



MULTI-REGIONAL CLINICAL TRIALS

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

Rebecca Li, PhD, Executive Director

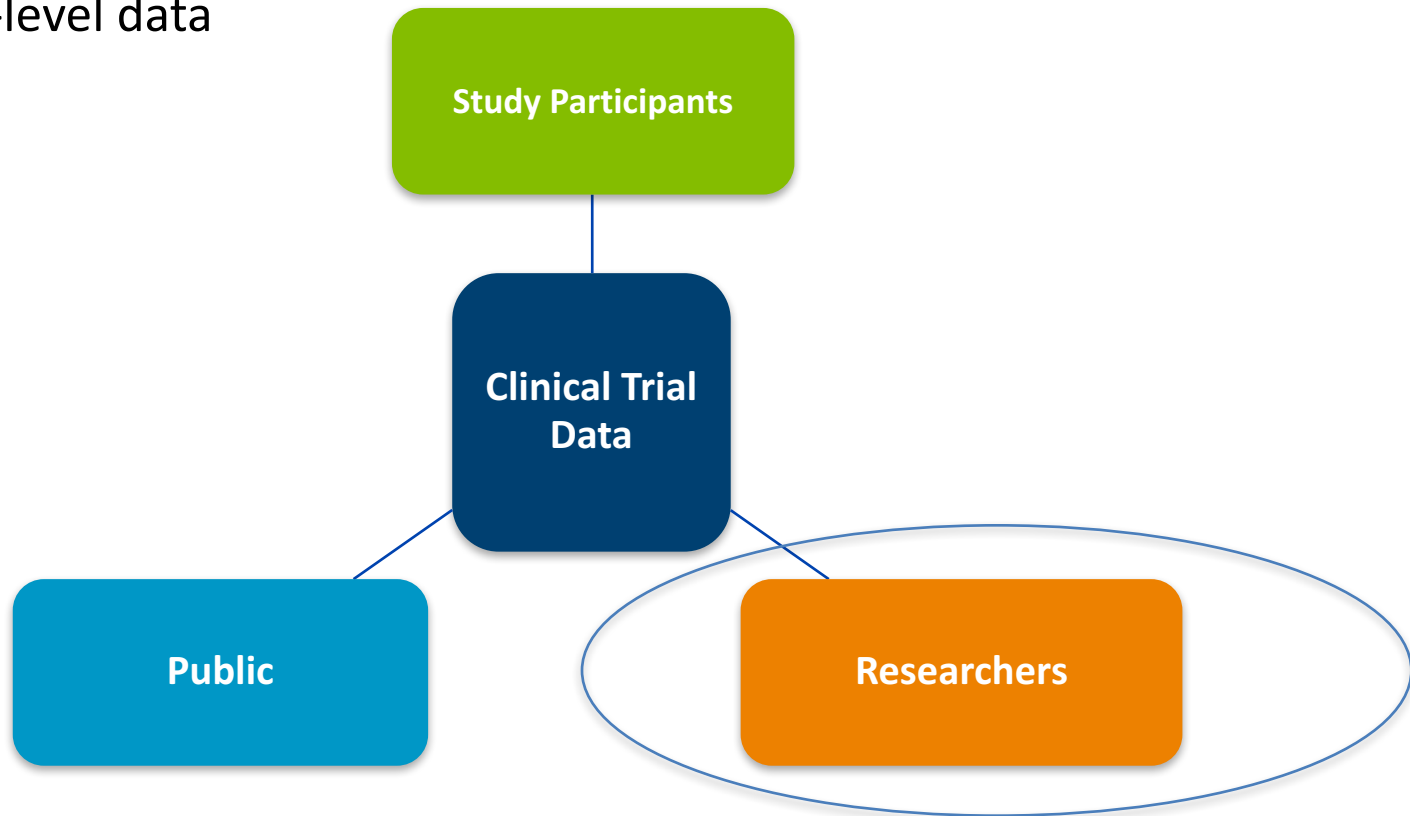
MRCT Center Mission

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



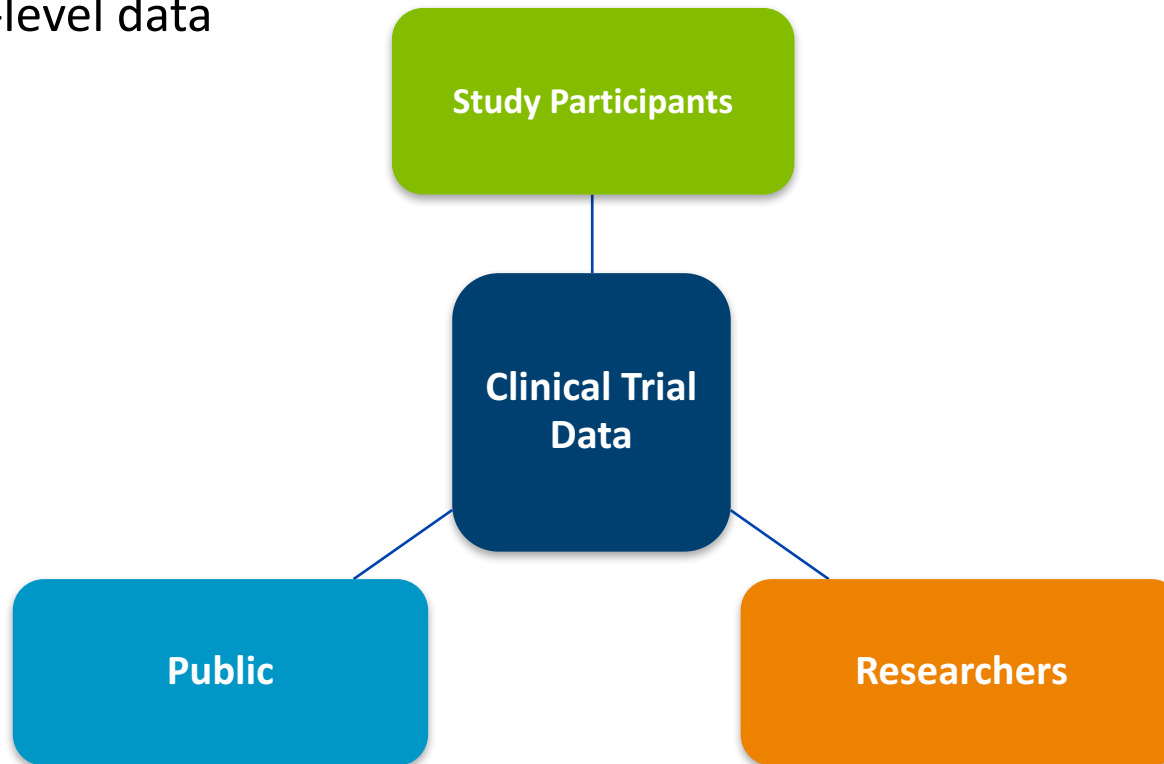
Clinical Trials Data Sharing: Audiences

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



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European Regulation

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: 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.

EU Requires posting laypersons summary to EU
Portal – by 2017/2018



Returning Results - 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**.

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



The MRCT Center Tools & Deliverables

An **ROR Guidance Document** for groups wishing to return results including:

- Logistics and detailed processes for results sharing
- Content of research result summaries
- Cultural and health literacy considerations
- Timing

An **ROR Toolkit** including:

- Templates for Phase 1, 2 & 3, studies ending early
- Neutral language guide
- Endpoints language guide

Go to: mrctcenter.org -- Resources – Return of aggregate results

<http://mrctcenter.org/news/updated-versions-of-return-of-results-guidance-document-and-toolkit-released/>

Aligned with HRA guidelines which refers to these documents

Participant Clinical Trial Results Summaries - Process

- Write in unbiased and not promotional language
- Obtain review by independent and objective editor(s) and patient representative(s) when possible
- Translate into additional languages consistent with translations of informed consent
- Make available an individual from the study site or neutral informed third party to answer questions for participants
- Make provisions for vulnerable populations and other instances
- Consider as to whether to inform, and whom to inform, in the event of a participant's death
- Use plain language (sixth-eight grade reading level)
- Apply health and numeracy principles



Return of results templates

Template for Communication of Study Results

SPONSORS: This template helps create clear summaries of clinical trials. Replace the *[guidelines in red brackets]* with your text; delete this heading.

[If written to study participants, include the following:]

Thank you for participating in this study.

You and other volunteers helped researchers answer important health questions.

Here we describe the results of this study.

[If written for the general public, start here:]

This summary was completed on *[month/year]*. Newer information since this summary was written may now exist. This summary includes only results from one single study. Other studies may find different results.

Phase 1 Study

This study searched for a safe dose of *[interventions/treatments]* for people with *[disease/condition]*.

[Place a simple title for the study in the box above. Sponsors may consider using the same simple title as in the registry. If drug names are used, list both generics and also where brand names® can be found.]

Phase 2 and 3 Studies

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.]

