ECHO
Environmental influences on Child Health Outcomes
A program supported by the NIH

IDeA States Pediatric Clinical Trials Network

Managing a Multicenter RCT Lessons Learned

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Learning Objectives

- Understand the roles and responsibilities of research protocol chairs
- Review ways to enhance collaboration between research protocol chairs, the study team, and site research teams
- Identify ways to project and mitigate risk throughout the development, implementation, and conduct of a multicenter clinical trial
- Review lessons learned by protocol chairs after the development, implementation, and conduct of a multicenter clinical trial

Disclosures

- Nothing to disclose

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Roles and Responsibilities of Research Protocol Chairs

Study Development

- Develop a research protocol
  - Time intensive
  - Multiple revisions will be needed
  - Protocol must convey a clear and complete account of how the study will be implemented
- Submit and resubmit the protocol for review and approval
  - Full study team
  - Protocol review committee (PRC)
  - Data safety monitor committee (DSMC)
  - IRB

Study Development

- Oversee the development of:
  - The manual(s) of operation (MOP)
  - Case report forms and other study materials
  - The informed consent document(s)
  - All participant facing study related materials
  - All educational materials for the research sites
- Finalize a budget
- Oversee the selection of study sites

Study Implementation

- Work with the data coordinating center(s) to train and certify research coordinators and site primary investigators in the implementation of the study
- Typically, this is accomplished with a 2-day onsite meeting where the study team reviews:
  - Protocol
  - Manual of Operations (MOP)
  - Case report forms (CRFs)
  - Electronic Data Entry (EDC)

Study Implementation

- Training typically includes a discussion of:
  - Eligibility criteria
  - The randomization process
  - Consent, recruitment, and retention strategies
  - The system for the distribution of centrally ordered materials
  - Data entry procedures
  - May also include:
    - Use of required equipment and/or drugs
    - Specimen or test result shipping procedures
    - Pharmacy set-up

Study Conduct

- Participation in frequent coordinator teleconferences which
  - Unify communication across study sites
  - Provide clarity for study definitions
  - Facilitate discussion of coordinator questions and issues
  - Communicate MOP and protocol changes
  - Help sites identify ways to maximize recruitment and retention
- Answer questions and address concerns from the research study sites, study team, and the NIH

Dissemination of Study Results

- Organize the writing team for the primary manuscript
  - Work with the DCC to develop clear expectations for authorship prior to study initiation
  - Communicate expectations for authorship with participating sites
  - Present study findings and encourage confidentiality of study findings
- Develop table/figure shells for the statistician
- Write abstract and develop research presentation(s) for the primary outcomes for the study

