Society for Clinical Trials

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COMMUNITY BASED CLINICAL TRIALS: INNOVATIVE REGULATORY PROCEDURES TO ENHANCE TRANSLATION

COMMUNITY BASED TRIALS WORKING DEFINITION

- The clinical trials involve a research topic of practical relevance to the community and is carried out in community settings
- Involves partnerships and coalitions that help mobilize resources
  - Community partners can include organized groups, agencies, institutions or individuals representing common interests, needs or concerns
- Community settings: where the clinical trial is conducted. Usually health care clinics, hospitals or private practice offices
  - VERY BUSY
  - Provides clinical care
  - No time for research

COMMUNITY ENGAGEMENT (CENR) GOALS*

- Create collaborations
- Build trust
- Enlist new resources/allies
- Create better communications
- Improve overall health as time evolves
- Long term goal for research to leave a legacy, both in terms of the utilization of research results, as well as in the future collaboration among partners

*Principles of Community Engagement, 2nd Ed, 2011

WHY COMMUNITY BASED TRIALS

Improve Health Care!

Address highly relevant public health issues

- Smoking, obesity, cancer, heart disease, diabetes, etc.

- Current initiatives
  - CER (Comparative Effectiveness Research)
  - NIH Collaboratory https://commonfund.nih.gov/hcscollaboratory/
  - PCORI (Patient Centered Outcomes Research Institute)

WHAT COMMUNITY PARTNERS BRING TO THE TABLE?

- Research question
- Study design
- Feasibility of the protocol/procedures
- Recruitment
- Retention
- Dissemination

WHO REGULATES THE TRIALS?

Regulations are the same as always….

Main Agencies involved:

- FDA
- OHRP (Office for Human Research Protections)
- OCR (HIPAA)

Others

- ORI (Office of Research Integrity)
- DEA (Drug Enforcement Agency)

Local Regulations: IRB, Institution, State, etc.

More if studies include international sites, drug import

WHAT REGULATIONS?

FDA: Regs are related to GCP (ICH E6)

- 21CFR
  - Part 11 Electronic Records
  - 50, 56, Human Subjects
  - 54, COI
  - Drugs: 312= IND; 314= NDA
  - Devices: 812= IDE; 814= PMA
- BM
- Guidance Documents

WHAT REGULATIONS? (OHRP)

- CFR 45 part 46 (Under revision fall 2011)
  - IRB Registration, FWA
  - Safety (Adverse Events Vs. Unanticipated Problems)
- 45 part 46 ANPRM Issues:
- Data security, Biospecimens
- Application to all studies, regardless of funding
- Central system for AE reporting
- Consent form too long
- Single IRB of record
- Issues about IRB review
- http://www.hhs.gov/ohrp/humansubjects/anprmchangetable.html
  - Guidance Documents

OTHERS

- Office of Research Integrity (ORI) – Research Misconduct http://ori.dhhs.gov/
- NIH
  - Follows FDA and OHRP, additional rules for grants

http://grants.nih.gov/grants/policy/nihgps_2012/index.htm

ETHICS IN CENR

- Same principles/issues as any other research
  - Belmont Report 1979
- Ethical issues that may (or will) evolve during the project, since many of the sites are research naïve
  - IRB review: risk benefit of community vs. individuals
  - Issues of privacy/confidentiality
  - Issues of clinical care Vs. research procedures (therapeutic misconception)
  - Research Equipoise
- Need for regular training (more than just once)
- Need for good relationships

IRB SPECIAL CONSIDERATIONS

- Community vs. individuals
- Training needs
- Membership
- Privacy/Confidentiality
- Additional documents needed for review- site and protocol specific- such as letters of support, other to attest to partnership, resources, assurances, etc.

SUD CLINICAL TRIALS NETWORK

- NIDA established in 1999
- Conduct multi-site trials on substance use treatment interventions
- Incorporate many of the CEnR Principles
  - CBPR with American Indian & Asian American partners
- Researchers & treatment providers at table
  - Protocol concept, design, review, implementation
- Many providers research naïve
- Researchers had little experience in multi-site trials, or FDA regulated trials

LESSONS LEARNED

- Understanding each other
  - Sponsors
  - Researchers
  - Community providers
- Takes a long time to agree
  - 2-3 years from concept to recruitment start
- Need for training at both sides of the table
  - need to be frequent and ongoing
- Site performance monitoring – should be done from start of the study, more frequent at the beginning, then as needed

LESSONS CONT.