Why the study was done

Phase 1 Study

This was the first time this *[treatment/drug/device/intervention]* was studied in humans. This study was done to find the highest *[dose/amount]* of the drug/treatment that people could take without having severe side effects. Side effects include unexpected medical

- Located in MRCT Return of Results Toolkit
- Templates for Phase 1, Phases 2 and 3, and Trials ending early
- Includes examples
- Incorporates principles of Health Literacy and Numeracy

Participant Clinical Trial Results Summaries - Example

Content	Example
Why the study was done (cont.)	<p>For clinical trials that stop early:</p> <p>This study was stopped earlier than planned. This can happen for many reasons.</p> <p>This study stopped early because <i>[add one of the possible statements below, or your own simple explanation, to this sentence. If there is more than one reason, list all that apply.]</i></p> <p>... too many participants had side effects (see below).</p> <p>... <i>[drug generic name]</i> did not improve patient results.</p> <p>... <i>[drug generic name]</i> was not as effective as expected <i>[comparator]</i>.</p> <p>... <i>[drug generic name]</i> was much more effective than expected. <i>[if applicable, add]</i> The study was stopped so all participants had a chance to take <i>[drug generic name]</i>.</p> <p>... not enough people joined the study.</p> <p><i>[Include a statement about what will happen next. ...</i></p> <ul style="list-style-type: none">• <i>For side effects ..</i>• <i>For efficacy ...</i>• <i>For futility ...</i>• <i>Low accrual:]</i>

Neutral Language Guide

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>.
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> is better tolerated than <Drug B>.	In this study, fewer patients who took <Drug A> had <list specific adverse events> than patients who took <Drug B>.

Similar principles have been suggested by TransCelerate BioPharma:

[Recommendations for Drafting Non-Promotional Lay Summaries of Clinical Trial Results](#)



Endpoint Descriptions and Examples

Endpoint	Description of the type of endpoint	Example in simple, plain language
Composite	<p>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.</p>	<p>“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.</p> <p>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.</p> <p>The study found that there was no change in the number of events for [patients/people] in Group A or Group B.”</p>

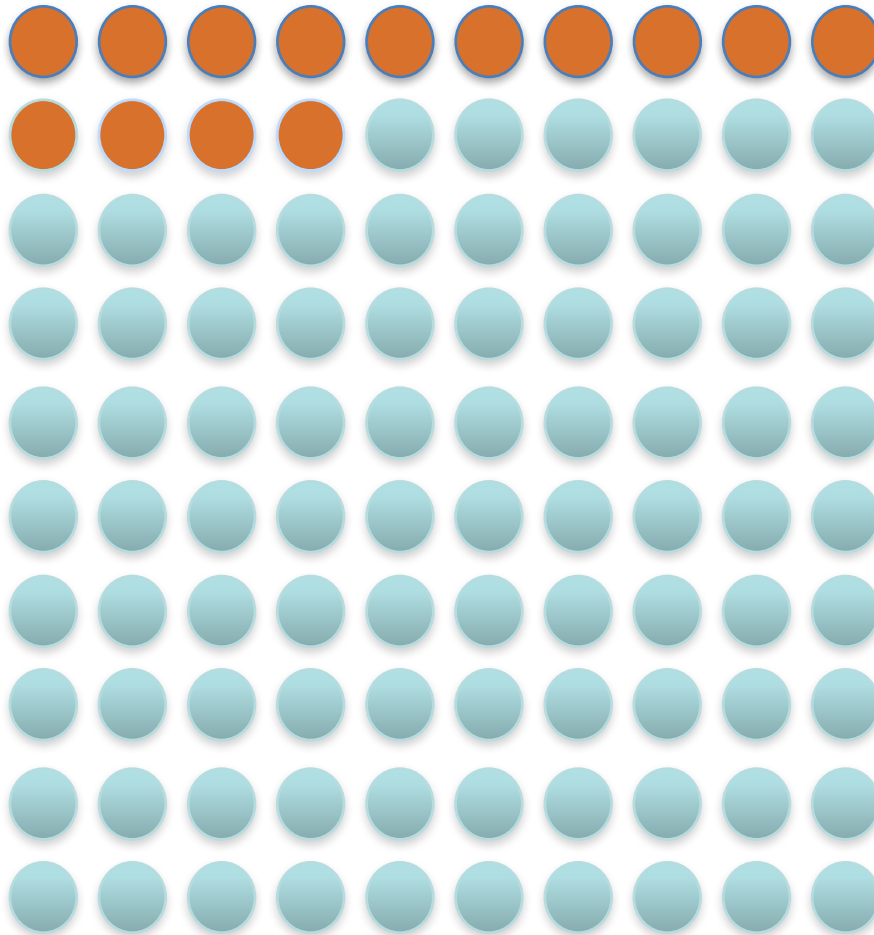
Numeracy: Overview

- The ability to use basic probability and mathematical concepts to explain mathematical and statistical terms.
- Numeracy principles in health literacy focus on simple explanations, instead of using complex fractions, percentages or statistical terms.

