MULTI-REGIONAL CLINICAL TRIALS

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

Clinical Trial Data Sharing

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Health Law Year in P/Review

Petrie-Flom Center Harvard Law School

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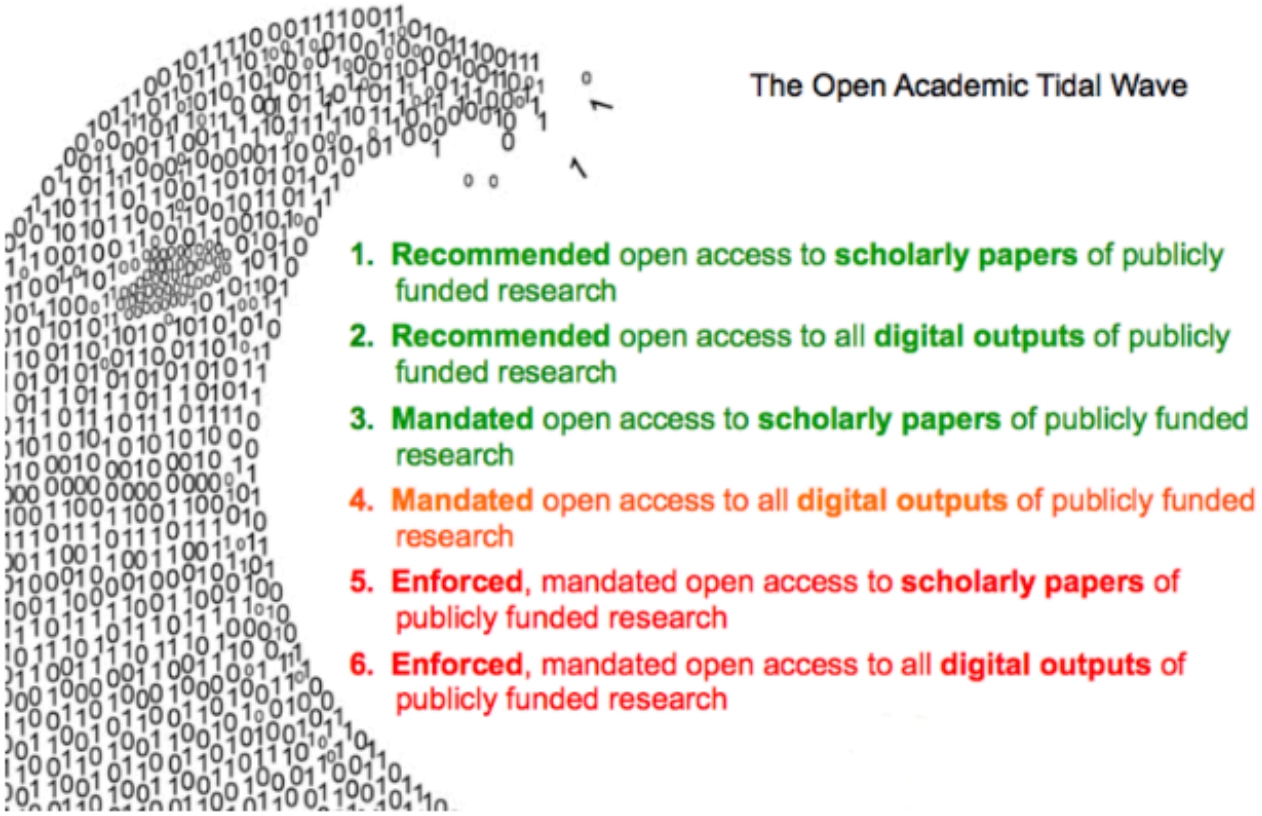
Changes in the Data Sharing Culture

- Transparency mandates for research data in publically funded programs
- Archiving mandates in 2015: 12 UK, 10 North America, 5 Europe
- Coinciding with:
  - The rise in 'big data'
  - Awareness of re-identification risks that come with big data and data combination



https://figshare.com/blog/2015_The_year_of_open_data_mandates/143

Goodbye Obama

"22 Federal departments and agencies accounting for more than 99% of U.S. Federal R&D expenditures now have public access plans in place."

