Welcome!

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Demystifying Cancer Clinical Trials

Clinical Trial Oversight

March 24, 2017

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Neely Center for Clinical Cancer Research

Elizabeth Grimm, JD, CHRC

Supervisor, Cancer Clinical Trials
Neely Center for Clinical Cancer Research
Tufts Medical Center

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Neely Center for Clinical Cancer Research (NCCCR)

- Cancer Center's clinical trials office
- Main offices are in South 7.

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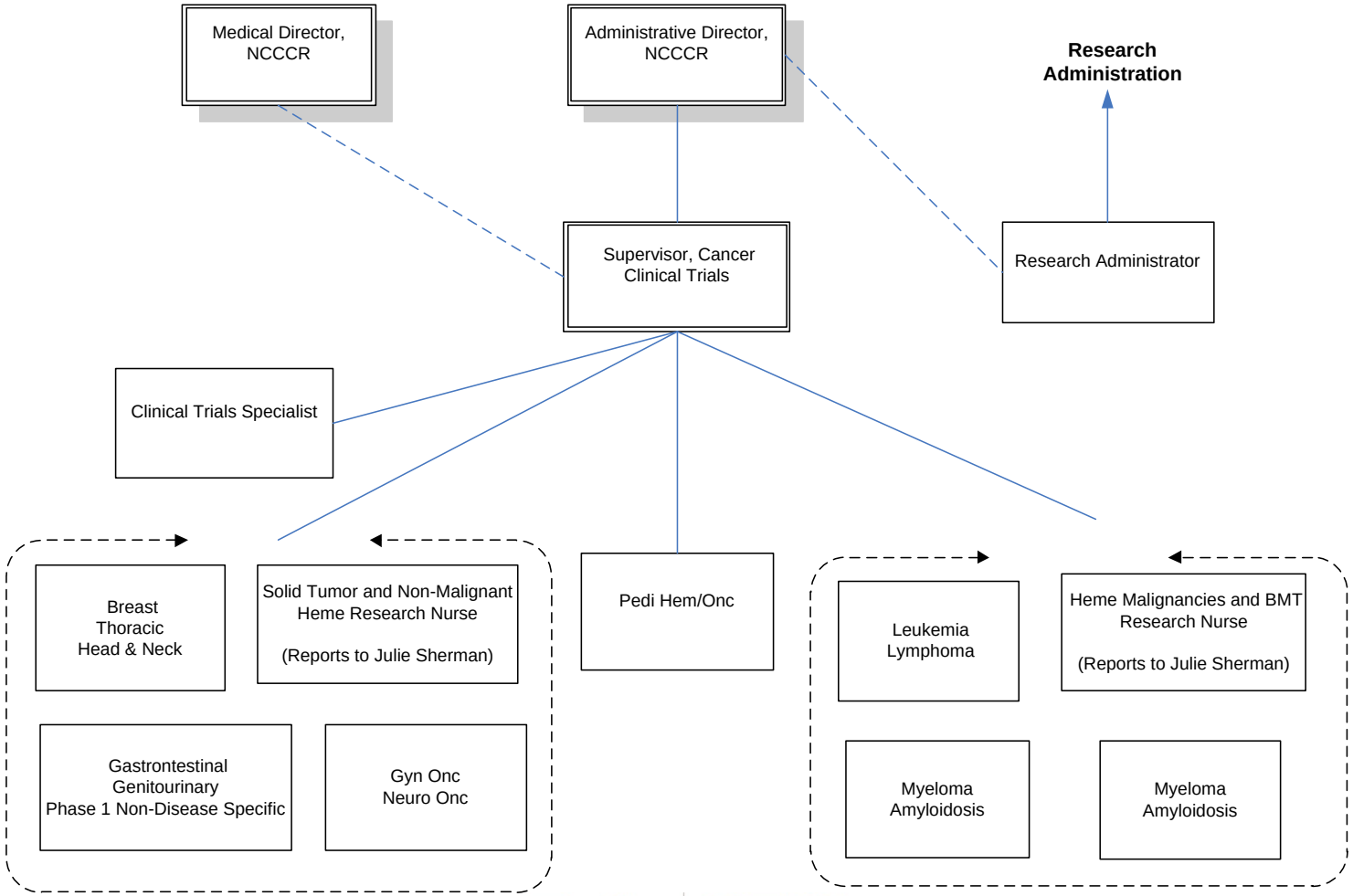
Office Structure

Neely Center for Clinical Cancer Research



NCCCR Involvement in Studies

- Collaborations at various levels:
  - Track subjects enrolled (*e.g.*, prospective blood collection and analysis)
  - Assistance with IRB work, but the actual research (*e.g.*, chart reviews) is done by someone else

- Bulk of our work is “cradle to grave” support for clinical cancer interventional trials.

IRB Approval

- IRB submissions including:
  - Initial submissions
  - Continuing reviews
  - Amendments
  - Unanticipated problems

- Multiple IRBs may be used

- HIPAA waivers for screening so patient records can be reviewed for “pre-screening” purposes.

Finding Subjects

- Pre-screen patients, including:
  - Review at tumor board
  - Regular team meetings to discuss next week's clinic patients
- Consent, screen, register patients, including:
  - Non-English speaking
  - Impaired decision making capacity, and
  - Children.

Study Activity

- Coordinate study visits, including
  - Ensure procedures are done within window
  - All results are recorded on source documentation
  - Process and ship blood, urine, and tumor tissue

- Attend regular team meetings
  - discuss the coming week's patients, and
  - if any are on study, remind team of required study procedures.

Interactions with the Sponsor

- Sponsor reporting – data, adverse events
  - Some reports are time sensitive
  - Some data entry has cut-offs for planned interim analysis

- Monitoring visits
  - Scheduling
  - Managing the monitor on-site, and
  - Responding to queries in real-time.

Administrative Support

- Coordinate PRMC and Cancer Center SRC
- Compassionate use/emergency use
  - IRB and FDA filings are required even though this is not technically considered “research” per 45 CFR 46
- Renew annual NCI investigator registration
- Maintain up to date CVs, licenses, and training for all doctors.

Store all the Paperwork

This is a stack of safety reports from a single study with an FDA approved agent.

We received more reports after this picture was taken.

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Audit Support

- Support in the event of an audit from:
  - Internal offices (*e.g.*, local IRB)
  - Sponsor
  - Cooperative group (*e.g.*, ECOG-ACRIN)
  - Government agencies (*e.g.*, FDA)

Multi-Center Trial Support

- Multi-center clinical trial coordination through Tufts Community Cancer Coordinating Program managed by Livia Gjylameti, including:
  - Collect regulatory documents from all sites
  - Train and activate sites
  - Monitor data and issue queries
  - On-site or remote monitoring plan based on the study
- Multi-center trials require additional support and planning.

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Questions?

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Multi-Center Clinical Trials

Karen Freund, MD, MPH

Director KL2 CTSI
Vice Chair, Department of Medicine

Susan Parsons, MD, MRP

Founding Director, Reid R. Sacco Adolescent and Young Adult Program for Cancer and Hereditary Blood Diseases
Director, The Center for Health Solutions at the Institute for Clinical Research and Health Policy Studies
Professor, Tufts University School of Medicine

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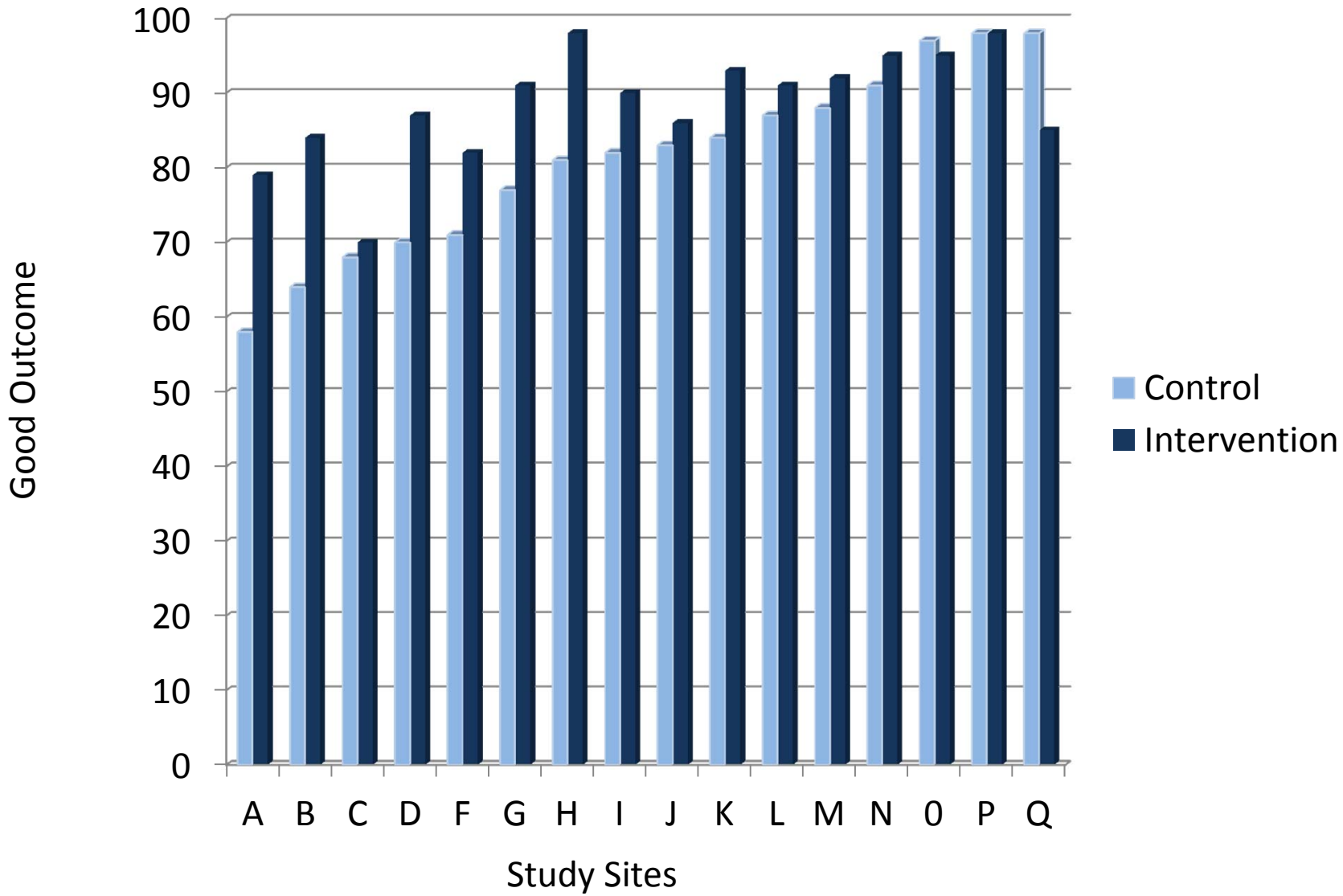
Making Multi- Site Trials Work