Dissemination of Primary Study Results

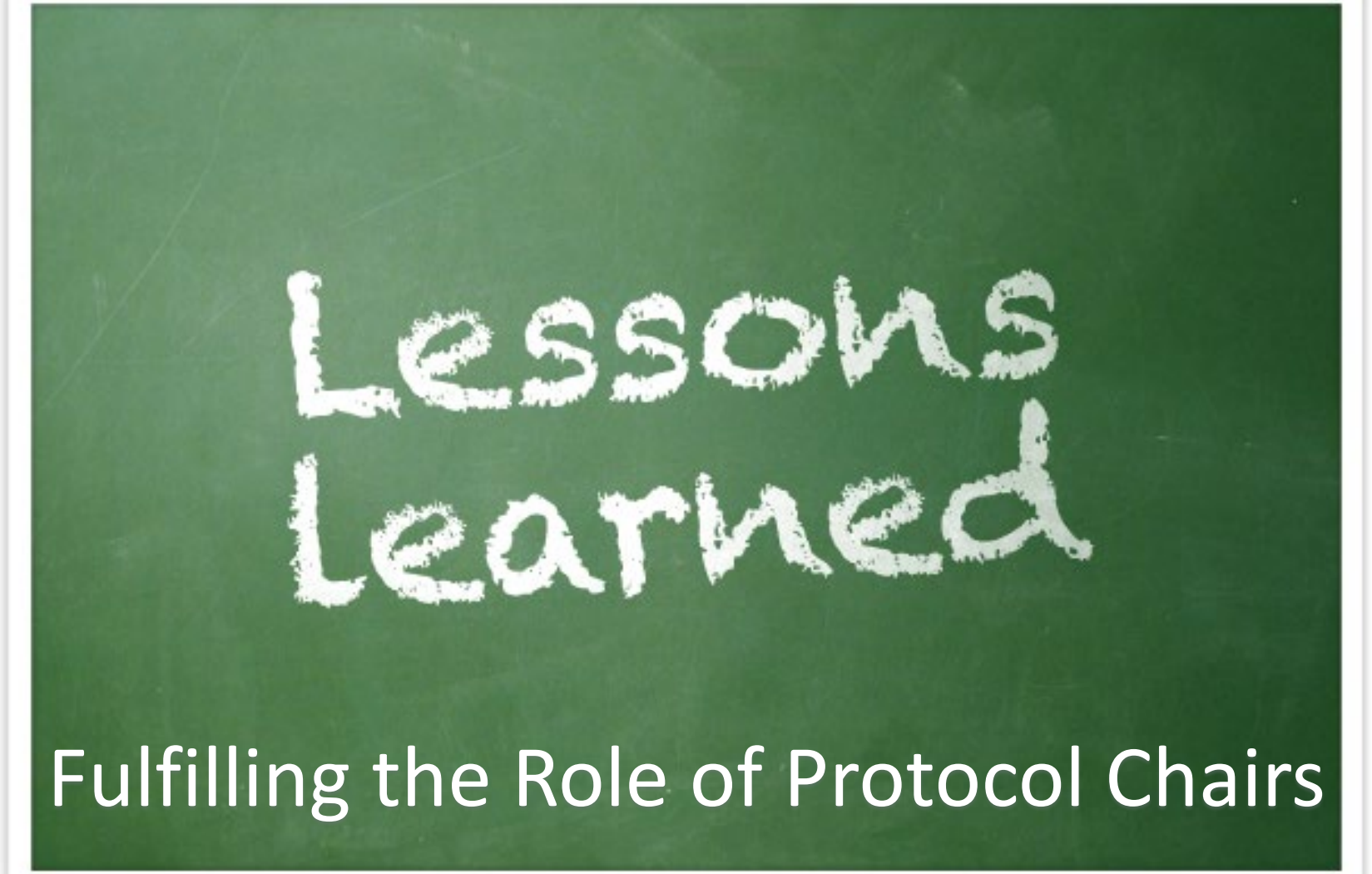
- The Primary Research Manuscript
  - Write the first draft of the manuscript
  - Integrate critical reviews from the writing team into the final manuscript
  - Submit the manuscript to the preferred journal
    - Typically serve as the corresponding author
    - Respond to reviewers' comments and update the manuscript
    - Resubmitting the manuscript
    - If the manuscript is not accepted by the preferred journal - repeat
- Work with public relations for press release, talking points, etc.