NIH Plans: https://grants.nih.gov/grants/NIH-Public-Access-Plan.pdf

Scope of Personal Data

Any information:

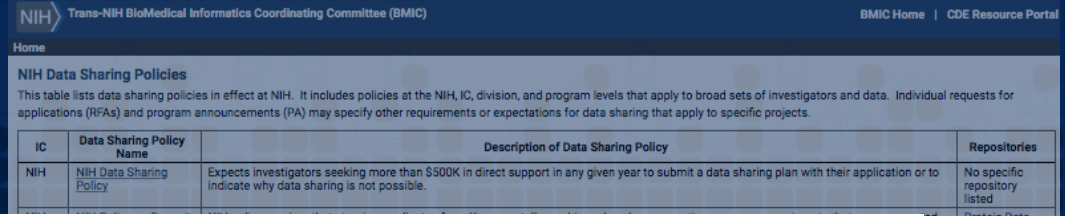
- Relating to a natural, living person
- Who can be identified, directly or indirectly, in particular by reference to an identifier such as:
  - a name
  - an identification number
  - location data
  - online identifier, or
  - one or more factors specific to the physical, physiological, genetic, mental, economic, cultural or social identity of that person.

US Government funders

Data Sharing Plan requirements:
Institutions, Foundations, NSF, DOD, DOE etc. as a condition of *review* of application

18 agency specific policies
>65 Repositories

Required data


Trans-NIH BioMedical Informatics Coordinating Committee (BMIC)

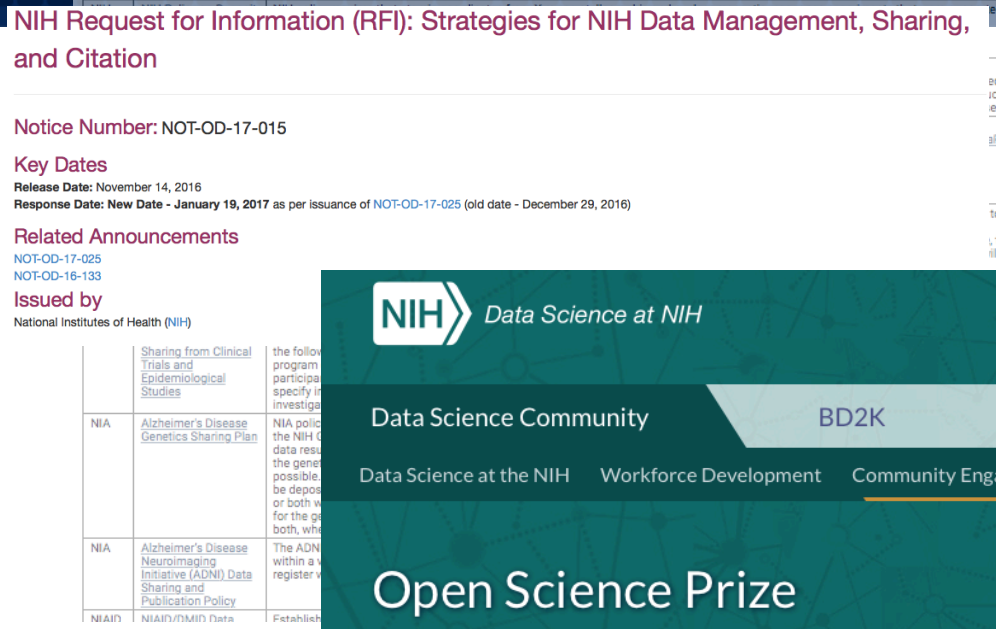
BMIC Home | CDE Resource Portal

Home

NIH Data Sharing Policies

This table lists data sharing policies in effect at NIH. It includes policies at the NIH, IC, division, and program levels that apply to broad sets of investigators and data. Individual requests for applications (RFAs) and program announcements (PA) may specify other requirements or expectations for data sharing that apply to specific projects.

