Comparative Effectiveness Clinical Trials in the Elderly: Practical and Methodological Issues

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Overview of Talk

- Background on CER clinical trials
- Methodological issues
- Practical considerations
- Future directions

Key Themes

- Making CER more efficient and generalizable
- Strengthening the research infrastructure

Comparative Effectiveness Clinical Trials

- Head to head comparisons of treatments
  - Randomized or observational
- Treatments could be very different
  - Drugs vs. behavioral therapy
  - Drugs vs. surgery
  - Surgery vs. devices
- CER long history in clinical trials
  - Pragmatic (effectiveness) vs. explanatory (efficacy)
  - Schwartz/Lellouch 1967

Pragmatic vs. Explanatory Trials

Pragmatic (Effectiveness)

- Real world
- Community based pts
- Larger sample size
- Broader eligibility criteria
- Patient centered outcomes
  - Mortality, morbidity, QOL
- Strategy trial: different management strategies

Explanatory (Efficacy)

- Mechanistic
- Academic /specialized centers
- Smaller sample size
- Tighter eligibility criteria
- Surrogate outcomes
  - Biomarkers
- Double-blind, placebo-controlled drug trial

Pragmatic vs. Explanatory Trials (Cont'd)

- Distinction between pragmatic and explanatory studies not always clear
  - Most trials have elements of both – hybrid designs
  - Thorpe, et al. A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help design trials. J Clin Epidemiolol 2009; 62: 464-475.

CER Goal: Enhance Generalizability

- Design studies to apply to broader population of patients
  - Expand eligibility criteria
- Include sites more representative of general population
  - Generally select sites based on recruitment, research experience, etc.
    - Large metropolitan medical centers
  - Need to consider – small sites, community hospitals/clinics, rural areas

Enhancing Generalizability (Cont'd)

- Make trials larger to study important subgroups
  - Gender and race
- Simplify treatments to be easily applied in general clinical practice
  - Uncomplicated protocols
  - Little or no monitoring of adherence
- Use easily ascertained endpoints that don't require central adjudication

Enhancing Generalizability (Cont'd)

- Simplify data collection
- Use electronic data bases
- Revisit large simple trial concept
  - Physicians Health Study – 2x2 factorial design
    - ASA on CV events and beta carotene on cancer
    - Two studies for price of one

Key point: achieve generalizability through simplicity

Methodological Considerations

I. Management of risk factors
II. Maintaining clinical equipoise across sites
III. Accounting for patient preferences
IV. Incorporating evolving technology
V. Issues with usual care as a comparator

I. Management of Risk Factors

- Often single disease mentality by clinical trialists
  - Focused on disease under study
- Elderly have multiple conditions (syndromes) that need to be managed to avoid spurious treatment effects
- Example: VA CSP Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) Trial
  - Frequently cited study as an example of CER

COURAGE Trial (1999 - 2006)

- Determine best strategy to treat stable CAD
- ~2300 pts from 50 US/Canadian centers randomized to
  - Optimal medical therapy (OMT): intensive pharmacological therapy + lifestyle intervention (diet, weight loss, regular aerobic exercise)
  - OMT + angioplasty
- Strategy of initial angioplasty did not reduce death/MI rate when added to OMT

COURAGE Trial (1999 - 2006)

- OMT worked: aggressive management CV risk factors in both study arms based on clinical practice guidelines
  - Elements of efficacy design = hybrid design

I. Management of Risk Factors (Cont'd)

Key point: Management strategy trials will require optimal management of all conditions for treatments to work

II. Clinical Equipoise Across Sites

- Clinical equipoise: general uncertainty whether or not treatments being tested will be beneficial
  - Fundamental principle of clinical trials
- Maintaining equipoise challenging in studies which
  - Primarily test established therapies where
  - Clinical opinions about trt preferences more entrenched
- Particularly when different treatment cultures and practices across geographic areas
- Example: VA CSP Options in Management of Antiretrovirals (OPTIMA) Trial

OPTIMA Trial (2001- 2007)

- VA, Canada, UK trial evaluate 2 strategies for treating patients with advanced HIV disease (salvage therapy)
- 2x2 factorial design
  - Drug intensification (> 5 drugs) vs. std HAART (≤ 4 drugs)
  - Antiretroviral drug-free period (3 mo.) vs. no drug-free
- Canada: certain regions preferred drug intensification vs. drug-free period preferred in other regions
  - Difficult to recruit to both treatment arms in Canada

II. Clinical Equipoise Across Sites (Cont'd)

Key point: lack of geographic wide equipoise can affect trial conduct

III. Patient Preferences

- Patients often have treatment preferences, particularly in studies of established therapies
- Preferences need to be considered in trial design
  - Can affect recruitment and adherence
- Examples
  - VA CSP OPTIMA Trial
  - NIMH Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Study

VA CSP OPTIMA Trial

- UK patients had preference for drug free period or no drug free period, but not intensity of antiretroviral therapy
- Result: factorial design changed to allow patients to opt out of drug free phase but still participate in drug phase
- Highlights need for flexible designs

NIMH STAR*D Study (2001-2006)

