trial results, but also enable adequate evaluation of the impact of intrinsic and extrinsic factors by applying the same quality standard for trial conduct in all regions.
- In addition, planning and conducting high quality MRCTs throughout drug development will build up trial infrastructure and capability, which over time will result in a strong environment for efficient global drug development.

Careful consideration

- To increase acceptability of MRCT data in the review by multiple regulatory agencies for drug approval, a sponsor should carefully consider the planning and design of MRCTs in advance.
  - Ethnic factors are a major point of consideration
  - They should be identified during the planning stage, and information about them should also be collected and evaluated when conducting MRCTs.
  - Based on the understanding of accumulated knowledge about these intrinsic and extrinsic factors, MRCTs should be designed to provide information to support an evaluation of whether the overall treatment effect applies to subjects from participating regions.

Pooled Population

- Introduce a new use of "pooled population" to help regulatory decision making
  - Some regions may be pooled at the design stage, if subjects in those regions are thought to be similar enough with respect to intrinsic and/or extrinsic factors relevant to the disease area and/or drug under study.
  - Consideration could also be given to pooling a subset of the subjects from a particular region with similarly defined subsets from other regions to form a pooled subpopulation whose members share one or more intrinsic or extrinsic factors important for the drug development program.
  - Both pooled subpopulations and pooled regions should be specified at the study planning stage and be described in the study protocol.

Sample size allocation

- The guiding principle for determining the overall sample size in MRCTs is that the test of the primary hypothesis can be assessed, based on combining data from all regions in the trial.
- The sample size allocation to regions or pooled regions should be determined such that clinically meaningful differences in treatment effects among regions can be described without substantially increasing the sample size requirements based on the primary hypothesis.

  - The guideline provides some more details how to allocate sample size to region in the guideline

Discussions with regulatory agencies

- Encourage discussions with regulatory authorities in the planning stage
  - In the planning and design of MRCTs, it is important to understand the different regulatory requirements in the concerned regions.
  - Efficient communication among sponsors and regulatory authorities at a global level can facilitate future development of drugs. These discussions are encouraged at the planning stage of MRCTs.

Discussion in Osaka

Key Themes of Comments - >800 received

- Harmonization among regulatory authorities
  - How can this be facilitated with company at the table
  - How to best accomplish given different HA's resources and priorities
  - Currently different guidances exist for same topics/diseases
- Consistency across regions
  - How to define consistency
  - Interpretation of variability – in light of biological plausibility, consistency of findings internally and externally, strength of evidence, statistical uncertainty

Key Themes of Comments - >800 received

- Definition of Region and Subpopulation
  - Geographic, regulatory regions
  - Subpopulation can be defined by variety of factors – race, etc. in future more molecular/genotypic categorization
- Sample Size Requirement for Region
  - Need to reconcile current country requirements
  - Pooling pre-specified like populations – still likely “underpowered”
  - Avoid inflating of overall sample size

Members of E17 (as of November 2016)

EU	EMA	Canada	Health Canada
	EFPIA	WHO	WHO
Japan	PMDA	GCC	Saudi Food and Drug Authority
	JPMA	Brazil	Brazilian Health Surveillance Agency
US	FDA	Singapore	Health Sciences Authority (HSA)
	PhRMA	Korea	Ministry of Food and Drug Safety (MFDS)
		Chinese Taipei	Center for Drug Evaluation (CDE)

ICH-E17 EWG

Data transparency today and tomorrow
Harvard MRCT Annual Meeting

December 7, 2016

Murray Stewart, **DM FRCP**
Chief Medical Officer, Global Medical
GlaxoSmithKline

Data transparency today and tomorrow: current state, issues, and vision

What are we trying to do with data sharing?

Why share clinical trial information?

- We can further science and improve patient care
- Decrease risk to trial participants by avoiding enrollment in duplicate trials
- Enable the review of results from individual clinical trials to validate the results

Why share clinical trial information?

- We hope to rebuild our reputation as an industry
- Transparency can help regain trust

Sharing our data with researchers may improve trust and speed discovery

- We can be better partners in innovation

Proof is in our behavior – what actions are we taking?

Search Go

Home | Find Studies | Patient Level Data | Products | Metrics | Research | Contact GSK

Quick Search

Medical Condition

Product Name

Enter GSK ID Go

Advanced search

Useful Links

Paroxetine Information

Patient Level Data Request System

ClinicalTrials.gov

clinicaltrialsregister.eu

European Public Assessment Reports

FDA Approved Drug Products

FDA Postmarket Drug Safety Information for Patients and Providers

For more information on this register please call +1.877.379.3718

About the GSK Clinical Study Register

The GlaxoSmithKline (GSK) Clinical Study Register provides an easily accessible repository of data from GSK-Sponsored Clinical Studies, supplementing communication in journals, at scientific meetings, in letters to healthcare professionals, and in approved prescribing information. It is important to emphasise that approved prescribing information must continue to guide appropriate use of GSK medicines. This information may vary from country to country. **Before prescribing any product mentioned in the Register, Healthcare Professionals should consult prescribing information approved in their country.**

PROTOCOL SUMMARIES | SCIENTIFIC RESULTS SUMMARY | PLAIN LANGUAGE RESULTS SUMMARY

PROTOCOL | CLINICAL STUDY REPORT | PUBLICATION

PATIENT LEVEL DATA FOR RESEARCHERS

REGULATORY OVERVIEW DOCUMENTS

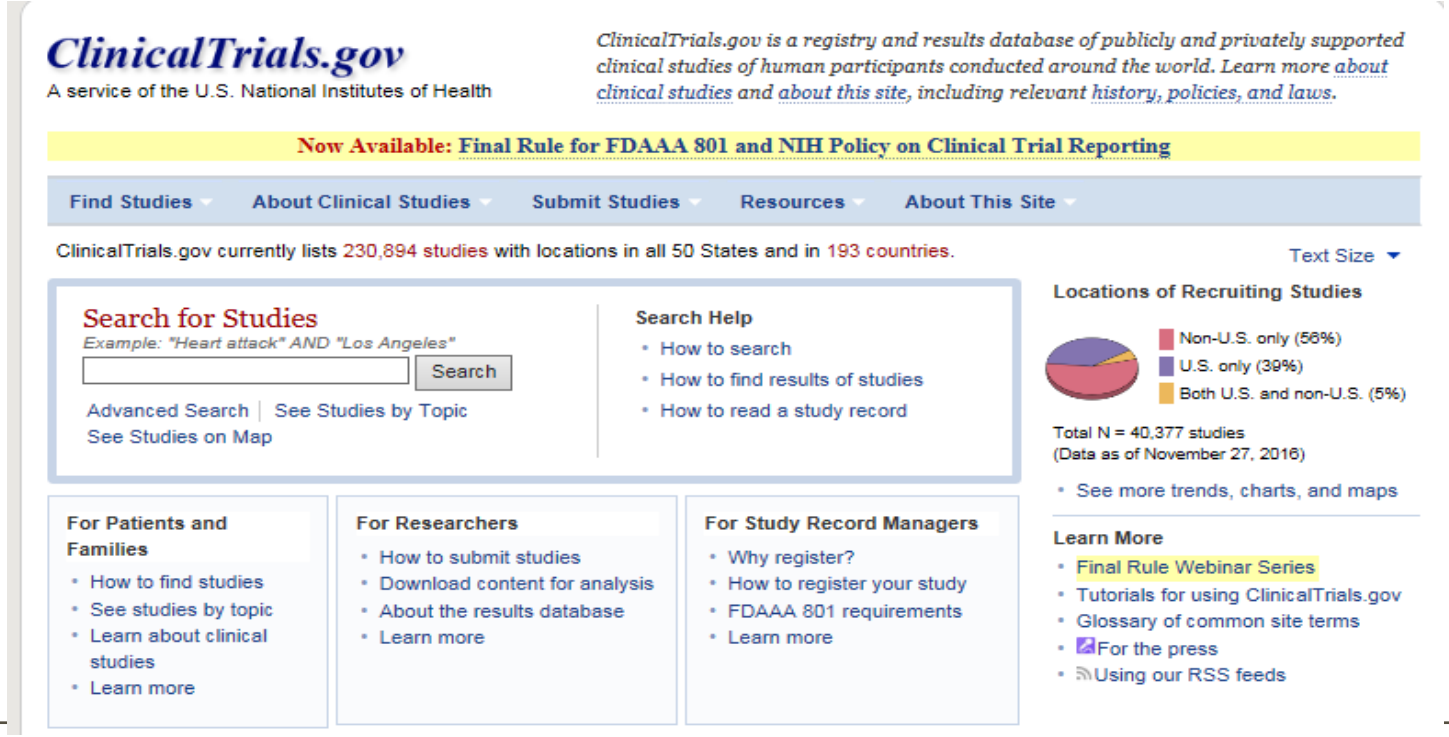
We publish data to our register, is this enough?

- It's fragmented and people are not looking at individual registers or systems.

- This relates to patient level data as well - If we don't utilize one system, people will not know

- Which then contributes to the appearance of not being transparent (undermining trust)

But this isn't where people are looking for results, for example, so we are responding…



ClinicalTrials.gov
A service of the U.S. National Institutes of Health

ClinicalTrials.gov is a registry and results database of publicly and privately supported clinical studies of human participants conducted around the world. Learn more about clinical studies and about this site, including relevant history, policies, and laws.

Now Available: Final Rule for FDAAA 801 and NIH Policy on Clinical Trial Reporting

Find Studies | About Clinical Studies | Submit Studies | Resources | About This Site

ClinicalTrials.gov currently lists 230,894 studies with locations in all 50 States and in 193 countries.

Text Size

Search for Studies
Example: "Heart attack" AND "Los Angeles"
Search
Advanced Search | See Studies by Topic
See Studies on Map

Search Help
- How to search
- How to find results of studies
- How to read a study record

Locations of Recruiting Studies
- Non-U.S. only (56%)
- U.S. only (39%)
- Both U.S. and non-U.S. (5%)

Total N = 40,377 studies
(Data as of November 27, 2016)

- See more trends, charts, and maps

For Patients and Families
- How to find studies
- See studies by topic
- Learn about clinical studies
- Learn more

For Researchers
- How to submit studies
- Download content for analysis
- About the results database
- Learn more

For Study Record Managers
- Why register?
- How to register your study
- FDAAA 801 requirements
- Learn more

Learn More
- Final Rule Webinar Series
- Tutorials for using ClinicalTrials.gov
- Glossary of common site terms
- For the press
- Using our RSS feeds

Where do we hope to be with patient level data sharing in the future?