Numeracy Principles: Implementation

- Less is more – how critical are the numbers?
- Provide fewer choices – choose strategically which options to show
- Do the math – calculate or convert numbers, readers are unlikely to conduct even basic math
- Give numbers meaning and context – explain what numbers mean
- Use common terms and imaginable formats
- Use visuals
- Use whole numbers
- Use consistent denominators and timeframe
- Natural frequencies vs percentages – “1 out of 10” may be more useful than percentages because it gives context and imagery

Example

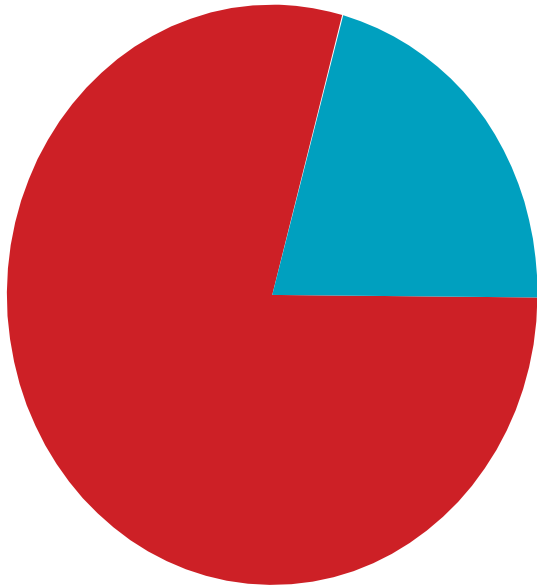


14%

Or

About 1 in 7

Example



In **20% (or 1 in 5)** of patients,
tumors got at least 30% smaller

In **80% (or 4 in 5)** of patients,
tumors did not get at least 30% smaller

Return of results: MRCT Center workgroup

Academic/Medical Center:

Carmen Aldinger – MRCT Center

Mark Barnes - Ropes & Gray, LLP / MRCT Center

Barbara Bierter - Brigham & Women's Hospital/MRCT

Assunta De Rienzo - Brigham & Women's Hospital

Alla Digilova – MRCT Center

Rebecca H Li – MRCT Center

Holly Fernandez Lynch - Harvard Law School

Pearl O'Rourke - Partners HealthCare

Nesri Padayatchi - Univ. of KwaZulu-Natal

Amish Shah - MRCT / Harvard Law School

Zachary Shapiro – MRCT/ Harvard Law School

Patrick Taylor - Children's Hospital, Boston

Sarah White - Partners HealthCare

Elizabeth Witte – Harvard Medical School

Sabune Winkler – Harvard Medical School

Industry/Trade Associations:

Salvatore Alesci – PhRMA

Richard Bergstroem – EFPIA

Elizabeth Garofalo - Novartis Pharma AG

Laura Hagan - Merck Serano

Sandra Hayes-Licitra – Johnson & Johnson

Angelika Joos – Merck Sharp & Dohme

Barbara Kress – Merck

Sarah Larson – Biogen Idec

David Leventhal – Pfizer

Craig Lipset – Pfizer

Laurie Myers – Merck (CO-CHAIR)

Alex Nasr – AbbVie

Mary Ann Plummer – J&J (prior CO-CHAIR)

Sandy Prucka – Lilly

Ben Rotz – Lilly

Beth Roxland – Johnson & Johnson

Jessica Scott – GSK

Institutional Review Boards:

David Forster - WIRB Copernicus Group

Mary Oster – NE IRB

Jim Saunders - NE IRB

Nonprofit:

Behtash Bahador – CISCRP

Phyllis Frosst - Personalized Medicine Coalition

Zach Hallinan – CISCRP

Marc Wilenzick – International AIDS Vaccine Initiative

Patient Advocates:

Nicola Bedlington – European Patients Forum

Deborah Collyar – PAIR (COCHAIR)

David Haerry – European AIDS Treatment Group

Cheryl Jernigan - Susan G. Komen

Yann LeCam – EURODIS

Marcello Losso - HIV RAMOS

Jane Perlmutter – Gemini Group

Research/Consulting Firms:

