CRDSA

Clinical Research Data Sharing Alliance

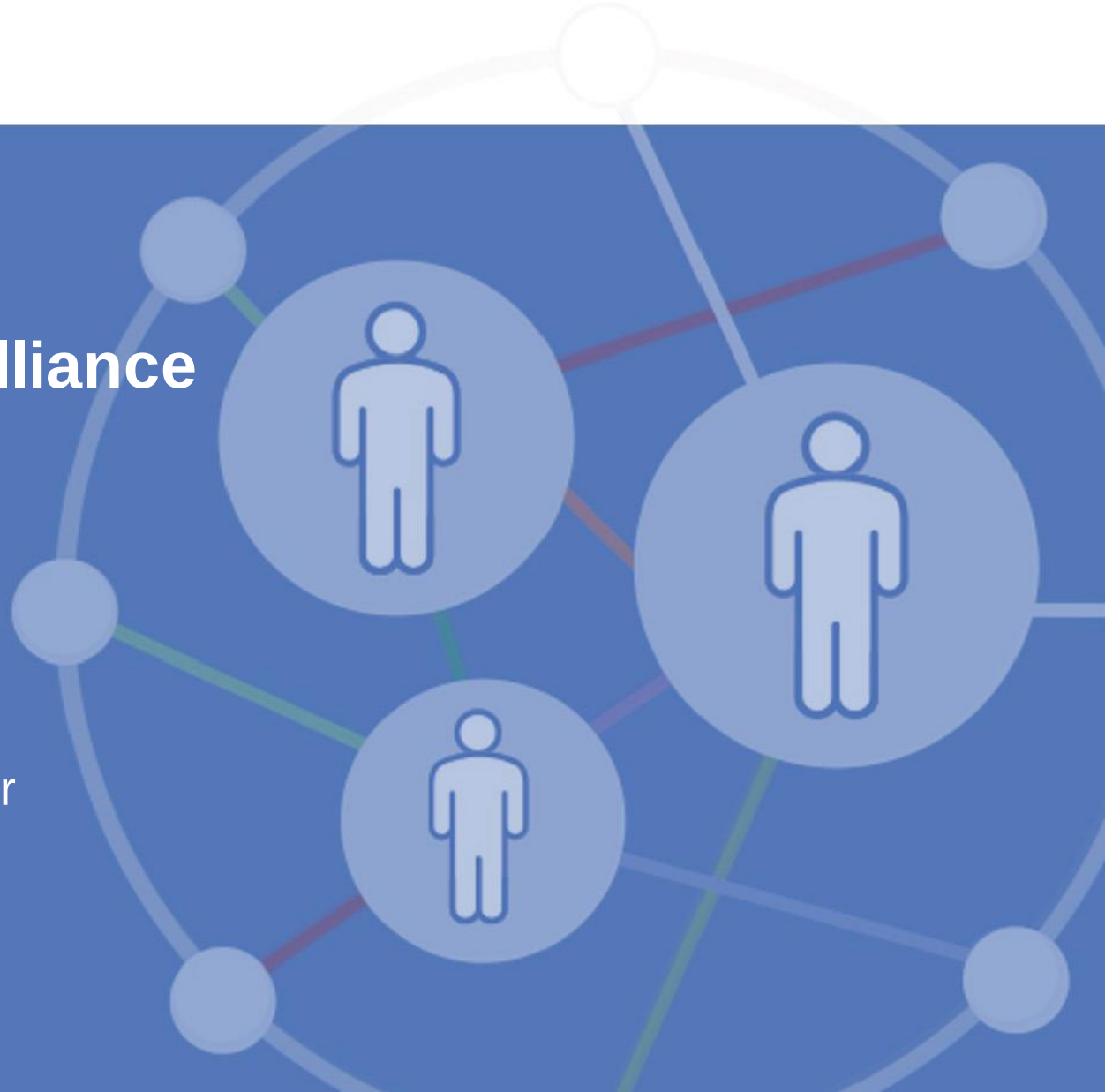
Clinical Research Data Sharing Alliance

Avenues for Collaboration

Liver Forum 16

Presented by: Aaron Mann, Chief Executive Officer

March 22, 2022



Agenda

1. CRDSA Overview
2. Clinical Trial Data Sharing: Standards Development
3. Supplemental and External Controls (pCTD and RWD)
    a) Regulatory Considerations
    b) Supplemental Controls Demonstration Project
    c) Data Platform Principles Development
4. Avenues for Collaboration