- Learning curve is long
- Some concepts hard to understand
  - RCT, GCP principles
  - FWA, IND
  - Research protocol vs. clinical care
  - Protocol violations
  - Adverse events
  - Need for oversight and regulations
    - Need for training on human subject protection
    - FWA process
    - HIPAA
- Budget
- Timelines?

EVOLUTION

- Central data management/coordinating centers
  - Standard CRFs for data collection
  - Same data system for all sites/protocols
- Safety reporting
  - Central safety monitoring
  - From all to necessary
- Site visits
  - From QA monitoring only to site management
  - From several visits by multiple monitors to target visits by central monitors
- Training
  - More targeted
  - Providers as trainers

ISSUES

Because clinic settings are extremely busy….

- Need for short/targeted training
- Need for simple protocols
- Need for short/essential only data collection
  - Maybe use of existing electronic tools to assist with these issues
    - What about regulations and confidentiality/privacy?
- Budget
  - Include cost for partners time, travel, etc.

MORE….

- Study design: how many arms, what to use as control, what to compare, issues about treatment as usual/standard of care, generalizability of results, funding (clinical care Vs. research), etc.
  - Incentives example
- Study results: dissemination (what to disseminate & how), implementation, sustainability
  - Need to wait for publication before implementation

AND…

Need for shorter informed consent document!

- Part of OHRP ANPRM issues
- M.E. Enama et al., Contemporary Clinical Trials 33 (2012) 895–902 (Study at NIH CC)

  Standard, 10 pages Vs. Concise, 5 pages

  "… no differences in study comprehension or satisfaction with the consent form."
- Matsui K, et al., J Epidemiol 2012;22(4):308-316 (Japan)

  Standard, 11 pages Vs. Short, 5 pages

  "A short informed consent form was no less valid than a standard form with regard to fulfilling ethical requirements and securing the scientific validity of research"

AGENDA

- Experience from academic center staff in establishing partnerships and how they implemented clinical trials in community settings. Lessons learned, recommendations
- Experience from clinical providers involved in clinical trials, lessons learned, recommendations for
- Questions/Discussion

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SCTR

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DISCLOSURE

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NIDA CTN: SOUTHERN CONSORTIUM NODE

- The CTN is a NIH, National Institute on Drug Abuse (NIDA) cooperative agreement to bridge the gap between research & practice through bi-directional collaboration between Academic Medical Centers (AMCs) & Community Treatment Programs (CTPs).
- The Medical University of South Carolina (MUSC), an AMC, participates in the NIDA CTN as the Regional Research and Training Center (RRTC) for the Southern Consortium (SC) Node.
- Assuring regulatory compliance in addition to conducting successful research trials with scientific rigor presents unique challenges for research naïve sites.
- A Project Management model is used to facilitate successful conduct of research trials at Community Treatment Program (CTP) research naïve sites while maintaining regulatory compliance & scientific rigor.

ACADEMIC MEDICAL CENTER (AMC): ONE NODE'S PERSPECTIVE

- Our Node
  - Academic Medical Centers (AMCs)
    - MUSC – 1 of 17 (1 of 13) Nodes across the United States
    - South Carolina (urban and rural areas), NC (Duke), GA
  - 4-5 Community Partner Sites (Readiness/Good Fit)
    - Community Treatment Programs (CTPs) in SC
    - Inpatient and Outpatient programs
  - Partnership between AMCs and CTPs & other sites
  - Bidirectional Relationship
    - AMC - research expertise (grant writing, study design, etc.)
    - CTPs and other sites – real world clinical experience

DEVELOPING A NODE: AMC RRTC

- Set up a Regional Research and Training Center (RRTC)
- TEAM: Experienced Research Investigators, Epidemiologists, Pharm.Ds, Biostatisticians, nurses, counselors, clinical research management professionals – many who are also addiction specialists
- **Mission** - to develop capacity and support research at the CTPs through research development, grant administration, training, regulatory compliance, quality assurance, and data management activities.
- Governance structure:
- leadership, decision making, conflict resolution, advisory board,
- communication, dissemination, meetings/retreats, newsletter, websites
- shared vision and values (evidenced based practice, respect, research),
- goals & objectives (type studies, patient populations, special interests), affiliations with community & organizations (AHEC, Advocacy Groups)