IC	Data Sharing Policy Name	Description of Data Sharing Policy	Repositories
NIH	NIH Data Sharing Policy	Expects investigators seeking more than $500K in direct support in any given year to submit a data sharing plan with their application or to indicate why data sharing is not possible.	No specific repository listed


NIH Request for Information (RFI): Strategies for NIH Data Management, Sharing, and Citation

Notice Number: NOT-OD-17-015

Key Dates

Release Date: November 14, 2016

Response Date: New Date - January 19, 2017 as per issuance of NOT-OD-17-025 (old date - December 29, 2016)

Related Announcements

NOT-OD-17-025

NOT-OD-16-133

Issued by

National Institutes of Health (NIH)

	Sharing from Clinical Trials and Epidemiological Studies	
NIA	Alzheimer's Disease Genetics Sharing Plan	
NIA	Alzheimer's Disease Neuroimaging Initiative (ADNI) Data Sharing and Publication Policy	

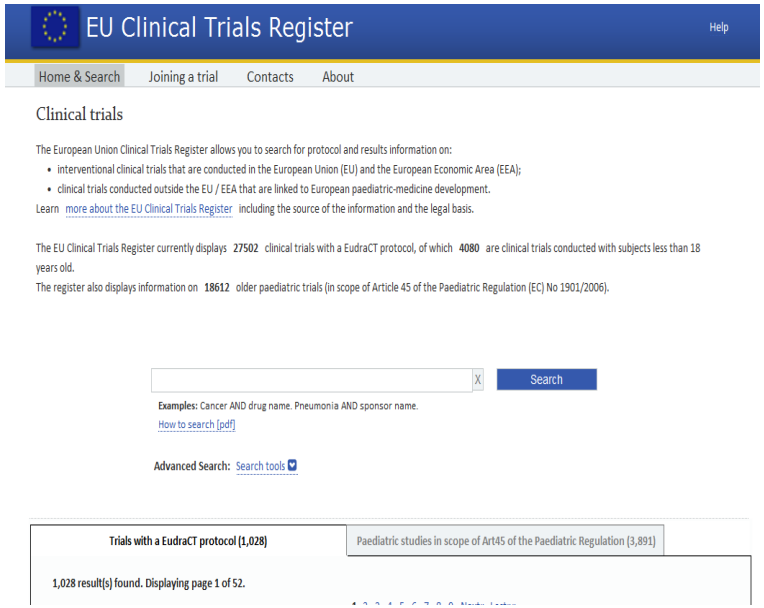
Data Science Home / Open Science Prize

The Cloud, dbGaP and the NIH

Vivien Bonazzi / 03.27.15

	ceive a cost estimate for deposition of materials at ZIRC. Plans to share materials generated by projects under the FOA through uding but not limited to mutant fish, embryos, and sperm, genetic screens, mutagenesis protocols, mutagenesis vector constructs, tic and phenotypic data for all mutant strains, should include evidence/documentation of coordination with staff at the Resource. A le time frame for periodic deposition of mutants, sperm, reagents, and data should be specified in the application and will be d during the review of the plan for sharing.	
	data for all NIDA-funded human genetics studies to be available for sharing, independent of direct costs, membership in the NIDA Consortium, or the type of genetics data generated.	NIDA Genetics Consortium, NIDA Center for

Clinical Trials Registries



Publishing Clinical Reports

EU Transparency legal requirements: Clinical Trials Regulation

- Article 81(4) of Regulation (EU) No. 536/2014
  - EU database *publically accessible by default*, irrespective of the Marketing Authorisation Procedure (national, central, mutual recognition, decentralised), with exceptions justified on any of the following grounds:
    - Protection of personal data;
    - Protection of commercially confidential information (in particular taking into account the manufacturing and technical specifics of the medicinal product, unless there is an overriding public interest in disclosure);
    - Protecting confidential communication between manufacturers and EMA in relation to the preparation of the assessment report;
    - Ensuring effective supervision of the conduct of a clinical trial.

