Yale-Medtronic Experience

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Medtronic INFUSE (rhBMP-2) Evidence and Reporting Challenge Background (1)

- INFUSE approved by the FDA in July, 2002
  - rhBMP-2 is used to accelerate bone growth
  - Indicated for 1-level anterolateral lumbar interbody fusion (ALIF)
- Base of evidence for FDA approval (MDT-sponsored ALIF indication)
  - ALIF indication dossier: 1 Pilot RCT, 2 Pivotal RCTs
- Peer-reviewed publications (MDT sponsored)
  - Most published after 2002 (last 2011)
  - ALIF indication: 3 Pilot RCTs, 4 Pivotal RCTs
  - Non-ALIF indications: 2 Pilot RCTs, 3 Pivotal RCTs
- June 2011: Major challenge was made regarding the validity of all published evidence for INFUSE, and unreported harms
  - Principal focus was on the results presented in the peer-reviewed literature (compared to the FDA data on file from the 2002 INFUSE dossier tables), and on general study designs and endpoint concerns
  - Challenge published in medical journal: dedicated issue with >10 articles

Medtronic INFUSE (rhBMP-2) Evidence and Reporting Challenge Background (2)

- June 2011:
  - MDT announces decision to contract with Yale as the independent review coordinator
- August 2011
  - Yale announces its plan to establish an independent steering committee and contract 2 systematic review organizations
  - MDT agrees to supply Yale with:
    - all de-identified rhBMP2 data (patient level data), including non-label studies
    - all FDA correspondence and adverse event reports
  - MDT agrees to allow Yale to establish a public transparency policy and process for the entire INFUSE patient level dataset

Fall-Winter 2012

Systematic Review reports to be finalized, summary manuscripts prepared and submitted for publication in Annals of Internal Medicine

Yale University
Open Data Access Project

A Model for Dissemination and Independent Analysis of Clinical Trial Program Data

Yale University
Center for Outcomes
Research and Evaluation

Funded by a contract with Medtronic, Inc

Project Leadership

- **Harlan Krumholz, MD, SM**
  Principal Investigator
  Yale University
- **Cary Gross, MD**
  Co-Investigator
  Yale University
- **Joseph Ross, MD, MHS**
  Co-Investigator
  Yale University
- **Kevin J. Bozic, MD, MBA**
  Associate Professor and Vice Chair
  University of California, San Francisco
- **Ezekiel J. Emanuel, MD, PhD**
  Vice Provost and Levy University Professor
  University of Pennsylvania

Rationale

- A substantial number of clinical trials are conducted, but never published
- Even among published clinical trials, a limited portion of the collected data is reported on
  - Particularly relevant for safety information
- Thus, patients and physicians frequently make treatment decisions with access to only a fraction of clinical research data

Focus on Industry

- Issues relevant to clinical trials conducted both publicly and privately, but are particularly important among industry trials
  - Industry funds majority of clinical trial research about drugs, devices and other products, both pre-market and post-market
  - Industry research is proprietary, no requirement for publication or dissemination
  - Public perception: industry has a financial interest in promoting “supportive” research, not publishing rest