What is the ideal situation?

Our Vision

A broad, independent global solution to allow access to data from clinical trials conducted by multiple companies and organisations.

Aim for one system

- Aim for one system (realistically get a few, less is better)
- Bring the ecosystem together
- Be responsive to current landscape

Data transparency today and tomorrow: current state, issues, and vision

What are the challenges we are facing?

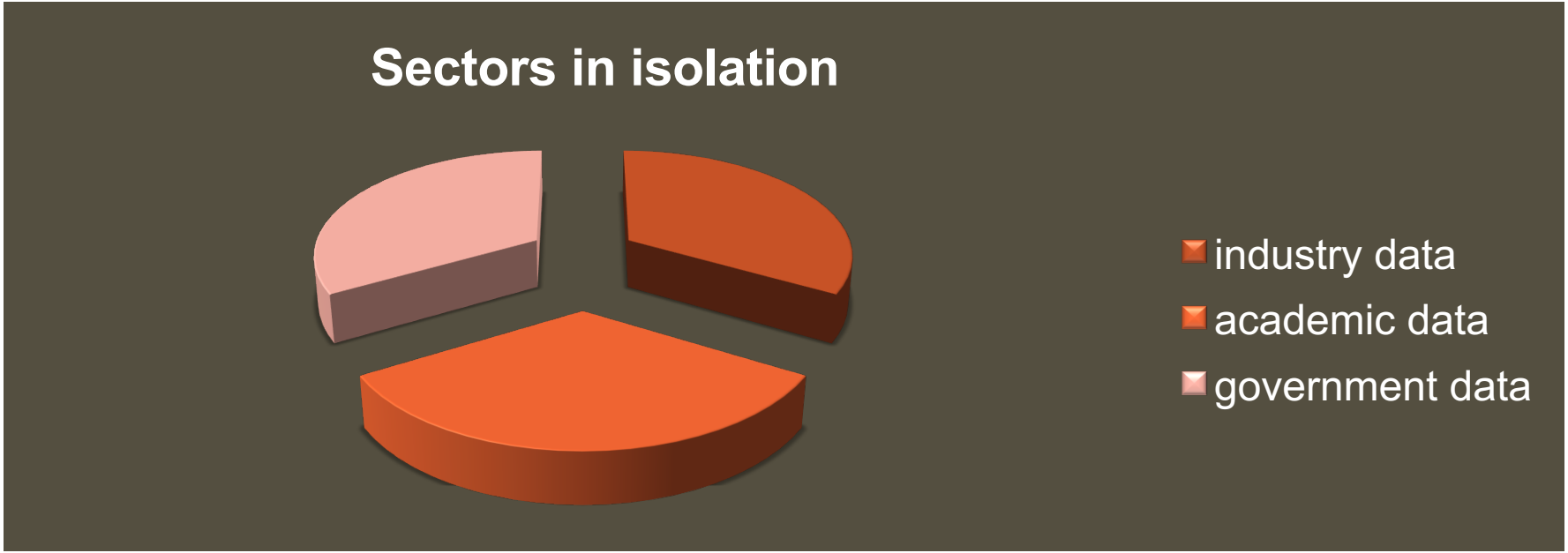
What challenges do we face?

Everyone agrees with principle but how to put data sharing into practice:

- How do we ensure valid science
- How do we protect privacy yet maintain data utility
- Funding and equitable distribution of cost
- Should there be monitoring and oversight
- Cultural changes are needed – “Once you have collected your data, you want to keep it”

Are we each going to solve our “own” problems with data sharing?

Can we come together for the public good?

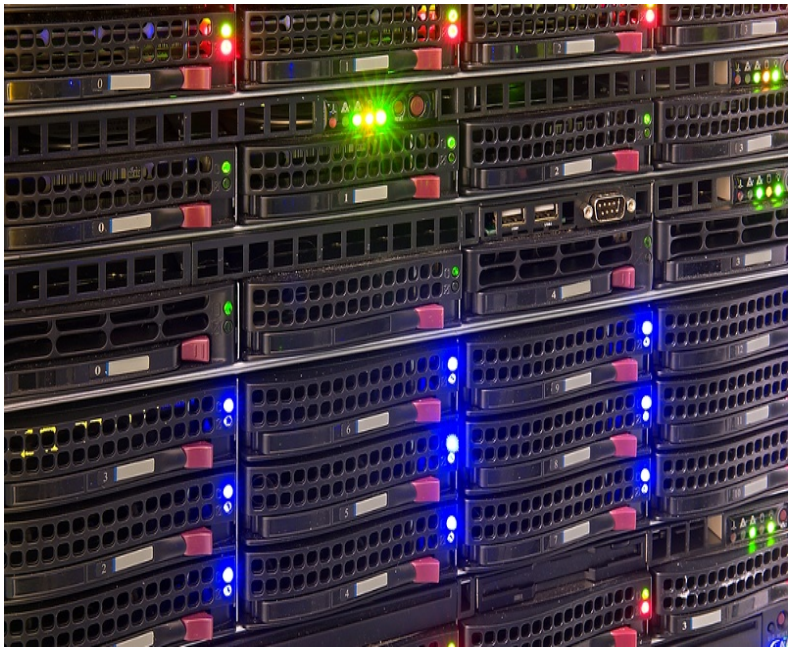


Not intended to be representative proportions

Can we convert data into an interoperable format?

There is a need for common standards for storing and retrieving data.

How can industry and academia work together toward this critical goal for data sharing and secondary research?



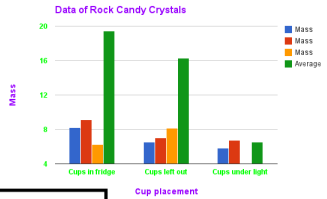
Skeptics can be vocal

Is the demand there?

- Used by some to show limited value

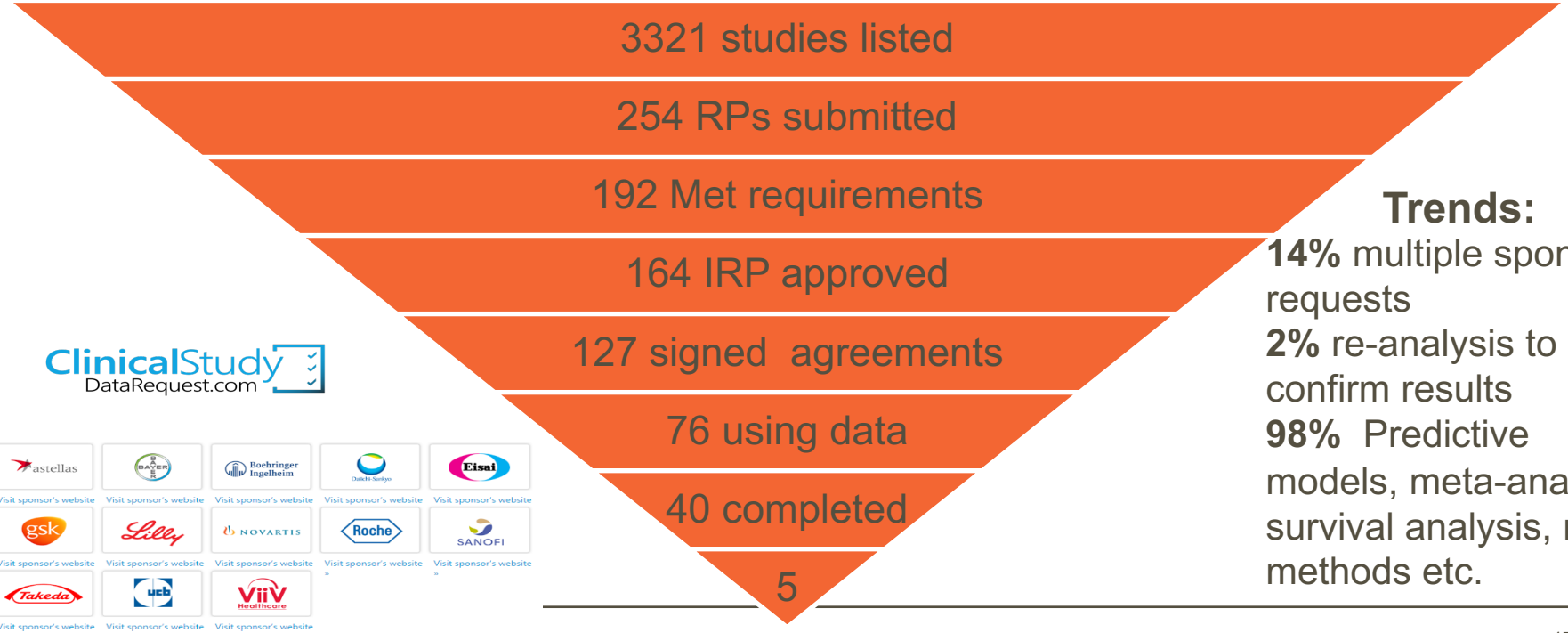
We need people to ask the questions

- People with skill set necessary



DATA		
Trial	Brand X – number of chips in 5 cookies	Brand Y – number of chips in 5 cookies
1	14	16
2	16	17
3	17	18
4	21	16
5	8	14
total number	76	81
number per cookie	15.2	17.2

ClinicalStudyDataRequest (CSDR)*
5 publications since May 2013 to Sept 2016



ClinicalStudy DataRequest.com

astellas Visit sponsor's website
BAYER Visit sponsor's website
Boehringer Ingelheim Visit sponsor's website
Daiichi-Sankyo Visit sponsor's website
Eisai Visit sponsor's website
gsk Visit sponsor's website
Lilly Visit sponsor's website
NOVARTIS Visit sponsor's website
Roche Visit sponsor's website
SANOFI Visit sponsor's website
Takeda Visit sponsor's website
ucb Visit sponsor's website
ViiV Healthcare Visit sponsor's website

Trends:

14% multiple sponsor requests

2% re-analysis to confirm results

98% Predictive models, meta-analysis survival analysis, new methods etc.