EU Transparency legal requirements: Clinical Trials Regulation

Article 81(4) of Regulation (EU) No. 536/2014

Results of trials are proposed to be made public:

- 12 months after the end of the trial – summary results and layperson summary
- 30 days after the decision on marketing authorization or its withdrawal by the applicant – the clinical study report of trials authorized under this Regulation and included in a EU marketing authorization application (central or national)
- Timing of release of details of phase I trials may be deferred until 12 months after the trial (and published with the summary results)
- Protocols, subject information sheets, IMPDs and investigator brochures, may be deferred differentially dependent on the nature of the IMP and of the trial.

"*End of trial*" is defined in Article 2(26) 'End of a clinical trial' as the last visit of the last subject, or at a later point in time as defined in the protocol.

EU Policy 70: Clinical Report Publishing

- Commercially confidential information (CCI) EMA position: majority of clinical report content is not CCI
- Redaction principles set out in the policy
- Two sets of data prepared: (1) scientific review and (2) publication
- Justification table required: company justifies each redaction, EMA reviews redactions & decides if accepted or not

Anonymisation

Data utility: important for researchers, EMA encourages utmost data utility, balance to protect personal data, EMA guidance recommends methodology to avoid (re)identification of clinical trial participants, various techniques, evolving area.

Journals

Annals of Internal Medicine EDITORIAL

Sharing Clinical Trial Data: A Proposal From the International Committee of Medical Journal Editors

The International Committee of Medical Journal Editors (ICMJE) believes that there is an ethical obligation to responsibly share data generated by interventional clinical trials because participants have put themselves at risk. In a growing consensus, many funders around the world–foundations, government agencies, and industry–now mandate data sharing. Here we outline ICMJE's proposed requirements to help meet this obligation. We encourage feedback on the proposed requirements. Anyone can provide feedback at www.icmje.org by 18 April 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. Further details may be found in the *Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals* at www.icmje.org.

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-

added an element to its registration platform to collect data-sharing plans. We encourage other trial registries to similarly incorporate mechanisms for the registration of data-sharing plans. Trialists who want to publish in ICMJE member journals (or nonmember journals that choose to follow these recommendations) should choose a registry that includes a data-sharing plan element as a specified registry item or allows for its entry as a free-text statement in a miscellaneous registry field. As a condition of consideration for publication in our member journals, authors will be required to include a description of the data-sharing plan in the submitted manuscript. Authors may choose to share the deidentified IPD underlying the results presented in the article under less restrictive, but not more restrictive, conditions than were indicated in the registered data-sharing plan.

ICMJE already requires the prospective registration of all clinical trials prior to enrollment of the first participant. This requirement aims, in part, to prevent selective publication and selective reporting of research outcomes, and to prevent unnecessary duplication of research effort. Including a commitment to a data-sharing plan is a logical addition to trial registration that will further each of these goals. Prospective trial registration currently includes documenting the planned primary and major secondary end points to

NEJM

The SPRINT Data Analysis Challenge

To explore the potential of clinical trial data sharing, the New England Journal of Medicine (NEJM) is hosting a challenge: use the data underlying a recent NEJM article to identify a novel clinical finding that advances medical science.

Share

Home | About | How To Enter | Rules | FAQs | News & Submit | Judges | NEJM Data Sharing Collection

Qualifying Round deadline has been extended to February 8, 2017

Call for Entries: SPRINT Data Analysis Challenge

Clinical trials drive medical advances and have a direct impact on health outcomes. Thoughtful, transparent systems for the responsible sharing of clinical trial data are important in maximizing the contribution of the patients who put themselves at risk by participating in clinical trials. The *New England Journal of Medicine* (NEJM) is committed to working with the global medical community to make the sharing of clinical trial data an effective, efficient and sustainable part of biomedical research.

To initiate an open conversation among researchers, data analysts, and patient participants, NEJM is hosting a web event, *Aligning Incentives for Sharing Clinical Trial Data* summit, on April 3-4, 2017. Leading up to the event, NEJM is sponsoring a SPRINT Data Analysis Challenge to demonstrate how clinical trial data can be used to identify additional advances in human health.