Public Health Need

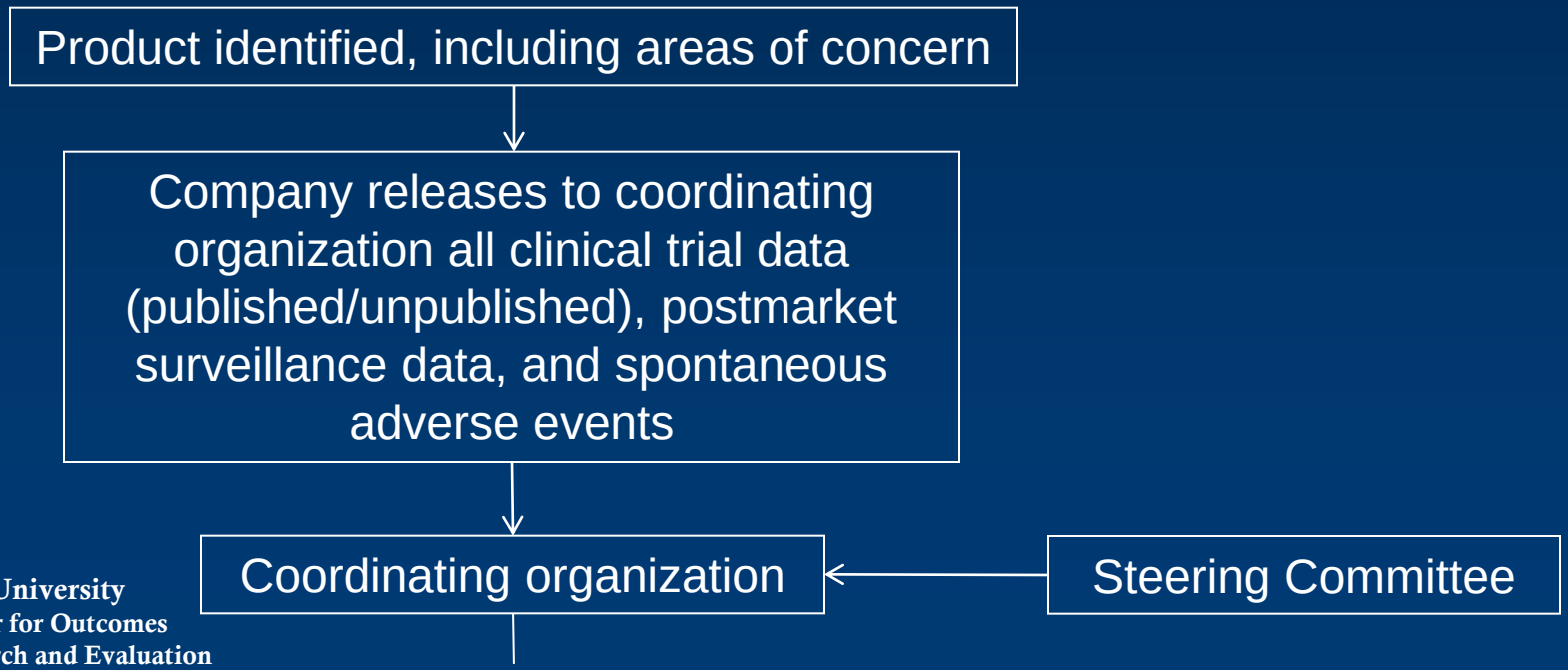
- Steps must be taken to align the interests of industry and the public, particularly when concerns arise about safety or effectiveness
- The public has a compelling interest in having the entirety of the data available for independent analysis
- Industry has legitimate concerns

Objective of the YODA Project

- The project's goal is to promote clinical trial program data access more widely, increasing transparency, protecting against industry influence, and accelerating the generation of new knowledge
- Patients, providers, and industry will be better informed
  - They will be able to facilitate the independent assessment and dissemination of data relevant to the benefits and harms of industry products
- Physicians and patients can base their decisions on the most comprehensive and contemporary evidence available

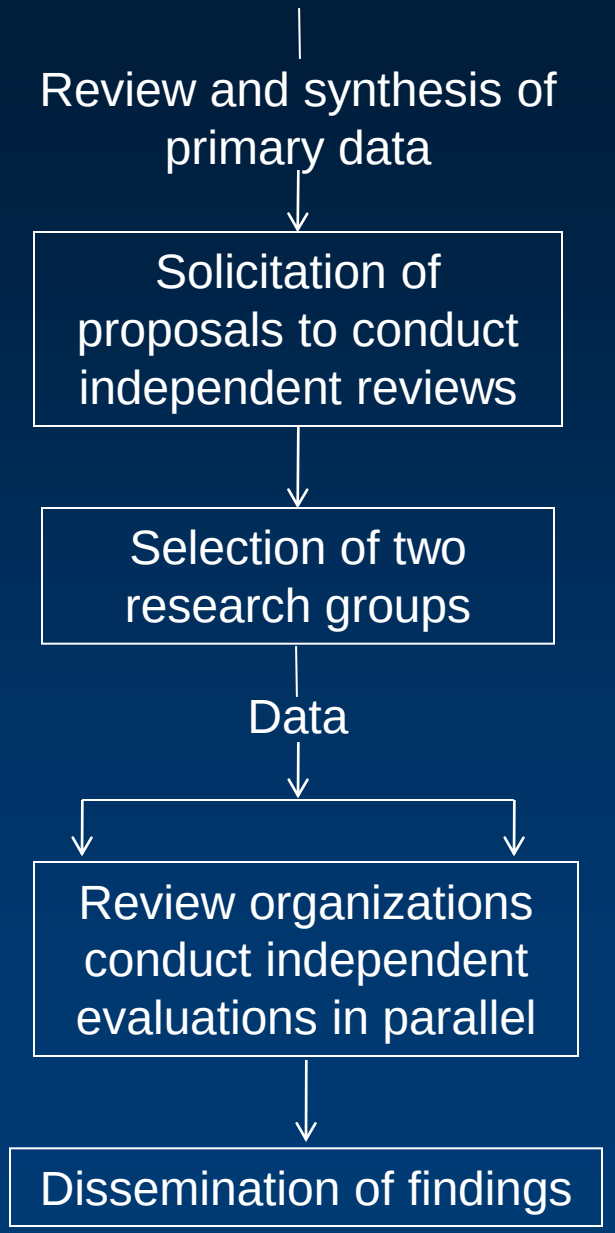
YODA Project Model

- Designed to facilitate the release of data, ensure high quality reviews of the evidence, and provide the public with the scrutiny of independent review
- Begins with company release of data to coordinating organization, which is overseen by steering committee