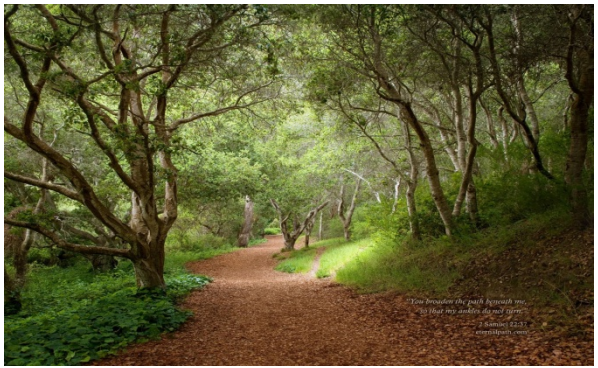
*Metrics as of September 30, 2016

And, do we really share a common goal?

Is the minimum enough or are we committed at a higher-level to make this work?

Data transparency today and tomorrow: current state, issues, and vision

How do we get to ideal (or as close as possible)?



Getting to ideal

Or as close as possible?

Where might Vivli fit into this long term vision?

- Now that we are over hurdle of deciding that we will share, then no reason *not* to share
- Unlikely to be one platform in 10 years that everyone uses but without this ideal, then we *will* be very fragmented
- How can we best connect existing platforms (CSDR, Yoda-J&J, DCRI-BMS) and non-industry platforms (NIH and others)
- Neutral entity might help increase academic data sharing and agree on standards?

Thank you

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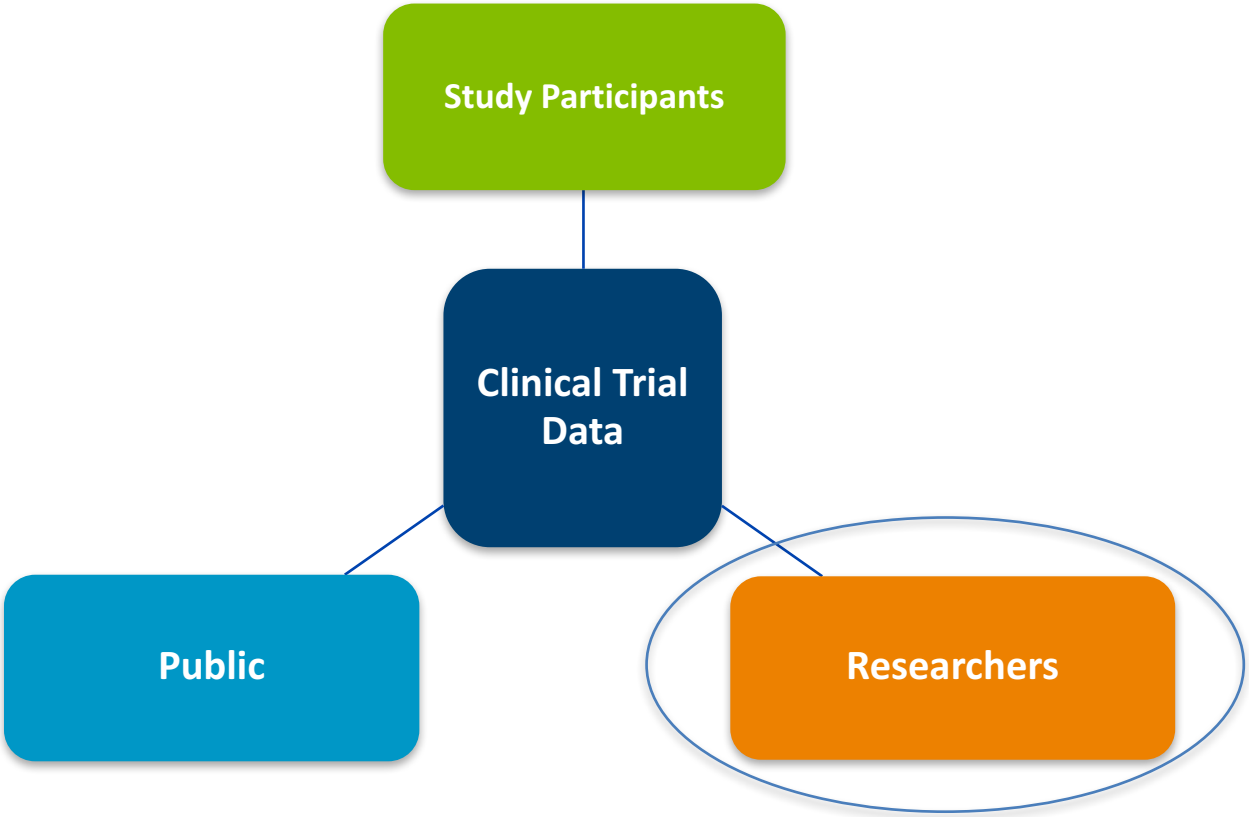
THE MRCT CENTER of BRIGHAM AND WOMEN'S HOSPITAL and HARVARD

Reducing Barriers to Clinical Trials Data Sharing: Cooperative Science to Improve Public Health

Valuing patient contributions, respecting existing research communities, and increasing discovery

Clinical Trials Data Sharing: Audiences

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



Purpose-driven Data Sharing Will Enhance Scientific Discovery And Public Trust

Benefits:

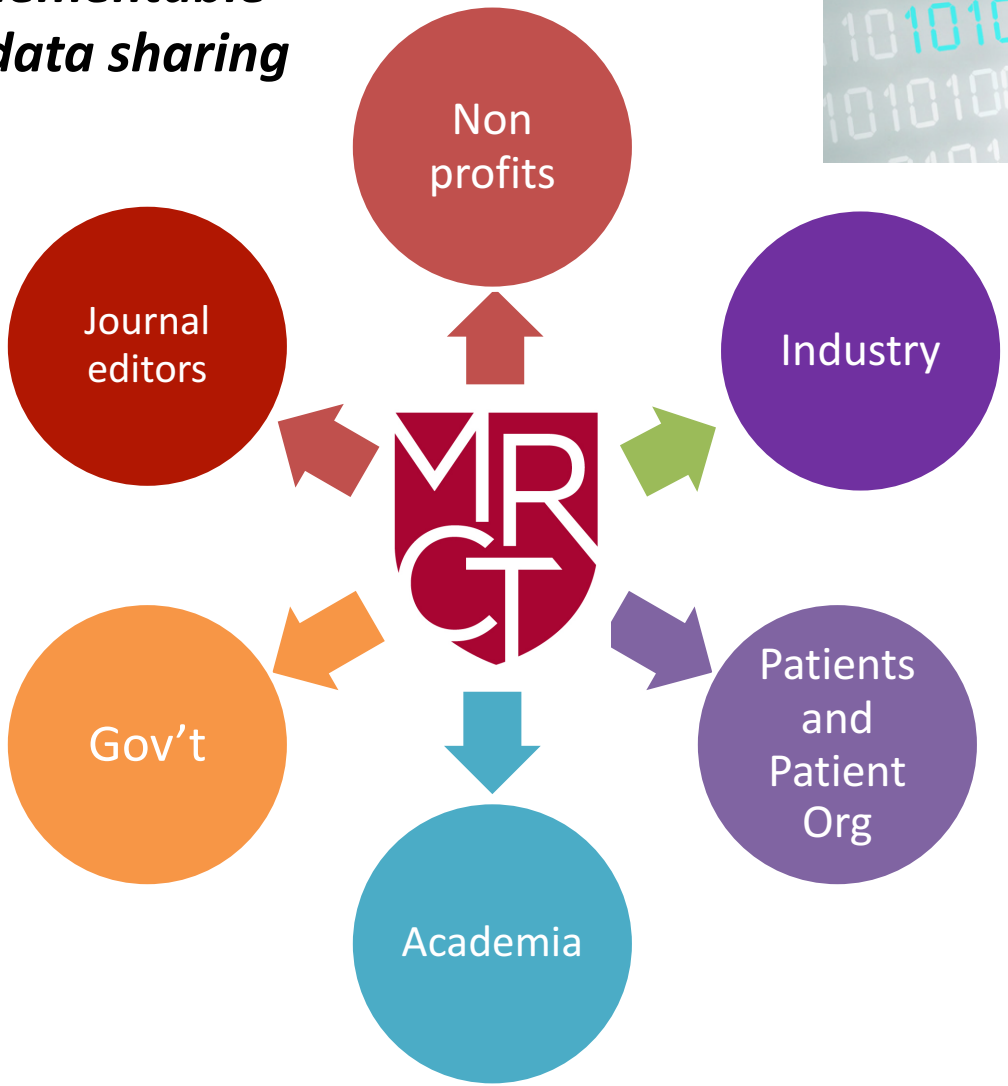
- Eliminate duplicative trials
- Evaluate common adverse events by compound class or subpopulation
- Identify surrogate endpoints
- Enhance correlative and explanatory science

Benefits only realized if

- Risks are minimized, with attention to participant safety and privacy
- Wide participation including academia, biotech, government, non-profits
- Data are interoperable and data sets can be pooled
- State-of-the-art security is in place

MRCT Center as a Neutral Convener

To create implementable solutions for data sharing



The MRCT Center's Data Sharing Workgroup Members

Governance Work Stream	IT Work Stream	Business Models Work Stream
Co-Chairs: **MRCT Center** **Wellcome Trust** **Arnold Foundation**	**Co-Chairs:** **Ida Sim (UCSF)** **Barbara Bierer (MRCT)**	**Co-Chairs:** **Wellcome Trust** **MRCT Center**
Team Members: Mark Barnes **(MRCT Center)** Barbara Bierer **(MRCT Center)** Stuart Buck **(Arnold Foundation)** Marla Jo Brickman **(Pfizer)** Nina Hill **(Pfizer)** Rebecca Li **(MRCT Center)** Nick Lingler **(Deloitte Consulting)** Justin McCarthy **(Pfizer)** Kris Bolt **(MRCT Center)** Sandra Morris **(Johnson & Johnson)** Jennifer O'Callaghan **(Wellcome Trust)** Nicola Perrin **(Wellcome Trust)** Paul Seligman **(Amgen)** Ida Sim **(UCSF)** Jessica Scott **(GlaxoSmithKline)** Catrin Tudur Smith **(University of Liverpool)** Natalie Zaidman **(Pfizer)**	Team Members: George Alter **(U of Michigan)** Munther Baara **(Pfizer)** Barbara Bierer **(MRCT Center)** Kris Bolt **(MRCT Center)** Brian Bot **(Sage Bionetworks)** Anne Claiborne **(IOM)** Khaled El Emam **(U of Ottawa)** Ghassan Karam **(WHO)** Michael Khan **(U of Colorado)** Sean Khozin **(FDA)** Rebecca Kush **(CDISC)** Rebecca Li **(MRCTCenter)** Gene Lichtman **(HCRI)** Michelle Mancher **(IOM)** Heather Marino **(MRCT Center)** Chris Mavergames **(Cochrane)** Eric Perakslis **(Takeda)** Frank Rockhold **(Duke, prior GSK)**	Team Members: Barbara Bierer **(MRCT Center)** Patrick Cullinan **(Takeda)** Rebecca Li **(MRCT Center)** Peter Lyons **(Deloitte)** Kris Bolt **(MRCT Center)** Nicola Perrin **(Wellcome Trust)** Rohin Rajan **(Deloitte)**