Are you up to the SPRINT Challenge to explore the potential from sharing clinical trial data? If so, NEJM challenges you to analyze the dataset underlying the SPRINT article — A Randomized Trial of Intensive versus Standard Blood-Pressure Control (N Engl J Med 373: 2103-2116) — and identify a novel scientific or clinical finding to advance medical science.

Proposal:

- A plan for data sharing as a component of clinical trial registration
- Sharing deidentified IPD required, 6 months following publication

White House & USG Proponents

The White House Office of Science and Technology Policy (OSTP) issued a Memorandum on Feb. 22, 2013 entitled ***Increasing Access to the Results of Federally Funded Research*** directing each Federal agency that conducts over $100 million annually in research and development expenditures to develop a plan to support increased public access to the results of that research. In response to the OSTP Memorandum, the NOAA Research Council issued the *NOAA Plan for Increasing Public Access to Research Results* (PARR) in February 2015. Among other requirements, the NOAA PARR Plan instructs the NOAA Environmental Data Management Committee (EDMC) to revise its existing *NOAA Data Sharing Policy for Grants and Cooperative Agreements*; this document (version 3.0) is the revised directive and supersedes the previous version (2.0). **"Data sharing" means making data publicly visible and accessible in a timely manner at no cost (or no more than the cost of reproduction), in a format which is machine-readable and based on open standards, along with metadata necessary to find and properly use the data.**

Recommendation 1:

Create culture in which data sharing expected norm

- **Funders and Sponsors** should require data sharing and provide appropriate support
- **Journals** should require sharing of analytic data set supporting the published results of a trial
- **Universities** should require data sharing and consider in promotion
- Research ethics committees
- Regulatory agencies

Specifics are important: “deidentified IPD”

- Anonymization:
  - Information which does not relate to an identified or identifiable natural person
  - Data rendered anonymous in such a way that the data subject is not, or no longer, identifiable
- Pseudonymization:

  Processing of personal data in such a way
  - that the data can no longer be **attributed** to a specific data subject
  - without the use of **additional information**
  - as long as that information is kept **separately** and subject to **technical and organisational measures**
  - to **ensure non-attribution** to an identified or identifiable person
- Deidentification
  - code may be maintained

Goal of Mandates and Policies: Utility of Research Data

- Leverage existing data for new scientific questions
- Combine from across:
  - Disease
  - Regions
  - Data generators

Rise in Data Repositories and Sharing Platforms

- New options for publishing data are being created
- Not all designed for secondary use or analysis
- Not all designed or capable of holding IPD data
- Multiplicity of repositories may challenge objective

The Dataverse Project

Open source research data repository software

OpenTrials
All the Data, on All the Trials, Linked

Open Science Framework
A scholarly commons to connect the entire research cycle

+AllTrials

ClinicalStudy DataRequest.com

Major Clinical Trials Data Sharing Platforms

- **CSDR -** leading industry multi-sponsor request site
- **Clinicaltrials.gov** – searchable database including summary results, not IPD
- **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