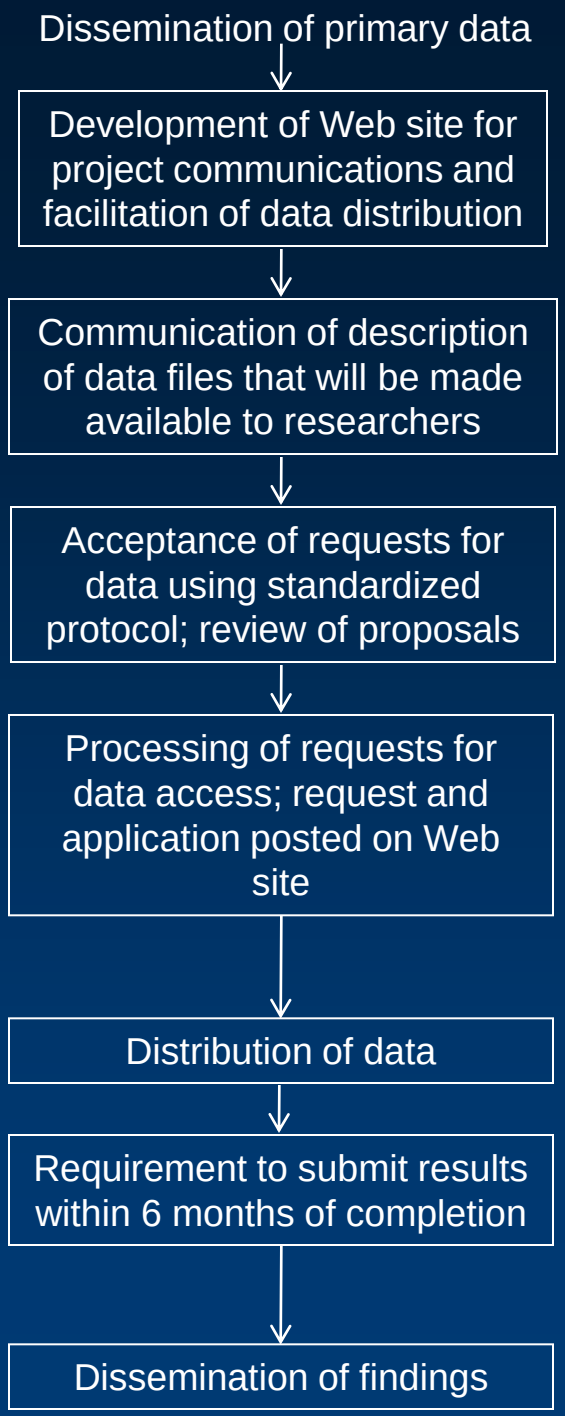
Formal Independent Analysis

- Coordinating organization contracts with two research groups that independently systematically review and synthesize clinical trial data
  - Industry and non-industry research
  - Uses individual-level data, in addition to trial summary-level data
- Advantages:
  - Distance between company and reviewers
  - Reproducibility and validity via two reviews



Data Dissemination

- Coordinating organization makes industry's individual-level data available to other external researchers
  - Via a Web site, requiring a registration process, commitment to results reporting
- Advantages:
  - Complete transparency



Yale University
Center for Outcomes
Research and Evaluation

Why Should Industry Participate?

- Allows for fair and objective assessment of product research data, as opposed to speculative analysis based on incomplete data
- Promotes transparency
- Supports scientific competition, not marketing
- Untenable to withhold information about product effectiveness and safety

2011 YODA Project Accomplishments

- Contract signed with Medtronic, Inc (Aug)
- Request for Proposals (RFP) drafted & released (Sept)
- Steering and Clinical Committees selected (Sept-Oct)
- Commentary: "A Model for Dissemination and Independent Analysis of Industry Data" published in *JAMA* (Oct)
- Applications received, scored and Centers selected (Sept-Nov)
- Manuscript: "Promoting Transparency in Pharmaceutical Industry-Sponsored Research" published in *AJPH* (Nov)
- Data received from Medtronic, Inc and distributed to Centers (Dec)
- Centers commenced independent analyses (Dec)
- Process established for fielding questions from Centers (Dec)

2012 YODA Project Accomplishments

- Manuscript: "Open Science and Data Sharing in Clinical Research: Basing Informed Decisions on the Totality of the Evidence" published in *Circulation: Cardiovascular Quality and Outcomes* (March)
- Manuscript: "The Importance of Clinical Trial Data Sharing: Toward More Open Science" published in *Circulation: Cardiovascular Quality and Outcomes* (March)
- Data sharing conference held at Yale (June)
- Final reports received from research Centers (Aug)
- Peer review of reports (Aug-Sept)