Our Work in Data Sharing

Policy

- Harmonizing language & agreements among sponsors

Advocacy

- Lowering barriers to data sharing
- Academic credit for data sharing

Implementation

- Creating a platform for data sharing
- Making data on other platforms more discoverable

Policy

••Harmonizing language & agreements among sponsors

- Data Contributor agreement
- Data Use agreement
- Informed consent agreement language
- IRP Principles document defined for participating IRPs

Advocacy

••Lowering barriers to data sharing

- Convening stakeholders who are currently sharing and those who do not currently share
- Lower the barriers for those who do not have the resources or knowledge to share data
- Advance policy changes that enable academic credit for data that is made widely available for the advancement of science and medicine

Advocacy

- Academic credit for data sharing

- Problem statement: Current system of academic recognition does not acknowledge or honor investigators who share their data
- **Aim: Develop practical, comprehensive recommendations on how data generators should be recognized for the design, curation, completion and dissemination of quality data sets**

"Data Authors"

Advocacy

- Data Authors

- Responsible for integrity and curation of data
- Data consistent with FAIR principles
- Listed on the primary publication
- Cited in Medline
- Searchable through NLM (and other search engines)
- Reflected on CV
- Utilized for promotions, tenure decisions, funding decisions
- Metrics to be developed over time

Implementation

Create a sustainable global data-sharing platform

- Launch Vivli, a non-profit center for global data sharing
- Making data on other platforms more discoverable through a robust search engine

Current Gap

We and others have identified significant current challenges to utilizing existing data on clinical trials for further research:

- Many academicians and others do not have a means to make data available in a turn-key fashion.
- Although technology has made it easier to make data available, data remain difficult to discover.
- A robust centralized search engine does not exist to locate data across the different data generators and data platforms.
- Combing datasets from different generators is resource- and time-intensive due to inconsistent adoption of data standards, data requirements, security standards and policies.
- Datasets are on different platforms, under different governance, and cannot be combined

Significant variability in stakeholder positions

- **Industry**
  - Data sharing on “multi-sponsor” or single institution platforms
  - At the leading edge of data sharing
  - All require review for data
- **Academic**
  - No institutional solution; creating URLs or using other (e.g. NIH) resources
  - Individuals: (1) If share, prefer to delegate management with open access or (2) closely held under strict controls for access
- **Non-profit and patient advocacy groups**
  - Generally encouraging of data sharing with appropriate participant information and consent
  - Appreciate that “stand alone platforms” lose the value of interoperability and of collective advantage of “big data”

Vivli Mission

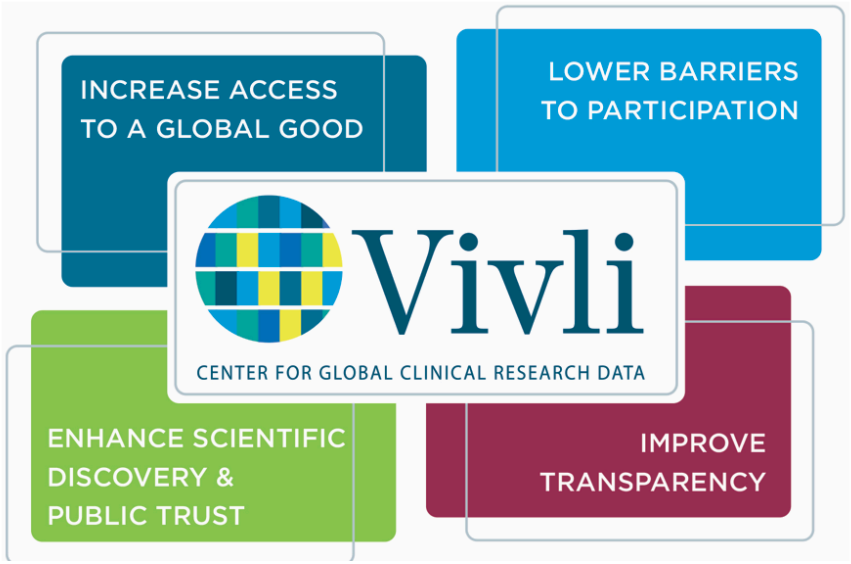
Vivli
CENTER FOR GLOBAL CLINICAL RESEARCH DATA

Promote, coordinate, and facilitate clinical research data sharing through the creation and implementation of a sustainable global data-sharing enterprise

Vivli has been incorporated to provide governance and management of a platform—agnostic to disease, country, sponsor and funder—to reduce barriers to clinical trials data sharing.

Vivli: Scope

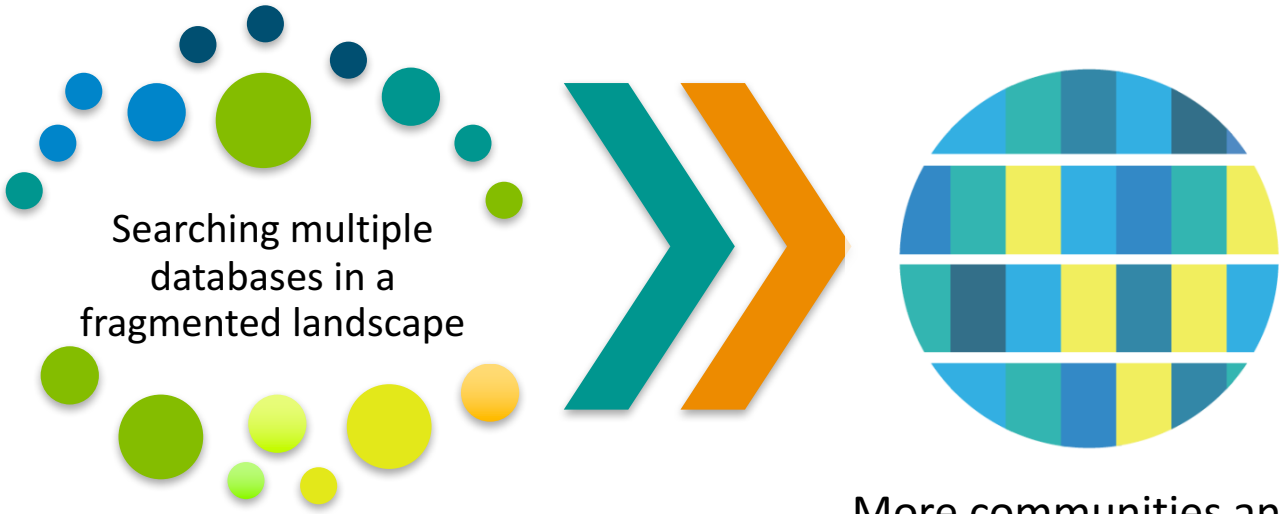
1) Hosting data for stakeholders that do not have the ability to do so;
2) Enabling interoperability of data from multiple sources;
3) Coordinating and integrating existing data-sharing initiatives, policies, and processes as appropriate;
4) Promoting reasoned solutions to challenges of data sharing.



The Unique Remit of Vivli

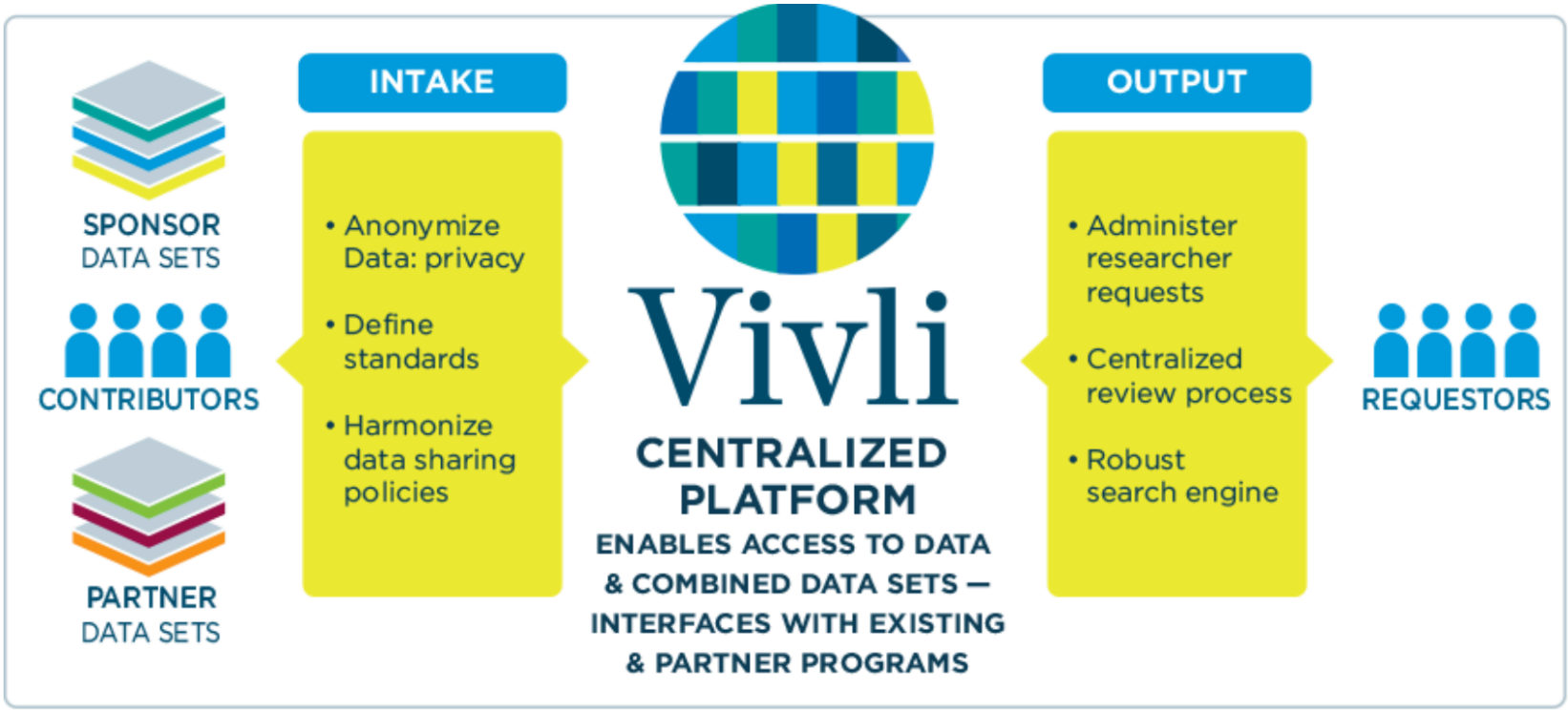
Advanced **metadata search** and **discovery** capability

