Design, Conduct, and Analysis of Clinical Trials

Course Slides

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Preface

The slide facsimiles contained herein are the product of various lectures and course offerings bearing on the design, conduct, and analysis of clinical trials as offered in a variety of settings in the Johns Hopkins School of Hygiene and Public Health and elsewhere.

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Design, Conduct, and Analysis of Clinical Trials

Course Slides

1 Introduction

1 Introduction

Clinical trial definition

An experiment designed to assess the efficacy of a test treatment by comparing its effects with those produced using some other test or control treatment in comparable groups of human beings.

Essential requirements

- Designed
- Test and control treatment
- Comparable treatment groups
- Followup for a specified outcome

Book of Daniel comparative study

Prove thy servants, I beseech thee, ten days; and let them give us pulse to eat, and water to drink. Then let our countenances be looked upon before thee, and the countenance of the children that eat of the portion of the King's meat; and as thou seest, deal with thy servant. So he consented to them in this matter, and proved them ten days. And at the end of ten days their countenances appeared fairer and fatter in flesh than all the children which did eat the portion of the King's meat.

Chapter 1, Verses 12-15
King James Version[2]

Before and after observation of Paré

I raised myself very early to visit them, when beyond my hope I found those to whom I had applied the digestive medicament, feeling but little pain, their wounds neither swollen nor inflamed, and having slept through the night. The others to whom I had applied the boiling oil were feverish with much pain and swelling about their wounds. Then I determined never again to burn thus so cruelly the poor wounded by Arquebuses

Ambroise Paré (1510-1590)[43]

1 Introduction

Lind's scurvy experiment

On the 20th of May, 1747, I took twelve patients in the scurvy, on board the Salisbury at sea. Their cases were as similar as I could have them. They all in general had putrid gums, the spots and lassitude, with weakness of their knees. They lay together in one place, being a proper apartment for the sick in the fore-hold; and had one diet common to all, viz., watergruel sweetened with sugar in the morning; fresh muttonbroth often times for dinner; at other times puddings, boiled biscuits with sugar, etc; and for supper, barley and raisins, rice and currants, sago and wine, or the like.

Two of these were ordered each a quart of cyder a-day. Two others took twenty-five guts of elixir vitriol three times a-day, upon an empty stomach; using a gargle strongly acidulated with it for their mouths. Two others took two spoonfuls of vinegar three times a-day, upon an empty stomach; having their gruels and their other food well acidulated with it, as also the gargle for their mouth. Two of the worst patients, with the tendons in the ham rigid, (a symptom none of the rest had), were put under a course of sea water. Of this they drank half a pint every day, and sometimes more or less as it operated, by way of gentle physic.

Two others had each two oranges and one lemon given them every day. These they ate with greediness, at different times, upon an empty stomach. . . The two remaining patients, took a bigness of a nutmeg three times a-day, of a electuary recommended by an hospital surgeon, made of garlic, mustard-seed, red raphan, balsam of Peru, and gum myrrh; using for common drink, barley-water well acidulated with tamarinds; by a decoction of which, with the addition of cremor tartar, they,were gently purged three or four times during the course.

. . . the most sudden and visible good effects were perceived from the use of oranges and lemons, one of those who had taken them being at the end of six days fit for duty.

Lind's Treatise on Scurvy, 1753[33]

1 Introduction

Lind's design[33]

No of treatments	6
Test treatments	5
Cyder, 1 qt / day	
Elixir vitriol, 25 gutts, 3 times / day	
Vinegar, 2 spoonfuls, 3 times / day	
Oranges (2); lemon (1) / day	
Bigness of nutmeg 3 times / day	
Control treatment	1
Sea-water, 1/2 pt / day	
Length of followup	6 days
Outcome measure	Fit for duty

Landmark events

- Untreated comparison group (Lind, 1747)[33]
- Sham procedure (Haygarth, 1800)[27]
- Placebo treatment (Gull & Sutton, 1863)[52]
- Randomization as a research tool (Fisher & Mackenzie, 1923)[21]
- Medical Research Council call for clinical trials (1931)[34]
- Randomization in medical experiment (Amberson et al, 1931)[1]
- Multicenter trial (Patulin Clinical Trials Committee, 1944)[44]
- Consent guideline (USPHS, 1966)[32]
- Congressional mandate regarding valid analysis for gender and ethnic origin treatment interactions (US Congress, 1993)[54]

1 Introduction

Types of trials covered

- Controlled trials
- Concurrent enrollment and followup
- Uncrossed treatments
- Groups created by random assignment
- Patient as randomization unit
- Clinical event (eg, MI, recurrence of cancer, or death) as outcome measure

Characteristics of trials covered

- Large sample size
- Multiple clinics to achieve recruitment goal
- Long period of patient recruitment and followup
- Followup period extends well beyond close of patient recruitment

Trials not considered

- Uncontrolled trials
- Trials with historical controls
- Crossover trials
- Animal trials
- In vitro trials

Essential design features

- Statement of purpose
- Specified study treatments (test and control treatments)
- Treatment plan
- Stated recruitment goal
- Bias free procedure for treatment assignment
- Procedures for bias control
- Explicit plan for data collection and patient followup
- Measurable outcome

1 Introduction

Design mistakes

- Ill conceived objective
- Outcome measure not specified
- Sample size of convenience
- No recruitment goal
- Equating data collection requirements for patient care to those of the trial
- Being in a hurry!

2 Bias control

2 Bias control

Bias: General definition

Systematic error introduced into sampling or testing by selecting or encouraging one outcome or answer over others

Webster's New Collegiate Dictionary, 1981

Treatment related bias

A bias related to treatment assignment that affects the treatment differences observed in the trial

Minimal requirements for bias free trials

- Establish comparable study groups that are free of selection bias
- Data collection schedule where probability of observing an event is the same for all patients
- Use defined treatment procedures that are reproducible

Examples of bias

- Use of schedules in which assignments are known or revealed before patients are enrolled (eg, with an open assignment list or with most systematic schemes)
- Sealed envelopes that are illuminated or opened to reveal assignments before they are issued
- Differential treatment refusal or dropout rates
- Use of different exam schedules by treatment groups
- Individualized treatment procedures that vary from physician to physician in unmasked trials
- Use of a subjective outcome and where outcome measurements and assessments are performed by treatment personnel in unmasked trials

2 Bias control

Methods of bias control

- Randomization
- Masking
- Standardization
- Surveillance

Masking

A condition imposed on a specified procedure (eg, administering study treatments, evaluating patient status, interpreting ECG's, coding cause of death) that is intended to keep knowledge of the treatment assignment, course of treatment, or previous observations on individual patients from a specified set of individuals (eg, patients, treating physician, laboratory technician, Treatment Effects Monitoring Committee)

Levels of treatment masking

- **Single**: Physician is informed of treatment assignment but patient is not
- **Double**: Neither patient nor physician is informed of treatment assignment
- **Triple**: Double masked trial with masked treatment monitoring group

Masking principles

- Masked administration of treatment preferable to unmasked administration
- Masked data collection preferable to unmasked data collection
- Treatment assignments in masked trials should be revealed only to those who have a need to know

2 Bias control

Masking problems

- Practical problems in treatment administration
- Side effects that unmask
- Accidental unmasking
- Deliberate unmasking

Mask maintenance

- Withhold data that may unmask
- Use unique bottle numbers in masked drug trials
- Minimize possibilities for unmasking

Other masking considerations

- Separation of treatment administration and evaluation, and data collection and evaluation functions in unmasked trials
- Use of special devices, such as the random zero muddler to measure blood pressures
- Masked readings and codings

Standardization for bias control

- Written treatment protocol
- Tested data forms, handbooks, and manuals of operations
- Written definitions
- Standard equipment
- Training and certification of study personnel
- Independent data center

2 Bias control

Possible indicators of treatment related bias

- Lack of baseline comparability of treatment groups
- Breakdowns in the treatment assignment process
- Differential treatment refusal rate
- Differential dropout rate
- Differential rate of interim examinations
- Differential rate of hospitalizations
- Unnecessary or differential unmasking
- Differential treatment protocol violations
- Differential error rates
- Differential variance of key measurements

"Corrections" for bias

- Early detection and correction
- "Worst case" analyses (Note: No mathematical models for adjustment exist)
- Data purges
- Abort trial
- Report in publications

3 Variance control

3 Variance control

Variance

[MF *variaunce,* fr MF, fr L *varianita,* fr *variant-, varians,* prp of *variare* to vary]

General: 1. The fact, quantity, or state of being variable or variant. 2. The fact or state of being in disagreement.

Statistics: 1. A parameter equal to the second moment of the underlying variable or its associated distribution function. 2. A measure of dispersion of a frequency distribution that is the square root of the arithmetic mean of the squares of the deviations of the values represented in the distribution from the mean of the distribution; a similar quantity using n - 1 rather than n as a divisor

Sources of variation in trials

- Patients
- Treaters
- Data collectors
- Data coders and keyers
- Data analysts
- Paper writers and printers

3 Variance control

Variance control strategies

Via design
- Crossover designs
- Matching

Via patient selection
- Selectivity
- Exclusion

Via execution
- Stratification
- Blocking
- Standardization

Via analysis
- Use of baseline covariates for adjustment
- Subgroup analyses

Variance reduction strategies

- Increased sample size
- Replication of the same measurement
- Ongoing surveillance and quality control
- Ongoing data editing
- Standardization

Variance control aids

- Written protocol
- Procedures handbook
- Outlier detection and trimming procedures
- Standardized equipment
- Central readings and determinations
- Training and certification
- Site visits

3 Variance control

Replication for variance reduction

Remember

- Independent replications are more costly then dependent replications
- Dependent replications are not as useful for variance reduction as independent replications
- The number of replications required for variance reduction is a function of the underlying variance of the measure
- Many measures in the trial setting are repeated needlessly, eg, most laboratory determinations

Examples

- Double data entry
- Duplicate laboratory determinations
- Duplicate measurements, eg, 2 blood pressure measurements with 30 second rest between measurements

3 Variance control

Stratification terminology

stratum, **strata**: [NL, fr L spread, layer, bed, fr neut of *stratus*, pp of *sternere* to spread out] A series of distinct levels or layers. In trials, generally subgroups of persons formed by classification on some variable or set of variables, usually baseline variables. Not to be confused with blocks.

stratification: 1. An active ongoing process of stratifying, eg, as in placing patients into strata as they arrive at a clinic as a prelude to enrollment and randomization to treatment in a trial. 2. post-stratification

post-stratification: The act or process of classifying observations or treatment units into strata after the fact, eg, as in classification as a prelude to a subgroup analysis.

stratification variable: A variable believed to influence treatment outcome, observed at or prior to randomization, and used to create assignment strata consisting of defined subgroups of patients

stratified randomization: The process of controlling the distribution of a variable (eg, sex, age at entry, baseline blood pressure) among treatment groups by using that variable to define assignment strata

assignment stratum: A stratum formed by a stratification variable and involving blocked randomization

Stratification examples

- Clinic in a multicenter trial
- Demographic characteristics, such as sex, race, or age at entry
- Baseline laboratory measurements, such as fasting blood glucose level
- Physiologic characteristics, such as blood pressure at entry
- Clinical characteristics, such as history of MI at entry

3 Variance control

Stratification considerations

- Select variables believed to influence treatment outcome
- Limit choice to small number of variables
- Gain in precision minimal in trials involving >50 patients per treatment group
- Stratification does not eliminate need for adjustment for differences in the baseline composition of the study groups
- Use of patient characteristics for stratification increases logistical complexities of the assignment process
- The larger the number of assignment strata the greater the chance of a sizable departure from the expected assignment ratio (Note: One can guard against such departures by using blocks of small size but the pattern, if discovered, may allow study personnel to predict assignments)

When to stratify

- Expected quantitative interaction (exclude if qualitative)
- Different treatment regimens or dosage requirements depending on strata
- Variance control of a variable assumed to be predictive of outcome
- Logistical simplicity (eg, regarding drug supply)
- Designed comparisons within specified strata

Sample stratification variables

- Demographic characteristics, eg, sex, race, age at entry
- Baseline characteristic
- Disease history or state
- Prior treatment
- Geography or surrogate (eg, clinic)

3 Variance control

Stratification foolishness

- Too much stratification; too much is like none at all
- Assuming that use of a stratification variable obligates one to make comparisons and to draw conclusions regarding treatment within the various strata defined by the variable
- Treating strata as having required samples sizes, eg, as in the notion of recruitment quotas based on sex or race

The politics of stratification

- There is the likelihood you will be judged to be "stupid" if you fail to stratify on variables perceived as important, especially if they turn out to be maldistributed
- It is sometimes easier to stratify on something than to have to explain why you did not
- People who believe stratification is a good idea will not understand scientific arguments having to do with gains and losses

Stratification vs post-stratification

Difference

Stratification is an active process carried out as a prelude to enrollment; post-stratification is a passive process performed as a prelude to analysis

Similarity

Both are done for the same reason — variance control in regard to the variable(s) used for classification

Notes and observations

- Use *stratification* to refer to the active process and *post-stratification* to refer to the passive process
- Subgroup analyses using characteristics observed at or prior to randomization are forms of post-stratification
- Post-stratification is a poor man’s approach to other more sophisticated forms of adjustment for baseline differences in the composition of the treatment groups
- There are profound operational differences between stratification as a prerequisite to randomization and post-stratification

3 Variance control

Variance reducing analysis procedures

- Trimming and Winsorization
- Subgroup analyses
- Repeated measures designs
- Multiple regression analyses

4 Funding

4 Funding

Methods of funding

Research grant: A gift to an institution to support research in a specific area; to be carried out under the direction of a named investigator.

Research contract: An agreement between sponsor and the receiving institution to carry out a specified activity and to deliver at its conclusion a specified end product; performed under the direction of a named individual.

Grant vs contract

Research grant
- Fixed funding ceiling
- Award may cover up to 5 years
- Designed to produce or promote research in some area
- Investigator controlled

Research contract
- Usually cost reimbursement
- Funded in yearly increments
- Designed for delivery of a product
- Sponsor controlled

Methods of initiation

Investigator
- Unsolicited grant application (R 01)
- Unsolicited contract proposal (rare)

Sponsor
- Request for (grant) application (RFA)
- Request for (contract) proposal (RFP)

4 Funding

Single vs multicenter clinical trial

	Single center	Multicenter
Initiative	Investigator	Sponsor
Funding	Grant	Grant or contract
Fund distribution	NA	Direct or indirect
Sponsor	Nondirective	Directive

Impediments to multicenter trials

- Inadequate design
- Negative attitudes of colleagues
- Cost
- Publication and promotion policies
- Logistical difficulties, especially in planning
- No planning grants
- NIH structure and nature of review process
- Conversion to contract or cooperative agreement

Investigator vs sponsor initiated trials

Investigator initiated

- Key investigators self-selected and specified in grant applications
- Research plan developed by investigators
- Investigators organize and operate the trial
- Communications with sponsor during preparation of applications

Sponsor initiated

- Investigative group chosen by sponsor and unknown to applicants at time of application
- Basic research plan developed by sponsor
- Sponsor usually has major role in organization and operation of trial
- No or limited communication with sponsor during preparation of response to RFA or RFP

4 Funding

RFAs and RFPs: Investigator perspective

- Unnatural constraints on communications with sponsor, especially during response
- Unrealistic specifications or expectations
- Short response time
- Absence of information concerning qualifications of other applicants
- Business mentality applied to research

Questions of RFAs and RFPs

- Is the request genuine?
- Is the problem proposed worthy of investigation?
- Is the project likely to achieve its stated aim?
- Does the project have a realistic timetable?
- Does the sponsor desire input in the design and operation of the trial?
- Are the suggested staffing and budgeting guidelines realistic?
- Is the project office experienced in clinical trials?
- Does the RFA or RFP indicate the amount of money available for the trial?

Funding principles

- Request what is needed
- Request adequate support for start up and close down
- Make certain there is balance in the allocation of funds for data generation vs data intake and analysis
- Monitor expenditures and project future costs

4 Funding

Budget items

Personnel
- Center director and co-director
- Study physicians
- Center coordinators
- Lab technicians
- Biostatisticians
- Programmers
- Data coordinators
- Data entry personnel
- Research assistants
- Administrative assistants
- Secretaries
- Clerks
- Other as needed

Consultants

Equipment
- Office
- Clinic
- Data processing

Supplies
- Office
- Clinic
- Data processing

Travel
- Staff
- Consultants
- Committee members
- Patients

Patient related expenses

Alterations and renovations

Other expenses
- Equipment maintenance
- Telephone
- Copying and reproduction charges
- Data entry
- Study insurance
- Books and journals
- Page charges
- Study forms
- Clinic fees (eg, lab charges)
- Space rental
- Moving charges
- Indirect costs

NIH inventory of clinical trials

Fiscal year	No of trials	Total cost	Cost/pt/yr of trial
1975	755	$87,817,682	$878
1976	926	120,626,279	923
1977	746	105,322,375	1,377
1978	845	122,339,823	1,715
1979	986	136,160,116	Unavail

4 Funding

NIH multicenter vs single center cost (FY 1975)†

	No. of trials	millions $	Cost/pt/yr of trial
Single center	653	$42.0	$931
Multicenter	102	45.8	544
Total	**755**	**87.8**	**878**

† *1975 NIH Inventory of Clinical Trials, multicenter trials identified from entries with multiple awards*[40]

Funding type: Multi vs single center trials†

	No of trials	Grant	Contract	Both
Single center	536	77.6%	22.0%	0.4%
Multicenter	102	26.5%	26.5%	47.0%
Total	638	69.4%	22.7%	7.8%

† *1975 NIH Inventory of Clinical Trials, multicenter trials identified from entries with multiple awards*[40]

Sources of private support

- Drug and biotechnology firms
- Device manufacturers
- Research foundations

4 Funding

Clinical trials: Drug company model

- Initiative from drug company
- Company recruits clinical centers
- Company monitors performance and does data analysis
- No or loose collaborative structure
- No publication guidelines or requirements

PARIS as a model for industry funding†

- Separation of trial leadership from drug firm
- Separation of data center from drug firm
- Investigators responsible for clinic selection and operation of trial
- Responsibility for fund dispersal outside control of drug firm
- Publication requirements according to study guidelines
- Written agreement with drug firm regarding separations and trial procedures

† *PARIS Research Group, 1980*[45]

5 Study protocol

5 Study protocol

Natural history of a treatment modality

- Early positive reports
- Widespread use without adequate testing
- Emerging doubts
- Initiation of trials
- Restricted use of the treatment

Factors in the timing of trials

- Availability of treatment and skill to apply treatment
- Ethical climate conducive to a trial
- Availability of suitable population for study
- Necessary financial support

Impediments to trials

- Reluctance to randomize
- Inadequate FDA requirements for licensure
- Lack of incentives
- Insufficient financial support
- Resistance from the scientific community
- Absence of demand for trials from the lay community
- Third party payment procedures

5 Study protocol

Considerations in the choice of the test treatment(s)

- Prior evidence on safety and efficacy
- Practicability of the treatment
- Availability of the treatment
- Amount of interest in the treatment
- Length of treatment and followup
- Representative nature of the treatment when a member of a family of treatments
- Method of administration
- Degree to which administration approximates a real world use
- Level of masking desired
- Treatment adherence measures to be used

Questions in the choice of the control treatment

- Is there an accepted standard treatment? If so, in what sense is it standard?
- Should the control treatment be active or inactive?
- Should there be more than one control treatment (eg, both a positive and negative control)?
- Is it ethical to withhold treatment or to use an inactive control treatment, such as a placebo or sham treatment?
- Is the proposed control treatment ethical?
- Is the choice consistent with the aims of the trial?
- Is the control treatment different from the test treatment?
- Could any patient in the trial receive either the test or control treatment?
- Is it possible to select a control treatment that permits masked administration of the test treatment?

5 Study protocol

Problems peculiar to drug trials

- Preliminary testing for toxicity and carcinogenicity
- Choice of route of administration (eg, IV, oral, patches)
- Dose level (ie, fixed vs variable)
- Bioavailability of the drug
- Drug purity
- FDA approval via IND
- Availability of the drug
- Packaging and dispensing
- Special reporting requirements
- Type and nature of financial support
- Conflicts of interest

Essential prerequisites

- Specified treatment procedures
- Specified procedures as contained in study handbook and manual of operations
- Specified data collection procedures and related data forms
- Specified examination and data collection schedule
- Specified informed consent procedure
- Funding

Elements of the treatment protocol

- Specification of treatments and methods of application
- Patient eligibility and exclusion criteria
- Indications for termination of assigned treatment and for implementing alternative treatments during the trial
- Specification of conditions for unmasking treatment in masked trials
- Indications of conditions or events that are to be regarded as endpoints for cessation of treatment or followup
- Safeguards for protecting patient welfare

5 Study protocol

Considerations in specifying eligibility criteria

- Homogeneity vs heterogeneity
- Select vs representative study population
- Real world vs experimental setting
- Desired population mix with regard to age, sex, race, etc
- Presumed treatment mechanism
- Nature and evidence of previous disease
- Other treatments; previous and current
- Contraindications for use of the test treatment; the control treatment
- Method of determining eligibility
- Time required for eligibility determination

Common mistakes concerning eligibility criteria

- Imposition of demographic restrictions, such as age, sex, or race, without a medical basis
- Use of medical exclusions not related to the study treatments
- Undue emphasis on homogeneity
- Elimination of a subgroup of patients because of size of the subgroup

Special problems

- Changes in admission criteria
- Addition or deletion of a treatment during the trial
- Publications from other studies on the same treatment during the trial
- Changes in community treatment patterns during the trial
- Changes in formulation or administration of test or control drug

5 Study protocol

Monitoring requirements

- Recruitment performance
- Protocol violations
- Data deficiencies
- Untoward events and serious side effects
- Beneficial treatment effects

6 Sample size

6 Sample size

Importance of sample size calculation

- Forces specification of primary outcome measure and estimated event rates for trial
- Leads to a recruitment goal
- Encourages development of timetable for the trial
- Discourages conduct of small inconclusive trials

Sample size mistakes

- No sample size calculation at all
- Calculation made with unrealistic assumptions
- No exploration of sample size characteristics for range of likely values
- Failure to compensate for losses due to dropouts, noncompliance, etc
- Failure to adjust sample size during the trial for unexpected problems
- Power not stated for completed trial that did not produce a treatment difference

NIH sponsored trials†

Median size	115
20th to 80th percentile	50 - 300
No. of trials	670

† *NIH 1979 Inventory of Clinical Trials*[42]

Factors leading to undersized trials

- Failure to make any sample size calculation
- Sample size of convenience
- Avoidance of multicenter collaborative structures
- Inadequate financial support
- Reward system for small trials and publish or perish mentality of academic institutions
- Lack of rigorous editorial policy of medical journals

6 Sample size

Elements needed for sample size calculation

- Number of treatments to be evaluated
- Outcome used to measure success of treatment
- Length of followup for outcome measure
- Type I and II error levels
- Assumed event rate for control treated group
- Treatment difference to be detected

HPT treatments

Na	Dietary counseling for Na restriction
NaK	Dietary counseling for Na restriction and K increase
Cal	Dietary counseling for calorie restriction
NaCal	Dietary counseling for Na and calorie restriction
Ct	No dietary counseling

HPT Research Group, 1989[28]

HPT eligibility criteria

- Men and women aged 25 through 49 at entry
- BL 1 diastolic BP $\geq$ 76 but < 100 mmHg
- BL 2 diastolic BP $\geq$ 78 but < 90 mmHg
- Quetelet's index (Wt/Ht^2) < 0.0500
- Informed consent

HPT Research Group, 1989[28]

Design parameters for HPT phase 2

α = 0.05 (Type I error, 2-sided)
β = 0.15 (Type II error)
P_c = 0.15 (5 yr conversion rate to hypertension)
P_t = 0.105 (30% reduction)
DO = 0.25 (5 yr dropout rate)

6 Sample size

Sample size requirements for HPT phase 2

1,268	Na
1,268	Cal
1,268	NaCal
2,196	Ct
6,000	**Total**

CDP sample size specifications

α = 0.01 (Type I error, 1-sided)
β = 0.05 (Type II error)
P_c = 0.30 (5 yr death rate for plbo treated group)
P_t = 0.225 (5 yr death rate for test treated group)
Do = 0.30 (5 yr loss rate per treatment group)

Computed sample size:

CPIB	1,117
DT-4	1,117
ESG1	1,117
ESG2	1,117
NICA	1,117
PLBO	2,793
Total	**8,378**

6 Sample size

AMIS sample size specifications†

- Test treatment: Aspirin, 1g/day
- Control treatment: Matching placebo
- Primary outcome: Death
- Minimum followup: 3 yrs
- Presumed study population: 85% male, 3 yr death rate: 12.8/100; 15% female, 3 yr death rate: 11.3/100
- Treatment difference: 30% reduction in mortality
- Test statistic: One tailed test, $\alpha = 0.05$ and $\beta = 0.10$
- Treatment lag: none
- Compliance: 90% yr 01, 82% yr 02, 74% yr 03
- Crossovers from placebo to aspirin: 8% per yr

† *USPHS NIH Publ 80-2106, June 1980*[4]

PARIS sample size specifications†

- Length of followup: 2 yr minimum
- Type I error level: 0.05 (2-sided)
- Primary outcome: Death
- Secondary outcome: Coronary incidence (fatal plus nonfatal MI)

- Sample size

PR/A	800
ASA	800
PLBO	400

- Power for primary outcome
  - 0.80 with 50% reduction
  - 0.30 with 25% reduction

- Power for secondary outcome
  - 0.80 with 40% reduction
  - 0.60 with 25% reduction

† *PARIS Research Group, 1980*[45]

6 Sample size

Sample size methods

- Exact method: P_c , P_t between 0 and 1
- Normal approximation: P_c , P_t between 0.20 and 0.80; N_cP_c , N_cQ_c , N_tP_t , and N_tQ_t all $\geq$ 15
- Arcsin approximation: P_c , P_t between 0.05 and 0.95; N_cP_c , N_cQ_c , N_tP_t , and N_tQ_t all $\geq$> 15
- Poisson approximation: P_c , P_t < 0.05 or > 0.95 and N_cP_c and $N_tP_t \geq 10$

Exact method

- Published tables for equal sample size (Casagrande et al, 1978[6])
- Computer program required for unequal sample size

Normal approximation

α = Type I error (2-sided)
β = Type II error
$\Delta = P_c - P_t$

P_c = Event rate in control treated group
P_t = Event rate in test treated group
$P_. = (N_cP_c + N_tP_t)/(N_c + N_t)$
$Q_c = 1 - P_c$
$Q_t = 1 - P_t$
$Q_. = 1 - P_.$

N_c = Number in control treated group
N_t = Number in test treated group
$N_c = N_t$ (Uniform assignment ratio)
$N_T = N_c + N_t$

$$N_c = [Z_{\alpha/2} (2P.Q.)^{1/2} + Z_\beta(P_cQ_c + P_tQ_t)^{1/2}]^2/\Delta^2$$

Example

α = 0.05 (2-sided)
β = 0.20
Δ = 0.13

P_c = 0.33
P_t = 0.20
$\dot{P}$ = 0.265
$\dot{Q}$ = 0.735

$$N_c = \{1.96[(2)(0.265)(0.735)]^{1/2} + 0.84\,[(0.33)(0.67) + (0.20)(0.80)]^{1/2}\}^2 / 0.13^2$$

$N_c = N_t = 180$
$N_T = 180 + 180 = 360$

Arcsin approximation

$$N_c = (Z_{\alpha/2} + Z_\beta)^2/2[\mathrm{Sin}^{-1}(P_c)^{1/2} - \mathrm{Sin}^{-1}(P_t)^{1/2}]^2$$
$N_c = N_t$ (Uniform assignment ratio)
$N_T = N_c + N_t$

Example

$$N_c = (1.96 + 0.84)^2/2[\mathrm{Sin}^{-1}(0.33)^{1/2} - \mathrm{Sin}^{-1}(0.20)^{1/2}]^2$$
$N_c = N_t = 178$
$N_T = 178 + 178 = 356$

6 Sample size

Poisson approximation

$N_c = (Z_{\alpha/2} + Z_\beta)^2(P_c + P_t)/(P_c - P_t)^2$
$N_c = N_t$ (Uniform assignment ratio)
$N_T = N_c + N_t$

Example
$P_c = 0.02$
$P_t = 0.01$
$\alpha = 0.01$ (2-sided)
$\beta = 0.05$
$Z_{\alpha/2} = 2.576$
$Z_\beta = 1.645$

$N_c = (2.576+1.645)^2(0.02/0.01+1)/(0.02/0.01 - 1)^2/0.01$
$N_c = 5{,}345$
$N_T = 5{,}345 + 5{,}345 = 10{,}690$

Power formulas

β = Type II error
Power = $1 - \beta = 1 - \Phi(A)$
$\Phi(A)$ = Proportion of area of N(0,1) curve to left of point A on the abscissa

Normal
$A = \{Z_{\alpha/2}[P_\cdot Q_\cdot(1/N_c + 1/N_t)]^{1/2} - |P_c - P_t|\}/(P_cQ_c/N_c + P_tQ_t/N_t)^{1/2}$

Arcsin
$A = Z_{\alpha/2} - 2|\mathrm{Sin}^{-1}(P_c)^{1/2} - \mathrm{Sin}^{-1}(P_t)^{1/2}|/(1/N_c + 1/N_t)^{\mathbf{1/2}}$

Poisson
$A = Z_{\alpha/2} - |P_c - P_t|/(P_c/N_c + P_t/N_t)^{1/2}$

6 Sample size

Power example

$N_c = 100$
$N_t = 100$
$P_c = 0.46$
$P_t = 0.30$
$\dot{P} = 0.38$
$\Delta = P_c - P_t = 0.16$
$\alpha = 0.05$ (2-sided)

$$A = \{Z_{\alpha/2}[\dot{P}\dot{Q}(1/N_c + 1/N_t)]^{1/2} - |P_c - P_t|\}/(P_cQ_c/N_c + P_tQ_t/N_t)^{1/2}$$

$$A = \{1.96[(0.38)(0.62)(1/100 + 1/100)]^{1/2} - 0.16\}/[(0.46)(0.54)/100 + (0.30)(0.70)/100]^{1/2}$$

$$A = (0.13 - 0.16)/0.07 = -0.40$$

Power = 1 - Q(- 0.40) = 1 - 0.35
Power = 0.65

Factors in the choice of alpha, beta, and delta

- Cost of new treatment vs standard treatment
- Risk vs benefit of new treatment
- Side effects associated with new treatment
- Acceptability of the new treatment
- Motivation of the investigators and sponsor
- Clinical importance of the treatment difference to be detected

Special problems in sample size calculations

- Treatment lag time
- Dropouts
- Adherence to treatment
- Multiple comparisons
- Multiple outcomes

6 Sample size

Reporting adequacy of 93 breast cancer trials†

Description of treatment assignment	39%
Statistical methods described	42%
Trial double masked	22%
Power discussed	2%
Informed consent mentioned	10%

† *Mosteller et al, Controlled Clinical Trials, 1980*[38]

Reporting adequacy of 83 GI trials†

Description of study population	76%
Description of treatment regimens	76%
Description of treatment assignment	34%
Checks for baseline comparability	49%
Sample size calculation	0%

† *Chalmers et al, Nat Comm on Dig Dis, 1978*[7]

7 Randomization principles

7 Randomization principles

Random: Lay definition

Having no specific pattern or objective; lacking causal relationships; haphazard (fr ME, *randoun*, fr OF *randon*, meaning, haphazard, fr *randir*, meaning to run).

American Heritage Dictionary, 1976

Random: Scientific definition

A selection or assignment process in which there is associated with every legitimate outcome a known probability.

Randomization - The actual process of carrying out a random selection or assignment procedure.

Uses of randomization in clinical trials

- Assignment of patients to treatment
- Selection of patients for special procedures
- Determination of order for reading or analyzing a set of records or laboratory specimens
- Construction of analytic procedures for assessing differences among treatment groups through use of a Monte Carlo simulation process
- Selection of quality control samples

Reasons for random treatment assignment

- Eliminate selection bias
- Provide study groups with known statistical properties regarding baseline composition
- Provide a statistical basis for certain tests of significance

7 Randomization principles

CDP sample assignment schedule

Trt	Bottle no.	ID no.	Patient's name or name code
CPIB	29	( )	( )
NICA	14	( )	( )
PLBO	26	( )	( )
ESG2	2	( )	( )
ESG1	27	( )	( )
NICA	19	( )	( )
DT-4	15	( )	( )
CPIB	16	( )	( )
PLBO	13	( )	( )
PLBO	25	( )	( )
ESG1	10	( )	( )
ESG2	4	( )	( )
PLBO	24	( )	( )
PLBO	23	( )	( )
DT-4	9	( )	( )
ESG2	30	( )	( )
DT-4	17	( )	( )
DT-4	20	( )	( )
PLBO	11	( )	( )
CPIB	6	( )	( )
PLBO	5	( )	( )
ESG1	28	( )	( )
CPIB	22	( )	( )
ESG1	18	( )	( )
ESG2	7	( )	( )
NICA	8	( )	( )
PLBO	1	( )	( )
PLBO	12	( )	( )
PLBO	21	( )	( )
NICA	3	( )	( )

7 Randomization principles

Hallmarks of a sound assignment scheme

- Reproducible order of assignment
- Documentation of methods for generation and administration of assignments
- Release of assignments prevented until essential conditions satisfied
- Assignments remain masked to all concerned until needed
- Future assignments not predictable from past assignments
- Clear audit trail for assignments
- Ability to detect departures from established procedures

Characteristics of CDP assignment scheme

- Separate schedules by clinic and risk group within clinic
- Assignment ratio of 1:1:1:1:1:2.5
- Blocking to ensure balance in numbers assigned to treatment groups after every 15th assignment within a risk group within a clinic
- 30 bottle numbers
- Central administration of the schedule
- Assignment not released until key data provided and patient consent obtained
- Defined entry point

Alternatives to randomization

- Quasi-randomization schemes based on social security or hospital number, birth date, or coin flips
- Systematic schemes such as alternation schemes based on date or order seen
- Deterministic schemes such as minimization and some adaptive (dynamic) procedures
- Outcome adaptive schemes such as play the winner or related variants
- "Haphazardization"

7 Randomization principles

Schemes to avoid

- Systematic assignment schemes
- Quasi-randomization schemes
- Unmasked assignment schemes
- Self administered envelope assignment schemes
- Informal assignment schemes such as coin flips and other schemes that cannot be audited
- Use of schemes in which it is possible to predict future assignments from past assignments

Misconceptions regarding randomization

- A haphazard procedure is the same as a random procedure
- Randomization ensures comparable study groups
- Differences in the baseline composition of the study groups is evidence of a breakdown in the randomization process
- It is possible to test for "randomness"
- A study that does not involve random treatment assignments is invalid

Positive features of randomization

- Protects against selection bias in the assignment process
- Provides predictable sampling variation for differences in the baseline composition of the treatment groups, and for subgroups of the treatment groups, formed using variables that are independent of treatment assignment (eg, sex, ethnic group, and all baseline observations)
- Expected degree of baseline comparability for an unobserved variable is the same as for an observed variable

7 Randomization principles

Definitions for fixed treatment assignment designs

treatment assignment probability: The probability of assignment to a given treatment group

expected treatment assignment ratio: The desired ratio of the treatment assignment probability for the test treatment to that of the control treatment as specified in the design of the trial (eg, 1: 1 for a design with equal assignment probabilities)

observed treatment assignment ratio: The ratio of the actual number of patients assigned to the test treatment to the number assigned to the control treatment

simple randomization: Randomization in which assignments are independent of one another and where all assignments have the same probability of selection (ie, schemes not involving blocking or stratification). Also referred to as complete randomization

restricted randomization: Randomization in which some assignments are determined from previous assignments (eg, a scheme in which assignments are issued so as to yield an observed treatment assignment ratio equal to the expected treatment assignment ratio after specified numbers of assignments)

block: A specified number of treatment assignments that satisfy the expected assignment ratio when that number of assignments has been issued

block size: The number of treatment assignments required so that the observed assignment ratio equals the expected assignment ratio

blocked randomization: Randomization that is carried out within a defined block

stratification variable: A variable believed to influence treatment outcome, observed at or prior to randomization, and used to create assignment strata consisting of defined subgroups of patients

stratified randomization: The process of controlling the distribution of a variable (eg, sex, age at entry, baseline blood pressure) among treatment groups by using that variable to define assignment strata for blocked randomization

assignment stratum: A stratum formed by a stratification variable and involving blocked randomization

7 Randomization principles

Blocking considerations

- Importance of agreement between observed and expected assignment ratios
- Likelihood of protocol changes (eg, in the eligibility criteria) during randomization
- Likelihood of time related changes in the composition of the study population or data collection procedures
- Fixed vs variable block sizes
- Small vs large blocks

Stratification considerations

- Select variables believed to influence treatment outcome
- Limit choice to small number of variables
- Gain in precision minimal for large studies involving >50 patients per treatment group
- Stratification does not eliminate need for adjustment for differences in the baseline composition of the study groups
- Use of patient characteristics for stratification increases logistical complexities of the assignment process
- The larger the number of allocation strata the greater the chance of a sizable departure from the expected assignment ratio (Note: One can guard against such departures by using blocks of small size but the pattern, if discovered, may allow study personnel to predict assignments)

Blocking versus stratification

Definitions

Block: Broadly, a group of elements or objects acting or regarded as a unit. In the context of trials, a group of treatment assignments purposefully arranged so as to be in the exact same proportions as those called for in the design of the trial, eg, the arrangement, ABAB (or any of the other 5 possible arrangements), in a trial involving blocks of size 4 and calling for a 1:1 treatment assignment ratio (ie, a design in which the proportion of assignments to A is to be the same as that for B).

Blocking: Broadly, the act or process of arranging elements or objects into blocks. In the context of treatment assignment in trials, typically characterized by a process involving the imposition of restrictions on the assignment scheme so as to ensure that the desired assignment ratio is satisfied when the last assignment comprising a block is designated or issued.

7 Randomization principles

Definitions

Strata: Broadly, a series of distinct levels or layers. In trials, generally subgroups of persons formed by classification on some variable or set of variables, usually baseline variables.

Stratification: Broadly, the act or process of stratifying; an active ongoing process of stratifying, eg, as in placing patients into strata as they arrive at a clinic as a prelude to randomization to treatment in a trial; the act or process of classifying observations or treatment units into strata after the fact, eg, as in classification as a prelude to a subgroup analysis, also referred to as post-stratification. In the context of trials and treatment assignment, the act of stratifying so as to be able to perform stratified treatment assignment.

Stratified treatment assignment: The act or process of arranging assignment units (usually persons) into strata and of creating and administering assignments within individual strata designed so as to satisfy a common assignment ratio, eg, a scheme involving stratification on sex and assignment within each sex subgroup such that the assignment ratio is the same within both strata.

Purpose

Blocking: To control for secular trends in the nature of the population enrolled into a trial; changes in the nature of people enrolled over the course of a trial, unless controlled via blocking, can confound treatment comparisons, if the mix is different by treatment group.

Stratification: To control the source of variation represented by the stratification variable(s) as expressed in relation to the outcome measure of interest by use of procedures to ensure that the populations represented in the treatment groups have the same distribution with regard to the stratification variable(s).

Usage notes and cautions

Blocking: Not to be confused with stratification. The number of assignments represented in a block may be the same for all blocks, eg, as required for a crossover design and as used in simple blocking schemes for parallel treatment designs. The number will be equal to the number of study treatments in the case of complete crossover designs. The minimum number for parallel treatment designs will be the sum of the numbers represented in the assignment ratio (eg, 2 for a design involving two study treatments and a uniform treatment assignment ratio and 15 for a design involving 6 study treatments and an assignment ratio of 1:1:1:1:1:2.5). The usual strategy in parallel treatment designs is to have a mix of blocks of different sizes, themselves randomly ordered, with all blocks being some multiple of the smallest possible block size. The actual number of blocks represented in an executed parallel design will depend on the block size or sizes used and on the number of blocks only partially filled when enrollment is stopped. That number will increase as a function of the number of strata represented in the design.

Usage notes and cautions

Stratification: Stratification and blocking in the treatment assignment process serve different purposes as noted above and, hence, should not be confused. In addition, there is confusion regarding the meaning and impact of stratification on the design and operation of a trial. Often the act of stratification is taken as evidence of the need to perform treatment comparisons within the various strata represented in the stratification. Though that may be desirable, such comparisons are not necessary. Valid comparisons of the treatment groups can be performed by pooling across strata, ie, by ignoring the stratification. As a rule, the mix of persons recruited to a trial is allowed to float, ie, to be determined by the mix of persons seen and ultimately judged eligible for enrollment. Hence, the numbers to be represented in the various strata will be a variable having values known only after completion of enrollment. The imposition of a sample size requirement for one or more of the strata in addition to one for the trial extends the time required for recruitment and should not be imposed unless there are valid scientific or practical reasons for doing so. Confusion also arises from use of the term stratification in two distinctly different contexts, one referring to an active process as a prelude to enrollment and the other referring to a passive process performed in relation to analysis. Use post-stratification for uses in the latter sense.