DEVELOPING A NODE: CTP RESEARCH SITE

- Identify Leadership, Gatekeepers, & Staff
  - + Site Investigators, existing staff, counselors
  - – Hire Staff (AMC or CTP research staff?)
    - – Our experience typically was that research staff hired by the CTP were able to integrate with CTP staff for study success
- Negotiate Subcontract Agreement & Budget
- Identify Space, Set up research office, Work hours
  - + Office space, furniture, computer, phone for consenting, administering assessments, & data entry
  - + Space for drawing blood, taking vital signs, exams
  - + Secure drug and record storage, petty cash
  - + Issues – FWA, CLIA, rent space, petty cash, vendors)

SELECTING A PROTOCOL

- AMC/CTPs review protocols for research interest
- Identify protocol related to research interest
- Assess CTP for recruitment, feasibility & logistics
  - Do they have the patient population?
  - Can they recruit enough patients for the study?
  - Do they have access to the personnel and facilities required to conduct the study?
    - Inpatient facility, laboratory, physicians
- Submit for Site Selection consideration
  - Site Selection Survey
  - Site Visits

IMPLEMENTING A PROTOCOL

Identify a protocol team

- RRTC
  - Principal Investigator at the AMC (IRB of Record)
  - Co-Investigators, Biostatistician
  - Regulatory Coordinator, Quality Assurance Monitor, Trainers, Counselor Supervisors
- CTP
  - Site Investigator at the CTP
  - Co-Investigators, Physician
  - Study Staff, Counselors, other staff

IMPLEMENTING A PROTOCOL

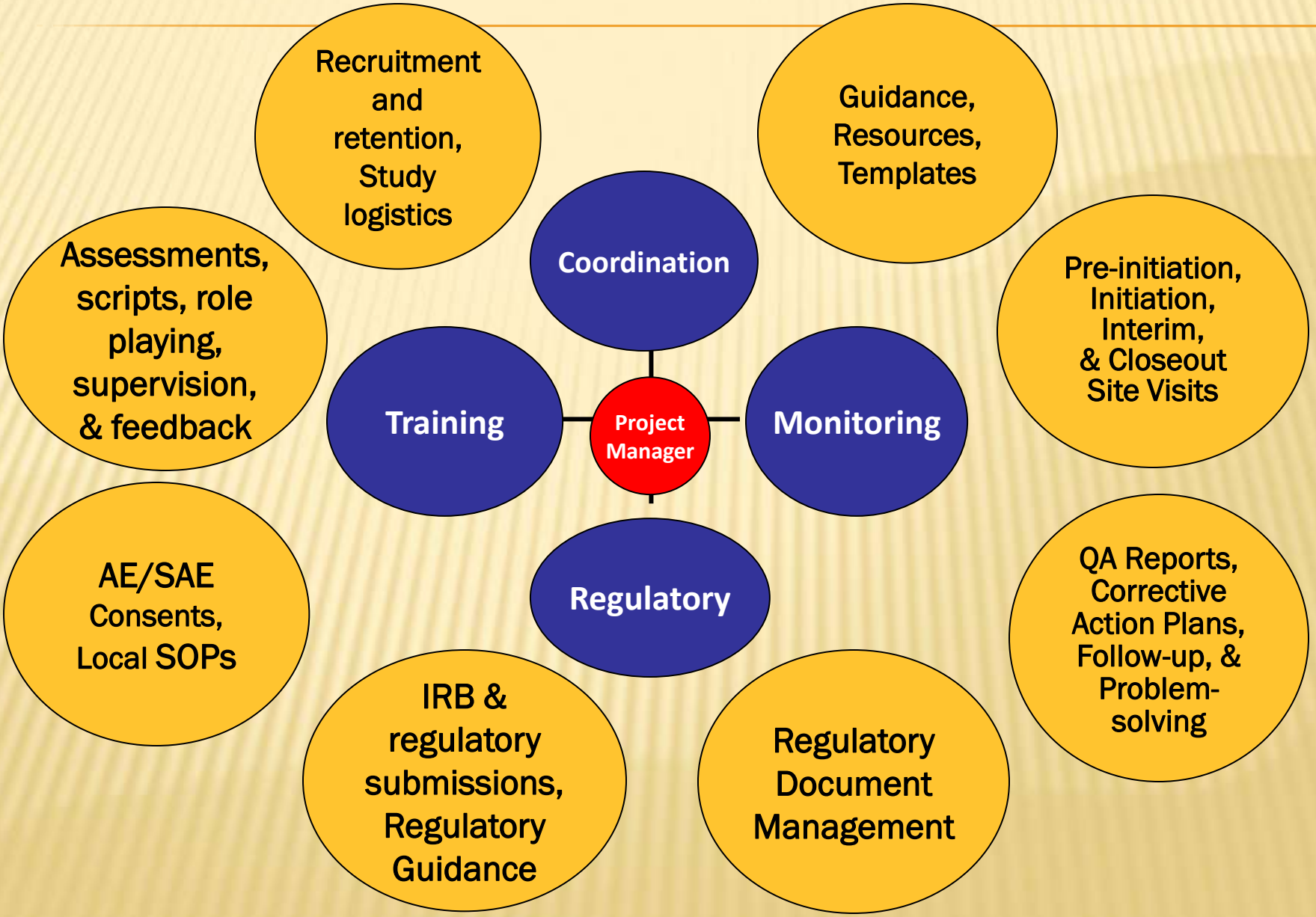
- To support the CTPs to successfully implement, conduct, & closeout clinical trials, the MUSC RRTC developed a project management approach
- Project Managers (PM) typically are masters prepared, experienced research professionals with specific training in quality assurance monitoring & regulatory compliance & frequently are also certified assessment trainers or counselor supervisors.