Simplified **access request** system to data residing on **other platforms**



As the enhanced metadata catalog matures, more data, including externally hosted data, will be discoverable through Vivli

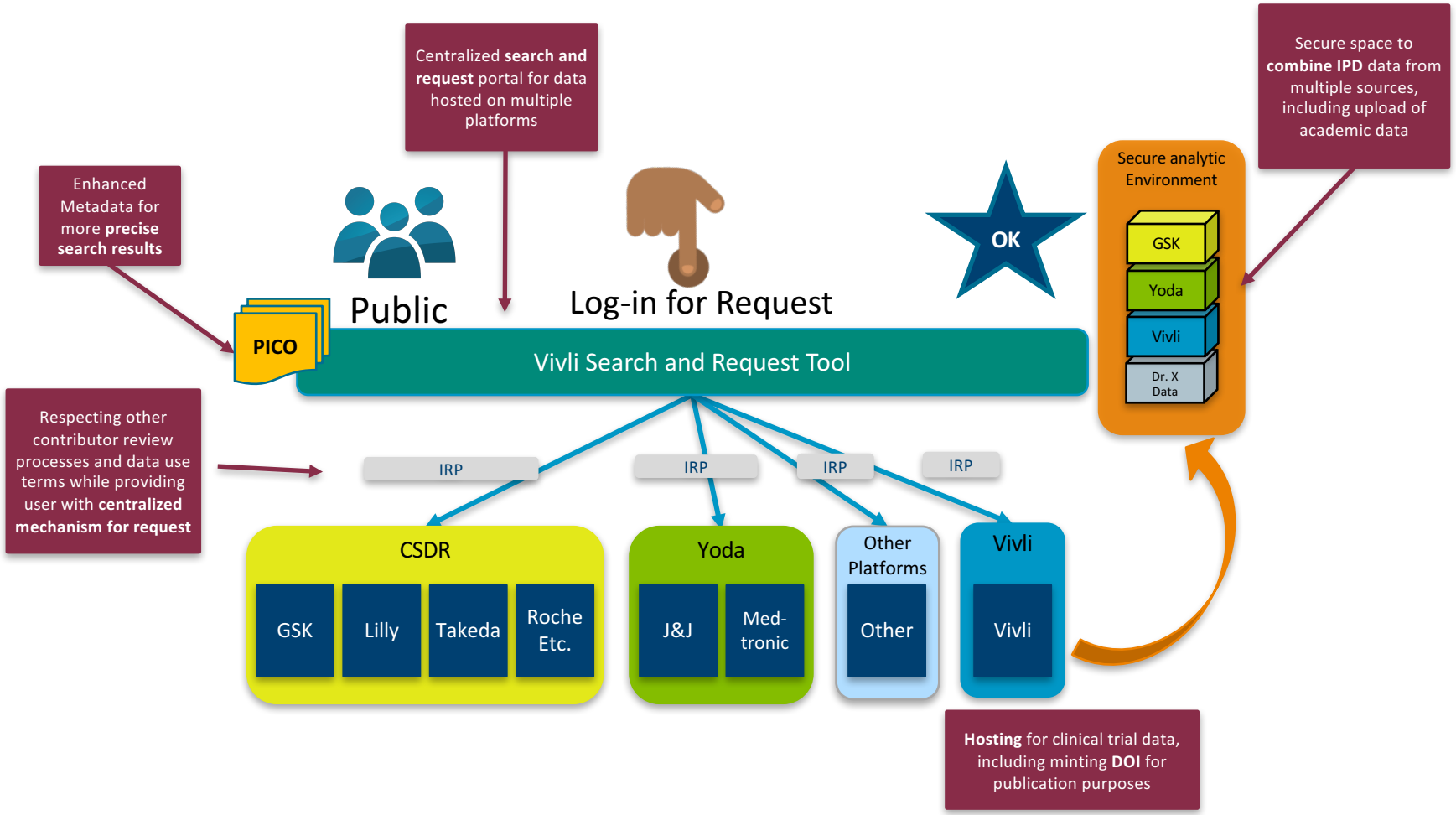
The Unique Remit of Vivli



Combined **Industry, Academic, and Biotech** data discoverable through one search engine

Anonymized Individual Participant-Level Data (IPD) available for request

Vivli Workflow



Vivli

Example of New Search Functionality

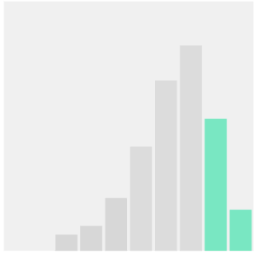
1. Question

Do anticholinesterase drugs slow dementia progression in patients over 65 without Parkinsons?

Population | Intervention / Comparator | Outcome

2. Additional criteria

3. Query Results (93 studies)



Study ID: 00451435

Title: The Effect of Anticholinesterase Drugs on Sleep in Alzheimer's Disease Patients

Lead Researcher: Walter AS Moraes, MD PhD

Sponsor: AFIP

More information…

IPD: Hosted on Vivli | Curated: CSV

Non-IPD: Hosted on Vivli | Curated: SAS

Packages: Full, Post-Pub, Post-Reg

Select

Value Proposition for Vivli

- Driving new discovery by sharing data outside of disease-specific enclaves
- Promoting harmonized approach to governance, including unifying data use agreements, data contributor agreements, informed consent language, etc.
- Hosting data as well as connecting existing systems to allow inter-digitation of data
- Starting with clinical trials data but growing to real world patient data, outcomes data, and public health data allowing:
  - Substantiation of safety & efficacy of medical and public health interventions
  - Real-time public health decision-making using aggregated public health data

3-Year Platform Development Roadmap: Next Steps

Year 1

- Pilot
- Metadata intake from registries
- Machine Assisted Metadata Curation
- User interface for Search, & Request, execute DUAs
- Combine datasets: Academic upload, Pharma from another platform
- Analyze in secure workspace
- Basic open source analytical tools (e.g. R)

Year 2

- Dynamic User interface
- Repository Dataset Identifiers
- Analytic Tools on platform
- Secure hosting for clinical and SNP data
- Centralized Review and Agreements Processes
- External APIs for analytic tools

Year 3

- Hosting for Full Genomic studies
- Dataset Citation for Academic Credit
- Anonymization Services
- Data Mapping services
- User Training
- Community Verticals
- Automated data provisioning
- Advanced Data Visualizations

Needs assessment for launch

Year 1	Year 2	Year 3
• Phase 1 technical build of platform: $3.5M • Vivli hosting, staffing, legal and marketing: $1M	• Advancements to platform for phase two: $3M • Vivli hosting, staffing, legal and marketing: $2M	• Advancements to platform for phase three: $2M • Vivli hosting, staffing, legal and marketing: $3M

Total Launch requirements = $12-15M

Intention: Capital build from non-profit sources and unrestricted donations

Fundraising strategy to Launch

MRCT is currently seeking funding for Vivli launch and has applied for 501c3 status

- Founders ≥ $3M (e.g. $1M per year for 3 years)
- Champions $750K - $3M (e.g. $250K – IM per year for 3 years)
- Supporters $300K - $750K (e.g. $100-250K per year for 3 years)

Execution and use: Planning for sustainability

- Subscription levels:
  - Annual Base membership (industry and bio)
  - Not for profit
  - Academic (individual and institutional)
  - Pay-per-use models for non-subscribers
- Certain services at cost (academic/non-profit) or cost+ (for-profit)

*In Year One: Academics and not-for-profit data users would not be charged for introductory use; for-profit organizations will be charged

Vivli Board of Directors

- *Stuart Buck, Laura and Arnold Foundation*
- *Justin McCarthy, Pfizer*
- *Sharon Terry, Genetics Alliance*
- *Murray Stewart, GSK*

- *Ex Officio:*
- *Mark Barnes, JD LLM*
- *Barbara E. Bierer, MD*
- *Rebecca Li, PhD*
- The ex officio members of the Board of Directors were appointed in order to incorporate Vivli as an entity in the US. It is intended that one ex officio member will be replaced annually over the course of the first three years of launch by election of the then current members of the Board.