Introduction to CRDSA

Delivering Collaborative Solutions

CRDSA

Biopharma

NOVARTIS
Roche
AMGEN
ucb
AstraZeneca
Takeda

Data Platforms

CRITICAL PATH INSTITUTE
Vivli
CENTER FOR GLOBAL CLINICAL RESEARCH DATA
HDRUK
Health Data Research UK
Project Data Sphere
ASCO CancerLinQ
KNOWLEDGE CONQUERS CANCER
COTA

Academic and Non-Profit

Duke Clinical Research Institute
THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH
Flinders University
THE UNIVERSITY OF CHICAGO PEDIATRIC CANCER DATA COMMONS

Service and Technology

parexel
d-wise
An Instem Company
PRIVACY ANALYTICS
an IQVIA company
Real Life Sciences
atorus
Your Complete Data Solution

Partner Organizations

phuse

Our Work

CRDSA

Accelerating drug discovery and delivery by expanding the research value of secondary use data.

Standards

Establishing standards to ensure the integrity, quality, and usability of secondary data and promoting responsible research use.

- Data contribution standards responsive to end-user research needs
- Standards for researchers to ensure analysis validity and integrity of results

Policy

Advancing the regulatory acceptance of trial designs enhanced by data reuse and promoting governance policies supporting broad secondary data use.

- Regulatory acceptance of supplemental and external control trial designs
- Advancing trial sponsor data-sharing participation and governance practices