A Project Management Model: (Ownership/Site Support)

(Mentoring: supportive, proactive, training approach)

- Regulatory Compliance & Data Management
- Training & Intervention Supervision
- Site Management / Study Coordination
- Quality Assurance & Data Monitoring

THE PROJECT MANAGER SUPPORTS THE CTPS WITH SITE MANAGEMENT, STUDY COORDINATION, QA & DATA MONITORING, REGULATORY COMPLIANCE AND TRAINING.



IMPLEMENTING A PROTOCOL (CON'T)

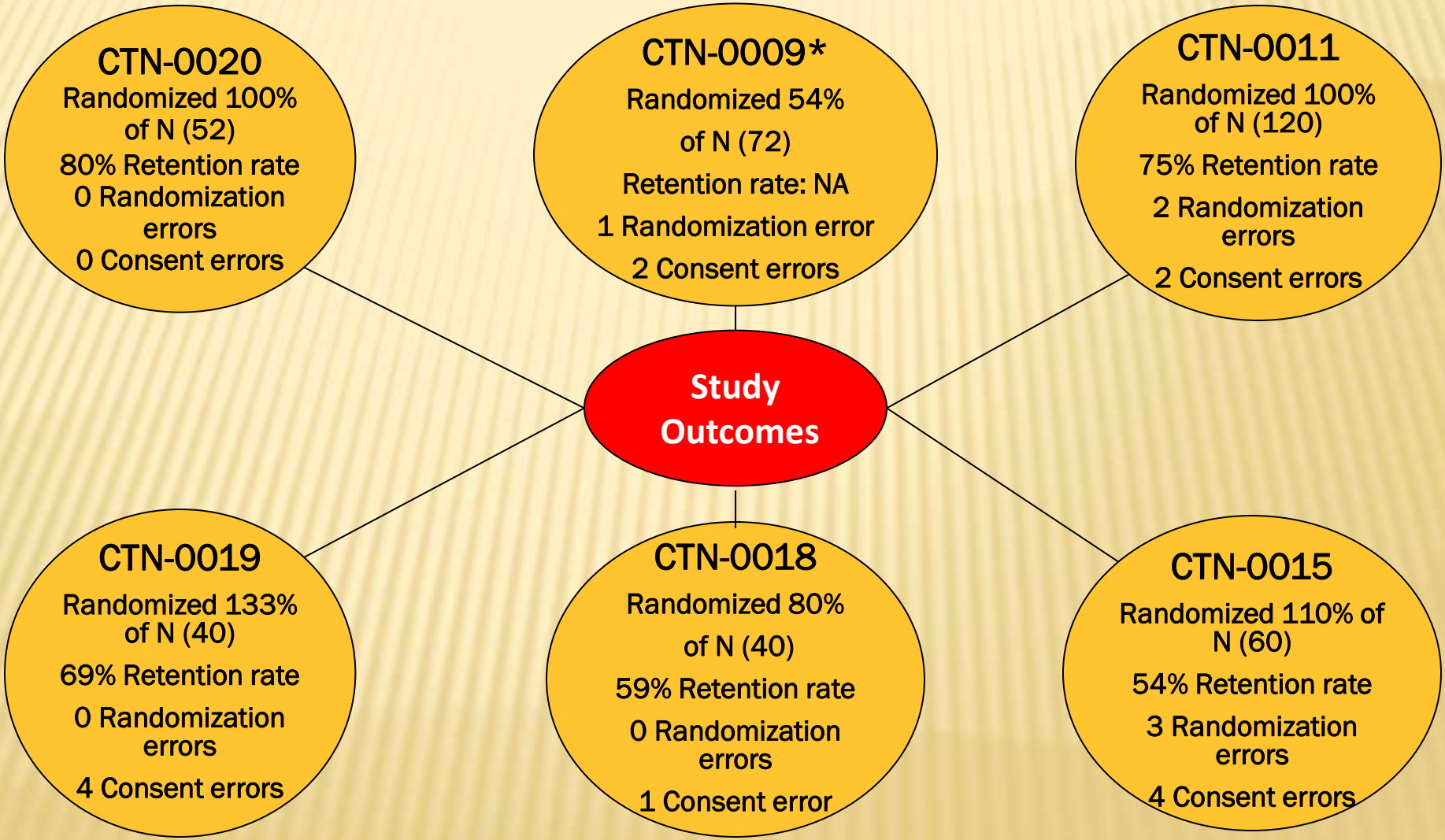
- Regulatory Compliance, IAA, FWA, CoC
  - Identification of all IRBs and IRB of record
  - Complete IRB and other regulatory submissions
  - Coordinate between multiple IRBs & Lead Node
  - Amendments, AE reporting, Protocol deviations
  - Regulatory document management
- Training & Intervention Supervision
  - Core Clinical Research Training (GCP, CITI, informed consent, AE/SAE, didactic, role playing, discussion)
  - Protocol specific training; supervision & feedback
  - Assessment & instrument training and certifications