Barbara Godlew - The FAIRE Company, LLC

Pierre Gervais - QT Research

Paulo Lacativa - CCBR Clinical Research

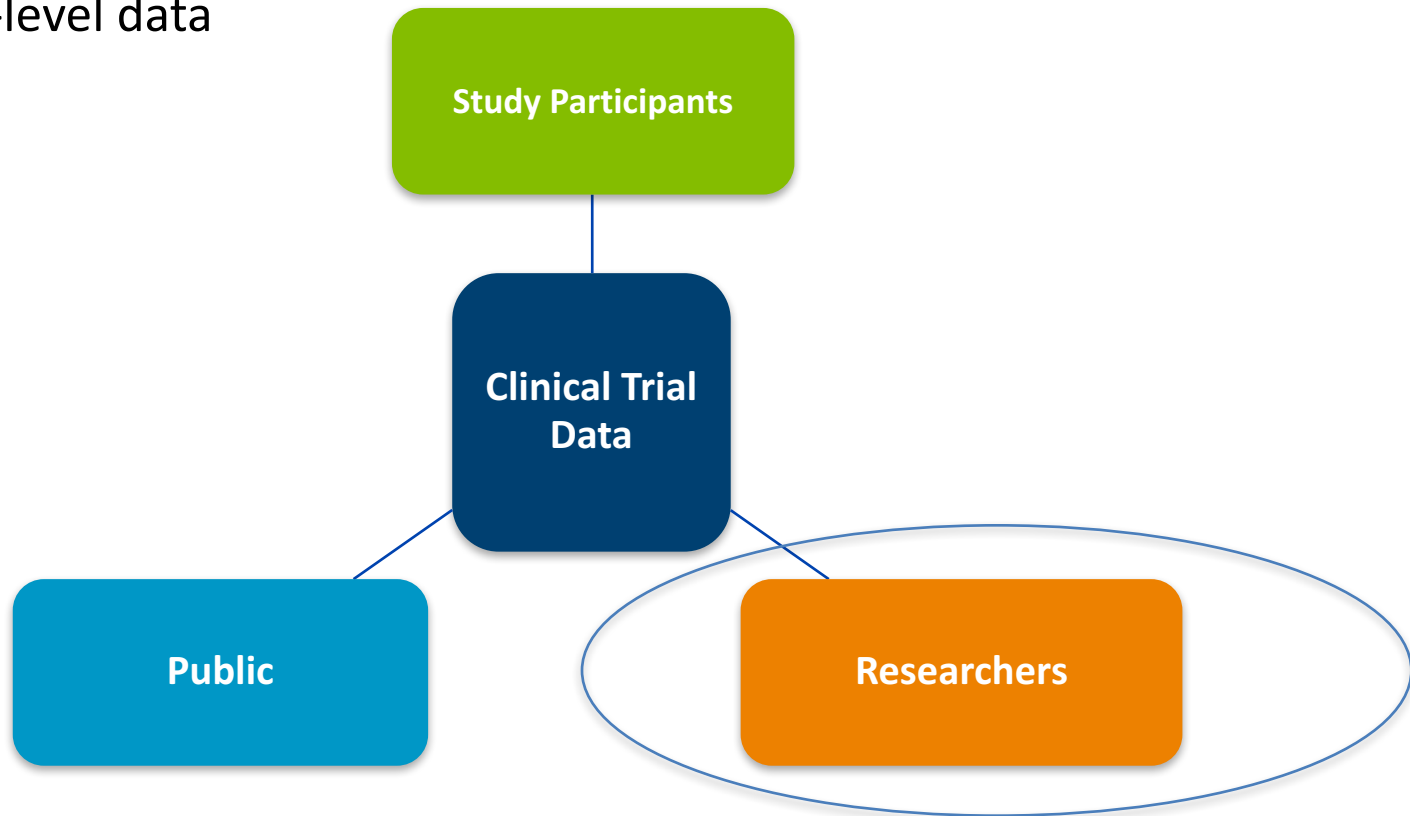
David Walling – Collaborative NeuroScience



Questions on Plain Language Summaries?

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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

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

Major Clinical Trial Data Sharing: Platforms

- **CSDR PLATFORM** - leading industry multi-sponsor request site
- **Clinicaltrials.gov** – searchable database including summary results
- **J&J - YODA** project - Yale partners with J&J /Medtronic
- **Duke** Clinical Research Institute – Bristol Myers Squibb Strategic Initiative (SOAR), which supports open access to clinical trials data
- **Project Datasphere** – cancer comparator data, and more
- **NIH** data repositories and (BIOLINCC and 60+ others)
- **FDA** Oncology's data aggregation effort - Information Exchange and Data Transformation (INFORMED).
- **OPENTRIALS** – indexes all freely available information, no IPD
- **EMA Database** – CSRs submitted to the agency as part of a MAA

Current Platform Differentiating Factors

FACTOR	VARIABLES	
Data types	Summary level data	IPD data*
Review process	No review	Discretionary Review
Data Standards	Specific format required	Multiple formats accepted
Contributor	Members only	Any researcher
Requestor	Researcher/Expert	Public/no qualifications
Hosts data	No	Yes
Downloadable data	No	Yes
Review of request	None	Discretionary
Analysis space	None provided	Space and licensed tools provided
Specificity of platform	Specific to sponsor type, geography or therapeutic area	Multi-stakeholder, global, all therapeutic areas
Connect/search other platforms	No	Yes

Current Platform Differentiating Factors

FACTOR	VARIABLES	Vivli
Data types	Summary level data	IPD data*
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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 are still 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.