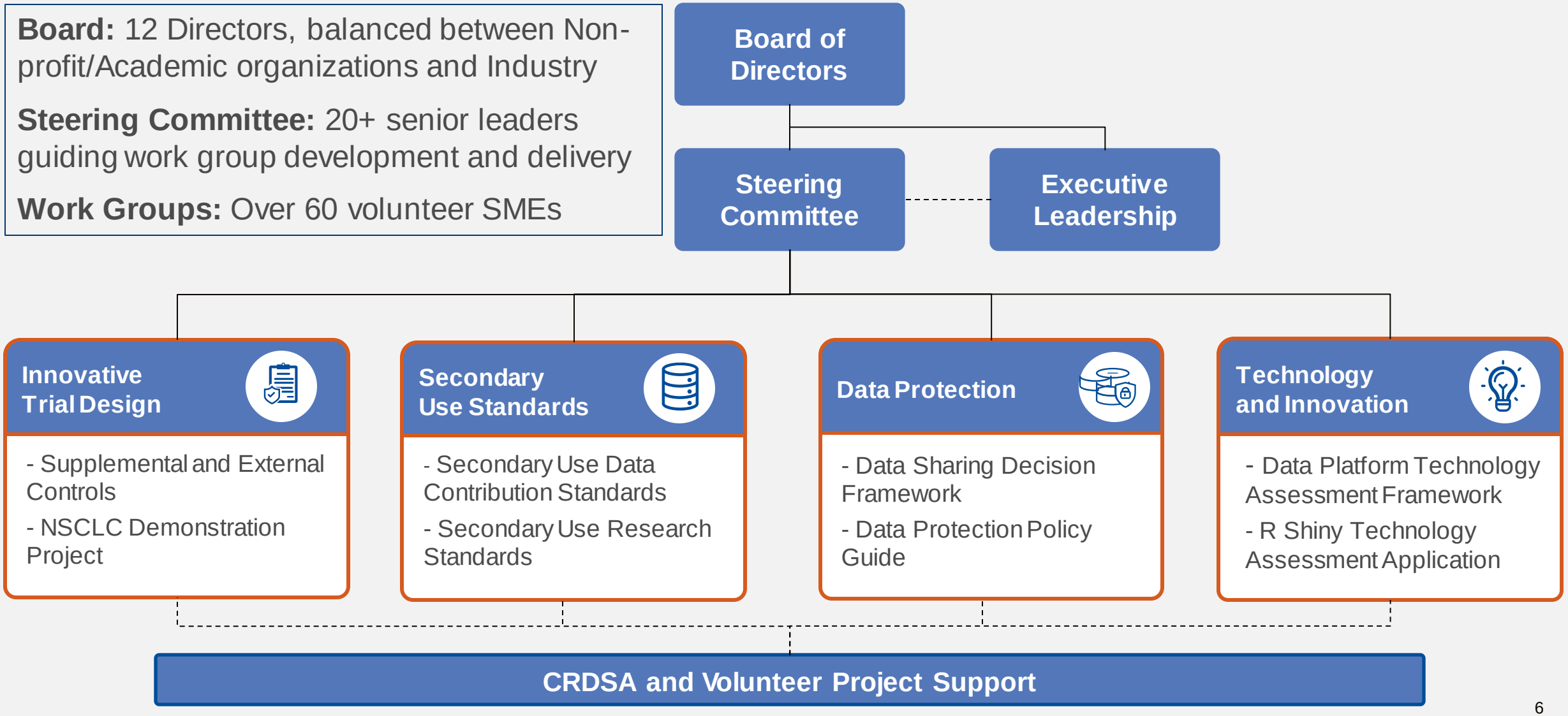
Governance and Work Groups

CRDSA

Board: 12 Directors, balanced between Non-profit/Academic organizations and Industry

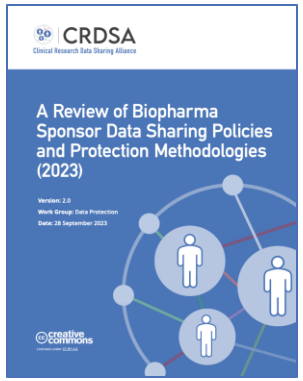
Steering Committee: 20+ senior leaders guiding work group development and delivery

Work Groups: Over 60 volunteer SMEs



Clinical Trial Data Sharing Standards

Standards Development



To enable good science with shared data:

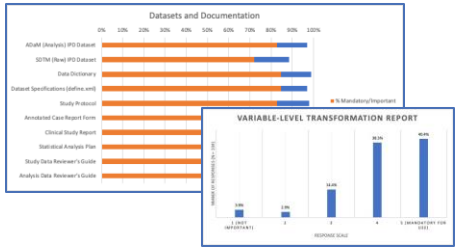
1. Contributed data must protect privacy and meet researchers' needs
2. Secondary analyses must be scientifically robust

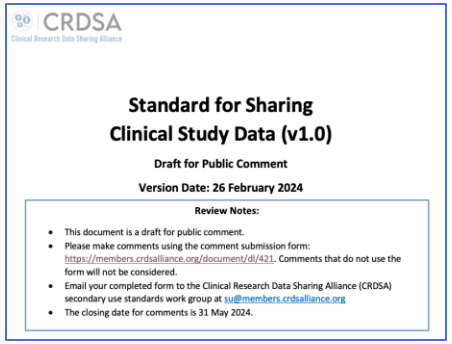
Data Contribution Standard

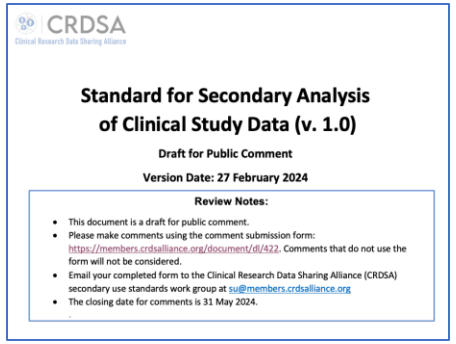
- Clinical Trial Datasets and Documentation

Secondary Use Research Standard

- includes team, data management, study/data understanding, analysis, quality control, interpretation, and transparency.