Facilitating the Return of Results

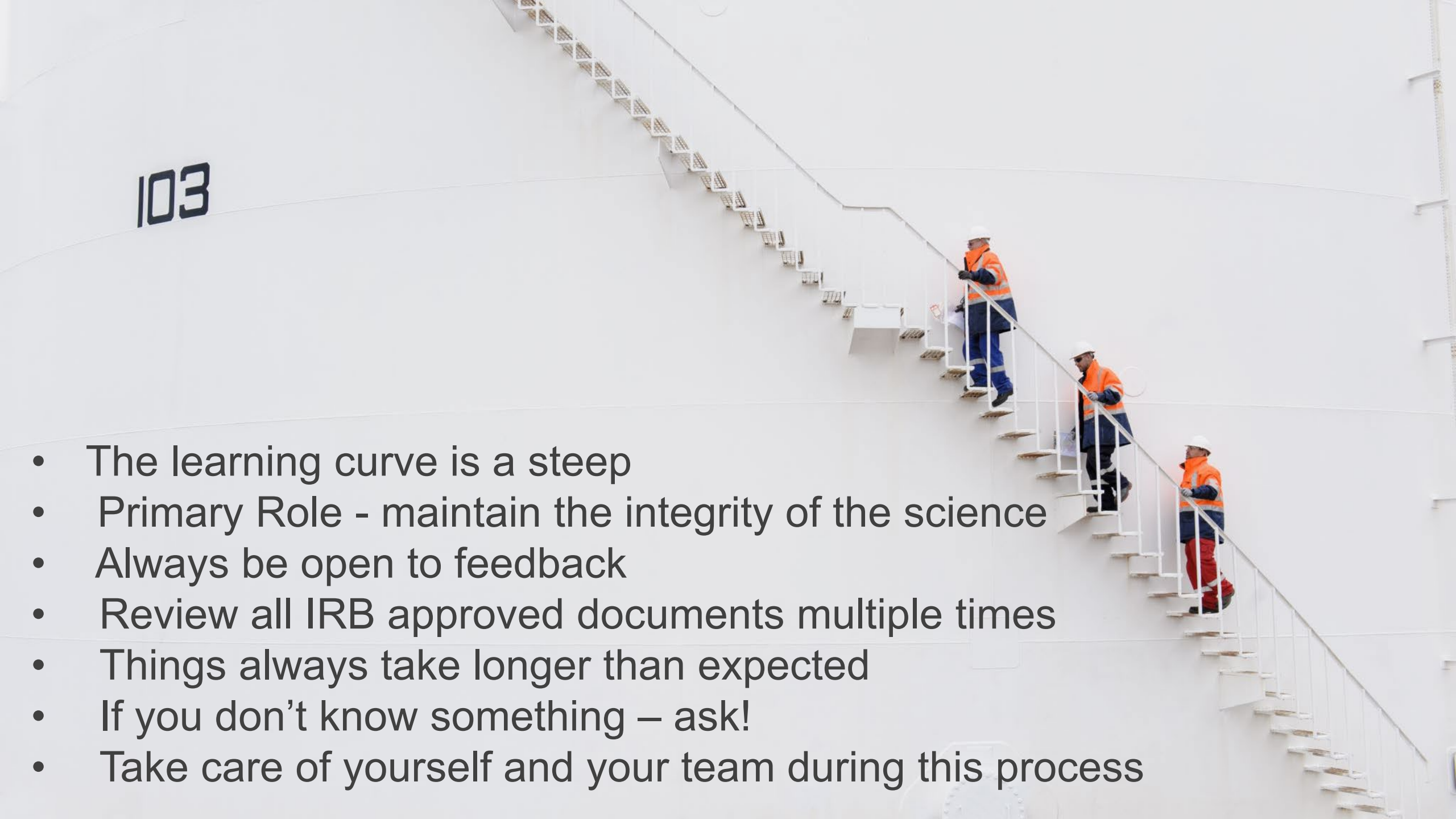
- Providing results back to the research teams and study participants and thank them for their participation
- Dissemination of results to medical providers and other stake holders to inform clinical care

Dissemination of Secondary Study Results

- Presentation and support of abstracts and manuscripts
  - Lead or participate on the writing team
  - Coordinate or participate in critical reviews from the writing team
  - If primary author, submit the manuscript to the journal
    - Primary author typically serves as the corresponding author
    - Respond to reviewers' comments and updates the manuscript or support the process
    - Primary author resubmits the updated manuscript
    - If the manuscript is not accepted by the preferred journal - repeat



Fulfilling the Role of Protocol Chairs



- The learning curve is a steep
- Primary Role - maintain the integrity of the science
- Always be open to feedback
- Review all IRB approved documents multiple times
- Things always take longer than expected
- If you don’t know something – ask!
- Take care of yourself and your team during this process

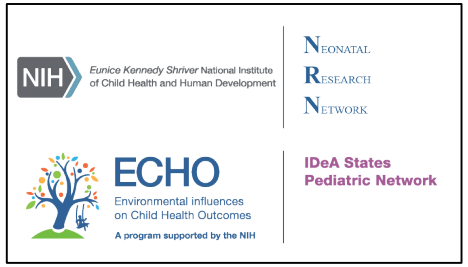
Collaborating with Your Study Team

Team Science

- Across all research fields, teams now produce more frequently cited and higher impact research than individual authors
- Teams are better able to address increasingly complex scientific problems through the application of sophisticated and innovative conceptual and methodologic approaches
- Teams often include collaborators across geographic space and organizational boundaries with expertise that span multiple disciplines and fields
  - Increase the number and magnitude of the challenges a team must navigate