7 Randomization principles

Examples of stratification variables

- Clinic in a multicenter trial
- Demographic characteristics such as sex, race, or age at entry
- Baseline laboratory measurements, such as fasting blood glucose level at entry
- Physiologic characteristics, such as blood pressure at entry
- Clinical characteristics, such as history of MI at entry

Other considerations

- Dynamic vs fixed treatment assignment
- Centrally administered vs locally administered assignment schemes
- Quotas vs goals

8 Randomization mechanics

8 Randomization mechanics

Random permutations of 16[†]

12	6	13	4	5	7	2	1	9	2	5	1	15	2	14
6	11	4	15	12	12	6	15	6	15	6	3	12	5	15
13	5	1	6	7	6	13	5	7	8	15	6	4	15	1
11	1	11	7	8	15	8	4	12	13	16	9	3	10	7
3	7	3	14	15	4	12	11	4	10	8	12	1	4	16
10	12	15	11	4	13	5	10	3	14	11	2	9	11	2
15	9	16	16	9	2	16	2	15	6	7	15	8	1	8
14	15	2	13	3	16	10	14	13	9	10	7	14	9	6
1	2	12	9	1	8	15	3	8	11	2	5	10	3	3
5	10	5	3	13	9	9	13	10	1	3	8	7	8	9
7	14	9	2	11	14	11	6	14	12	9	10	16	12	13
9	8	10	1	6	3	3	8	5	5	14	16	2	7	12
2	3	7	5	10	1	1	12	2	7	1	4	6	16	10
16	13	14	10	2	5	7	16	1	16	13	11	11	6	5
4	4	6	8	14	10	14	7	11	3	4	13	13	13	11
8	16	8	12	16	11	4	9	16	4	12	14	5	14	4

[†] *Lines 17 through 32, columns 1 through 15, p 584, Cochran and Cox,* ***Experimental Designs****, 2nd ed, 1957*[8]

8 Randomization mechanics

Permutation assignment worksheet

Specifications	Notation	Documentation
_____ Trt grps		_____ Page no
_____ Blk size		_____ Line no
_____ Ratio		_____ Col no

Line no	Random no	Treatment assignment
1	_____	_____
2	_____	_____
3	_____	_____
4	_____	_____
5	_____	_____
6	_____	_____
7	_____	_____
8	_____	_____
9	_____	_____
10	_____	_____
11	_____	_____
12	_____	_____
13	_____	_____
14	_____	_____
15	_____	_____
16	_____	_____

8 Randomization mechanics

Permutation assignment: 1

Specifications		Notation		Documentation
2	Trt grps	*M=Med, nos 1-7*	_____	Page no
14	Blk size	*S=Surg, nos 8-14*	_____	Line no
1:1	Ratio		_____	Col no

Line no	Random no	Treatment assignment
1	_____	_____
2	_____	_____
3	_____	_____
4	_____	_____
5	_____	_____
6	_____	_____
7	_____	_____
8	_____	_____
9	_____	_____
10	_____	_____
11	_____	_____
12	_____	_____
13	_____	_____
14	_____	_____
15	_____	_____
16	_____	_____

8 Randomization mechanics

Permutation assignment: 2

Specifications		Notation	Documentation	
2	Trt grps	*M=Med, nos 1-7*	*584*	Page no
14	Blk size	*S=Surg, nos 8-14*	*17*	Line no
1:1	Ratio		*7*	Col no

Line no	Random no	Treatment assignment	Random Permutation
1	*2*		2
2	*6*		6
3	*13*		13
4	*8*		8
5	*12*		12
6	*5*		5
7	*10*		16
8	*9*		10
9	*11*		15
10	*3*		9
11	*1*		11
12	*7*		3
13	*14*		1
14	*4*		7
15			14
16			4

8 Randomization mechanics

Permutation assignment: 3

Specifications		Notation	Documentation	
2	Trt grps	*M=Med, nos 1-7*	*584*	Page no
14	Blk size	*S=Surg, nos 8-14*	*17*	Line no
1:1	Ratio		*7*	Col no

Line no	Random no	Treatment assignment	Random Permutation
1	*2*	*M*	2
2	*6*	*M*	6
3	*13*	*S*	13
4	*8*	*S*	8
5	*12*	*S*	12
6	*5*	*M*	5
7	*10*	*S*	16
8	*9*	*S*	10
9	*11*	*S*	15
10	*3*	*M*	9
11	*1*	*M*	11
12	*7*	*M*	3
13	*14*	*S*	1
14	*4*	*M*	7
15			14
16			4

8 Randomization mechanics

Random numbers†

	0 12345	1 67890	1 12345		0 12345	1 67890	1 12345
00	08149	14776	83594	25	96114	58859	90474
01	69393	16793	26625	26	67430	57097	39476
02	07127	28219	15917	27	06964	90193	70344
03	67488	61562	40266	28	89983	69718	33004
04	86214	53821	81970	29	60718	80714	47399
05	21568	19342	07821	30	74024	90794	99100
06	80376	95821	97763	31	37033	17764	59482
07	04265	23100	73964	32	49246	59630	43635
08	52382	67432	94394	33	52978	20248	07296
09	41948	99708	55353	34	31425	39865	60729
10	09201	35481	83003	35	04402	26377	19057
11	12379	36696	08556	36	45389	43993	28279
12	96328	82959	31874	37	74187	62120	63159
13	33004	64495	76596	38	65624	31299	63494
14	56796	12936	76308	39	58428	17582	18339
15	20887	43157	74092	40	50626	40047	41078
16	58773	50675	68623	41	35706	97649	32802
17	17542	12554	64286	42	87633	10424	93235
18	95002	80153	31722	43	83126	63377	81018
19	57807	77433	65367	44	70090	05750	43225
20	78394	97930	72476	45	17382	39493	85125
21	36010	00874	61554	46	22214	57511	99807
22	35736	49271	60789	47	51139	50509	66346
23	25323	56652	55557	48	18864	71938	84707
24	85278	21251	40588	49	40108	66030	03600

† *Rows 00 through 49, columns 1 through 15, pg 391 of* ***1,000,000 random digits****; Rand Corporation, 1955*[46]

Moses-Oakford assignment worksheet†

Specifications		Notation		Documentation		
____	Trt grps		Pg	____	Row	Col
____	Blk size			Start	____	____
____	Ratio			Stop	____	____

1	2	3	4	5
Line	Interim assignments		Random	Final
no	Initial	Replacements	no	assign
1	____	_____	_____	_____
2	____	_____	_____	_____
3	____	_____	_____	_____
4	____	_____	_____	_____
5	____	_____	_____	_____
6	____	_____	_____	_____
7	____	_____	_____	_____
8	____	_____	_____	_____
9	____	_____	_____	_____
10	____	_____	_____	_____
11	____	_____	_____	_____
12	____	_____	_____	_____
13	____	_____	_____	_____
14	____	_____	_____	_____
15	____	_____	_____	_____
16	____	_____	_____	_____

Reading instructions:

† *Moses and Oakford, 1963*[37]

8 Randomization mechanics

Moses-Oakford assignment worksheet: 1

Specifications		**Notation**	**Documentation**		
2	Trt grps	*M = Med trt*	____	Row	Col
14	Blk size	*S = Surg trt*	Start	____	____
1:1	Ratio		Stop	____	____

1	2	3	4	5
Line	Interim assignments		Random	Final
no	Initial	Replacements	no	assign
1	*M*			
2	*M*			
3	*M*			
4	*M*			
5	*M*			
6	*M*			
7	*M*			
8	*S*			
9	*S*			
10	*S*			
11	*S*			
12	*S*			
13	*S*			
14	*S*			
15				
16				

Reading instructions:

8 Randomization mechanics

Moses-Oakford assignment worksheet: 2

Specifications		**Notation**	**Documentation**		
2	Trt grps	*M = Med trt*	*391*	Row	Col
14	Blk size	*S = Surg trt*	Start	*00*	*1*
1:1	Ratio		Stop	____	____

1	2	3	4	5
Line	Interim assignments		Random	Final
no	Initial	Replacements	no	assign
1	*M*			
2	*M*			
3	*M*			
4	*M*			
5	*M*			
6	*M*			
7	*M*			
8	*S*			
9	*S*			
10	*S*			
11	*S*			
12	*S*			
13	*S*			
14	*S*			
15	____			
16	____			

Reading instructions: *Read down using pairs of digits for lines 14 through 10. Use only left hand member of pair for lines 9 through 2.*

Random nos

00	*08	25	96
	69		67
	07		06
	67		89
	86		60
05	21	30	74
	80		37
	04		49
	52		52
	41		31
10	09	35	04
	12		45
	96		74
	33		65
	56		58
15	20	40	50
	58		35
	17		87
	95		83
	57		70
20	78	45	17
	36		22
	35		51
	25		18
	85		40

8 Randomization mechanics

Moses-Oakford assignment worksheet: 3

Specifications		**Notation**	**Documentation**		
2	Trt grps	*M = Med trt*	*391*	Row	Col
14	Blk size	*S = Surg trt*	Start	*00*	*1*
1:1	Ratio		Stop	____	____

1	2	3	4	5
Line	Interim assignments		Random	Final
no	Initial	Replacements	no	assign
1	*M*			
2	*M*			
3	*M*			
4	*M*			
5	*M*			
6	*M*			
7	*M*			
8	*S*	*S*		
9	*S*			
10	*S*			
11	*S*			
12	*S*			
13	*S*			
14	*S*		*08*	*S*
15	____			
16	____			

Reading instructions: *Read down using pairs of digits for lines 14 through 10. Use only left hand member of pair for lines 9 through 2.*

Random nos

00	*08	25	96
	69		67
	07		06
	67		89
	86		60
05	21	30	74
	80		37
	04		49
	52		52
	41		31
10	09	35	04
	12		45
	96		74
	33		65
	56		58
15	20	40	50
	58		35
	17		87
	95		83
	57		70
20	78	45	17
	36		22
	35		51
	25		18
	85		40

8 Randomization mechanics

Moses-Oakford assignment worksheet: 4

Specifications		**Notation**	**Documentation**		
2	Trt grps	*M = Med trt*	*391*	Row	Col
14	Blk size	*S = Surg trt*	Start	*00*	*1*
1:1	Ratio		Stop	____	____

1	2	3	4	5
Line	Interim assignments		Random	Final
no	Initial	Replacements	no	assign
1	*M*			
2	*M*			
3	*M*			
4	*M*			
5	*M*			
6	*M*			
7	*M*	*S*		
8	*S*	*S*		
9	*S*			
10	*S*			
11	*S*			
12	*S*			
13	*S*		*07*	*M*
14	*S*		*08*	*S*
15				
16				

Reading instructions: *Read down using pairs of digits for lines 14 through 10. Use only left hand member of pair for lines 9 through 2.*

Random nos

00	08	25	96
	69		67
	*07		06
	67		89
	86		60
05	21	30	74
	80		37
	04		49
	52		52
	41		31
10	09	35	04
	12		45
	96		74
	33		65
	56		58
15	20	40	50
	58		35
	17		87
	95		83
	57		70
20	78	45	17
	36		22
	35		51
	25		18
	85		40

8 Randomization mechanics

Moses-Oakford assignment worksheet: 5

Specifications		**Notation**	**Documentation**		
2	Trt grps	*M = Med trt*	*391*	Row	Col
14	Blk size	*S = Surg trt*	Start	*00*	*1*
1:1	Ratio		Stop	____	____

1 Line no	2 Interim assignments: Initial	Replacements	4 Random no	5 Final assign
1	*M*			
2	*M*			
3	*M*			
4	*M*	*S*		
5	*M*			
6	*M*			
7	*M*	*S*		
8	*S*	*S*		
9	*S*			
10	*S*			
11	*S*			
12	*S*		*04*	*M*
13	*S*		*07*	*M*
14	*S*		*08*	*S*
15				
16				

Reading instructions: *Read down using pairs of digits for lines 14 through 10. Use only left hand member of pair for lines 9 through 2.*

Random nos

00	08	25	96
	69		67
	07		06
	67		89
	86		60
05	21	30	74
	80		37
	*04		49
	52		52
	41		31
10	09	35	04
	12		45
	96		74
	33		65
	56		58
15	20	40	50
	58		35
	17		87
	95		83
	57		70
20	78	45	17
	36		22
	35		51
	25		18
	85		40

8 Randomization mechanics

Moses-Oakford assignment worksheet: 6

Specifications		**Notation**	**Documentation**		
2	Trt grps	*M = Med trt*	*391*	Row	Col
14	Blk size	*S = Surg trt*	Start	*00*	*1*
1:1	Ratio		Stop	____	____

1 Line no	2 Interim assignments Initial	Replacements	4 Random no	5 Final assign
1	*M*			
2	*M*			
3	*M*			
4	*M*	*S*		
5	*M*			
6	*M*			
7	*M*	*S*		
8	*S*	*S*		
9	*S*	*S*		
10	*S*			
11	*S*		*09*	*S*
12	*S*		*04*	*M*
13	*S*		*07*	*M*
14	*S*		*08*	*S*
15	____			
16	____			

Reading instructions: *Read down using pairs of digits for lines 14 through 10. Use only left hand member of pair for lines 9 through 2.*

Random nos

00	08	25	96
	69		67
	07		06
	67		89
	86		60
05	21	30	74
	80		37
	04		49
	52		52
	41		31
10	*09	35	04
	12		45
	96		74
	33		65
	56		58
15	20	40	50
	58		35
	17		87
	95		83
	57		70
20	78	45	17
	36		22
	35		51
	25		18
	85		40

8 Randomization mechanics

Moses-Oakford assignment worksheet: 7

Specifications		**Notation**	**Documentation**		
2	Trt grps	*M = Med trt*	*391*	Row	Col
14	Blk size	*S = Surg trt*	Start	*00*	*1*
1:1	Ratio		Stop	____	____

1	2	3	4	5
Line	Interim assignments		Random	Final
no	Initial	Replacements	no	assign
1	*M*	_____	_____	_____
2	*M*	_____	_____	_____
3	*M*	_____	_____	_____
4	*M*	*S*	_____	_____
5	*M*	_____	_____	_____
6	*M*	*S*	_____	_____
7	*M*	*S*	_____	_____
8	*S*	*S*	_____	_____
9	*S*	*S*	_____	_____
10	*S*		*06*	*M*
11	*S*		*09*	*S*
12	*S*		*04*	*M*
13	*S*		*07*	*M*
14	*S*		*08*	*S*
15	____	_____	_____	_____
16	____	_____	_____	_____

Reading instructions: *Read down using pairs of digits for lines 14 through 10. Use only left hand member of pair for lines 9 through 2.*

Random nos

00	08	25	96
	69		67
	07		*06
	67		89
	86		60
05	21	30	74
	80		37
	04		49
	52		52
	41		31
10	09	35	04
	12		45
	96		74
	33		65
	56		58
15	20	40	50
	58		35
	17		87
	95		83
	57		70
20	78	45	17
	36		22
	35		51
	25		18
	85		40

8 Randomization mechanics

Moses-Oakford assignment worksheet: 8

Specifications

2 Trt grps
14 Blk size
1:1 Ratio

Notation

M = Med trt
S = Surg trt

Documentation

391 Row Col
Start *00* *1*
Stop ____ ____

1 Line no	2 Interim assignments: Initial	Replacements	4 Random no	5 Final assign
1	*M*			
2	*M*			
3	*M*			
4	*M*	*S*		
5	*M*			
6	*M*	*S*		
7	*M*	*S*		
8	*S*	*S S*		
9	*S*	*S*	*8*	*S*
10	*S*		*06*	*M*
11	*S*		*09*	*S*
12	*S*		*04*	*M*
13	*S*		*07*	*M*
14	*S*		*08*	*S*
15				
16				

Reading instructions: *Read down using pairs of digits for lines 14 through 10. Use only left hand member of pair for lines 9 through 2.*

Random nos

00	08	25	96
	69		67
	07		06
	67		*89
	86		60
05	21	30	74
	80		37
	04		49
	52		52
	41		31
10	09	35	04
	12		45
	96		74
	33		65
	56		58
15	20	40	50
	58		35
	17		87
	95		83
	57		70
20	78	45	17
	36		22
	35		51
	25		18
	85		40

8 Randomization mechanics

Moses-Oakford assignment worksheet: 9

Specifications		**Notation**	**Documentation**		
2	Trt grps	*M = Med trt*	*391*	Row	Col
14	Blk size	*S = Surg trt*	Start	*00*	*1*
1:1	Ratio		Stop	____	____

1 Line no	2 Interim assignments: Initial	2 Interim assignments: Replacements	3 Random no	4 Final assign
1	*M*			
2	*M*			
3	*M*			
4	*M*	*S*		
5	*M*			
6	*M*	*S S*		
7	*M*	*S*		
8	*S*	*S S*	*6*	*S*
9	*S*	*S*	*8*	*S*
10	*S*		*06*	*M*
11	*S*		*09*	*S*
12	*S*		*04*	*M*
13	*S*		*07*	*M*
14	*S*		*08*	*S*
15	____	____	____	____
16	____	____	____	____

Reading instructions: *Read down using pairs of digits for lines 14 through 10. Use only left hand member of pair for lines 9 through 2.*

Random nos

00	08	25	96
	69		67
	07		06
	67		89
	86		*60
05	21	30	74
	80		37
	04		49
	52		52
	41		31
10	09	35	04
	12		45
	96		74
	33		65
	56		58
15	20	40	50
	58		35
	17		87
	95		83
	57		70
20	78	45	17
	36		22
	35		51
	25		18
	85		40

8 Randomization mechanics

Moses-Oakford assignment worksheet: 10

Specifications		**Notation**	**Documentation**		
2	Trt grps	*M = Med trt*	*391*	Row	Col
14	Blk size	*S = Surg trt*	Start	*00*	*1*
1:1	Ratio		Stop	____	____

1 Line no	2 Interim assignments Initial	Replacements	4 Random no	5 Final assign
1	*M*			
2	*M*			
3	*M*			
4	*M*	*S*		
5	*M*			
6	*M*	*S S*		
7	*M*	*S*	*7*	*S*
8	*S*	*S S*	*6*	*S*
9	*S*	*S*	*8*	*S*
10	*S*		*06*	*M*
11	*S*		*09*	*S*
12	*S*		*04*	*M*
13	*S*		*07*	*M*
14	*S*		*08*	*S*
15	____			
16	____			

Reading instructions: *Read down using pairs of digits for lines 14 through 10. Use only left hand member of pair for lines 9 through 2.*

Random nos

00	08	25	96
	69		67
	07		06
	67		89
	86		60
05	21	30	*74
	80		37
	04		49
	52		52
	41		31
10	09	35	04
	12		45
	96		74
	33		65
	56		58
15	20	40	50
	58		35
	17		87
	95		83
	57		70
20	78	45	17
	36		22
	35		51
	25		18
	85		40

8 Randomization mechanics

Moses-Oakford assignment worksheet: 11

Specifications		**Notation**	**Documentation**		
2	Trt grps	*M = Med trt*	*391*	Row	Col
14	Blk size	*S = Surg trt*	Start	*00*	*1*
1:1	Ratio		Stop	____	____

1	2	3	4	5
Line	Interim assignments		Random	Final
no	Initial	Replacements	no	assign
1	*M*			
2	*M*			
3	*M*	*S*		
4	*M*	*S*		
5	*M*			
6	*M*	*S S*	*3*	*M*
7	*M*	*S*	*7*	*S*
8	*S*	*S S*	*6*	*S*
9	*S*	*S*	*8*	*S*
10	*S*		*06*	*M*
11	*S*		*09*	*S*
12	*S*		*04*	*M*
13	*S*		*07*	*M*
14	*S*		*08*	*S*
15	____	____	____	____
16	____	____	____	____

Reading instructions: *Read down using pairs of digits for lines 14 through 10. Use only left hand member of pair for lines 9 through 2.*

Random nos

00	08	25	96
	69		67
	07		06
	67		89
	86		60
05	21	30	74
	80		*37
	04		49
	52		52
	41		31
10	09	35	04
	12		45
	96		74
	33		65
	56		58
15	20	40	50
	58		35
	17		87
	95		83
	57		70
20	78	45	17
	36		22
	35		51
	25		18
	85		40

8 Randomization mechanics

Moses-Oakford assignment worksheet: 12

Specifications		**Notation**	**Documentation**		
2	Trt grps	*M = Med trt*	*391*	Row	Col
14	Blk size	*S = Surg trt*	Start	*00*	*1*
1:1	Ratio		Stop	____	____

1 Line no	2 Interim assignments Initial	Replacements	4 Random no	5 Final assign
1	*M*			
2	*M*			
3	*M*	*S*		
4	*M*	*S M*		
5	*M*		*4*	*S*
6	*M*	*S S*	*3*	*M*
7	*M*	*S*	*7*	*S*
8	*S*	*S S*	*6*	*S*
9	*S*	*S*	*8*	*S*
10	*S*		*06*	*M*
11	*S*		*09*	*S*
12	*S*		*04*	*M*
13	*S*		*07*	*M*
14	*S*		*08*	*S*
15				
16				

Reading instructions: *Read down using pairs of digits for lines 14 through 10. Use only left hand member of pair for lines 9 through 2.*

Random nos

00	08	25	96
	69		67
	07		06
	67		89
	86		60
05	21	30	74
	80		37
	04		*49
	52		52
	41		31
10	09	35	04
	12		45
	96		74
	33		65
	56		58
15	20	40	50
	58		35
	17		87
	95		83
	57		70
20	78	45	17
	36		22
	35		51
	25		18
	85		40

8 Randomization mechanics

Moses-Oakford assignment worksheet: 13

Specifications		**Notation**	**Documentation**		
2	Trt grps	*M = Med trt*	*391*	Row	Col
14	Blk size	*S = Surg trt*	Start	*00*	*1*
1:1	Ratio		Stop	____	____

1 Line no	2 Interim assignments: Initial	2 Interim assignments: Replacements	3 Random no	4 Final assign
1	*M*			
2	*M*			
3	*M*	*S M*		
4	*M*	*S M*	*3*	*S*
5	*M*		*4*	*S*
6	*M*	*S S*	*3*	*M*
7	*M*	*S*	*7*	*S*
8	*S*	*S S*	*6*	*S*
9	*S*	*S*	*8*	*S*
10	*S*		*06*	*M*
11	*S*		*09*	*S*
12	*S*		*04*	*M*
13	*S*		*07*	*M*
14	*S*		*08*	*S*
15				
16				

Reading instructions: *Read down using pairs of digits for lines 14 through 10. Use only left hand member of pair for lines 9 through 2.*

Random nos

00	08	25	96
	69		67
	07		06
	67		89
	86		60
05	21	30	74
	80		37
	04		49
	52		52
	41		*31
10	09	35	04
	12		45
	96		74
	33		65
	56		58
15	20	40	50
	58		35
	17		87
	95		83
	57		70
20	78	45	17
	36		22
	35		51
	25		18
	85		40

8 Randomization mechanics

Moses-Oakford assignment worksheet: 14

Specifications		**Notation**	**Documentation**		
2	Trt grps	*M = Med trt*	*391*	Row	Col
14	Blk size	*S = Surg trt*	Start	*00*	*1*
1:1	Ratio		Stop	____	____

1 Line no	2 Interim assignments: Initial	2 Interim assignments: Replacements	3 Random no	4 Final assign
1	*M*			
2	*M*			
3	*M*	*S M*	*3*	*M*
4	*M*	*S M*	*3*	*S*
5	*M*		*4*	*S*
6	*M*	*S S*	*3*	*M*
7	*M*	*S*	*7*	*S*
8	*S*	*S S*	*6*	*S*
9	*S*	*S*	*8*	*S*
10	*S*		*06*	*M*
11	*S*		*09*	*S*
12	*S*		*04*	*M*
13	*S*		*07*	*M*
14	*S*		*08*	*S*
15	____			
16	____			

Reading instructions: *Read down using pairs of digits for lines 14 through 10. Use only left hand member of pair for lines 9 through 2.*

Random nos

00	08	25	96
	69		67
	07		06
	67		89
	86		60
05	21	30	74
	80		37
	04		49
	52		52
	41		31
10	09	35	04
	12		45
	96		74
	33		65
	56		58
15	20	40	50
	58		*35
	17		87
	95		83
	57		70
20	78	45	17
	36		22
	35		51
	25		18
	85		40

8 Randomization mechanics

Moses-Oakford assignment worksheet: 15

Specifications		**Notation**	**Documentation**		
2	Trt grps	*M = Med trt*	*391*	Row	Col
14	Blk size	*S = Surg trt*	Start	*00*	*1*
1:1	Ratio		Stop	____	____

1	2	3	4	5
Line	Interim assignments		Random	Final
no	Initial	Replacements	no	assign
1	*M*	*M*	_____	_____
2	*M*		*1*	*M*
3	*M*	*S M*	*3*	*M*
4	*M*	*S M*	*3*	*S*
5	*M*		*4*	*S*
6	*M*	*S S*	*3*	*M*
7	*M*	*S*	*7*	*S*
8	*S*	*S S*	*6*	*S*
9	*S*	*S*	*8*	*S*
10	*S*		*06*	*M*
11	*S*		*09*	*S*
12	*S*		*04*	*M*
13	*S*		*07*	*M*
14	*S*		*08*	*S*
15	____	_____	_____	_____
16	____	_____	_____	_____

Reading instructions: *Read down using pairs of digits for lines 14 through 10. Use only left hand member of pair for lines 9 through 2.*

Random nos

00	08	25	96
	69		67
	07		06
	67		89
	86		60
05	21	30	74
	80		37
	04		49
	52		52
	41		31
10	09	35	04
	12		45
	96		74
	33		65
	56		58
15	20	40	50
	58		35
	17		87
	95		83
	57		70
20	78	45	*17
	36		22
	35		51
	25		18
	85		40

8 Randomization mechanics

Moses-Oakford assignment worksheet: 16

Specifications		**Notation**	**Documentation**		
2	Trt grps	*M = Med trt*	*391*	Row	Col
14	Blk size	*S = Surg trt*	Start	*00*	*1*
1:1	Ratio		Stop	*45*	*1*

1	2	3	4	5
Line	Interim assignments		Random	Final
no	Initial	Replacements	no	assign
1	*M*	*M*		*M*
2	*M*		*1*	*M*
3	*M*	*S M*	*3*	*M*
4	*M*	*S M*	*3*	*S*
5	*M*		*4*	*S*
6	*M*	*S S*	*3*	*M*
7	*M*	*S*	*7*	*S*
8	*S*	*S S*	*6*	*S*
9	*S*	*S*	*8*	*S*
10	*S*		*06*	*M*
11	*S*		*09*	*S*
12	*S*		*04*	*M*
13	*S*		*07*	*M*
14	*S*		*08*	*S*
15				
16				

Reading instructions: *Read down using pairs of digits for lines 14 through 10. Use only left hand member of pair for lines 9 through 2.*

Random nos

00	08	25	96
	69		67
	07		06
	67		89
	86		60
05	21	30	74
	80		37
	04		49
	52		52
	41		31
10	09	35	04
	12		45
	96		74
	33		65
	56		58
15	20	40	50
	58		35
	17		87
	95		83
	57		70
20	78	45	17
	36		22
	35		51
	25		18
	85		40

8 Randomization mechanics

Masked treatment assignment: 1

Specifications		Notation	Documentation		
6	Trt grps	*A,B,C,D,E =*	____	Row	Col
15	Blk size	*Test trts*	Start	____	____
1:2.5	Ratio	*F = Ctrl trt*	Stop	____	____

1	2	3	4	5
Line	Interim assignments		Random	Final
no	Initial	Replacements	no	assign
1	*A*	_____	_____	_____
2	*A*	_____	_____	_____
3	*B*	_____	_____	_____
4	*B*	_____	_____	_____
5	*C*	_____	_____	_____
6	*C*	_____	_____	_____
7	*D*	_____	_____	_____
8	*D*	_____	_____	_____
9	*E*	_____	_____	_____
10	*E*	_____	_____	_____
11	*F*	_____	_____	_____
12	*F*	_____	_____	_____
13	*F*	_____	_____	_____
14	*F*	_____	_____	_____
15	*F*	_____	_____	_____
16	____	_____	_____	_____

Reading instructions:

8 Randomization mechanics

Masked treatment assignment: 2

Specifications		Notation	Documentation		
6	Trt grps	*A,B,C,D,E =*	____	Row	Col
15	Blk size	*Test trts*	Start	____	____
1:2.5	Ratio	*F = Ctrl trt*	Stop	____	____

1 Line no	2 Interim assignments Initial	3 Interim assignments Replacements	4 Random no	5 Final assign	**Random permutation set** (Col 3, Slide: *Permute*)
1	*A-13*				13
2	*A-04*				04
3	*B-01*				01
4	*B-11*				11
5	*C-03*				03
6	*C-15*				15
7	*D-02*				16
8	*D-12*				02
9	*E-05*				12
10	*E-09*				05
11	*F-10*				09
12	*F-07*				10
13	*F-14*				07
14	*F-06*				14
15	*F-08*				06
16	____				08

Reading instructions:

8 Randomization mechanics

Masked treatment assignment: 3

Specifications		**Notation**	**Documentation**		
6	Trt grps	*A,B,C,D,E =*	*391*	Row	Col
15	Blk size	*Test trts*	Start	*00*	*4*
1:2.5	Ratio	*F = Ctrl trt*	Stop	*34*	*4*

1	2	3	4	5
Line	Interim assignments		Random	Final
no	Initial	Replacements	no	assign
1	~~*A-13*~~	~~*F-08 G-15*~~ *F-14*		*F-14*
2	~~*A-04*~~	~~*F-07 D-12*~~ *C-03*	*2*	*C-03*
3	~~*B-01*~~	~~*E-05*~~ *C-03*	*2*	*D-12*
4	~~*B-11*~~	~~*F-14*~~	*1*	*C-15*
5	*C-03*		*3*	*E-05*
6	*C-15*		*1*	*F-08*
7	~~*D-02*~~	~~*F-10*~~	*7*	*F-10*
8	*D-12*		*2*	*F-07*
9	*E-05*		*3*	*B-01*
10	~~*E-09*~~		*10*	*E-09*
11	*F-10*		*07*	*D-02*
12	*F-07*		*02*	*A-04*
13	*F-14*		*04*	*B-11*
14	~~*F-06*~~	*F-08*	*01*	*A-13*
15	*F-08*		*14*	*F-06*
16				

Reading instructions: *Read down using pairs of digits for lines 15 through 10. Use left hand member of pair for lines 9 through 2.*

Random nos

00	49	25	*14
	93		*30
	27		64
	48		83
	*14		*18
05	68	30	*24
	76		33
	65		46
	82		78
	48		*25
10	*01	35	02
	79		89
	28		87
	*04		24
	96		28
15	87	40	26
	73		06
	42		33
	*02		26
	*07		90
20	94	45	82
	*10		14
	*36		39
	*23		64
	*78		08

8 Randomization mechanics

CDP sample schedule

Trt	Bottle no.	Id no.	Patient's name or name code
CPIB	29	[ ]	[ ]
NICA	14	[ ]	[ ]
PLBO	26	[ ]	[ ]
ESG2	2	[ ]	[ ]
ESG1	27	[ ]	[ ]
NICA	19	[ ]	[ ]
DT-4	15	[ ]	[ ]
CPIB	16	[ ]	[ ]
PLBO	13	[ ]	[ ]
PLBO	25	[ ]	[ ]
ESG1	10	[ ]	[ ]
ESG2	4	[ ]	[ ]
PLBO	24	[ ]	[ ]
PLBO	23	[ ]	[ ]
DT-4	9	[ ]	[ ]
ESG2	30	[ ]	[ ]
DT-4	17	[ ]	[ ]
DT-4	20	[ ]	[ ]
PLBO	11	[ ]	[ ]
CPIB	6	[ ]	[ ]
PLBO	5	[ ]	[ ]
ESG1	28	[ ]	[ ]
CPIB	22	[ ]	[ ]
ESG1	18	[ ]	[ ]
ESG2	7	[ ]	[ ]
NICA	8	[ ]	[ ]
PLBO	1	[ ]	[ ]
PLBO	12	[ ]	[ ]
PLBO	21	[ ]	[ ]
NICA	3	[ ]	[ ]

8 Randomization mechanics

Steps in treatment assignment: CDP

- Baseline data forms received at Coordinating Center
- Forms edited for completeness and stop conditions
- Patient's name and ID number entered on appropriate treatment assignment schedule
- Treatment assignment form completed and mailed to clinic in sealed envelope
- Treatment envelope opened at clinic during Initial Visit 3

Sample schedule for clinic 56

Trt	Bottle no.	Id no.	Patient's name or name code
CPIB	29	[*56-001*]	[*JAFul*]
NICA	14	[*56-002*]	[*ASJon*]
PLBO	26	[*56-007*]	[*HLBak*]
ESG2	2	[ ]	[ ]
ESG1	27	[ ]	[ ]
NICA	19	[ ]	[ ]
DT-4	15	[ ]	[ ]
CPIB	16	[ ]	[ ]
PLBO	13	[ ]	[ ]
PLBO	25	[ ]	[ ]
ESG1	10	[ ]	[ ]
ESG2	4	[ ]	[ ]
PLBO	24	[ ]	[ ]
PLBO	23	[ ]	[ ]
DT-4	9	[ ]	[ ]

8 Randomization mechanics

CDP treatment assignment form

We have received your request for a treatment allocation for

Mr. _____

whose identifying number is _____

This person should receive medication from bottles identified by the following number:

The sealed tear-off portion of the label on each bottle should be removed prior to dispensing. The patient's name, treating physician, date and prescription number should be recorded on the tear off portion of the label prior to filing with the patient's prescription record. The treatment should be initiated at initial visit 3 and should be administered on the following schedule:

One capsule three times a day after meals from initial visit 3 through initial visit 4;

Two capsules three times a day after meals from initial visit 4 through initial visit 5;

Three capsules three times a day after meals after initial visit 5 throughout the remainder of the study on the above named person unless clinically contraindicated.

NOTE: If the date on which the treatment allocation envelope has been opened is more than four months after the date of initial visit 1 (which, as indicated on Form 01, is_____), this allocation must be returned unused to the CDP Coordinating Center and this patient must start anew with initial visit 1.

Date of Allocation _____

CDP Coordinating Center
Baltimore, Maryland 21201

8 Randomization mechanics

CDP treatment assignment envelope (face)

Coronary Drug Project

Treatment Allocation for

Mr. _____ ID no. _____

DO NOT OPEN until instructed to do so on Form 02 (at initial visit 3).

If not opened within four months following the date of initial visit 1, this envelope should be returned to the CDP Coordinating Center.

9 Patient recruitment

9 Patient recruitment

Recruitment "facts of life"

- Early estimates of patient availability are usually unrealistically high
- The likelihood of achieving the stated recruitment goal is small and takes a major effort
- Patients presumed eligible for study during planning can be expected to "mysteriously" disappear as soon as the trial starts
- Recruitment will be more difficult, cost more, and take longer than planned
- Patients recruited will be healthier than planned in the sample size calculation

Preparatory steps

- Collect reliable data to estimate patient availability
- Decide on general recruitment approach
- Outline steps in recruitment process
- Establish network for recruitment

Approaches

Direct patient contact

- Via primary care clinic
- Screening
- Direct mailings or telephoning

Indirect patient contact

- Patient referrals
- Record review
- Indirect appeals via newspaper, radio, and TV publicity, announcements, or ads

9 Patient recruitment

Mistakes and problems

- No recruitment goal
- Redefining the recruitment goal during the trial to avoid failure
- Recruitment quotas
- Use of recruitment logs for characterizing the underlying study population in trials with multiple entry points
- Unrealistic timetable
- Competing with private physicians for patients
- Providing primary care rather than referring patients to primary care physician
- Failing to maintain adequate contact with referring physicians
- Attempting recruitment without the support of colleagues
- Taking access to medical records for granted
- Unenthusiastic staff
- Inadequate publicity

Groups requiring special consideration

- Children
- Elderly
- Pregnant women
- Mentally incompetent
- Culturally or economically deprived
- Prisoners

Other recruitment considerations

- Stability of study population
- Reliability of study participants
- Ethnic balance of study population
- Aids to recruitment such as incentive payments
- Policy on payments for care
- Need for Certificate of Confidentiality

9 Patient recruitment

Principles of consent

- Allow patient time to assimilate information presented and to obtain answers to questions regarding the trial
- Supplement with written and visual material regarding the design and purpose of the trial
- Test consent statement and related informational material for readability
- Document the consent process
- Update consent (when applicable)
- Monitor the consent process

Items to be covered in consent process

Design information

- Purpose of trial
- Test treatments
- Control treatment
- Method of treatment assignment and reason
- Level of treatment masking and reason
- Outcome of primary interest
- Length of treatment and followup
- Methods of followup for major events
- Clinic visit and contact schedule
- Methods of locating and following dropouts

9 Patient recruitment

Items to be covered in consent process

Risk-benefit information
- Risks vs benefits of treatments
- Possible treatment side effects
- Invasive procedures to be used, frequency of use, and associated risks

Safeguards
- Specification of:
  - Right to withdraw at any time
  - Confidentiality procedures
  - Right to privacy
  - Procedures for protection from injury
- Mechanisms to limit exposure to harmful treatment

Other information
- Patient responsibilities
- Limits on access to treatment information
- Amount of information available during and at conclusion of trial

Mistakes in the consent process

- Inadequate time for consent exchange
- Failure to specify required procedures
- Inadequate documentation
- Vague or inaccurate statements in the consent material
- Making commitments that cannot be met
- Fabrications or "white" lies to protect the study design
- Viewing the consent statement as a legal document
- Consent after the fact

Concerns related to consent

- Impact on recruitment
- Staff time
- IRB clearance
- Differential dropout rate
- Selection bias

9 Patient recruitment

Consent aids

- Written and visual material
- Adequate time
- Opportunity for questions
- Inclusion of "significant other" in consent process

Quality control of consent process

- After the fact assessments
- Required knowledge tests as a prerequisite to enrollment
- Spot sampling of consent process
- Periodic reviews and updates of the consent statement and process

10 Followup

10 Followup

Followup aids

- Dedicated pleasant staff
- Convenient data collection schedules
- Clinic hours geared to patient needs
- Pleasant clinical setting, located in a safe area
- Dedicated equipment
- Payment of fees for special procedures
- Payment of transportation and other related costs
- Attending to medical needs of patient
- Periodic phone and mail contacts with patient

Treatment adherence aids

- Exclusion of noncooperative or unreliable patients from entry
- Emphasis on treatment adherence during consent process
- Staff training to ensure familiarity with the treatment protocol
- Staff commitment to maintaining adherence
- Use of adherence aids and measures
- Ongoing checks for treatment protocol departures
- Periodic reports on adherence

Adherence measures

- Pill dispensers
- Pill counts
- Tracer substances, such as tocopherol (vitamin E)
- Blood or urine tests for drug product
- Treatment effect on secondary outcome(s)
- Adherence scores

10 Followup

Methods of minimizing losses to followup

- Use of followup aids outlined earlier
- Maintenance of up-to-date locator information
- Special provisions, such as: clinic transfers, reduced clinic visit schedule, home visits, transport to and from clinic

Mortality followup principles

- Provide for reports of deaths as they occur
- Follow all patients for mortality regardless of outcome of interest
- Set up mechanisms that avoid losses to followup for mortality, such as regular contact with dropouts

Mortality followup procedures

- Make concerted effort to maintain contact with all patients during the trial
- Primary responsibility for maintaining contact and for re-establishing contact, when lost, resides with clinic staff
- Contacts for a patient should be via the clinic, whenever feasible
- Extraordinary search procedures should not be implemented until routine searches have been performed
- Respect and honor patient's right to privacy in searches

Resources for determining mortality status

- National Death Index
- Social Security Administration
- Veterans Administration
- Federal Civil Service
- Credit agencies
- Special search agencies

10 Followup

Key data for mortality followup

- Full name including given and assumed surname for women†
- Sex
- Date of birth
- Place of birth
- Social security number
- Veteran's Id number
- Current place of residence and telephone number†
- Name, address, and tel no of present employer†
- Name, address, and tel no of close relative or friend†
- Driver's license number
- Other Id numbers, such as hospital number

† *Collect on entry and update periodically*

Methods of close-out

Common closing date

Common period of followup

10 Followup

Features of the two close-out methods

- Methods similar when recruitment takes place over short time period
- Common closing date preferred because approach:
  - Maximizes followup information
  - Easier to implement
  - Avoids patient and staff attrition sometimes associated with phased shut-down
- Common period of followup necessary when patients are to be treated and followed for only a specified period of time

Steps in the close-out process

General

- Decide on method of close-out
- Design and test close-out data collection forms
- Formulate treatment recommendations for patients

Patient

- Prepare patient for termination of trial by:
  - Providing advance warning of termination
  - Making provisions for subsequent care
  - Preparing summary medical record
  - Informing patient of study results
  - Recommending future course of treatment
- Outline future followup plans, if any
- Update locator information for future followup

Referring physician

- Discuss treatment recommendations and care requirements with referring physician
- Provide preprint of manuscript containing study results and conclusions

Housekeeping and administrative

- Collect and dispose of unused drugs in drug trial
- Provide lead time for staff to find alternative employment
- Document patient close-out process, including list of materials and information given to patient
- Cancel INDA, if applicable

10 Followup

Steps in the closeout process

Data storage and deposition

- Finalize dataset
- Carry out final data checks before clinics cease to function
- Outline and implement study archive procedures
- Designate secure storage areas for medical records to be retained and dispose of unwanted medical records
- Outline procedures for gaining access to study database after close of trial
- Outline policy on public access to study files and records

Considerations for premature close out

- Method of patient recall
- Type of treatment recommendation
- Impact on other study patients
- Method of disseminating study information prior to publication
- Method of documenting that a change has been made
- Method of informing patients of design changes
- Circumstances under which a new consent is required

11 Data collection

11 Data collection

Types of examinations

- Baseline
- Treatment application and adjustment
- Followup
- Close-out
- Post close-out

CDP examination schedule

Mos fr entry	Exam	Purpose
-2	BL 1	Baseline data; eligibility assessment
-1	BL 2	Baseline data; eligibility assessment
0	BL 3	Baseline data; eligibility assessment; randomization; start treatment
1	Trt 1	Increase dose from 3 to 6 caps/day
2	Trt 2	Increase dose from 6 to 9 caps/day
4	FU 1	Followup evaluation and data collection
8	FU 2	Followup evaluation and data collection
12	FU 3	Followup evaluation and data collection
16	FU 4	Followup evaluation and data collection
20	FU 5	Followup evaluation and data collection
24	FU 6	Followup evaluation and data collection
28	FU 7	Followup evaluation and data collection
32	FU 8	Followup evaluation and data collection
36	FU 9	Followup evaluation and data collection
40	FU 10	Followup evaluation and data collection
44	FU 11	Followup evaluation and data collection
48	FU 12	Followup evaluation and data collection
52	FU 13	Followup evaluation and data collection
56	FU 14	Followup evaluation and data collection
60	FU 15	Followup evaluation and data collection
61	CO 1	Stop treatment and data collection
62	CO 2	Post treatment data collection

11 Data collection

Factors influencing the data collection schedule

Prior to randomization
- Time required to assess eligibility
- Stability of baseline data
- Urgency of treatment
- Importance of shakedown period
- Time required for informed consent
- Convenience and practicability

After randomization
- Need for treatment application and adjustment
- Patient care requirements
- Expected event rate
- Maintenance of patient interest
- Convenience and practicability

Purpose of different examinations

Baseline examinations
- Determine eligibility
- Exclude unsuitable patients
- Provide information to patients for obtaining informed consent
- Establish baseline for evaluation of subsequent changes
- Provide descriptive data on entry characteristics of the study population

Treatment application and adjustment examinations
- Initiate treatment
- Adjust and "touch up" treatment
- Record details of treatment and related events
- Observe events in the early treatment period
- Provide initial followup data

11 Data collection

Purpose of different examinations

Scheduled followup examinations
- Provide essential care to patients
- Evaluate course of treatment for modification if necessary
- Provide uniform basis for observing and recording clinical events
- Provide data to assess differences in treatment procedures
- Provide data for evaluating changes over time from entry
- Maintain patient contact

Unscheduled interim followup examinations
- Provide essential care to patients
- Provide data on circumstances surrounding need for interim exam
- Assess treatment side effects

Close-out examinations
- Provide data surrounding termination of treatment
- Provide documentation of exit procedures and information supplied to patient on exit
- Check for occurrence of untoward events during termination of treatment

Post close-out examinations
- Provide data on events following close out and cessation of treatment
- Maintain contact with patient for subsequent followup

Design principles for the examination schedule

- Allow sufficient time for assessment of eligibility
- Provide adequate time for informed consent
- Strive for a common followup exam schedule that is independent of treatment assignment
- Consider a common closing date for followup regardless of the length of time required for patient recruitment

11 Data collection

Principles of form construction

- Distinguish between data needed for the trial and those needed for patient care
- Avoid the "Christmas Tree" approach to data collection
- Strive for forms that are self-contained
- Include essential instructions and definitions on form
- Avoid linked or interdependent forms
- Use separate forms for procedures or activities that are separated in time or that are performed at sites that are geographically or administratively distinct from the primary data collection site
- Make certain that there is a correspondence between baseline and followup data for variables that are to be used to assess changes over time
- Know and state the purpose of each form proposed
- Have an explicit rationale for each item on a form
- Test all forms before use

Form lay-out

- Arrange items in order of use
- Collect related items into sections and label with appropriate headings
- Number each item
- Use vertical rather than horizontal format for check lists
- Right or left align check spaces
- Maintain uniformity in the order of check responses
- Use symbols, arrows, etc., to guide respondent around conditional items
- Allow adequate space for completion of individual items (≥ 1/4 inch between lines)

Item construction principles

- Avoid the use blanks or skips as a response
- Use check lists in place of unformatted responses when feasible
- Use "stop" items as reminders of protocol requirements
- Distinguish between no, don’t know, and unknown as responses
- Use conventional units of measure
- Distinguish between response lists that are to be read as written from those to be used as checklists for recording responses volunteered by patients

Other form suggestions and considerations

Suggestions

- Name and number each form
- Number each item
- Date and number each version of a form (including the original); display the information in a standard location (eg, in headers or footers) on each page of the form
- Standardize the location of patient name (or name code) and Id number across forms; Choose a location that is consistent with filing procedures
- Provide space for recording patient Id number and visit number on each page of a form (standardize location across pages and forms)
- Use page numbering schemes that indicate both page number and total number of pages (eg, page 3 of 10)
- Include items to record date form is completed and name of individual completing form
- Allow adequate right, left, top, and bottom margins for binding and photocopying
- Box instructions and definitions or set off in some other way (eg, by use of a special font)
- Precode where possible

Considerations

- Paper size and weight
- Page orientation (portrait vs landscape)
- Printed vs typed forms
- Photocopy masters vs printed supply
- Carbon vs NCR paper vs photocopying for duplicates of completed forms
- Centralized vs distributed approach to supply of forms
- Full page vs multiple column lay-out
- Color coding vs none for identification of related forms
- Blanks vs no blanks in the item numbering scheme to allow for additions
- Decimal vs integer numbers for item numbers

11 Data collection

Key data items

All forms

- Identifying information
  - Patient Id number
  - Patient name or name code
  - Check digit
  - Visit or examination number
- Times and dates for designated procedures
- Names or certification numbers of personnel responsible for designated functions
- Version number

Baseline forms

- Documentation of eligibility
- Stratification variables
- Population characteristics
- Disease characteristics
- Risk factors
- Baseline for assessing subsequent changes
- Locator and tracing information

Followup forms

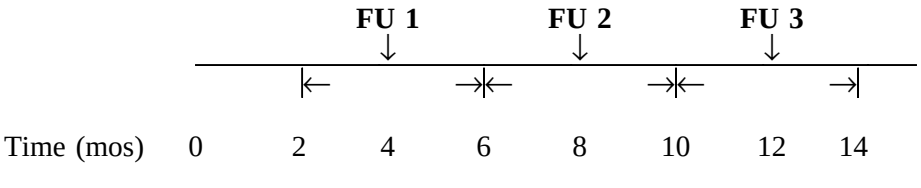
- Particulars of treatment
- Treatment changes
- Treatment adherence
- Time and nature of events
- Change from baseline for change measures
- Update locator and tracing information

11 Data collection

Data collection principles

- Defined entry point
- Specified examination schedule
- Ideal and permissible times for examinations
- Contiguous time windows
- Operational definitions for missed visit, dropout, lost-to-followup
- Test before implementing data collection procedures
- Test sites and lead clinics
- Separate test data from real data
- Test cohort of patients
- Gradual start-up (vs the "Big Bang" approach)
- Phased clinic enrollment
- Personnel training, certification, and recertification
- Continuous data flow
- Ongoing data entry, editing, and analysis

CDP data collection time windows



Housekeeping responsibilities

- OMB clearance of data forms for trials done under federal contracts
- Supply clinics with forms and other essential documents
- Equipment acquisition and distribution
- Documenting changes to forms, handbooks, and manuals of operations
- Filing and storage of completed forms
- Disposal of completed forms
- Microfilming and archiving
- Inventorying, data entry, and editing

12 Quality control

12 Quality control

Definitions

Quality control: Any procedure, technique, or method carried out during the trial, that maintains or enhances the reliability, reproducibility, or accuracy of the data from the trial.

Performance monitoring: Any method of summarizing data during the course of the trial, that is designed to detect deficiencies in the performance of specific activities in the trial.

Examples of quality control procedures

- Use of zero muddler to record blood pressure
- Duplicate lab determinations
- Repeat readings of ECGs
- Separation of the treatment and data collection functions in unmasked trials
- Special committee to code cause of death
- Edit of data for missing, inconsistent, or outlier values
- Independent reprogramming of an analysis procedure
- Double data entry

Examples of performance monitoring

- Comparison of recruitment experience vs stated goals
- Count of missed exams over time by clinic
- Counts of dropouts over time by clinic
- Counts of treatment protocol departures over time by clinic
- Data entry error rates over time by operator

12 Quality control

Quality control credos

- To err is human
- No one purposely sets out to collect poor quality data
- Data that are collected without ongoing quality checks are best left uncollected
- The only way to have any assurance regarding data quality is to check, check, check
- Perfection is impossible
- Quality control is everyone's responsibility

Requirements

- Quality conscious staff
- Timely data flow from clinic to processing site
- Expeditious data processing
- Computer hardware and software
- Organizational structure for implementing correction procedures

Quality control aids

- Reference handbooks and manuals
- Numbered policy and procedure memos
- Standardized equipment and procedures
- Tested data forms
- Trained and certified data collectors
- Clinic coordinators
- Site visits
- Conference phone calls and meetings
- On-site data entry

12 Quality control

Electronic vs paper forms

Electronic forms

Advantages

- Eliminates lag time between generation and entry
- Reduces need for filing space
- May help to promote good form design and editing procedures

Disadvantages

- Front loaded labor intensive
- Can be expensive to acquire and maintain needed equipment
- Absence of a paper record for documentation
- Down time and lost files

Paper forms

Advantages

- User friendly
- Forms provide basis for audit trail
- Data collection not dependent on functioning hardware
- No down time because of computer malfunctions

Disadvantages

- Filing space required for storage
- Lag in data entry

Data entry considerations

- On line vs off line entry
- Direct from form vs transcription for entry
- Distributed vs centralized entry
- Single vs double entry

12 Quality control

Paper based data generation and entry

- Forms should be checked for deficiencies at the time of completion
- Data forms should take the shortest time route to the entry site
- All data should be entered as they appear on the forms
- Conversion of data to computer readable electronic form should take place as soon after generation as feasible, and preferably by personnel associated with data acquisition
- Entries should be made directly from the form if possible
- All items on a form should be keyed at the same time
- Data entries should be checked for accuracy

General edit rules

- Computer checks are preferable to hand checks
- Edit queries should be directed to the persons responsible for data collection
- Changes made to a data files as a result of edit queries should be documented
- Entries in the electronic file with outstanding edit queries should be flagged

Types of edit checks

- Improper record linkage
- Unanswered items
- Impossible answers
- Inconsistent information (within or across forms)
- Abnormal and outlier values
- Suspicious changes from one exam to the next
- Inadmissible codes
- Uncertified technician
- Improper treatment or protocol violation

12 Quality control

Schemes for quality control

Fixed time

- Repeat measurement by the same or different person during an examination
- Aliquot determinations (in the same or different runs)
- Replicate readings by the same individual within a short period of time or by two different individuals at the same time

Over time

- Periodic submission of masked laboratory samples containing a known or fixed concentration of a substance
- Resubmission of previously read records to the same individual or reading center for rereading

Clinic performance data[†]

- No. of patients enrolled and recruitment rate
- No. of ineligible patients enrolled
- No. of patients enrolled with missing baseline data
- No. of dropouts
- No. of treatment departures by treatment group
- No. of patients lost to followup by treatment group
- No. of missed examinations
- No. and percent of forms received free of error

- Treatment adherence patterns
- List of major protocol violations (eg, unauthorized unmasking, improper lab tests, failure to administer treatment properly)
- Analysis of laboratory data for secular trend
- Inter-aliquot variability
- Count of abnormal and outlier values
- Edit error rates by person
- No. of delinquent forms

[†] *Counts and tabulations by clinic and time period*

12 Quality control

Purpose of performance monitoring

- Provides descriptive data on clinic performance
- Provides measures of relative standing of clinics
- Facilitates the identification of practices that may need correction
- Provides the database to support corrective actions taken

Pitfalls to avoid

- Over-reliance on editing system for detecting forged data
- Over-reliance on ranking as a means of identifying poor performers
- Artificial definition of outliers
- Overemphasis on one aspect of quality control while overlooking other more important aspects

Quality control design considerations

- Cost allocation for quality control
- Identification of the processes and procedures that require quality control
- Permissible error levels

Quality control planning aids

- Outline desired quality control procedures for each element of the data generation and analysis process
- Evaluate importance of each procedure to overall objectives of the trial
- Choose the procedures to be implemented using a "top down" approach

13 Record auditing

13 Record auditing

Terms

Record audit
Audit trail
Source document
Primary document
Secondary document
Medical record
Case report form

13 Record auditing

Definitions

audit *n* - [ME fr L *auditus* act of hearing, fr *auditus*, pp] A systematic examination or review of an organization, activity, or procedure; a careful step by step review of some method or process.

record audit *n* - 1. A comparison of data recorded in one document with those recorded in another document made to determine the accuracy or reliability of data; in the context of trials, often the comparison of data in study records with those in medical charts. 2. A comparison of information keyed with that recorded on the study form for the purpose of determining the accuracy or reliability of the keying process. 3. An audit of records by the FDA in relation to an INDA or NDA. 4. A search for external evidence that a person purported to have been enrolled into a study actually exists, eg, by locating the person's medical chart at the site of enrollment.

audit trail *n* - The sequence of transactions linking two events or actions. In data processing, the sequence of transactions linking data in a finished dataset to those recorded in source documents, such as data collection forms or medical records.

source document *n* - The document from which other things flow or arise

primary document *n* - The main or principle document in relation to some process or procedure; source document

secondary document *n* - A document of secondary importance or relevance in relation to some specified use, process, or procedure, or in relation to a primary document or source document; a document completed from a primary or source document.

medical record *n* - A collection of written and tabular information and related documents, such as reports of laboratory tests, x-ray films, and ECG tracings, concerning a specific person and related to that person's diagnosis or care in a specified setting. syn: medical chart, patient record, patient chart

case report form *n* - A collection of individual data forms related to a person enrolled into a study, especially when arranged in order of use and completed in totality before submission to the center or sponsor responsible for receiving such forms.