Why Vivli is Needed

- Data hosting capacity
 - VIVLI is a general access data platform that flexibly designed to meet global capacity needs
- Analytic functionality / value
 - current federated architectures (e.g., SENTINEL, PCORnet) offer only limited analytic capabilities (e.g., counts)
 - To enable meta-analysis and other aggregated analyses, datasets need to be held in a single host environment
 - The greater the proportion of IPD datasets held by one host, the greater the ability to do aggregated analyses
 - No other platform aims for Vivli's scale and scope of IPD hosting

Center and Background

The Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard University (MRCT Center) has championed efforts to enhance sharing of, and access to, clinical trials data around the world.



Vivli is being formed to provide governance and management of a platform—agnostic to disease, country, sponsor and funder—to reduce barriers to clinical trials data sharing.

Various 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**

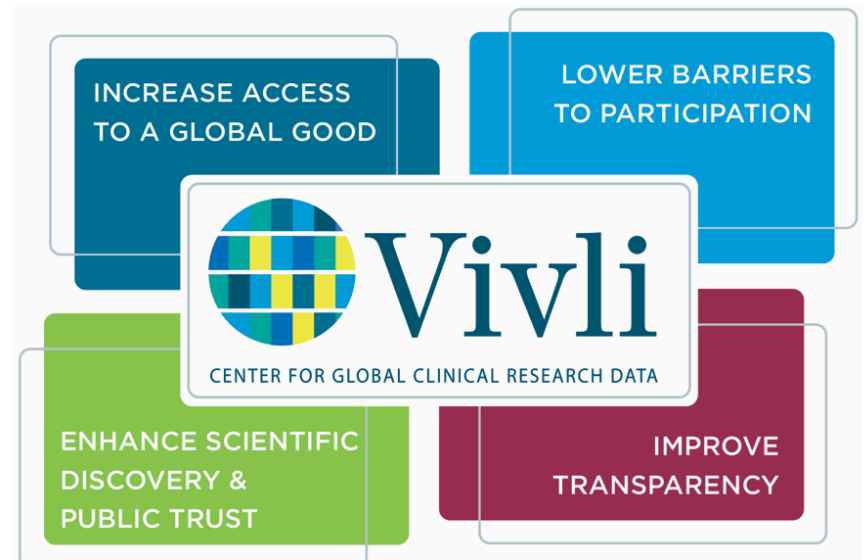
- No institutional solution; creating URLs or using other (e.g. NIH) resources
- Individuals: (1) If share, prefer to delegate management with open access or (2) closely held under strict controls for access

- **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”