Vogel, AL . *Am J Prev Med*. 2013. https://doi.org/10.1016/j.amepre.2013.09.001

National Institutes of Health



Data Coordinating Centers

RTI International

- EDC System
- NRN site management, contracting

University of Arkansas for Medical Sciences

- Central IRB
- Training
- Statistics

Duke Clinical Research Institute

- ECHO ISPCTN and other site management, contracting

Study Team

Lead Study Investigators

- Leslie Young, University of Vermont
- Lori Devlin, University of Louisville
- Stephanie Merhar, University of Cincinnati

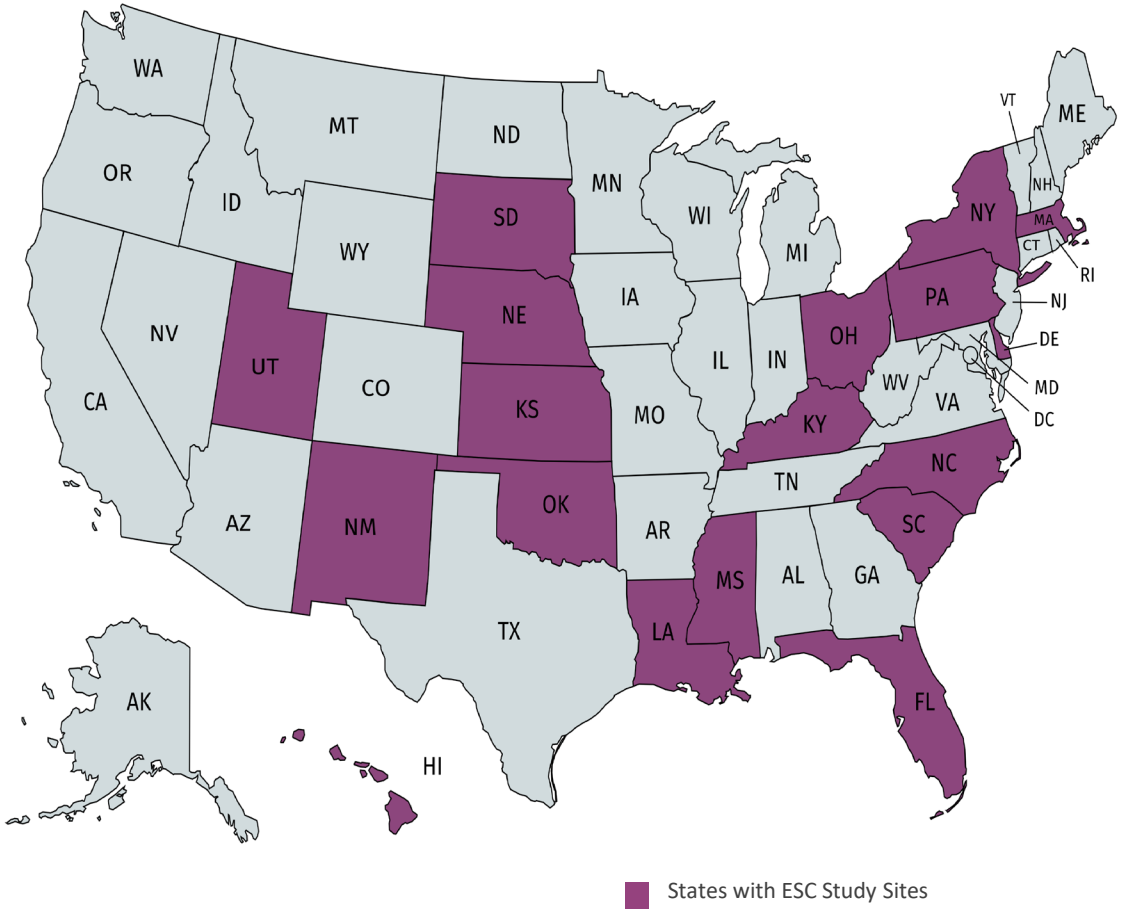
Subcommittee

- Brian Smith, Duke
- Rachel Greenberg, Duke
- Jessica Snowden, UAMS
- Jeannette Lee, UAMS
- Songthip Ounpraseuth, UAMS
- Alan Simon, NIH
- Andrew Bremer, NICHD NRN
- Brenda Poindexter, NICHD NRN
- Abhik Das, RTI, NRN