A Look Ahead

- Fall 2012/ Winter 2013
  - Manuscripts submitted to *Annals* for simultaneous publication
  - Centers' reports locked
  - Public release of data

Yale Review Project

Medtronic

Principles & Processes

Communication Principles

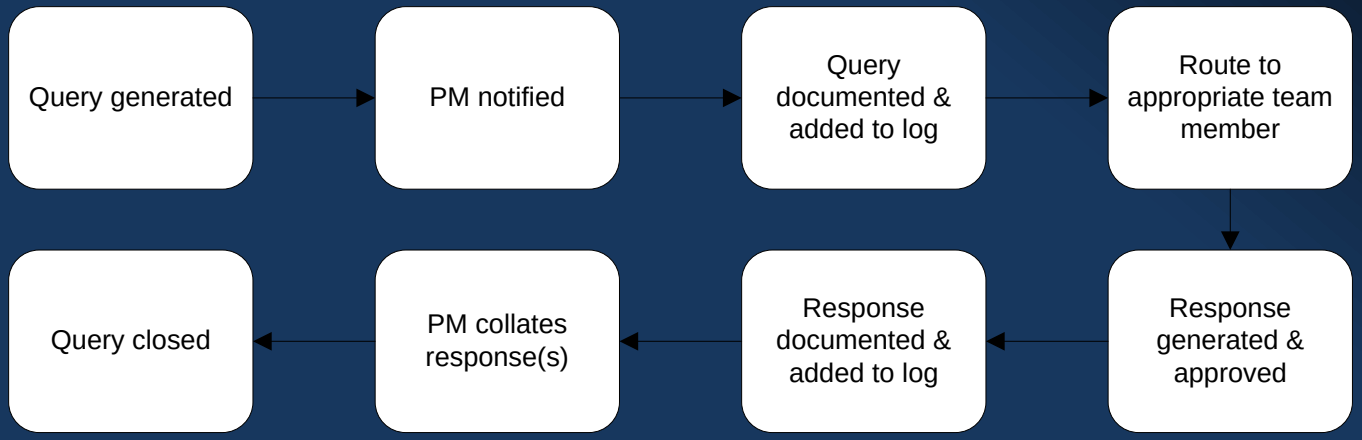
The primary tenets of the project are

- *Transparency*
- *Independence*

To maintain both, we need:

- Formal documentation of Yale-to-MDT questions & MDT-to-Yale responses
- Clarity around what types of discussions we can & cannot have

Communication logistics & boundaries



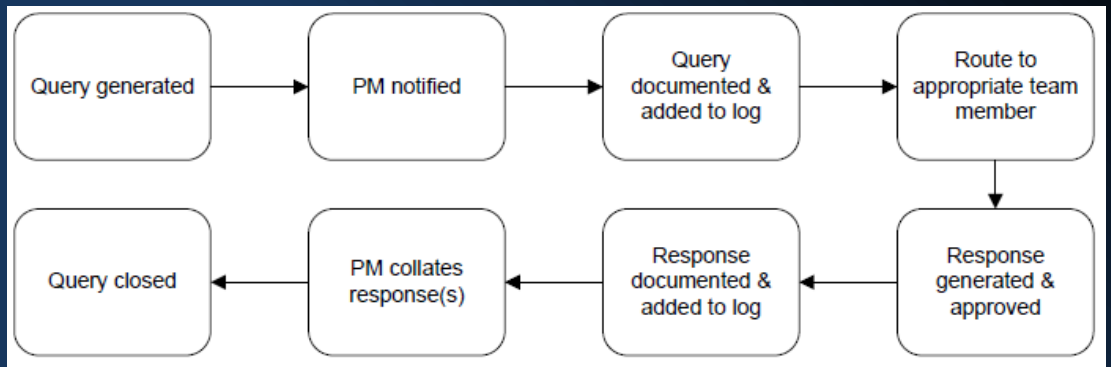
Team CAN communicate re:

- Study conduct
- Data clarity
- Data content
- Study report

Team CANNOT communicate re:

- Review contractors
- Evaluation methods
- Evaluation criteria

Query Management Process



3RD PARTY REVIEW REQUEST TRANSMITTAL FORM

Part A - Requestor to complete

Date of request: 9-Nov-11

Request type: Internal _____ External _____

Requestor: _____ Contact _____

Request:

Part B - MDT mailbox recipient to complete & forward to Functional Expert

Date logged: _____

Request type: _____

Forwarded to: _____

Part C - MDT Functional Expert to complete & forward to Approver(s)