13 Record auditing

Record auditing as a rigorous check?

... the most rigorous check of data in a multisite study is auditing at the trial site by comparison of the trial's case report forms with original patient records. On-site auditing is the only type of monitoring intended to seek out sloppiness, carelessness, and fraud by comparing the patient's clinical record with the data entered in the trial.

Cohen J: Clinical Trial Monitoring: Hit or Miss? Science 264:1,534 - 1,537, **1994**.

Misconceptions in Cohen statement

Predicated on a false assumption (that there is a one-to-one relationship between the medical record and study forms)

The claim that record auditing is the most rigorous check of data

Factually incorrect (most editing and monitoring procedures are intended to ferret out sloppiness, carelessness, and fraud)

Limitations of record auditing

- After the fact, hence of limited value as a corrective procedure
- High false positive rate (ie, lots of discrepancies but few indicative of sloppiness, carelessness, or fraud)
- Largely useless in finding telltale patterns indicative of fraud
- Ignores electronic file used for data analysis

13 Record auditing

The reality of trials

- Often the study form is the "medical record"
- Only a fraction of phase III and IV trials are hospital-based
- Real-time record auditing, even if useful, is impossible
- Most discrepancies do not affect conclusions

Observations regarding data fraud from the perspective of a trialist

- Difficult to detect and still more difficult to prove
- Most discoveries are serendipitous
- Most data fraud goes undetected
- It takes less energy to collect data than to fabricate them
- A good analyst is likely to detect fraud that is consistently practiced
- One is not smart enough to invent data having the right variance and covariance characteristics

Facts of life

- The more you look the more you find
- The more you find the more doubts you create
- Counts without denominator data are misleading
- Ignorance is bliss

13 Record auditing

Why the emphasis on record auditing?

- Erroneous assumption that the *clinical* in **clinical trial** is synonymous with something done in a clinic or hospital
- The tendency to regard clinical trials and drug trials as an overlapping set
- Failure to differentiate between medical record and study forms
- The tendency in the FDA to assume that case report forms are completed from medical records
- Industry "standard" for pivotal NDA studies
- The case report form of data collection

Good and bad uses of record audit

Good

- Ongoing quality assurance process
- Spot checks reminding treaters and data collectors that people are watching
- Concerted efforts to find the smoking gun
- Verification of the existence of a named patient

Bad

- Mindless discrepancy detection
- Reconciliation in favor of the record
- 100% checks in the absence of reason

13 Record auditing

Data transcription and entry rules

Transcription

- Record what you see or what the patient tells you
- Review the form after completion
- Insist on dated signature of responsible study person
- View the completed form as a legal document
- Proscribe use of white out and require initials and dates for any change made to the form after completion

Entry

- Key what is recorded on the form, even if believed to be wrong
- Maintain an audit trail for any change made to the electronic file
- Flag "dirty" data awaiting response to edit query

Reasonable checks

- Date checks
- Consent documents
- Spot check of lab reports
- Drug records
- Internal consistency checks over time

Audits more important than record audits

- Randomization audit
- Count audits
- Electronic dataset audits
- Deaths and censoring events
- Serious and unexpected adverse events

13 Record auditing

Audit philosophy

Audit data most important to the conclusion
Address and resolve queries raised in an audit
Do not assume discrepancies are the result of carelessness, sloppiness, or fraud without evidence

The 64 dollar question

What fraction of the quality assurance dollar should the trialist spend on record auditing?

14 Organization and management

14 Organization and management

Management functions

- Leadership
- Direction
- Decision making
- Delineation of functions
- Delegation of responsibilities
- Communication

Management mistakes

- Failure to designate who is in charge
- Delegation of responsibility without authority
- Overlapping responsibilities
- Overlooking areas of responsibility
- Ill defined communication channels
- Undefined decision making structure

End results of faulty management

- Poor quality data
- Staff dissatisfaction or indifference
- High staff turnover
- Conflicting decisions, false starts, wasted efforts
- Inefficiency

Organizational elements

- Study chairperson
- Steering Committee
- Executive Committee
- Treatment Effects Monitoring Committee
- Advisory Review Committee

14 Organization and management

Definitions

center: An autonomous unit in the structure of a clinical trial that is responsible for performing a defined function in one or more stages of a trial and that is functionally and administratively independent of other units in the trial. Centers include clinics, coordinating centers (data and treatment), central laboratories, procurement and distribution centers, project office, reading centers, and quality control centers.

study chairperson: The titular head of the study, usually chairperson of the Steering Committee.

steering committee: A committee that is responsible for conduct of the trial; usually constituted to provide representation from all or selected centers in the trial.

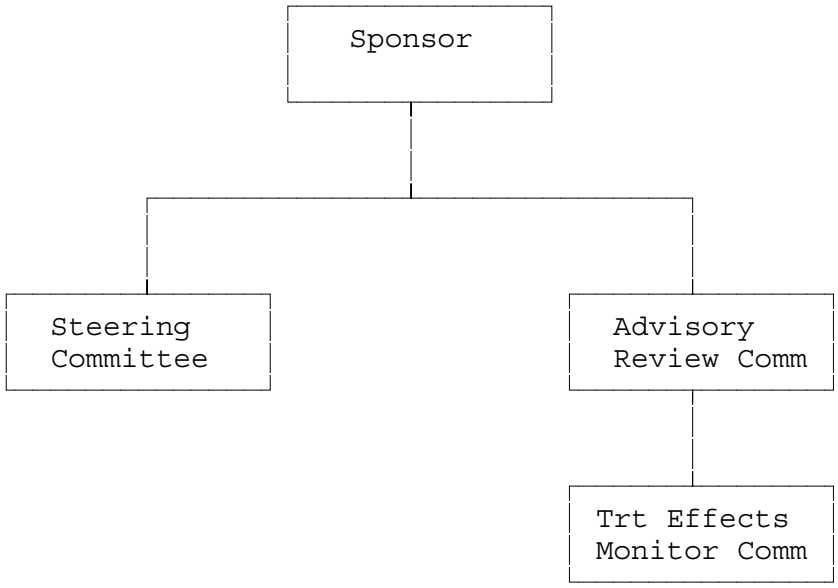
executive committee: A committee responsible for direction of the day-to-day affairs of the trial on behalf of the Steering Committee. Usually composed of the officers of the trial (eg, Chair and Vice Chairpersons, Director of the Coordinating Center, Project Officer) and perhaps others selected from the Steering Committee.

advisory review committee: A committee that is responsible for providing external review of the trial and for advising the Steering Committee and the sponsor on the general operation of the trial. Usually composed of individuals not involved in patient care or administration of treatments in the trial.

treatment effects monitoring committee: A committee responsible for reviewing data during the trial for evidence of adverse or beneficial treatment effects and for recommending termination of a treatment when deemed appropriate. Usually composed of individuals not involved in patient care or administration of treatments in the trial.

14 Organization and management

Typical organizational structure



HPT centers

Center	Location
Clinics (4)	Birmingham Ala; Davis Calif; Minneapolis Mn; Jackson Miss
Data Coord Center	Baltimore Md
Trt Coord Center	Minneapolis Mn
Food Coding Center	Pittsburgh Pa
Central Laboratory	Van Nuys Calif
Project Office	Bethesda Md

14 Organization and management

CDP centers

- 53 clinical centers
- Coordinating center (Baltimore)
- Central laboratory (Atlanta)
- ECG reading center (Minneapolis)
- Project office (Bethesda)
- Drug distribution center (Perry Point Md)

CDP committees

- Policy Board
- Data Monitoring Committee
- Steering Committee
- Executive Committee
- Treatment Criteria Committee
- Natural History Committee
- Laboratory Committee
- Mortality Classification Committee
- Editorial Review Committee

Desirable separations

- Patient and physician
- Treater and evaluator (unmasked trials)
- Clinical centers and data coordinating center
- Sponsor and data coordinating center (especially if sponsor has proprietary interest in product being tested)
- Sponsor and investigators of trial (especially if sponsor has proprietary interest in product being tested)

14 Organization and management

Organizational principles

- Formulate organizational structure before starting trial
- Delineate and separate functions of key committees
- Specify relationship of one committee to another
- Specify committee membership and voting rules
- Delineate disclosure requirements for protection against conflicts of interest
- Review and revise organizational structure as trial proceeds

Considerations in selecting study chairperson

- Scientific qualifications
- Method of selection and appointment
- Length of office
- Responsibilities
- Replacement
- Vice chair

Steering committee design considerations

- Membership (eg, center directors vs other members of the study group)
- Number of representatives per center
- Mix of permanent vs elected members
- Length of membership for elected members

Executive committee design considerations

- Size (should be small to be effective)
- Time of creation (should be at outset)
- Membership conditions

14 Organization and management

Treatment effects monitoring and advisory review committee

- Odd number of voting members
- Appointment for duration of trial
- Balance of disciplines
- Free from conflicts of interest and of treatment responsibilities
- Appointment by sponsor or investigators

Examples of structural flaws

- Too much or too little centralization of control
- Too much democracy
- Too much control by the sponsor
- No method for revitalizing committee structure
- Ill defined decision making structure
- No mechanism for transfer of power

Policy issues

- Mechanisms for protection against conflicts of interest
- Payments for Advisory Review and Treatment Effects Monitoring
- Authorship and presentations procedures
- Policies and procedures for access to study data
- Data analysis policies and rights of individual centers
- Training and certification procedures
- General guidelines on employee responsibilities for protection of patient rights
- Backup systems for data records and files

15 Policy considerations

15 Policy considerations

Policy issues

- Authorship of papers
- Presentation and publication policies
- Internal editorial review procedures
- Publicity
- Policy on ancillary studies
- Degree of public access to study documents
- Policies on access to study data

Authorship principles and goals

- Formulate authorship policy with input from all interested parties
- Establish policy early in course of trial
- Provide ample opportunity for review and modification before adoption
- Review and modify policy as trial proceeds
- Avoid needlessly rigid or inflexible authorship rules
- Develop plan that stimulates individual initiative
- Avoid use of authorship as a vehicle for rewards or credits
- Persons listed as authors should have a role in writing and should be able to testify to the content and veracity of paper
- Persons instrumental in the design, execution, or analysis of the study, not listed as authors of paper, should be acknowledged or listed in credit roster in the paper

Authorship formats

conventional authorship: A form in which individual authors are listed in the masthead of the paper

Title: *Results from the XYZ Trial*
Authors: *Ann L Jones, Fred A Brown, and Ian F Smith*

modified conventional authorship: A form in which individual authors and the corporate name of the study group are listed in the masthead of the paper

Title: *Results from the XYZ Trial*
Authors: *Ann L Jones, Fred A Brown, and Ian F Smith*
for the XYZ Research Group

15 Policy considerations

corporate authorship: A form that attributes authorship to a corporate entity or group and in which individual authors are not named

Title: *Results from the XYZ Trial*
Authors: *The XYZ Trial Research Group*

modified corporate authorship: A form that attributes authorship to a corporate entity or group in the masthead of the paper but in which individual authors are named in a footnote to the title page or in the credit roster to the paper

Title: *Results from the XYZ Trial*
Authors: *The XYZ Trial Research Group*

Footnote: *Ann L Jones, Fred A Brown, and Ian F Smith for the XYZ Trial Research Group*

Credit roster formats[†]

Nonspecific credit: Undifferentiated listing of personnel arranged in alphabetic order. Listing does not indicate role or location of listed personnel (format not recommended).

Ann J Brown, MD
Frank M Curran, MD
Kate S Duran, RN
Raymond V Ellison, PhD
Beth L Grant
Milton J Handly, BS
Etc

15 Policy considerations

Discipline/activity specific credit

Physicians
Ann J Brown, MD
Frank M Curran, MD
William J Dutton, MD

Nurses
Kate S Duran, RN
Estelle N Lawson, LPN
Carol J Morrison, RN

Data processors
Raymond V Ellison, PhD
Nancy L Harrison, MSc

Etc

Position specific credit

Center directors
Ann J Brown, MD
Frank M Curran, MD
William J Dutton, MD
Raymond V Ellison, PhD
Etc

Clinic coordinators
Kate S Duran, RN
Emily N Eaton, BS
Marie K Fisher
Etc

Etc

15 Policy considerations

Credit roster formats

Center/committee specific credit (recommended format for multicenter trials)

Clinics
University of California, Davis
Ann J Brown, MD (Director)
Van H Ho, MD (Deputy director)
Amy B Butler, BS (ECG technician)
Kate S Duran (Clinic coordinator)
Joe T Mews, BS (Lab technician)
Etc for other clinics

Coordinating Center
University of Minnesota, Mpls
Raymond V Ellision, PhD (Director)
Mary W Baker, MD (Deputy director)
S Kern Forster, PhD (Sr statistician)
Elaine B Garrison, MSc (Coordinator)
Edward N Hartman, MSc (Programmer)
Grace R Zelier, BA (Secretary)
Etc for other resource centers

Steering Committee
Ann J Brown, MD (Chair)
Raymond V Ellision, PhD (Vice chair)
Frank M Curran, MD
Kate S Duran, RN
William J Dutton, MD (nonvoting)
Etc
Etc other committees

† *Credits may appear in footnote to title page or elsewhere in the manuscript, eg, in a section at the end of the manuscript*

15 Policy considerations

Conventional authorship

Advantages
- Identifies authors
- Preferred by most journal editors
- Recognized by promotions committees
- Compatible with National Library of Medicine indexing procedures

Disadvantages
- Difficult to devise equitable system for authorship
- May lead to bickering and dissent
- May discourage young investigators from participation in the trial

Recommended usage
- Small single center trials
- Approved ancillary studies in multicenter trials
- Special investigations or studies prompted by the trial but not directly related to it

Corporate authorship

Advantages
- Avoids association of study with specific individuals
- Avoids bickering over authorship rights and ordering
- Enables all personnel with documented role to cite in C.V.

Disadvantages
- Does not directly identify responsible authors
- Complicates retrieval by author via MEDLINE and not recognized in the SCI
- May discourage individual initiative
- Unfair to key people

Recommended usage
- Multicenter trials, especially for mainline papers
- Single center trials with 6 or more investigators
- Papers reflecting a corporate activity or point of view

15 Policy considerations

Considerations affecting authorship approach

- Number of investigators and centers involved
- Number and types of papers to be written
- Authorship needs of study personnel
- Skills and expertise needed for writing efforts
- Equity in distribution of authorship credits
- Method of identifying published papers

Writing committee considerations

- Number of members
- Mix of members
- Choice of chairperson
- Appointing authority
- Number of active committees

Types of papers produced

- Design and methods
- Baseline results
- Interim or final treatment results
- Descriptive and natural history
- Ancillary studies
- Methodological
- Review and summary

15 Policy considerations

Presentation and publication policy issues

Presentations
- Who may present
- What may be presented
- When to present (eg, before or after publication) and to whom
- Mechanism for review and submission of abstracts for proposed presentations

Publications
- When to publish
- Where to publish
- Format (eg, monograph vs individual papers)
- Before or after presentations

Other issues
- Type and amount of data that may be presented to investigators during the course of the trial
- When and where to present treatment results
- Dealing with criticisms or publicity from a presentation or publication

- Guarding against premature or unauthorized release of confidential treatment results
- Establishing a central referral point for press inquires and data requests
- Monitoring adherence to study presentation and publication guidelines

Presentation and publication mistakes

- Presentation or publication of results determined by events external to trial
- Hurried preparation of a major presentation or publication
- Presentation of major findings prior to publication
- Interim presentation or publication of treatment results not related to a protocol change

15 Policy considerations

Contributors to premature data releases

- Undisciplined investigators with access to treatment results
- Members of treatment effects monitoring or advisory review committees with loose tongues
- Special committees or probes
- News reporters
- Freedom of Information Act
- Journal policy on release of articles to the press

General guidelines for data release

- Limit access to treatment data during the trial to those responsible for monitoring treatment effects
- Prohibit release of individual listings or records that may compromise patient rights
- Provide access to unpublished supplementary tables for all major publications on treatment effects
- Limit release of data listings during the period of active support to those portions of the data file where analyses have been completed or no further analyses are planned
- Be sensitive to requests for data or added analyses that arise from outside the study
- Provide access to all data files used in publications from the trial after termination of active support

Special data access and analysis policy questions

- Decide on resources to be committed to responding to criticisms of the study design
- Provide opportunities for independent data analyses by investigators in the study
- Decide on level of analysis support to be provided for ancillary studies
- Establish equitable guidelines for data and information access

15 Policy considerations

Guidelines for ancillary studies[†]

- Funding (if needed) should be independent of that for the trial
- Data collection procedures should not interfere with recruitment, treatment, or data collection
- Arrangements for data analysis and access to main data file should be spelled out prior to start of ancillary study
- Limitations on time of publication or amount of information that can be presented or published should be agreed upon prior to start of ancillary study

[†] *An investigation carried out in one or more of the participating centers, utilizing resources arising from the trial but with objectives that are distinct from the primary objectives of the trial*

Internal editorial review issues

- Formal vs informal review procedures
- Types of papers subject to internal editorial review and approval
- Authority of the review group
- Standing editorial review committee vs ad hoc review committees

Study information policy

- Establish a central referral point for inquiries concerning the study
- Place design documents such as manuals, data forms etc. in the public domain
- Inform all investigators of publicity ground rules
- Limit constraints on information flow to those required for:
  - Protection of patient welfare
  - Protection of design integrity
  - Treatment monitoring
- Be forthright and honest in dealing with information requests

16 Analysis procedures

16 Analysis procedures

Basic analysis principle

The initial comparison of treatment groups should include all patients assigned to the respective treatment groups, should be by original treatment assignment, and should include all recorded events for the outcome of interest.

Reasons for the principle

- Conservative
- Approach compatible with design
- Avoids selection bias in forming comparison groups

Examples of violations of analysis principle

- Comparison restricted to patients who received assigned therapy
- Using the treatment actually administered to determine the group into which a patient is placed
- Excluding from analysis, patients with low treatment adherence
- Using only "evaluable" patients
- Exclusion of patients who fail to meet study eligibility criteria when the assessment is not independent of treatment assignment
- Counting only clinical events that occur after a specified period of treatment

Other analysis mistakes

- "Shopping" for an event merely to achieve statistical significance (eg, use of a contrived composite event)
- Use of hypothesis testing and p-values as the sole analysis approach
- Use of an adjustment variable related to treatment
- Selection of an adjustment variable with knowledge of the effect it has on the observed treatment difference
- Failure to describe data collection and analysis methods

16 Analysis procedures

Preliminaries to data analysis

- "Freeze" the data set
- Define a cutoff point beyond which additions to the data set are not accepted
- Establish rules regarding use of outlier values and "dirty" data
- Assemble data in a format designed for data analysis
- Edit for errors in linkage and time sequence
- Check accuracy of the treatment designation
- Generate backup data files
- Test analysis programs
- Document data analysis procedures

Types of comparisons

- At a specified point in the examination schedule
- At a specified calendar time
- Cross-sectional over time
- Cohort over time

Common descriptive procedures

- Simple counts
- Proportions or means
- Rates per unit of time
- Frequency distributions

Descriptive statistics

- Mean
- Median
- Standard deviation and variance
- Range
- Percentile, decile, etc
- Standardized treatment differences

16 Analysis procedures

Statistical procedures

- Fisher's exact test
- Chi square test
- t-test
- Standardized differences
- Analysis of variance
- Log rank test
- Relative betting odds

UGDP dropout status as of 7 Oct 1969†

	Plbo	Tolb	Istd	Ivar
No. enrolled	205	204	210	204
Alive	22	22	26	23
Status unknown	2	1	0	2
Total dropouts	24	23	26	25
% of enrolled	**11.7**	**11.2**	**12.4**	**12.3**

† *UGDP Research Group, 1970b*[56]

16 Analysis procedures

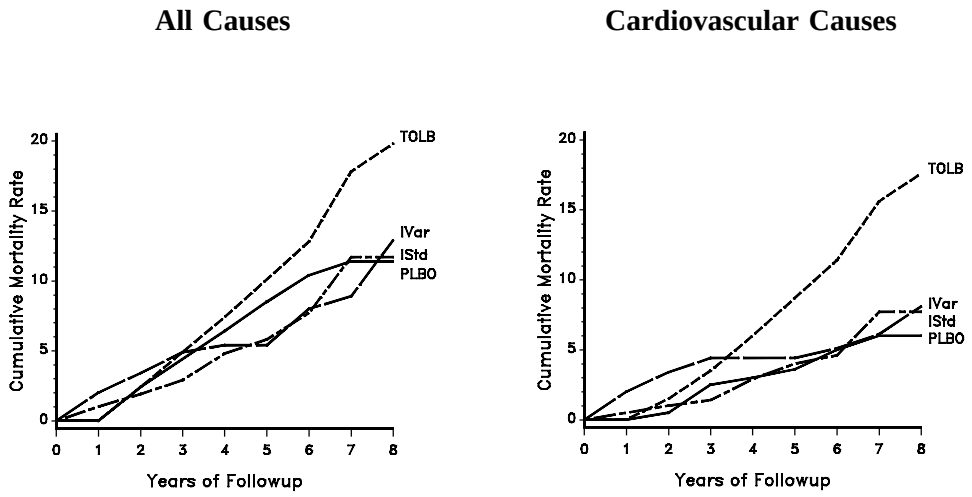
UGDP baseline SUM GTT Distribution[†]

Sum GTT mg/dl	Plbo	Tolb
< 500	3.6	9.0
500 - 649	36.6	24.0
650 - 799	21.3	22.0
800 - 949	14.2	18.0
950 - 1,099	9.6	10.5
≥ 1,100	14.7	16.5
Total no.	197	200
Mean	790.3	814.2

† *UGDP Research Group, 1970a*[55]

16 Analysis procedures

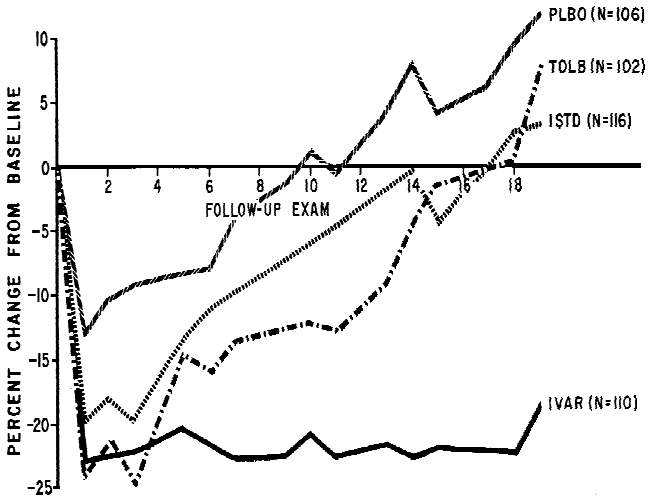
UGDP cumulative mortality rates†



† *UGDP Research Group, 1970b*[56]

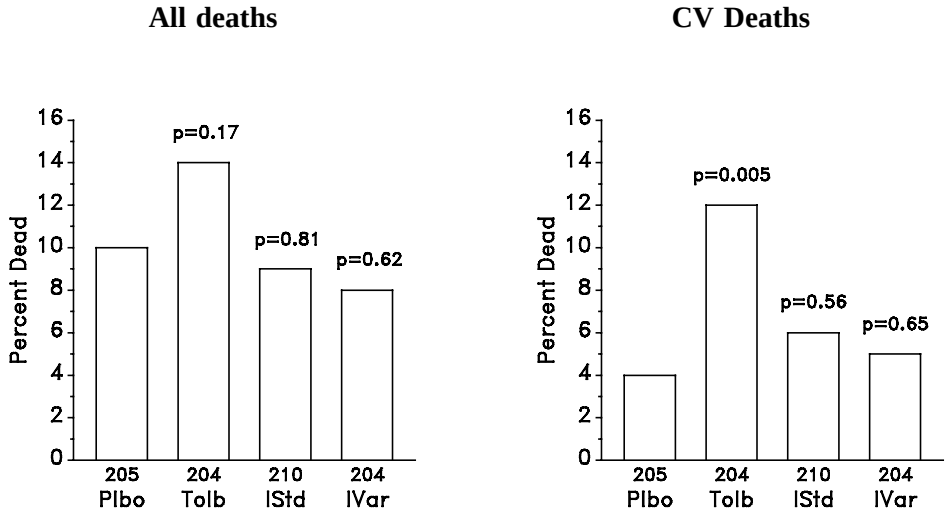
16 Analysis procedures

UGDP fasting blood glucose levels[†]



[†] *UGDP Research Group, 1970b*[56]

UGDP percent dead†



† *UGDP Research Group, 1970b*[56]

UGDP treatment difference (mortality)†

	Tolb vs Plbo	Istd vs Plbo	Ivar vs Plbo
Diff in % dead	4.5	-0.7	-1.4
p-value	0.17	0.81	0.62
Diff in % CV dead	7.8	1.3	1.0
p-value	0.005	0.56	0.65

† *UGDP Research Group, 1970b*[56]

16 Analysis procedures

UGDP Tolb vs Plbo RBOs†

	All causes	CV causes
Difference in % dead	4.5	7.8
RBO for 25% alternative	0.90	0.20

RBO (Relative Betting Odds): Ratio of posterior odds for H_0 to prior odds for H_1

† *UGDP Research Group, 1970b*[56]

UGDP demographic characteristics†

	Plbo	Tolb	Istd	Ivar	p-value
Age ≥ 55	41.5	48.0	46.2	46.1	0.58
Female	69.3	69.1	72.9	77.5	0.20
White	50.2	52.9	49.0	59.3	0.16

† *UGDP Research Group, 1970b; p-values for X^2 (3df)*[56]

PARIS side effects and z values†

	Pr/A	ASA	Plbo	Pr/A vs Plbo	ASA vs Plbo
No. of patients	798	800	403		
Stomach pain	15.8	17.2	7.7	3.74	4.41
Heartburn	9.6	9.4	5.2	2.58	2.43
Vomiting	2.5	3.2	1.0	1.59	2.37
Constipation	4.0	4.7	2.0	1.71	2.34
Dizziness	8.5	6.5	5.2	2.12	0.82
Headaches	9.6	4.1	3.7	4.01	0.27

† *PARIS Research Group, 1980*[45]

16 Analysis procedures

Adjustment

An attempt, through analytic procedures, to remove the effect of differences in baseline composition of the treatment groups on the outcome of interest.

Reasons for adjustment

- Randomization does not guarantee the baseline comparability of the treatment groups for variables not controlled at the time of randomization
- Only a small number of variables can be controlled at the time of randomization
- Small but systematic differences in the baseline composition of the treatment groups may explain the observed treatment difference

Adjustment procedures

- Subgroup analysis using demographic or baseline characteristics for subgrouping
- Multiple regression (linear or logistic) using a variety of demographic and baseline characteristics as regressors

Subgrouping definitions

subgrouping variable: A variable that is used to separate patients in a treatment group into two or more specified subgroups.

baseline subgrouping variable: A variable observed at or prior to treatment assignment that is used for subgrouping.

subgrouping cut point: The value of the subgrouping variable that represents the boundary between two subgroups (eg, 55 for age at entry to form two subgroups of patients: Those ≤ 55 at entry and those above 55 at entry).

16 Analysis procedures

UGDP subgroup mortality[†]

Baseline characteristic	Subgroup size		% dead	
	Plbo	Tolb	Plbo	Tolb
Hypertension				
Absent	127	139	11.0	12.9
Present	74	60	9.5	16.7
Hx digitalis use				
No	193	183	8.3	13.1
Yes	9	15	55.6	33.3
Hx of angina				
No	192	187	9.4	13.9
Yes	10	14	30.0	21.4
Entry ECG abn				
No	193	193	9.3	13.0
Yes	6	8	33.3	50.0
Entry cholesterol				
< 300 mg/100ml	181	169	10.5	14.8
≥ 300 mg/100ml	17	30	11.8	13.3
Composite				
None of above	98	100	9.2	11.0
≥ 1 of above	88	92	12.5	17.4

[†] *UGDP Research Group, 1970a*

16 Analysis procedures

UGDP regression model[†]

$$y = 1/(1 + e^{-A})$$
$$A = b_{00} + b_{01}x_{01} + b_{02}x_{02} + \cdots + b_{17}x_{17}$$

Where

$b_{00}, b_{01}, \cdots, b_{17}$ are regression coefficients

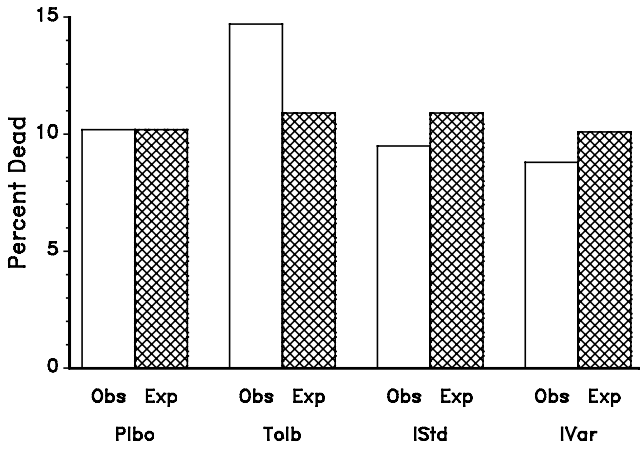
and

x_{01} = Treatment assignment
x_{02} = Treatment assignment
x_{03} = Treatment assignment
x_{04} = Sex
x_{05} = Race
x_{06} = Age
x_{07} = Digitalis use
x_{08} = Angina pectoris
x_{09} = ECG abnormality
x_{10} = Systolic blood pressure
x_{11} = Diastolic blood pressure
x_{12} = Serum cholesterol
x_{13} = Fasting blood glucose
x_{14} = Relative body weight
x_{15} = Visual acuity
x_{16} = Vascular calcification
x_{17} = Serum creatinine

[†] *UGDP Research Group, 1970b*[56]

16 Analysis procedures

UGDP observed and expected mortality (as of 7 Oct 1969)†

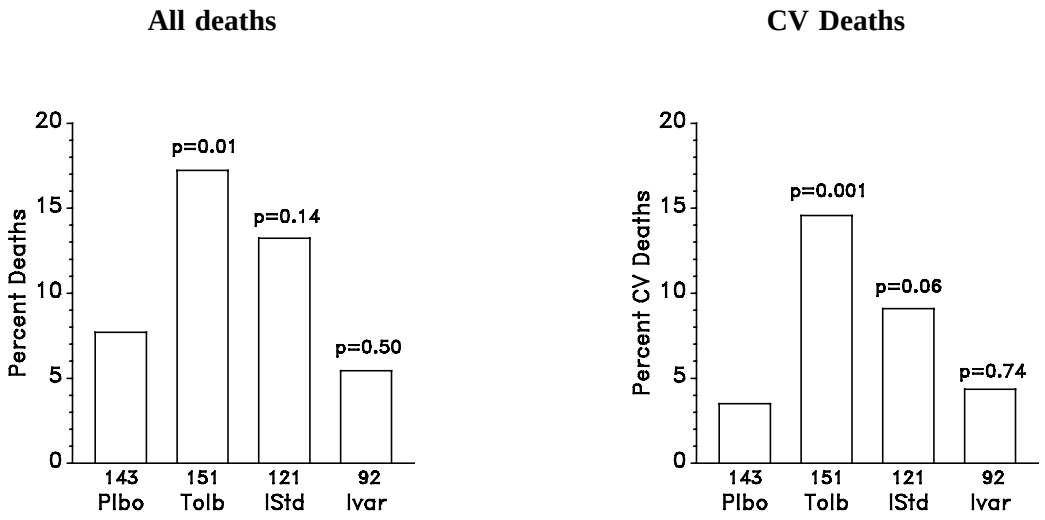


Exp (shaded bars) based on logistic model for total population of 823 patients

† *UGDP Research Group, 1970b*[56]

16 Analysis procedures

UGDP percent dead: High adherers†



† *UGDP Research Group, 1970b*[56]

17 Analysis questions

17 Analysis questions

Factors in analysis and interpretation of data

- Ineligible patients
- Missing data
- Uncollected data
- Unreliable or erroneous data
- Falsified or forged data
- Outlier values
- Loss of data due to missed exams and dropouts
- Death
- Unknown followup status
- Treatment noncompliance
- "Early" events
- Subgroup identification
- Significance testing

Enrolled ineligible patients

Recommended approach

Perform initial analyses with all patients counted, regardless of eligibility. Do other analyses counting only eligible patients.

Considerations

- How and when ineligibility was determined
- Length of treatment and followup before final determination was made
- Treatment following determination of ineligibility
- Number of ineligible patients

Missing data

Recommended approach

Restrict analysis to subset of patients with desired data or estimate missing values.

Considerations

- Amount of data missing
- Relationship to treatment assignment
- Need for full data complement

17 Analysis questions

Uncollected data

Recommended approach

Punt, since there is no way to create something out of nothing! Data collection scheme may be modified during trial to correct oversight. Retrospective data collection may be considered if reliable information can be obtained in this way – usually not the case. Minimize problem by proper review procedures during the development of the data collection forms.

Considerations

- Presumed baseline comparability of treatment groups with regard to unobserved variables
- Importance of the variable to subsequent analyses
- Feasibility and cost of obtaining the desired information from existing medical records vs directly from study patients

Unreliable or erroneous data

Recommended approach

Questionable data that are suspicious but where obvious errors cannot be ruled out should be retained in the initial analysis. Subsequent analyses may be done excluding questionable data. Carry out ongoing editing procedures during the trial to identify and correct problems.

Considerations

- Amount of data in question
- Relationship of data to treatment assignment
- Importance of data to overall evaluation of the trial results
- Biological or clinical "reasonableness" of the values in question

17 Analysis questions

Falsified or forged data

Recommended approach

Data may be retained for analysis if falsification or forgery is limited to data collected prior to treatment assignment, otherwise purge. Extent of purge should include all questionable data and should be made without regard to treatment assignment or outcome. Purge all falsifications or forgeries that occur after treatment assignment or that are likely to be treatment related. Report nature of problem and action taken to appropriate Institutional Review Boards, sponsoring agencies, and in publications.

Considerations

- Time in relation to treatment assignment
- Amount of data and patients affected
- Importance of affected data
- Size of purge required to ensure containment of affected data

Outlier values

Recommended approach

Use appropriate trimming procedures, such as Winsorization, when dealing with means or variances; or use measures that are insensitive to extremes such as the median or rank order. Carry out ongoing editing procedures during the trial to identify and correct procedures that lead to erroneous extreme values.

Considerations

- Influence of outliers on the analysis
- Biological or clinical plausibility of outliers
- Relationship of outliers to treatment assignment
- Method of data analysis and presentation
- Amount of trimming to be performed
- Impact of trimming on observed treatment difference

17 Analysis questions

Loss of data due to missed exams and dropout

Recommended approach

Perform "best" and "worst" case analyses to determine whether or not losses explain the observed result, especially if losses are large or differential by treatment group.

Considerations

- Number of missed exams or dropouts
- Effect of missing an exam or of dropping out on treatment compliance
- Difference in missed exam rate or dropout rate by treatment assignment
- Characteristics of patients who miss exams or drop out

Loss to followup due to death

Recommended approach

Compare treatment groups for difference in number of deaths. If the difference is small, proceed with comparisons involving other variables, ignoring losses due to death. If the difference is large use methods that take account of censoring due to death when analyzing nonfatal event data or other kinds of data.

Considerations

- Number of deaths
- Randomization unit
- Relationship of deaths to treatment assignment
- Relationship of deaths to the variable of interest
- Timeliness of death reporting

Unknown vital status

Recommended approach

Perform "best" and "worst" case analyses to determine effect on mortality comparisons.

Considerations

- Number of patients with unknown status
- Relationship to treatment assignment
- Baseline and demographic characteristics contrasted with those under active followup

17 Analysis questions

Treatment noncompliance

Recommended approach

Analyze and report by original treatment assignment. Base conclusions on this analysis. Perform other analyses with adherence as a subgrouping or adjustment variable for comparison with primary analysis.

Considerations

- Degree of noncompliance
- Nature of noncompliance (eg, no. of "crossovers")
- Effect of noncompliance
- Characteristics of noncompliers

Merits of approach to treatment noncompliance

- Compatible with study design
- Avoids treatment related selection bias in the composition of the treatment groups
- Provides "real world" measure of treatment effect (ie, the effect remaining after losses due to patient or physician rejection)
- Usually conservative

"Early" events

Recommended approach

Primary analysis should be based on all events regardless of time of occurrence. Results of this analysis may be compared with one in which "early" events are ignored to determine effect on results.

Considerations

- Number of "early" events
- Relationship to treatment assignment
- Biological explanation

17 Analysis questions

How not to count events

- By excluding "early" events from count (eg, 7 day rule in ART or by counting only post operative deaths in surgical trial)
- By counting only certain classes of events (eg, CV deaths count, all others ignored)
- By excluding noncompliers
- By counting only "evaluable" patients

Subgroup identification

Recommended approach

Restrict search to subgroups defined by variables that are known to be independent of treatment assignment (ie, invariant demographic characteristics, such as sex and race, and all observations made prior to treatment assignment). Exercise extreme caution in formulating any conclusion derived from subgroup analyses.

Considerations

- Number of subgroups of interest
- Means of identifying variables to be used for subgrouping
- Biological plausibility of defined subgroups

Ground rules for subgroup analyses

- Limit choice of subgrouping variables to invariant demographic characteristics or variables observed prior to treatment assignment
- Look at all subgroups defined by a variable
- Distinguish between a-priori and a-posteriori selected subgrouping variables
- Choose cut point for subgrouping without regard to observed treatment differences
- Avoid conventional interpretation of significance tests
- When possible, validate subgroup results before reporting when based on a-posteriori selected subgrouping variable
- Report methods and procedures
- Be cautious regarding all subgroup conclusions!

17 Analysis questions

Cornfield on multiple significance testing†

Just as the Sphinx winks if you look at it too long, so, if you perform enough significance tests, you are sure to find significance even when none exists.

† ***Am J Epidemiol*** *104: 408-21, 1976*[12]

Anscombe on multiple significance testing†

The probability of obtaining a significant result (eg, A p-value ≤ 0.05) with conventional tests of significance approaches unity as the number of interim analyses increases.

† ***Biometrics*** *10:89-100, 1954*[3]

Problems with conventional significance testing

- Assumptions for interpretations rarely satisfied (eg, single "look" for a single outcome)
- Encourages binary view of results as either "significant" or "nonsignificant"
- May contribute to publication bias
- May block more searching and biologically informative data analyses
- May lead to erroneous interpretations or conclusions

Alternatives to conventional tests of significance

- Focus on point and interval estimation rather than on hypothesis testing
- Use methods that focus on trend, direction, and consistency of results rather than on "significance"
- Use Bayesian rather than frequentist approach to data interpretation
- Employ procedures to adjust p-values for multiple looks or comparisons

17 Analysis questions

Cornfield on research principles[†]

On being asked to talk on the principles of research, my first thought was to arise after the chairman's introduction, to say, "be careful", and to sit down.

[†] ***Am J Ment Defic*** *64: 240-52, 1959*[11]

18 Treatment effects monitoring

18 Treatment effects monitoring

Treatment effects monitoring

An ongoing process of reviewing accumulated outcome data during the trial to assess treatment effects for the purpose of determining whether to allow the trial to continue unaltered.

Trials requiring monitoring

Any trial in which the treatments have the potential for producing an adverse or beneficial treatment effect and where it is possible to detect and act upon such effects during the course of the trial.

NIH recommendations†

- Every clinical trial should have provision for data and safety monitoring
- Provision should be approved by IRB
- A multicenter trial should have an independent treatment effects monitoring committee
- Monitoring committee should include clinicians with expertise in disease under study, biostatisticians, and scientists from other pertinent disciplines. Physicians in the study engaged in patient care should be excluded from membership

† ***NIH Guide for Grants and Contracts***, *Vol. 8, No. 8, 5 June 1979*[41]

Monitoring prerequisites

- Direct and timely flow of data from clinic to data center
- Up-to-date database
- Computer hardware and programs for data analysis
- Mechanism for review and acting upon interim analyses

18 Treatment effects monitoring

Sequential vs fixed sample size designs

Sequential designs

Open sequential design: A design in which patient enrollment continues until the test - control treatment difference exceeds a specified upper or lower boundary limit and where the limits are computed so as to have specified statistical properties.

Closed sequential design: A design in which patient enrollment continues until the test - control treatment difference either exceeds the upper or lower boundary limits or until the observed treatment difference enters the region of "no difference".

Fixed sample size design

A design in which the intent is to continue patient enrollment for a stated period of time or until a specified recruitment goal (usually the result of a sample size calculation) is achieved.

Interim analysis

An analysis carried out during the course of the trial that is designed to determine whether the trial should be altered because of observed treatment effects.

Desired approach to treatment monitoring

Multidisciplinary review team with appropriate medical, biostatistical, and bioethical expertise in which:

- At least one team member has first hand clinical experience with the treatments under study and is familiar with the nuances of the treatment protocol
- No voting member is dependent on funding from the trial
- No member stands to gain or lose financially from recommendations concerning the study treatments
- All members freely disclose all arrangements and associations that could be construed as constituting a conflict of interest

18 Treatment effects monitoring

"NIH approach" to treatment monitoring

- Committee (5 to 7 voting members) appointed by investigators or NIH with advice and consent of NIH or investigators
- Periodic meetings held to review data with frequency determined by study needs (usually at least twice a year)
- Membership limited to individuals not responsible for administration of treatment(s)
- Membership includes expertise in appropriate medical area and biostatistics, and usually includes at least one nonhealth professional
- Members usually chosen so as to exclude any with conflict of interest, however no uniform policy on disclosure exists

Treatment monitoring characteristics of the CDP

- Semiannual reports prepared by the Data Coordinating Center for distribution to the Treatment Effects Monitoring Committee (TEMC)
- Semiannual meetings of TEMC with provision for special meetings when necessary
- Recommendations from TEMC reviewed by Advisory Review Committee (ARC) before being passed to the Steering Committee for implementation

General guidelines

- Carry out analyses by treatment group
- Concentrate on comparisons involving the primary and secondary outcome variables
- Perform simplest analyses first
- Use plots to describe data trends and changes
- Do not combine outcome events before considering each one alone
- Search for discrepancies and deficiencies in the data that may explain the observed treatment difference
- Relate data on side effects and general health status to comparisons of primary and secondary outcome variables
- Search for inconsistencies in the data

18 Treatment effects monitoring

CDP treatment monitoring reports

Primary outcomes
- Death, all causes
- Death, CV causes

Secondary outcomes
- MI
- Stroke
- Intermittent claudication, incidence
- Angina pectoris, incidence
- TIA, incidence
- Congestive heart failure

Side effects or complications
- Elevated bilirubin
- Elevated alkaline phosphatase
- Abnormal hematocrit
- Patient complaints or symptoms
- Reasons for change in treatment

Baseline characteristics
- Age
- Race
- Risk group
- Smoking status
- Plus various others (50+)

Indicators of exposure to treatment
- Pill count
- Adherence score
- Laboratory measures of adherence

Indicators of completeness of data collection
- Missed examination rate
- No. of dropouts or losses to followup

18 Treatment effects monitoring

CDP treatment monitoring reports

Indicators of data quality
- No. of edit queries generated
- No. of outstanding edit queries
- No. of protocol violations
- Repeat lab determinations
- Repeat ECG readings

General indicators of health status
- Hospitalization
- Physical activity
- Occupational status
- Exam findings
- Blood pressure
- Body weight
- Drugs taken
- Cholesterol level
- Change in smoking status

Considerations when terminating a treatment

- Trend of results over time
- Reversals of a trend during the course of the trial
- Internal consistency of the data
- Importance of the treatment being tested
- Risk vs benefit of stopping
- Size and clinical importance of the observed treatment difference observed
- Statistical significance

Cornfield on interim results and p-values†

If maintenance of the significance level interferes with the release of interim results (of clinical trials), all I can say is so much the worse for the significance level.

† *Cutler et al, 1966*[19]

18 Treatment effects monitoring

Arguments against stopping rules

- Impossible to specify conditions at outset that may lead to premature termination
- Rules tend to be unrealistic and mechanistic
- Does not encourage meaningful data analysis
- Over emphasizes significance testing as an analysis approach

Alternatives to conventional p-values

- Bayesian approach (eg, RBOs)
- Frequentist approach using Monte Carlo procedures
- Bonferroni's Inequality
- p-value adjustments

Relative betting odds (RBOs)

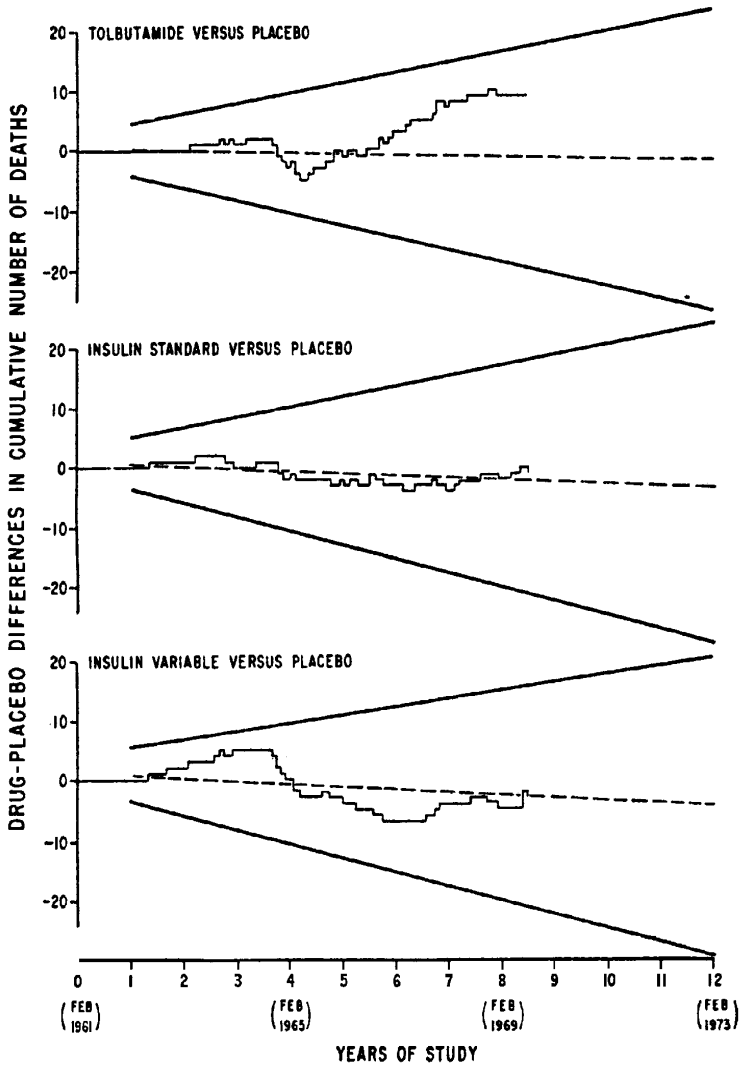
Comparison of the likelihood of an observed treatment difference for the test vs the control treatment, as calculated under the null hypothesis of no beneficial effect for the test treatment, and under an alternative hypothesis for a specified beneficial treatment effect. RBOs < 1.0 favor the alternative hypothesis; RBOs ≥ 1.0 favor the null hypothesis.