- Oversight (site selection, initiation, closeout)
- Data management (collection, online tools)
- Safety reporting and compliance

What is wrong with this picture?



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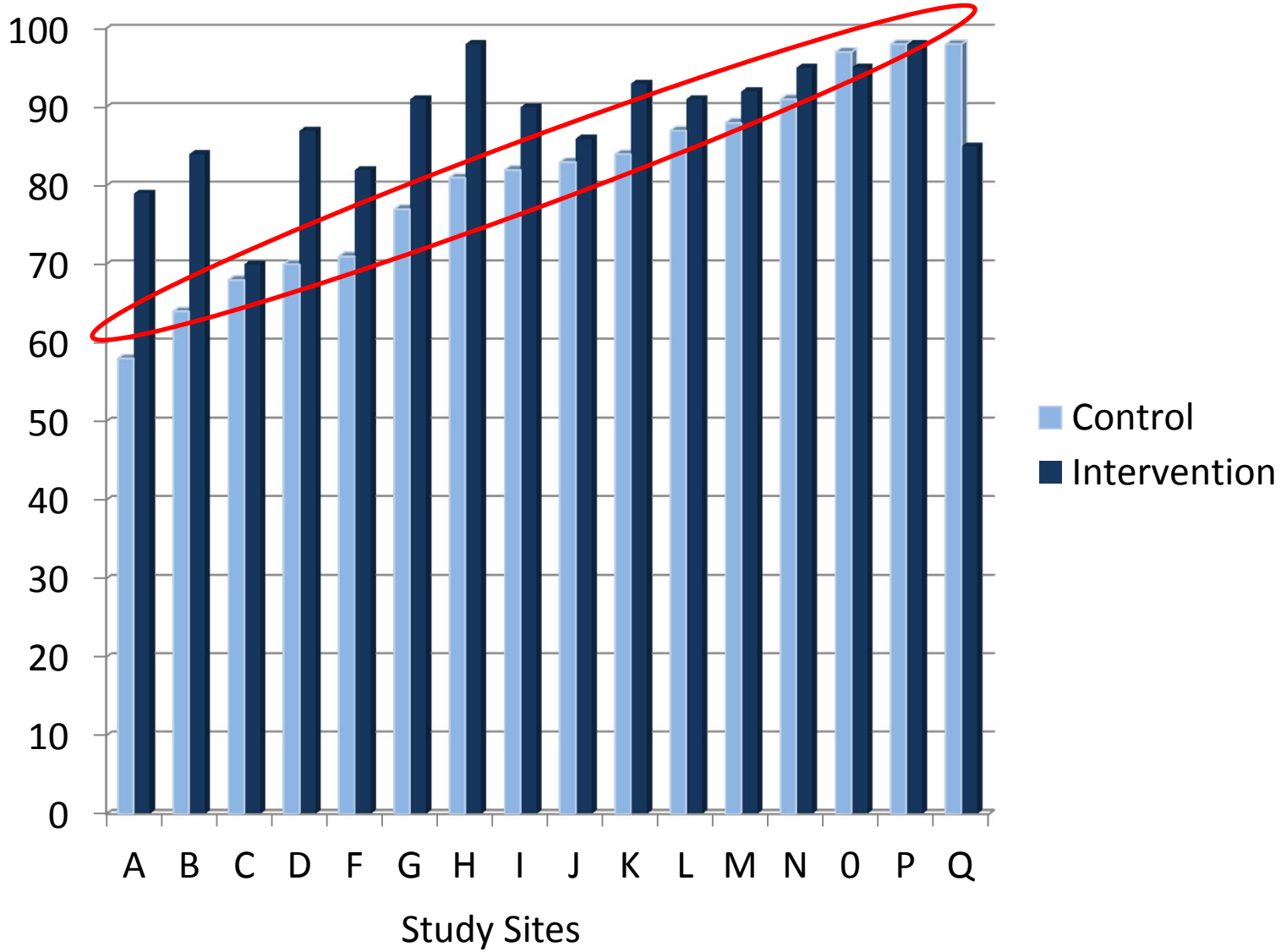

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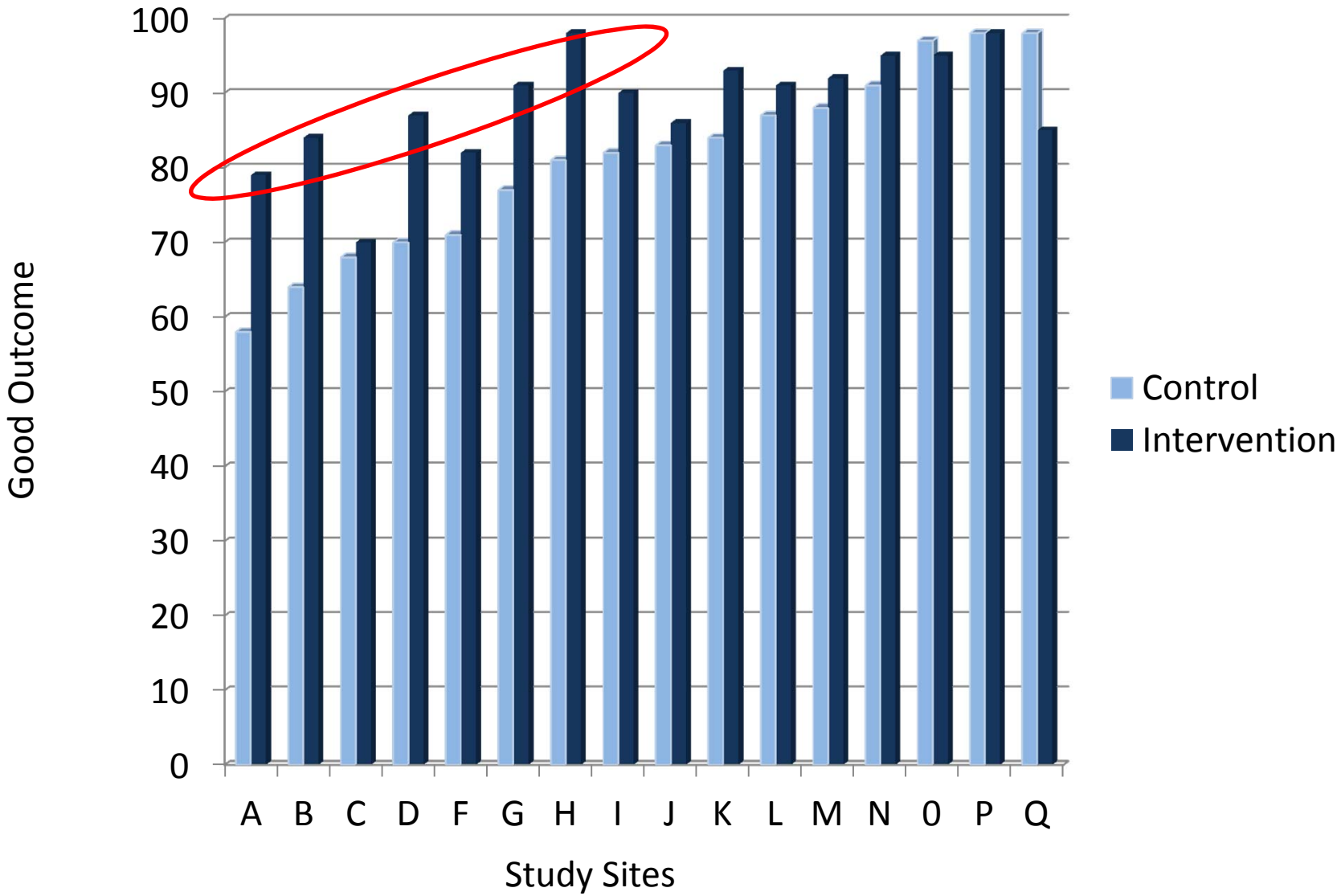