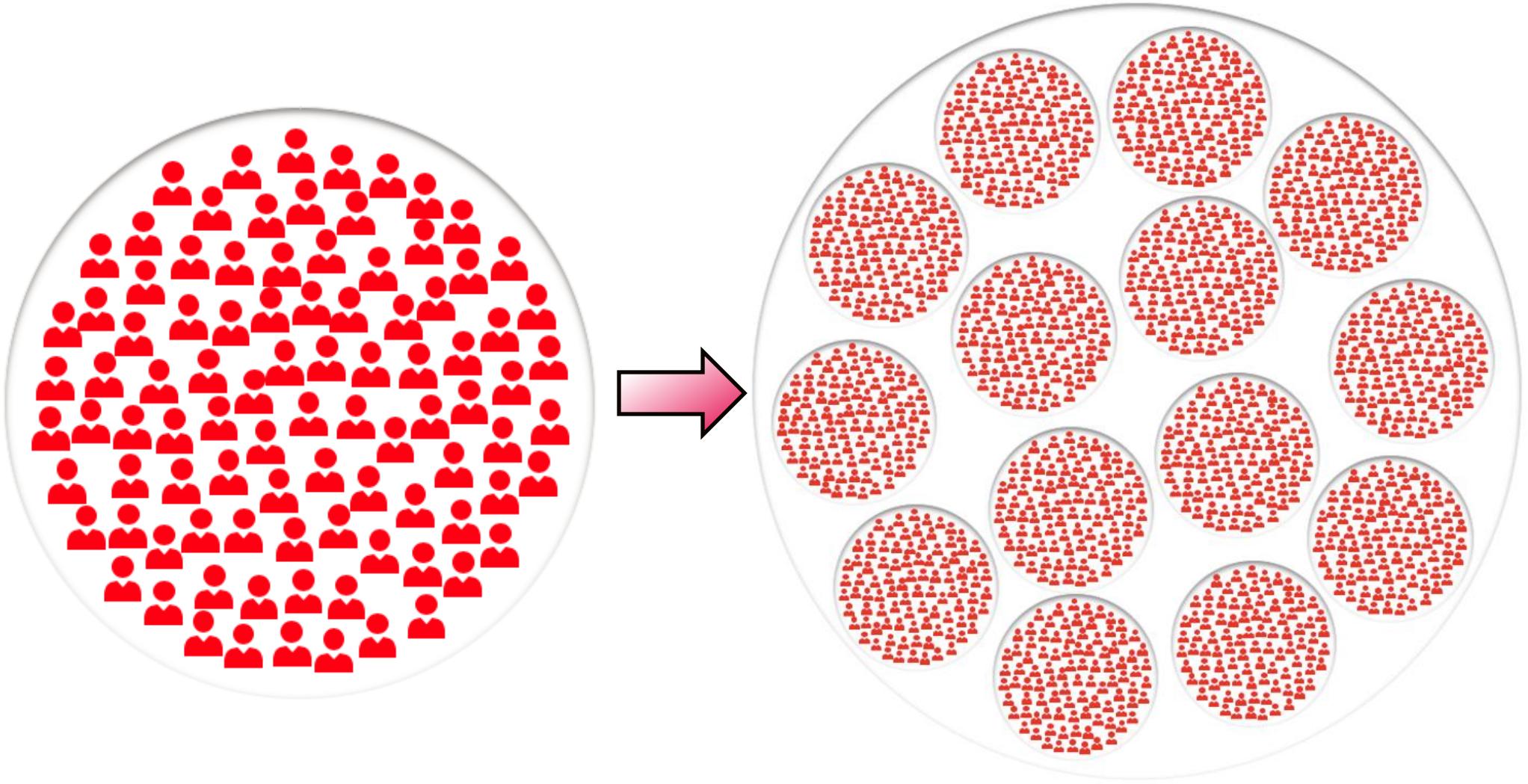
"Establishing a Basis for Secondary Use Standards for Clinical Trials"
Odame, et al (Applied Clinical Trials 2023)

The Data Contribution and Research Standard work together to enable good science

The draft standards are available for public comment (through May 31, 2024) at: https://crdsalliance.org

Supplemental and External Controls

Scientific advances mean…



…that everything starts to look like a rare disease.

SEC Trial Design

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Traditional RCT

- Concurrent control

Single Arm Trial

- No concurrent control
- External data may augment SAT
- Reference: "Reflection paper on establishing efficacy based on single-arm trials submitted as pivotal evidence in a marketing authorization" (EMA, 17 April 2023)