RBOs for Tolb vs Plbo comparison; 25% alternative hypothesis[†]

Year	All causes	CV causes
1	1.00	1.00
2	1.12	1.00
3	1.21	1.10
4	1.27	0.87
5	1.32	0.52
6	1.30	0.39
7	0.69	0.21
8	0.51	0.15

† *UGDP Research Group, 1970b*[56]

UGDP 5% tolb vs plbo monitoring bounds†



† *UGDP Research Group, 1970b*[56]

18 Treatment effects monitoring

Bonferroni's inequality†

If A_1, A_2, · · ·, A_k are k independent events, each occurring with probability p, then

Prob(1 or more events occur simultaneously) <kp.

† *Feller:* ***Introduction to Probability Theory and its Applications***[20]

Multiple comparisons and Bonferroni's inequality

If k independent statistical tests are done, each with a type I error level of p, then:
Prob (1 or more "chance" differences)
= $1 - (1-p)^k < kp$

Example: k = 10, p = 0.05
Prob (1 or more "chance" differences)
= $1- (0.95)^{10}$
= $0.401 < 10(0.05) = 0.5$

Application: Choose level of significance for k tests such that combined risk of a type I error is ≤ p
Choose p* = p/k, such that
Prob (1 or more "chance" differences) < kp*
= k(p/k) = p

Example: k = 10, p = 0.05
p* = 0.05/10 = 0.005

18 Treatment effects monitoring

Myths and misconceptions

- It is inappropriate to carry out interim analyses because of their impact on p-values
- You should not start a trial without stopping rules
- There is no need to worry about stopping once patient recruitment is completed
- You should not stop until you achieve statistical significance for the primary comparison
- The same difference, regardless of direction, should lead to the same action
- The quality of decision making is enhanced by masking the treatment effects monitoring committee
- A difference that is insignificant will lead to an inconclusive finding
- The statistician should be responsible for decision making
- The quality of interim analyses is not affected by limiting participation on the treatment effects monitoring committee to individuals not involved in the trial

19 Publication

19 Publication

Paper writing considerations

- Purpose of paper
- Type of paper (manuscript vs monograph)
- Journal for submission
- Authors
- Data to be included and methods of analysis
- Internal review procedures

Parts and sections

- Title
- Authors
- Credits and acknowledgements
- Disclosures
- Abstract and key words
- Introduction
- Methods
- Results
- Discussion
- Conclusions
- References
- Appendixes

Title

Considerations

- Numbered titles?
- Design terms in title (eg, such as, *randomized*)?
- Subtitles?
- Study name as part of title?

Create titles that:

- Are succinct but informative
- Indicate purpose
- Telegraph content and type of study

19 Publication

Title

Avoid titles that:
- Contain too much detail
- Contain redundant terms, such as, *prospective*, in the phrase *prospective clinical trial*
- Are "cute" but uninformative

- Contain jargon, undefined abbreviations, or acronyms
- Contain uninformative words or terms, such as, *study, project, program, collaborative, cooperative*, as substitutes for more precise informative terms, such as, *clinical trial, multicenter*
- Contain terms of presumption or arrogance, such as, *definitive, unique, innovative*

Remember
- Importance of title as identifier and descriptor
- Use of title by indexers

Authors

General requirements for authorship (at least one of the following):
- Participation in the study at a level sufficient to enable taking responsibility for contents of the manuscript
- Involvement in the conception or design of the trial, or in the analysis and interpretation of data
- Involvement in writing the manuscript or in providing intellectually important input for the manuscript
- Review and approval of the manuscript prior to submission for publication

Suggestions
- List senior author first; list other authors in descending order of importance or in alphabetic order
- List full name of each author, including middle initial, and surname qualifiers such as Jr, II, and III (as well as degrees even though not included in MEDLINE)
- List institutional affiliation of authors in a footnote to title page or elsewhere in the manuscript

19 Publication

Authors

Remember

- Corporate authors are not listed in author field of MEDLINE database
- All listed authors indexed in MEDLINE thru 1983; 1984 thru 1995: first 10 authors indexed, "et al" used to indicate presence of unindexed author; starting in 1996: 25 authors indexed; if > 25 authors, first 24 and last in listing indexed, "et al" used to indicate presence of unindexed authors
- Only two initials per author in MEDLINE and *Index Medicus*
- Variation from paper to paper in use of middle initials, surname qualifiers, or hyphenated names may create problems for users of MEDLINE

Credits and acknowledgements

- Distinguish between credits and acknowledgements
- Credit listing should include personnel involved in design, conduct, or analysis of the trial as well as responsible committees and membership
- Acknowledgement listing should include those to be thanked or noted
- Include institutional affiliations in listings for multicenter trials
- Check accuracy of listings and inform people of how they will be listed prior to publication
- List credits and acknowledgements in footnote on first page or at the end of the manuscript

Disclosures

- Name and address of funding agencies and associated grant or contract numbers in the case of Federal funding+
- Name and address of agencies contributing drugs, equipment, or other supplies†
- Name and address of person or office responsible for filling requests for reprints†
- Listing of persons or agencies having proprietary interest in test treatment(s) or in some other aspect of the study
- Mechanism for disclosure and review of potential conflicts of interest
- List of documents, such as study forms, manuals, and handbooks available via a study center or on deposit at NTIS or some other public repository
- Method of obtaining data included in manuscript; intended release time if not available at time of publication

† *Items usually listed in footnote to first page*

19 Publication

Abstract and key words for trials†

Abstract to include statements concerning:
- Purpose of trial
- Study treatments (control and test treatments)
- Level of treatment masking
- Method of treatment assignment
- Number of patients enrolled (total and per treatment group)
- Length of followup
- Primary outcome measure
- Main result
- Conclusion

Abstract should:
- Be short (ie, ≤ 200 words)
- Be succinct
- Be factual
- Include key words to telegraph subject matter and content of paper; use design as well as content terms (some journals may also ask authors to suggest Medical Subject Headings (MeSH) for NLM indexers)

Remember:
- Abstracts are part of MEDLINE and may be electronically searched
- Abstracts are written by authors, not by editors or indexers
- Key words are of limited value to NLM indexers; their main purpose is for readers
- Author listed MeSH may not be used by indexers

† *See also A Proposal for More Informative Abstracts of Clinical Articles,* ***Ann Int Med*** *106: 598-604, 1987*[59]

Introduction

- Motivation and rationale for study
- Developments leading to initiation of trial and history of trial
- Review of pertinent literature and reference to previous pertinent work

19 Publication

Methods: Study population

- Eligibility and exclusion criteria
- Method of identification and recruitment
- Time period for patient recruitment (ie, enrollment dates of first and last patients)

Methods: Treatment

- Study treatments and rationale for choice
- Treatment administration procedures
- Level and method of masking
- Conditions under which treatment may be stopped or changed
- Method of measuring adherence to treatment

Methods: Outcome

- Primary and secondary outcome measures, definitions, methods of measurement, and rationale for choice
- Definition of events comprising outcome measures
- Methods for recording, coding, and classifying events

Methods: Design specifications

- Method of treatment assignment including description of safeguards to ensure the integrity of the assignment process, stratification, blocking intervals, and method of packaging and dispensing medications in case of masked drug trials
- Recruitment goal (planned sample size)
- Type I and II error level protection with planned sample or power with sample size of convenience
- Proposed and actual length of followup and rationale
- Number of patients enrolled (total and by treatment group)

19 Publication

Methods: Patient safeguards

- Outline of steps for obtaining patient consent
- Method of updating consent where applicable
- Measures taken to protect confidentiality
- Description of safeguards to protect patients against exposure to ineffective or harmful treatments

Methods: Data collection

- Baseline and followup examination schedule and rationale
- List of types of data collected at baseline and followup exams
- Definitions of missed examination and dropout
- Methods for locating patients lost to followup and for mortality followup (when applicable)

Methods: Data processing and analysis

- Center or group responsible for data processing
- Method of data entry (eg, at clinic from paper forms)
- Average time from generation of data to entry
- Cutoff date for data included in publication
- Analysis principles (eg, by treatment assignment)
- Description of methods of analysis, including relevant references
- Methods for judging statistical importance of observed differences

19 Publication

Methods: Quality control and performance monitoring

- General data editing procedures
- Laboratory and reading quality control procedures
- Checks on data entry, programming, and analysis procedures
- Other quality control procedures, such as site visits to clinics, and training and certification
- Measures used for performance monitoring
- Frequency of performance assessment
- Methods for reviewing performance and for implementing corrective action

Methods: Treatment monitoring

- Frequency of interim analyses for assessment of treatment effects
- Analysis procedures
- Data used for treatment monitoring
- Individuals or group responsible for carrying out interim analyses
- Procedures for implementing a decision arising from interim analyses

Methods: Organization

- No. and location of participating centers
- Location of data center
- Committee leadership structure and interrelationships
- Funding structure (eg, consortium vs individual grants or contracts in case of multicenter trials)

19 Publication

Methods: Miscellaneous

- Language conventions and terminology used, including glossary (if appropriate)
- Detailed accounting of any actions taken that affect the database including:
  - Addition or deletion of clinics or other centers
  - Addition or deletion of a treatment
  - Additions or deletions to the study forms
  - Changes in definitions or coding procedures during the trial
  - Data purges for whatever reason, including those related to known or suspected falsification or due to questions concerning data accuracy or validity

Results: Descriptive and baseline

- Number of patients enrolled (total and by treatment group)
- Comparison of study population with larger population via use of data from screening logs or other sources (useful when attempting to generalize findings)
- Means, medians, variances, frequency distributions, etc for selected demographic and baseline variables
- Assessment of treatment comparability for selected demographic and baseline characteristics
- Indicators by treatment group of the completeness of followup, such as:
  - No. of missed examinations
  - No. of dropouts
  - No. lost to followup
- Indicators of treatment adherence such as:
  - Comparison of treatment groups using an adherence score or a laboratory measure of adherence
  - Count of the number of patients in each treatment group who received little or none of the prescribed treatment
  - Count of the number of patients in each treatment group who received an alternative treatment

19 Publication

Results: Outcome

- Number and proportion of deaths by treatment group
- Number and proportion of deaths by cause and treatment group
- Number and proportion of other events by treatment group
- Treatment comparisons related to the occurrence of selected morbid events
- Comparison of treatment groups for the primary and secondary outcome measures using various analytic techniques, including comparisons of proportions and lifetable analyses for event data
- Treatment comparisons related to:
  - Occurrence of side effects during followup
  - Hospitalization during followup
  - Changes in health during followup
- Changes over time by treatment group for continuous variables such as blood pressure or laboratory measures

Results: Explanatory

- Comparisons of treatment groups for the outcome of interest within subgroups of patients formed using selected demographic and baseline characteristics
- Multiple regression analyses using selected demographic and baseline characteristics to provide adjusted treatment comparisons
- Comparisons of treatment groups by level of adherence to determine if increased adherence enhances the treatment effect
- Best and worst case analyses to determine effects of different analysis approaches and assumptions on observed treatment effects
- Analyses aimed at attempting to identify treatment related biases or artifacts in the data
- Analyses aimed at identifying inconsistencies in the data via comparison of results for one outcome with another or comparison of the same outcome across different subgroups (including treatment comparisons for the primary outcome by clinic in the case of multicenter trials)
- Other analyses relating trends for one variable (eg, cholesterol level) to an outcome event, such as death

19 Publication

Discussion

- Commentary on important findings by referring to tables and figures presented in results section
- Qualifiers and cautions to be noted when interpreting results of trial
- Commentary on consistency of observed treatment results across subgroups and outcomes
- Review of findings in relation to other studies, noting findings that are consistent with earlier studies and those that are not
- Clinical implication of the findings

Conclusions

- Conclusions reached and reason
- Limitations of the study and of the conclusions
- Discussion of validity vs generalizability
- Future research and analyses needed

References

- Check accuracy of citations against source document; do not copy citations from other papers
- Reference indexed journals (when possible), as opposed to similar information contained in government publications, chapters in books, or unindexed proceedings
- Use textbooks to reference general information concerning medical conditions, standard analysis procedures, etc
- Cite original as opposed to secondary source, except where source resides in obscure location
- Provide complete listing for each citation (ie, all authors, complete title, and beginning and ending pages for journal articles; total number of pages for books, monographs, and proceedings)
- Use NLM journal abbreviations unless otherwise instructed
- Arrange and number references in order of use or alphabetize and number sequentially; cite number or author and year in text

Remember
- Importance of accurate and complete referencing
- Use of references in the Science Citation Index
- Citation of inappropriate references is often the result of careless reading, haste, or use of secondary sources
- Errors in citations once published reflect badly on authors and stand unaltered for time immemorial

Appendixes

- Use appendixes for material not of interest to the majority of readers
- Each appendix should be clearly labeled as such, titled, numbered (if more than one), and listed in the table of contents

Remember
- Not all journals accept manuscripts with appendixes
- Alternatives to published appendixes include depositing material at a national repository or providing the material on request to the authors
- Material in appendixes tends to be "lost"

Other parts

- Table of contents
- Subject and author index
- History of manuscript
- Glossary

20 Clinical trials: How to read

20 Clinical trials: How to read

Clinical trial definition

An experiment designed to assess the efficacy of a test treatment by comparing its effects with those produced using some other test or control treatment in comparable groups of human beings.

Types of trial designs

Treatment structure
- Crossover
- Parallel

Assignment ratio
- Fixed
- Dynamic; adaptive

Sample size
- Fixed
- Sequential

Types of trials

By focus on disease
Treatment trial (GLT, SOCA trials)
Secondary prevention trial (UGDP, CDP)
Primary prevention trial (HPT, MRFIT, PHS)

By focus on type of treatment
Drug trial
Surgery trial
Dietary trial
Etc

By focus on number of centers
Single center trial
Multicenter trial

20 Clinical trials: How to read

Treatment trials as the focus

Definition: A trial involving treatment in the usual sense; generally characterized by enrollment of patients having a disease or health condition requiring treatment or considered to be likely to benefit from treatment in the long term

Examples
- FDA licensure trials
- Phase III and IV drug trials
- Any trial involving treatment of clinical disease

Usual features

- Designed
- Parallel treatment design
- Fixed assignment ratio
- Fixed sample size design
- Two or more study treatments
- Generally a control treatment (eg, standard medical treatment, sometimes a placebo or sham treatment)
- Comparable treatment groups
- Baseline data collection
- Followup over a defined period for the outcome(s) of interest

Finding trials of interest

- The old fashioned way via the eye ball approach
- MEDLINE
- Current Contents

20 Clinical trials: How to read

How to succeed in trials

- Use surrogate outcome to reduce sample size and impress cost conscious funding agency
- Data dredge until you find a "significant" result
- Use a composite outcome when none of the outcomes alone yield "significant" results
- Consider only "evaluable" patients in analyses
- Discard certain events in analyses
- Perform analyses by treatment received
- Test a new (and preferably high tech) treatment and show it to be superior to the current standard treatment
- Reach a conclusion people want to hear
- Do a lot of small scale short term trials and publish only those that yield positive results
- Do only trials in which you are 1st (if not sole) author
- Do an underpowered trial to accept the null hypothesis
- Use self laudatory language in describing your trials (eg, definitive, unique, landmark)

Ways to fail at trials

- Test an established treatment and show it to be useless
- Attempt to answer a question the medical profession does not want answered
- Do long term multicenter trials with corporate authorship of papers
- Use performance goals (eg, for patient recruitment) as imposed by review group or funding agency

Reading sequence

- Title
- Abstract
- Fine print
- Tables and figures
- Methods
- Discussion
- Introduction
- Results

20 Clinical trials: How to read

Features of a good clinical trial

- Randomized
- Adequate sample size
- Meaningful outcome measure
- Adequate period of followup
- Analysis by original treatment assignment
- Adequate bias control procedures
- Adequate performance

Essential counting and analysis rules

Study population

- Count as enrolled when randomized
- Count as randomized when assignment revealed to clinic
- Count in treatment group to which randomized, regardless of subsequent course of treatment and followup, including dropouts and noncompliant patients

Count of events

- Count from time of randomization forward, ie, count regardless of when an event occurs after randomization and initiation of treatment
- Count all higher order events (eg, deaths in an MI study) even if treatment not expected to have effect on such events
- Count events separately before combining to create a composite outcome measure

Analysis principles

Basic principle: The initial comparison of treatment groups should include all patients assigned to the respective treatment groups, should be by original treatment assignment, and should include all recorded events for the outcome of interest

- Primary analysis should be by original treatment assignment; include all patients randomized and outcomes observed regardless of course of treatment or time from randomization
- For trials not involving death as the primary outcome: comparisons for higher order outcomes should be performed before proceeding to the comparison of primary interest
- Comparisons for individual events or outcomes measures should be performed before presenting analyses for a composite event or outcome measure

20 Clinical trials: How to read

Telltale clues regarding rule violations

- Absence of specific statements regarding counting or analysis principles employed
- Unexplained varying denominators
- Telltale words in the abstract or methods, such as "evaluable" patients
- Large differences in baseline comparability of the groups
- Large departures from the expected assignment ratio

The title

- Informative, short, and succinct
- Use of key design terms such as trial and randomized
- Communicates something about the treatments being evaluated and the disease or population under study

Abstract

- Second only to the title in importance
- The best abstracts are short, succinct, and structured
- A good abstract should provide the following:
  - Purpose of trial
  - Study treatments (control and test treatments)
  - Level of treatment masking
  - Method of treatment assignment
  - Number of patients enrolled (total and per treatment group)
  - Length of followup
  - Primary outcome measure
  - Main result
  - Conclusion

20 Clinical trials: How to read

Design and operational integrity

- Adequacy of bias control procedures
- Method of treatment assignment and vulnerability to abuse
- Adequacy of separations, especially of sponsors with proprietary interests in the outcome
- Data analysis independent of the sponsor, especially for sponsors with proprietary interest in the outcome
- Independent treatment monitoring board

Methods

- Method of bias control, especially in relation to masking
- Method of treatment assignment
- Landmark event defining enrollment of a person into the trial
- Method of ongoing monitoring
- p-value philosophy in relation to multiple looks and subgroup analyses
- Statement of counting and analysis principles

Analysis issues and questions

- Was the outcome measure of primary interest in the manuscript selected prior to the start of data collection?
- Were higher order events or outcomes taken into account in the analysis and interpretation of that measure?
- If the focus is on a subgroup, was it identified by some means other than data dredging?
- Were differences in the baseline composition of the treatment groups taken into account in the analysis?
- If results were published prior to the end of the trial, do the authors offer a reasonable rationale for that action?

20 Clinical trials: How to read

Looking for that which is not there

- Reading the fine print of footnotes
- Credits and acknowledgments
- Sources of support
- Affiliations and conflict of interest disclosures
- Statements regarding counting and analysis principles

Validity versus generalizability

- Validity and generalizability are different concepts
- A comparison from a trial is valid so long as there is a legitimate basis for comparison of the different treatment groups
- Design maneuvers such as randomization, masking, and standardized data collection procedures are all designed to help ensure valid treatment comparisons
- The ability to generalize requires a sampling frame (usually absent by definition in the clinical trial setting) or must be done on the basis of judgment

Data dredging as an art form

- Do an almost countably infinite number of subgroup analyses, largely without regard to size of your dataset
- Select only those subgroups yielding differences that are statistically significant, measured with a conventional p-value of ≤ 0.05, blithely ignoring any need for conservatism
- Where possible, choose cut points for subgrouping variables that maximize differences
- Combine two or more variables for subgrouping if doing so increases the difference
- Report results only for the subgroups with the largest differences, without any indication as to the process for identification or of the number of analyses performed yielding trivial differences
- Submit the manuscript containing dredged results with the suggestion that the subgroups identified are original with you and that the factors defining them carry major medical implications for treatment
- Stay near the phone awaiting a call regarding your nomination for the Noble Prize in Medicine, promoting your candidacy for the prize while waiting

20 Clinical trials: How to read

Non issues

- Lack of representativeness
- Inability to define the population from which patients were recruited
- The size of the population approached for study not agreeing to participate
- Minor imbalances in the treatment groups
- Minor changes in procedures over the course of the trial
- Departures from normal practice procedures
- The lack of perfection

Publication bias

An inclination or tendency toward publication of results that support conclusions favoring a particular hypothesis or position

Meta-analysis

An analysis performed on data or results from two or more similar studies for the purpose of drawing a conclusion concerning the implications of those studies with respect to the usefulness of some procedure or treatment, the contribution of some risk factor to a disease, or the role of some condition in the etiology of a disease

Remember!

- Criticism is easier than craftsmanship
- There are no perfect studies — only imperfect ones
- No one sets out to do a bad study
- Receiving criticism can be painful

20 Clinical trials: How to read

Qualities of a good critic

- Honest
- Fair
- Sensitive to the feelings of others
- Listens
- Alters stand when indicated by available data or arguments
- Admits mistakes
- Polite and courteous
- Discloses conflicts of interest

Questionable tactics

- Playing to the gallery by appealing to emotions, or by being "cute", clever, or frivolous
- Being condescending, derisive, abusive, insulting or destructive
- Emotional outbursts or personal attacks
- Imputation of study or investigator integrity by innuendo
- Use of buzz words or emotionally laden words or phrases
- Use of generic criticism as if unique to a specific trial
- Reference to data or results that cannot be checked
- Use of secondary sources of information without checking their accuracy

Sources of criticism open to suspicion

- Publications with direct or indirect financial interests in specific treatments or philosophies
- Criticisms from individuals or business firms with proprietary interests in one of the treatments
- Television "news" reports offered primarily for their entertainment value
- Special interest lobbying groups

20 Clinical trials: How to read

Universal criticisms

- Wrong study population
- Study population not representative of general patient population
- Conclusions not valid or irrelevant because of select nature of study population
- Treatment groups not comparable at entry
- Sample size or length of followup inadequate
- Treatment difference (or lack of one) accounted for by unidentified subgroup of patients
- Data collection or processing errors
- Important data overlooked in collection or analysis
- Wrong or inadequate analyses
- Wrong treatments or method of administration
- Wrong or inadequate diagnostic or evaluation procedures
- Results of the trial are not clinically relevant

Myths and misconceptions

- The randomization process is invalid if there are significant differences among the treatment groups with regard to one or more baseline characteristics
- Results of the trial should be ignored if there is a difference in the baseline comparability of the treatment groups
- The failure to find a significant treatment difference should lead to acceptance of the null hypothesis
- Unmasked trials are invalid
- Only conclusions based on the primary outcome measure identified as such before initiation of the trial are valid
- Marked heterogeneity of the study population makes it impossible to draw conclusions from the trial

20 Clinical trials: How to read

A readers evaluation guide

1. Was the trial done under a legitimate state of equipoise?
2. Are the investigator trustworthy?
3. Do I believe the investigators to be free of financial and philosophical conflicts of interest in regard to the treatments under evaluation?
4. Did the authors adhere to the principle, *once randomized always counted*?
5. Is there reason to believe all events (outcomes) observed have been counted and in the treatment group to which patients were assigned regardless of course of treatment?
6. Did the design include adequate provisions for bias control?
7. Are variations in denominators for treatment comparisons explained and are the explanations consistent with good practice principles of trials?
8. Do the authors recognize and discuss potential weaknesses of their design and execution?
9. Is the primary analysis by original treatment assignment (intention to treat)?
10. Have the authors done adequate analyses to explain their results?

The 64 dollar question

Do I believe the results to be reproducible in spite of weaknesses in design and execution?

21 Critiquing trials

21 Critiquing trials

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- There are no perfect studies — only imperfect ones
- No one sets out to do a bad study
- Receiving criticism can be painful

Functions of criticism

- Fosters development and maintenance of improved research methods
- Stimulates new research
- Focuses attention on important medical and research issues
- Increases public awareness and sophistication with regard to medical research

Qualities of a good critic

- Honest
- Fair
- Sensitive to the feelings of others
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21 Critiquing trials

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- Reference to data or results that cannot be checked
- Use of secondary sources of information without checking their accuracy

Useful qualities for recipients of criticism

- Listens without becoming defensive, taking criticisms personally, or sulking
- Knows when to remain silent
- Resilient
- Persistent and persevering
- Stoutness of heart

Sources of criticism open to suspicion

- Publications with direct or indirect financial interests in specific treatments or philosophies
- Criticisms from individuals or business firms with proprietary interests in one of the study treatments
- Television "news" reports offered primarily for their entertainment value
- Special interest lobbying groups

21 Critiquing trials

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- Wrong or inadequate diagnostic or evaluation procedures
- Data collection or processing errors
- Wrong or inadequate analyses
- Treatment difference (or lack of one) accounted for by unidentified subgroup of patients
- Clinical relevance of findings in question
- Conclusions not valid or irrelevant because of select nature of study population
- Results of the trial are not clinically relevant

Myths and misconceptions

- The randomization process is invalid if there are significant differences among the treatment groups with regard to one or more baseline characteristics
- Results of the trial should be ignored if there is a difference in the baseline comparability of the treatment groups
- The failure to find a significant treatment difference should lead to acceptance of the null hypothesis
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21 Critiquing trials

UGDP criticisms

- Patients assigned to the tolbutamide treatment group were at a higher risk for CV disease than those assigned to other treatments
- Dosage schedules for oral agents should have been flexible
- Study population consisted of individuals who were not really diabetic
- Trial was not designed with mortality as the primary outcome
- "High" data entry error rate
- Coding criteria for ECGs were changed during the trial
- Clinically relevant data were overlooked
- Majority of deaths occurred in three clinics
- Analysis by original treatment assignment was inappropriate
- Blood sugar levels were not controlled

Areas of legitimate concern

- Baseline comparability of the treatment groups
- Completeness and adequacy of followup
- Adequacy of adherence to the treatment protocol
- Appropriateness of the treatments
- Quality of the data collected
- Reliability and clinical relevance of the primary outcome measure
- Power of the trial to detect a treatment difference when none is observed
- Legitimacy of the conclusions reached

Considerations in responding to criticisms

- Resources required
- Source of criticism and method of dissemination
- Risk of remaining silent vs making a response
- Advocacy vs dispassionate approach
- Method of responding and of disseminating response

22 Ethics

22 Ethics

22 Ethics

22 Ethics

Introduction

- General frame of reference
- Required mind set
- Principles of medical ethics
- Codes of conduct
- State of equipoise

Frame of reference

- **Clinical** trials involving fixed sample size parallel treatment designs
- Multicenter
- Continuous treatment and monitoring
- Extended recruitment and enrollment period
- Extended followup well beyond the close of enrollment

Basic research standards

- Documentation
- Protocol
- Surveillance
- Monitoring
- Objectivity
- Integrity

Questionable research practices

- Knowingly proposing and carrying out a grossly underpowered study
- Duplication of research (as distinct from replication)
- Proposing a study to "prove" or promote a point of view, position, or cause
- Doing a study that encourages illegal or bad practices

22 Ethics

Ethical principles

- Respect for persons
- Beneficence
- Justice
- Competence

Required state of mind

- Equipoise
- Nonpromotional
- Nonemotional regarding direction of outcome
- Show me

Facts of life

- Codes of conduct and ethical standards change with time
- Ethical standards are situation dependent
- Standards for trials vary depending on type of patients, setting for treatment, and purpose
- There is no such thing as a 100% safe treatment
- Generally, standards of care are declared rather than deduced
- There are no free lunches
- Perfection is an imaginary state
- Secrecy is dangerous

Warning signals

- Demonstration trial
- Stated position regarding treatment
- Conflict of interest relationships
- Blind obedience

22 Ethics

Personal tests

- Would you enroll yourself or a loved one into the trial?
- Would you expose yourself or a loved one to the procedures to be performed in the trial?
- Do you believe that if you or a loved one enrolled that the benefits would outweigh the risks?
- Do you believe you could follow the procedures required of patients in the trial without undue hardship or inconvenience?
- Would you be willing to be a patient in your clinical setting, without any special handling or care?
- Do you believe that the trial, as designed, with the sample size proposed, will yield useful new information regarding the use of the treatments?
- Do you trust all your collaborators?
- Do you trust the motives of your institution and the funding agency in relation to the proposed trial?
- Is your primary reason for doing the trial based on motives other than self serving ones (eg, need for employment or self aggrandizement)?

Analysis and reporting standards

- Accuracy
- Detailedness
- Maturity of analysis and conclusions
- Disclosure
- Uniqueness of publications
- Public access to finished result

22 Ethics

Legal and ethical record storage and access

Record retention

- Depends on funding agency and funding vehicle; for financial records, minimum of 3 years following termination of support
- Local conventions as set forth by investigator's institution
- Secure, monitored storage; especially for records containing personal ID data
- Destruction according to local laws

Public access

- Legal requirement: Depends on funding agency and funding vehicle; None required with NIH grant support, may be specified or implicit in NIH contract support
- Proposed norm: Public access regardless of funding source or vehicle on or before termination of funding

Good and bad record policies

Good

- One-to-one correspondence between data record and electronic dataset
- Entry of all that is recorded
- Deposit of electronic dataset in public repository

Bad

- Undocumented, modified, or altered data records
- Premature, partial, or total record destruction
- Cold, unsupervised, record storage
- Monitored or discriminatory public access

22 Ethics

Unethical procedures

- Fabrication and falsification
- Deceitful noncompliance to IRB requirements
- Conducting unapproved research
- Plagiarism
- Pirating
- No or improper attribution
- Wishful data collection
- Complicity
- "Censored" data, analyses, or conclusions
- Simultaneous submission of manuscripts to two or more journals

Consequences of misconduct

- Loss of credibility and respect
- Dismissal
- Public censure
- Criminal charges
- Jail

Investigator grant assurance statement

Item 17 of title page of Grant Application, PHS form 398 (Rev 10/88)

Principal investigator / Program director assurance: I agree to accept responsibility for the scientific conduct of the project and to provide the required progress reports if a grant is awarded as a result of this application. Willful provision of false information is a criminal offense (U.S. Code, Title 18, Section 1001).

22 Ethics

Institutional safeguards

- IRBs and ethics committees (Committee on Human Research Ethics)
- Disclosure and review of external working and financial relationships (JHU SHPH Policy Memorandum Faculty (4): Conflicts of interest and commitment, 23 Jan 1990)
- Committee to deal with charges of malfeasance (JHU SHPH Policy and Procedure Memorandum Faculty No. 7: Fraud in research, 28 Feb 1989)

Nuremberg Code

1. Voluntary consent
2. Scientific validity
3. Prior knowledge
4. Humane conduct
5. Death and injury proscription
6. Risk / benefit
7. Proper facilities and preparation
8. Investigator competence
9. Right to withdraw
10. Termination

See Levine, Ethics and Regulation of Research[32]

22 Ethics

The Nuremberg Code

1. The voluntary consent of the human subject is absolutely essential.

   This means that the person involved should have legal capacity to give consent; should be situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

   The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

3. The experiment should be designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problems under study that the anticipated results will justify the performance of the experiment.

4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

5. No experiment should be conducted where there is an *a priori* reason to believe that death or disabling injury will occur except, perhaps, in those experiments where the experimental physicians also serve as subjects.

6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.

22 Ethics

The Nuremberg Code

8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.

9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.

10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment in any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

From Levine, Ethics and Regulation of Research[32]

22 Ethics

General references

Committee on Human Research Ethics: *Policy and Procedures Manual for the Protection of Human Subjects*. The Johns Hopkins School of Hygiene and Public Health, Baltimore, **1990**.[9]

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National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research: *The Belmont Report: Ethical principles and guidelines for the protection of human subjects of research*. OPRR Reports, **18 April 1979**.[22, 39]

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Silverman WA: *Human Experimentation: A Guided Step into the Unknown*. Oxford University Press, New York, **1985**.[48]

Tuskegee Syphilis Study Ad Hoc Advisory Panel: *Tuskegee Syphilis Study Ad Hoc Advisory Panel: Final Report*. United States Public Health Service, Washington, **1973**.[53]

22 Ethics

Ethics of design

- Acceptable and unacceptable purposes
- Issues in the choice of the control and test treatments
- Masking principles and standards
- Sample size issues

Acceptable and unacceptable purposes

Acceptable

- Test of new and promising treatment
- Test of an established treatment having doubtful efficacy
- Test to determine short or long term efficacy
- Replication of a trial because of legitimate doubts concerning its conclusions

Unacceptable

- Demonstration that a treatment is harmful
- Promotion of a treatment via a trial
- Test of a treatment already shown to be efficacious
- Duplication of a trial absent any legitimate doubt concerning its conclusion

High "risk" trials

- Trials of established treatments
- Trials of high tech, established, care procedures, such as CCUs
- Trials testing a fundamental premise of treatment
- Trials that produce results challenging established dogma
- Trials that are likely to tell the medical profession or society in general something it does not want to hear
- Trials that are likely to challenge the existence of some professional group

22 Ethics

Standards for choice of study treatments

- Medical relevancy
- Acceptability
- Prior knowledge regarding safety and efficacy
- Reasonable doubt regarding relative merits

Standards for choice of test treatments

- Ethically acceptable
- Use consistent with care standards
- Prior studies and evidence suggesting treatment may be beneficial
- For drug and device trials: Prior animal studies failing to indicate carcinogenicity, mutagenicity, or teratogenicity
- Presence of skill and expertise necessary to administer the treatments

22 Ethics

Types of control treatments and when to choose

Active control treatment: A treatment having the capability of producing a positive or negative treatment effect in excess of that produced with an inactive control treatment

- **Positive control treatment**: A treatment having the capability of producing a positive treatment effect in excess of that produced with an inactive control treatment; use when the standard of care precludes use of an inactive control treatment

- **Negative control treatment**: A treatment having the capability of producing a negative treatment effect in excess of that produced with an inactive control treatment; use limited to settings where there is no risk of harm arising from use of a treatment intended to produce an effect opposite from the one desired

Inactive control treatment: A treatment not having any known biological, medical, or pharmacological effect; use limited to settings devoid of established standards for care, ie, settings characterized by legitimate disagreements as to whether treatment is needed

- **Placebo control treatment**: An inactive control treatment involving the administration of a placebo or use of a sham procedure; use limited to settings characterized by legitimate disagreement as to whether treatment is needed and where masked administration of treatment is desired and possible

- **Null control treatment**: An inactive control treatment not involving the administration of a placebo or any other form of intervention (other than observation); use limited to settings where treatment is not indicated by current medical standards and where masked treatment administration is not desired or possible

22 Ethics

Types of control treatments

Active control
- Best medical judgment
- Best medical care
- Current standard of care

Inactive control
- Placebo treatment
- Sham procedure
- No treatment
- No control treatment

Negative control
- Test treatment opposite
- Test treatment reverse

Considerations in choosing control treatment

- Current standards of care and treatment
- Desire for masked administration, data collection, or outcome assessment
- Outside influences and contamination (eg, availability of test treatment outside trial; community influence on behavior of participants)
- Other aims (eg, study of natural history of disease)

22 Ethics

Placebo and sham treatment standards

Drug placebo

- May be used only when there is no accepted drug treatment and legitimate doubt in the medical community as to whether any form of drug treatment is useful
- Cannot be used once there is an accepted or established drug treatment
- Use not feasible or appropriate when method of treatment administration is incompatible with masking
- Questionable when use carries risk, even if only minimal

Sham procedure

- Use with caution; use likely to be challenged by IRBs if use requires subterfuge and absence of candor in relation to the enrollment and consent processes
- Use normally limited to procedures considered to be risk free; generally not recommended where procedure carries risk, even if only minimal
- Use best limited to settings involving double-masked administration of treatment

Treatment administration requirements and goals

Requirements

- Use of a treatment protocol consistent with existing medical standards
- A treatment protocol sufficiently detailed to allow personnel to administer treatments in uniform fashion
- Recording of sufficient information to allow study monitors to measure adherence to the treatment protocol
- Treatment procedures sufficiently flexible to allow study personnel to choose in favor of patients, rather than the treatment protocol, when their well-being is at stake
- Access to sufficient information during the trial to allow study personnel to provide high quality care to all patients enrolled

Goals

- "Real world" treatment protocol
- Just and equitable patient selection
- Valid results
- Results that are generalizable
- Robust findings

22 Ethics

Levels of masking

Full: Designs in which patient, treater, data collector, assessor, analyst, and monitoring committee are masked

Partial: Designs that involve masking of some individuals or groups

None: Designs in which no one is masked

Masking by type of individual

	Single	Double	Triple	Full	None
Patient	y	y	y	y	n
Treater	n	y	y	y	n
Data collector	?	y	y	y	n
Assessor	?	y	y	y	n
Analyst	?	?	?	y	n
TEMAC member	?	n	y	y	n

Masking principles

- Design with the highest level of masking possible
- Masked administration of treatment preferable to unmasked administration
- Masked data collection preferable to unmasked data collection
- Masked outcome assessment preferable to unmasked assessment, except for outcome measures not subject to observation error

22 Ethics

Masking standards and practices

Standards
- Mask only if doing so does not threaten patient well-being or reduce quality of care
- Be prepared to unmask to protect patients
- Be prepared to unmask in the case of life threatening emergencies

Practices
- Do not mask when the act is little more than a charade
- Unmask only on a "need to know" basis
- When possible, stop treatment without unmasking
- Set up system for immediate unmasking in case of emergencies

Sample size standards and ethics

Standards
- Designate a particular outcome measure for use in making the calculation
- Perform sample size or power calculation before starting
- Check calculations during trial using observed data and modify enrollment and followup strategy accordingly
- Base sample size on calculation using a reasonable α, β, and Δ; proposed sample size should provide adequate power for reasonable alternatives to null hypothesis

Questionable ethics
- Doing obviously underpowered trial, except where participants informed as to questionable value of trial
- Performing purposely underpowered trial to avoid rejecting null hypothesis
- Shopping for the "right" outcome
- Sample size game

Sample size no nos

- No recruitment goal
- No sample size or power calculation
- Use of composite outcome to "reduce" sample size requirement
- Miracle treatment difference (Δ) to justify sample size
- Shopping for α and β in order to obtain "correct" sample size
- Changing to some other outcome measure during the trial to justify a smaller trial

22 Ethics

Ethics of recruitment

- Special populations
- Inclusion / exclusion standards
- Population demographics
- Questionable enrollment practices

Special populations

- Infants
- Children
- Pregnant women
- Mentally incompetent persons
- Institutionalized persons
- Prisoners
- Students
- Infirm elderly

22 Ethics

Demographic selection questions

Is the selection process consistent with the demographics of the disease or condition being investigated?

Is the selection process "demographically neutral"? If not, is there a scientifically or logistically sound and defensible rationale for the lack of neutrality?

Is there a fair distribution of the potential risks and benefits across the various demographic groups approached for study?

Do those approached for study, and not enrolled, have the same rights and access to care as those enrolled for study?

If participants are offered pay for participation is such pay consistent with current practice and is it small enough so as to be unlikely to cause a person to agree to submit to high risk procedures simply to receive the pay?

If selection is limited to one sex or ethnic group is such selection justified by the epidemiology of the disease or condition being investigated?

If pregnant women are excluded can exclusion be justified on the grounds that the known or likely risks to the woman outweigh the likely benefits?

Questionable practices

- Finders incentive fees
- Large patient incentive fees
- Head payments
- Scare tactics
- Quick sell

22 Ethics

Indicators of trouble

- Town and gown tensions
- Sniping
- Institutional distancing
- Community hostility
- Claims of restraint of trade
- Bad "press"

Inclusion / exclusion standards

- Demographic equity
- Realism (ie, patients enrolled typical of those treated)
- Safety (ie, those enrolled can be safely treated with any of the study treatments)
- Medical legality (ie, usage of treatment consistent with labeled indications or medical standards)
- Representativeness (ie, that those enrolled are representative of real world population of patients)
- Selectivity and purity (ie, that study population is homogeneous)

22 Ethics

Inclusion / exclusion dos and don'ts

Do

- Exclude patients for whom a study treatment is contraindicated
- Exclude patients not likely to follow the treatment or data collection protocol
- Be as inclusive as medically and legally practical

Don't

- Exclude on the basis of age, sex, or race unless there are valid medical reasons for doing so
- Concentrate on mentally, emotionally, economically, or culturally disadvantaged as a recruitment ploy
- Concentrate on a foreign population because it is less knowledgeable or because the trial cannot be performed locally because of risk considerations

Remember

- That the rate of recruitment slows as the number of exclusions increases
- That homogeneity of study groups can be achieved by subgroup analyses
- That groups of patients excluded cannot be studied

Population demographic goals

- Absence of subtle exclusions that work to the disadvantage of some demographic group
- Racial, ethnic, sex, and age heterogeneity
- Socioeconomic cross section
- Absence of concentration of the emotionally, culturally, economically, or mentally deprived

22 Ethics

Trials and "isms"

"Isms": Denying enrollment to a sex, race, ethnic, or age group when such an action is not justifiable on medical or legal grounds

De facto "isms": Limiting enrollment to a sex, race, ethnic, or age group because of clinic location, referral patterns, or clinic personnel

Examples
- Sexism: Enrolling only males (eg, into a CV trial) or females (eg, into a breast cancer trial) because of sex predominance of disease
- Racism: A trial involving only whites or blacks where the condition to be treated is common in both races; Tuskegee Syphilis Study (involved poor black males)
- Ageism: Enrolling only adults because it is easier than including children (eg, in AIDS trials); excluding beyond an upper age limit

Questionable enrollment practices

- Coercion
- Obscenely large rewards
- Company store treatment access
- After the fact consent

Ethics of consent and enrollment

- Reasons for consent
- Types of consent
- Hallmarks of a sound consent
- Post-randomization partial consent
- Deferred consent
- Consent aids
- General rights
- Consent content checklist for trials
- General disclaimers
- Promises and responsibilities
- False and questionable assurances

22 Ethics

Reasons for consent

- Ethical
- Understanding and bonding
- Commitment
- Preventative

Types of consent

Full active: All aspects of the trial, including a discussion of all treatment options open to the patient before asking for consent (conventional approach in clinical trials)

Partial active: Some options or choices discussed or offered only to certain patients prior to enrollment; only patients to be treated in certain ways are given the option of refusal (post randomization consent in trials)

Passive implied: Purpose of trial explained but consent not formally requested; considered to be given if participant continues dialogue (commonly used in low risk telephone or face-to-face interviews in which it is clear the individual being interviewed is free to terminate the dialogue at any time)

Full active consent

- Default mode of consent; all other forms must be justified
- Generally required or preferred mode for clinical trials
- Advantages include participant bonding to study, patient / physician partnership exchange, knowledgeable participants
- Disadvantages include front end time expenditure, increased participant anxiety and confusion, increased enrollment refusal rate

22 Ethics

Active consent process

Do

- Be honest and direct
- Proceed in stages
- Provide time for participant to make informed decision
- Whenever possible allow at least 24-hours for person to decide on enrollment
- Provide patient with written description of the trial and requirements for participation prior to requesting consent
- Provide a copy of the consent statement for review prior to requesting enrollment
- Provide a private setting that is conducive to an informed exchange and to questioning of study personnel regarding the trial
- Check on the adequacy of the consent
- Have signing witnessed
- Provide participant with signed statement

Don't

- Perform a hard sell
- Proceed as a door-to-door sales person
- Misinform or distort
- Be evasive
- Ignore real or implied questions or concerns

Hallmarks of a sound consent process

- Performed in stages
- Not hurried, not coerced
- Thorough, with ample opportunity for dialogue
- Informed

22 Ethics

Post-randomization partial consents

Definition: A consent obtained after randomization and prior to treatment for patients assigned to the test treatment; patients assigned to the control treatment are not informed of being in a trial or that their course of treatment was determined by randomization

Use: Limited to special circumstances such as the following:
- The control treatment is the accepted standard of treatment
- Investigators are in a true state of equipoise concerning the relative merits of the study treatments
- The condition being treated is likely to be terminal

Note
- Most IRBs reluctant to approve such consents, except in special cases
- Advantages include time conservation, reduced patient anxiety, and increased enrollment
- Disadvantages include investigator "conflict of interest" in dialogues with patients assigned to test treatment who refuse the assignment, paternalism, unbalanced nature of information, and choices offered to control vs test assigned patients

Deferred consent

Definition: A consent obtained after the initiation of the assigned treatment. Treatment terminated for patients not consenting. Treatment continued for consenting patients.

Use: Primarily in emergency situations in which treatment must be started promptly or where patient is unconscious or incoherent.