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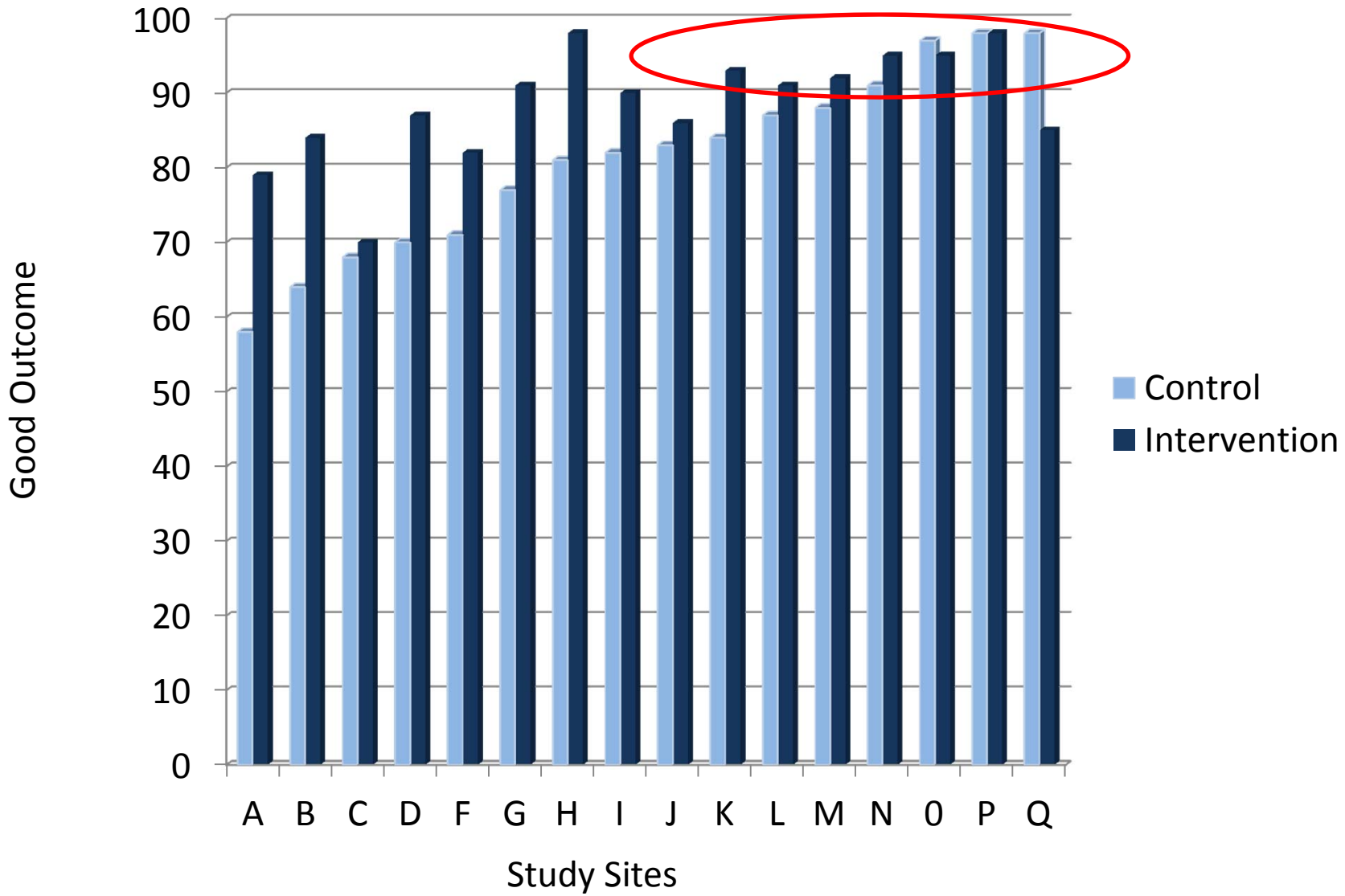

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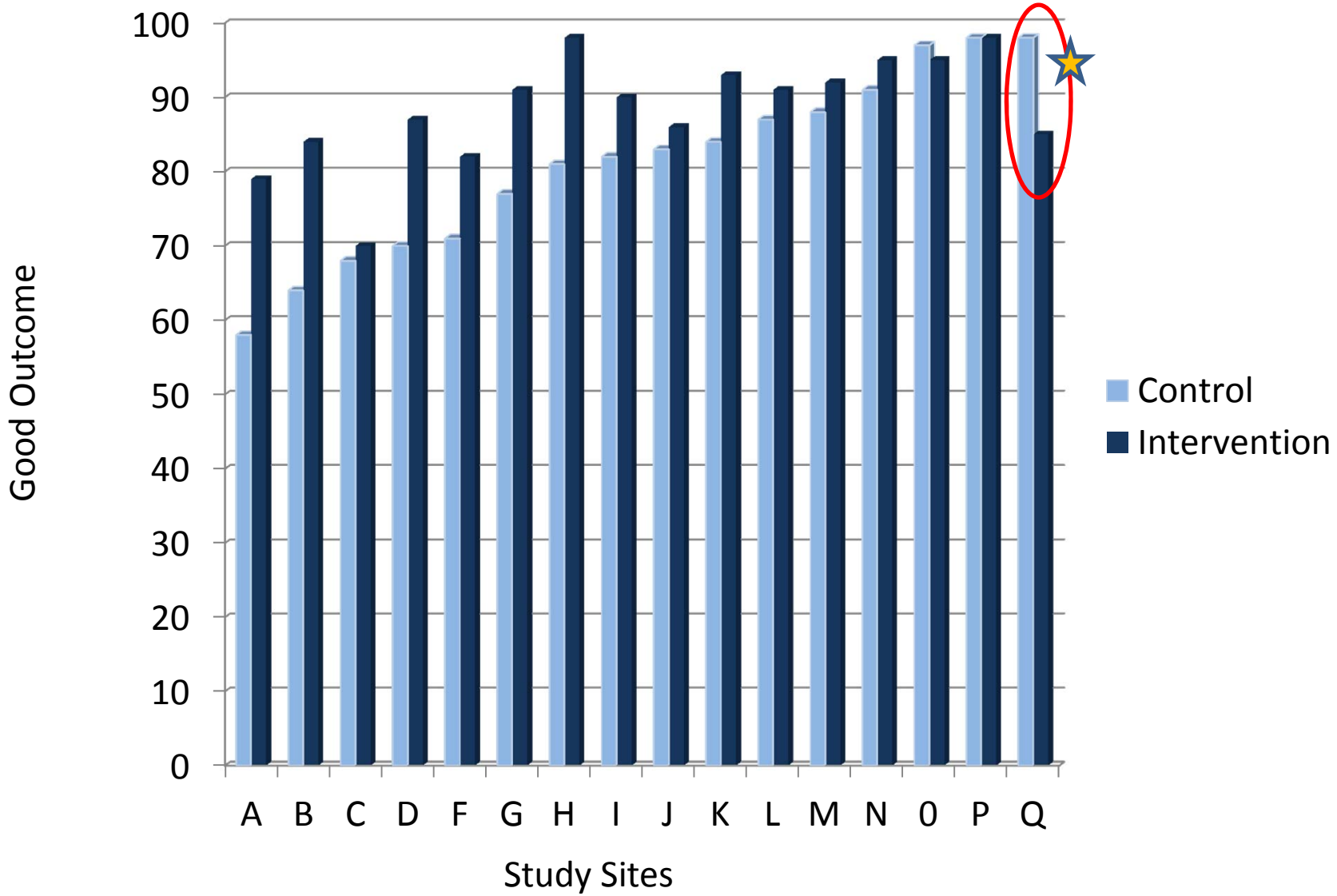
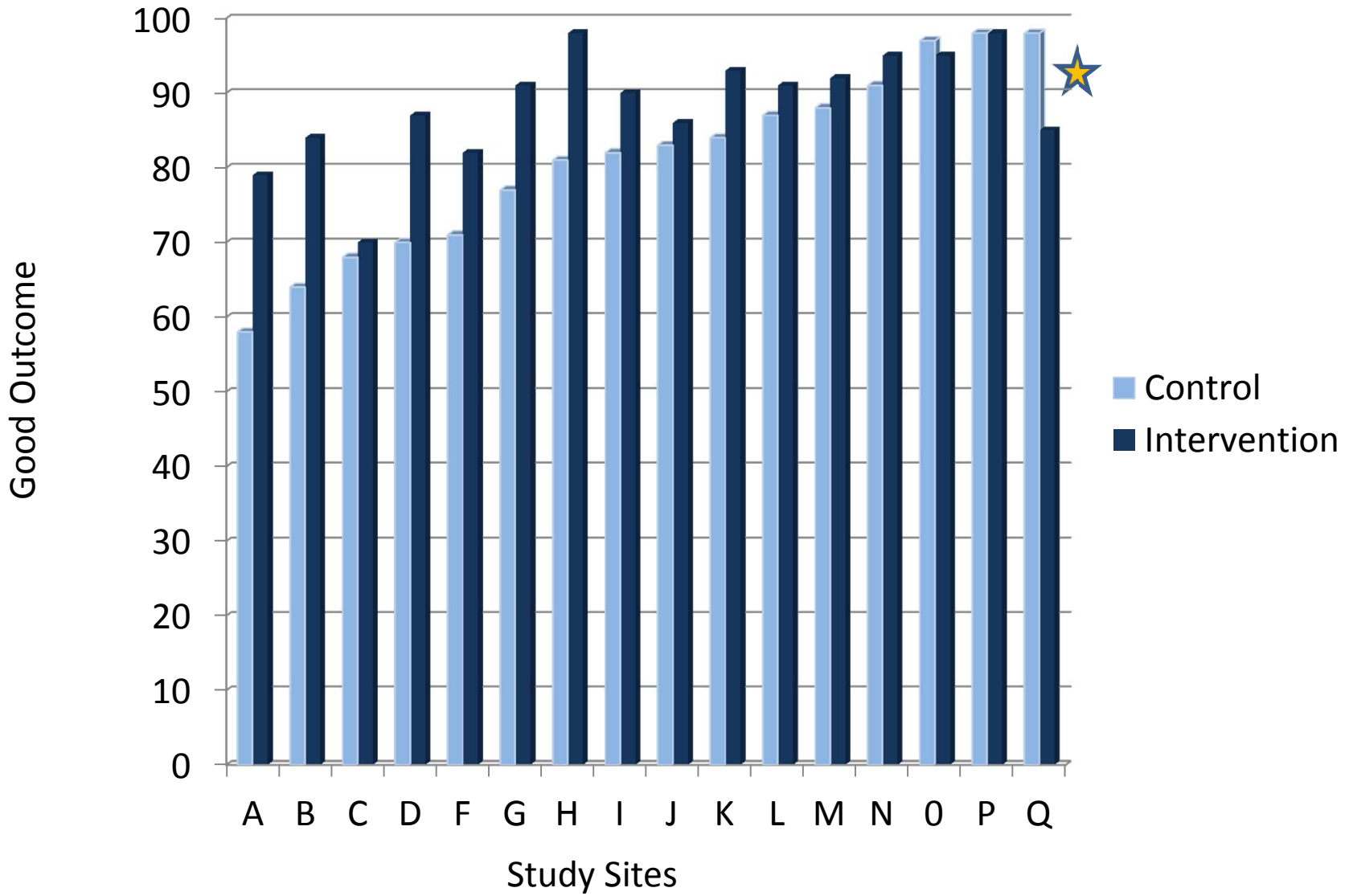
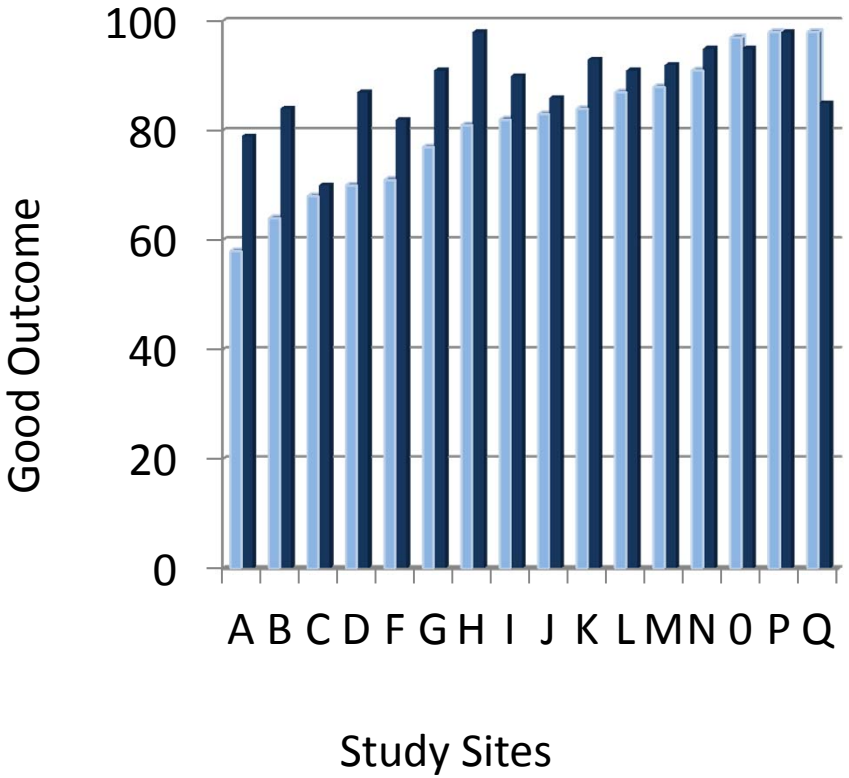