Study Sites

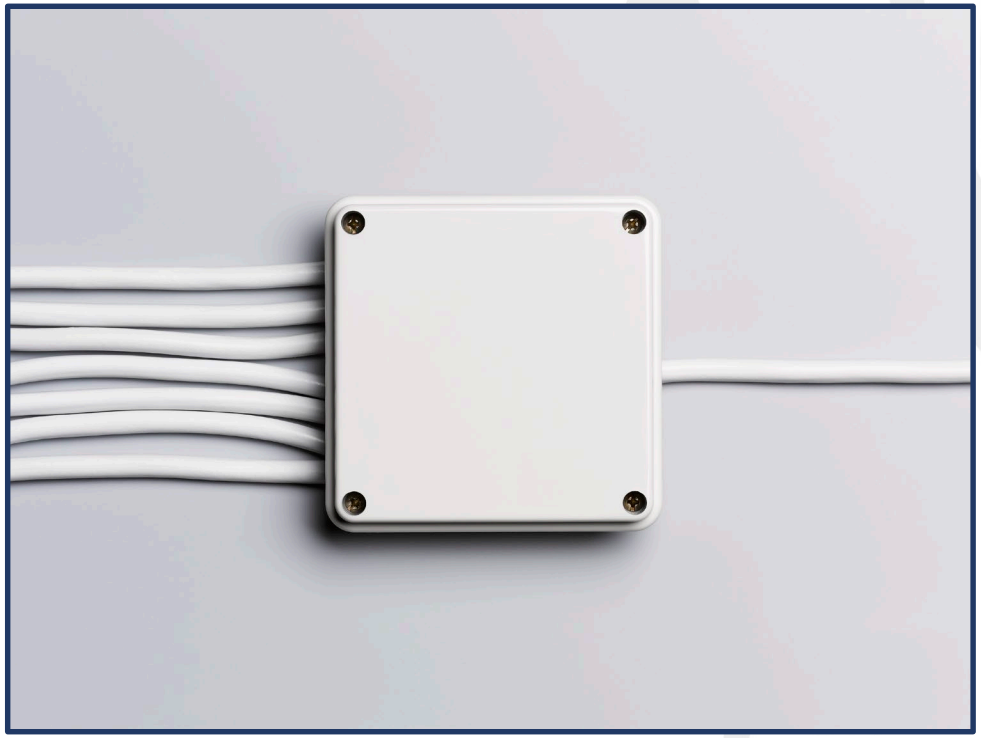
Site PI and Coordinator
26 sites

ESC Study Sites



Understanding Your Study Team

- Identify the expertise and responsibilities of each member of your research team
- Identifying and utilizing the strengths of the members of your research team to enhance the research study, increase efficiency, and foster collaboration across the team
- It is important that each member knows that their contributions are valued and that their time is appreciated



Groover, S. *Nature*. 2020

Communicating with Your Study Team

- Communication is the key to success
- The study team needs to be on the same page
- Listening to the needs and viewpoints of your study team is essential during the development, implementation and conduct of an RCT