Supplemental Control

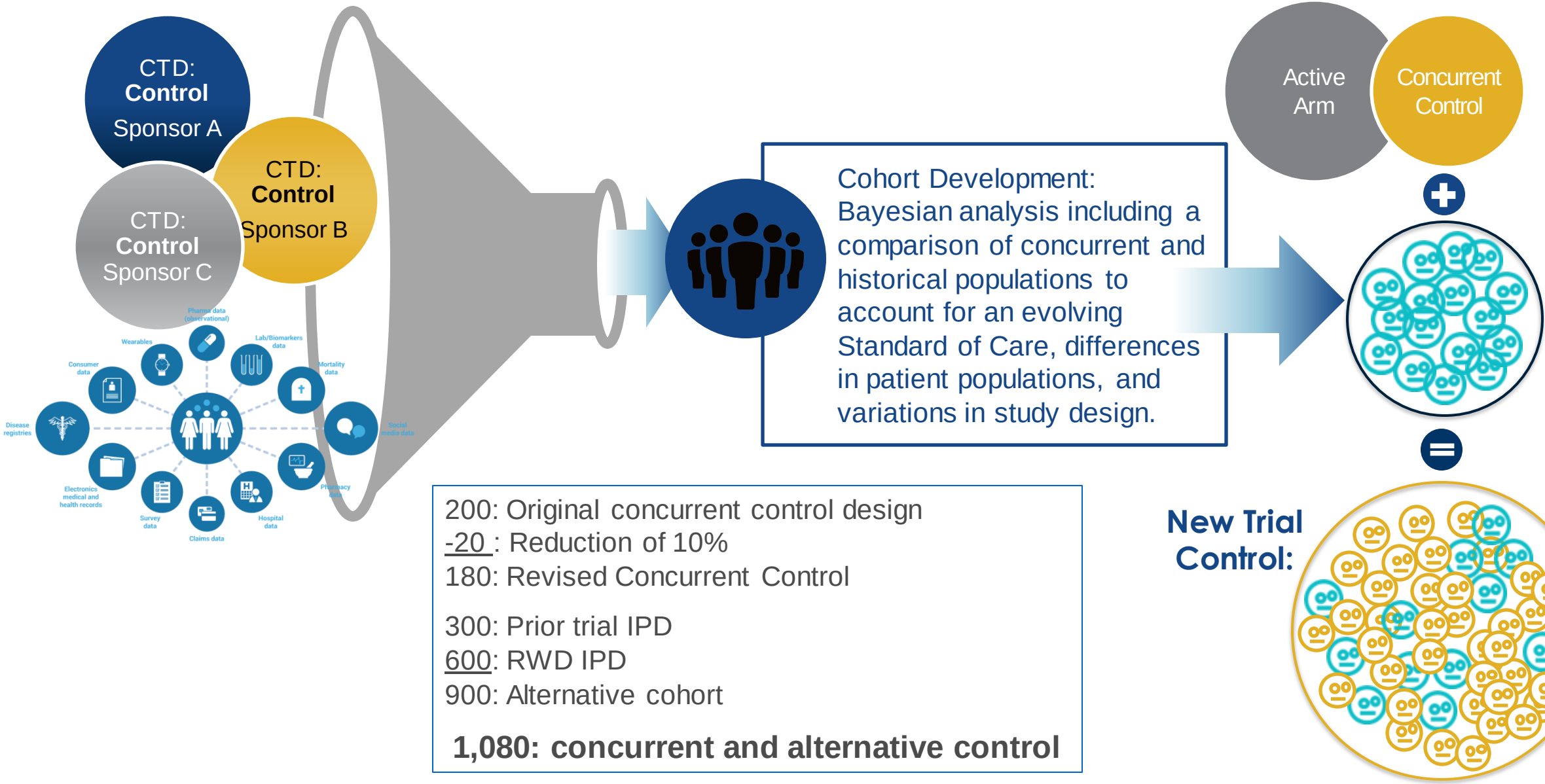
- Concurrent control, power limited by design and/or patient population considerations

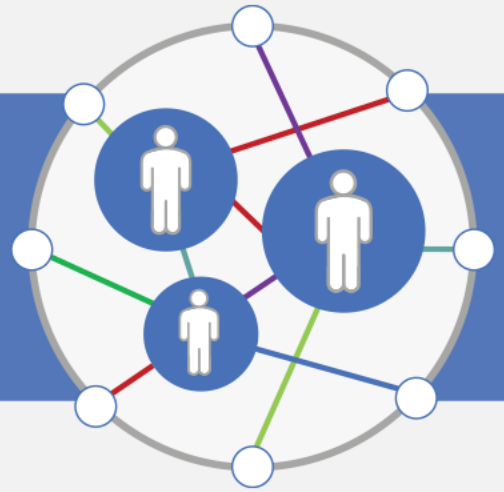
Externally Controlled Trial

- No concurrent control
- Reference: "Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products – Draft Guidance for Industry" (FDA, February 2023)

Same Data Provenance and Selection Methodology Considerations

Evolving an Evidence Mindset





Regulatory Considerations

FDA Draft External Controls Guidance

The FDA posted the draft guidance on January 31, 2023, and comments closed on May 2, 2023
- https://www.regulations.gov/docket/FDA-2022-D-2983/document
- The guidance encompasses both prior clinical trial and real-world data
- 205 comments received

- CRDSA-sponsored draft guidance roundtable (July 2023)
- "FDA Draft External Controls Guidance: Situation Analysis and Recommendations" (Aug 2023)
  - https://crdsalliance.org/resources
- Data Platform Workshop (Jan 2024)