Notes
- May introduce treatment related selection bias, especially with unmasked treatment administration
- IRB likely to be cautious in approving

22 Ethics

Consent aids

- Patient information booklet
- Written consent statement
- Consent statement tested for:
  - Content
  - Accuracy
  - Readability
- Video display
- Translation to other languages
- Knowledge assessment questionnaire

General rights

Patient

- Right to confidentiality
- Right to privacy
- Right to care without prejudice
- Right to withdraw without prejudice
- Right to not cooperate or respond without prejudice

Investigator

- Right to refuse enrollment
- Right to terminate participation
- Right to expect cooperation and compliance

22 Ethics

Consent content checklist for trials

General
- Purpose of trial
- Reason for contact
- Known or suspected condition or illness
- Options or choices to be offered
- Sources of funding and reasons for funding

Organization and operation
- Responsible institution
- Other participating sites
- Location and responsibility of data center
- Leadership structure and decision-making process
- Operational division of labor and rationale

Design choices and rationale
- Proposed sample size and rationale
- List of test treatments to be studied and reasons for study
- List of control treatments to be used and reasons for choice
- Treatment design and reason (eg, parallel; crossover)
- Route or mode of treatment administration and reason
- Treatment masking procedure (eg, use of placebo or sham procedure) and reasons
- Other masking and reasons
- Primary and secondary outcomes measures and reasons for choice
- Length of participation (followup) and reason

Methods and rationale
- Procedures to be performed and rationale
- Inconvenience, discomfort, and risks associated with procedures
- Data collection procedures and schedule
- Contact schedule and rationale
- Clinic visit schedule and rationale
- Method of treatment assignment and rationale
- Method of treatment administration and rationale
- Methods of masking (treatment, data collection, data analysis)
- Methods of outcome followup and rationale
- Method of locating dropouts and losses to followup
- Methods of ensuring and protecting confidentiality
- Method of communication with parents and surrogates when children are enrolled
- Method of protecting patient from prolonged exposure to useless or harmful treatment
- Method of providing patient access to beneficial treatment
- Method of ongoing monitoring for treatment group differences and use of interim results
- Anticipated method of close-out

Risk - Benefit
- List of invasive procedures to be used, rationale, frequency of use, and associated risks and discomfort
- Risks associated with procedures and treatments
- Expected side effects
- List of adverse events or consequences of treatment and rough approximation of chance of occurrence
- Benefits of treatments
- Short and long term benefits of participation
- Risk/benefit analysis

Patient and surrogate safeguards and rights
- Right to confidentiality
- Right to care regardless of decision regarding participation
- Right to withdraw without prejudice
- Right to refuse to answer questions
- Right to benefit from new information emerging during the trial
- Parent and guardian rights in the case of children

Investigator rights and expectations
- Right to terminate participation
- Right to follow participant unobtrusively after data collection ends or after dropping out
- Expectation of cooperation and compliance

Disclaimers and conditions
- Limits on protection of confidentiality
- Limits on injury protection
- Right of FDA to inspect records

Other

- Nature of knowledge assessment and reason for assessment
- Incentive payments and reason for such payments
- Extent to which treatment and care procedures differ from standard care procedures
- Limits on access to treatment information during participation
- Limits on access to personal study data during trial
- Amount of information on study results available to investigator during and at conclusion of trial
- Method of communicating results of trial to participants and study physicians
- Method of communicating and implementing treatment recommendations emanating from trial
- Costs to patient for care and procedures
- Presumed value of research
- Intentions regarding publication
- Extent of public access to results and database on completion of trial

General disclaimers

Limitations on ability to protect confidentiality

Recommended wording: Every effort will be made within the limits of the law to preserve the confidentiality of your records and data collected in this study

Rights of FDA to record review in IND drug trials

JHU JCCI statement: If the study uses a new drug or device that is under the jurisdiction of the Food and Drug Administration (FDA), the FDA government official may look at the relevant part of your medical record as part of their job to review new drug and device studies

22 Ethics

Limitations on protection from injury

JHU JCCI statement: If you want to talk to anyone about this research study because you think you have not been treated fairly, or you have been hurt by joining the study, or you have questions about the study, you should call the principal investigator, (name), at (phone no), or call the Office of the Joint Committee on Clinical Investigation at 955-3008 or call the Francis Scott Key Medical Center Institutional Review Board for Human Research at 550-1853. Either the investigator or the people in the Committee office or IRB office will answer your questions and/or help you find medical care for an injury you feel you have suffered. The Johns Hopkins University, The Johns Hopkins Hospital, The Francis Scott Key Medical Center, (other) and the Federal Government do not have any program to provide compensation to you if you experience injury or other bad effects which are not the fault of the investigator

Promises and responsibilities

- Do not make promises or commitments in matters over which you have little or no control
- Do not make time specific promises (eg, the time at which the trial will be completed) absent 100% assurance that they can be kept
- Promises and commitments made to patients should be honored; patients should be informed of those that cannot be kept
- Do not use benefit to society arguments as an enrollment inducement unless there is an unswerving commitment to publication regardless of the outcome of the research

False and questionable assurances

- Locked data storage as an assurance of confidentiality
- Separation of ID data from remaining dataset
- Time driven severed record linkage
- Time limited data retention
- Time driven data destruction

22 Ethics

Investigator responsibilities to IRBs

- Submission of proposal before initiation
- Implementation only after approval
- Communication of protocol amendments or changes
- Communication of untoward events and faulty or fraudulent activities
- Communication of potentially embarrassing or disqualifying conflicts of interest
- Honesty
- Responsiveness

IRB ongoing interactions

- Annual renewals
- Protocol amendments as they occur
- Report untoward events as they occur
- Inform of misconduct or faulty operations as discovered
- Notify of termination or completion

Ethics of data collection and execution

- Data collection standards
- Ethics of masking and censoring
- Consent updates
- Desired separations
- Conflicts of interest
- Treatment effects monitoring

Data collection standards

- Form driven data collection
- Trained and certified data collectors
- Record what is observed
- Enter what is reported
- Audit trail for modifications
- Ongoing quality control and surveillance

22 Ethics

Patient care and clinical trials

- Requirement for good care takes priority over requirement for adherence to treatment protocol of trial
- Investigators in trials have a responsibility to deliver good care to the patient or to have them obtain such care for conditions or illnesses not treated in the trial but that have adverse health implications for the patient
- Generally it is a mistake to equate the data collection requirements of a trial to those required for patient care
- Generally those procedures performed in a trial that are also needed for care should be covered from sources other than the research grant or contract
- Procedures that are performed primarily for their research value should be covered by the research grant or contract

Treatment no nos

- Withholding a known beneficial treatment
- Continuing to administer a treatment known to be useless or harmful
- Unmasking a treatment assignment when other actions that preserve the mask would accomplish the same end
- Failing to unmask a treatment in the case of life threatening emergencies where the treatment information is needed to determine the proper course of treatment
- Using of a drug beyond its IND or NDA approved indications
- Changing of a drug formulation or route of administration without adequate bioavailability data or without proper approvals

Ethics of masking and censoring

- Do not mask that which needs to be known for patient care or safety
- Do not censor or withhold information essential to patient care or well-being
- Do not maintain a mask by lying or deception
- Do not maintain a mask or censoring beyond the point of patient well-being or safety

22 Ethics

Consent updates

Purpose: To inform people already enrolled in trial or prospective followup study of changes in the study design or procedures

When: As dictated by course of events over the course of the study and as soon after those events as is prudent and practical

Method: Letter, telephone, or in person depending on circumstances

Reasons: Treatment terminated because of lack of efficacy or harm; treatment terminated because of better alternative; discovery of an at "risk" subgroup; broken promise or commitment; introduction of new procedure; discovery of fraudulent activities

Desired separations

- Patient and physician
- Treater and evaluator (unmasked trials)
- Clinical centers and data coordinating center
- Sponsor and data coordinating center (especially if sponsor has proprietary interest in product being tested)
- Sponsor and investigators (especially if sponsor has proprietary interest in product being tested)

22 Ethics

Conflict of interest

Definition: Any activity, relationship, association, or position that influences or is likely to influence one's judgment, course of action, or position in relation to exercising some specified function or role

Examples

- Academic researcher being paid a retainer by a pharmaceutical firm while evaluating one of their drugs
- Member of a TEMAC committee who owns or buys stock in the company whose product is being tested
- Researcher who does a trial of a treatment to promote its use

Preventative measures

- Establish policy on what constitutes a conflict of interest prior to starting the trial; maintain the policy over the course of trial
- Educate investigators as to the adverse effects of real or perceived conflicts of interest on the creditability of trial
- Establish a system for disclosure of conflicts of interest and for reviewing and acting upon the disclosures
- Require members of key committees, such as the SC and TEMAC, to be free of conflicts
- Provide public access to individual disclosure statements

Treatment effects monitoring

Definition: An ongoing process of reviewing accumulated outcome data during the trial to assess treatment effects for the purpose of determining whether to allow the trial to continue unaltered

When: Any trial in which the treatments have the potential of producing an adverse or beneficial treatment effect and where it is possible to detect and act upon such effects during the course of the trial

How: Interim analyses presented to a specially constituted committee to review and, when necessary, to recommend actions based on the results

22 Ethics

Current monitoring approach

Multidisciplinary review team with appropriate medical, biostatistical, and bioethical expertise in which:

- At least one team member has first hand clinical experience with the treatments under study and is familiar with the nuances of the treatment protocol
- No voting member is dependent on funding from the trial or sponsor
- No member stands to gain or lose financially from recommendations concerning the study treatments
- All members freely disclose all arrangements and associations that could be construed as constituting a conflict of interest

Monitoring issues

- Who can look
- Frequency of looks
- Outcomes of interest
- Whether the monitors are masked to treatment assignment
- Whether or not to use a formal stopping rule
- How long to continue in the face of negative, nil, or positive results
- P-value philosophy
- What and when to tell clinical investigators; patients

Ethics of close-out

- Close-out procedures and consents
- Close-out housekeeping requirements
- Patient close-out rights and safeguards

22 Ethics

Close-out

Definition: The process of separating patients from a trial and shutting the trial down

When: Scheduled (eg, on completion of the trial) or unscheduled (eg, as a result of failure to obtain funding to continue or because of negative or positive findings); speed determined by situation

How: Normally in person, but in special circumstances by telephone or letter

Types: Common closing date or common followup period

Close-out procedures and consents

General procedures

- Provide advance verbal as well as written notice of close-out and reason
- Indicate results of the trial or how and when participants will be informed of results and conclusions
- Obtain signed evidence of acknowledgement of close-out, especially in settings where treatment has been provided
- Arrange for alternative sources of patient care if patients were being cared for in the study; provide written evidence of transfer for patient and physician to whom care is being transferred; provide, where appropriate, a written or tabular summary of pertinent data collected in the study relevant to the patients future care

Added procedures for trials

- Inform the patient of the treatment to which assigned (masked trials)
- Discuss results of trial with patient and implications for future care
- Provide a recommended course of treatment if indicated by results of trial
- Arrange, if possible, for access to beneficial study drug(s) if not presently available as a licensed drug
- Debrief, answer questions, and administer close- out data collection visit, including questions to assess adequacy of masking, when indicated

Close-out consents

- Used to document close-out and transfer of care responsibilities
- Used to update locator information if renewed contact likely
- Indicate possibility of re-contact and reasons for wanting to do so

22 Ethics

Close-out housekeeping requirements

Patient
- Positive confirmation of separation
- Transfer medical record, where appropriate
- Re-contact consent statement
- Update personal locator information
- Special data collection

Records and data
- Final editing
- Final data set and analysis file
- Data summary for patient or primary care physician
- Data retention, storage, and ultimate disposition
- Data and record ownership

Notifications
- IRB on termination
- FDA in case of IND or IDE
- Sponsor
- Suppliers

Other
- Decommission study committees
- Designation of official repositories for official study records and documents
- Update of study curriculum vitae
- Disposal of unused drugs
- Disposition of special equipment
- Data deposit in public archive
- Destruction of "duplicate" files and documents

22 Ethics

Patient close-out rights and safeguards

Right to:
- Advance notice
- Orderly separation
- Explanation as to reason for close-out
- Transfer of care responsibilities
- Findings of trial in relation to subsequent course of treatment
- Knowledge of treatment to which assigned in the case of masked treatment administration
- Confidentiality, privacy, and to be left alone
- Subsequent updates or recalls if new and important information emerges following separation

Safeguards:
- Secure record storage, complete with linkage capabilities
- Ability to recall a patient after separation if dictated by subsequent findings or analyses
- Continuing structure and analyses

Ethics of reporting and publication

- Publication requirement and responsibility
- Presentation and publication principles
- Information access standards
- Archiving responsibilities
- Author responsibilities
- Editor responsibilities

22 Ethics

Publication requirements and responsibilities

Minimal requirement: At least one publication at conclusion of trial regardless of outcome or reason for stopping the trial

General responsibilities

- Description of design and methods
- Description of the study population
- Baseline comparability data
- Denominator data by original treatment assignment
- Treatment results by original treatment assignment
- Disclosure of real or potential conflicts of interest
- Disclaimers and qualifiers, including enumeration of data deficiencies, errors, or purges

Other responsibilities

- Publication of results leading to major treatment protocol changes as they occur
- Preparation of important publications likely to impact on the practice of medicine with deliberate speed, compatible with the production of accurate quality publications
- Publication of changes affecting data collection, interpretation, or analysis of results

Presentation and publication principles

- Publish first, present later
- Publish in peer reviewed, indexed journals
- Findings not revealed to medical community or public at large until published
- Implementation of findings for patients prior to publication
- Advance notice to investigators, sponsor, FDA, and manufacturer
- Access to underlying analyses on publication

22 Ethics

Information access standards proposed for academic research institutions

Public documents and records

Foundation documents

- Funding initiative (on release)
- Funding proposal (on funding)
- Funding award and level (on award)
- IRB submission and approval (on approval)
- IND or IDE application (on approval)

Design and operating documents

- Trial protocol (on approval by IRB)
- Trial manuals of operations (on release to investigators)
- Trial handbooks (on release to investigators)
- Numbered policy and procedure memos (on distribution)
- Trial forms (on release for use)
- Consent procedure, statement, and related documents (on IRB approval)

Papers and presentations

- Manuscripts on presentation at open national meetings
- Manuscripts on publication
- Documents placed in public repositories when so deposited

Other documents and records

- Conflict of interest disclosure statements
- OMB clearance of forms for government contract supported research
- Protocol amendments submitted to IRB (on IRB approval)
- Other assurances, such as certificate of confidentiality, animal safety, etc (on granting or approval)

22 Ethics

Information access standards proposed for academic research institutions

Restricted or limited public access
- Trial results and analysis database, until publication or termination of funding
- Data listings without personal ID
- Performance monitoring reports
- Treatment monitoring reports
- Papers submitted for publication

Public access proscribed
- Patient medical record
- Patient data record
- Data listings with personal ID information
- Personal identifying data of any member of the study population or those screened for enrollment
- Personal identifying data of investigator other than that related to research credentials
- Personal salary data contained in funding proposals

Level of restriction optional
- Minutes of committee meetings
- Trial progress reports
- Study internal correspondence related to design, operation, or analysis of results

Archiving responsibilities

Design and operating documents
- Trial protocol
- Description of design and methods, unless published
- Consent statement and procedure
- Manuals of operations and handbooks
- Treatment administration documents
- Data collection forms

Results
- Supporting analyses (unpublished) for papers published as a result of treatment protocol change
- Electronic or paper listings of dataset on termination of funding

22 Ethics

Publication no nos

- Simultaneous submission of a manuscript to two or more journals
- Presentation of key findings prior to publication
- Publication of key findings of a trial in places other than indexed medical journals
- Duplicate publications
- Salami publications
- Half baked papers
- Erroneous results
- Manipulated, "censored", forged, or falsified results

Author responsibilities and no nos

Responsibilities

- Accuracy, honesty, and thoroughness
- Medical and analytic competence
- Capable of vouching for the veracity of results presented
- Active role in the writing or generation of manuscript
- Disclosure of conflicts of interest

No nos

- Use of author listing as a credit roster
- Listing an individual as an author without his/her knowledge
- Removing someone as an author without his/her knowledge
- Changing the order of listing without knowledge of all concerned
- Adding authors without knowledge of other authors
- Acknowledging the creative or analytic input or help of persons without their knowledge

22 Ethics

Editor responsibilities and no nos

Responsibilities
- Timely, confidential, peer review
- Reasoned actions
- Expedited review and publication when necessary
- Communication and follow through

No nos
- Release of manuscript to media prior to publication without knowledge of authors
- Disclosure of reviewers without their permission
- Publication without author assurances

Other ethical considerations

- Credibility issues
- Falsified or forged data
- Retractions and errata
- Disclosure ethics
- Clinical researcher's oath

Credibility problems

Design
- Wrong motivation for trial
- Unacceptable control treatment
- Inadequate consent process
- Ineffective or unnecessary masking
- Discriminatory recruitment or enrollment
- Over or under collection of data
- Inadequate patient care

Execution
- Stopping too soon; continuing too long
- Sloppy treatment or data collection procedures
- Informal treatment assignment schemes, or formal schemes that are not followed
- Undocumented protocol changes
- Denominator and counting "problems"

Data processing and analysis
- High data entry error rate
- Inadequate audit trail for data changes
- No interim monitoring, especially when trial is criticized for continuing beyond the point of prudence
- No primary analysis by original treatment assignment
- Analysis mistakes, especially those discovered by others
- Failure to perform "demolition" analyses related to treatment difference

Reporting and publication
- Reporting via the media
- Retractions
- Corrections or additions
- Multiple publications of the same thing
- Discovered reporting "lapses"
- Failure to disclose conflicts of interest, especially when discovered

Falsified or forged data

Prevention
- Choose collaborators carefully
- Create and maintain environment of integrity and of mutual trust and respect
- Educate, remind, and admonish

Detection
- Ongoing monitoring
- Pursuit of all suspicious data or explanations, no matter how small or trivial
- Paying attention and listening

Action
- Dismissal and or legal action
- Purging of forged or falsified data
- Report occurrences to IRB, local ethics committee, and sponsor
- Report occurrence and actions taken in any publication of results

22 Ethics

Retractions and errata

Publish retraction or modification when:
- Conclusion in previous paper is changed by new results of a continuing trial
- Conclusion or key findings are found to be in error because of mistakes in data processing or analysis
- Results published were forged or falsified

Publish errata when:
- Error that is not obvious in some statement, such as an equation or formula, that when followed leads to the wrong result or conclusion
- Wording errors that alter the meaning or implication of key statements in the paper
- Errors in reported results that are misleading or that lead to the wrong conclusion

Prevention and defense
- Collaborating, picky, probing authors
- Like wine, publish no paper before its time
  - Wait until there is something worth saying
  - Wait to publish until trial is finished, or in the case of a continuing trial, until results are stable and not likely to change, such that the present conclusion would change with the accumulation of more data
  - Allow manuscript to mature prior to submission
- Independent replication of analyses
- Internal review prior to submission

Action
- Verify that a retraction or errata is required
- Correspond with editor as to procedure
- Inform appropriate parties and groups regarding nature of error or reason for retraction
- Submit material for publication in journal

Disclosure ethics

- Need for disclosure increases as a function of the position and influence of individual in decision-making processes
- Disclose prior to starting an activity and update disclosures as activity proceeds
- Disclose what a reasonable person would want to know and that which, if undisclosed, is likely to reduce the credibility of the individual and study in question
- Provide public access to disclosures statement

22 Ethics

Clinical researcher's oath

Whereas engaging in research on human beings is a privilege, not a right, is performed to expand the base of knowledge concerning our collective health and well-being, and should be performed only in settings that are free and open, be it recognized that such research represents a form of public trust that is diminished whenever:

- Those who are approached for participation or who are enrolled are not treated with respect and dignity
- One proposes or carries out a research activity that is so poorly designed or executed that it is not capable of yielding useful information
- One fails to provide those who volunteer or their surrogates with the information needed to make an informed decision regarding participation
- One engages in practices restricting the flow and exchange of information, except where needed for proper conduct of the research, and then only with the knowledge and consent of participants
- One has interests, financial or otherwise, that are undisclosed and that, among reasonable people are or can be viewed as constituting conflicts of interest
- One fails to set and adhere to standards of integrity that foster and ensure the honest collection, analysis, and reporting of results

Therefore, I will:

- Consider, propose, and conduct only such research that is scientifically sound and that, when completed, will contribute to the general knowledge base
- Recognize my trust to patients and those who volunteer by treating them as I would wish to be treated and in so doing will:
  - Provide them with information presented in a manner that provides them with a basis for making an informed decision regarding participation
  - Inform those who are enrolled of changes to study procedures in order to allow them to renew or reaffirm their willingness to continue or to terminate their participation
  - Respect their right to privacy, confidentiality, and to withdraw as they see fit
  - Err on the side of the patient in matters of doubt, including departing from the study protocol and procedures if the safety or well-being of the patient is in question

22 Ethics

Clinical researcher's oath

- Recognize my trust to fellow collaborators by:
  - Meeting my responsibilities
  - Being open and direct with them
  - Doing my best in following study procedures and protocol
  - Honoring restrictions and guidelines imposed by the collaboration including matters of publication and presentation

- Recognize my trust to patients, fellow collaborators, the medical community, and public at large by:
  - Freely disclosing conflicts of interest
  - Adhering to high standards of moral and ethical conduct
  - Pursuing and exposing any irregularities in the study, its data, analyses, or reports, such as falsification of data or other fraudulent acts, that demean, detract, or otherwise destroy the study and its product
  - Publishing the results of the work and by considering the work unfinished until published

23 Objectivity vs competency in clinical trials

23 Objectivity vs competency

Competency

Competency is the state or quality of having the necessary skill, expertise, and knowledge to act or perform as necessary in the absence of constraint or barrier

Measurement elusive since competency lies in the collective body of knowledge, skills, and experiences represented by those doing a trial

Objectivity

Objectivity is the product of rules and procedures imposed for the purpose of rendering a process or procedure immune to emotion, surmise, bias, or personal prejudice

Objectivity constructs:
- Randomization
- Masked treatment administration
- Masked data collection
- Censoring to maintain masking
- Shielding investigators from results (imposed state of equipoise)
- Masked monitoring
- Apartheid treatment effects monitoring
- Preordained monitoring stopping rules
- Constraints on number and types of looks
- Exclusion of treating investigators and other study personnel on basis of "conflict of interest"

Reasons for objectivity

- Desire to reduce risk of treatment-related bias
- Concern regarding "conflicts of interest"
- Need to be "scientific"
- Desires of funding agencies and FDA

23 Objectivity vs competency

Forces for objectivity over competency

- Exaggerated fear of treatment-related bias
- Misguided worries regarding "conflicts of interest"
- The investigators as a technician
- The protocol as a blueprint
- Money power
- "Tradition"
- The view that analysis is "cut and dried"

Practices at odds with competency requirements

- Masked monitoring
- Apartheid treatment effects monitoring
- Frozen state of equipoise
- Useless or risky masking

Pressures for frozen state of equipoise

- Dilemma sparing of physician
- Conflict of interest sparing
- Bias reducing
- Objectivity increasing

23 Objectivity vs competency

Duties

- To do no harm
- To ensure a positive benefit to risk ratio for patients
- To maintain consents
- To monitor by "looking" as often as necessary

Nuremberg Code

Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

Monitoring imperative

Investigators and Institutional Review Boards (IRBs) are obliged to ensure that risks to subjects are minimized "*...by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk*" and that risks "*...are reasonable in relation to anticipated benefit*" (§46.111 (1)(i) and (2))

23 Objectivity vs competency

Apartheid treatment effects monitoring

Treatment effects monitoring performed in such a way as to keep study clinic personnel and study patients from seeing or knowing interim treatment results; typically done by constituting a treatment effects monitoring committee absent study clinic personnel, by closed deliberations, and by proscription of dissemination or discussion of interim results (except within the committee) until the trial is completed or until it has produced an actionable interim treatment result.

The Director of the NHLBI on treatment effects monitoring

Because the DSMB is advisory to the NHLBI, and not to investigators, the NHLBI retains the responsibility for determining which recommendations are appropriate for dissemination.

Letter dated 21 July 1995 in response to one from Meinert on policy of NHLBI on monitoring

Dangerous practices?

- No treatment effects monitoring
- Closed treatment effects monitoring
- Masked treatment effects monitoring
- Allowing sponsors to dictate when a recommendation may be implemented
- Marginalization of investigators' duty to patients and IRBs
- Marginalization of IRBs

23 Objectivity vs competency

Preferred model of monitoring

- Balance of conflicts of interest rather than "absence" of conflicts of interest
- Balance of power among investigators and IRBs, sponsors, and TEMCs
- Openness
- Unconstrained freedom to act as needed

Forces/situations leading back to more balanced structures

- Less passive IRBs
- More assertive investigators
- Legislation and regulation
- Disasters
- Real-time data sharing via Internet

Issues in the mix of funding agencies, investigators, TEMCs, IRBs, and patients

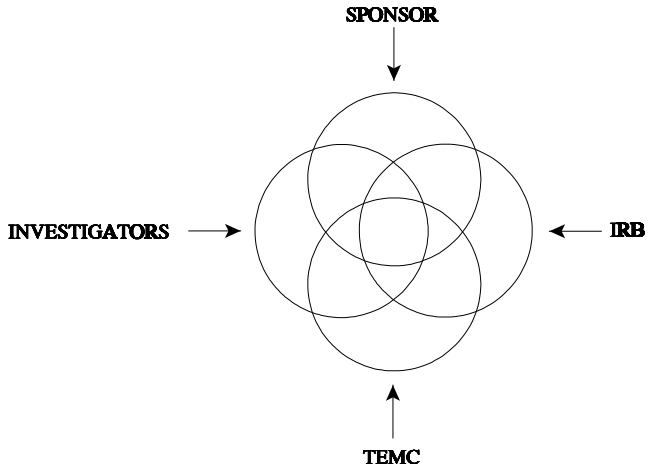
- Access to treatments and care
- Money
- Rights of primacy
- Prerogatives and rights of ownership
- Duties and responsibilities to patients
- Concern regarding conflicts of interests

23 Objectivity vs competency

Adequate monitoring

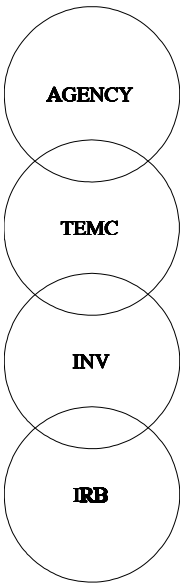
- Timeliness
- Completeness
- Competency
- Freedom

The fully interactive model



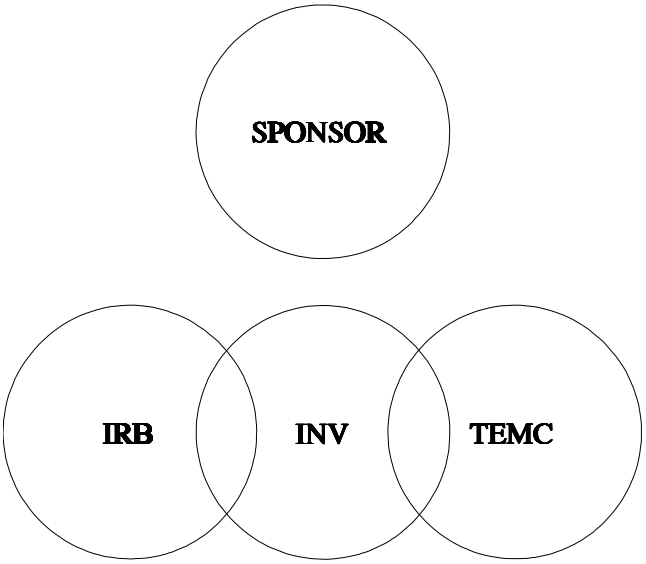
23 Objectivity vs competency

Linear interaction model



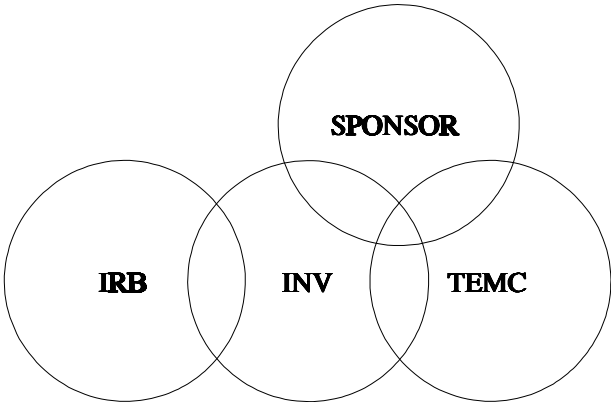
23 Objectivity vs competency

R0 1 interaction model



23 Objectivity vs competency

Cooperative agreement interaction model



24 Integrity and research

24 Integrity requirements of research

Fisher's tale

Once upon a time they apprehended a slovenly pickpocket in the far reaches of the kingdom with a fresh-picked wallet in his hand. They called the king's ministers who ordered him tapped on the wrist of his misguided extremity. They forbade him to put his hand in any pocket for a full eight days. Then, after confiscating the wallet, they ordered the owner executed for not shouting "Stop, thief!" loud enough .

James Holland, Mt Sinai Medical Center
The Cancer Letter, 15 April 1994

Our culture

A little lying is OK ("white" lies and institutional lies)
We should not steal, but it is OK to avoid paying what we owe (beat the IRS)
Everybody cheats a little so it is OK for me to do likewise
Rules are made to be broken (Catch-22 rules made for political reasons)
You have to beat the system to survive (moonlight requisitions)
The Bible says that the meek shall inherit the earth but we see them as inheriting the dirt

24 Integrity requirements of research

Truth vs reality in regard to data fraud and trials

Truth

- Fraud comes in varying shades of grey
- Multicenter trials are reasonably fraud robust
- Most data fraud is inconsequential in impact on results or conclusion
- To be of consequence in trials, fraud must be widespread and treatment related
- There are no fool proof procedures for detecting fraud

Reality

- There is no such thing as a little fraud in the eyes of the public
- Any fraudulent act, regardless of how trivial, will be seen by the public as bad
- The public tends to equate the allegation of fraud to the fact of fraud
- Every act of fraud serves to erode public trust in the research enterprise of the Nation

Mind set for research on human beings

That being able to do such research is a privilege, not a right, and having that privilege granted is, in and of itself, a form of public trust that is diminished or violated by any act that is insensitive or disrespectful of that trust

Observations

It used to be that: There were lies, damned lies, and statistics; now we have lies, damned lies, and fraud

Fraud and pornography: We can't define it but we know it when we see it

24 Integrity requirements of research

Fraud

Oxford English Dictionary 1. The quality or disposition of being deceitful; faithlessness, insincerity. 2. Criminal deception; the using of false representations to obtain an unjust advantage or to injure the rights or interests of another. 3. An act or instance of deception, an artifice by which the right or interest of another is injured, a dishonest trick or stratagem. 4. A method or means of defrauding or deceiving; a fraudulent contrivance; in modern colloquial use, a spurious or deceptive thing.

Black's Law Dictionary: An intentional perversion of truth for the purpose of inducing another in reliance upon it to part with some valuable thing belonging to him or to surrender a legal right. A false representation of a matter of fact, whether by words or by conduct, by false or misleading allegations, or by concealment of that which should have been disclosed, which deceives and is intended to deceive another so that he shall act upon it to his legal injury. Anything calculated to deceive, whether by a single act or combination, or by suppression of truth, or suggestion of what is false, whether it be by direct falsehood or innuendo, by speech or silence, word of mouth, or look or gesture.

Other related terms

conflict of interest
error
falsify
systematic error
plagiarize

24 Integrity requirements of research

Other related terms

conflict of interest - Any interest, deriving from financial holdings, proprietorship, a post held or position taken that is acknowledged to constitute a conflict or that is perceived to have that potential.

error - A mistake, slip, lapse, or blunder; a deviation from truth or accuracy, as in the difference between an observed and expected value; variation in measurement or observation of a quantity due to factors or conditions not controlled or that cannot be controlled, or due to mistakes. ***Usage note***: Generally the term and its synonyms, such as mistake, slip, lapse, or blunder, imply the absence of motive or intent to depart from truth or accuracy. Hence, usage in scientific writing and discourse should be reserved for instances where motive is absent or not suspected. Appropriate, non-neutral terms, such as falsehood, untruth, lie, or fabrication, should be used when motive is presumed or present.

falsify - 1. To state untruthfully; misrepresent. 2. To make false by altering or adding to. 3. To makeup; fabricate; forge.

systematic error - Error due to some systematic process or bias; not to be confused with random error. ***Usage note***: Error connotes absence of motive. Avoid as a euphemism for fraudulent acts.

plagiarize - 1. To steal and pass off the ideas or words of another as one's own. 2. Use of someone else's words or documents in such a way as to imply creation and ownership; use of such words or documents, especially verbatim uses, without crediting the source. 3. To present as new and original an idea or product known by the presenter to have been developed or derived from someone else.

Adapted from Clinical Trials Dictionary: Terminology and Usage Recommendations; C Meinert

Recent "celebrated" violations of norms of honesty

- NBC News: Staged fire of GMC pickup truck
- ABC News: Staged taping run as news (transfer of briefcase in spy story)
- 60 Minutes: Mike Wallace hidden camera interview of reluctant reporter
- Connie Chung interview of Newt Gingrich's mother ("just between you and me" in Eye to Eye interview)
- Volvo: Reinforced frames for crashes filmed for ads promoting safety

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Perceptions

- Epidemic of fraudulent acts
- Multicenter trials are sloppy and prone to bad acts
- The researcher will do anything for fame or fortune
- No one can be trusted
- Everyone lies

Office of Research Integrity (ORI)

An office within the National Institutes of Health responsible for protecting the integrity of the extramural and intramural research programs of the USPHS. The office has its origins in the Health Extension Act of 1985. Responsibilities include conducting investigations and rendering judgments regarding alleged scientific misconduct in federally funded research. The office conducts investigations of alleged misconduct at applicant or awardee institutions and in the intramural research program of the USPHS and presents findings in administrative hearings before the Department of Health and Human Services Departmental Appeal Board. The office was established as part of the NIH Revitalization Act of 1993. Prior to 1993 responsibilities for investigations of misconduct resided in the Office of Scientific Integrity (OSI), in the Office of the Director of the NIH, and in the Office of Scientific Integrity Review (OSIR), in the Office of the Assistant Secretary for Health.

ORI on large clinical trials

In its final report on Poisson, ORI noted that until recent years, "a certain 'sloppiness' had been considered 'acceptable' in large clinical investigations"

Washington Post, 13 April 1994

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Misconceptions about trials

- That fraudulent data automatically invalidates trials
- That there is a demarcation line for fraudulent acts
- That all fraudulent acts involving data collection have the same consequence
- That the failure to detect fraudulent acts is due to a failure to look
- That we can make sense out of numerator data without denominator data

Fraudulent act vs error

Error is inadvertent; fraudulent act is purposeful

Motive is absent with error but necessary for establishing an act to have been fraudulent

The evidence required to establish the fact of error is different than that needed to establish an act as fraudulent

There is no smoking gun with error whereas, absent confession, it is essential for establishing an act as fraudulent

Dangers in the current environment

- Debilitating public distrust
- Star chamber interrogations
- Ruined careers
- Verdicts of guilt without due process
- Coverups
- Divergence of resources and energies
- Avoidance of trials

24 Integrity requirements of research

Classes of events triggering a call to ORI

- Documents believed to be falsified (eg, the St Luc Hospital, Poisson, NSABP case, involving different versions of the same record, or a "halo" around dates suggesting alteration)
- Patterns of misreported or undocumented data (eg, the COMS Cleveland Clinic where visits were "stacked" near the close of time windows)
- Interviewee responses where contact with interviewers cannot be verified

As communicated in letter (dated 25 October 1995) from Dorothy K Macfarlane, Deputy Director, Division of Research Investigations, ORI in response to written query for general advice

Investigator responsibility

- Set a good example
- Provide an environment conducive to integrity
- Be watchful
- Inform local IRB and appropriate body or committee in the case of suspected fraud and the CC
- Meet periodically with staff to discuss individual and collective responsibility

Employee responsibilities

- Be familiar with the norms and expectations of researchers
- Report suspected fraudulent acts to the appropriate person or body
- **Do not** follow orders involving lies or leading to fraudulent data
- **Do not** engage in wishful data collection or data entry
- **Do not** alter records or forms in the absence of a documented basis for the alterations
- **Do not** use erasure or white out on study forms or records
- **Do not** cut corners

24 Integrity requirements of research

Clinic-patient responsibilities

- Emphasize need and reasons for accuracy and integrity with patient (especially important in settings where patient completes forms or keeps diaries used for data entry; Note: Fraud is fraud regardless of source; ORI has investigated cases of patient perpetrated fraud)
- Make certain patient understands requirements and procedures of study
- **Do not** suggest by action or innuendo that it is OK to say or record something that is false
- Set a good example
- **Do not** cut corners or take liberties with the protocol to "beat" the system

Coordinating center obligations in reporting suspected fraud

- To have some assurance that a report is justified
- Ensure that there is a report to ORI, ideally in concert with the funding agency and initially via a three-way phone call with ORI
- To inform its IRB and ensure that affected IRBs are informed
- To inform funding agencies and product sponsor, such as drug companies contributing drug for a trial
- To coordinate on-site audit
- To ensure the creation and maintenance of a documented audit trail in relation to communications, actions, and transactions occurring following the suspected event
- To carry out action plan as dictated

Operating procedures in cases of suspected fraud

Suspicious patterns identified by CC

- CC internal review and "2nd opinion" as to nature of pattern
- Clinic queried by phone or letter (except in cases where evidence is considered strong and "coverup" a possible scenario)
- Site visit to clinic if queries do not produce a plausible explanation
- Report to CC IRB, Sponsor, and ORI if queries or site visit leave doubt as to whether or not fraud occurred
- Report to study officers, SC, and TEMC

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Operating procedures

Modified or altered records consistent with fraud
- CC internal review and "2nd opinion" as to nature of evidence
- Alert sponsor and study officers to the possibility of fraud
- Alert ORI; if by phone, ideally in a 3-way conversation (ORI, sponsor, and CC)
- Alert at risk IRBs
- Visit of site
- Report from site visit
- Implement actions, if any, of report
- Update at risk IRBs, officers of study, SC, and TEMC

Notified by clinic of suspected fraud
- Notify officers, sponsor, and ORI
- Remind clinic of local reporting requirements and of need to inform IRB
- Inform CC IRB and proceed as above for modified or altered records consistent with fraud

Written account of suspected fraud by disgruntled employee
- Notify officers, sponsor, and ORI
- Ask ORI to investigate and report to study

CC informed of a clinic director suspected of fraud
- Alert sponsor and ORI and proceed as indicated by ORI

Clinic suspects employee of CC of fraud
- Seek counsel of clinic director as to course of action
- Director of clinic discuss concern with sponsor and proceed accordingly

Director of center suspected of fraud by employee of center
- Seek counsel of appropriate university body and proceeds accordingly

Director of center suspected of fraud by employee of another center
- Seek counsel of a study officer or CC director (unless under suspicion) and proceed accordingly

24 Integrity requirements of research

Consequences of scientific misconduct

- Loss of credibility and respect
- Dismissal
- Public censure
- Criminal charges
- Jail

PI assurance; grant applications

Item 17 of title page of Grant Application, PHS form 398, Rev 10/88)

Principal investigator / Program director assurance: I agree to accept responsibility for the scientific conduct of the project and to provide the required progress reports if a grant is awarded as a result of this application. Willful provision of false information is a criminal offense (U.S. Code, Title 18, Section 1001).

The NIH blacklist

NIH Guide to Grants and Contracts: An online publication of the NIH; announces cases under investigation by ORI and outcome of investigations; a dozen or so cases per year

Reasons for "making" the list
- Fabricated data
- Fraudulent credentials
- False information in grant applications
- False interview data

Consequences
- Debarred from federally funded research for a specified period of time
- Criminal proceedings

24 Integrity requirements of research

Summary of ORI findings and actions

Findings by year (as of September 1997)

1993	15
1994	7
1995	20
1996	18
1997	13
Total	73

Usual consequence

3 to 5 voluntary exclusion from receiving NIH support and from sitting on NIH advisory or review panels

25 Subgroup differences

25 Subgroup differences

Definitions

baseline subgroup: A subgroup defined by a baseline variable.

baseline subgroup treatment effect: 1. A heterogeneous treatment effect. 2. A treatment effect that differs across related, mutually exclusive, baseline subgroups (eg, as for the two subgroups formed using sex as the subgrouping variable). syn: baseline subgroup treatment difference

baseline variable: 1. A variable measured, observed, or assessed at baseline. 2. Any time invariant variable, regardless of when measured, observed, or assessed, such as one's place of birth, sex, or ethnic origin.

baseline subgrouping variable: A baseline variable used for subgrouping.

heterogeneous treatment effect: A treatment effect that differs depending on some characteristic(s) of the treatment or observation unit; especially any characteristic(s) that is (are) independent of treatment (such as those that are invariant (eg, sex or ethnic origin) or those that are observed prior to the start of treatment). syn: nonhomogeneous treatment effect; treatment interaction effect ant: homogeneous treatment effect

homogeneous treatment effect: A treatment effect that is the same, or that is considered to be the same, across all identifiable baseline subgroups; either assumed to be so without any baseline subgroup analyses or demonstrated to be credible by the failure to find noteworthy subgroup treatment differences via such analyses. ant: heterogeneous treatment effect

qualitative interaction treatment effect: An interaction treatment effect in which the direction or sign of the relationship depends on the value assumed by the variable of interest. Related terms: heterogeneous treatment effect, quantitative interaction

quantitative interaction treatment effect: An interaction treatment effect in which the sign of the slope for the different levels of the variable of interest is the same, but the magnitude of the slope is different. Related terms: heterogeneous treatment effect, qualitative interaction

subgrouping variable: A variable, such as age, used to classify observation units or treatment units into subgroups; usually a baseline characteristic for most subgroup analyses in trials.

25 Subgroup differences

Types of subgrouping variables

Treatment independent

- Invariant demographic characteristics such as sex or ethnic origin
- Disease state or history on entry
- Baseline measurement or observation

Treatment dependent

- In a rigorous sense, any observation made following treatment assignment; in a less rigorous sense any observation made following the initiation of treatment
- Any measure of treatment adherence or compliance
- Any variable made treatment dependent or likely to be made so because of the method of observation or interpretation, including any baseline variable subject to readings or interpretations following treatment assignment by persons not masked to treatment assignment

Note: Subgroup analyses aimed at identifying treatment differences must, of necessity, be restricted to treatment independent variables

Reasons for subgroup analyses

- Check for homogeneous treatment effect
- Exploratory data analysis
- Establishing a subgroup hypothesis or conclusion
- Testing an a-priori subgroup hypothesis

25 Subgroup differences

Grant application package on gender and minority inclusion[†]

Applications for grants and cooperative agreements that involve human subjects are required to include minorities and both genders in study populations so that research findings can be of benefit to all persons at risk of the disease, disorder, or condition under study; special emphasis should be placed on the need for inclusion of minorities and women in studies of diseases, disorders, and conditions which disproportionately affect them. This policy applies to **all** research involving human subjects and human materials, and applies to males and females of all ages. If one gender and/or minorities are excluded or are inadequately represented in this research, particularly in proposed population-based studies, a clear compelling rationale for exclusion or inadequate representation should be provided. The composition of the proposed study population must be described in terms of gender and racial/ethnic group, together with a rationale for its choice. In addition, gender and racial/ethnic issues should be addressed in developing a research design and sample size appropriate for the scientific objectives of the study.

Assess carefully the feasibility of including the broadest possible representation of minority groups. However, NIH and ADAMHA recognize that it may not be feasible or appropriate in all research projects to include representation of the full array of United States racial/ethnic minority populations (ie, American Indians or Alaskan Natives, Asians or Pacific Islanders, Blacks, Hispanics). Provide the rationale for studies on single minority population groups.

Applications for support of research involving human subjects must employ a study design with gender and/or minority representation (by age distribution, risk factors, incidence/prevalence, etc.) appropriate to the scientific objectives of the research. It is not an automatic requirement for the study design to provide statistical power to answer the questions posed for men and women and racial/ethnic groups separately; however, whenever there are scientific reasons to anticipate differences between men and women, and racial/ethnic groups, with regard to the hypothesis under investigation, applicants should include an evaluation of these gender and minority group differences in the proposed study. If adequate inclusion of one gender and/or minorities is impossible or inappropriate with respect to the purpose of the research because of the health of the subjects, or other reasons, or if in the only study population available, there is a disproportionate representation of one gender or minority/majority group, the rationale for the study population must be well explained and justified.

[†] *Application for Public Health Service Grant (Form PHS 398; 9/91 revision)*

25 Subgroup differences

US racial and ethnic groups[†]

Native American (American Indian or Alaskan Native): A person having origins in any of the original peoples of North America, and who maintains cultural identification through tribal affiliation or community recognition

Asian or a Pacific Islander: A person having origins in any of the original peoples of the Far East, Southeast Asia, the Indian subcontinent, or the Pacific Islands. This area includes, for example, China, India, Japan, Korea, the Philippine Islands and Samoa

Black (not of Hispanic origin): A person having origins in any of the black racial groups of Africa

Hispanic: A person of Mexican, Puerto Rican, Cuban, Central or South American or other Spanish culture or origin, regardless of race

White (not of Hispanic origin): A person having origins in any of the original peoples of Europe, North Africa, or the Middle East

[†] *NIH instruction and information memorandum (OER 90-5; 11 December 1990); Office of Extramural Research*

Myths and misconceptions

- That the absence of statements in published manuscripts regarding subgroup analyses means that none were done
- That subgroup analyses are not justified, except for a-priori specified subgroups
- That stratification variables must be used for subgroup analyses
- That investigators have a responsibility to report results by sex and ethnic origin

25 Subgroup differences

Characteristics of proper subgroup analyses

- Restricted to subgrouping variables that are operationally independent of treatment assignment and course of treatment
- Treatment comparisons by original treatment assignment and based on data obtained from all patients enrolled, regardless of course of treatment or length of followup
- All events counted regardless of course of treatment or length of followup
- Temperate interpretation of observed treatment differences, especially when subgroup differences identified via data dredging

Congressional mandate re gender and minority subgroup analyses†

In the case of any clinical trial in which women or members of minority groups will under subsection (a) be included as subjects, the Director of the NIH shall ensure that the trial is designed and carried out in a manner sufficient to provide for a valid analysis of whether the variables being studied in the trial affect women or members of minority groups, as the case may be, differently than other subjects in the trial.

. . . the Director of NIH, in consultation with the Director of the Office of Research on Women's Health and the Director of the Office of Research on Minority Health, shall establish guidelines regarding the requirements of this section.

. . . the guidelines shall provide that the costs of such inclusion in the trial is not a permissible consideration in determining whether such inclusion is inappropriate.

. . . the guideline may provide that such inclusion in the trial is not required if there is substantial scientific data demonstrating that there is no significant difference between: (i) the effects that the variable to be studied in the trial have on women or members of minority groups, respectively; and (ii) the effects that the variables have on the individuals who would serve as subjects in the trial in the event that such inclusion were not required.

† *Clinical Research Equity Regarding Women and Minorities; Part I:* ***Women and Minorities as Subjects in Clinical Research***[54]

25 Subgroup differences

Facts of life regarding trials and baseline subgroup differences

- Most trials are underpowered in regard to detecting main effects, let alone baseline subgroup treatment effects
- Virtually all trials are profoundly underpowered for detecting subgroup differences
- The most likely outcome of a trial is a nil result
- Most baseline subgroup differences that are reported are not reproducible
- Most baseline subgroup differences that are found relate to the disease state or history of the persons being studied; few relate to sex or ethnic origin

Subgroup identification in β-blocker trials†

65	No. of trials reviewed
8	No. of trials reporting a BL subgroup difference
1	No. related to demographic characteristic (age on entry)
7	No. related to disease state
20	Presumed number of subgroups examined per trial
1,300	Estimated number of subgroups examined (20x65)
0.69	Yield per 100 subgroups examined
0	No. of subgroups considered to be verified by independent replication

† *Based on review of 65 randomized trials of β-blocker agents; Yusuf et al,* ***JAMA****, 1991*[60]

A priori identification of important baseline subgrouping variables

- A priori identification usually not practical; few so identified yield subgroup differences
- Simply because a variable is predictive of the outcome interest does not necessarily mean it has any utility as a base subgrouping variable
- Most subgroup differences that are reported are the result of post hoc identification

Prognostic importance of baseline variables for death in the CDP

	Simple t-value	adj t-value 5	10	20	40
1 ST segment dep	9.44	7.17	6.10	5.17	3.24
2 Cardiomegaly	9.20	5.86	5.43	5.07	4.81
3 NYHA class	6.34	4.54	3.32	2.81	1.83
4 Vent cond defect	4.36	4.44	4.17	3.88	3.93
5 Diuretics	7.32	4.09	3.92	2.87	1.73
6 Hx of int claud	5.61		3.71	3.11	3.11
7 Cholesterol	3.61		3.66	3.88	3.95
8 Fq vent ect beats	4.06		3.08	2.81	2.93
9 Inactivity	5.30		2.98	2.73	2.33
10 Q or QS finding	5.30		2.84	2.61	2.01
% of var		7.3	8.9	10.2	10.6

Source: CDP Research Group[17]; see also Schlant et al[49]

Subgroup reproducibility as seen via followup†

Variable	Group	Patients benefited	Prior hyp?	Con-firmed?
Heart rate	Barber et al	HR > 100 beats/min	No	No
CV risks	MIAMI	High risk patients	No	No
Age	Anderson et al	Aged > 65	No	No
Heart rate	Hjalmarson et al	HR > 65 beats/min	No	No
ECG	Wilhelmsson et al	Elect or mechanical defect	No	No
MI type	Multicenter In't	Anterior MI	No	No
Time of trt	Taylor et al	Start trt within 6 mos of MI	No	No
ECG	BHAT	Electrical or mechanical defect	No	No

† *Based on review of 65 randomized trials of β-blocker agents; Yusuf et al, **JAMA**, 1991*[60]

25 Subgroup differences

Subgroup differences as seen via published multicenter randomized trials as identified via MEDLINE search

334	No. of trials identified (as identified via MEDLINE search restricted to multicenter trials published in the first half of 1993; multicenter trials identified by searching abstract for multicenter, multi-center, cooperative, or collaborative)
27	No. of abstracts containing the terms *sex*, *sex*, *interaction*, *subgroup*, or *contraindication* (24 of the trials involved both men and women, 3 of the trials were women only trials)
5	No. of trials reporting a subgroup difference
4	No. of subgroups related to disease state or concomitant treatment
1	No. of subgroups related to age

Features of plausible subgrouping variables

- Treatment independence
- Biological or medical plausibility
- Statistical plausibility
- Internal consistency
- External consistency
- Reproducibility

Stratification versus subgrouping variables

- The purposes of stratification and subgrouping are different; stratification is done for variance control, subgrouping (and the accompanying subgroup analyses) is done as a means of screening for nonhomogeneous treatment effects, hence, a "good" stratification variable may be useless as a subgrouping variable and vice versa
- Both kinds of variables must be independent of treatment assignment, ie candidates should be limited to those invariant over time or to those observed at or prior to treatment assignment
- The utility of a stratification variable depends on its ability to **predict** a designated outcome measure; the utility of a subgrouping variable depends on its ability to **explain** an observed treatment difference for a designated outcome measure
- Stratification using a designated variable does not obligate one to carry out a subgroup analysis using that variable

25 Subgroup differences

Subgrouping "facts"

- A good clinical trialist has an obligation to dredge for subgroup differences
- The notion that the response to treatment is moderated by subgrouping variables is intellectually and clinically appealing
- Reproducible subgroup differences are hard to find
- Many subgroup differences are reported, few are substantiated by other trials
- Most subgrouping variables are found via ad hoc data dredging as opposed to having been identified in advance
- The most fertile fishing grounds are those involving variables relating to the disease state or prior history of disease

Age, sex, and ethnic origin vs other subgrouping variables

- Of the three, age and sex have more biological content than ethnic origin
- Generally, variables related to disease and prior treatment are more likely to be useful for subgrouping than are age, sex, or ethnic origin, ie, disease is the big homogenizer
- Age is often more useful than either sex or ethnic origin as an explanatory variable
- Sex and ethnic origin may be more useful in accounting for treatment differences in primary prevention trials than in secondary prevention trials or in treatment trials
- Sex and ethnic origin may be useful for subgrouping if those variables account for behavior or practice differences capable of influencing treatment and outcome

Factors affecting the plausibility of demographic characteristics as explanatory variables

- Biologic plausibility (eg, generally differences based on sex or age have more biological plausibility than differences based on ethnic origin)
- Medical, behavioral, or operational plausibility
- The nature and extent of previous corroborating evidence or data
- Internal consistency
- Size of the difference observed

25 Subgroup differences

Defects in the Congressional mandate

- Lacking in scientific, biological, and medical rationale
- Lacking in practicality
- Simplistic view of trials and of the degrees of freedom available to trialists
- Motivated by erroneous perceptions of reality; reality distorted by partisan reports such as the GAO report and by a few large male only heart trials
- Imposes corrective measures on the mere presumption that they are needed
- Imposes the requirement for valid interaction analysis on a study by study basis
- Ignores cost

Risks inherent in the mandate

- Reduction in the number of trials done
- Inherently divisive to the extent that it encourages a sex specific partisan approach to trials
- Creates an environment in which "male only" trials are socially unacceptable and politically risky
- Further increases the bureaucracy surrounding the review and approval processes for trials thereby increasing their cost and the time required to carry them out

25 Subgroup differences

Society for Clinical Trials Petition re the mandate[†]

We, the undersigned, ascribe to the value of demographic heterogeneity in clinical trials. We do so in the belief that the value of such trials as a research tool for improving the collective health and well-being of the world's population is enhanced by their being as broadly inclusive as possible and practical. We also ascribe to the principle that exclusions from clinical trials, on the basis of age, gender, or ethnic origin, should not be imposed, except where required by medical-legal restraint, or where justified on scientific or practical ground.