Groover, S. *Nature*. 2020

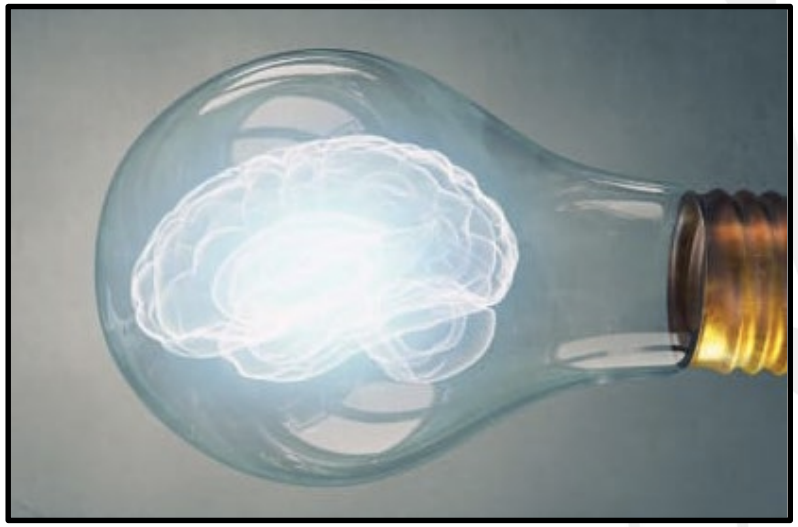
Commitment and Reliability

- Your responsiveness can facilitate success
  - Organize your inbox because it will be overflowing
  - Don't be afraid to ask for help
  - Develop a plan for when you are not readily available
- Meet your deadlines
  - Understand your bandwidth and the breath/depth of what needs to be done
  - Divide primary leadership responsibilities
  - Perfect is often the enemy of progress

Groover, S. *Nature*. 2020

Adaptability

- Be flexible and innovative
  - Emergencies will occur
  - Resources will be limited
  - Be prepared to pivot
- Don’t be afraid to step out of your comfort zone and learn something new