- Different treatment options for major depressive disorder
- Patient treatment preferences accommodated as part of equipoise stratified randomization design
- 7 treatment options divided into groups that would be acceptable to both patients and physicians
  - “equipoise stratum”
- Each equipoise stratum had several treatment options
- Patients randomized to treatment options within each equipoise stratum

III. Patient Preferences (Cont'd)

Key point: Flexible designs that accommodate patient preferences in studies of established therapies may become more relevant in CER era

IV. Evolving Technology

- Much CER discussion focuses on established therapies
- However, therapies can evolve during course of trial (devices) and new therapies introduced (drugs)
- Example: VA CSP Open vs. Endovascular Repair (OVER)

OVER Trial (2002 - 2011)

- Designed to determine best strategy for treating AAA
  - Open surgery vs. any approved endovascular repair device
- Because trial duration was 10 years, designed to incorporate new devices
- Not designed to test any particular device, but devices in general, so it could accommodate device modifications and changes

IV. Evolving Technology (Cont'd)

Key point: Evolving technology needs to be considered at design phase to ensure trials remain relevant when completed, particularly in CER where study durations will be longer

V. Issues with Usual Care as a Comparator

- UC often used as control comparator therapy when active control not available
- Standardization of UC needs careful consideration
  - Can result in treatment different from usual clinical practice
    - E.g., controlling for contact time in behavioral studies
  - Inferences would apply to something other than usual clinical practice

V. Issues with Usual Care (Cont'd)

- Scientific and ethical issues surrounding usual care complex (NIH Conference 2005)
  - Designs incorporating usual care need to be based on scientific validity, consideration of risks and benefits, relevance to clinical care community and feasibility

V. Issues with Usual Care (Cont'd)

Key point: inferences to clinical practice need to be considered when using usual care as the control comparator therapy; changes to usual care may not equate to clinical practice

Practical Considerations

A. Elderly patient populations
B. Study site selection
C. Sample Size
D. Treatment fidelity

A. Issues with Elderly Patient Populations

- Comorbidity common
  - Conditions other than one under study need to be managed to avoid spurious treatment effects (COURAGE Trial)
- Physical and cognitive limitations
  - Lack of mobility, frailty
  - Surrogates and caregivers
- Environmental factors
  - Transportation issues – how to get patients to treatment

Key point: These issues contribute to recruitment, adherence, study execution/logistic problems

B. Issues with Broadening Site Selection

- Inclusion of small/rural sites to enhance generalizability can be problematic
  - Lack of research experience and trained personnel - need more training and oversight
  - Fewer number of eligible patients
  - Underrepresented subpopulations, e.g., race
- E.g., VA healthcare system is single nationwide system
  - Studies typically conducted at sites based on size and research experience
  - May not be representative of broader VA population

B. Issues with Broadening Site Selection

Key Point: Broadening site selection enhances generalizability but has practical limitations

C. Issues with Sample Size

- Studies of established treatments often result in testing smaller effect sizes
- Broadening inclusion criteria creates more heterogeneous populations, introduces more variability
- Net effect to increase sample size
- To achieve adequate power to test subgroups requires further increases in sample size

Key point: trials usually lag in recruitment, larger CER trials will exacerbate this problem

D. Issues with Treatment Fidelity

- In pragmatic trials usually little or no measurement of compliance with treatment
- However, cases in which maintaining treatment fidelity critical, particularly in strategy trials
- When treatments look more alike, it becomes harder to detect differences in effects
- Example: VA/NIH Acute Renal Failure Trial Network (ATN) Study

ATN Trial (2003 - 2007)

- Designed to determine best strategy to treat critically ill hospitalized patients with acute kidney failure:
  - Usual treatment with dialysis every other day
  - Intensive treatment: dialysis every day
- Strict monitoring of adherence resulted in good separation of treatments

Key point: monitoring adherence can be critical for maintaining treatment fidelity: element of efficacy design

Future Directions

- Many more treatments available for testing than can be possibly evaluated
  - Consider more efficient use of observational studies for screening of treatments
- To increase number of geriatric CER studies will require
  - Making studies more efficient
  - Strengthening research infrastructure

Making Studies More Efficient

- CER studies will be larger and to be feasible will need to be more efficient
- Revisit large simple trial concept
  - Enroll large numbers of patients and sites
  - Use broad eligibility criteria
  - Collect minimal amounts of data with greater use of centralized follow-up using electronic data bases
    - Use data already available rather than collecting it again

Making Studies More Efficient (Cont'd)

- Plan ahead for studies using same infrastructure rather than re-creating it again
  - Run concurrent and sequenced studies
- Take advantage of natural experiments
  - Radiation therapy for prostate cancer – sites predominately use one form of radiation treatment or the other
    - Observational approach in addition to RCT
- Consider adding observational components to randomized studies to better assess generalizability

Strengthening Research Infrastructure

- Create stable infrastructure
  - Permanently funded centers
  - Expertise for conducting RCTs and observational studies
  - Methodologists to work alongside collaborating scientists
    - Develop novel designs and analytical methods
    - Improve logistics for conducting studies (overlooked issue)
  - Provide for certification/training programs
  - Protect investigators' time
- Consider VA CSP model

Summary

- A strategy to enhance the potential number CER geriatric studies would include
  - Investing in a stable infrastructure of specialized centers
  - Simplifying studies