We do not, however, ascribe to the notion that every trial of a condition affecting both genders or peoples of different ethnic origins must be "designed and carried out in a manner sufficient to provide for a valid analysis of whether the variables being studied in the trial affect women or members of minority groups, as the case may be, differently than other subjects in the trial." We believe the imposition of such a requirement by the 103rd Congress of the United States of America to be unwise, impractical, and lacking in scientific rationale. It is unwise because its most likely effect is to reduce the number of trials that can be done, thereby reducing the benefits derived from trials to all peoples, regardless of gender or ethnic origin. It is impractical because of the increased requirement of size and cost imposed by the mandate for valid interaction analyses. It is lacking in scientific rationale because it is predicated on the supposition that we, as people, are fundamentally different in the way we respond to treatments, when our collective biology and experience indicates otherwise. Therefore, we respectfully request that the interaction analysis mandate be reconsidered.

† *Circulated and signed at the 24 - 27, May 1993 Annual Meeting of the Society in Orlando, Florida; sent to the Director of the NIH by the President of the Society*

On demographic neutrality in trials

Investigator level

- Avoid exclusions based on sex, ethnic origin, and age (except for children vs adults)
- Justify all demographic-based exclusions on scientific or pragmatic grounds
- Default to the passive mix model, especially in treatment trials
- Avoid mandative mix models in treatment trials
- Use restrictive mix models with caution; generally best restricted to feasibility trials or primary prevention trials

25 Subgroup differences

On demographic neutrality in trials

IRB level

- Establish demographic neutrality as a desired norm; review individual studies against that norm
- Do not approve studies aimed at a particular demographic group, except where justified by the proposing investigator with convincing written scientific or practical arguments
- Expand the annual review and renewal of an approved project to include data on the demographic composition of the study population recruited
- Develop and maintain an ongoing database capable of tracking the demographic mix of approved studies and of generating reports characterizing the nature of the combined research effort of institutions with regard to the mix of demographic specific diseases and conditions

National level

- Promulgate, via the OPRR, IRB review criteria aimed at establishing demographic neutrality as a norm
- Establish a nationwide system for registration of trials on initiation
- Establish a nationwide database (based on data from individual general assurance IRBs) that enables its operators to generate reports to the scientific and lay communities on the nature of the combined research agenda of the Nation in regard to the demographic nature of peoples studied and for assessing the extent to which it, in a collective sense, meets tests for demographic neutrality
- Repeal the portion of the 1993 NIH Revitalization Act pertaining to subgroup analyses

Observations on the Congressional mandate and its implementation

Observations

- Unrealistic in that it imposes requirements for valid subgroup analyses on a trial by trial basis
- Counterproductive in that its most likely effect is to reduce the number of trials that are done and to increase the cost of those that are done several fold
- A-scientific rationale in that it requires investment of inordinate resources for protection against unlikely outcomes
- Dangerous use of the political process to "rewrite" the rules of science re trials
- Problem being "corrected" is largely perceptional

25 Subgroup differences

On implementation of the legislative mandate

Suggestions

- Strive for operational interpretation of the phrase *valid analysis* (as opposed to strict statistical interpretation), ie, tend toward interpretation in which emphasis is on recruitment of sufficiently heterogeneous population to allow for desired sex and ethnic origin subgroup analyses
- Avoid interpretations that will lead to imposition of sex or ethnic origin quotas, especially in the setting of treatment trials
- Tend toward interpretations in which *valid analysis* refers to the broad collection of trials of a particular treatment or condition, as opposed to a single trial
- Develop an approach that errs on the side of nonrestriction absent scientific rationale for sex or ethnic origin subgroup effects
- Develop rules for implementation involving an escalating scale for sex and ethnic coverage as the collective number of trials relating to a specific treatment and condition increases, ie, allow the first trial to proceed unencumbered re sex or ethnic origin coverage, allow the 2nd one to proceed with only minor encumbrances, etc, with each succeeding trial being required to provide coverage not yet provided in the collective set of trials reported
- Establish global measures of coverage that are based on analyses of all preceding trials of a particular disease or condition

Worries

- That trials, especially large-scale, multicenter trials, will become still more difficult and time consuming to carry out
- That the system of implementation will make it still more appealing to do small-scale, single center, trials as opposed to large-scale, multicenter, trials, in part because of the likelihood that the requirement for *valid analyses* is only viable when the sample size is adequately large
- That Study Sections will become enforcers of a questionable mandate
- That RFPs and RFAs will be written with sex and ethnic origin quotas

26 Clinical trials: Subgroup analysis vs data dredging

26 Subgroup analysis vs data dredging

The traditional construct for a trial

- Choose a test treatment and a control treatment
- Choose an outcome measure for judging success of the treatment
- Specify the null hypothesis and an alternative
- Use the alternative to determine the required sample size
- Design and carry out the trial
- Test the hypothesis
- Publish the results with emphasis on p-values

Problems with the hypothesis testing construct

- Simplest, binary view of nature
- Encourages analyses and presentations aimed at showing "significance" as measured by p-values
- Causes one to concentrate on a single outcome measure to the exclusion of all others
- Tends to encourage an "endpoint" mentality in regard to treatment and followup

The duty of the trialist

- To do no harm
- To perform interim analyses and to modify the design when indicated
- To produce valid findings
- To explore and probe accumulated data
- To explain with parsimony

26 Subgroup analysis vs data dredging

The purpose of exploring and probing

- To "know" the data
- To "explain away" a treatment difference (eg, as being due to differences in the baseline composition of study groups or due to some artifact or defect in the way data were generated or recorded)
- To assess the internal consistency of the findings (eg, as done by looking at different, but related, outcomes)
- To assess the robustness of an observed treatment effect by subgroup analyses
- To assess the homogeneity of the observed treatment effect by subgroup analyses

Definitions

Treatment effect: An effect (adverse or beneficial) attributed to the test treatment; in trials, usually inferred or estimated from a comparison of the test- and control-assigned groups.

Subgroup analysis: Assessment of a treatment effect in a subgroup of persons as defined by one or more demographic or entry (baseline) characteristics.

Data dredging: Ad hoc subgroup analyses done for the purpose of finding a noteworthy treatment effect as measured by p-value and then presented as "proof" or "refutation" of some hypothesis or contention.

26 Subgroup analysis vs data dredging

Subgroup analysis vs data dredging

Similarities

- Both ad hoc, but for different reasons
- Both involve the same analytic approaches
- Both concerned with demographic and entry characteristics

Differences

- Subgroup analysis is done to explain or dispel; data dredging done to proclaim or refute
- The subgroup analyst is p-value cynical as an indicator of "truth"; the data dredger is p-value fixated and uses it as an indicator of truth
- The subgroup analyst is reluctant to conclude in favor of a subgroup; the data dredger is predisposed to conclude

On reasons for caution re subgroup analyses in clinical trials

- Rarely reproducible
- Often lacking medical plausibility
- Generally not consistent with laws of parsimony in regard to treatment effect
- Lacking in precision due to size of subgroups

Subgroup reproducibility as seen via followup[†]

Variable	Group	Patients benefited	Prior hyp?	Con-firmed?
Heart rate	Barber et al	HR > 100 beats/min	No	No
CV risks	MIAMI	High risk patients	No	No
Age	Anderson et al	Aged > 65	No	No
Heart rate	Hjalmarson et al	HR > 65 beats/min	No	No
ECG	Wilhelmsson et al	Elect or mechanical defect	No	No
MI type	Multicenter In't	Anterior MI	No	No
Time of trt	Taylor et al	Start trt within 6 mos of MI	No	No
ECG	BHAT	Electrical or mechanical defect	No	No

[†] *Based on review of 65 randomized trials of β-blocker agents; Yusuf et al,* ***JAMA****, 1991*[60]

26 Subgroup analysis vs data dredging

Subgroup differences seen in published multicenter randomized trials identified via MEDLINE search

334	No. of trials identified (search restricted to multicenter trials published in the first half of 1993; multicenter trials identified by searching abstract for multicenter, multi-center, cooperative, or collaborative)
27	No. of abstracts containing the terms *sex*, *interaction*, *subgroup*, or *contraindication* (24 of the trials involved both men and women, 3 of the trials were women only)
5	No. of trials reporting a subgroup difference
4	No. of subgroups related to disease state or concomitant treatment
1	No. of subgroups related to age

Data dredging as an art form

- Do an almost countably infinite number of subgroup analyses, largely without regard to size of your dataset
- Select only those subgroups yielding differences that are statistically significant, measured with a conventional p-value of ≤ 0.05, blithely ignoring any need for conservatism
- Where possible choose cut points for subgrouping variables that maximize differences
- Combine two or more variables for subgrouping if doing so increases the difference
- Report results only for the subgroups with the largest differences, without any indication as to the process for identification or of the number of analyses performed yielding trivial differences
- Submit the manuscript containing dredged results with the suggestion that the subgroups identified are original with you and that the factors defining them carry major medical implications for treatment
- Stay near the phone awaiting a call regarding your nomination for the Nobel Prize in Medicine, promoting your candidacy for the prize while waiting

26 Subgroup analysis vs data dredging

Interim analysis for treatment effects monitoring vs data dredging

Interim analysis: Analysis aimed at assessing treatment effect as carried out at different points in the conduct of a trial

Monitoring
- Essential for safety and well-being of study subjects
- Used to decide whether it is prudent to continue the trial unaltered
- Subgroup analyses used primarily for probing and plumbing observed treatment effects
- General reluctance to attribute an effect to a subgroup, unless evidence is overwhelming
- Results not presented or published except where they lead to a protocol change

Data dredging
- Done more for curiosity than for monitoring
- Results likely to be presented or published
- Tendency to accept subgroup differences even when not statistically convincing

On the value of subgroup analyses when monitoring

- Indicator of homogeneity of treatment effect or lack thereof
- Indicator of robustness of finding
- Indicator of degree of "generalizability" of finding
- Indicator of internal consistency of results

On indicators of data dredging

- Concocted outcome measure
- Composite outcome, absent presentation of component parts
- Ad hoc look presented as if planned
- Asymmetrical presentation, ie, presentation of subgroups reinforcing "proof" to the exclusion of those that do not
- Presentation emphasizing conventional use and interpretation of p-values

26 Subgroup analysis vs data dredging

On indicators of worship at the altar of p-values

- View a finding yielding a p-value of 0.05 as true and reproducible
- Present results as significant or non-significant
- Label results in tables as S or NS
- Rely on the hypothesis testing approach for analyzing and presenting results

Remember!

The trialist has a duty to analyze by subgroup and to shun data dredging

27 Validity vs generalizability

Validity vs generalizability

Definitions

generalizability *n* - The state or quality of being able to draw a general conclusion that extends beyond the strict confines of a study.

validity *n* - The state or quality of being sound, well-founded, or justified.

The scientific basis for generalization (sampling from a defined population) is absent in trials, hence, generalizations must be made on judgmental, nonstatistical, grounds. Generalizability in the context of trials relates to the extent to which the conclusions derived from a trial can be generalized beyond the setting of the trial.

Validity relates to comparisons within a trial and to the extent to which the treatment differences can be legitimately attributed to the treatment variable. Validity derives from design and execution. Treatment comparisons are considered to be valid if the most likely explanation for the observed differences is the treatment variable.

Source: Adapted from reference 36.

Validity vs generalizability

Validity: The ability to reliably compare and draw conclusions regarding one treatment group vs another without regard to other explanatory variables

Generalizability: The ability to reliably extend the findings of a trial regarding a treatment to general use in the population at large

Observations

The validity of a trial does not depend on having a representative study population

A trial may be valid but not generalizable

Efforts to ensure validity center on the use of methods aimed at ensuring bias free treatment assignment and data collection

Validity vs generalizability

Validity and trials

A trial provides a valid basis for assessing treatment effect only to the extent to which it is reasonable to attribute the effect to the assigned treatment (experimental variable)

Validity and bias

The validity of a trial is robust against selection bias and all other forms of bias, except those that are treatment related

Validity assurance procedures

- Informed consent
- Compliant investigators
- Random treatment assignment (randomization or operational equivalent)
- Masking
  - Masked treatment assignment and absence of any means of predicting assignments before issue
  - Masked treatment administration
  - Masked data collection
  - Masked readings
- Separations
  - Treaters and data collectors
  - Data collectors and processors
  - Investigators and sponsors
  - Investigators and treatments effects monitors
- Surveillance for error and protocol deviations and associated corrective procedures

Validity vs generalizability

Validity gremlins

- Haphazardization
- "Peeking" (including being able to predict the next assignment)
- Differential rate of observation or of loss to followup
- Analysis by treatment received
- Not playing with a full deck (evaluable patients only or not counting certain events)

On the nature of generalization

- Lonesome (accept when made possible by sampling)
- Risky
- Judgmental
- Necessary

The first two tests of generalization re trials

1st: Do you believe the finding? That is, do you believe that someone else doing the same trial in the same kind of patients would get the same result?

2nd: Do you believe that the treatment effect is large enough and important enough to make a difference to patients and their well-being?

Direction of generalizations

- To similar patients
- To dissimilar patients
- To the broader spectrum of disease
- To different modes of administration or delivery
- To new indications
- To related members of a class of drugs

Validity vs generalizability

Generalization hierarchy

The risk of generalization (ie, the likelihood of being wrong) increases as a function of the number of assumptions required

Usually a treatment that works on some patients can be assumed to work across the larger spectrum of patients

For the most part, it is reasonable to assume that a treatment that works in one gender or ethnic origin group works in the other gender or other ethnic origin groups

It is reasonable (but open to challenge on scientific grounds) to assume that related compounds produce similar effects

Myths and facts regarding trials

Myth

- That it is possible to provide a scientific basis for generalization
- That it is possible to avoid selection bias
- That selection bias leads to invalid results
- That steps to ensure "representativeness" enhance validity or one's ability to reliably generalize

Fact

- All trials involve select study populations
- There is no scientific basis for generalization of findings beyond the confines of a trial

28 Food and Drug Administration

28 Food and Drug Administration

FDA terms

biologic
drug
effective
generally regarded as safe and effective (GRASE)
investigational device
Investigational Device Exemption (IDE)
Investigational New Drug Application (INDA)
Investigational New Drug (IND)
new drug
New Drug Application (NDA)
orphan drug
phase I drug trial
phase II drug trial
phase III drug trial
phase IV drug trial
pioneer drug
pivotal trial
post marketing surveillance
safe
vaccine

28 Food and Drug Administration

Drug

drug: ME *drogge*, fr OF *drogue*, chemical material, possibly from MLG *droge*, dry goods] A chemical compound or noninfectious biological substance which is or may be administered to human beings or other animals as an aid in the diagnosis, treatment, or prevention of a disease or clinical condition for the relief of pain or suffering, or to control or modify a physiological or pathological condition. According to the Food, Drug and Cosmetic Act: 1. A substance recognized in an official pharmacopoeia or formulary. 2. A substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease. 3. A substance, other than food, intended to affect the structure or function of the body. 4. A substance intended for use as a component of a medicine but not a device or a component, part, or accessory of a device.

new drug: 1. A new or existing drug being evaluated as an Investigational New Drug. 2. A drug not generally classified as **GRASE** by the Food and Drug Administration and that has no record of use prior to 1938 that matches the use for which it is now being proposed. Usage note: In the parlance of the Food and Drug Administration *new* refers to the application or use being proposed for a drug rather than to the drug itself.

Biologic

Any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment or cure of diseases or injuries of man

28 Food and Drug Administration

Safe and effective

safe *adj* - [ME *sauf*, fr OF, fr L *salvus* safe, healthy; akin to L *salus* health, safety, *salubris* healthful, *solidus* solid, Gk *holos* whole, safe] Free from harm or risk; not threatening danger.

safety *n* - [ME *saufte*, fr MF *sauveté*, fr OF, fr *sauve*, fem of *sauf* safe] The condition of being safe from undergoing or causing harm or injury.

effective *adj* - 1. Producing a desired effect. 2. Being in effect, operative.

efficacy *n* - 1. The power to produce an effect, especially a desired beneficial **effect**, effectiveness. 2. The extent to which a treatment or procedure serves to produce or is capable of producing a desired beneficial effect or result.

FDA requirements for adequate and well-controlled trial

- Clear statement of objective and methods of analysis
- Description of the study design and method for comparing treatments
- Appropriate study population having the disease or condition of interest
- Bias free method of treatment assignment and methods intended to ensure comparability of treatment groups
- Minimization of bias in observations
- Well-defined and reliable outcome assessment
- Appropriate analysis

Types of controls mentioned in FDA CFR

- Placebo concurrent control
- Dose-comparison concurrent control
- No treatment concurrent control
- Active treatment concurrent control
- Historical control

28 Food and Drug Administration

Factors affecting the approval process

- Political pressure
- Social climate
- Amount of prior experience and data available
- Population to be treated
- Availability of alternative treatments
- Quality of studies done

Common complaints

- Slow
- Bureaucratic
- Insensitive
- Noncommittal
- Inconsistent

Questionable practices

- p-value fixation
- Discouraging interim looks because of p-value concerns
- Stopping rule "requirements"
- The supposition that only outcome measures specified before the trial started can be used in analyses

Bad practices

- Approving drugs without benefit of any trials
- Bowing to political pressure
- The "privatization" of the FDA
- "Easy" access to unapproved drugs via "compassionate" use
- Having a short term view of safety or efficacy for drugs used long term

28 Food and Drug Administration

Toward a better process

- A better trained, more experienced FDA staff
- Required separations for industry sponsored trials
- Conditional approval with requirement for long term phase IV trials for long term use
- A more open process including registration of trials and access to results supporting successful NDAs
- Better "enforcement" of label conditions
- More immediate remedial action in the event of questionable treatments or claims

29 Summary

29 Summary

General mind set regarding research on human beings

That being able to do such research is a privilege, not a right, and having that privilege granted is a form of public trust that is diminished or violated by any act related to the conduct of such research that is insensitive, disrespectful, or contemptuous of that trust

That a legitimate state of equipoise is a necessary prerequisite for doing trials falling into the class broadly referred to as treatment trials

Treatment trials are undertaken with the hope of showing benefit, hence, they are not routinely undertaken, except where such hope exists; they are not routinely undertaken to prove harm or to demonstrate something already known

A trial known to be so underpowered so as to be inadequate for answering the relevant questions is unethical

A treatment trial should be terminated once the results obtained provide convincing evidence that the underlying state of equipoise no longer holds

29 Summary

General mind set regarding trials

Given the choice, a big "messy" trial is preferable to a little "clean" one, especially when addressing questions of clinical relevance

Recruitment of participants for a trial almost always takes longer than planned

Retention of participants in any long term trial takes a continuing effort

The consent process is an essential part of the enrollment process from an ethical as well as a practical perspective

The bonding process that takes place during a quality consent process is essential in maximizing adherence to the study protocol and minimizing losses to followup during the trial

Clinical trials are best conducted using tested techniques and approaches for measurements and assessments; ie, avoiding use of evolving, state of the art, technology

Studies designed to achieve multiple ends, such as those involving both a trial and a natural history epidemiological component, are, of necessity, more complicated and costly than single purpose studies

Validity vs generalizability

Validity: The ability to reliably compare and draw conclusions regarding one treatment group vs another without regard to other explanatory variables

Generalizability: The ability to reliably extend the findings of a trial regarding a treatment to the broader population of participants and settings in which the treatment is used

- The validity of a trial does not depend on having a representative study population
- A trial may be valid but not generalizable
- Efforts to ensure validity center on the use of methods aimed at ensuring bias free treatment assignment and data collection

29 Summary

Selectivity vs representativeness

All trials involve select study populations, if for no other reason than only those who consent can be studied

The population from which participants are recruited cannot be defined (except in cases in which participants are recruited from a defined cohort) and hence the issue of representativeness cannot be addressed

The internal validity of a trial does not depend on having a representative population

The greater the degree of selectivity, as imposed by eligibility criteria, the greater the difficulty in finding suitable people for study

Mandated that specify a certain "mix" of people (ie, the imposition of age, sex, or ethnic recruitment quotas), have costs and logistical and ethical implications, and should be imposed only when justified on scientific grounds

The imposition of recruitment quotas, in addition to increasing the cost of recruitment, is likely to increase the time needed to recruit participants

Homogeneity vs heterogeneity re participant selection

Fact

The more homogeneous the population, the more precise the comparison, but the less valuable for subgroup analyses

The greater the selectivity, the longer it will take to achieve the stated sample size

Exclusions based on demographic characteristics, for the purpose of achieving homogeneity, may raise serious social and ethical issues regarding equity and justice

It is hopeless to control variability via imposition of homogeneity requirements on enrollment

Opinion

It is better to do a big dirty trial than a little clean one

The broader the enrollment criteria, the more realistic and relevant the trial

29 Summary

Bias control and reduction

In the context of comparative trials, the biases of primary concern are those known or believed to have the potential for being treatment-related

Biases operating prior to randomization in randomized trials, such as the selection bias arising from the fact that only those who consent can be enrolled, are independent of treatment assignment

The tools and techniques used by trialists to design and carry out trials are robust against treatment-related biases. They are:

- Use of treatment assignment schemes free of treatment-related biases; randomization or some other scheme arguably free of treatment-related bias
- Double masked treatment administration and data collection, and failing that, other forms of masking such as separation of treaters, data collectors, and readers
- Standardization, such as use of common treatment and data collection protocols to reduce the amount of variation arising from differences in the way procedures are performed
- Ongoing quality control and surveillance of all aspects of the treatment, data collection, data processing, data analysis, and publication procedures to detect, correct, and eliminate, sources of bias

The minimal requirements for a bias free trial are:

- Establishment of comparable study groups that are free of selection bias
- Establishment and maintenance of a data collection schedule in which the probability of observing an event is the same for all participants regardless of treatment assignment
- Use of defined, reproducible, treatment procedures

29 Summary

Variance control and reduction

Variation due to differences in the baseline composition of participants enrolled, or due to variation in the treatment or observation processes employed, even if not differential by treatment group, reduces the precision of the trial — as measured by confidence intervals around estimates of the observed treatment effects

The primary tools of the trialist for variance control include the following:

Via design
- Crossover designs
- Matching

Via participant selection
- Selectivity
- Exclusions

Via execution
- Stratification of treatment assignments
- Blocking of treatment assignments within strata
- Standardization of procedures and data collection schedules

Via analysis
- Use of baseline covariates for adjustment
- Subgroup analyses

The primary tools of the trialist for variance reduction include the following:
- Increased sample size
- Replication of the same measurement
- Ongoing surveillance and quality control
- Ongoing data editing
- Standardization

29 Summary

Masking principles and beliefs

- All other things being equal, masked administration of treatment is preferable to unmasked administration
- Masked data collection is preferable to unmasked data collection
- Treatment assignments in masked trials should be revealed only to those who have a need to know
- In general, masked treatment administration or data collection is possible only to the extent that it is feasible, and then only to the extent that it is ethical
- Masked treatment administration should not be imposed if it is little more than a charade (eg, the side effects of the treatments are such so as to make the treatment obvious)
- There are real logistical and practical problems in imposing and maintaining double-masked drug treatments
- Masking should not be imposed if doing so leads to reduced quality of participant care or increases risks for participants
- Treatment effects monitoring by treatment effects monitoring committees should be performed without masking

29 Summary

Philosophy and views regarding treatment assignment

There are various approaches to treatment assignment, among them simple or restricted randomization

Essential hallmarks of sound assignment schemes are those that:
- Provide a reproducible order of assignment (eg, a randomization scheme produced using a table of random numbers or a computer based pseudorandom number generator)
- Are documented in writing and in adequate detail to allow someone else to reproduce the assignment scheme
- Have adequate provisions and built-in safeguards to prevent the release of an assignment until essential eligibility requirements are satisfied and essential baseline data have been collected and recorded on study forms
- Contain safeguards preventing anyone from knowing the identity of an assignment until it is issued
- Make it impossible to predict future assignments from past assignments
- Provide clear and indelible audit trails for use by the SC and other review groups, including FDA auditors or other external review groups

Positive features of randomization for treatment assignment include the following:
- Protect against selection bias in the assignment process
- Provide predictable sampling variation for differences in the baseline composition of the treatment groups, and for subgroups of the treatment groups formed using variables that are independent of treatment assignment (eg, sex, ethnic group, and all baseline observations)
- Expected degree of baseline comparability for an unobserved variable is the same as for an observed variable

Other facts:
- Haphazardization is not the same as randomization
- Randomization does not ensure baseline comparability
- Large differences in baseline composition of the study groups can occur even if the randomization process is valid (ie, has been produced by a procedure known to be random and has been administered without any breaches)
- Large differences in the baseline composition of the treatment groups cannot be used as evidence of a breakdown in the treatment assignment process without other accompanying information documenting breaches in the assignment process

29 Summary

Stratification views and philosophy in relation to treatment assignment

- The purpose of stratification is to ensure the comparability of the treatment groups with regard to the variable or variables used for stratification
- The choice of variables should be limited to those known to be or likely to be related to outcome
- Only a small number of variables can be controlled via stratification at design time, all the rest must be "controlled" at analysis time via post-stratification and subgroup analyses or via use of multiple regression procedures
- The gain in statistical precision diminishes as the sample size of the trial increases; the gain is minimal once the per treatment sample size is 50 or larger
- Use of participant characteristics for stratification increases the logistical complexities of the assignment process
- The larger the number of assignment strata the greater the chance of sizable departures from the expected assignment ratio (Note: One can guard against such departures by using blocks of small size, but the pattern of blocking, if discovered, may allow study personnel to predict assignments)
- Stratification by clinic is generally a good idea, even if the statistical gain is nil because clinic populations and local customs and procedures vary; such stratification also has logistical advantages in double-masked drug trials in relation to packaging, labeling, and supplying drug to individual clinics
- The notions of stratification and recruitment quotas are different
- Stratification does not obligate one to recruit a specified number to the different strata nor does it require one to carry out treatment comparisons within the different strata (though one usually does)

29 Summary

Blocking of treatment assignments

Blocking in the treatment assignment process is generally imposed:

- To force the design to yield assignment ratios near those specified in the design
- To ensure that the distribution of assignments prior to a change in the study protocol (eg, one affecting the eligibility criteria) is the same as that after the change (ie, intended to yield schemes robust to protocol changes)
- To protect the design against time-related changes in the nature of participants enrolled or in the way the protocol and data collection procedures are performed

General procedures for blocking include use of variable sized blocks to reduce the likelihood of clinic personnel being able to predict future assignments

The notions of stratification and blocking are different; both are performed to control variance across treatment groups but via different approaches

The proximity of the observed assignment ratio to the one specified in the design will be a function of the blocking scheme imposed; the degree of the departure will be a function of the number of partially filled blocks when enrollment is stopped

Views on publication vs presentation of key results

Investigators have a responsibility to publish, regardless of the nature or direction of the results, as soon as possible after a trial is completed or stopped

The most responsible and reliable way to communicate the main results of a trial is via peer reviewed, indexed journals

Generally, the best course of action in relation to key study findings is to *publish first and present later*; ie, no public presentation of key results until they have been published

29 Summary

Views on authorship policies and practices

There is no ideal method of authorship attribution for multicenter trials; only varying degrees of imperfection

Rules and procedures for publication and authorship should be set by the study steering committee and should be debated and reviewed by the entire research group before they are adopted

Such rules and procedures should be developed and adopted early in the course of activities, long before the first paper is written

Corporate forms of authorship, though not warmly embraced by some journal editors, are preferred over conventional forms of authorship for primary papers, ie, those containing the main results or conclusions of a trial

Philosophy on outcome measures

The importance of masking depends, to some degree, on the risk of treatment-related bias in measuring or recording the outcomes of interest; the less the risk the less the importance

A trial with a clinical event as the outcome of interest has greater relevance and importance in the treatment evaluation process than one based on a surrogate outcome measure

The fact that a variable is correlated with a clinical event is not sufficient to justify use of that variable as a primary outcome measure for in the design of a trial until or unless it can be conclusively shown that that correlation is highly predictive of the clinical outcome for the particular population being studied

Trials performed using a surrogate outcome and indicating a beneficial treatment effect, should be followed by trials and studies demonstrating a predictive relationship between that measure and relevant clinical events or outcomes

Any drug, biologic, or device proposed for approval should be supported by trials with sufficient power and length of followup to provide assurance as to safety based on assessments using clinical outcome measures

29 Summary

Data access

- Limit access to treatment data during the trial to those responsible for monitoring treatment effects
- Prohibit release of individual listings or records that may compromise participant rights
- Provide access to unpublished supplementary tables for all major publications on treatment effects
- Limit release of data listings during the period of active support to those portions of the data file where analyses have been completed or no further analyses are planned
- Be sensitive to requests for data or added analyses that arise from outside the study
- Provide access to all data files used in publications from the trial after termination of active support

Followup

As a rule, all persons, once enrolled, should be followed according to the indicated data collection schedule, regardless of course of treatment and regardless of whether or not the person is considered to be adherent to the assigned treatment

All persons enrolled into a trial, including those who drop out, should be accounted for in the final data set

Persons who drop out should be subject to some minimal level of followup simply as a means of accounting for their whereabouts and for providing counts as to life-death status of the population randomized

To the extent possible and medically prudent, all persons, regardless of treatment assignment, should be subject to the same frequency of clinic visits and data collection schedule

The data systems devised for trials should provide counts of all participant-study personnel contacts involving evaluation or data collection (scheduled or unscheduled) to allow one to determine whether the differences observed among the treatment groups can be explained by differential rates of observation

29 Summary

Close-out

Common date close-out: Close out that occurs at approximately the same time for all persons enrolled in a trial, regardless of when enrolled

Anniversary date close-out: Close out that occurs after the same period of followup

All things being equal, common date close-out systems are preferable to anniversary date close-out systems because:

- Followup information is maximized
- Logistical ease
- Participant and staff attrition sometimes associated with anniversary close-outs are avoided
- Allows one to provide more useful information and advice to participants on departure than is possible with anniversary close-out (eg, all participants can be informed of the treatment they were receiving in the case of masked trials and can be informed of the results of the trial)

29 Summary

Subgroup analysis and interaction

Interaction: A relationship in which response to treatment is moderated or influenced by some demographic characteristic, such as age, sex, or ethnic origin

Qualitative interaction: One in which the direction or sign of the relationship depends on the value assumed by the demographic variable (eg, one in which there is a beneficial treatment effect for males and a harmful effect for females)

Quantitative interaction: One in which the sign or direction of the relationship is the same for the different values of the demographic variable, but where the magnitude of the effect is different

Observations of the trialist

- Biologically, it is more plausible to expect the existence of sex by treatment interactions than it is to expect ethnic origin by treatment interactions
- It easier to postulate the existence of a demographic by treatment interaction than it is to demonstrate its existence
- The frequency of quantitative interactions is higher than qualitative interactions
- There are likely to be thousands of quantitative demographic by treatment interactions, but few of them are likely to be large enough or of sufficient medical importance to warrant trials aimed at detecting them

Reminders

- The likelihood of finding a qualitative interaction in treatment trials is low
- Most sample size calculations for trials are made assuming a homogeneous treatment effect across the demographic spectrum represented in a trial
- The sample size required to detect clinically meaningful demographic by treatment interactions is usually beyond the range of what is reasonable

29 Summary

Analysis and counting rules and principles

Analysis

The initial comparison of treatment groups should include all participants assigned to the respective treatment groups, should be by original treatment assignment, and should include all recorded events for the outcome of interest.

Treatment comparisons involving a composite outcome measure, should be preceded by analyses providing comparisons of the treatments for the individual component parts of the composite outcome measure

All higher order outcome measures (eg, death or some clinically morbid event), regardless of whether or not considered in designing the trial, should be taken into account in any analysis involving lower order outcome measures (eg, progression of retinitis or change in CD4 counts)

Counting rules

A person should be counted as randomized and as part of the denominator for the treatment group to which assigned when the assignment is issued and should be so counted regardless of subsequent course of events in the care and treatment of that person

Count all events occurring from the point of randomization (ie, the point in time at which the treatment assignment is revealed to the clinic) forward, regardless of when they occur

Count a person in the group to which assigned regardless of subsequent course of treatment or level of adherence to that treatment

Organizational philosophy

- Formulate organizational structure before starting trial
- Delineate and separate functions of key committees
- Specify relationship of one committee to another
- Specify committee membership and voting rules
- Delineate disclosure requirements for protection against conflicts of interest
- Review and revise organizational structure as trial proceeds
- There are real operational and logistical costs associated with creating and maintaining committee structures and interactions
- Avoid the creation of more committees than necessary

29 Summary

Philosophy regarding ancillary studies

ancillary study: An investigation carried out in one or more of the participating centers, utilizing resources arising from the trial but with objectives that are distinct from the primary objectives of the trial.

General points and suggestions regarding ancillary studies

- Funding (if needed) should be independent of that for the trial
- Data collection procedures should not interfere with recruitment, treatment, or data collection for the trial
- Arrangements for data analysis and access to main data file should be spelled out prior to start of ancillary study
- Limitations on time of publication or amount of information that can be presented or published should be agreed upon prior to start of ancillary study

30 University Group Diabetes Program

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UGDP

University

Group

Diabetes

Program

Timetable

1959	First meeting of investigators
1960	NIH funding initiated
1961	First patient enrolled
1962	Phenformin treatment added to design
1962	Six additional clinics enrolled
1966	NIH funding renewed
1966	Patient enrollment completed
1969	Tolbutamide treatment stopped
1971	Phenformin treatment stopped
1975	Patient followup terminated
1978	NIH funding renewed
1981	NIH funding ends

Objectives

- To evaluate the effects of hypoglycemic agents on vascular complications of adult-onset diabetes
- To study the natural history of adult-onset diabetes
- To develop methodology for clinical trials

30 University Group Diabetes Program

Design features

- Random treatment assignment
- Double-masked evaluation of oral hypoglycemic agents
- Common study protocol
- Long-term followup
- Ongoing quality control

Randomization features

- Stratification by clinic
- Balance of assignments within clinic
- Assignments issued by CC on request

Treatment assignment by clinic

	Plbo	Tolb	IStd	IVar	Phen	All
Baltimore	24	21	21	20	0	**86**
Cincinnati	23	22	24	21	0	**90**
Cleveland	19	19	20	20	0	**78**
Minneapolis	22	24	24	24	0	**94**
New York	22	21	21	22	0	**86**
Williamson	23	23	24	24	0	**94**
Boston	16	16	16	15	23	**86**
Birmingham	12	12	12	12	38	**86**
Chicago	11	11	12	11	35	**80**
St. Louis	10	11	12	11	35	**79**
San Juan	12	13	13	13	40	**91**
Seattle	11	11	11	11	33	**77**
All	**205**	**204**	**210**	**204**	**204**	**1,027**

30 University Group Diabetes Program

Number per treatment group

Plbo	205
Tolb	204
IStd	210
IVar	204
Phen	204
Total	**1,027**

Eligibility criteria

- Adult-onset diabetes (diagnosis within 12 mos of enrollment)
- Sum GTT ≥ 500 mg/dl
- Nonketotic on diet alone
- Life expectancy ≥ 5 yrs
- Willing to participate

Study treatments

Placebo (**Plbo**)	Dosage schedules same as for **Tolb** or **Phen**
Tolbutamide (**Tolb**)	1.5 gm (split)
Insulin standard (**IStd**)	10, 12, 14, 16 units depending on body surface
Insulin variable (**IVar**)	Amount required to maintain "normal" glucose levels
Phenformin (**Phen**)	100 mg (split)

30 University Group Diabetes Program

UGDP examination schedule

Time fr entry	Repeat cycle	Study Examination	Procedures
< -1 yr	NA	NA	1st diagnosis
< -1 mo	NA	Qualifying exam	GTT
0	None	Eye, heart, kidney, peripheral vascular	Randomization
3 mos	Yearly	Eye	Fundus photos
6 mos	Yearly	Heart	ECG
9 mos	Yearly	Kidney	Cr clearance
12 mos	Yearly	Peripheral vascular	x-rays, GTT

Clinics

30 University Group Diabetes Program

Data collection principles

- Time windows for scheduled exams
- Central masked readings of ECGs, fundus photos, and x-rays
- Central cause of death coding
- Central data entry

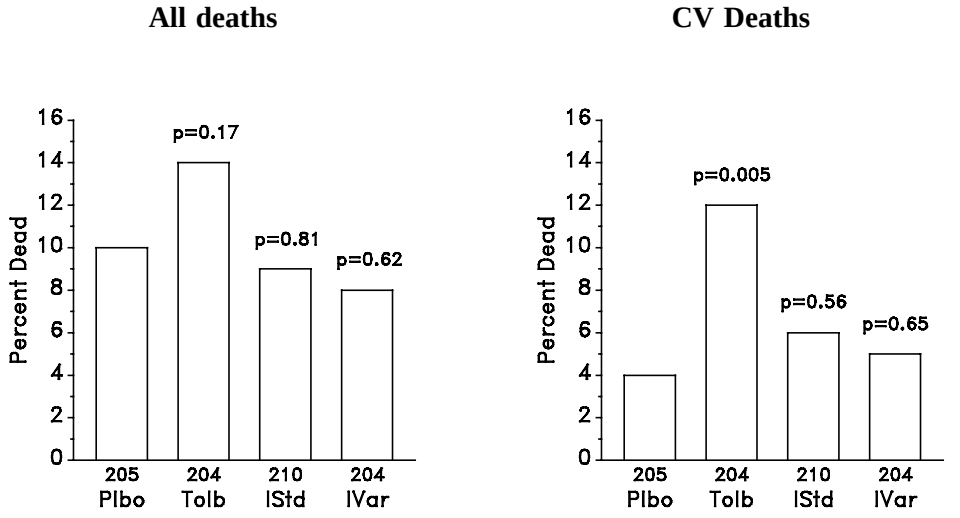
Dropouts (as of 7 Oct 1969)

	Plbo	Tolb	IStd	IVar
No. enrolled	205	204	210	204
Alive	22	22	26	23
Status unknown	2	1	0	2
Total dropouts	24	23	26	25
% of enrolled	**11.7**	**11.2**	**12.4**	**12.3**

Reference 56

30 University Group Diabetes Program

Percent Dead (as of 7 Oct 1969)

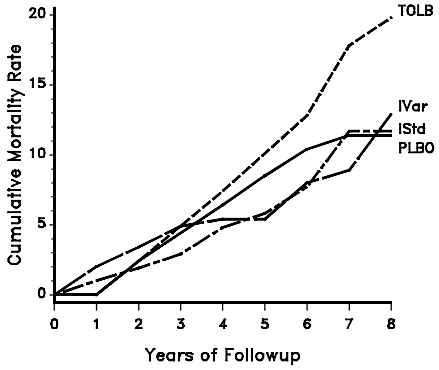


Reference 56

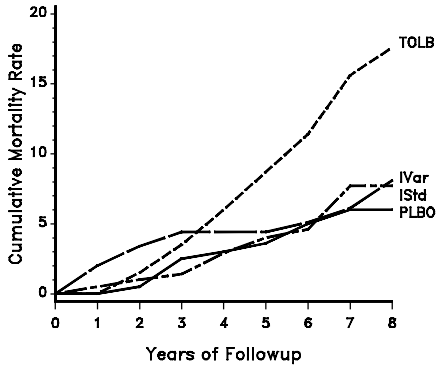
30 University Group Diabetes Program

Cumulative Mortality Rates (per 100 pop, as of 7 Oct 1969)

All Causes



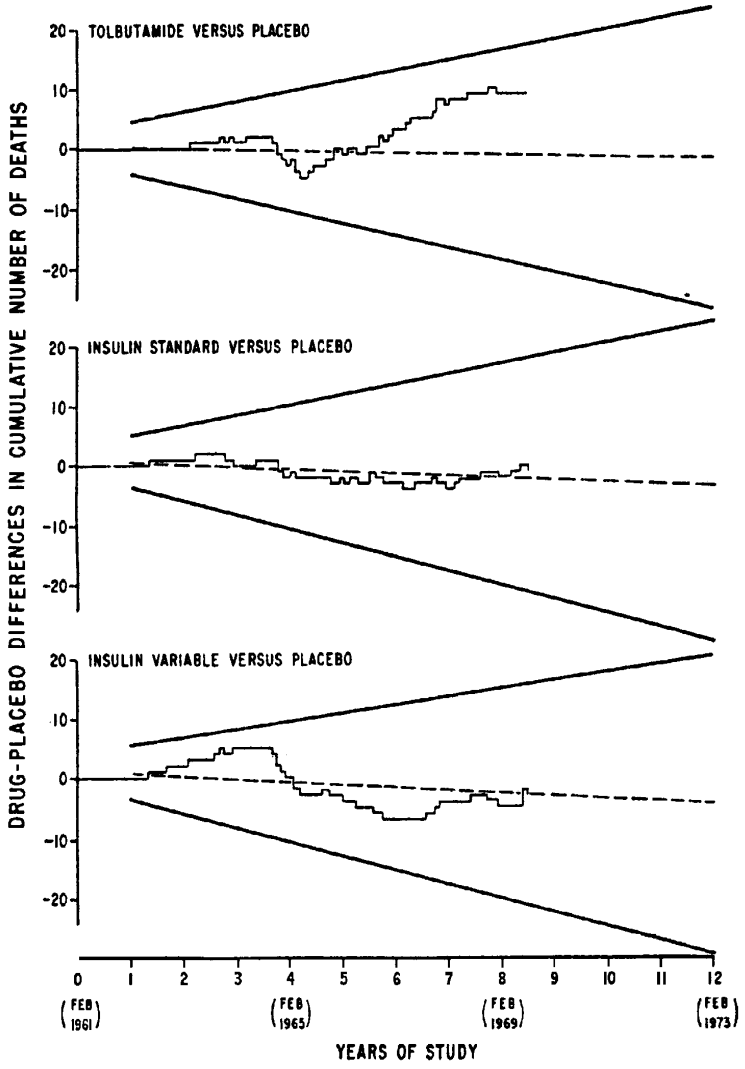
Cardiovascular Causes



Reference 56

30 University Group Diabetes Program

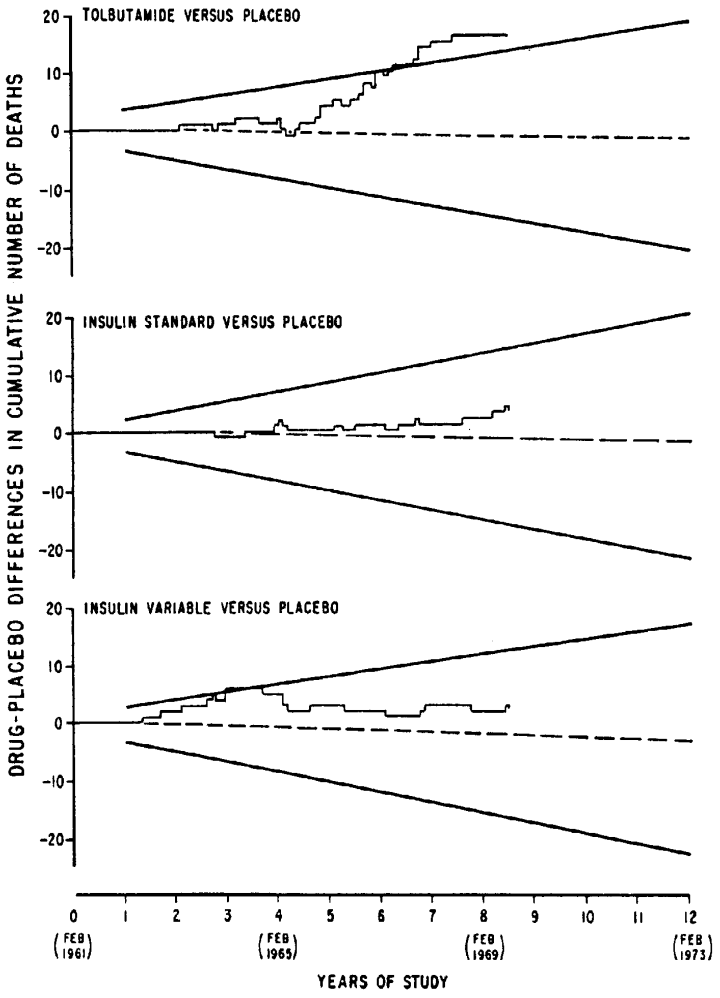
Monitoring bounds (5%) for deaths (as of 7 Oct 1969)



Reference 56

30 University Group Diabetes Program

Monitoring bounds (5%) for CV deaths (as of 7 Oct 1969)



Reference 56

30 University Group Diabetes Program

Entry demographic characteristics

	Plbo	Tolb	IStd	IVar	p
Age ≥ 55	41.5	48.0	46.2	46.1	0.58
Female	69.3	69.1	72.9	77.5	0.20
White	50.2	52.9	49.0	59.3	0.16

Entry cardiovascular characteristics

	Plbo	Tolb	IStd	IVar	p
Hypertension	36.8	30.2	30.9	28.1	0.28
Digitalis use	4.5	7.6	5.8	5.0	0.56
Angina	5.0	7.0	7.7	3.5	0.26
Abn ECG	3.0	4.0	5.3	4.0	0.72
Chol ≥ 300	8.6	15.1	16.4	13.4	0.11
One or more	47.3	47.9	50.2	41.5	0.35