Currently not interoperable nor are most of these systems integrated

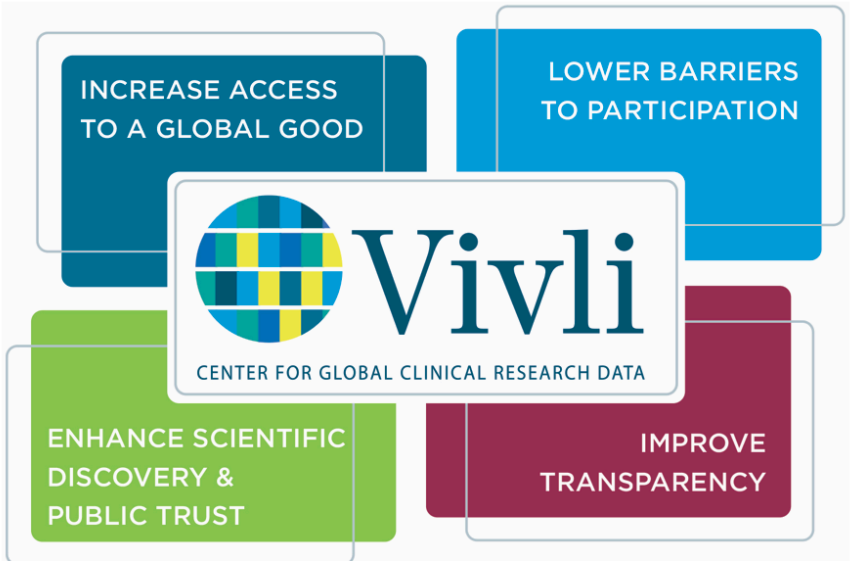
Current Gap

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.

Scope

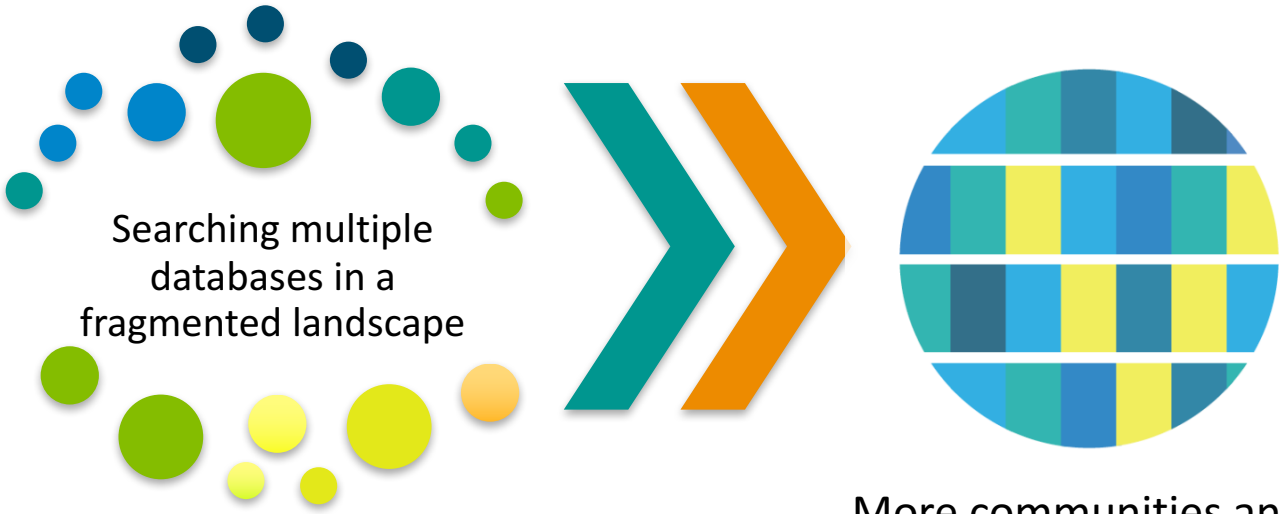
1) Enabling interoperability of data from multiple sources;
2) Hosting data for stakeholders that do not have the ability to do so;
3) Coordinating and partnering with existing data-sharing initiatives, policies, and processes as appropriate;
4) Promoting reasoned solutions to challenges of data sharing.