Don’t let this happen to you!



How Could this Happen?



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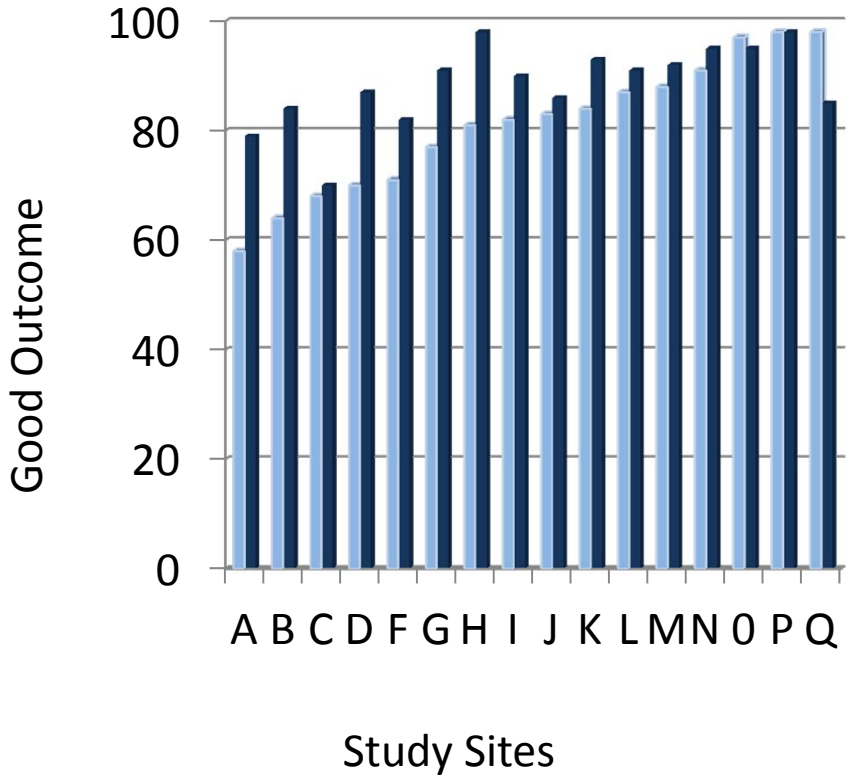
How Could this Happen?



- Inappropriate allocation to intervention or control
- Inconsistent inclusion/ exclusion criteria
- Incomplete/ incorrect outcome assessment

Benefits and Challenges of Multi-site Clinical Trials

Benefits

-
-
-

Challenges

-
-
-

Benefits and Challenges of Multi-site Clinical Trials

Benefits

- Any one site unlikely to have sufficient cases
- Efficiency of recruitment
- Generalizability

Challenges

- Standardization
- Standardization
- Standardization

Site Selection Issues

- Evidence of personnel with expertise in clinical trials
- Evidence of study population
- Prior successful in clinical trial recruitment, adherence, retention
- Champion at the institution

Addressing Challenges in Trial Site Selection

Case: You are 9 months into recruitment, with 10 open sites. You have provided funds to each site for start up, including IRB approval, hiring study personnel

5 sites have enrolled and randomized 2 – 5 patients

2 sites have enrolled 1 patient

3 sites have no enrollement (2 have not completed IRB

What do you do?

Addressing Challenges in Trial Site Selection

- Guidelines for retaining sites
- Potential of back up sites

- At trial meeting, you announce that sites must have 1 patient enrolled within 3 months, or would come off study
- You invite 3 other sites to complete IRB process
- Will require new resources for the start up

Specific Areas of Challenges

- Recruitment
  - Clear eligibility/ exclusion criteria
  - Clear timeframe for enrollment
- Trial Conduct
  - Completion of all data collection
  - Accuracy of data collection
  - Fidelity to the intervention/ control

Addressing Challnege of Trial Enrollment and Conduct

How can you ensure each site following the protocol?

Addressing Challenges of Trial Enrollment and Conduct

How can you ensure each site following the protocol?

- Start up processes – in person meetings to develop consensus on inclusion/ exclusion/ protocol/ measures
- Standard operation procedures – standardized protocol for all locations
- Training – standardized, followed by assessment

Addressing Challenges of Trial Enrollment and Conduct

How can you ensure each site following the protocol?

- On line enrollment forms – real time monitoring for completeness, accuracy, missing fields
- Site visits – review of study documentations, standard operating procedures, observe study processes

Addressing Challenges of Trial Enrollment and Conduct

How can you ensure each site following the protocol?

- Opportunities for discussion / questions
  - Place to pose questions
  - Monthly meeting to adjudicate questions about protocol, measurement, criteria for enrollment
  - Easy access to FAQ

Questions?

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Break!