Date received: _____

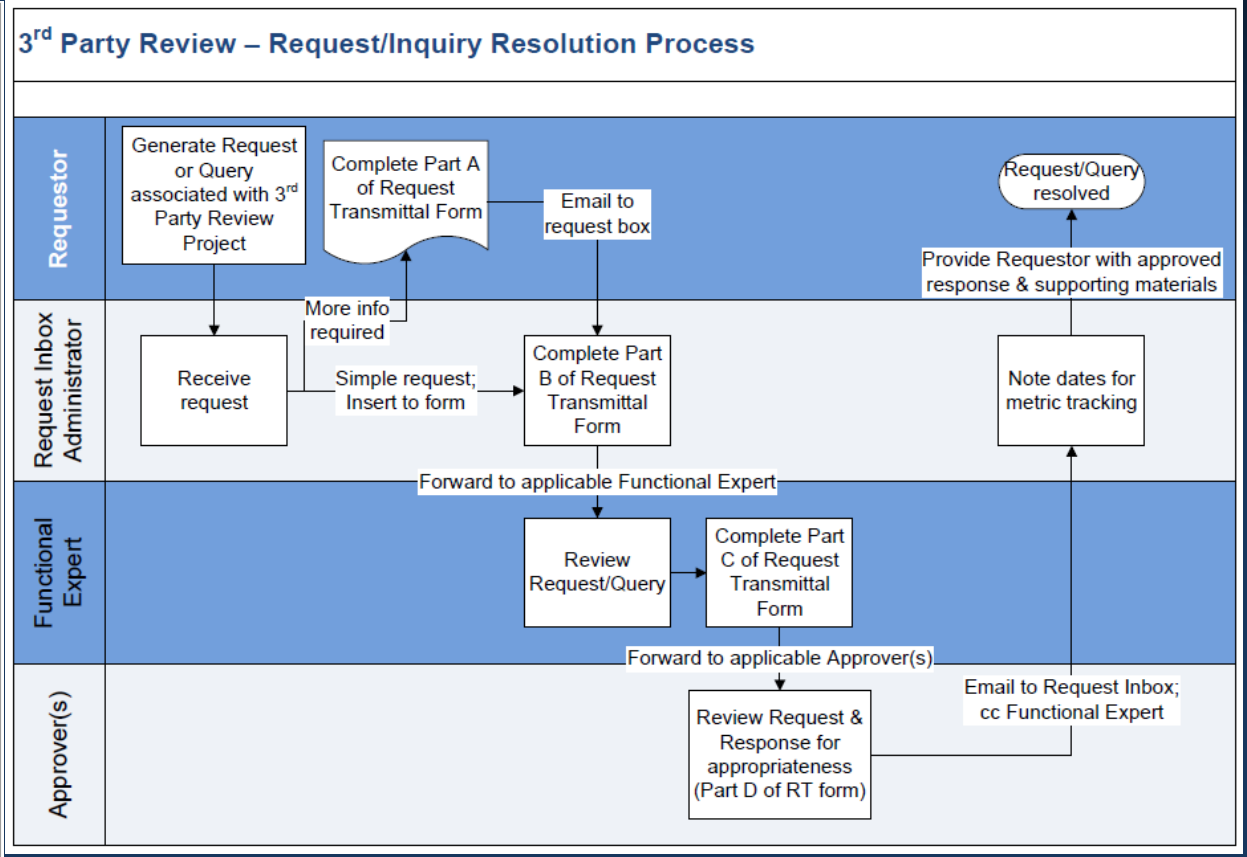
Resolution comments &/or attachments:

Part D - MDT Approver(s) to review & return to MDT mailbox, cc: Functional Expert

Approver _____ Name _____ Title _____ Date

Approver _____ Name _____ Title _____ Date

Approver _____ Name _____ Title _____ Date



Yale Review De-Identification Process

- Overview of de-identification process
  - Guiding principles
  - Documents
  - Datasets
  - MDRs
  - Certification