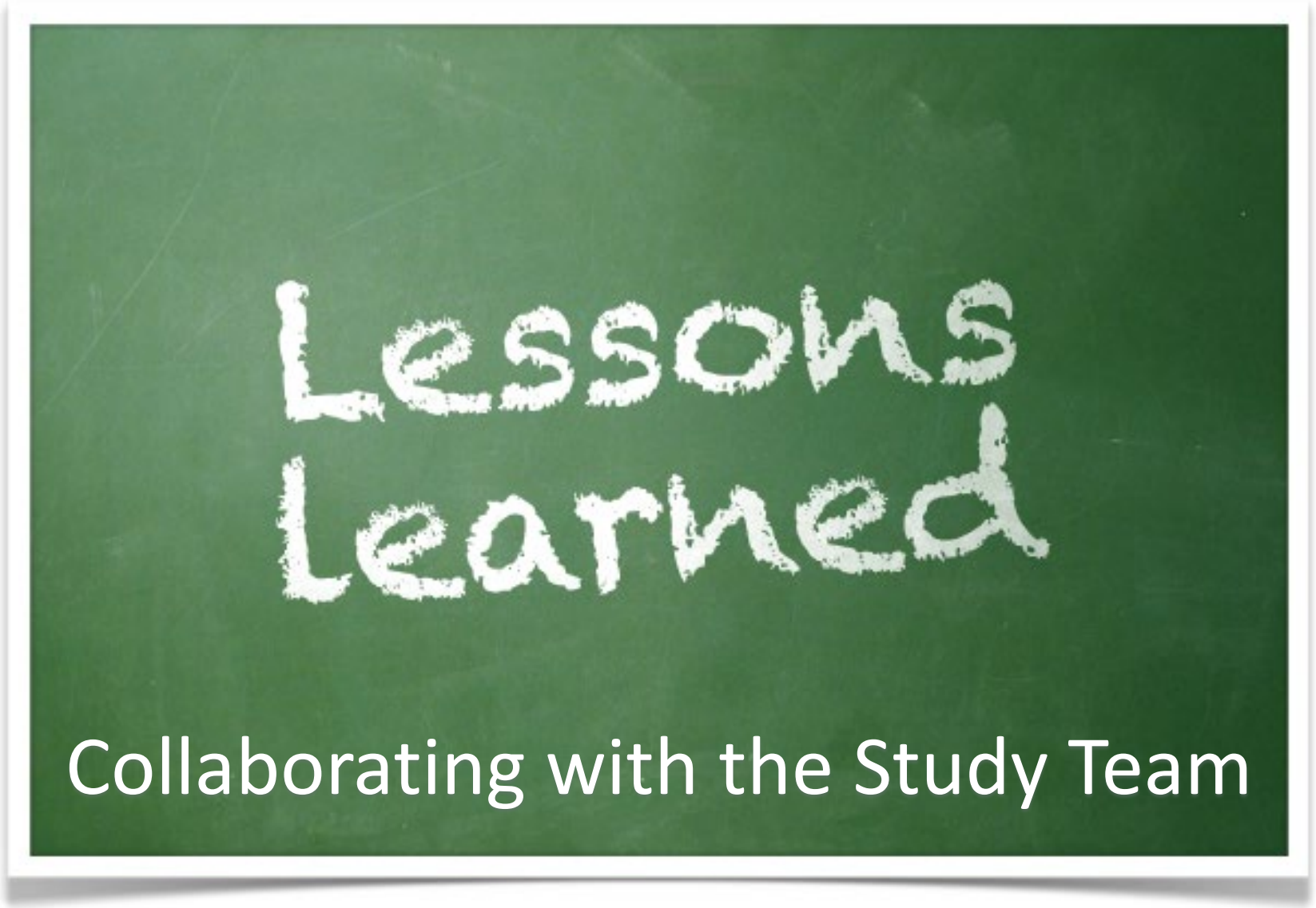


Groover, S. *Nature*. 2020

Keep an Open-Mind and Convey Empathy

- The most productive scientific groups are diverse and capitalize on their group's ability to bring different, creative or unconventional solutions to difficult questions
- Be open to feedback
- Ensure that all voices are heard
  - The softest voices may be those that lead to the solution of the problem

Groover, S. *Nature*. 2020



Collaborating with the Study Team

Get	Get to know and value each member of your study team
Have	Have a coordinator on your study team
Keep	Keep communication open and close the communication loop
Meet	Meet deadlines
Ensure	Ensure that all voices on the study team are heard and appreciated
Develop	Develop a process to integrate new members of the team who join mid-study

Projecting and Mitigating Risk

Projecting and Mitigating Risk

- Protocol Development
  - Ensure that the protocol is concise and clear
  - Be precise when you need to, but stay broad where you can
  - Review each section in detail and pull in others to review
- Put the details in the Manual of Operations (MOP)
  - Address potential ambiguity that may cause confusion
  - Include best practices
  - It is much easier to change the MOP than the protocol
  - Read the MOP carefully
    - Have 1-2 research coordinators review and critique the MOP