Scope

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



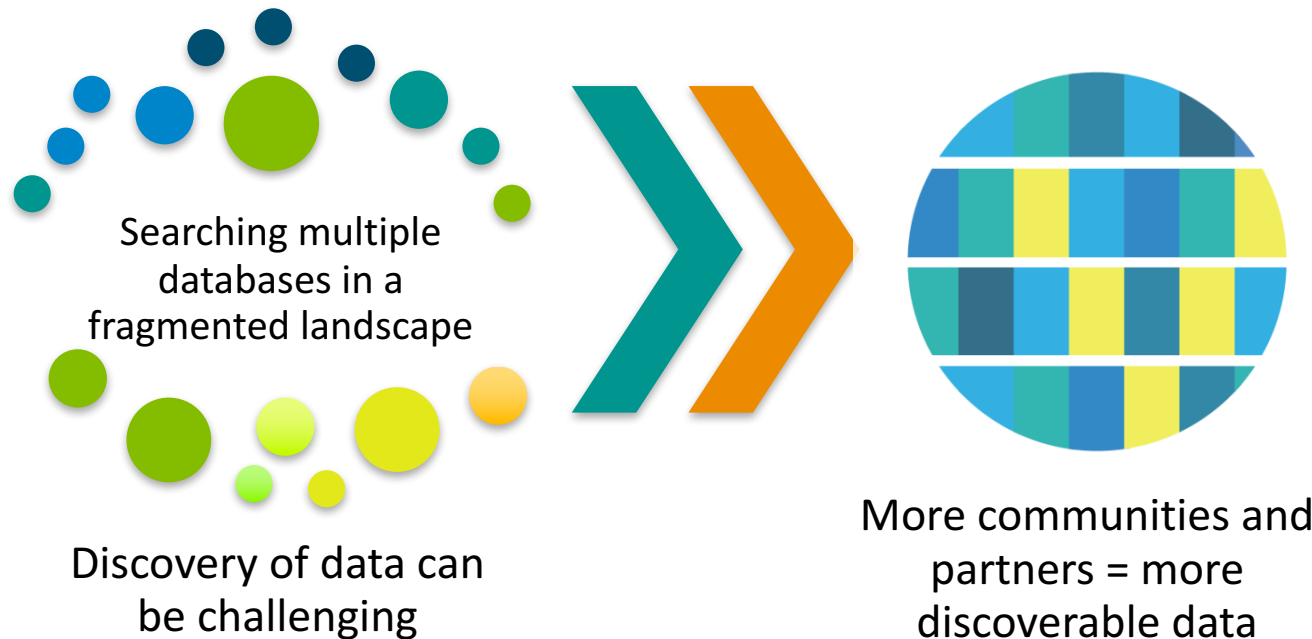
Mission

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

The Unique Remit of Vivli – Enhancing Discovery

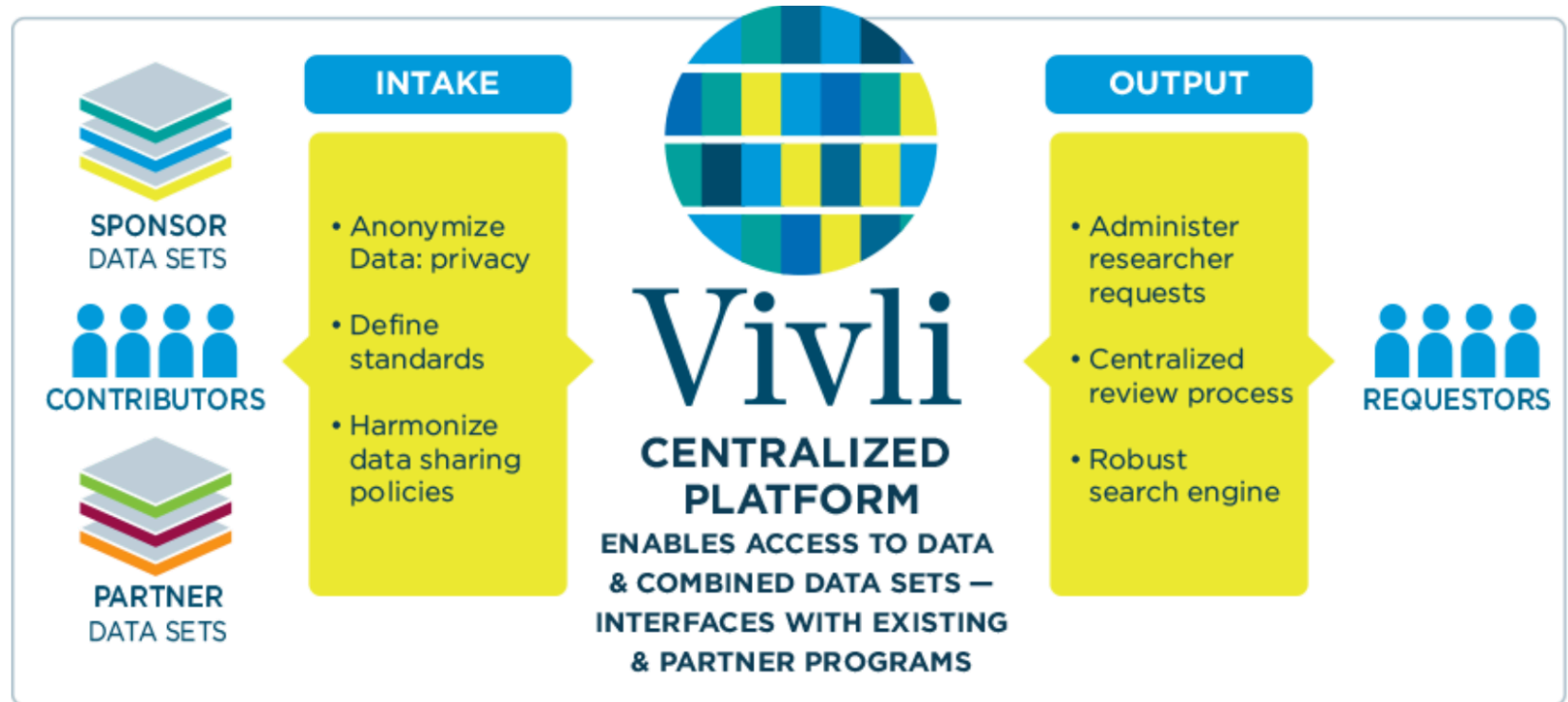
Advanced **metadata search** and **discovery** capability