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Cooperative Group Studies

Susan Parsons, MD, MRP

Founding Director, Reid R. Sacco Adolescent and Young Adult Program for Cancer and Hereditary Blood Diseases
Director, The Center for Health Solutions at the Institute for Clinical Research and Health Policy Studies
Professor, Tufts University School of Medicine

Jack Erban, MD

Clinical Director, Tufts Cancer Center
Medical Director, Neely Center for Clinical Care Research

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Participation in Cooperative Group Research

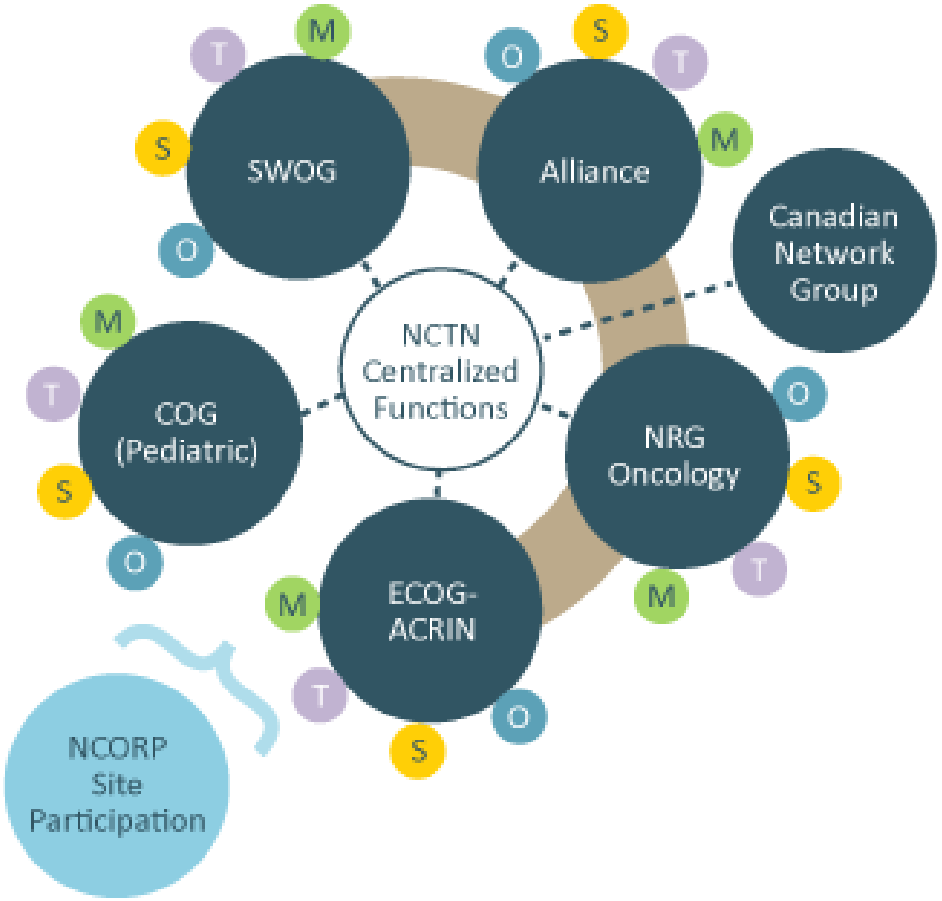
Susan Parsons, MD, MRP

3/24/17

The Landscape

- Nine formerly geographically based adult cooperative groups now consolidated to four:
  - Alliance
  - ECOG-ACRIN
  - NRG Oncology
  - SWOG
- Four pediatric groups now consolidated to one.
  - Children's Oncology Group

NCI National Clinical Trials Network Structure



LEGEND

- Centralized Functions:
  - Centralized Institutional Review Board
  - Cancer Trials Support Unit
  - Imaging and Radiation Oncology Core (IROC) Group
  - Common Data Management System Central Hosting
- 30 Lead Academic Participating Sites (LAPS)
- O — Operations
- S — Statistics & Data Management
- T — Tissue Banks
- M — Member Sites

Types of Participation

- Attend the open annual meeting
- Join a disease group or topical area of interest
  - E.g., Hodgkin Lymphoma, Cancer Control, AYA
- Join a study team
  - Currently leading two embedded studies within an upfront trial
- Lead a trial
- Lead a group or discipline
- Represent the research base at NCI on scientific steering committee

Advantages of Participation

- Establish national collaborations
  - Informational
  - Relational
  - Social
    - Opportunities for leadership and professional networking
- Access to patients, specimens, and outcomes from broad geographic reach

Disadvantages

- Lots of cooks in the kitchen
  - Unspoken queue: Whose turn is it?
- Process can be slow
- Can be political at every level
- May not provide sufficient resources to do every type of study: supplemental funding may be required

AHOD 1331

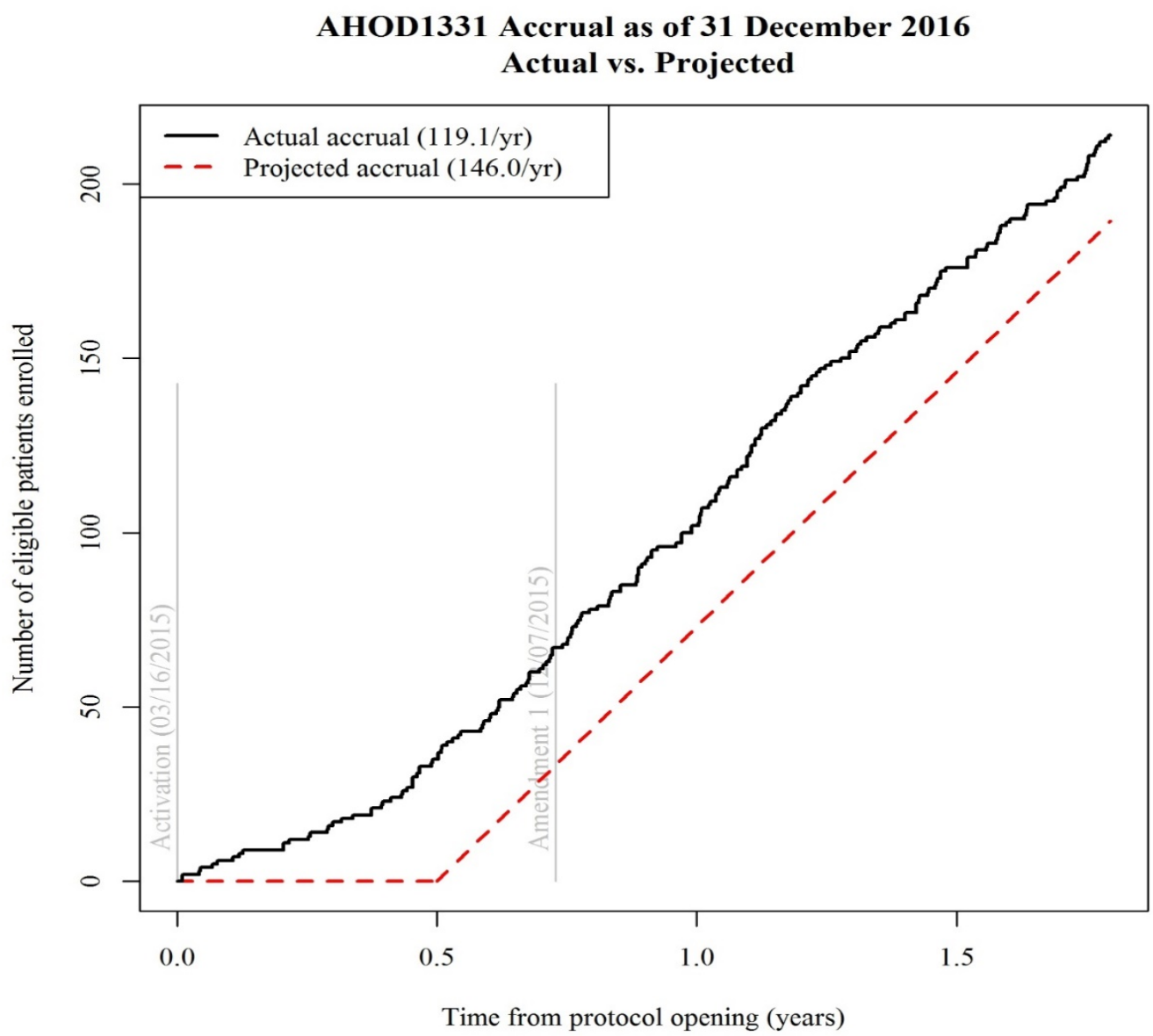
- Phase III RCT comparing the addition of Brentuximab vedotin into the chemotherapy backbone of advanced stage HL in children and young adults
- PET-adapted study: informed use of IFRT
- Bv associated with ↑ peripheral neuropathy
- Bv costs $16,000 per dose (x 5 planned doses)