Regulatory Considerations

CRDSA-Sponsored Workshops and Demonstration Project Scope

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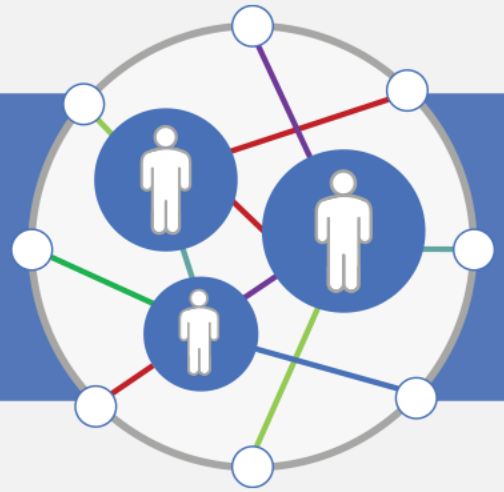
Data Provenance (Generating confidence in the integrity and suitability of the secondary use data used to construct an external/supplemental control)		Selection Methodology (Acceptable technical and/or process approaches to minimize or eliminate selection bias)	Statistical Methodology (The case-by-case approach to determining and adjusting for sources of bias)
Category	**Consideration**		
Completeness	Secondary Use Datasets (and documentation) are sufficient to support the intended analysis and ensure data relevance and reliability.	**Data Selection:** The process for determining which datasets (e.g., studies) will be used to construct the applicable cohort.	• Time periods • Geographic regions • Assessments • Treatments • Intercurrent events • Index date / Immortal time
Transparency	Criteria to promote health authority confidence in source data collection processes and secondary use data management, including data transformations and quality assurance processes.	**Subject Selection** Application of Inclusion/Exclusion Criteria	Illustrative only, not an exhaustive list.
Audit Trail (Traceability)	A transparent and traceable audit trail for the secondary use data is available to regulators, including methods to ensure data integrity		



Supplemental Controls Demonstration Project

Demonstration Project Summary and Sponsors

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Background:
The Supplemental Controls Demonstration Project aims to expand the body of knowledge and address gaps in current sponsor guidance when using diverse data types and methods to construct supplemental, external, or hybrid controls.

Objective:
Establish clear regulatory guidelines for data provenance and selection methodologies to ensure confidence in the integrity and trustworthiness of the data at source and as selected for use in constructing a supplemental control.

Project Data:
Non-small cell lung cancer datasets

- RWD: Curated and harmonized NSCLC patient records
- Clinical Trial Data: NSCLC IPD from trial sponsors

Status:
- Data Sharing and Research Use agreements in final review
- Initial source data and data platform workshop held January 2024, draft output in process

