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Developing Scientific Research Proposals (Grant Writing)

2003 Epidemiology and Biostatistics Summer Session



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Session 5

Methods Continued

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Measures

Include many types of parameters:

- Lifestyle (smoking, exercise, diet)
 - Demographic (age, gender)
 - Medical history (cancer, surgery)
 - Family history (colon cancer, diabetes)
 - Work history (job exposures, duration)
 - Physical exam (blood pressure)
 - Biochemical parameters (CRP, Chol. Level)
 - Genetic and genomic information
 - etc.
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Measures

From many sources:

- Self-report
- Next of kin
- Medical records
- Work records
- National registries
- Benefits lists
- Work records
- Etc.

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Measures

Classify variable types

- Independent variables from specific aims (exposure)
- Dependent variable from specific aims (outcome/endpoint)
- Covariates (confounding variables)

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Measures: Baseline collection

- Sets the tone for future collections
- Get everything you need in the beginning because it's hard to go back

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Measures: Exposures / Other Data

Propose to collect only what you need

- Participant burden
- Costs
- Relevance to specific aims
- Invasiveness
- Risk

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Measures

Describe assessments

- Questionnaire
- Self/interviewer-administered
- Biological samples
- Medical or other records
- Vital registries

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Validity/Feasibility

Questionnaire

- Previously used (hopefully well-characterized)
- New instruments, based on other instruments
- New instruments, valid by pilot study
- New instruments, validated within study

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Measures: Outcomes / End Points

- Ascertainment
- Confirmation/validation
- End points committee

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Measures: Outcomes / End Points

Ascertainment

- Self report
- Physical measurements
- Medical records
- Registries

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Measures: Outcomes / End Points

Confirmation/validation

- Should you obtain records?
- Do you need an endpoints committee?
- Blinded confirmation is essential
- Multiple opinions
- Well defined process

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Specimen Collection

- Is it necessary?
- How will it enhance the study?
- DNA
- Consent issues

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Laboratory Assays

Laboratory assays

- Reference laboratory
- Standardized kits
- Up-and-running assay
- Established procedure, to be established

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Follow-up

- Mechanism – mail, phone, in person
- How often?
 - monthly
 - yearly
- What to do with no response?
- What do you need to collect?

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Follow-up plan

- Clinic visits
- Mail
- Phone
- Administrative or clinical databases
- Death indexes

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Data Management / Quality Assurance

- Flow of data
- Quality assurance
- Quality control
- Archiving
- Storage

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Human Subjects Issues

Define the Consent process

- Who will inform?
- Witnesses?
- Proxies needed?
- How do you document consent?

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Human Subjects Issues

Issues addressed in the document and in your discussion of the consent process

- Expectations of participation
- Sub-studies (optional)
- Risk to subjects
- Alternatives

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Human Subjects Issues

Issues addressed in the document and in your discussion of the consent process

- Confidentiality
- HIPPA
- Rights of participants to withdrawal and information

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Limitations

- Don't shoot yourself in the foot
- Have an answer for every limitation

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Institutional Infrastructure

- Space
- Informatics support
- Equipment
 - computing system
 - data storage
 - backup systems

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Example: The Physicians' Health Study Aspirin Component

Overview:

The PHS is a large-scale, placebo-controlled, double-blind, factorial-design, randomized trial of aspirin and beta carotene in the primary prevention of cardiovascular disease and cancer among 22,071 US male physicians. The study is conducted entirely by mail.

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Physicians' Health Study

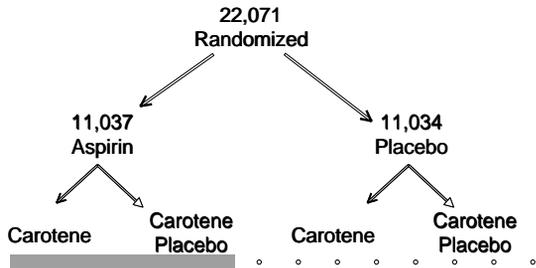
Design:

- placebo-controlled, double-blind, randomized trial
- 2x2 factorial design (4 treatment groups)
 - Aspirin (ASA) alone
 - Beta carotene alone
 - Aspirin and beta carotene
 - Both placebos

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Physicians Health Study

Randomized Scheme



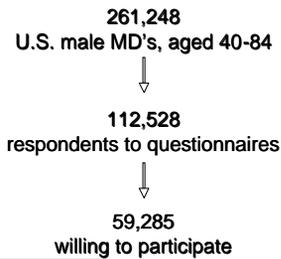
Physicians' Health Study

Study Population:

- US male physicians
- Age 40 to 84 years at baseline
- No ASA or BC allergy
- No prior history of MI, stroke, cancer or liver disease
- Willing to avoid outside ASA and BC
- Compliant with run-in

Physicians Health Study

Population Hierarchy



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Physicians Health Study

Run-In Phase

33,223

willing and eligible MD's
enrolled in run -in
(18 weeks on active aspirin and
beta-carotene placebo)



22,071
Randomized

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Physicians' Health Study

Treatment:

- Aspirin 325mg (Bayer) on alternate days
 - Beta carotene 50 mg (BASF) on alternate days
 - Delivered in calendar packs
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Physicians' Health Study

Endpoints:

- Primary for ASA:
 - MI (WHO criteria)
 - Stroke
 - Important CVD events (MI, Stroke, CVD death)
- Primary for BC:
 - Total epithelial cancer excluding non-melanoma skin cancer

Physicians' Health Study

Follow-up:

- Entirely by mail and phone
- Questionnaires were sent at 6 months and 1 year after randomization, then yearly.
- Six month post cards were sent between yearly questionnaires.
- Non-response was followed with subsequent mailings and then telephone calls.
- Follow-up rates were extremely high: 100% for mortality, % for morbidity.

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Physicians' Health Study

Measures:

- Endpoints
- Compliance with study pills
- Use of outside ASA or BC
- Potential effect modifiers: NSAID use, et
- Brief food frequency questionnaires.
- Potential side effects
- Various exposure variables

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Physicians' Health Study

Specimen Collection:

- Specimens were collected by mail at baseline.
- Kits with instructions were mailed to participants.
- Blood specimens were shipped via over night express mail.
- Upon arrival they were processed and stored in freezers for future use.

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Physicians' Health Study

Data management / Quality Assurance:

- All data management was done in house at BWH.
- Questionnaires were date stamped on arrival.
- Manual scanning was done to check for completeness and for new endpoint reports.
- Complete forms were entered twice.
- Incomplete forms often require mail or phone clarification.
- Forms with new endpoints were given priority.

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Physicians' Health Study

Data management:

- Forms with new endpoints were given priority.
- Medical records were requested for all major endpoints and other events of interest.
- Medical records were processed and sent to the endpoints committee for adjudication.
- Endpoint data was then coded and entered.

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Physicians' Health Study

Analysis:

- All analysis were conducted using SAS.
- Analysis were based on intention to treat.

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Physicians' Health Study

Power / Sample Size Consideration:

- The projected power of the study to detect differences for ASA on various CVD outcomes was overestimated.
- This was likely due to the healthy volunteer effect and to the excellent access to health care of physicians reducing overall CVD events dramatically. The observed CVD mortality rate was 15% of expected.

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Physicians' Health Study

Human subjects issues:

- Consent was obtained by mail
- Both study agents are very safe
- Physicians understood well the issues involved in participation

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Physicians' Health Study

Limitations:

- All male population
- All healthy physicians
- Minorities under represented

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Physicians' Health Study

Infrastructure:

- Adequate space
- In house computing and data storage system with back up
- In house mail room to ship study pills and receive blood specimens
- In house laboratory for specimen processing and long-term storage

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Physicians' Health Study

Budget issues:

This study was conducted at extremely low cost. The cost for each participants treatment and follow-up was less than \$100. This compares favorable to other trials where costs can be as high as \$10,000 per participant.

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Physicians' Health Study

Findings:

Highly significant 44% reduction in first fatal MI.

Nonsignificant trend toward excess risk of stroke.

Effects were comparable in most subgroups.

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Methods Check List

- Is the overview clear?
- Is the design well thought out?
- Is the choice study population scientifically sound?
- Is the recruitment strategy feasible?

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Methods Check List

- Are the measurements clearly defined and instruments justified for all exposures, outcomes and other variables?
- Did you include the measurement instruments?
- Is specimen collection planned?
- Will the follow-up plan maximize follow-up and efficiency?

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Methods Check List

- Is the data management flow spelled out? Use a figure if necessary.
- Is the analysis plan spelled out for each aim?
- Can power / sample size be justified?
- Have all human subjects issues been address? Remember HIPPA.

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Methods Check List

- Are the major limitations mentioned and then addressed?
- Is the infrastructure described?
- Does the budget make sense?

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Methods Check List

For trials:

- Is the intervention / treatment clear, feasible, logical?
- Can you project good long term compliance?
- Are side effects and other risks minimal?
- Is a data and safety monitoring plan in place?

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