Other entry characteristics

	Plbo	Tolb	IStd	IVar	p
Fasting blood glucose≥ 110 mg/100 ml	63.5	72.1	63.6	68.0	0.20
Relative body wt ≥ 1.25		52.7	58.8	57.1	0.59
Visual acuity (either eye) ≥ 20/200	4.3	5.2	6.1	5.8	0.86
Serum creatinine≥ 1.5 mg/100 ml	2.6	2.5	1.9	2.0	0.96
Art calcification	14.3	19.7	17.2	15.9	0.52

30 University Group Diabetes Program

Deaths by CV risk factors (as of 7 Oct 1969)

	Plbo	Tolb	IStd	IVar	Avg N
Hypertension					
No	11.0	12.9	7.0	4.2	138
Yes	9.5	16.7	14.1	21.4	64
History of digital use					
No	8.3	13.1	7.1	7.9	190
Yes	55.6	33.3	41.7	30.0	12
History of angina					
No	9.4	13.9	6.7	8.8	192
Yes	30.0	21.4	43.8	14.3	12
ECG abnormality					
No	9.3	13.0	8.1	7.8	194
Yes	33.3	50.0	36.4	37.5	8
Cholesterol					
< 300 mg/100ml	10.5	14.8	8.7	6.9	174
≥ 300 mg/100ml	11.8	13.3	14.7	18.5	27
Any of above					
No	9.2	11.0	3.0	3.5	103
Yes	12.5	17.4	14.9	16.2	90

30 University Group Diabetes Program

CV deaths by CV risk factors (as of 7 Oct 1969)

	Plbo	Tolb	IStd	IVar	Avg N
Hypertension					
No	3.9	11.5	4.2	0.7	138
Yes	6.8	13.3	10.9	19.6	64
History of digitalis					
No	3.6	10.9	5.1	4.7	190
Yes	33.3	33.3	25.0	30.0	12
History of angina					
No	3.6	11.8	5.2	5.7	192
Yes	30.0	21.4	18.8	14.3	12
Significant ECG abnormality					
No	3.6	10.9	5.6	4.7	194
Yes	33.3	50.0	18.2	37.5	8
Cholesterol					
< 300 mg/100ml	5.0	12.4	4.6	4.0	174
≥ 300 mg/100ml	5.9	13.3	14.7	18.5	27
Any of above					
No	2.0	9.0	2.0	0.0	103
Yes	8.0	15.2	10.9	15.0	90

30 University Group Diabetes Program

Deaths by baseline characteristic (as of 7 Oct 1969)

	Plbo	Tolb	IStd	IVar	Avg N
Fasting blood glucose					
< 110 mg/100 ml	12.2	10.5	5.3	3.1	68
≥ 110 mg/100 ml	8.5	16.3	12.0	11.6	137
Relative body weight					
< 1.25	15.5	20.2	8.9	12.8	91
≥ 1.25	5.6	10.8	10.0	5.5	114
Visual acuity					
< 20/200	10.6	14.3	8.1	9.0	181
≥ 20/200	12.5	30.0	33.3	9.1	102
Serum creatinine					
< 1.5 mg/100 ml	8.5	12.9	7.9	8.7	195
≥ 1.5 mg/100 ml	20.0	20.0	50.0	0.0	4
Arterial calcification					
No	9.2	10.1	5.4	7.9	166
Yes	17.2	33.3	31.4	16.1	34

30 University Group Diabetes Program

CV deaths by baseline characteristics (as of 7 Oct 1969)

	Plbo	Tolb	IStd	IVar	Avg N
Fasting blood glucose					
< 110 mg/100 ml	5.4	8.8	2.6	3.1	68
≥ 110 mg/100 ml	4.7	14.3	8.3	7.2	137
Relative body weight					
< 1.25	7.2	15.5	6.7	9.6	91
≥ 1.25	2.8	10.8	5.8	2.7	114
Visual acuity					
>20/200	5.6	12.1	5.4	6.2	181
≤20/200	0.0	30.0	16.7	0.0	10
Serum creatinine					
< 1.5 mg/100 ml	4.2	10.8	5.0	5.6	195
≥ 1.5 mg/100 ml	20.0	20.0	25.0	0.0	4
Arterial calcification					
No	4.0	9.4	3.0	4.3	166
Yes	10.3	25.6	22.9	16.1	34

Deaths by demographic entry characteristics (as of 7 Oct 1969)

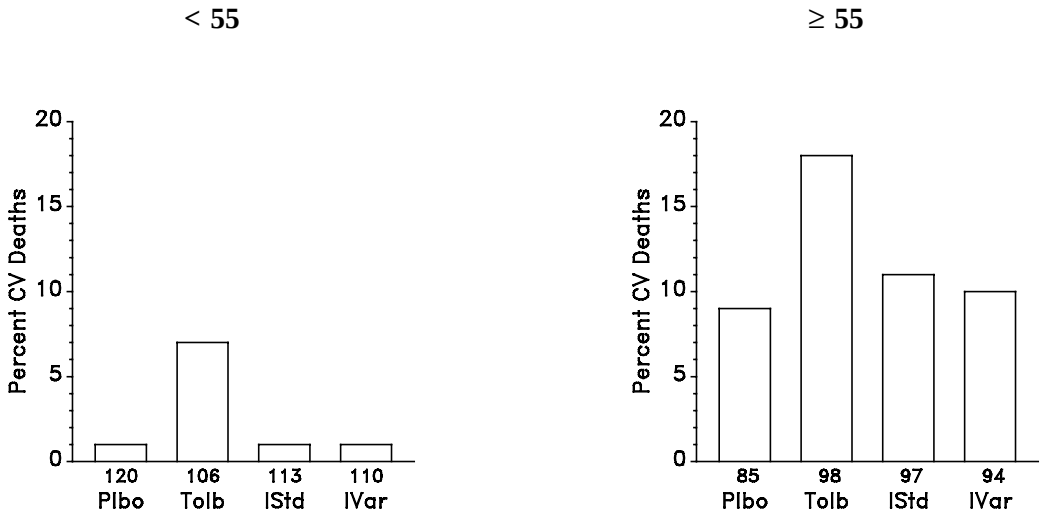
	Plbo	Tolb	IStd	IVar	Avg N
Age					
< 55	4.2	7.5	1.8	6.4	112
≥ 55	18.8	22.4	18.6	11.7	94
Sex					
Male	20.6	20.6	17.5	4.3	58
Female	5.6	12.1	6.5	10.1	148
Race					
White	10.7	20.4	14.6	9.1	108
Nonwhite	9.8	8.3	4.7	8.4	97

30 University Group Diabetes Program

CV deaths by entry demographic characteristics (as of 7 Oct 1969)

	Plbo	Tolb	IStd	IVar	Avg N
Age					
< 55	1.7	7.5	1.8	1.8	112
≥ 55	9.4	18.4	11.3	10.6	94
Sex					
Male	11.1	17.5	8.8	4.3	58
Female	2.1	10.6	5.2	6.3	148
Race					
White	5.8	16.7	7.8	7.4	108
Nonwhite	3.9	8.3	4.7	3.6	97

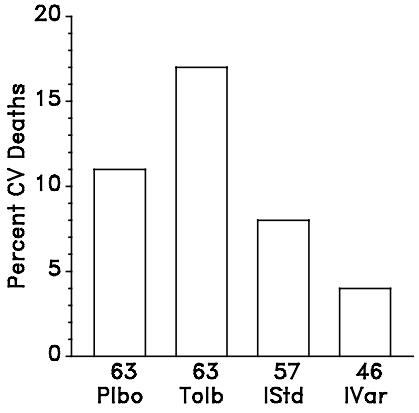
Mortality by age on entry (as of 7 Oct 1969)



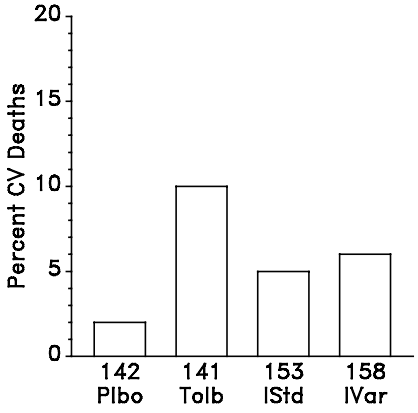
30 University Group Diabetes Program

Mortality by gender (as of 7 Oct 1969)

Male

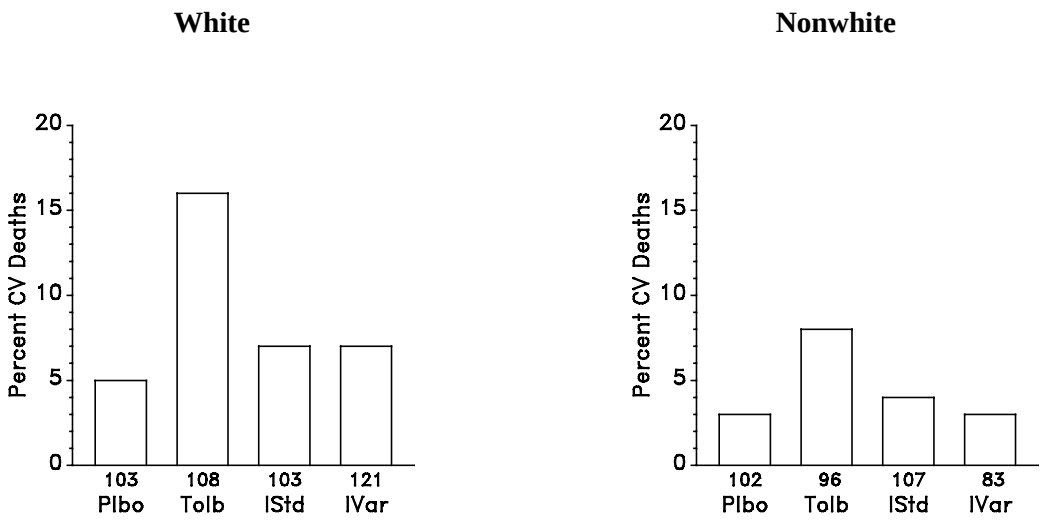


Female



30 University Group Diabetes Program

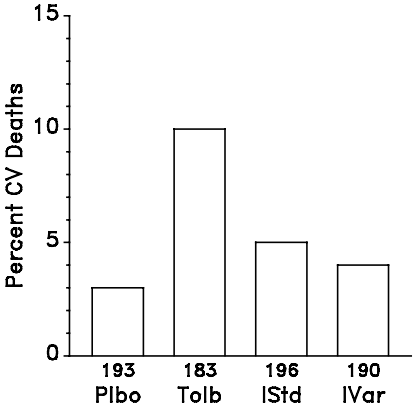
Mortality by race (as of 7 Oct 1969)



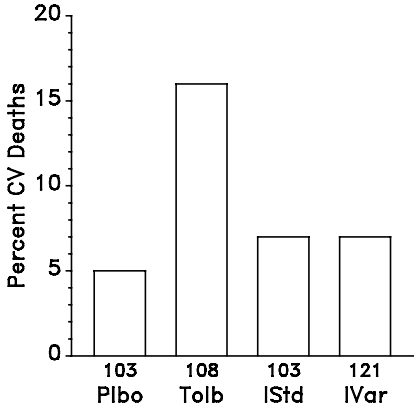
30 University Group Diabetes Program

Mortality absent history of angina or digitalis use on entry (as of 7 Oct 1969)

No angina pectoris



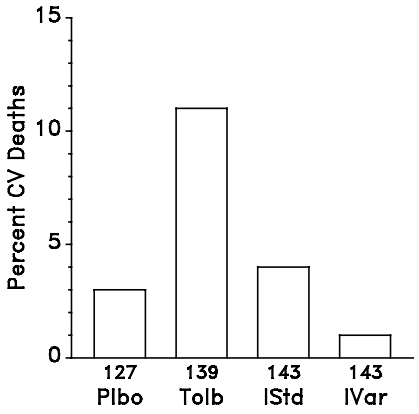
No digitalis use



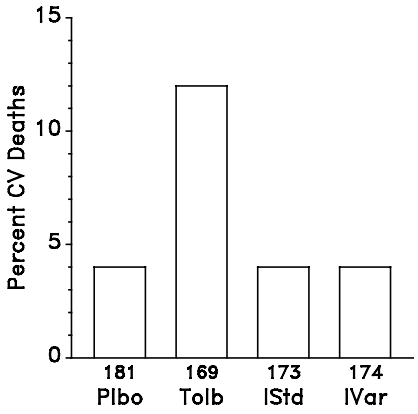
30 University Group Diabetes Program

Mortality absent hypertension and for subgroup having cholesterol < 300 mg/100ml on entry (as of 7 Oct 1969)

Definite hypertension, absent



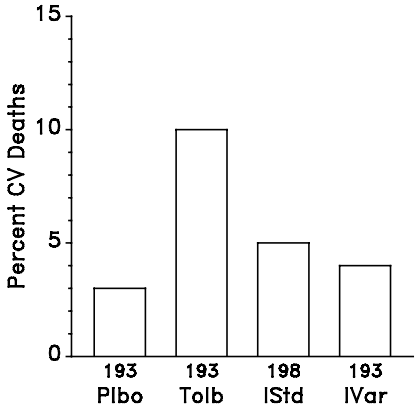
Cholesterol <300 mg/100 ml



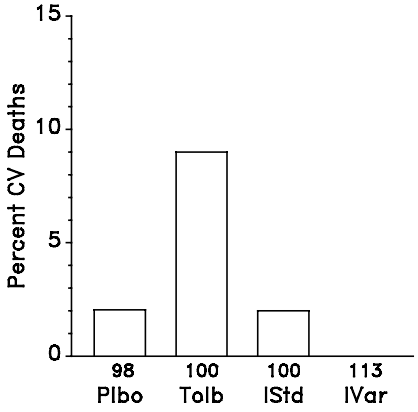
30 University Group Diabetes Program

Mortality absent ECG abnormality and CV risk factors on entry (as of 7 Oct 1969)

Significant ECG abnormality, absent



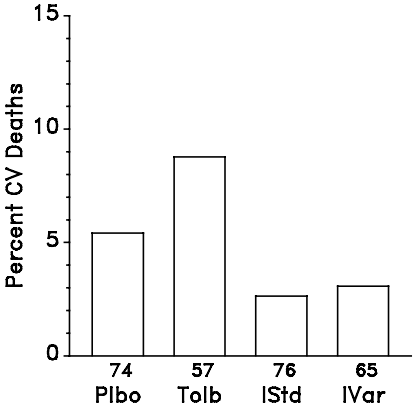
CV risk factors, none



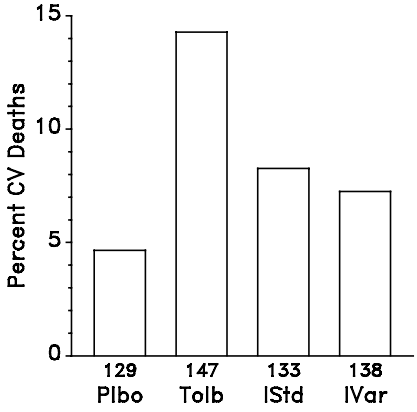
30 University Group Diabetes Program

Mortality by baseline fasting blood glucose level on entry (as of 7 Oct 1969)

< 110 mg/100 ml



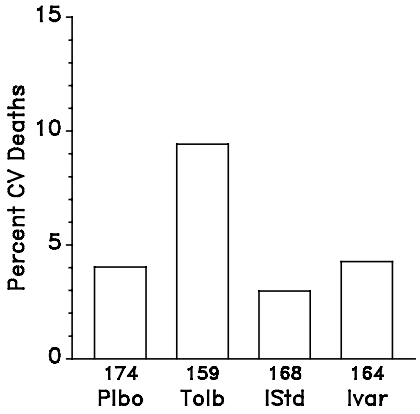
≥ 110 mg/100 ml



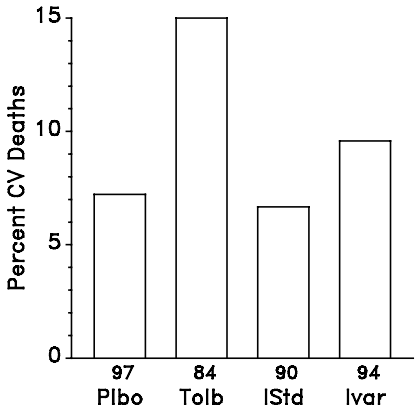
30 University Group Diabetes Program

Mortality absent arterial calcification and for subgroup having low relative body weight on entry (as of 7 Oct 1969)

Arterial calcification, absent



Relative body weight < 1.25



30 University Group Diabetes Program

Baseline adjustment variables

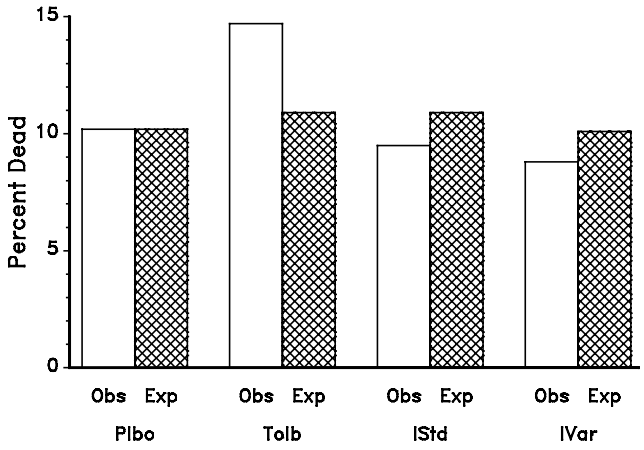
Demographic variables
Age
Sex
Race

History variables
Digitalis use

Baseline variables
ECG abnormalities
Systolic BP
Diastolic BP
Serum cholesterol
Serum creatinine
Fasting blood glucose
Relative body wt
Visual acuity
Vascular calcification

30 University Group Diabetes Program

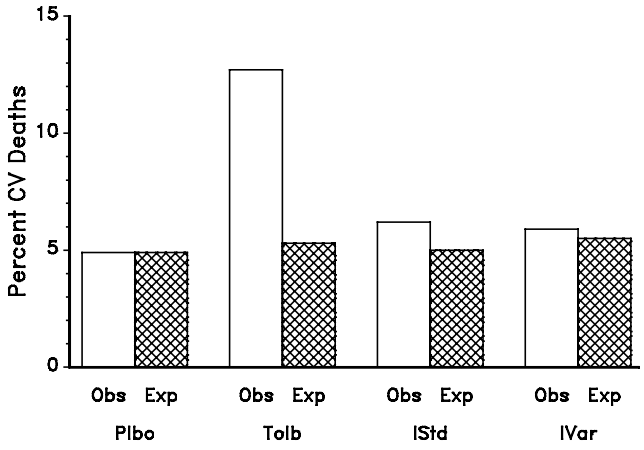
Observed and adjusted mortality (as of 7 Oct 1969)



Shaded bars correspond to adjusted control-treated mortality assuming the same baseline characteristics as those observed for the indicated treatment group[56]

30 University Group Diabetes Program

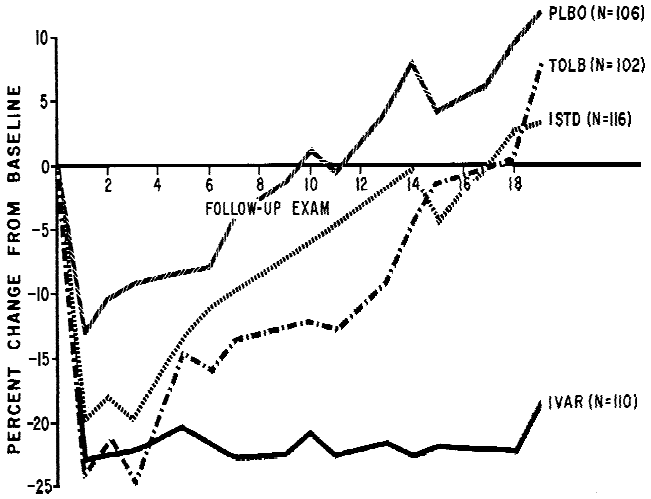
Observed and adjusted CV mortality (as of 7 Oct 1969)



Shaded bars correspond to adjusted control-treated mortality assuming the same baseline characteristics as those observed for the indicated treatment group[56]

30 University Group Diabetes Program

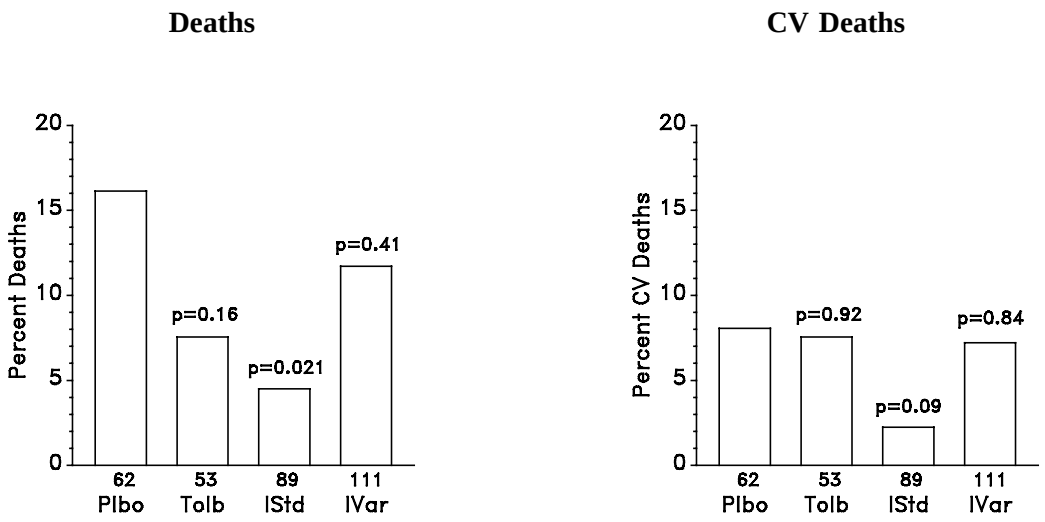
Fasting blood glucose levels for cohort completing 4.75 years of followup (as of 7 Oct 1969)



Reference 56

30 University Group Diabetes Program

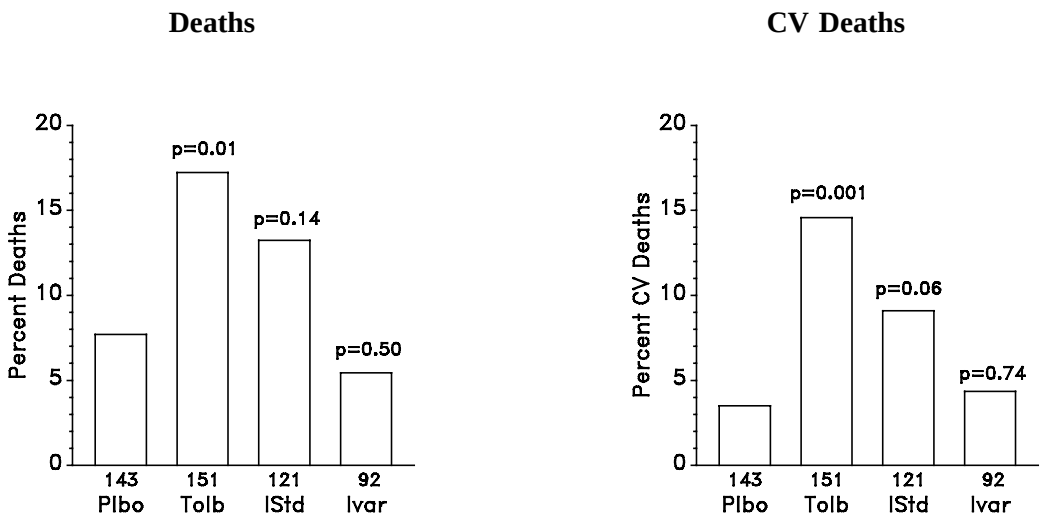
Mortality for low or intermediate adherers (as of 7 Oct 1969)



Reference 56

30 University Group Diabetes Program

Mortality for high adherers (as of 7 Oct 1969)



Reference 56

30 University Group Diabetes Program

Deaths by clinic (as of 7 Oct 1969)

	Plbo	Tolb	IStd	IVar	Deaths	Total
Baltimore	0.0	4.5	0.0	0.0	**1**	**87**
Cincinnati	30.4	31.8	16.7	23.8	**23**	**90**
Cleveland	5.3	5.6	0.0	10.0	**4**	**77**
Minneapolis	13.6	33.3	20.8	8.3	**18**	**94**
New York	13.6	10.0	9.5	13.6	**10**	**85**
Williamson	8.7	18.2	13.0	12.5	**12**	**92**
Birmingham	15.4	18.2	0.0	0.0	**4**	**49**
Boston	6.7	29.4	12.5	6.7	**9**	**63**
Chicago	9.1	0.0	8.3	9.1	**3**	**46**
St. Louis	10.0	0.0	8.3	0.0	**2**	**44**
San Juan	0.0	0.0	7.7	7.7	**2**	**52**
Seattle	0.0	0.0	9.1	0.0	**1**	**44**
Total	**10.2**	**14.7**	**9.5**	**8.8**	**89**	**823**

Reference 56

30 University Group Diabetes Program

CV deaths by clinic (as of 7 Oct 1969)

	Plbo	Tolb	IStd	IVar	Deaths	Total
Baltimore	0.0	4.5	0.0	0.0	**1**	**87**
Cincinnati	8.7	31.8	16.7	19.0	**17**	**90**
Cleveland	0.0	5.6	0.0	5.0	**2**	**77**
Minneapolis	9.1	25.0	8.3	8.3	**12**	**94**
New York	13.6	10.0	0.0	0.0	**5**	**85**
Williamson	4.3	13.6	8.7	12.5	**9**	**92**
Birmingham	0.0	18.2	0.0	0.0	**2**	**49**
Boston	6.7	23.5	6.3	6.7	**7**	**63**
Chicago	9.1	0.0	8.3	9.1	**3**	**46**
St. Louis	0.0	0.0	8.3	0.0	**1**	**44**
San Juan	0.0	0.0	7.7	0.0	**1**	**52**
Seattle	0.0	0.0	9.1	0.0	**1**	**44**
Total	**4.9**	**12.7**	**6.2**	**5.9**	**61**	**823**

Reference 56

Chronology

Yr	Mo	Day	Event
1959	Jun		1st meeting of investigators (7 clinics and coordinating center)
1960	Sep		Start of NIH
1961	Feb		Enrollment of 1st patient
1962	Sep		Addition of phenformin; 5 new clinics added
1966	Feb		Patient enrollment completed
1969	Jun	6	Investigators vote to stop use of tolbutamide
1969	Oct		Tolbutamide treatment stopped

30 University Group Diabetes Program

Chronology

Yr	Mo	Day	Event
1970	May	20	Tolbutamide results on Dow Jones ticker tape
1970	May	21-22	Wall Street Journal, Washington Post, New York Times articles on tolbutamide
1970	Jun	14	Tolbutamide results presented at ADA, St. Louis
1970	Oct		FDA distributes bulletin supporting findings
1970	Nov		Tolbutamide results published in **Diabetes**
1970	Nov		Committee for the Care of Diabetic (CCD) formed
1971	Apr		Feinstein criticism of UGDP published
1971	May	16	Investigators vote to stop phenformin
1971	Jun		FDA outlines labeling changes for sulfonylureas
1971	Aug	9	Preliminary report on phenformin published
1971	Sep	14	NIH Associate Director asks president of Biometrics Society to appoint committee to review UGDP
1971	Sep	20	Schor criticism of UGDP published
1971	Sep	20	Cornfield defense of UGDP published
1971	Oct	7	CCD petitions FDA to rescind proposed label change
1972	May		FDA reaffirms position on proposed labeling change
1972	Jun	5	FDA commissioner denies Oct 1971 request to rescind proposed label change
1972	Jul	13	CCD requests evidentiary hearing before FDA on proposed labeling changes
1972	Aug	3	Request for hearing denied
1972	Aug	11	CCD asks US District Court of Massachusetts to enjoin FDA from implementing labeling change
1972	Aug	30	Request denied by Judge Campbell of US District Court of Massachusetts
1972	Aug		Biometrics Society Committee starts work
1972	Sep		Seltzer criticism of UGDP published
1972	Oct	17	Motion for injunction against label change filed in US District Court of Massachusetts by CCD
1972	Oct		Response to Seltzer critique published
1972	Nov	3	Temporary injunction order granted by Judge Murray of US District Court of Massachusetts
1972	Nov	7	Preliminary injunction against proposed label change granted by US District Court of Massachusetts
1973	Jul	31	Preliminary injunction vacated by Judge Coffin of the US Court of Appeals for the First Circuit. Case remanded to the FDA.
1973	Oct		FDA hearing on labeling of oral agents

30 University Group Diabetes Program

Chronology

Yr	Mo	Day	Event
1974	Feb		FDA circulates proposed labeling change
1974	Mar-Apr		FDA holds meeting on proposed labeling change, then postpones action on change pending report of Biometrics Committee
1974	Sep	18-20	Testimony taken concerning use of oral hypoglycemic agents before the US Senate Select Committee on Small Business, Monopoly Subcommittee
1975	Jan	31	Additional testimony concerning use of oral hypoglycemic agents before the US Senate Select Committee on Small Business, Monopoly Subcommittee
1975	Feb	10	Biometrics Committee report published
1975	Feb		Final report on phenformin published
1975	Jul	9-10	Additional testimony concerning use of oral hypoglycemic agents before the US Senate Select Committee on Small Business, Monopoly Subcommittee
1975	Aug		Termination of patient followup
1975	Sep	30	CCD files suit against David Mathews, Secretary of Health, Education and Welfare et al, for access to UGDP raw data under Freedom of Information Act (FOIA) in US District Court of Columbia
1975	Oct	14	Ciba-Geigy files suit against David Mathews, Secretary of Health, Education and Welfare et al, for access to UGDP raw data under the FOIA in US District Court of Southern District of New York
1975	Dec		FDA announces intent to audit UGDP results
1976	Feb	5	US District Court of Columbia rules UGDP raw data not subject to FOIA
1976	Feb	25	CCD files appeal of Feb 5 decision in US Court of Appeals for the District of Columbia Circuit
1976	Sep		FDA audit of UGDP begins
1976	Oct		FDA Endocrinology and Metabolism Advisory Committee recommends removal of phenformin from market

30 University Group Diabetes Program

Chronology

Yr	Mo	Day	Event
1977	Mar	8	US District Court for the Southern District of New York rejects Ciba-Geigy request for UGDP raw data
1977	Apr	22	Health Research Group (HRG) of Washington, DC, petitions Secretary of HEW to suspend phenformin from market under imminent hazard provision of law
1977	May	6	FDA begins formal proceedings to remove phenformin from market
1977	May	13	FDA holds public hearing on petition of HRG
1977	Jul	25	Secretary of HEW announces decision to suspend New Drug Applications (NDAs) for phenformin
1977	Aug		CCD requests that US District Court of Columbia issue an injunction against HEW order to suspend NDAs for phenformin
1977	Oct	21	CCD request to US District Court of Columbia for injunction against HEW order to suspend NDAs for phenformin denied
1977	Oct	23	NDAs for phenformin suspended by Secretary of HEW under imminent hazard provision of law
1977	Dec		UGDP announces release of data listings for individual patients
1978	Jan		Appeal of Oct 21, 1977, phenformin ruling filed by CCD in US Court of Appeals for the District of Columbia Circuit
1978	Jul	7	Preliminary report on insulin findings published
1978	Jul	11	Judges Leventhal and MacKinnon of US Court of Appeals for the District of Columbia Circuit rule that public does not have right to UGDP raw data under the FOIA. Judge Bazelon dissents
1978	Jul	25	CCD petitions US Court of Appeals for District of Columbia Circuit for rehearing on July 11 ruling
1978	Oct	17	Petition for rehearing by US Court of Appeals for the District of Columbia Circuit denied
1978	Nov	14	Results of FDA audit of UGDP announced
1978	Nov	15	Commissioner of FDA orders phenformin withdrawn from market
1979	Jan	15	CCD petitions the US Supreme Court for writ of certiorari to the US Court of Appeals for the District of Columbia Circuit
1979	Apr	10	Appeal of Oct 21, 1977, ruling denied
1979	May	14	Writ of certiorari granted
1979	Oct	31	UGDP case of Forsham vs Harris argued before US Supreme Court

30 University Group Diabetes Program

Chronology

Yr	Mo	Day	Event
1980	Mar	3	US Supreme Court holds that HEW need not produce UGDP raw data in split (6 to 2) decision
1980	Apr		NIH grant support for UGDP expires
1982	Nov		Final report on insulin results published
1982	Nov		UGDP deposits patient listings at National Technical Information Service
1984	Mar	16	Revised label for sulfonylurea class of drugs released

Reference 35

Tolbutamide chronology

1969 Tolbutamide stopped

1970 Results presented; published
1971 FDA proposes labeling change
1972 Biometrics Society Committee formed

1973 Hearing on labeling change
1974 Hearings before US Senate Select Small Business Committee
1975 Biometrics Committee report published; CCD files suit under FOIA for access to raw data

1976 Suit denied; appeal filed; FDA starts UGDP audit
1977 Sec'y HEW announces decision to remove phenformin from market
1978 CCD request denied; petitions for rehearing on FOIA request; request denied; results of FDA audit announced; FDA Commissioner orders phenformin removed from market

1979 CCD petitions Supreme Court to hear case on FOIA; petition granted; case argued
1980 Supreme Court rules against CCD FOIA request (6 to 2)

1984 Label insert for sulfonylurea drugs issued by FDA

Reference 35

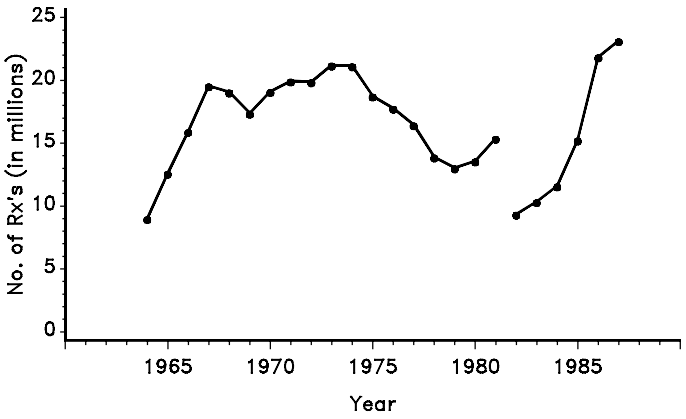
30 University Group Diabetes Program

Wholesale costs (millions of $)

Year	Phenformin	Tolbutamide	All oral agents
1964	2.3	22.4	28.9
1965	3.9	28.2	38.6
1966	3.5	35.1	47.2
1967	7.1	38.1	58.0
1968	7.9	35.3	58.9
1969	8.4	28.7	54.5
1970	10.5	29.0	62.1
1971	14.0	24.7	65.0
1972	15.2	21.8	65.8
1973	26.7	34.8	104.8
1974	28.3	34.1	112.0
1975	26.7	31.2	109.3
1976	25.2	28.4	114.9
1977	17.1	31.8	119.8
1978		30.9	109.8
1979		26.4	110.5

30 University Group Diabetes Program

Oral hypoglycemic prescriptions



Cook County Hospital (circa 1987)

Prescription	%
Diet	9.9
Insulin	55.0
Oral agent	35.1
Total	**100.0**
Number	111

30 University Group Diabetes Program

Antidiabetic drugs (1988 PDR)

Compound	Name	Manufacturer
Acetohexamide	Dymelor	Lilly
Chlorpropamide	Diabinese Glucamide	Pfizer Lemmon
Glipizide	Glucotrol	Roerig
Glyburide	DiaBeta Micronase	Hoechst-Roussel UpJohn
Tolazimide	Ronase Tolinase	Reid-Powell UpJohn
Tolbutamide	Orinase	UpJohn

Label insert contraindications

- Known hypersensitivity or allergy to drug
- Diabetic ketoacidosis
- Type I diabetes
- Warning of CV mortality based on UGDP (*Diabetes* 19 Suppl 2:247-830, 1970)
- Patients should be so informed
- Warning may apply to other sulfonylurea oral hypoglycemic agents in view of similar chemical structures

30 University Group Diabetes Program

Label insert warning

Special Warning of Increased Risk of Cardiovascular Mortality: The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with noninsulin-dependent diabetes. The study involved 823 patients who were randomly assigned to one of four treatment groups (DIABETES, 19 supp 2:747-830, 1970).

UGDP reported that patients treated for five to eight years with diet plus a fixed dose of tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately 2 1/2 times that of patients with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show increase in overall mortality. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and advantages of TOLINASE and of alternative modes of therapy.

Although only one drug in the sulfonylurea class (tolbutamide) was included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other oral hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

30 University Group Diabetes Program

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31 Coronary Drug Project

31 Coronary Drug Project

Purpose

To evaluate the efficacy of lipid influencing drugs in prolonging life in men with a prior history of myocardial infarction

Objectives

1. To evaluate the efficacy of several lipid-influencing agents in the long-term therapy of coronary heart disease in men of ages 30 through 70 with previous ECG-document myocardial infarction

2. To obtain information on the natural history and clinical course of coronary heart disease

3. To develop more advanced methodology for the design and conduct of long-term, large, multicenter clinical trials

CDP statistics

Cost	$40,000,000
Source of support	NHLBI
Mode of support	Grants
No of patients enrolled	8,341
Period of recruitment	3.5 years
Length of followup	5 year minimum
Length of study	15 years
Number of centers	60

31 Coronary Drug Project

Design features

- Random treatment assignment
- Double-masked treatment administration
- Placebo controlled
- Multicenter; common treatment protocol
- 5 year minimum followup
- Common closing date

Eligibility criteria

- Male
- Age 30 through 64 (subsequently raised to 70)
- History of MI
- NYHA class I or II
- Consent

Treatment regimens

	Drug	Dose/day
ESG1	Estrogen	2.5 mg
ESG2	Estrogen	5.0 mg
CPIB	Clofibrate	1.8 gm
DT-4	Dextrothyroxine	6.0 mg
NICA	Nicotinic acid	3.0 gm
Plbo	Lactose placebo	3.0 gm

31 Coronary Drug Project

Sample size specifications

α = 0.01 (type I error, 1-sided)
β = 0.05 (type II error)
P_c = 0.30 (5 yr death rate for plbo treated group)
P_t = 0.225 (5 yr death rate for test treated group)
Do = 0.30 (5 yr loss rate per treatment group)

Computed sample size:

CPIB	1,117
DT-4	1,117
ESG1	1,117
ESG2	1,117
NICA	1,117
PLBO	2,793
Total	**8,378**

31 Coronary Drug Project

Geographic location of participating sites

Participating centers

Center	No
Clinical centers	55*
Coordinating center	1
Central laboratory	1
ECG reading center	1
Drug distribution center	1
Project office	1
Total centers	**60**

*Including 2 that resigned

31 Coronary Drug Project

Organizational units

- Policy Board
- Data Monitoring Committee
- Steering Committee
- Executive Committee
- Treatment Criteria Committee
- Natural History Committee
- Laboratory Committee
- Mortality Classification Committee
- Editorial Review Committee

Randomization procedure

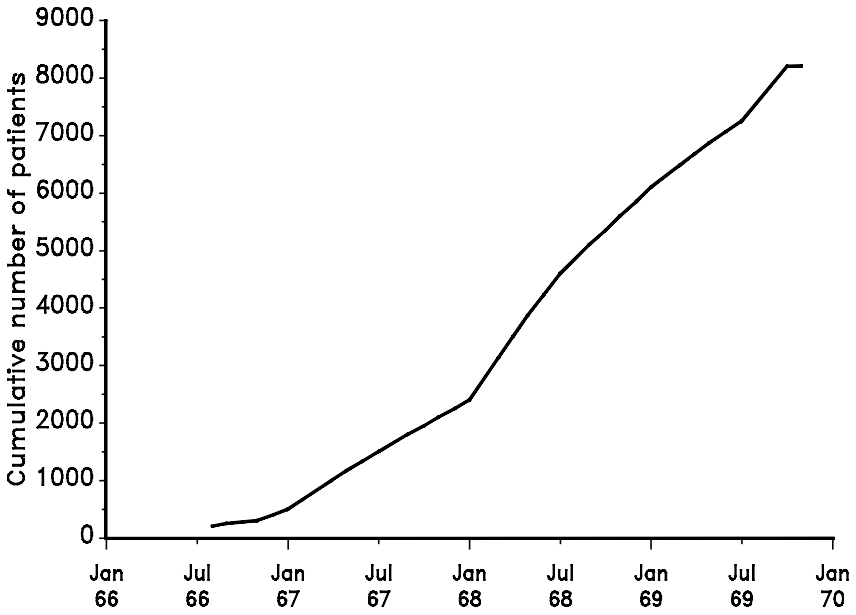
- Randomization schedule prepared and administrated by the Coordinating Center
- Assignments stratified by clinic and by risk group (2 groups) within clinic
- Assignments made in the ratio of 1:1:1:1:1:2.5
- Assignments within strata blocked after every 15 assignments
- Assignments sent to clinics in sealed envelopes after receipt of required eligibility and baseline data
- Once envelope opened at clinic, assignment counted and person for whom issued counted as enrolled

Observed sample size

	Risk 1	Risk 2	Total
ESG1	729	372	1,101
ESG2	740	379	1,119
CPIB	730	373	1,103
DT-4	731	379	1,110
NICA	737	382	1,119
Plbo	1,831	958	2,789
Total	**5,498**	**2,843**	**8,341**

31 Coronary Drug Project

Cumulative enrollment



31 Coronary Drug Project

Outcome measures

Primary
Death

Secondary
CV deaths
Coronary deaths
Myocardial infarction
Stroke
Acute coronary insufficiency
Transient ischemic attacks
Peripheral arterial occlusion
Peripheral arterial embolism
Pulmonary embolism
Arterial aneurysm

Tertiary
Cardiomegaly
Congestive heart failure
Intermittent claudication
Thrombophlebitis

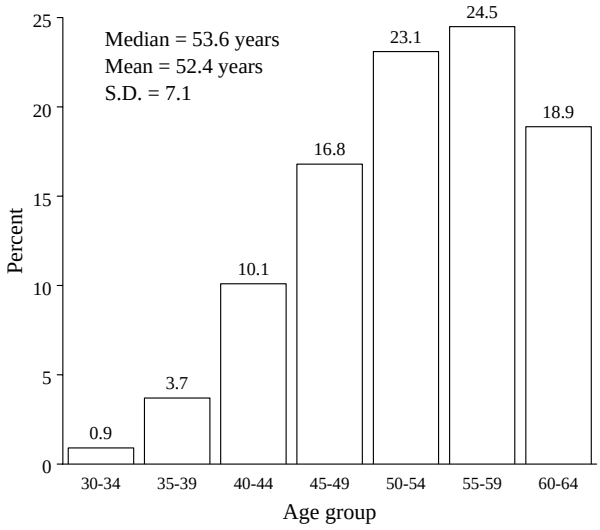
31 Coronary Drug Project

Visit schedule

Mos fr entry	Visit	Purpose
-2	BL 1	Baseline data; eligibility assessment
-1	BL 2	Baseline data; eligibility assessment
0	BL 3	Baseline data; eligibility assessment; randomization; start treatment
1	Trt 1	Increase dose from 3 to 6 caps/day
2	Trt 2	Increase dose from 6 to 9 caps/day
4	FU 1	Followup evaluation and data collection
8	FU 2	Followup evaluation and data collection
12	FU 3	Followup evaluation and data collection
16	FU 4	Followup evaluation and data collection
20	FU 5	Followup evaluation and data collection
24	FU 6	Followup evaluation and data collection
28	FU 7	Followup evaluation and data collection
32	FU 8	Followup evaluation and data collection
36	FU 9	Followup evaluation and data collection
40	FU 10	Followup evaluation and data collection
44	FU 11	Followup evaluation and data collection
48	FU 12	Followup evaluation and data collection
52	FU 13	Followup evaluation and data collection
56	FU 14	Followup evaluation and data collection
60	FU 15	Followup evaluation and data collection
	CO 1	Stop treatment and data collection
	CO 2	Post treatment data collection

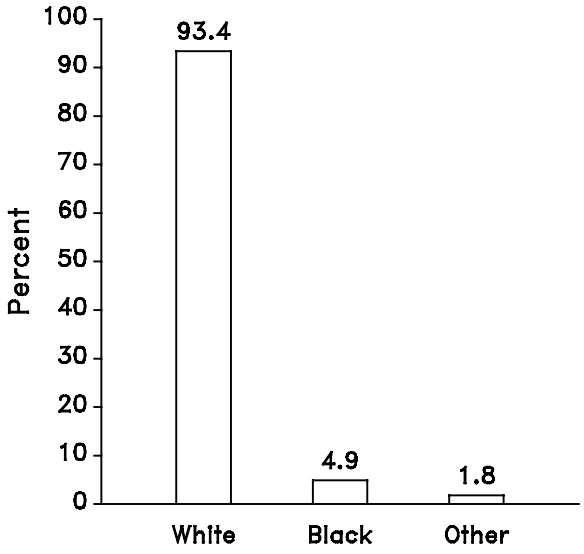
31 Coronary Drug Project

Age distribution on entry



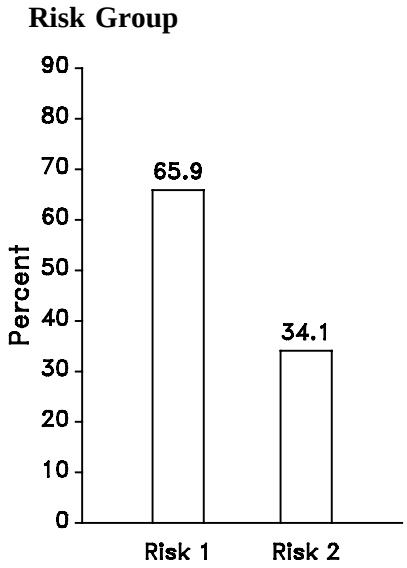
31 Coronary Drug Project

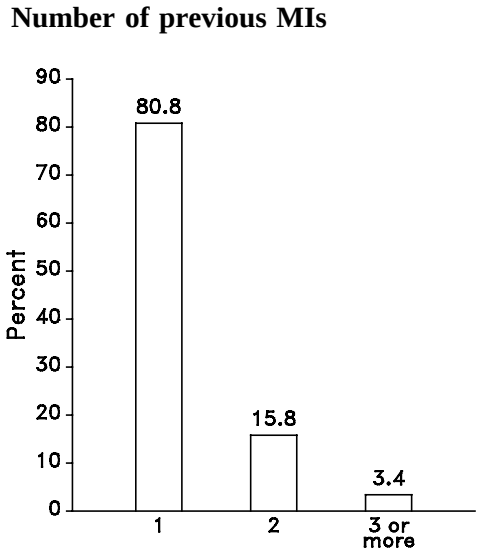
Race distribution



31 Coronary Drug Project

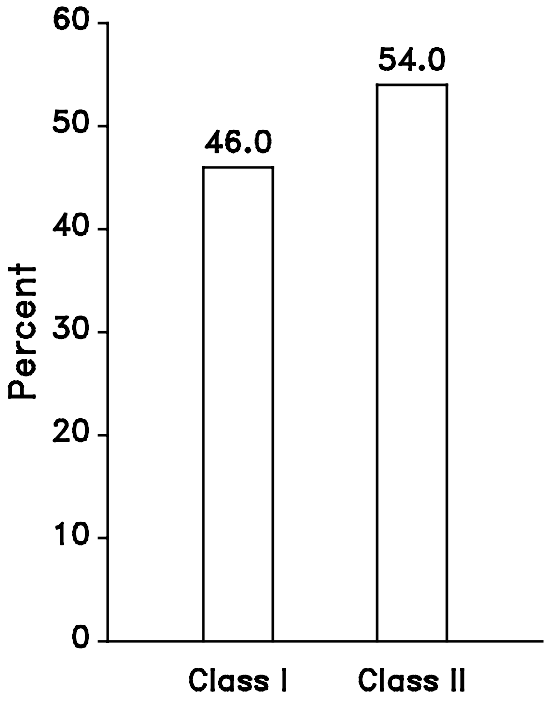
Risk distribution





31 Coronary Drug Project

New York Heart Association class on entry



31 Coronary Drug Project

Age distribution on entry by treatment group

Age	ESG1	ESG2	CPIB	DT-4	NICA	Plbo
30 - 44	15.9	14.8	14.8	15.4	12.8	14.8
45 - 54	41.8	40.3	41.7	42.7	42.2	42.2
55 - 59	26.0	24.3	24.8	25.3	24.4	23.5
≥ 60	16.3	20.6	18.7	16.6	20.6	19.5
Total	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**
n	**1,101**	**1,119**	**1,103**	**1,110**	**1,119**	**2,789**

p = 0.207; based on chi-square with 15 df

Risk factors on entry by treatment group

Risk factors†	ESG1	ESG2	CPIB	DT-4	NICA	Plbo
0	27.9	28.0	26.8	28.9	28.1	29.3
1	45.0	42.7	42.8	42.3	42.8	40.9
2	17.8	18.8	19.8	19.8	21.5	20.0
3	7.7	8.1	8.1	7.4	5.6	7.7
4 or 5	1.6	2.4	2.5	1.6	2.0	2.1
Total	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**
n	**1,101**	**1,119**	**1,103**	**1,110**	**1,119**	**2,789**

