Challenges in Setting up a Multicenter Study

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Why Multisite Research?

The nature of critical care necessitates timely intervention research.
Why Multisite Research?

- Allows the accrual of sufficient numbers of diverse patients in the shortest period of time (Prone: 102 patients/7 sites/2.5 years)
- Improves the generalizability of study results and augments the potential for subgroup analyses
- But - the complexity of clinical research exponentially increases

- Challenged to maintain
  - Internal validity of the study and
  - Sustained commitment and collaboration of numerous disciplines over the study period
Limit “Challenges”

- Begin with the end in mind
- Know that there are few absolutely right or wrong answers … but LOTS of trade-offs
- Ten essential points to consider when conducting multisite research
Clinical trials are launched from pilot studies
Pilot Study

- Answers important questions that can inform the design and conduct of a larger clinical trial
  - Evaluate subject availability
  - Guide sample size calculation
    - Effect of the intervention
    - Test assumptions on consent, dropouts and non-compliance rate to guide inflation factor
- Refine protocol
- Trial case report forms and analysis plan
- Project costs to help with budget preparation
Need pilot data and publications to obtain funding.

Need funding to ensure that adequate resources are available for a multisite clinical trial.
#2 Clinical research is a team sport

- Need collaborators, data coordination and, perhaps a specialized center (CRISMA center)
- Team = Multidisciplinary Co-investigators
  - Nurse-physician-respiratory therapist
  - Nurse-physician-clinical pharmacist
- Need several mentors
Choose Your Collaborators Wisely

- Experience in clinical trials
- Availability of appropriate subjects
  - Evidence of their capacity to enroll
  - Safely manage critically-ill patients on protocol
- Ability to devote time to the clinical trial
- History of successful collaboration
- Closed unit where few individuals manage the patient’s care
- Presence of a skilled study coordinator (smart, detail oriented, tenacious, single-minded)
Data Coordination Center

- Independent - No conflict of interest
- Expertise in biostatistics, “Good Clinical Practice”, computer programming, data management
- Help design and manage the clinical trial
  - Develop case report forms, manual of operations, randomization scheme
  - Carry out day-to-day communication with sites
  - Monitor IRB status and renewals at multiple centers
  - Collect, monitor, clean and analyze data from all collaborating centers
  - Conduct site visits
  - Facilitate interim analysis
#3 Well-defined organizational structure and processes are required

- Problems most often originate from inadequate and/or unclear communication between the principal and site investigators.

- Team expectations
  - Communication
  - Accountability

- Committee structure and processes
  - Steering
  - Operations
  - Data coordination
  - Independent data safety and monitoring board (DSMB)
Data Safety and Monitoring Board

- Independent oversight
  - Monitor data quality and center performance
  - Monitor baseline variables, adverse events, and outcomes

- Early stopping
  - Serious adverse event
  - Interim analysis
    - Greater than expected benefit
    - “Futility”
      - Probability of finding a significant difference is low
      - Logistical or data quality problems
      - Outside information makes the trial unnecessary
#4 All site investigators (and their colleagues) must agree to follow the study protocol.
“Equipoise”

- There is a reason to believe that a new treatment MAY be better than current treatment or than no treatment.
- There are 2 standard treatments but we don’t know which is better.
Protocol Development and Consensus

- Create initial drafts
- Circulate drafts to coinvestigators
- Trial the protocol in the clinical setting
  - Improve the logic until it becomes functional
- Review revised draft at the start-up meeting
- Steering Committee signs off on final protocol
- Data Safety Monitoring Board approves final and any revision
### Control - Randomized Clinical Trial

#### Intervention
- Prone Positioning
  - When to start and stop positioning
- Procedure
- Check list
- Supine Positioning

#### Cointerventions
*Reflect “usual” care*
- Lung protective ventilator protocol
  - Low Vt strategy
  - Permissive hypercapnea
  - PEEP/FiO2 grid
  - HFOV
- Sedation protocol
- Extubation readiness testing
- Hemodynamic, nutrition, skin care guidelines
#5 Data quality must be ensured

- Goal = collect high quality verifiable data that is relevant to the primary and secondary hypothesis
- Emphasis on standardization, certification, training, testing, and retraining
- Centers demonstrate competence before enrolling their 1st patient
Design …

to decrease inter-site variation

- Case report forms (CRF)
- Manual of operations (MOO)
  - All study activities (screening, randomization, data collection, interventions and co-interventions)
- Discipline-specific training (project initiation and with new staff)
  - Modules with post-test
  - Toolbox: Reminder cards, videos
  - IRR every 4 months
- Research database using data management software
#6 Monitor site performance

- Use a daily screening log
- Data collection and processing
- Protocol adherence
- Goal – improve a center’s performance so that each site contributes to the overall success of the project.
Monitor elements of a protocol that are critical to the validity of the study’s conclusions.
Monitoring Adherence

- Adherence reports
  - Generated quarterly from data coordinating center
  - Reviewed by the Steering and Operations Committee every 3 months
- Site Visits – External Auditor
  - Audit - All primary source documents (consents and randomization logs)
  - Audit – 10%+ randomly selected CRFs
  - Walk-through policies and procedures
- Reported to the Data Safety Monitoring Board
#7 Monitor finances

- Multicenter studies are expensive
- Limit expense by simplifying data collection
  - Easy to overbuild a trial – Avoid “interesting to know” items.
  - Reduce the number of tests
#8 Adhere to principles of data analysis

- Once randomized you must analyze
- *Primary analysis must be done according to an intention-to-treat analysis*
  - Every patient should be counted with the group that they were originally assigned (even if they never received treatment, did not comply with treatment, or the protocol was not followed)
#9 Be vigilant about adverse events

- All outcomes that occur after randomization are counted
- Report all events, even if unlikely to be related to the intervention or trial participation
#10 Foster a cohesive spirit

- Be generous with publication, presentation and authorship (determine in advance)

- Build a collective mission to achieve shared goals
  - Spread the wealth with co-investigator-driven ancillary studies
Conclusion

- Multisite clinical trials require vigilance to detail, comprehensive planning and multidisciplinary collaboration.

- While challenging, multisite clinical trials offer great potential for building a scientific base for the practice of critical care nursing.