Join us

- Partner with us - our mission to is to *accelerate your discoveries through integrating of data globally across platforms and databases*
- Please collaborate with us by making your data discoverable
- Consider learning more about supporting the Vivli effort

Development Advisors and Supporters

The MRCT Center would like to thank the following supporters and funders* for their contributions to the Vivli project:

- *Deloitte Consulting*
- *GlaxoSmithKline*
- *The Institute of Medicine*
- *The Laura and John Arnold Foundation*
- *Johnson & Johnson*
- *The Lyda Hill Foundation*
- *Pfizer Foundation*
- *Wellcome Trust*

*In alphabetical order

MULTI-REGIONAL CLINICAL TRIALS

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

MRCT Annual Meeting 2017: Transparency

Mark Barnes

Barbara Bierer

Rebecca Li

Carmen Aldinger

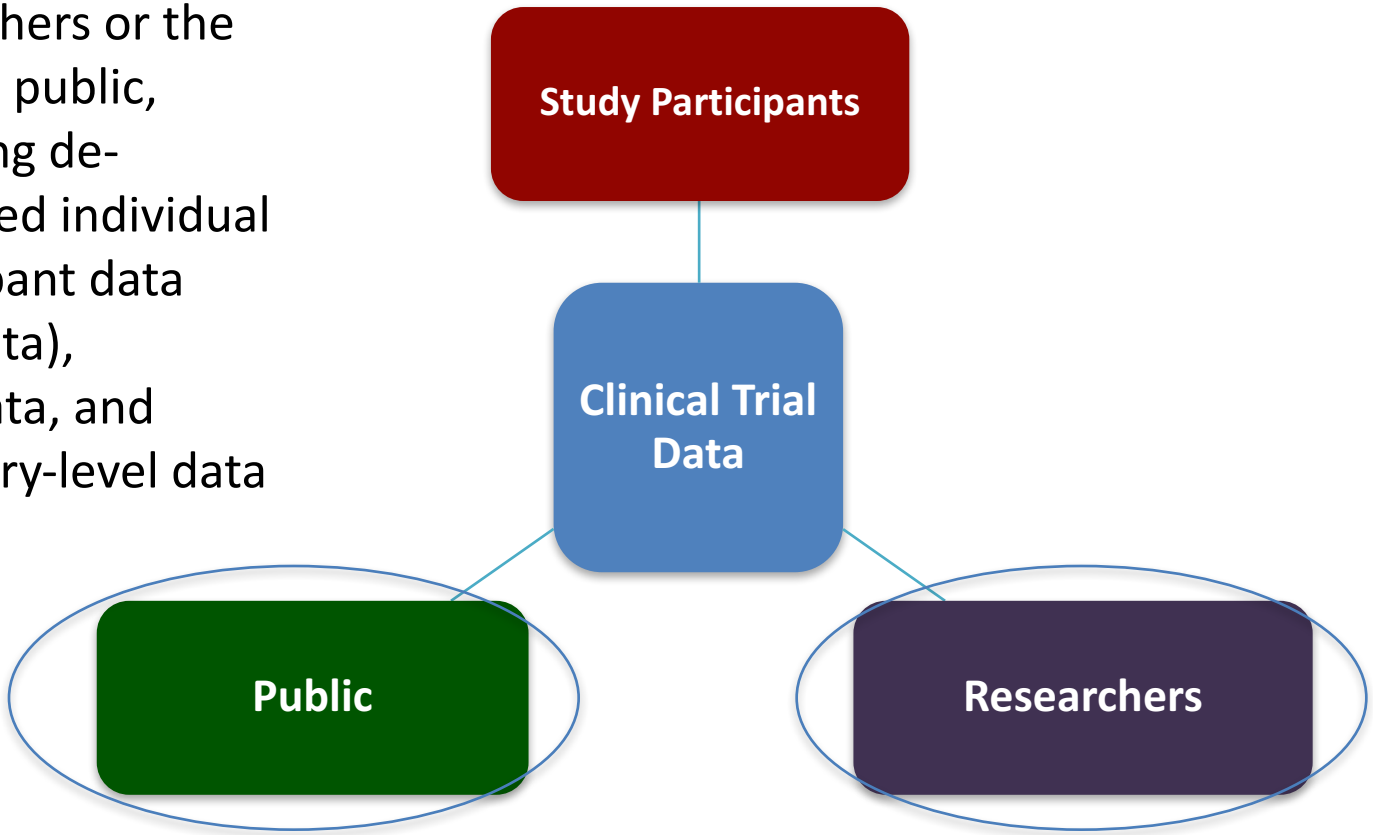
Kris Bolt

Christopher Kabacinski

Sarah Rich

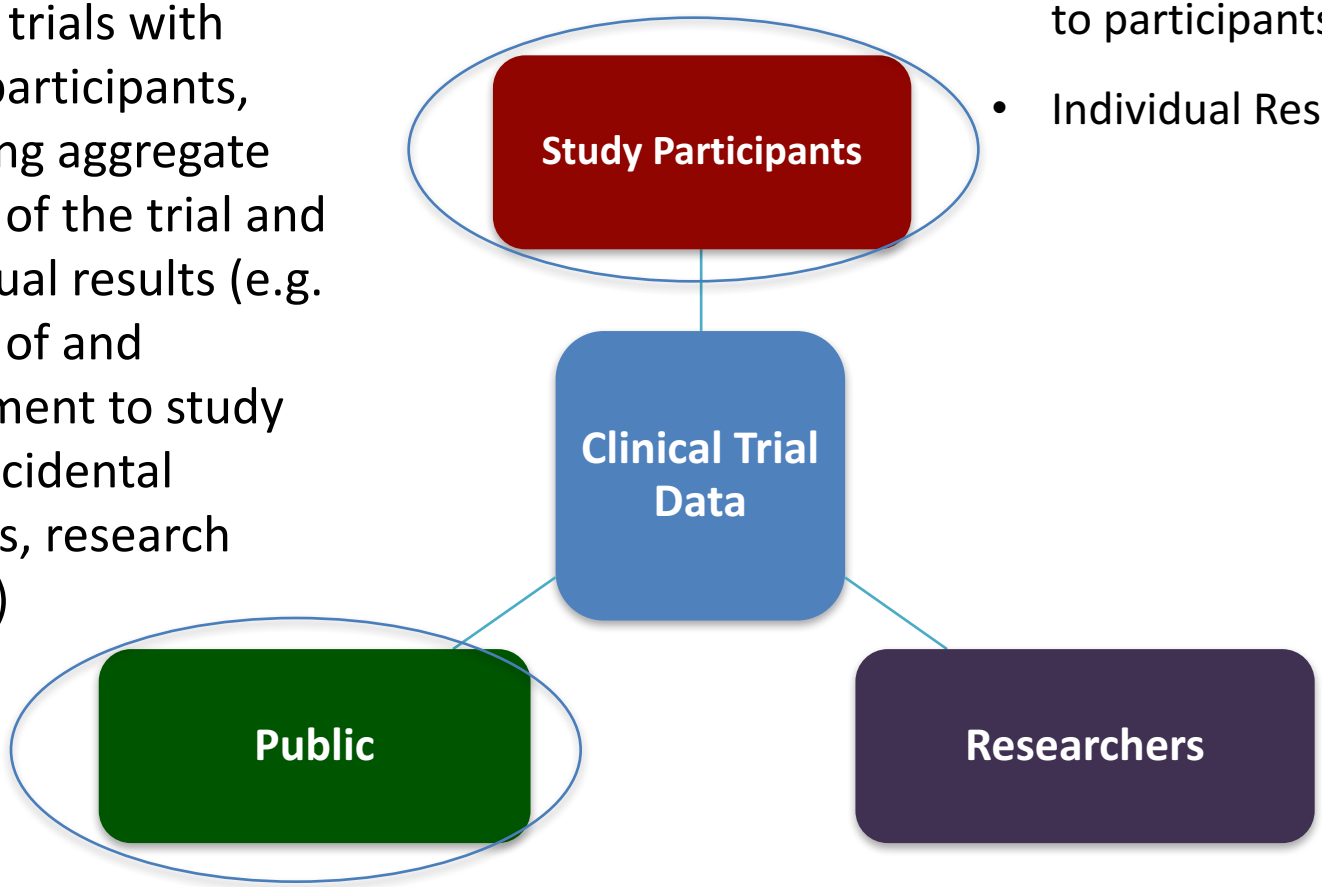
The various audiences of clinical trials data sharing

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



The various audiences of clinical trials data sharing

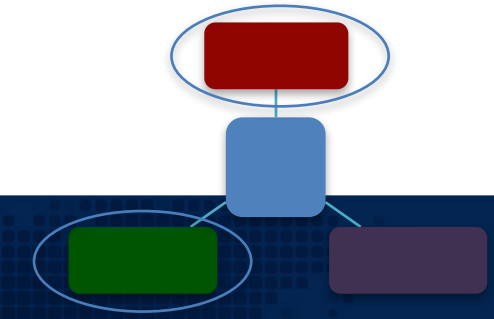
The sharing of research results from clinical trials with study participants, including aggregate results of the trial and individual results (e.g. results of and assignment to study arm, incidental findings, research results)



Return of

- Aggregate Research Results to participants
- Individual Results

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



Return of Individual Research Results

- Debra Mathews, Johns Hopkins University
- David Pulford, GlaxoSmithKline
- Sandra Prucka, Eli Lilly and Company
- Barbara Bierer, MRCT Center
- Rebecca Li, MRCT Center
- Carmen Aldinger, MRCT Center

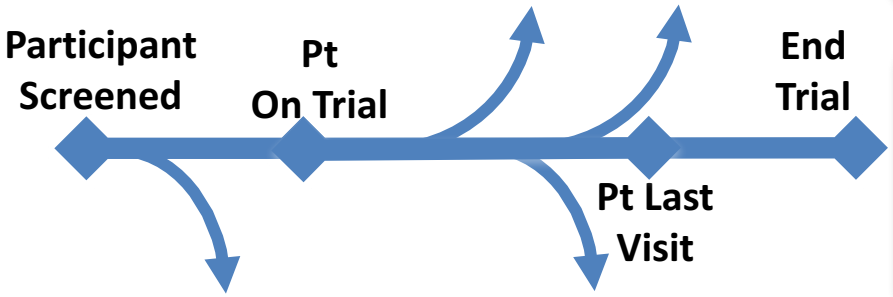
Project statement: returning individual research results

- **Problem:** Many patients desire to receive individual research data from clinical studies in which they have participated. Standards to facilitate the return of individual research results are lacking, making it difficult to determine whether, what, when, how, by whom and to whom results are to be returned.
- **Summary**: This project focused on return of *individual* research results to study participants.

Project statement: returning individual research results

- **Approach:** An international multi-disciplinary workgroup was launched, coordinated and organized by the MRCT Center, to provide a framework and recommendations as to the types of individual research results, benefits and risks, and related operational issues of returning individual level data.