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

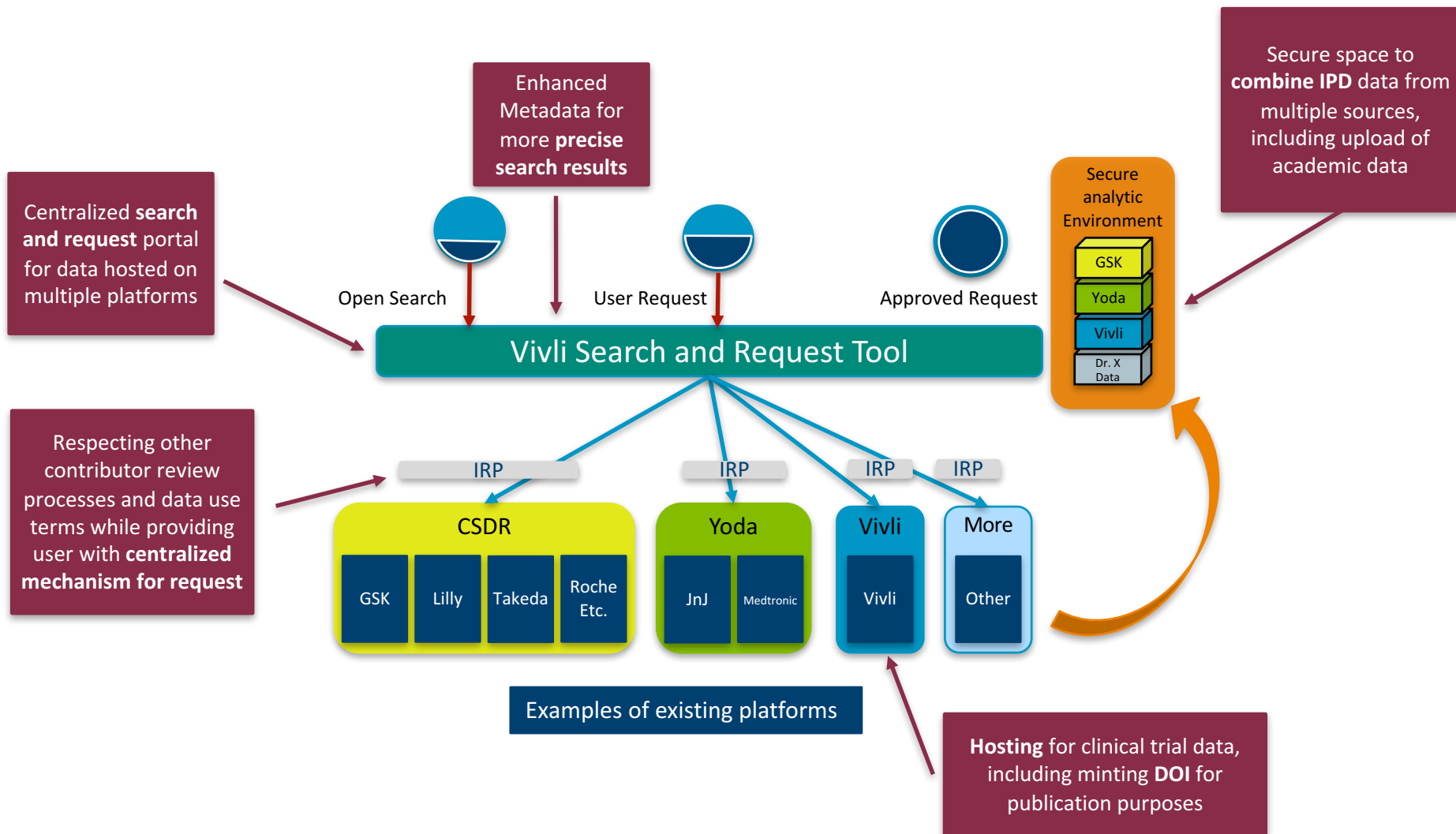
The Unique Remit of Vivli – Providing Visibility and Combining Data in a Centralized Platform



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

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

Vivli Solutions Offerings



Example of New Search Functionality

1. Question

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

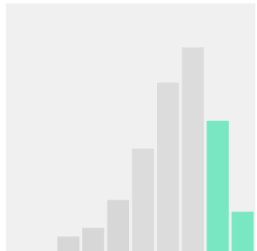
Population

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



Select



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

Challenges with Launching a New Platform

- Create incentive structures within Vivli for sharing with external mandates to require clinical trial data sharing
- Harmonizing requirements of diverse stakeholders
- Accelerating the Vivli timeline to launch
- Maintain low financial barriers to entry

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

THANK YOU