Embedded Studies

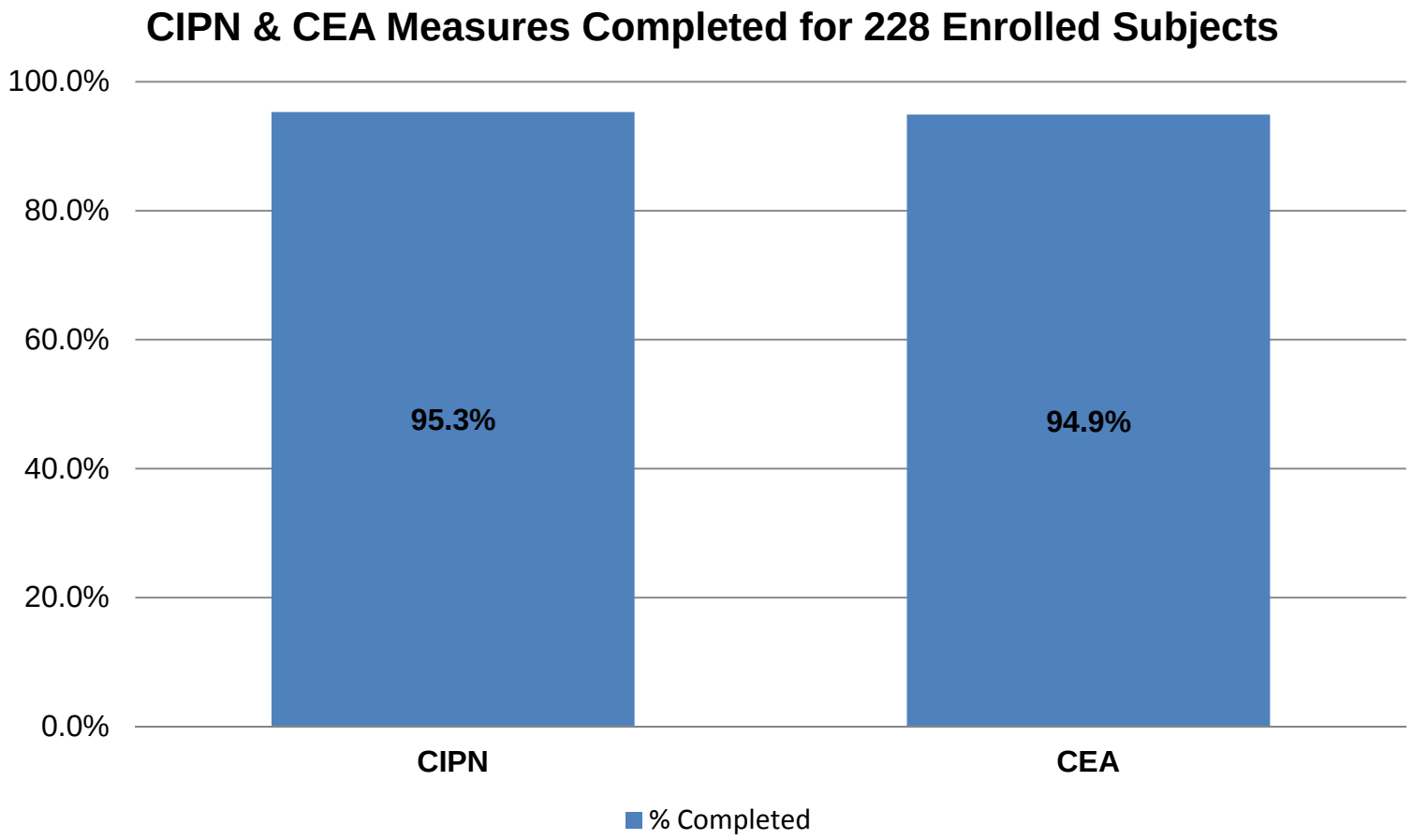
- Describe peripheral neuropathy during treatment and in the 1 and 3 years off treatment
  - Serial assessment of patient- and parent-reported peripheral neuropathy
- Create a cost effectiveness analysis of inclusion of Bv vs. standard care
  - Serial collection of healthcare utilization units
  - Monetize utilization through administrative data bases

Feedback from Council

- Great idea, but…..
- Hard to do either of these studies in cooperative group setting: burden to the sites
- Limited resources (to sites) from COG
- Recommendation: Seek outside support
  - 3-year grant from Leukemia & Lymphoma Society
  - Cancer control credit per enrollee from DCP
  - Project support from Seattle Genetics: CRA and site reimbursement


AHOD1331 Accrual as of 31 December 2016
Actual vs. Projected
Actual accrual (119.1/yr)
Projected accrual (146.0/yr)
Number of eligible patients enrolled
0
50
100
150
200
Activation (03/16/2015)
Amendment 1 (12/07/2015)
0.0
0.5
1.0
1.5
Time from protocol opening (years)

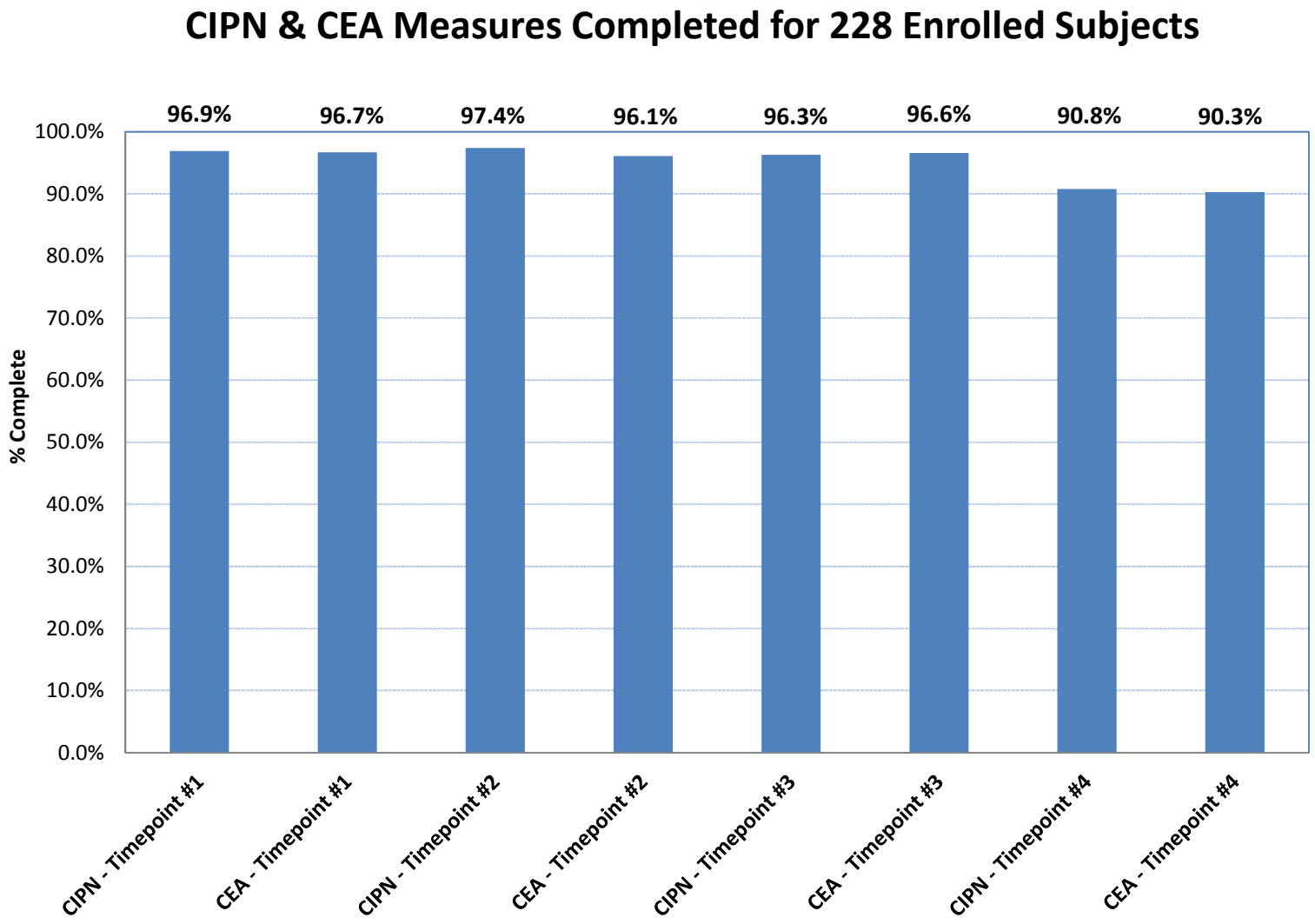
Where we are as of March 17, 2017



CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

Where we are as of March 17, 2017



CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

Follow up Studies

- Analysis of Massachusetts All Payer Claims Data: 2009-2013 to evaluate practice variability by site of care and patient factors
- Three-way collaboration with Kaiser Permanente, Seattle Genetics, and Tufts MC to explore initial and salvage therapy in a “real world” setting
- Pharmacogenomics study to explore genetic polymorphisms associated with peripheral neuropathy after vincristine and Bv, using banked specimens, clinical grading, and PROs.

Strategies for Collaboration in Cooperative Group

- Determine area (s) of interest
- Reach out to disease leaders locally (at Tufts)
- Consider attending annual meeting (young investigator awards generally available)
- Speak with local leaders about how to join project or protocol
- Be persistent! It can take a while.

Questions?

