

'Advanced' Clinical Trials Course

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|----------|---------------------------------|------------|
| 1. | Design | RP |
| 2, 3. | Implementation | AL, GA |
| 4. | Monitoring | GA |
| 5, 6, 7. | Analysis | GA, AL, AL |
| 8. | Communications | AL |
| 9. | Managing reaction to CT results | GA/AL |
| 10. | CT's in prevention research | RP |

Most presentation and discussion focused on Women's Health Initiative CT (Co-PI's of Clinical Coordinating Center)

Prevention Trial Design: Example of the Women's Health Initiative

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- OBJECTIVE
- Describe the basic set of assumptions needed, and related trade-offs in designing a large-scale prevention trial.

WHI Clinical Trial Design

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	Design	Actual
Dietary modification	(n = 48,000)	(48,836)
Hormone replacement therapy – E alone	(n = 12,375)	(10,739)
Hormone replacement therapy – E & P	(n = 15,125)	(16,608)
Calcium and vitamin D	(n = 35,000 to 45,000)	(36,282)

Major Trial Design Choices

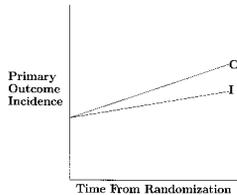
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- Study population
- Trial outcomes
 - Primary, secondary, adverse
- Study duration
- Sample size and power

Design Assumptions

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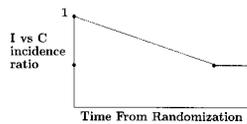
- Control group disease incidence rates
- Full adherence relative risk for intervention versus control subjects
- Intervention adherence
- Loss to follow-up and competing risk mortality rates
- Calculate probability of rejecting null hypothesis (power) if sample size
 - n (αn intervention, $(1-\alpha)n$ control) drawn from these curves.



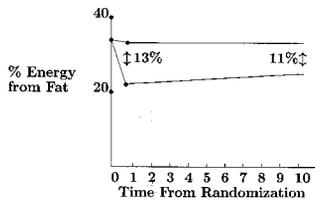
e.g., WHI Dietary Modification Component (Breast and Colorectal Cancer, and CHD)

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- Control group incidence rates as a function of age.
 - SEER data for years 1985-89
 - Age distribution:
 - 50-54 10%
 - 55-59 20%
 - 60-69 45%
 - 70-79 25%
 - Healthy volunteer effect (33% for CHD)
- Full adherence relative risk assumption



Intervention and Control Group Dietary Adherence (% Energy from Fat)



3% per year loss to follow-up and competing risk mortality.

Incidence Rates for Intervention and Control Groups

$$\lambda_I(t) = \lambda_C(t) [1 + X_I(t)\beta]$$

$$\lambda_C(t) = \lambda_C(t) [1 + X_C(t)\beta]$$

$$\text{where } X(t) = (-1) \int_{t-10}^t \{Z(u) - 35\} du$$

$$\text{and } \beta = .5/15$$

$$P_I(t) = \int_0^t \lambda_I(u) \exp - \int_0^u \{\lambda_I(w) + \Psi(w)\} du$$

$$P_C(t) = \int_0^t \lambda_C(u) \exp - \int_0^u \{\lambda_C(w) + \Psi(w)\} du$$

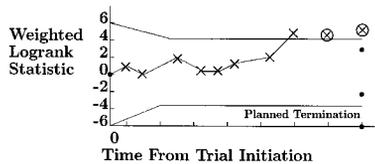
STATISTIC FOR TESTING NULL HYPOTHESIS

$$T = \sum w_i(O_i - E_i)$$

Power:

- Generate disease occurrence times and censoring times from above
- model for sample of size n , and compute T .
- Repeat many times. Estimated power is fraction of T values that
- exceed a certain critical value for the null hypothesis distribution of T .

Primary Outcome Intervention Versus Control Comparisons



- Probability of crossing bounding is .05 under null hypothesis
- Choice of boundary shape (O'Brien, Fleming, 1979 Biometrics)
- Most significance probability (.045) saved for planned termination

Additional Aspects of Trial Design and Development

- Randomization fractions, stratification
- Blinding
- Protocol development
- Cost projections
- Feasibility studies
- Funding

Aspects of Trial Planning

- Explicit protocol and procedures
- Database developments and periodic reporting
- Study organization and communications
- Monitoring of factors related to study power, and related innovations as needed
- Participant consent and safety
- Internal and external data and safety monitoring

RCT's in the Chronic Disease Prevention Setting

Challenges:

- Expensive, logistically difficult
- May require long follow-up period, with associated adherence uncertainties
- Possible interpretation issues if study subjects make changes beyond those intended
- Possible generalizability issues
- May be difficult to ensure safety

RCT's in the Chronic Disease Prevention Setting

Strengths:

- Permits study of treatments/interventions not self-selected by sufficient numbers of persons in populations of interest
- Provides 'clinical' context for unbiased outcome ascertainment and for meaningful benefit versus risk analyses
- **Ensure independence between treatment/-intervention and other risk factors, whether or not recognized or readily measured**