Data Types



A: Routine Results & Non-Urgent Incidental Findings

B: Urgent Results & Urgent Incidental Findings

C: Individual Study Results
- Study Arm
- 1° (and 2°) Endpoints
- Safety endpoints

D: Exploratory Results
- Includes exploratory endpoints
- During or after close of study
- May lead to future research

E: Aggregate Results
- 1° and 2° Endpoints
- Summary of Conclusions

In final document A and B will be reversed

MRCT Center organized efforts to return results to study participants

Return of aggregate Results Guidance Document and Toolkit

2014: Workgroup meetings

March 2015: Complete Version 1

July 2016: Version 2.1

Multi-disciplinary Stakeholder Workgroup Launched December 2015

45 international members

21 biweekly meetings and 2 In-person meetings

Presentation of IRR Recommendations Document and Toolkit: MRCT Annual Meeting 2016

>90 attendees

Academia, Industry, IRBs, Non-profits, Government, Patient Advocates and others

IRR Working Group Members

Leadership:
Debra Mathews, Johns Hopkins Berman Institute
Sandra Prucka, Eli Lilly and Company
David Pulford, GlaxoSmithKline
Carmen Aldinger, MRCT Center
Barbara Bierer, MRCT Center
Rebecca Li, MRCT Center

Team members:*
Academic/Medical Center:
Mark Barnes, MRCT Center
Juan Carmona, formerly MRCT Center
Arianna Franca, Johns Hopkins University
Michael Johnson, MRCT Center
Youngshin Kim, Beijing United Family Hospital
Gloria Mason, Harvard Medical School
P. Pearl O'Rourke, Partners HealthCare
Usharani Pingali, Nizam's Institute of Medical Sciences
Wasana Prasitsuebsai, GlaxoSmithKline
Lynn Sleeper, Harvard Medical School
Clinical Research Organization:
Jules Mitchel, Target Health Inc.
Dana Leff Niedzielska, August Research
Government/Regulatory:
Ricardo Eccard da Silva, Braz. Health Surv. Ag. - Anvisa
Carol Weil - NIH
Industry:
Mary Ellen Allen, Genentech, Inc.
Karina Bienfait, Merck
Karla Childers, Johnson & Johnson
Poorvi Chablani, Biogen Idec
Kelly Coulbourne, AstraZeneca
Patrick Cullinan, Takeda Pharmaceuticals
Lea Harty, Pfizer
Nicole Hinton, Biogen
Tab (Tabassum) Hoda, Amgen
Jaime Houde, EMD Serono
Barbara Kress, Merck
Sarah Larson, Biogen
David Leventhal, Pfizer
Megan McBride, Janssen/Johnson & Johnson
Lana Skirboll, Sanofi
Jessica Scott, GlaxoSmithKline
Jina Shah, Genentech/Roche
Max Springer, Eli Lilly & Company
Cris Woolston, Sanofi
Institutional Review Boards:
Linda Coleman, Quorum Review IRB
David Forster, WIRB Copernicus Group
Stephen Rosenfeld, Quorum Review IRB
Non-Profit:
Zachary Hallinan, CISCRP
Patient Advocates:
Deborah Collyar, Patient Advocates In Research
Elizabeth Frank, Dana Farber/Harvard Cancer Center
Cheryl Jernigan, Susan G. Komen
Jane Perlmutter, Gemini Group

*attending two or more meetings of IRR Working Group

Objectives

1. Determine types of individual research results (IRR) to be offered to participants
2. Develop principles for return of individual results that may be implemented and adopted by all sponsors, researchers and investigators involved in the clinical trial enterprise
3. Define methods to plan for return of individual results to participants
4. Develop relevant framework to manage IRR within the global context of clinical research trials

Two Major Deliverables

- **IRR Recommendations Document**
  - Terminology
  - Ethical Foundations
  - Principles and Recommendations
  - Considerations:
    - What should be returned?
    - When should results be returned?
    - Who should receive results? Who returns results?
    - How to return results to participants?
- **IRR Toolkit**
  - Clinical Trial Timeline
  - Tools for study planning and consent
  - Tools to assist the Institutional Review Board review
  - Tools for site staff who return results
  - Case studies

Methodology for Version 1.0 Draft

1. Solicit real-life case studies from working group
2. Evaluate submitted case studies to identify and categorize both ethical and practical issues
3. Based on categories create a master list of relevant specific issues to be addressed
4. Decide on guiding principles
5. Develop an IRR Recommendations Document and Toolkit ⇦ ⇦
6. Integrate commentary from MRCT Annual Meeting
7. Add two principles (IRB and Informed Consent)
8. Return to case studies to validate principles against the IRR Recommendations Document and Toolkit

Selected Case Studies

Content	Issue
HER-2 negative metastatic breast cancer	Some samples were incorrectly categorized as HER-2 negative; ICF did not allow for return
PfizerLink & Blue Button®	Online patient community / Returning clinical data to study participants post-trial
Returning genetic research data generated during international clinical trials	Practical and ethical challenges communicating individual genetic research data in prospective and retrospective studies
Discovering HIV status in healthy clinical trial participants in Hyderabad, India	"Healthy volunteer" who had participated in multiple studies, was identified as having HIV infection
Discovering sexually transmitted infections in a cohort study in Bangkok, Thailand	Tests revealed STIs in non-symptomatic participants; lack of PCP complicated clinical management

Methodology for Version 2.0

- Special considerations for genomic data
  - Constitute Genomics working group
  - Provide specific genomics recommendations
- Complete survey to understand communication architecture between sponsors, PIs, Providers, and Participants
  - Identify and disseminate best practices
  - Provide tools for communication
- Disseminate and create implementation plan for PIs and sponsors
- Create educational and training materials

Ethical Foundations

- Beneficence
- Non-maleficence
- Autonomy / Respect for persons
- Favorable Risk/Benefit Ratio
- Transparency

IRR Principles

1. The participants or their designees should be the **recipients** of individual research results.
   - Communication pathway must be planned to share results with participants
   - Considerations for providing individual results to a designee (legally authorized representative)

2. Providing individual research results responds to the **expressed interests and expectations** of many clinical trial participants that their individual results to be communicated to them.
   - Respect for participants' autonomy
   - Balancing autonomy with other values

IRR Principles

3. Considerations pertaining to the return of individual results to clinical trial participants should be integrated into the clinical trial and **proactively planned**.
   - Considerations for whether results will be offered and if so, who will deliver which result, when and how
   - Informed consent process should be clear on parameters and limitations

4. Participants should be able to **choose whether or not to receive** their individual clinical research results, if results are offered.
   - For most results, participants should have the opportunity to decide
   - Exception applies to critical results of immediate clinical importance

IRR Principles

5. Sponsors and investigators have an obligation to return individual research results responsibly, taking into account **analytical validity, medical actionability** and **personal utility**.
   - Validity of the test; medical, social, and/or personal usefulness of the results to participants should be considered
   - Sharing too much data without interpretation can result in overload and distress

6. Individual research results should be returned in ways and at times that maintain the **integrity of the study**, insofar as the safety and welfare of the research participants are not at risk
   - Returning results should strive to maintain the integrity of the study and its ability to attain its research aims
   - Safety and welfare of research participants take priority over the value of research

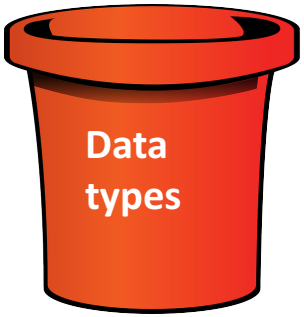
IRR Principles

7. The purpose of research is not clinical care, and return of individual research results **cannot substitute for appropriate clinical care** and advice.
   - Ethical framework pertaining to research-care distinction
   - Considerations when treating physician is also investigator, when the investigator is not a physician, and when participant does not have a primary care provider

8. Return of individual research results should be planned and executed in **compliance with institutional policies and** local, regional, and national **laws and regulations**.
   - Be aware of inconsistencies in national and local legislation
   - Each country may have unique considerations

Considerations for returning individual results

What?

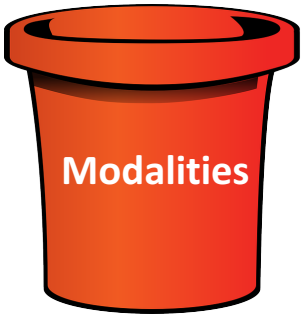


- What types of data should be returned?
- What differing international clinical guidelines need to be considered?

When?

- When should results be returned?
- Can results be returned without jeopardizing scientific aims?

How?



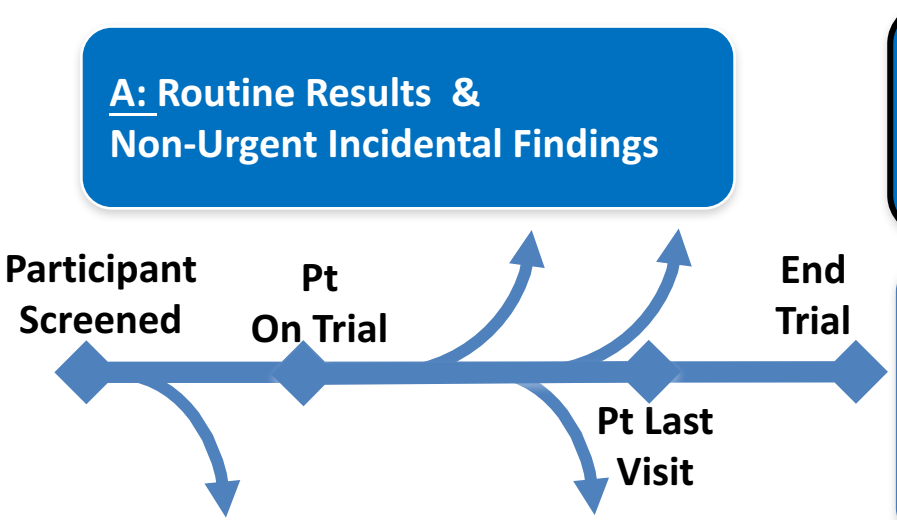
- Which delivery mechanisms should be used?
- What role does technology play in returning results?
- How feasible and affordable are the options?

Who?

- Who should communicate the results?
- Who should receive the results?

Overall Recommendations

- What to return?