ASCO CancerLinQ
KNOWLEDGE CONQUERS CANCER

Project Data Sphere

Roche

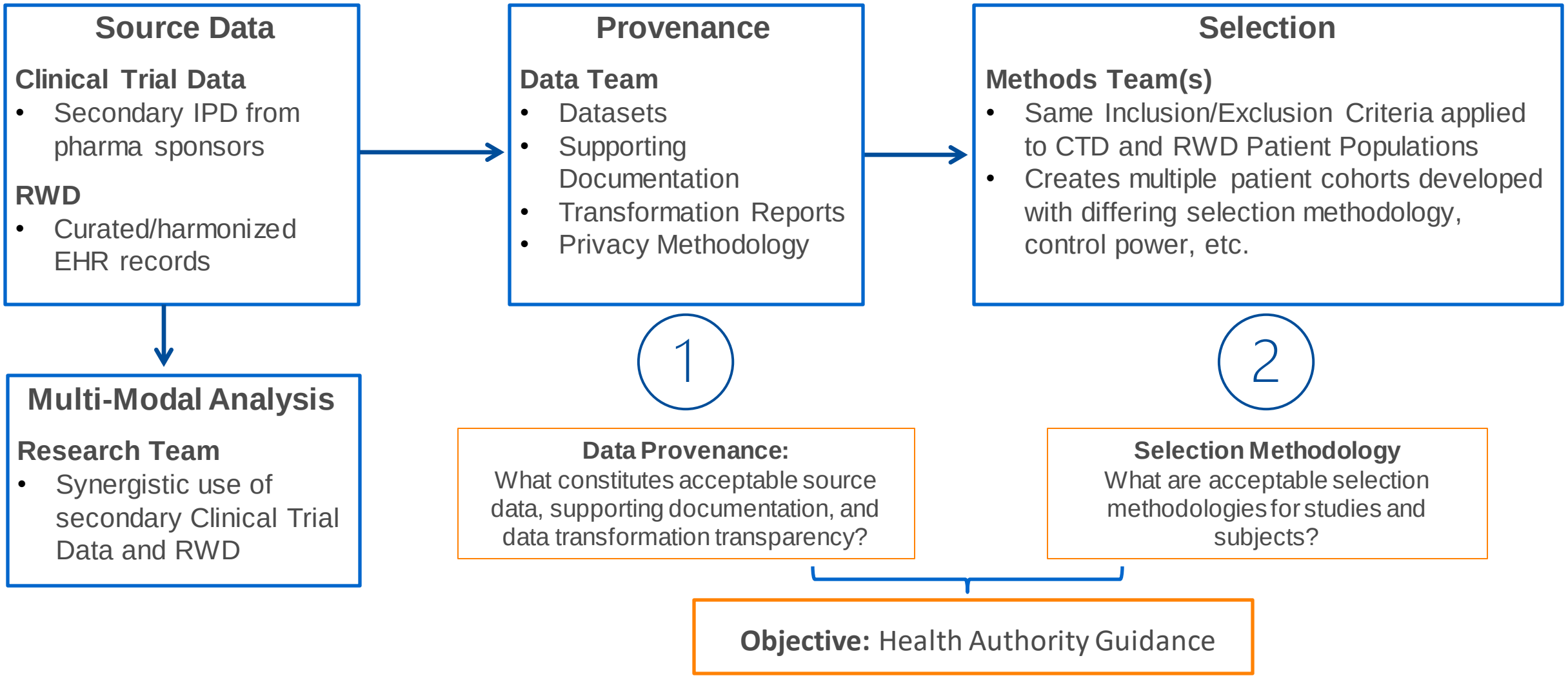
Takeda

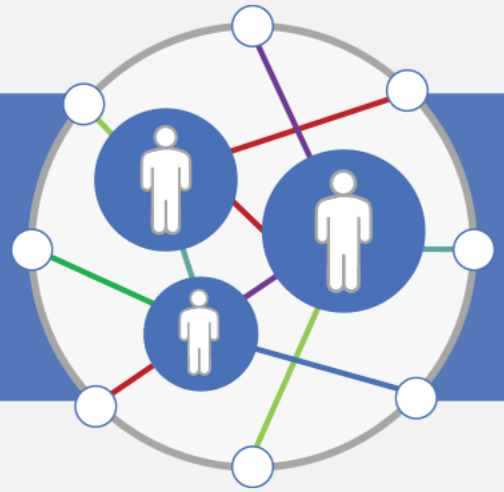
NOVARTIS

AMGEN

COTA

Project Design





Data Platform Principles For Regulatory Submissions

Overview

Scope: Data used to construct Supplemental and External Controls (SEC) for Regulatory Submissions

Source Data and Data Platform Workshop (11-January):

- 26 participants representing 14 organizations, including nine clinical trial and RWD data platforms
- Deliverable: Whitepaper or manuscript proposing data platform principles for health authority and public comment

Data Platform Principles:

- Objective: Develop principles to promote health authority confidence in data platforms, satisfying health authority "traceability" without requiring source data access (e.g., access to hospital or clinical trial site).
- Positioning: The principles are suggested practices to promote and facilitate SEC use in regulatory submissions. They are high-level concepts, not specific implementations or processes.

Definitions:

- **Source Data**: data and documents as collected for primary use (e.g., in a prior clinical trial or an electronic health record)
- **Secondary Use Data**: the datasets and documentation on the data platform available for secondary use (after data preparation by the data contributor and/or data platform)
  - RWD data preparation includes all processes after primary collection, including accrual, curation, transformation, and abstraction
- **Submission Data**: the final study analytic dataset submitted by the sponsor for regulatory review

Prior Clinical Trial Data

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Collection: Data Contributor /Original Sponsor

Individual Patient Data

Raw Dataset (SDTM)

Analysis Dataset (ADaM)

Statistical Analysis

Regulatory Submission

Anonymized Raw Dataset

Anonymized Analysis Dataset

Data Platform

Anonymized Raw Datasets

Anonymized Analysis Datasets

Clinical trial data platforms can be:

- Nonprofits
- Academic Institutions
- Patient Groups (e.g., MJFF)
- Health Authorities/Funders
- Sponsors (e.g., internal data warehouse)