IMPLEMENTING A PROTOCOL (CON'T)

- Site Management - Study Coordination (study plan)
  - Recruitment and Retention Plan
  - Logistics, SOPs, Source documents, and tracking logs
  - CRFs and data entry
  - Data management, storage of records and meds
- Quality Assurance & Data Monitoring
  - Monitoring Plan - Onsite visits per plan & identified need
  - More visits at start-up, decrease over time
  - Identify risks (study start, new staff, protocol deviations)
  - Supportive, proactive, training focused approach
  - Relationship building - Site Visits, Phone Calls, & Emails

METRICS

PROTOCOLS WITH RELATED METRICS IN WHICH THE PROJECT MANAGEMENT MODEL WAS UTILIZED



RESULTS

- Four of the six studies met or exceeded the target N; Three achieved the target N ahead of study timelines; Two continued to enroll participants, bolstering the national enrollment rate
- Although retention rates may appear low, they are above the retention rate expected for these substance use disorder trials
- Consent errors noted above were minor in nature (i.e. signing on the wrong line, omitting a date) & tended to occur at the beginning of the study with few subsequent errors
- Success was externally validated - External monitor reported that the study team was “proactive in managing the study and providing internal quality assurance” and additionally described the study as “well organized and closely monitored”
- All protocols were independently reviewed by sponsor contract monitors in addition to the local QA monitoring conducted by the Project Manager

CONCLUSIONS

- Participating sites were well-prepared for study implementation
- Able to immediately begin recruiting participants at study start
- Project Management Model allowed early identification of problems and prompt response with corrective action plans
- Model provided for continuity of support at these research naïve sites and facilitated building close relationships between the RRTC and CTP staff
- Initial support provided by the Project Manager enhanced the sites ability to function more autonomously as experience grew
- The Project Management Model facilitated efficient communication between Sponsor, Lead Investigator, PI & Site
- This model was effective in providing the research support necessary to help community sites participate in research and comply with the increasingly complex regulatory requirements.