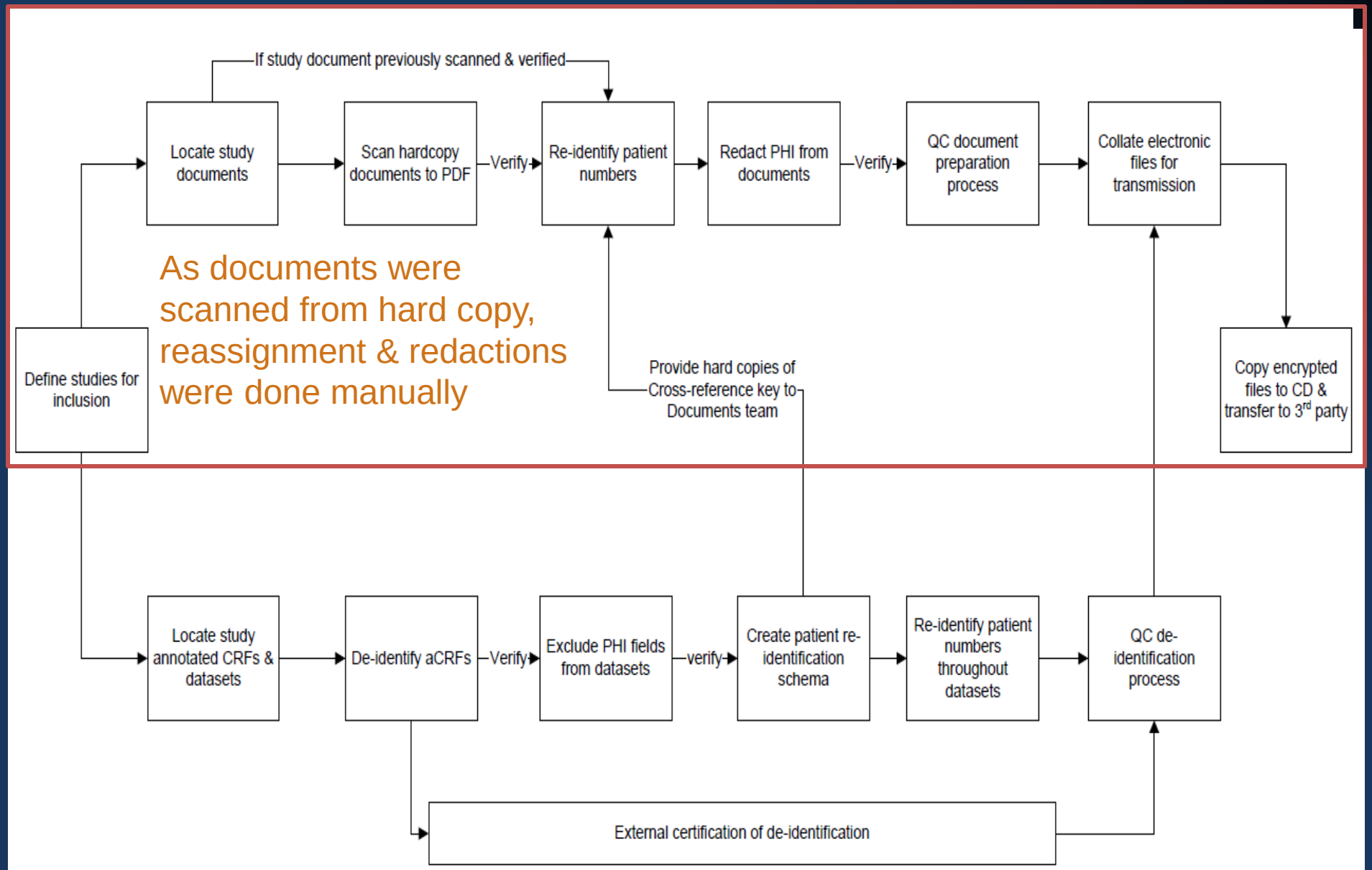
De-Identification Guiding Principles

- Not all 18 HIPAA identifiers were removed – dates of care were deemed significant for data interpretation
- Because dates were being maintained, an added level of protection was added by re-assigning the patient numbers to a randomly generated key known only to MDT