Projecting and Mitigating Risk

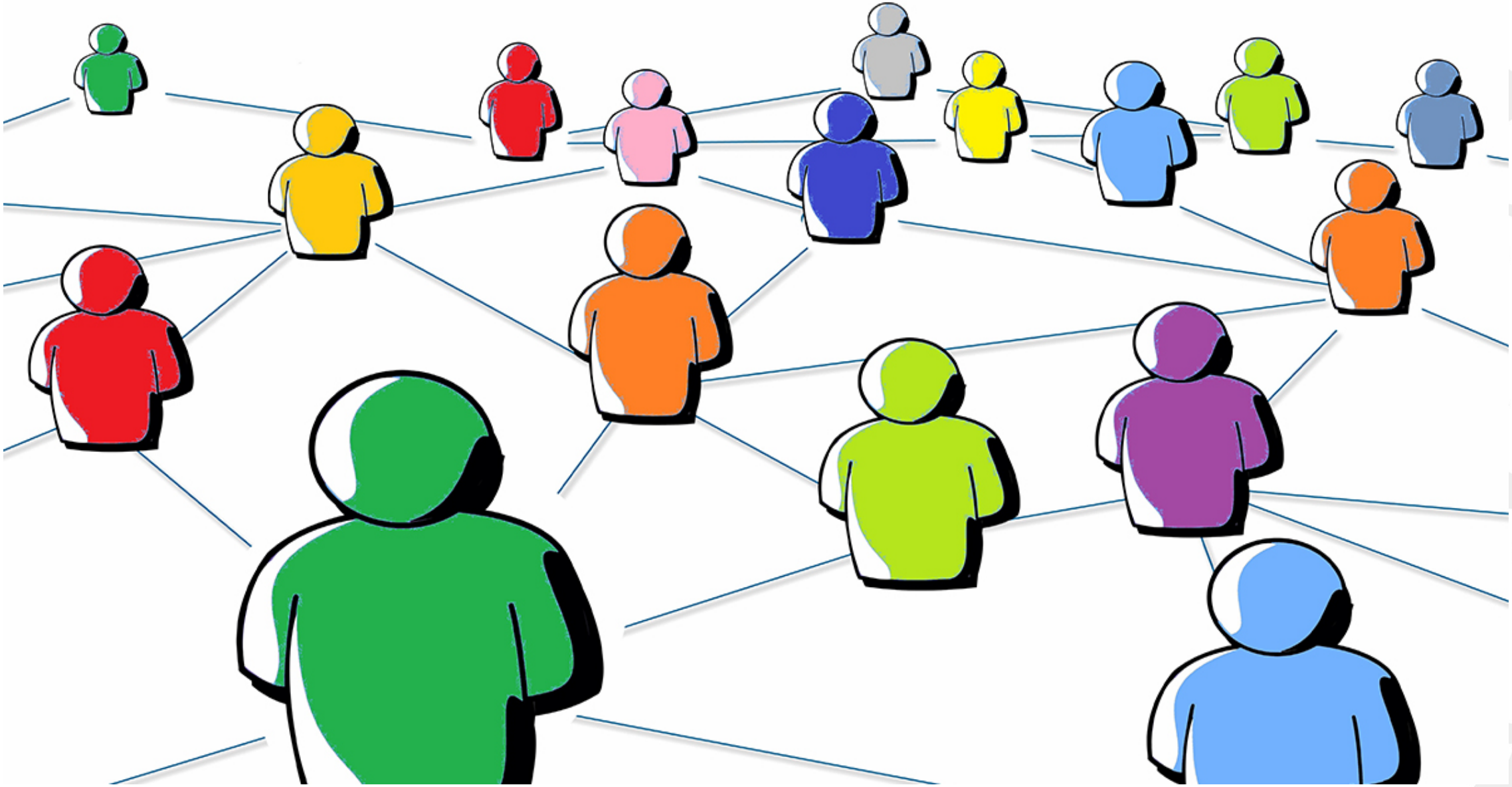
- Understanding the study sites
  - Keeping up with sites is challenging
  - If possible, meet with study leadership from each site
- Education on the intervention is key
  - Take the opportunity to educate at every contact
  - Utilize interactive and asynchronous educational methods
  - Provide time for feedback from the sites
  - May need to schedule educational meetings for site PIs

Projecting and Mitigating Risk

- Buy in from the study team and study sites
  - Communicate effectively
  - Admit when you do not know but, then find the answer
- Anticipate and mitigate potential barriers
  - Recruitment
    - Challenging study populations may require an alternative approach
  - Intervention
    - Pivot as needed if it does not impact the quality of the science
  - Team
    - Understand potential opportunities and limitations at study sites

Projecting and Mitigating Risk

- Develop a clear and concise research protocol
- Detailed MOP that has been reviewed by research coordinators
- Establish and reestablish buy in
- Always consider the utility of a personal phone call over multiple emails
- The solutions to barriers may only be seen through an alternative lens



Collaborating with Site Research Teams

Supporting Sites

- Ensure that the coordinators and PIs at each site understand their role and responsibilities during:
  - Study activation
    - Meeting with sites to hear concerns and answer questions
  - Enrollment and informed consent
    - Education on IRB updates including changes in the informed consent
  - Support recruitment and retention
    - Identifying best practices to support sites
  - Study implementation and conduct
    - Compliance with the protocol
    - Training on the intervention

Addressing Site Specific Concerns

- Site PI is ultimately responsible for acceptable conduct of research at their site
  - Personally responsible for study conduct and actions of personnel under their supervision
- Every site is unique

Helping Sites Optimize Study Conduct

- Data quality
  - Data re-abstraction
- Implementation of the intervention
  - Identify opportunities for improvement through training, peer mentoring, and innovation
- Recruitment and retention
  - Providing sites with data on their performance compared to other sites throughout the study
  - Allow sites to discuss concerns together and they find the solution

Collaborating with Research Sites

- Sites thrive when they problem solve together
- Consider developing an FAQ early to support consistent messaging across sites
- Actively engage the full research team at a site when concerns arise
- Be ready to pivot
- Appreciation and gratitude for a job well done!

Questions and Comments