FUTURE DIRECTIONS

- NIH CTSAs mission to facilitate and promote clinical & translational research to speed up health care discoveries (Community Readiness Toolkit)
- OHRP revising human subject regulations
- Much discussion about moving toward one centralized IRB for multi-site clinical trials may reduce regulatory burden and increase study oversight and patient protection
- Agreement on contract language to speed up the contracting process
- Logic Models & Process Improvement – mapping & removing 0 value steps
- Consent forms may benefit from decision science strategies to inform on risk/benefits and electronic platforms with video and 3-D modeling depictions.
- Electronic systems provide opportunities for more efficient and effective and types of research management and monitoring
  - Electronic consent platforms
  - Electronic data capture and IRB (assessments)
  - Electronic medical records and clinical data warehouses
  - Electronic Clinical trial listing and Voluntary Registries

Community Treatment Program Perspective on Implementing a Clinical Trial

Kimberly Pressley, MA
Site Principal Investigator
Protocol Manager
Quality Assurance Monitor
Medical University of South Carolina

Why become a CTP research site?

- We are always looking for new evidence based treatments but it is not always feasible to implement them in a real world treatment setting.
- The concept of testing new treatment options with the population we serve was intriguing and gave us the opportunity to work with the best researchers to determine how it could work in a CTP.
- The belief that participation in the study may benefit the clients who participate.
- The hope that the treatment could be integrated as apart of Treatment as Usual at the conclusion of the research that is assuming it is cost effective.
- The benefit of the CTP being affiliated with ground breaking research.
- There is some financial benefit to the CTP.

CTP FIRST STEPS

- Establishing an Infrastructure
  - Management Support, Time, & Effort
    - Integration of the research as apart of the CTP and into the established treatment programs
    - Assurance that facility space and resources are available to research staff
  - Finance Support
    - Contracts
    - Budgets
  - Human Resources
    - Hiring research staff
    - The use of CTP staff
  - Procurement
    - Purchasing equipment, office furniture, computers, supplies, petty cash
  - Technical Support
    - Computer Set-up and Maintenance, Software, Ability to access or install protocol specific programs for data entry or collection

Challenges and Barriers

- Resistance to Change
  - What's wrong with the way we are already doing things?
  - There is concern that it will disrupt Treatment as Usual.
- Mistrust in Research
  - This can be received from staff and clients.
  - Clinical staff can be protective of their clients and their time with them.
  - This can result in a lack of cooperation with referrals and have a negative impact on recruitment.
- Additional Work
  - No one wants any more added to their already heavy work load.

REGULATORY

- Working with the Institutional Review Boards
  - Community Treatment Programs may require working from multiple IRBs
    - University IRB (MUSC)
    - Secondary University (if applicable) or Agency IRB
    - Research and Development Committee
  - Review Process and Time Frames
    - eIRB systems and Traditional IRB systems
    - Impact on Study Start Up at CTP
  - Human Subjects Training
    - IRBs may require specific HST different from protocol required HST training
    - Staff time required

REGULATORY CONTINUED

- Reporting AE (SAE)s and Protocol Violations
  - IRB requirements
  - Protocol requirements
- Managing regulatory documents
  - Community Treatment Program (Electronic or Hardcopy)
  - Regulatory Specialist (Regulatory Tracking System)
  - Receiving updated regulatory documents in a timely manner
- Consents

CONSENTS

- Length and Time required
  - Witness Requirements
- Quizzes
  - Trick Questions
  - Additional Questions
- HIPAA Forms
  - Integrated into consent or separate form
- Behavioral Vs. Medication Trials
  - The staff and staff time required to complete consents.

After the Research

- Attempts are usually made to implement the treatments/interventions into TAU.
- Research staff are usually placed on other studies if possible, sometimes hired by the CTP, or let go at the end of the trial.
- The CTP is recognized in publications as contributors. Some CTP and research staff participate in writing the publications.
- The CTP staff does not usually hear any more about the study after the data collection has been completed.
- If a new research opportunity comes along immediately that is great but if it takes a while the CTP has to start over again.

Suggestions

- Federal Regulations for a specific Human Subjects Course that would be required/accepted by all institutions
  - The same renewal time required for all.
- More consideration of Community Treatment Program provider's time when determining training requirements
- More eIRB systems
  - Notifications Required
- A Regulatory Tracking System that would be more useful for CTPs
- A Simpler Consent Process
  - Shorter consents
  - Initials not required at the bottom of each page
  - An integrated HIPAA form
  - All comprehension assessment questions incorporated into one brief quiz
  - Clearer and more concise quiz questions
- The inclusion of more cost effective analysis in research studies.
- Information provided to all CTP staff after the publication of findings (e.g. presentation of findings, copies of the publications).
- More research opportunities to continue building on the infrastructure that has been established.

QUESTIONS?