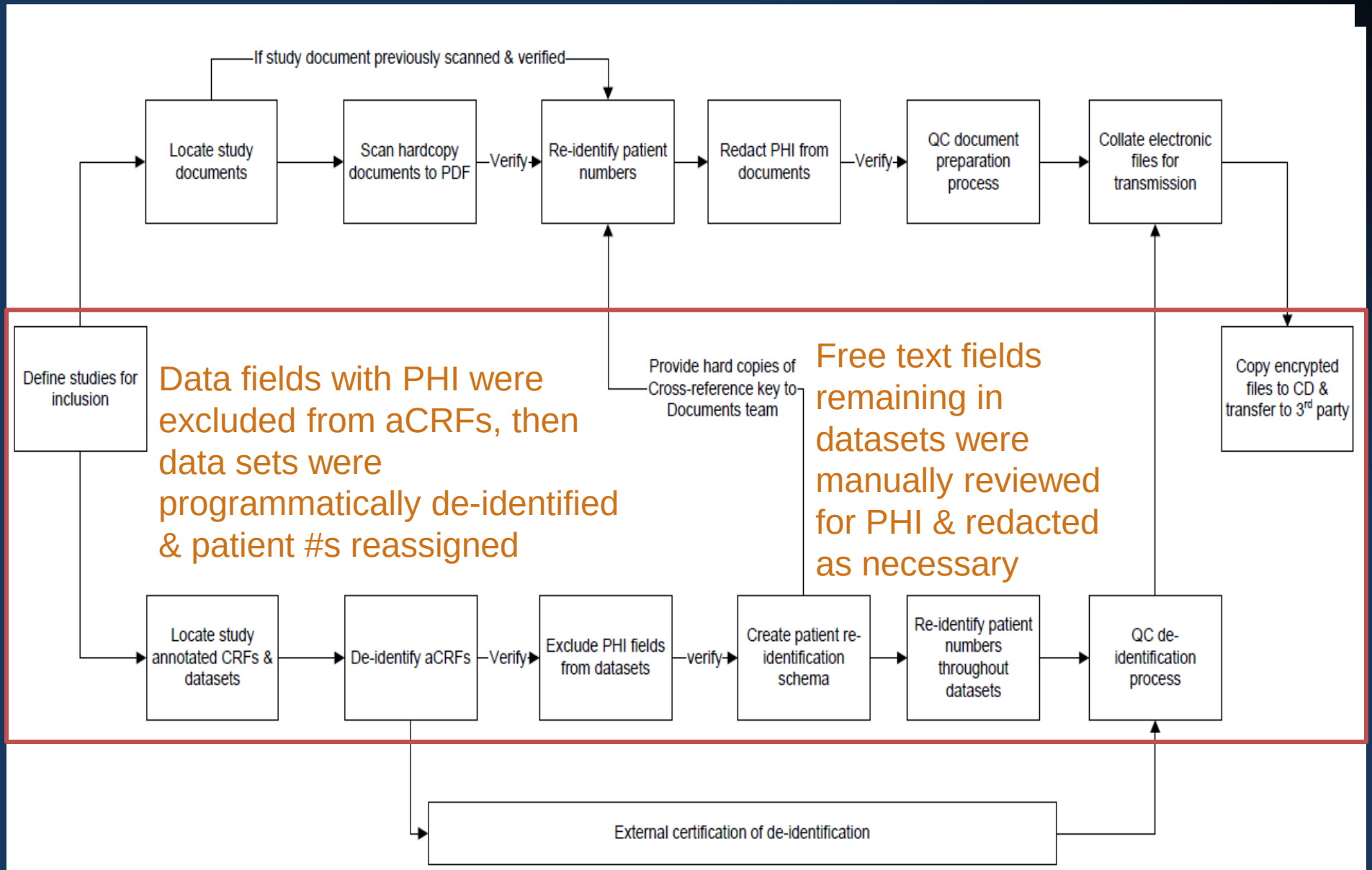
De-Identification Guiding Principles

- Statistical de-identification provision of HIPAA privacy rule was utilized.
  - A qualified statistician with appropriate knowledge of, and experience with, generally accepted statistical and scientific principles and methods for rendering information not individually identifiable:
    - Has applied such principles and methods, and determined that the risk is minimal that the information that could be used, alone or in combination with other reasonably available information, by a recipient of the information to identify the person whose information is being used; and
    - Has documented the methods and results of the analysis that justify such determination