Submitting Sponsor

Harmonization: Supplemental Control Cohort

Statistical Analysis

Supplemental Control Submission Dataset

New Regulatory Submission

Real-World Data

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Collection (also Data Accrual)

Individual Patient Data

e.g., EHR record

Data Platform

Data Management

- **Curation**: Application of standards and codes to patient records(e.g. HL7, ICD-10-CM)
- **Transformation**: includes extraction, cleansing, and integration (into a CDM)
- **Aggregation**:
- **Abstraction**:
- **Anonymization**

Real-World Data platforms can be:

- Commercial companies
- Health Authorities (e.g., DARWIN)
- Patient Groups
- Academic and Research Institutions
- Sponsors (in limited cases)

Anonymized IPD

Submitting Sponsor

Supplemental Control Cohort

Statistical Analysis

Supplemental Control Submission Dataset

New Regulatory Submission

Platform Principles: Primary References

- FDA Final Guidance (Dec 2023): Data Standards for Drug and Biological Product Submissions Containing Real-World Data (CDER/CBER)
- CRDSA Draft Standards (Feb 2024): Data Contribution Standard
- HMA/EMA (Dec 2023): Data Quality Framework for EU medicines regulation
- FDA Final Guidance (Aug 2023): Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products (CDER, CBER, OCE)
- FDA Draft Guidance (Dec 2023): Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices (CDRH/CBER)
- FDA Draft Guidance (Feb 2023): Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products (CDER, CBER)

Regulatory Submissions: Data Platform Principles

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DRAFT: For Discussion Only

Prior Clinical Trial Data	Real-World Data
Source Data: Collection	
(a) Clinical trial data are from trials that were used in regulatory submission and, therefore, have been subject to prior health authority review and possible audit.	a) The process for capturing, entering, or collecting data (e.g., EHR entry at the point of care) is subject to clearly defined and documented SOPs. b) Quality control procedures are documented and implemented
Secondary Use Data: Documentation	
a) Data Platforms should ensure that contributed trials include sufficient data and supporting documentation to facilitate secondary research and allow regulators to assess *Data Relevance* and *Data Reliability.* The CRDSA Standard for Sharing Clinical Study Data introduces requirements to support this principle. b) Data Platforms should ensure that datasets and supporting documentation are available to data users such that they can readily be used in a new regulatory submission (e.g., through data download)	a) The data management process is documented and available to end-users and other third-parties. Documentation should include process and quality control procedures for all data changes (including deletions, additions, and alterations) from the Source Data system to Secondary Use Data availability for platform end users. b) When RWD is to be used for regulatory submission, the Data Platform is to provide datasets to end-users in SDTM format with documentation at the domain and variable level of any changes, alterations, deletions, or transformations from the original value collected at source to the Secondary Use Dataset. Please reference the FDA guidance ”Data Standards for Drug and Biological Product Submissions Containing Real-World Data” issued December 2023. For these Data Platform principles: i. The Data Platform is responsible for documenting all data changes prior to secondary use by the end-user Sponsor ii. The Sponsor is responsible for documenting data changes from the data platform into the data model used for analysis

Regulatory Submissions: Data Platform Principles

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DRAFT: For Discussion Only

Prior Clinical Trial Data	Real-World Data
Submission Data: Quality Assurance	
a) Data Platforms will facilitate, through data access or other comparable method, audit of the Secondary Use Data used in the new submission such that regulators are able to validate that the data used to create the study analysis dataset is the same as that provided by the platform to the Sponsor.	(a) Data Platforms will facilitate, through data access or other comparable method, audit of the Secondary Use Data used in the new submission such that regulators are able to validate that the data used to create the study analysis dataset is the same as that provided by the platform to the Sponsor. (b) Data Platforms agree to be subject to data user (Sponsor) and/or regulator audits and inspections to ensure adherence to collection and data management SOPs.

Project Plan (WIP)

1. Principles alignment
   a) CRDSA internal and workshop participant review (in process)
2. Position paper development
   a) CRDSA internal review
   b) Select non-member organizations
3. Publication and socialization (including health authorities)

Avenues for Collaboration

Opportunities for Collaboration

CRDSA

Standards Development

Work Group Participation

- Develops draft standards
  - Data contribution v 2.0: Principles for data access, sharing scope, provision timing
- Reviews and reconciles internal and external document comments

CRDSA Steering Committee

- Review and comment drafts and final deliverables prior to public release

Supplemental and External Controls

- Data platform principles: project and authoring team (position paper development and drafting)
- Parallel MASH demonstration project development

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Thank you!

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