Challenges in Setting up a Multicenter Study

Martha A.Q. Curley, RN, PhD, FAAN
Associate Professor
University of Pennsylvania
School of Nursing
Anesthesia and Critical Care Medicine

Nurse Scientist
Cardiovascular and Critical Care Program
Children's Hospital Boston

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/7sites/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

#1 Clinical trials are launched from pilot studies

PRONE POSITIONING OF PATIENTS WITH ACUTE RESPIRATORY DISTRESS SYNDROME: A SYSTEMATIC REVIEW

By Martha

The Effects of Early and Repeated Prone Positioning in Pediatric Patients With Acute Lung Injury*

Martha
John H.

Effect of Prone Positioning on Clinical Outcomes in Children With Acute Lung Injury

A Randomized Controlled Trial

Martha A. Q. Curley, RN, PhD
Patricia L. Hibberd, MD, PhD
Lori D. Fineman, RN, MS
David Wypij, PhD
Mei-Chiung Shih, PhD
John E. Thompson, RRT
Mary Jo C. Grant, RN, PhD

Context In uncontrolled clinical studies, prone positioning appeared to be safe and to improve oxygenation in pediatric patients with acute lung injury. However, the effect of prone positioning on clinical outcomes in children is not known.

Objective To test the hypothesis that at the end of 28 days infants and children with acute lung injury treated with prone positioning would have more ventilator-free days than those treated with supine positioning.

Design, Setting, and Patients Multicenter, randomized, controlled clinical trial conducted from August 28, 2001, to April 23, 2004, of 102 pediatric patients from 7 US pediatric intensive care units aged 2 weeks to 18 years who were treated with supine

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 biostatisics, “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

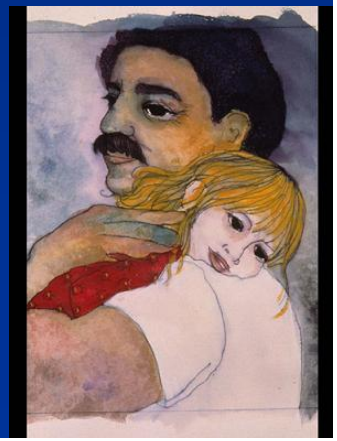
- Lung protective ventilator protocol
  - Low Vt strategy
  - Permissive hypercapnea
  - PEEP/FiO2 grid
  - HFOV
- Sedation protocol
- Extubation readiness testing
- Hemodynamic, nutrition, skin care guidelines

#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 coinvestigator-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.