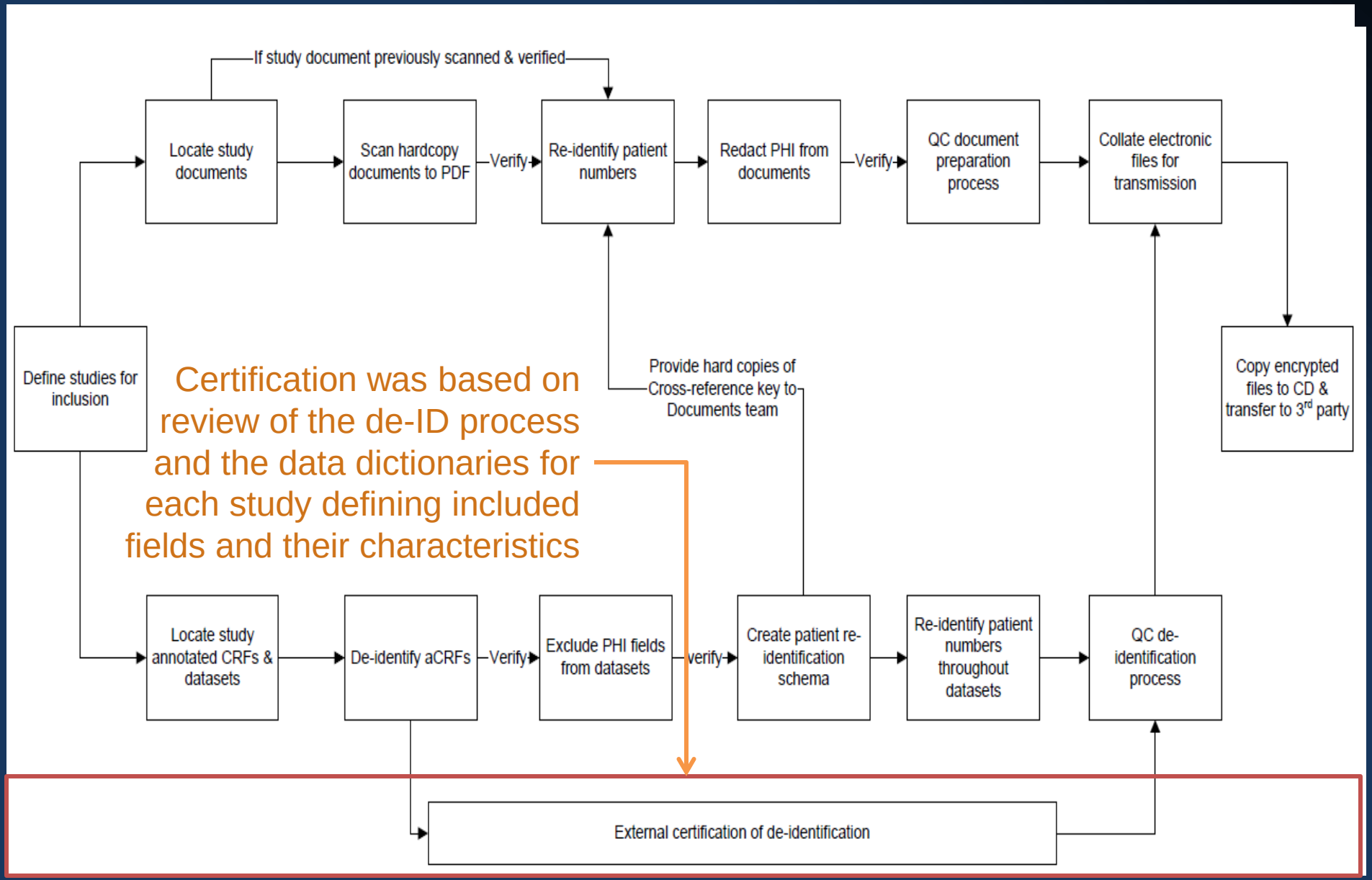
De-Identification Process - Documents



De-Identification Process - Datasets



De-Identification Process - Certification



De-Identification Process - MDRs

- MDR de-identification followed the same principles as the clinical documents & datasets
- MDR summaries and associated forms were reviewed for fields containing PHI
- Fields containing PHI (and MDT employee names & signatures) were electronically redacted
- MDRs did not contain patient numbers therefore reassignment was not applicable

De-Identification Statistical Expert

- Daniel C. Barth-Jones, M.P.H, Ph.D.

President, dEpid/dt Consulting, Inc. d.barth-jones@depiddt.com
and Assistant Professor of Clinical Epidemiology db2431@columbia.edu
Department of Epidemiology
Mailman School of Public Health
Columbia University

- Full de-identification certification provided to Yale

  File name: Medtronic_rhBMP-2_I_Stat_De-ident_Determination_9_12_11_Updated 10_10_2011.pdf
- Curriculum Vitae for Dr. Barth-Jones included as Appendix D, pg 397-417
- As a condition of de-identification certification, an addendum to the contract between MDT and Yale was executed on 12Sept2011 to ensure
  1. Yale complies with conditions of de-identification set by Dr. Barth-Jones
  2. Yale maintains statistical de-identification if they add any info or links to the data
  3. Users of the data would not attempt to re-identify the patients
  4. Yale will implement & maintain data security

Transparency Concerns: From Medtronic (1)

- Query
  - Who is asking the question and why?
    - Is there interest in the truth?
  - What is the question?
    - Does it serve the public, or perverse special interest?
  - Should query be limited to 1 question?
  - Should the methods pre-specified?
- Access
  - Should there be an initial time zone of propriety (academic & industry)
  - What level and portion of data is requested?
  - Should there be a time limit or license for data access?
  - Who controls data distribution?
- Methods
  - Are there *a priori* questions and hypotheses to be tested?
  - Is there interest in data exploration?
    - How to control multiplicity (Type I error)?

Transparency Concerns: From Medtronic (2)

- Analysis
  - Is the requester competent to do analysis?
    - Should a trusted 3rd party analytic center be contracted
  - Should the analytic methods used be transparent to the public?
- Secondary Data Sharing
  - May the requester share the data?
    - Should data be licensed?
- Dissemination of the Results
  - Should there be controls on results dissemination?
    - Unfettered dissemination
    - Dissemination only after peer-review publication
    - Full methodological review by dispassionate competent reviewer, contracted with data center, before dissemination
  - Attest to historical record of analyses performed?

Clinical Research Roles and Responsibilities Medtronic Concerns

- Industry Role:
  - Regulatory compliance
  - Ethical and competent contracting or execution of required clinical studies
  - Competent and timely filing of the data and results dossier
  - If approved, limited on-label promotion
  - Post-market studies and surveillance when required
  - Academic publications: methods/results, methodology
- Academia, Principal and Co-Investigators
  - Protocol oversight, lead steering committee and DSMB
  - Writing and peer-review publication
  - Free to discuss any results if not sponsored by industry
- Cross-roles and responsibilities
  - Peer-reviewed literature