The Unique Remit of Vivli – Enhancing Discovery

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

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

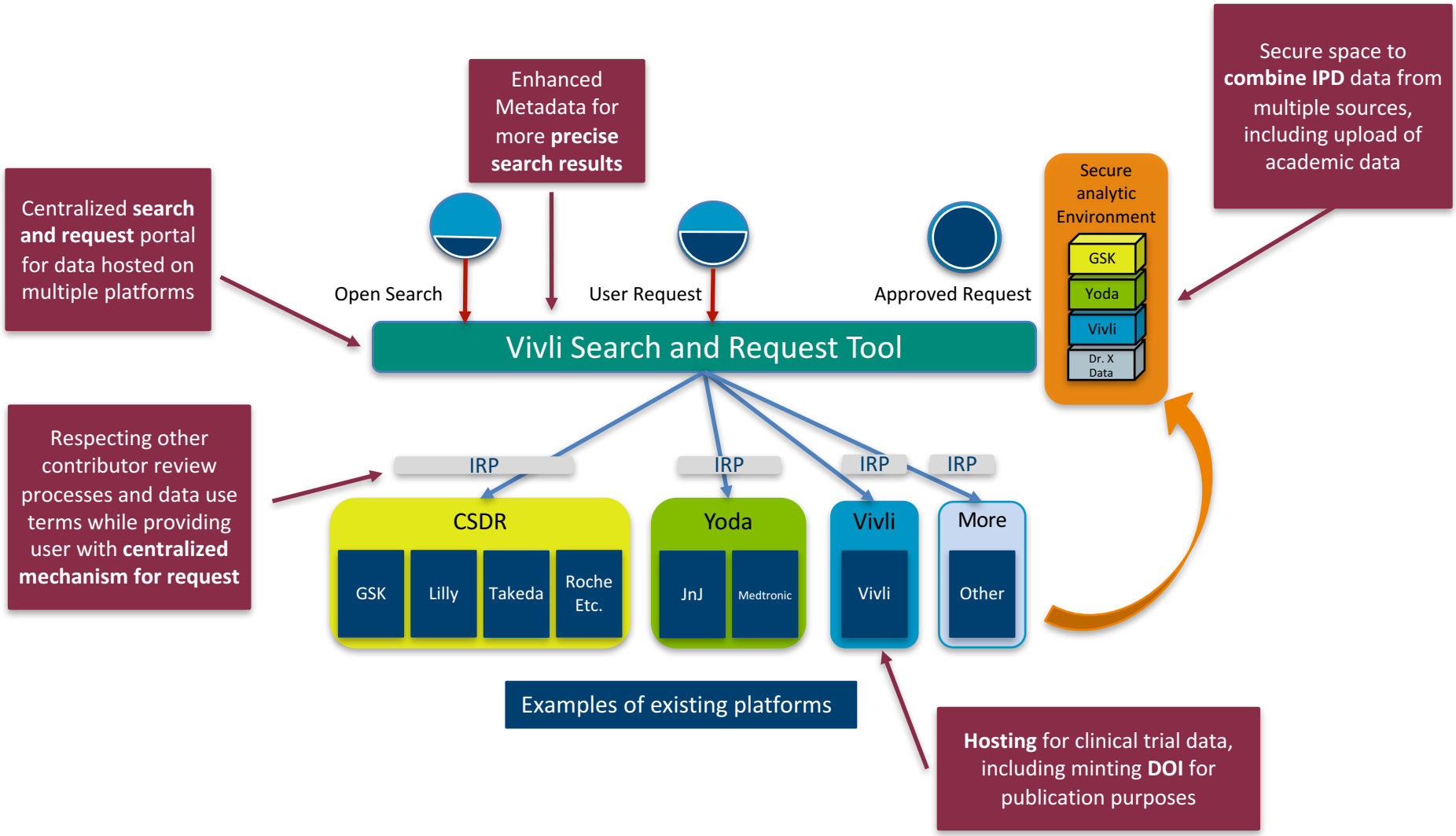


Discovery of data can be challenging

More communities and partners = more discoverable data

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

Vivli Solutions Offerings



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
  - Scale and scope of IPD hosting

Data Sharing: “Data Author” Designation

- 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

Closing Remarks

- Clinical trial data sharing, including sharing (deidentified) IPD, is rapidly becoming a reality
  - In 2017: anticipate final ICMJE policy
- Forward progress in sharing aggregate research results directly with participants (and public)
  - In 2017: anticipate final EMA policy with requirements to post summary results
  - Anticipate US FDA will not require sharing summary results
- Progress in sharing individual research results
  - In 2017: anticipate further guidance, no requirements

Discussion

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Thank you