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Thank You

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Data Management Tools

Robin Ruthazer, MPH

Assistant Professor of Medicine, Tufts Medical School
Associate Director, Biostatistics, Epidemiology, and Research Design (BERD) Center
Tufts Clinical and Translational Science Institute (CTSI)

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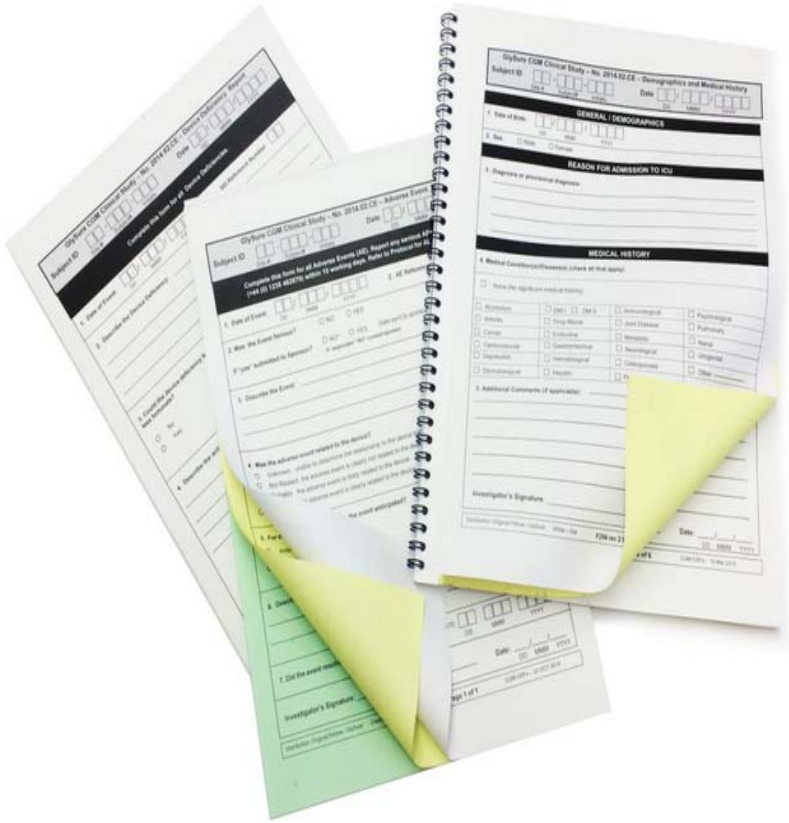
Goals for today's talk

Familiarize you with terminology and concepts that will help you make successful choices when choosing and designing data collection/management systems for your clinical studies

Introduce you to REDCap
(Research Electronic Data Capture)

A Little History

- Early systems (1970's)
  - Collect data on (NCR*) paper forms
  - Send data to sponsor for data entry into flat file (or other) on mainframe computer
  - Use statistical software to read data and do analysis



Trivia Question: What does NCR stand for?

Figure source: http://www.carbon.co.uk/category/latest-news/page/3/

A Little History

- Some problems with early systems
  - data copied many times leading to errors
  - errors not identified in timely manner
  - delay in ability for sponsors to review, monitor data

In 1980s, 1990s with personal computing, option of ‘remote data entry (RDE) ‘ started. RDE then evolved into electronic data capture (EDC) in the 1990s

EDC today

11Nov2014 *(and still current 16Mar2017)*
http://en.wikipedia.org/wiki/Electronic_data_capture

An **electronic data capture (EDC)** system is a computerized system designed for the collection of clinical data in electronic format for use mainly in human clinical trials. EDC replaces the traditional paper-based data collection methodology to streamline data collection and expedite the time to market for drugs and medical devices. EDC solutions are widely adopted by pharmaceutical companies and clinical research organizations (CRO).

EDC today

11Nov2014 *(and still current 16Mar2017)*
http://en.wikipedia.org/wiki/Electronic_data_capture

Typically, EDC systems provide:

- a graphical user interface component for data entry
- a validation component to check user data
- a reporting tool for analysis of the collected data

EDC today

- Some problems with EDC systems
  - Data may still needed to be entered into multiple systems since integration with electronic medical record (EMR) systems may not work (yet)
  - System setup can be resource intensive
  - There are a lot of EDC vendors and little standardization (*although organizations like Clinical Data Interchange Standards Consortium (CDISC) and others are trying to change this. [www.cdisc.org])*

Types of EDC Systems

- Custom Built (programmers make system for specific project)
- Hire a vendor to build (e.g. Medidata, Oracle InForm)
- 'User' built using software that allows non-programmers to build the system
  - *Open source*
  - *CTSI supported (e.g. REDCap)*
  - *Vendor supplied (e.g. ScienceTRAX)*

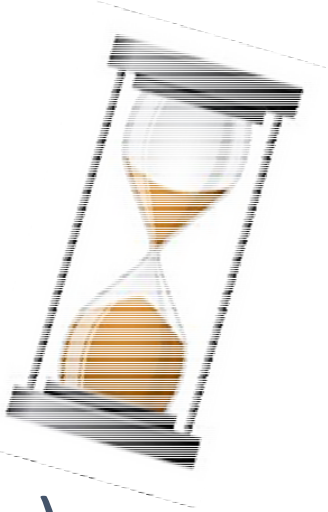
Types of EDC/Data Management Systems:
A hierarchy

System	Cost	Internet	21 CFR Part 11 compliant *	Developer	Relational Structure	Reporting Systems
Medidata Rave+	$$$	Yes	Yes	Company	Yes	Yes
StudyTrax+	$	Yes	Yes	Company or User	Yes	Yes
REDCAP	Free (if CTSI)	Yes	No	User	Yes	Yes
MS-Access	MS Office Pro	No	No	User	Yes	Yes
MS-Excel	MS Office	No	No	User	No	No

***FDA guidelines re: electronic medical records, electronic signatures, audit trails, and security*

+ These systems are discussed as examples because I have used them, not because they are better/worse than others

Building an EDC system

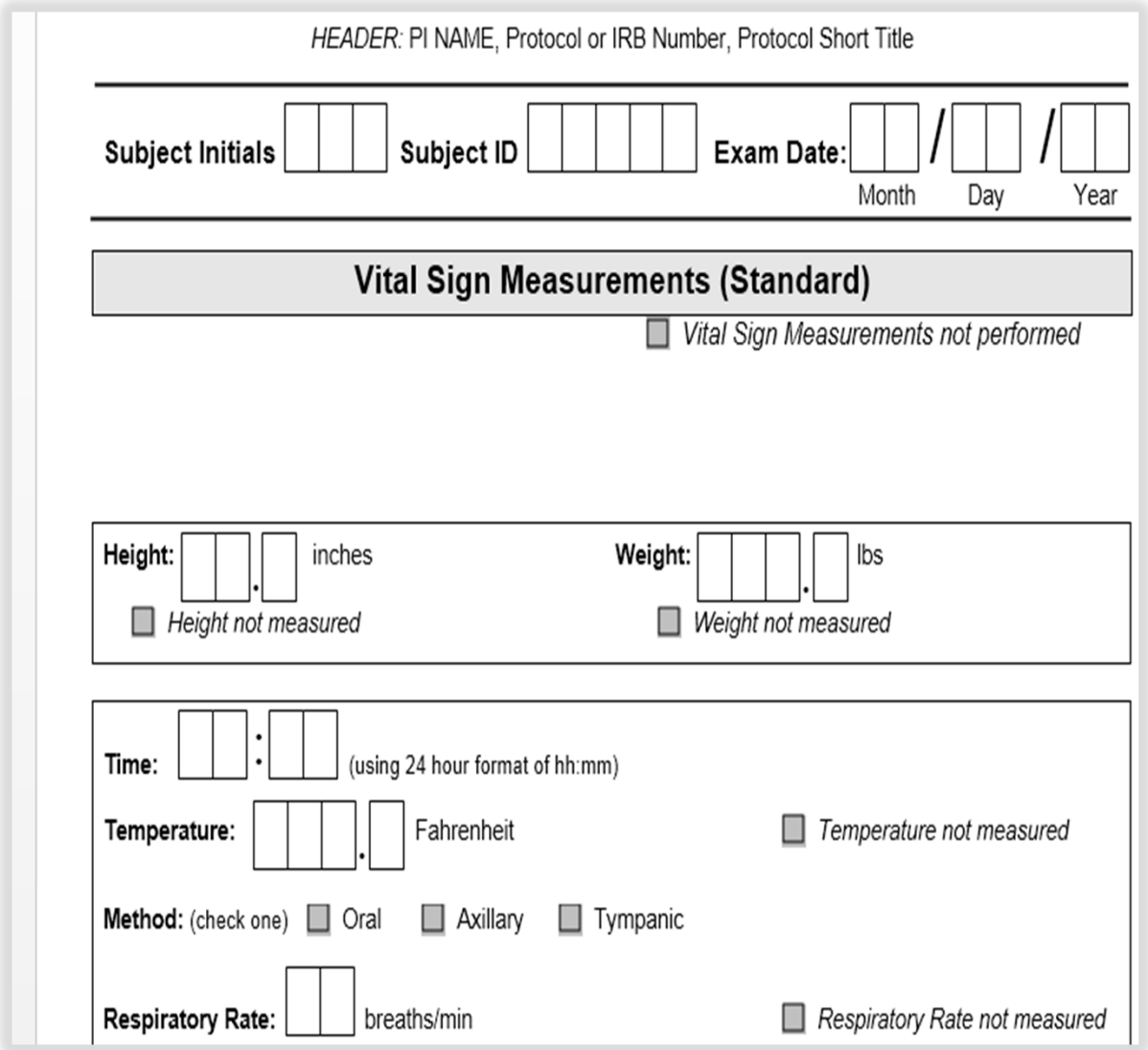


- Data capture forms (what data to collect)
- Variable and fields on each form (attributes)
- Underlying table structure (key fields; long/wide*)
- Data Quality (data checks, skip patterns)
- User Roles/Access
- System Utilities (reporting)
- Analysis datasets (structure of exported data)
- Other Considerations *(user interface, security, audit, backups…)*

** Examples shown on next couple of slides*

Building an EDC system

Example of Case Report Form (CRF) "Wide" vs. "Long"