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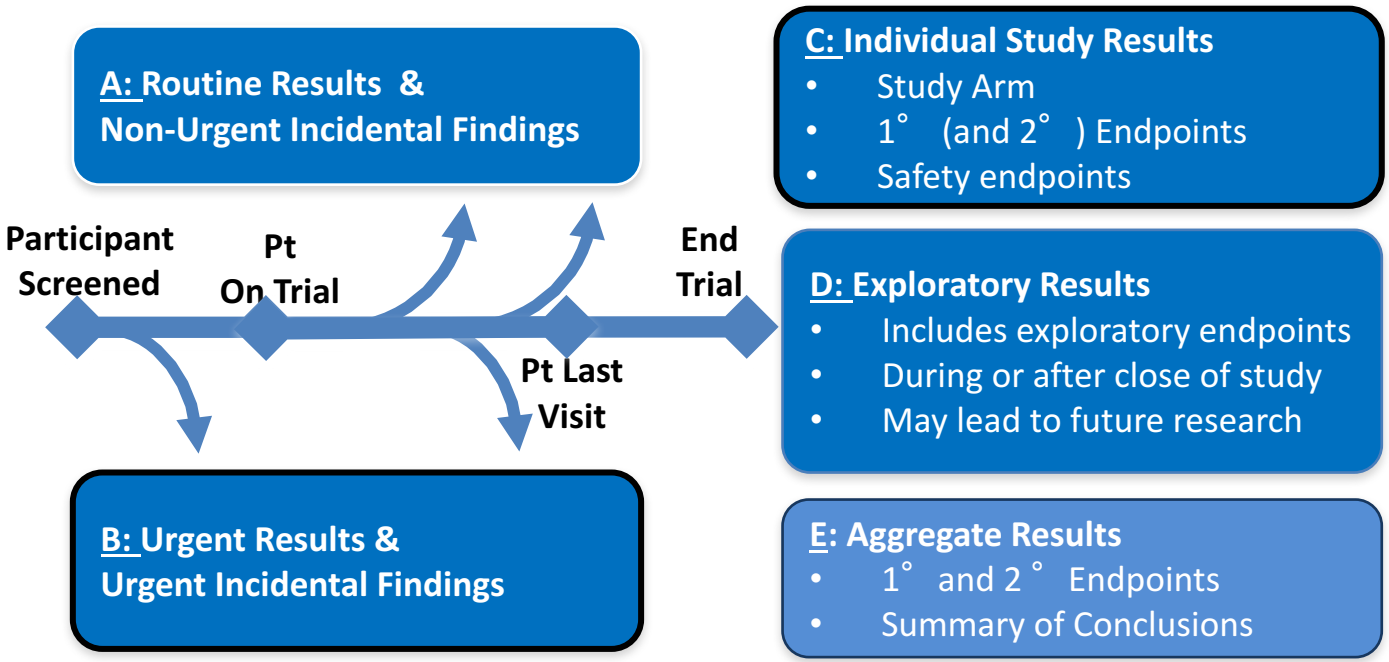
D: Exploratory Results
- Includes exploratory endpoints
- During or after close of study
- May lead to future research

E: Aggregate Results
- 1° and 2° Endpoints
- Summary of Conclusions

Overall Recommendations

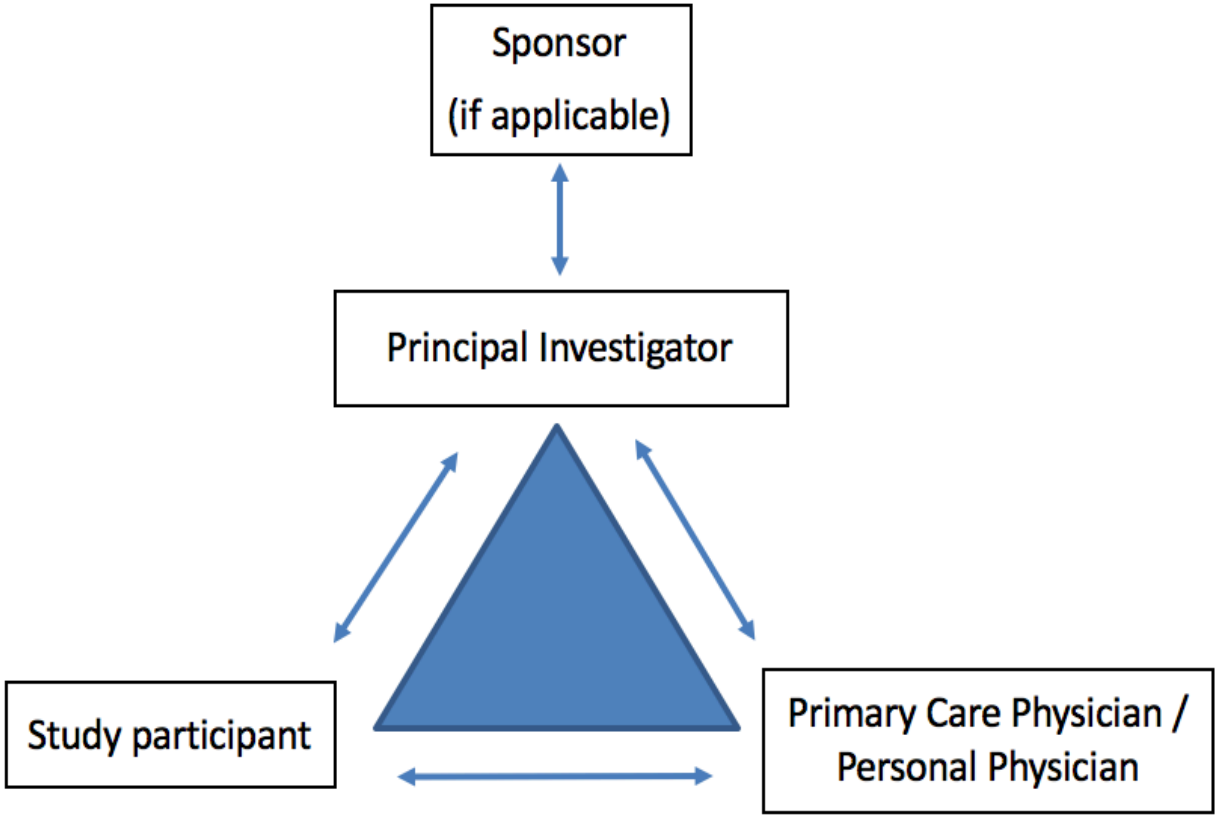
When?

Target for study arm and primary endpoints: 1 year after the study ends, consistent with return of aggregate results, provided return does not compromise the scientific integrity of the research. To enable this to occur, prospective planning is key (Principle 3).



Overall Recommendations

Who?



Overall Recommendations

How: Modalities for returning individual results

1. In-person meeting with physician or clinical research staff member or specialist
2. Telephone/video conference consultation with physician, clinical research staff member or specialist
3. Online patient community or portal
4. Confidential letter

All results return must incorporate health literacy principles.

Overview of Toolkit

	Planning and Design Phase	Protocol and IC Development Phase	Active Trial Phase	Post-Trial Publication Phase
IRR Tools and References	Tool 1: Rationale matrix for returning various types of data Tool 2: Points to Consider along the Clinical Trial Timeline Tool 3: Selected IRR Regulations and Resources	Tool 4: Informed Consent Language for Return of Individual Results Tool 5: Checklist for IRB and Ethics Committees	Tool 6: Designation of Third Party Recipient of Results Tool 7: End of Study Form	Tool 8: Communication of study results at the end of a trial (including study arm)

Next Steps

- Please forward comments, suggestions, tools, best practices
- Apply documents to new or hypothetical case studies
- Finalize Version 1.1 Recommendations Document and Toolkit
- Communicate and Disseminate; Feedback appreciated

- Develop implementation plans as without operational direction principles will remain aspiration and hypothetical
- We hope to drive a change in practice and culture

Respondents and Panel Discussion

Return of Individual Results: Response

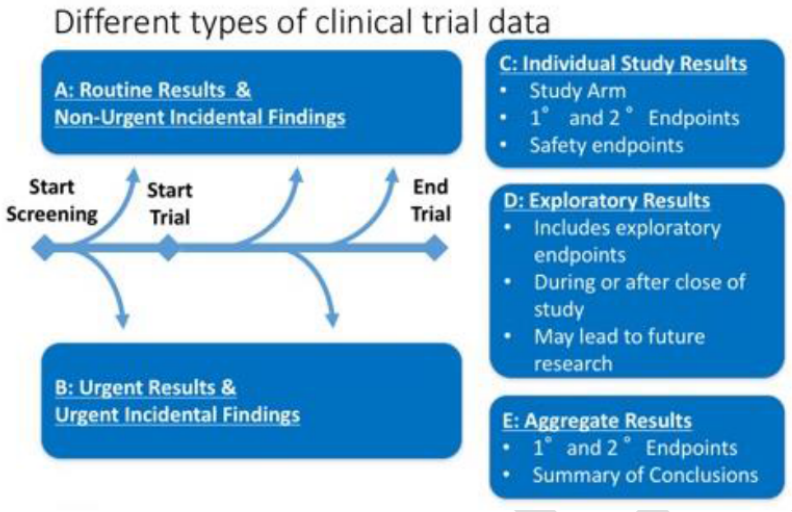
Holly Taylor, PhD, MPH

Johns Hopkins Bloomberg School of Public Health

Johns Hopkins Berman Institute of Bioethics

Overall Strengths

- *Living* document
  - Science moving target
- Comprehensive
  - Scope, complexity
- Repetition
  - Some discrepancies
- Case-based
  - Practical



Enhancing Ethics

- Justification for Approach
- Educational for End Users

Enhancing Ethics

- Autonomy
  - Right to receive or not receive information
    - Mediated by clinical action-ability and **personal utility**
    - Consent is a practical application
- Beneficence
  - Potential benefits of disclosure
  - Favorable Risk/Benefit Ratio (practical application)
- Non-Maleficence
  - Potential harms of disclosure

Enhancing Ethics

- Transparency

- *Accountability* (Principle 3)
  - Disclosure of options
  - Managing/tracking preferences

Enhancing Ethics

- *Integrity*
  - Physician commitment to well-being of patient, researcher commitment to welfare of subjects and future patients (mentioned under Autonomy, Principle 7, p. 25)
  - Of research enterprise (Principle 6)

Enhancing Ethics

- *Justice*
  - Equity introduced in Principle 2
- *Social Justice*
  - Avoid further disadvantaging populations already disadvantaged
    - What if clinically actionable but patient has no health insurance and no primary provider? (p. 25)
      - Baseline obligation is referral (Principle 2, 14)

Enhancing Ethics

- *Reciprocity* (p. 32)

Final Thoughts

- Scope
  - Trials only (p.12)
    - Applicable to observational studies as well
  - "Particularly participants" (p. 12)
  - International collaborations
    - Current draft draws from US-based ethics and policy and assumes functioning health system

Final Thoughts

- *Personal Utility* needs to be better defined
  - Reproductive decision making (pp. 8, 16, 22)
- Ethical justification could be used to be more directive in recommendations
  - Thresholds (p. 18)
  - When physicians are compelled to disclose (p. 20)
  - Whether genetic counseling required (p. 23)

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MRCT Center 2016 Annual Meeting

December 7, 2016