HEADER: PI NAME, Protocol or IRB Number, Protocol Short Title

Subject Initials ☐☐☐ **Subject ID** ☐☐☐☐☐ **Exam Date:** ☐☐ / ☐☐ / ☐☐
Month Day Year

Vital Sign Measurements (Standard)

☐ *Vital Sign Measurements not performed*

Height: ☐☐.☐ inches ☐ *Height not measured*

Weight: ☐☐☐.☐ lbs ☐ *Weight not measured*

Time: ☐☐:☐☐ (using 24 hour format of hh:mm)

Temperature: ☐☐☐.☐ Fahrenheit ☐ *Temperature not measured*

Method: (check one) ☐ Oral ☐ Axillary ☐ Tympanic

Respiratory Rate: ☐☐ breaths/min ☐ *Respiratory Rate not measured*

Web site with sample forms:
https://ictr.wisc.edu/clinical-research-toolkit/case-report-form-templates/

Building an EDC system

Example of Dataset/Table: “Wide” vs. “Long”

Subject ID	Exam data (mm/dd/yy)	Vital signs not done : 1=not done	height in inches	height not done : 1=not done	weight in pounds	weight not done: 1=not done	exam time (mm:ss) 24 hour	temp-erature (farenheit)	temp method 1=oral, 2=axillary, 3=tympanic	temp not done: 1=not done
SID	EX_Date	VSM_ND	HT_IN	HT_ND	WT_LBS	WT_ND	EX_TIME	TEMP	TEMP_METH	TEMP_ND
1	7/1/2017		70		170		13:10	98.2	1	
2	7/1/2017	1								
3	7/3/2017		64			1	10:45	99	1	

REDCAP

"REDCap is a mature, secure web application for building and managing online surveys and databases. Using REDCap's stream-lined process for rapidly developing projects, you may create and design projects using 1) the online method from your web browser using the Online Designer; and/or 2) the offline method by constructing a 'data dictionary' template file in Microsoft Excel, which can be later uploaded into REDCap. Both surveys and databases (or a mixture of the two) can be built using these methods." *https://collaborate.tuftsctsi.org/redcap/*

REDCAP

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REDCAP

RESEARCH ELECTRONIC DATA CAPTURE

Getting Started

Title	Description	Watch Video
Brief Overview	A quick summary of what REDCap is and what it can do.	4 minutes
Detailed Overview	This video provides an overview of basic functions and features within a REDCap project. It will serve as a starting point for learning about the basic concepts of REDCap, what REDCap projects are, how to create them, and how to use them.	14 minutes
Data Entry Overview	A focused exploration of basic data entry workflow. Suitable for training data entry staff.	16 minutes

There are a lot of other training videos too

REDCAP

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REDCAP

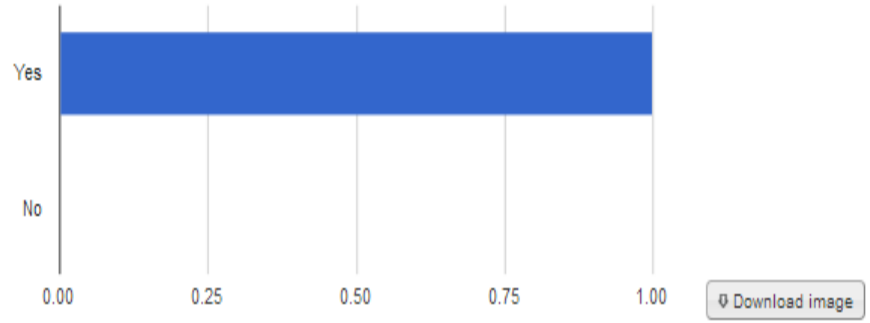
RESEARCH ELECTRONIC DATA CAPTURE

Finishing up – Exporting data, Reviewing reports

Have you used services provided by the Tufts CTSI BERD (Biostatistics, Epidemiology, and Research Design Center) in the past 6 months? Refresh Plot | View as Bar Chart

Total Count (N)	Missing	Unique
1	1 (50.0%)	1

Counts/frequency: Yes (1, 100.0%), No (0, 0.0%)



Exporting "All data (all records and fields)"

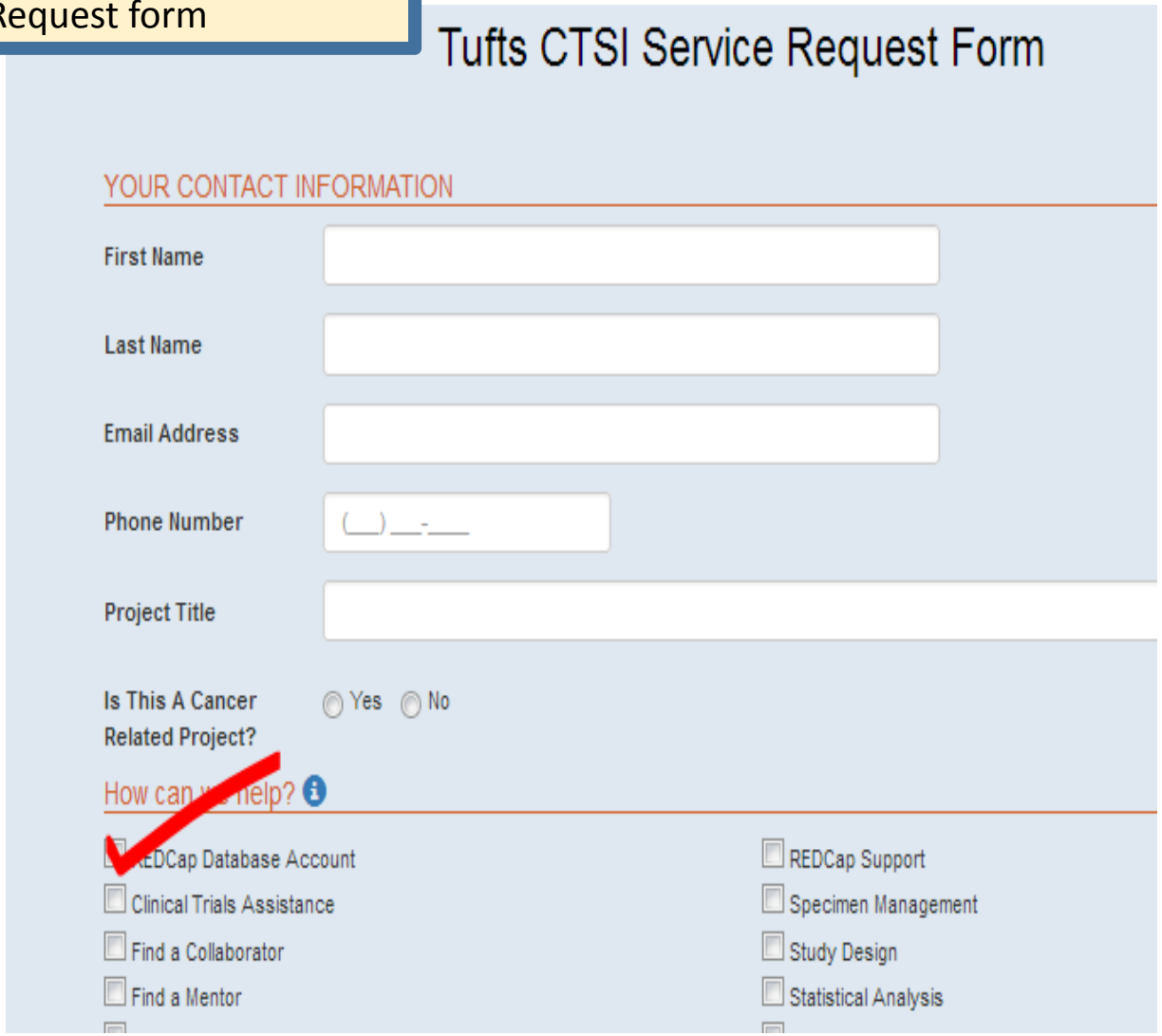
Select your export settings, which includes the export format (Excel set.

Choose export format

- CSV / Microsoft Excel (raw data)
- CSV / Microsoft Excel (labels)
- SPSS Statistical Software
- SAS Statistical Software
- R Statistical Software
- Stata Statistical Software
- CDISC ODM (XML)

How to get a REDCAP account

1. https://informatics.tuftsctsi.org/pims/request.htm#/
2. "Google" Tufts CTSI Service Request form



Other help:
BERD Drop-ins
Wednesday
morning 8am-9am
10th floor of 35
Kneeland Street

Other resources

- Slides from Society for Clinical Trials 24th Annual Meeting Workshop P5: “In-House vs. Open Source Electronic Data Capture (EDC) Software for Clinical Research – Build or Buy? May, 2013

http://www.sctweb.org/public/meetings/2013/slides/Workshop%20P5.pdf

Questions?

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Thank You

Email: RRuthazer@TuftsMedicalCenter.org
Telephone: 617-636-8819
Office: 35 Kneeland Street, 10th floor

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Panel Discussion

Andy Evans, DO, MSc

Andreas Klein, MD

Robert Martell, MD, PhD

Susan Parsons, MD

Wasif Saif, MD

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Demystifying Cancer Clinical Trials: Conclusion

Andrew Evans, DO, MSc

Director, Tufts Cancer Center
Chief, Division of Hematology/Oncology
Director, Lymphoma Program
Professor, Tufts University School of Medicine

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