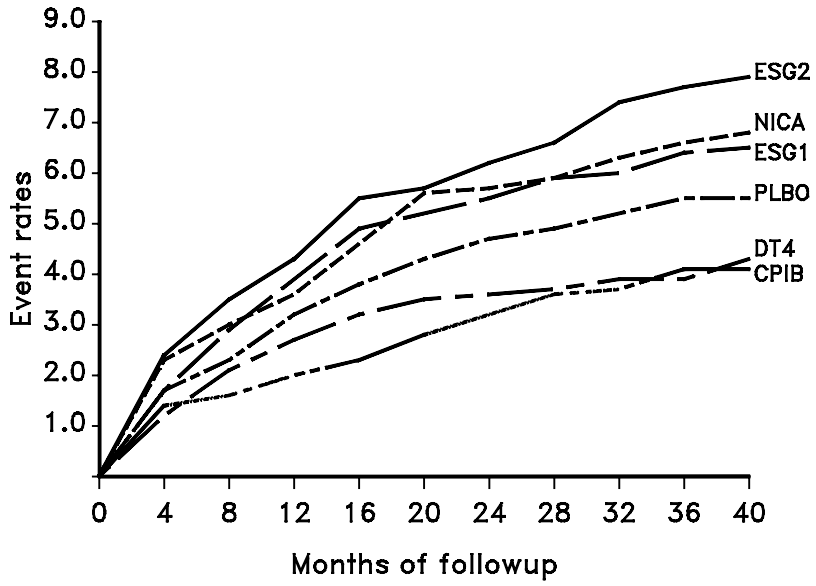
† *ST depression, suspect or definite cardiomegaly, suspect or definite intermittent claudication, diuretics use, cholesterol ≥ 250 mg/dl; p = 0.431; based on chi-square with 20 df*

31 Coronary Drug Project

Treatment terminations

	Reason	No of patients	Date
Premature			
DT-4	FEVBs at Bl	27	1970 May
ESG2	Excess mortality	1,011	1970 May
DT-4	Excess mortality	923	1971 Dec
ESG1	Excess mortality	882	1973 Mar
Scheduled			
CPIB	Scheduled end	822	1974 Oct
NICA	Scheduled end	846	1974 Oct
Plbo	Scheduled end	2,080	1974 Oct

Cumulative dropout rate

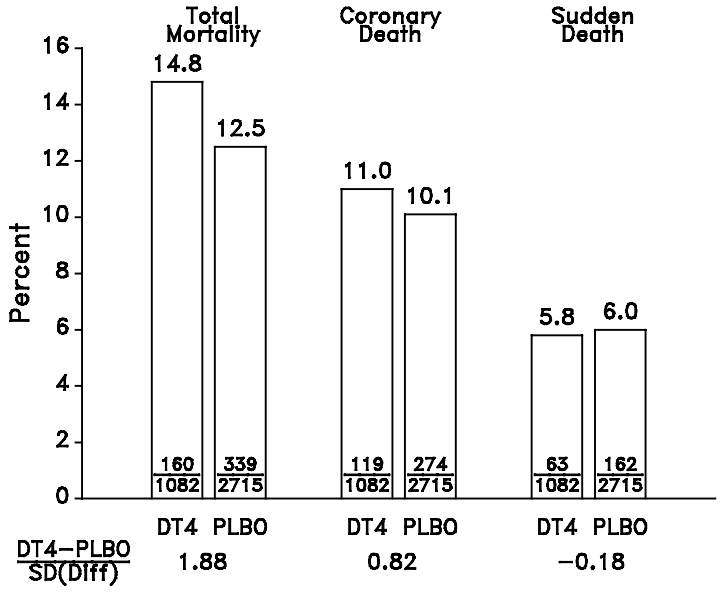


31 Coronary Drug Project

Treatment adherence

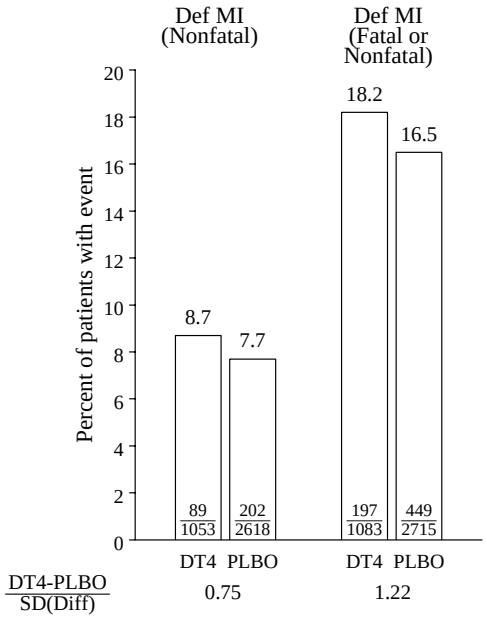
	ESG1	ESG2	CPIB	DT-4	NICA	Plbo
As of 1 Feb 1970						
0 caps	8.7	12.0	2.6	3.4	7.9	1.9
< 9 caps	33.2	43.8	10.6	13.4	23.3	9.1
As of 1 Aug 1971						
0 caps	17.8	7.0	4.1	7.2	13.5	3.7
< 9 caps	46.7	24.3	11.6	16.3	25.0	9.5

DT-4 - Placebo mortality



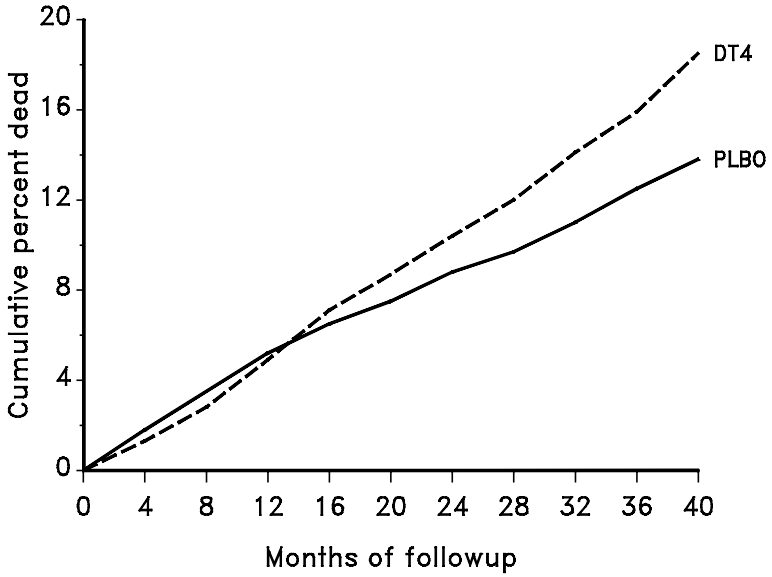
31 Coronary Drug Project

DT-4 - Placebo myocardial infarction



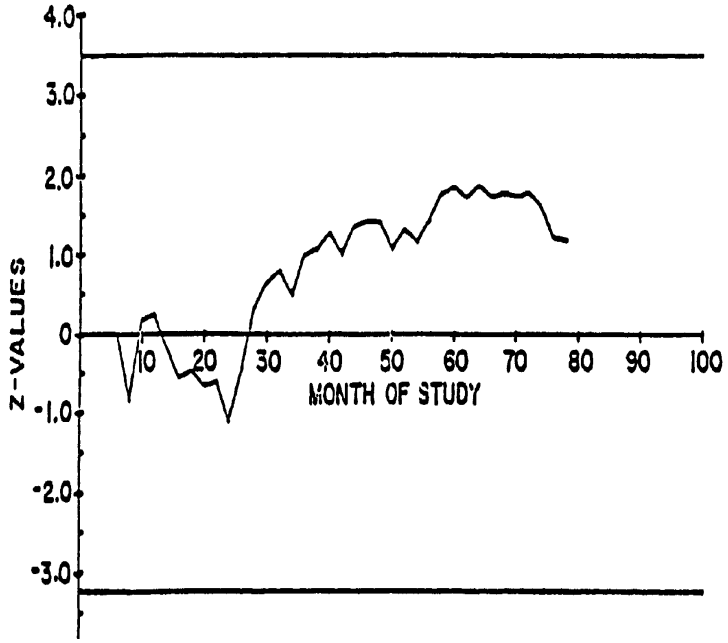
31 Coronary Drug Project

DT-4 and placebo cumulative mortality



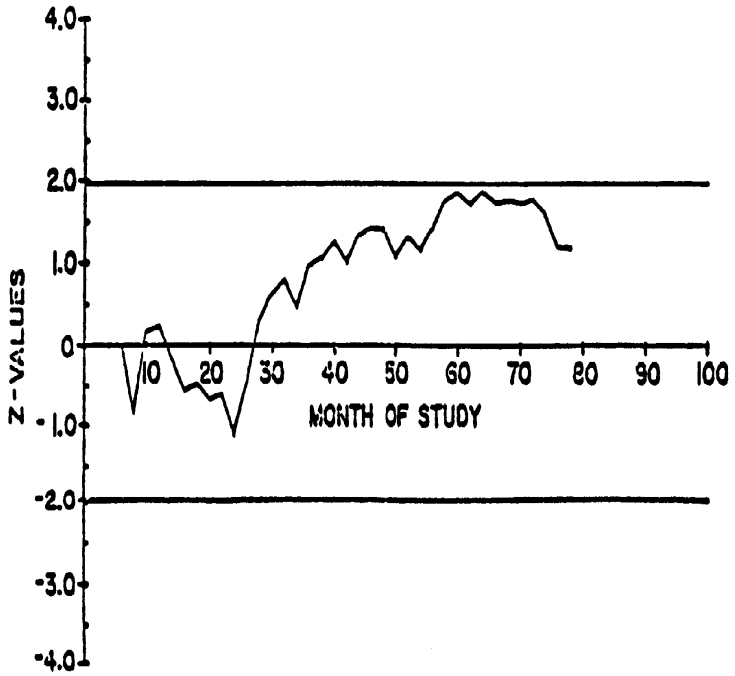
31 Coronary Drug Project

DT-4 - Placebo adjusted 5% monitoring bounds



31 Coronary Drug Project

DT-4 - Placebo conventional 5% monitoring bounds



31 Coronary Drug Project

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32 Foscarnet-Ganciclovir CMV Retinitis Trial

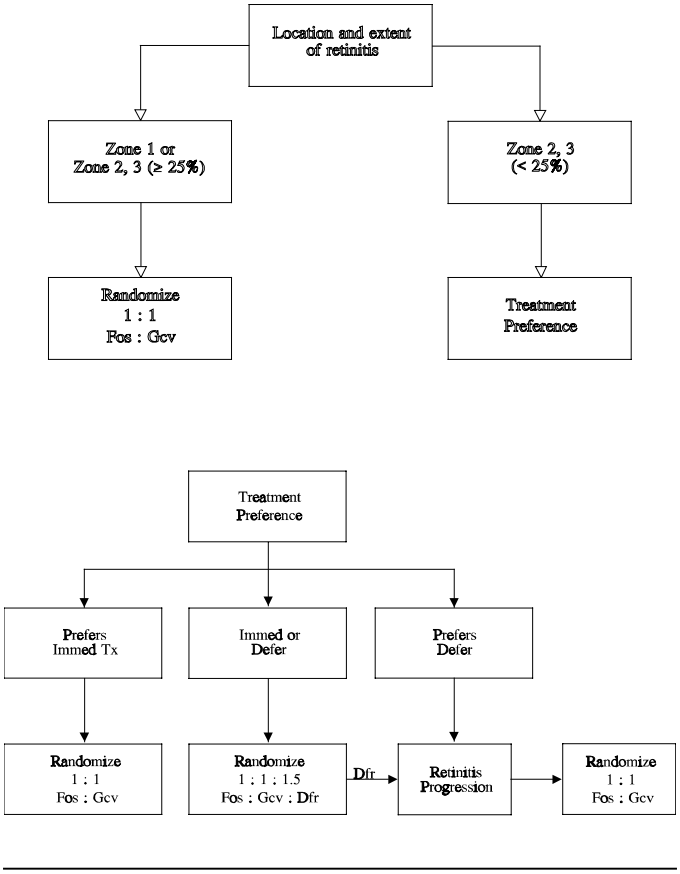
32 Foscarnet-Ganciclovir CMV Retinitis Trial

SOCA dates

25	Mar	88	Release of RFA from NEI
15	Aug	88	Funding initiated
17	Mar	89	Release of RFP from CC for clinics
15	Jun	89	Clinics selected
17	Nov	89	1st meeting of SOCA Research Group (Baltimore)
5	Jan	90	1st startup patient enrolled (Chicago)
13	Mar	90	1st trial patient enrolled
14	Dec	90	Reinduction dosage for foscarnet modified
30	Aug	91	Enrollment into stratum 1 closed
7	Oct	91	PDMB recommendation to suspend treatment protocol
11	Oct	91	Results presented to SOCA investigators

32 Foscarnet-Ganciclovir CMV Retinitis Trial

Design schematic



Objective

To evaluate the relative safety and efficacy of initiating treatment of AIDS-related CMV retinitis with ganciclovir vs foscarnet as assessed by differences in retinitis progression, visual function, or death

32 Foscarnet-Ganciclovir CMV Retinitis Trial

Ganciclovir and foscarnet

	Gcv	Fos
Generic name	Ganciclovir	Foscarnet
Trade name	Cytovene®	Foscavir®
Manufacturer	Syntex	Astra
Recommended dosage		
Induction	5 mg/kg/ 2x / day (2 weeks)	60 mg/kg 3x / day (2 weeks)
Maintenance	5 mg/kg/day	90-100 mg/kg/day
Cost (1991 figures)		
Induction	$58/day	$114/day
Maintenance	$29/day	$63/day
Annual cost (1991 figures)	$11,000	$23,900

Design summary

Test treatments: 2
Ganciclovir
Foscarnet

Control treatments: 0

Treatment structure: Parallel

Treatment preference option: Patient
Option: Immediate or deferred trt

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Design summary

Treatment assignment:	Random
Stratification variables:	2 (clinic & lesion)
Number of strata:	24 (12 x 2)
Blocking:	Within strata
Masking:	Fundus photo graders, yes Treating phy, no Patient, no Data collector, no PDMB, no
Sample size:	Goal; 240 Achieved; 240
Design outcome measures:	3 Retinitis progression Visual function Death
Sites:	Clinics; 12 Coordinating center Fundus photograph reading center Other resource centers; 3
Followup:	To death or a minimum of 1-year
Close-out design:	Common closing date

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SOCA cost (thousands of dollars)

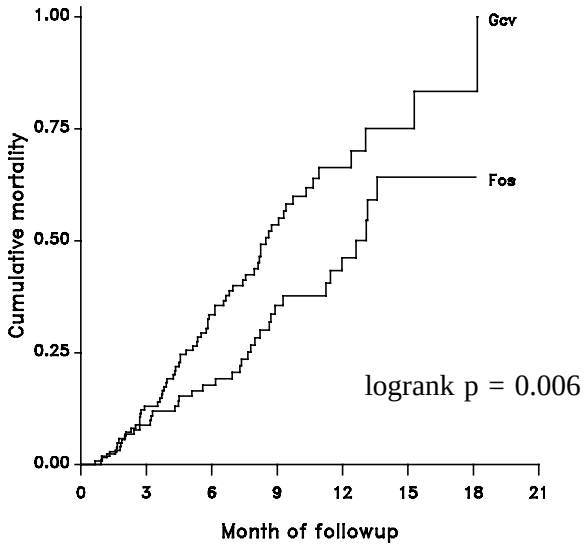
	Clinics	CC	FPRC	Chm off	Other	Total
Yr 1	76	631	190	415	0	1,312
Yr 2	1,486	971	215	377	15	3,064
Yr 3	2,229	1,031	242	359	184	4,045
Total	**3,791**	**2,633**	**647**	**1,151**	**199**	**8,421**

Interim mortality results

Date	Number enrolled	RR (G:F)	p
31 Aug 90	72	0.35	0.113
31 Oct 90	106	0.52	0.166
31 Dec 90	135	0.92	0.589
28 Feb 91	174	1.14	0.684
31 May 91	223	1.40	0.212
31 Jul 91	242	1.63	0.025
13 Sep 91	242	1.57	0.024
7 Oct 91	254	1.62	0.013

32 Foscarnet-Ganciclovir CMV Retinitis Trial

Mortality; Kaplan-Meier plot



Mortality by treatment exposure

	Adj RR	n	% time on Gcv	% time on Fos
Fos (reference)	1.00	61	0	97
Fos to Gcv	0.90	39	54	41
Gcv	2.04	105	94	0
Gcv to Fos	0.99	14	64	29

32 Foscarnet-Ganciclovir CMV Retinitis Trial

Sample size issues and strategies

Issues
- Surrogate vs clinical outcome
- Length of followup
- Patient access
- Homogeneity vs heterogeneity
- When to stop

Strategies
- Draw upon expertise and credibility as designers and executors of multicenter trials
- Clinical relevance and real world treatment protocol
- Big and heterogeneous rather than small and homogeneous
- Forge alliances between infectious disease and eye people

Sample size specifications

240 total (not counting startup patients)

Specification
$\alpha = 0.05$, 2-sided
$\beta = 0.1$

1-yr mortality = 0.65
1-yr visual loss ($\leq$ 20/200) = 0.40
6-mo retinitis progression = 0.42
10% jackup factor for loss of precision

Detectable difference (with power of 0.90)
1-yr mortality = 0.23
1-yr visual loss = 0.20
6-mo retinitis progression = 0.21

Method of calculation
Blackwelder WC, Chang MA: Sample size for "proving the null hypothesis", *Controlled Clinical Trials*, 5:97-105, 1984[439]

32 Foscarnet-Ganciclovir CMV Retinitis Trial

Design politics

Issues
- Children and adults
- IV drug users
- Females
- Affirmative action re blacks and other minorities
- Patient preference

Strategies
- Pay attention to the politics of enrollment!
- Local clinic option re children (13 to 18)
- No active IV drug users
- Females, if not pregnant or lactating on entry
- Neutral on ethnic makeup
- Patient preference allowed

FDA issues and strategies

Issues
- Designation of a single primary outcome
- Formal stopping rule
- Method of sample size calculation
- Specification of analysis procedures

Strategies
- Reiterate reasons for multiple outcomes
- Indicate reasons for not having formal stopping rules
- Demonstrate that FDA recommended method of sample size calculation yields same results as the one used
- Outline monitoring approach
- Indicate neutrality re NDA process

32 Foscarnet-Ganciclovir CMV Retinitis Trial

Clinic selection issues and strategies

Issues
- Who selects and how
- Selection limited to sites with ACTG
- ID person or ophthalmologist as clinic director
- Method of payment
- Additional support for ACTG

Strategies
- CC responsible for solicitation and selection
- Selection not limited to ACTG sites
- Ophthalmologist as clinic director
- CC contracts with clinics; negotiated sums
- Added $2,500 on enrollment and up to $2,500 additional to cover justified expenses

Money issues and strategies

Issues
- Coverage of patient care
- Buy or receive drugs
- Fiscal autonomy vs fiscal dependence
- How much money do we really have
- CC vs NEI in contracting process
- Pharmacist costs and other ACTG costs

Strategies
- 3rd party payments for ordinary care; study pays for those things required over and above ordinary care
- Drugs supplied by manufacturer free of charge
- Balancing act re fiscal autonomy
- CC and SHPH not an extension of NEI
- Clinics provided fixed sum for pharmacist and costs for special tests and procedures; $2,500 on entry and added $2,500 if needed

32 Foscarnet-Ganciclovir CMV Retinitis Trial

Sequence of events leading to and following recommendation

22	Jul	91	CC staff on state of alert (Mon)
28	Aug	91	Special mtg of PDMB; Chicago (11:00am - 4:00pm; Wed)
6	Sep	91	Mtg at CC with Syntex, Astra, and FDA (Fri)
12	Sep	91	Syntex agreed to reduced review period in exchange for data listing; similar agreement signed by Astra 13 Sep 91 (Fri)
19	Sep	91	Data listings sent to Syntex and Astra (Thu)
7	Oct	91	Mtg of PDMB; Baltimore, 10am - 4pm (Mon); conference call with representatives of Astra, Syntex, and FDA regarding PDMB recommendation (6:00pm; Mon)
8	Oct	91	SOCA investigators phoned to notify of PDMB recommendation and to invite to 11 Oct 91 (Tue)
9	Oct	91	Draft manuscript sent to Astra, BW, Syntex and FDA (Wed)
9	Oct	91	Conference call with ACTG Executive Committee (2:00pm; Wed)
11	Oct	91	Results presented to SOCA investigators; Baltimore (9:00am - 1:00pm; Fri)
11	Oct	91	Penultimate draft of clinical alert and press release reviewed by Officers of SOCA (1:00pm - 6:00pm, Fri)
17	Oct	91	CC notified that all patients contacted (Thu)
17	Oct	91	Clinical alert (40,000) mailed via NEI (Thu)
18	Oct	91	Press announcement distributed to media via NEI; embargoed to Mon 1:30pm 21 Oct 91 (Fri)
21	Oct	91	Results announced at NIH press conference; 12:30pm, NIH Clinical Center, Masur Auditorium (Mon)
29	Oct	91	Manuscript sent to NEJM (Tue)
30	Oct	91	Manuscript sent to SOCA investigators (Wed)
30	Oct	91	Manuscript sent to Astra, BW, Syntex, and FDA (Tue)
30	Oct	91	FDA officials briefed at CC (8:30 - 10:00am) (Wed)
4	Nov	91	Manuscript accepted for review by NEJM (Mon)
13	Nov	91	Manuscript conditionally accepted for publication
20	Nov	91	Revised manuscript sent to NEJM
22	Nov	91	Manuscript accepted for publication

32 Foscarnet-Ganciclovir CMV Retinitis Trial

Informed people and groups

Group/person	Date
CC staff	24 Jul 91
Study Chm	5 Aug 91
Chm PDMB	7 Aug 91
All SOCA officers	16 Aug 91
NEI Director	16 Aug 91
PDMB members	28 Aug 91
NIAID Director	29 Aug 91
Astra, Syntex, FDA rep	6 Sep 91
NEJM editor	6 Sep 91
FDA commissioner	16 Sep 91
ACTG executive committee	9 Oct 91
SOCA investigators	11 Oct 91
IRBs	14 Oct 91
Patients	17 Oct 91
Clinical alert	18 Oct 91
Press conference	21 Oct 91

Local people and groups informed

- Respective deans and department chairmen of CC and Chm office
- Respective public relations office
- SHPH IRB, then Medicine IRB
- CC Department and School business offices
- Colleagues consulted for advice or help

32 Foscarnet-Ganciclovir CMV Retinitis Trial

What, when, and how to monitor

Issues
- Stopping rules
- Adjustment of p-values
- Masked monitoring report
- Frequency of looks
- Representation

Strategies
- No formal stopping rules; no p-value adjustment
- Monitoring reports not masked
- Meet semiannually; more often if necessary; mailed interim reports between meetings
- Officers sit as non-voting members; drug companies not represented

Recommendation and rationale

Recommendation

Suspend the treatment protocol; continue followup

Rationale
- Difference large and probably reproducible
- No plausible explanation for difference other than treatment assignment
- No redeeming features of ganciclovir with regard to progression of retinitis, visual function, or morbidity
- Conclusion not likely to be different if trial continued to its scheduled end

Implementation issues

Issue	Action
When?	Starting 11 Oct
How?	Mtg in Baltimore
Who?	Study clinics
Reps from drug industry?	Yes
Mode of data presentation?	Slide
Draft manuscript distributed?	Yes
Press announcement?	No

32 Foscarnet-Ganciclovir CMV Retinitis Trial

Counting and analysis rules

- Primary analyses by original treatment assignment, regardless of course of treatment
- Patient considered to be randomized when assignment revealed to clinic
- Followup timed from date of randomization
- All deaths and morbid events counted regardless of when they occurred during the course of followup
- 20 startup patients excluded

SOCA presentation and authorship policy

Presentations

- No public presentation until manuscript published
- Standard slide set provided to investigators
- Central review and clearance of all official study presentations

Authorship

- Corporate masthead listing
- Writing committee not named in manuscript

Manuscript preparation

Issue	Action
When to start?	After 28 Aug
Who writes?	Officers (4)
Database update?	Yes
Journal?	NEJM
Draft distribution?	Limited

32 Foscarnet-Ganciclovir CMV Retinitis Trial

Manuscript facts

Date started	29 Aug 91
No of iterations	40+
Major	10+
Minor	30+
Length	
Pages	31
Words	3,229
Tables	5
Figures	1
References	47
NEJM dates	
Date submitted	29 Oct 91
Date accepted for review	4 Nov 91
Date provisional accepted	13 Nov 91
Date of final acceptance	22 Nov 91
Publication	23 Jan 92

Manuscript QC and review procedures

Quality control procedures

- Death verification and vital status update
- Independent death count
- Independent replication of key analyses
- Frequent CC meetings
- All numbers and tables triple checked in NEJM submitted versions

Manuscript review procedures

- Major and minor internal reviews
- Signed review by SOCA officers for mailed copies
- Investigator review of penultimate version
- ACTG review of penultimate version

32 Foscarnet-Ganciclovir CMV Retinitis Trial

Manuscript distribution

Version	SOCA	Drug	FDA	ACTG	NEJM	Other
8 Oct 91	✓	✓	✓	✓		✓
29 Oct 91	✓	✓	✓		✓	
20 Nov 91					✓	

Clinical alert

Issues
- Should there be one?
- When should it be issued?
- Who should receive it?

Strategies
- Avoid factual errors and statements at odds with published paper
- Careful and repeated reviews
- Distribute from NEI
- Wide distribution

Press conference

Issues
- Should there be a press conference?
- When and where should it be held?
- Who should run it?
- Who should be there?

Strategies
- Hold until patients informed and clinical alert mailed
- Hold at NIH
- Run by NEI
- NIH and SOCA officers

32 Foscarnet-Ganciclovir CMV Retinitis Trial

Dear Doctor letters from drug companies

Issues
- Preventative measures?
- Counter response?
- Passive or active posture?

Strategies
- Energy conservation
- Anti advertising clauses
- Communications

NEJM issues and strategies

Issues
- Length and content restrictions
- Authorship format
- Credit list
- Title

Strategies
- Cut to meet word limit; 3,300 maximum
- Cut one table, hold fast on others
- Stand pat on authorship format
- Ditto for credit list
- Compromise on title

Data access

Issues
- Electronic copy to Astra and Syntex?
- Public deposit of dataset?

Strategies
- Provide restricted access by Astra and Syntex under specified conditions
- Limit use by Astra and Syntex to meeting regulatory requirements
- Place data set in public archive in due course

32 Foscarnet-Ganciclovir CMV Retinitis Trial

Subgroup differences

Issues
- Variables to be used for subgrouping
- Size of difference required
- Weight to be attached to suggestive differences

Strategies
- Limit variables to BL set
- Be cautious re any difference!

References

Studies of Ocular Complications of AIDS Research Group in collaboration with the AIDS Clinical Trials Group: Studies of Ocular Complications of AIDS foscarnet-ganciclovir cytomegalovirus retinitis trial: 1. Rationale, design, and methods. Controlled Clin Trials 13:22 - 39, **1992a**.[50]

Studies of Ocular Complications of AIDS Research Group in collaboration with the AIDS Clinical Trials Group: Mortality in patients with the acquired immunodeficiency syndrome treated with either foscarnet or ganciclovir for cytomegalovirus retinitis. N Engl J Med 326:213 - 220, **1992b**.[51]

33 Hypertension Prevention Trial

33 Hypertension Prevention Trial

Objective

To determine whether by sustained dietary change, DBP can be lowered or prevented from increasing in persons who have DBP ≥ 78 but < 90 mmHg

Participating centers

Clinics

- Birmingham, University of Alabama (UAB)
- Davis, University of California (UCD)
- Jackson, University of Mississippi (UMC)
- Minneapolis, University of Minnesota (UMN)

Resource centers

- Data Coordinating Center (DCC); Baltimore, Johns Hopkins University
- Project Office (PO); Bethesda, National Heart, Lung, & Blood Institute
- Nutrition and Education Resources Center (NERC); Mpls, Univ of Minnesota
- Food Coding Center (FCC); Pittsburgh, University of Pittsburgh
- Central Laboratory (CL); Van Nuys, BioScience Laboratories

Treatments and counseling goals

Trt	Individual goal	Group goal
Cal	Achieve DBW	5% drop in mean body wt
Na	Urine Na ≤ 70 mEq/24hrs	50% drop in mean 24hr urine Na excretion
NaCal	Urine Na ≤ 70 mEq/24hrs	50% drop in mean 24hr urine Na & achieve DBW& 5% drop in mean body wt
NaK	Urine Na ≤ 70 mEq/24hrs	50% drop in mean 24hr urine Na & urine K ≥ 100 mEq/24hrs & mean urine Na:K of 1
Ctrl	None	None

33 Hypertension Prevention Trial

Inclusion and exclusion criteria

Inclusion

- Men or women aged 25 thru 49 on entry
- Initial DBP ≥ 76 mmHg but < 100 mmHg
- Qualifying DBP ≥ 78 mmHg but < 90 mmHg
- Consent

Exclusion

- Evidence of hypertension
- CV disease
- Obese (BMI ≥ 0.05 lbs/in^2)
- Heavy drinker (≥ 21 drinks/week)
- Special diet requirements
- Inability to meet treatment visit schedule
- Pregnant
- Involvement in another study with needs or treatments incompatible with HPT

Baseline demographic characteristics

	Na-Cal component		Na-K component	
	Mean	**p**	**Mean**	**p**
Males	65%	0.02	63%	0.73
Whites	80%	0.43	84%	0.46
Mean age (yrs)	39	0.22	39	0.58
Smoker (%)	18	0.61	15	0.85
≥ 7 drinks/wk	26%	0.80	30%	0.55
≥14 caf dks/wk	66%	0.79	64%	0.93
No.	**506**		**587**	

33 Hypertension Prevention Trial

Baseline BMI and urine Na and K excretion

	Na-Cal component		Na-K component	
	Mean	**p**	**Mean**	**p**
BMI (lbs/in^2) x 100				
Males	4	0.63	4	0.56
Females	4	0.04	4	0.04
Urine excretion (mEq/8hrs)				
Na	46	0.84	43	0.78
K	14	0.62	13	0.94
No.	**506**		**587**	

Baseline food intake (24-hr food record)

	Na-Cal component		Na-K component	
	Mean	**p**	**Mean**	**p**
Calories				
Males	2,575	0.94	2,640	0.74
Females	2,001	0.05	2,090	0.39
Na (mg)	3,375	0.93	3,448	0.82
K (mg)	3,128	0.16	3,218	0.86
No.	**506**		**587**	

33 Hypertension Prevention Trial

Baseline blood pressure

	Na-Cal component		Na-K component	
	Mean	**p**	**Mean**	**p**
DBP (mmHg)				
Males	83	0.19	83	0.04
Females	83	0.24	83	0.66
SBP (mmHg)				
Males	125	0.65	124	0.75
Females	124	0.66	124	0.91
No.	**506**		**587**	

Visit completion rates

	Ctrl	Cal	Na	NaCal	NaK
Sodium-calorie component					
FU visit completion (%)					
6 mos	96		90	87	88
3 yrs	92		94	90	90
Missed all 6			2	1	3
Counseling sessions (%)					
1 st session			na	84	86
12th session			na	58	57
Missed all 12			na	6	5
No.	**126**	**125**	**126**	**129**	
Sodium-potassium component					
FU visit completion (% of expected)					
6 mos	97			89	93
3 yrs	91			89	92
Missed all 6			1		4
Counseling sessions (% attending)					
1 st session			na		82
12th session			na		70
Missed all 12			na		4
No.	**196**		**196**		**195**

33 Hypertension Prevention Trial

Deaths and morbidity

	Ctrl	Cal	Na	NaCal	NaK	p
Sodium-calorie component						
Deaths (%)	1	0	1	1		0.57
DBP ≥90, any FU (%)	30	23	22	29		0.30
BP drug Rx (%)	7	7	8	6		0.96
DBP ≥95 or drug Rx (%)	15	15	17	13		0.64
No.	**126**	**125**	**126**	**129**		
Sodium-potassium component						
Deaths (%)	1		1		1	1.00
DBP ≥90, any FU (%)	26		21		20	0.21
BP drug Rx (%)	6		5		4	0.58
DBP ≥95 or drug Rx (%)	13		11		9	0.28
No.	**196**		**196**		**195**	

Net wt, Na, and K changes: Na-Cal component (N = 506)

	Na		Calorie		Na x Cal	
	Mean	p	Mean	p	Mean	p
Weight (lbs)						
6 mos	-0.5	0.24	-12.7	<0.01	4.2	<0.01
3 yrs	-2.6	0.10	-7.7	<0.01	5.9	<0.01
Sodium (mEq/8hrs)						
6 mos	-3.3	0.12	0.3	0.92	-0.9	0.99
3 yrs	-5.0	0.10	-2.6	0.11	-3.8	0.52
Potassium (mEq/8hrs)						
6 mos	0.6	0.71	-1.4	0.07	0.4	0.52
3 yrs	0.9	0.29	1.1	0.33	-2.9	0.05

Net BP changes: Na-Cal component (N = 506)

	Na		Calorie		Na x Cal	
	Mean	**p**	**Mean**	**p**	**Mean**	**p**
DBP (mmHg)						
6 mos	-0.9	0.47	-2.8	0.01	2.2	0.20
3 yrs	0.1	0.74	-1.8	0.04	0.4	0.51
SBP (mmHg)						
6 mos	-1.8	0.12	-5.1	<0.01	2.9	0.04
3 yrs	0.3	0.77	-2.4	0.03	1.1	0.47

Net wt, Na, and K changes: Na-K component (N = 587)

	Na		K	
	Mean	**p**	**Mean**	**p**
Weight (lbs)				
6 mos	-0.6	0.02	0.6	0.10
3 yrs	-1.4	0.18	0.4	0.52
Sodium (mEq/8hrs)				
6 mos	-5.5	<0.01	-2.0	0.45
3 yrs	-4.2	0.05	-1.6	0.33
Potassium (mEq/8hrs)				
6 mos	0.3	0.99	1.0	0.10
3 yrs	1.3	0.04	0.0	0.58

33 Hypertension Prevention Trial

Net BP changes: Na-K component (N = 587)

	Na		K	
	Mean	**p**	**Mean**	**p**
DBP (mmHg)				
6 mos	-0.4	0.66	-0.3	0.60
3 yrs	0.2	0.79	-0.9	0.40
SBP (mmHg)				
6 mos	-1.7	0.13	0.4	0.82
3 yrs	0.1	0.88	-1.3	0.16

Lessons learned

- It is feasible to recruit large numbers of healthy people over a short period of time with adequate planning, resources, and prior experience
- It is possible to maintain the interest and participation of those enrolled for three years or longer
- Implementing a dietary change is easy compared to the effort required to maintain the change
- Participants and staff alike suffer burnout as the trial proceeds
- Increased effort is required to simply "hold" a given dietary change as time progresses
- Blood pressure should have been measured two ways: Via random zero muddler and electronically
- It is likely that data collected via food records are biased
- Trials the size of the HPT are awkward to organize and manage

33 Hypertension Prevention Trial

Conclusions

- Weight reduction is associated with a drop in BP
- Reduced Na intake is associated with a modest drop in BP in both weight strata
- Sustaining dietary changes over an extended period of time is difficult
- It is easier to change Na or calorie intake than it is to change both Na and calorie intake
- Increasing K consumption, while reducing Na intake, is no better than Na restriction alone in reducing BP
- BP in all treatment groups, including the Ctrl treatment, dropped after enrollment
- A small drop in BP in the entire US adult population could result in a sizable reduction in CV events, such as stroke

References

Hypertension Prevention Trial Research Group: The Hypertension Prevention Trial (HPT): Design, Methods, and Baseline Results (C Meinert, J Tonascia, S Tonascia, editors). Controlled Clin Trials 10 (suppl):1S - 117S, **1989**.[28]

Hypertension Prevention Trial Research Group: The Hypertension Prevention Trial: Three-year effects of dietary changes on blood pressure. Arch Intern Med 150:153 - 162, **1990**.[29]

34 Glaucoma Laser Trial

34 Glaucoma Laser Trial

Objective

Compare initial treatment with ALT followed by topical medication if needed vs initial treatment with topical medication for controlling IOP in eyes with newly diagnosed POAG

Design

Test treatment: ALT followed by stepped topical medications as needed

Control treatment: Stepped topical medications

Treatment assignment: Random

Randomization unit: Eye

Outcome measures

- Number of medications (outcome used to calculate sample size)
- Change in visual field
- Change in optic disc
- Change in visual acuity
- Need for nonprotocol treatment
- Change in IOP

Criteria for changing medication

- Inadequate control of glaucoma; defined as
  - IOP ≥ 22 mmHg on 2 consecutive occasions
  - IOP <20% below baseline level on 2 consecutive occasions
  - Visual field deterioration
  - Optic disc deterioration
- Adverse ocular or systemic reaction

34 Glaucoma Laser Trial

GLT protocol

Laser
- Argon blue-green

Sessions
- 2 sessions spaced 4 weeks apart
- 180˚ of trabecular meshwork treated at each session

Burns
- 48 per session (45-50 allowed)
- Placed to saddle pigmented and nonpigmented anterior trabecular meshwork
- 50μ spot size

Power
- Power adjusted to achieve threshold of bubble formation
- 0.1 second duration

Immediate post ALT therapy
- Dexamethasone 0.1% 4 times per day for 6 days

Medication stepping regimen

1: Timolol
2: Dipivefrin
3: Low dose pilocarpine
4: High dose pilocarpine
5: Timolol with high dose pilocarpine
6: Dipivefrin with high dose pilocarpine
7: Best medical judgement

34 Glaucoma Laser Trial

Functioning units

Clinical centers (8)
- Emory Eye Center
- Massachusetts Eye and Ear Infirmary
- Medical College of Wisconsin
- New York Eye and Ear Infirmary
- Ohio State University
- Sinai Hospital of Detroit
- University of Illinois Eye and Ear Infirmary
- Wills Eye Hospital

Resource centers (5)
- Chairman's Office (Sinai Hospital of Detroit)
- Coordinating Center (Johns Hopkins University)
- Disc Stereophotography Reading Center (Wills Eye Hospital)
- Visual Field Reading Center (University of Illinois Eye and Ear Infirmary)
- Project Office (National Eye Institute)

Committees

- Steering Committee
- Executive Committee
- Design and Quality Assurance Committee
- Treatment Effects Monitoring and Advisory Committee

34 Glaucoma Laser Trial

Chronology

Date	Event
1983 Feb 1	Funding awarded for 7 clinics, CC and reading centers
1984 Feb 15	1st patient enrolled
1984 Oct	Tucson clinic resigns
1985 Feb	Funding for 5 additional clinics awarded
1985 Apr	Albany clinic resigns
1985 Jul	Los Angeles and New Orleans clinics resign
1987 Apr 30	Recruitment ends with 271 patients
1987 Jun 2	NEI approves funding for continuation of GLT through January 31, 1991
1989 Nov 15	End of GLT treatment phase
1991 Dec	Start of GLT Followup Study
1993 Aug	End of GLT Followup Study data collection
1994 Aug	End of funding for GLT Followup Study

34 Glaucoma Laser Trial

Clinic visit schedule

Visit	Time fr randomization
Baseline 1	-3 wks
Baseline 2	-2 wks
Treatment 1	0
Post-treatment 1	1 wk
Treatment 2	4 wks
Post-Treatment 2	5 wks
Follow-up 1	3 mos
Follow-up 2	6 mos
Follow-up 3	9 mos
Follow-up 4	12 mos
Follow-up 5	15 mos
Follow-up 6	18 mos
Follow-up 7	21 mos
Follow-up 8	24 mos
etc	

34 Glaucoma Laser Trial

Data collection schedule

Time fr randomization	Procedure				
	VA	IOP	VF	Slit lamp	Fundus photo
-3 wks	X	X	X	X	
-2 wks	X	X			X
1 wk	X	X		X	
4 wk	X	X		X	
5 wk	X	X		X	
3 mos	X	X	X	X	
6 mos	X	X	X	X	X
9 mos	X	X			
12 mos	X	X	X	X	X
15 mos	X	X			
18 mos	X	X	X	X	
21 mos	X	X			
24 mos	X	X	X	X	X
etc					

Randomization features

Stratification variables

- Clinic
- Eye with higher IOP at baseline visit 2 (if RE IOP = LE IOP, higher IOP eye is selected randomly)

Block size

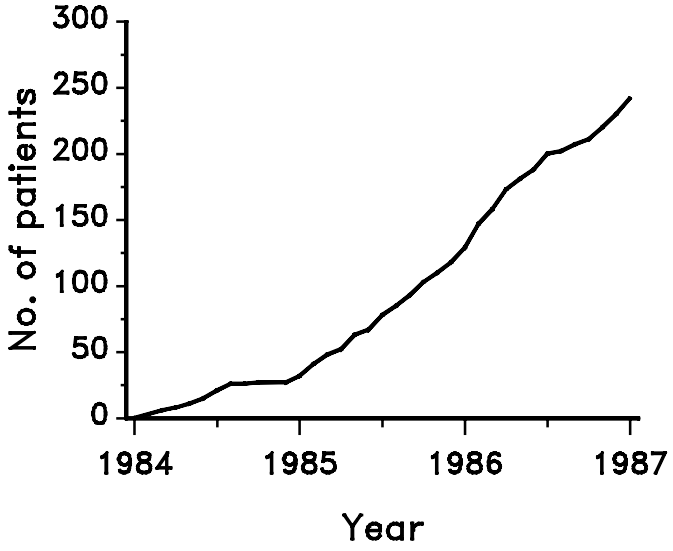
- Length 4, 6 or 8, selected randomly

34 Glaucoma Laser Trial

Data management features

- Centralized
- Paper-based
- Double data entry (same sitting)
- Separate inventory and data files
- Edit checks for consistency, completeness, and accuracy

Cumulative GLT recruitment



Losses

- 7 deaths
- 137 visits missed by patients classified as inactive (dropout patients)
- 114 visits missed by patients classified as active

34 Glaucoma Laser Trial

Completion of followup

Length of followup	Patients %	Patients No
< 1 yr	5.2	14
≥ 1 yr but < 2 yrs	8.9	24
≥ 2 yrs but < 3 yrs	36.9	100
≥ 3 yrs but < 4 yrs	37.3	101
≥ 4 yrs but < 5 yrs	11.1	30
≥ 5 yrs	0.7	2
Total	**100.1**	**271**

Demographic characteristics

	%
Age	
35-44	11
45-54	17
55-64	35
65-74	29
≥ 75	8
Race	
White	45
Black	43
Hispanic	9
Asian	1
Other	2
Sex	
Male	44
Female	56

34 Glaucoma Laser Trial

Baseline medical characteristics

	%
Glaucoma history	
Family history of glaucoma	27
Used glaucoma medication in past	7
Medical conditions	
Diabetes	15
Coronary heart disease	12
Peripheral vascular disease	10
Hypertension	48
Anemia	7
Hx of blood transfusion for uncontrolled bleeding	8
Medication usage	
Currently using α blocker	4
Currently using β blocker	6

34 Glaucoma Laser Trial

Baseline ocular characteristics

	Test	Ctrl
IOP (mmHg) at TR1		
≤ 21	8	8
22	4	3
23 - 25	38	37
26 - 30	27	28
31 - 40	20	21
≥ 41	4	3
Refractive error (D)		
< -4.0	6	6
-4.0 - -1.0	14	15
-1.0 - 1.0	47	45
1.0 - 4.0	32	33
> 4.0	1	1
Visual acuity at TR1		
20/20 or better	48	49
20/25 to 20/40	45	47
20/50 to 20/65	6	3
Pigmentation		
None	7	8
Mild	55	55
Moderate	34	34
Heavy	3	3
VF defect		
Absent	14	16
Present	86	84

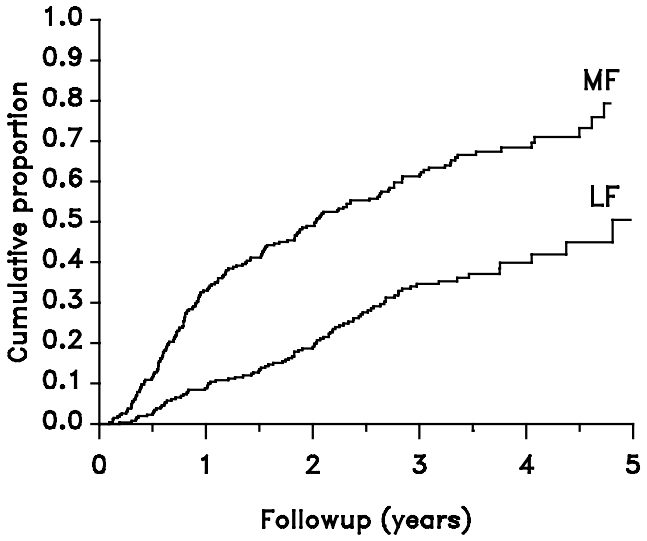
34 Glaucoma Laser Trial

Medication use after 2 years of treatment

	LF	MF
ALT only	44%	na
ALT or timolol	70%	30%
ALT or any single drop	84%	51%
ALT or single or multiple drops	89%	66%
Best medical judgment	11%	34%
No of patients	244	

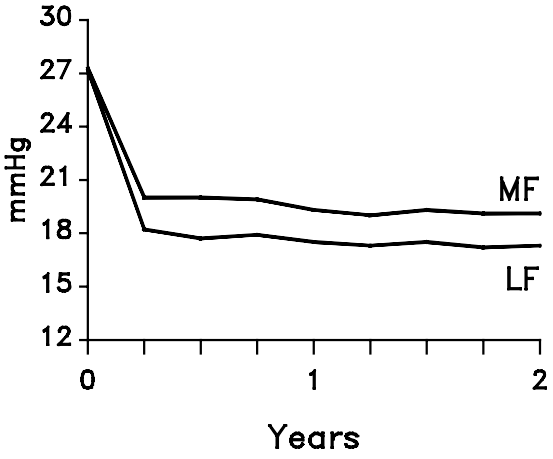
34 Glaucoma Laser Trial

Eyes prescribed 2 or more medications simultaneously

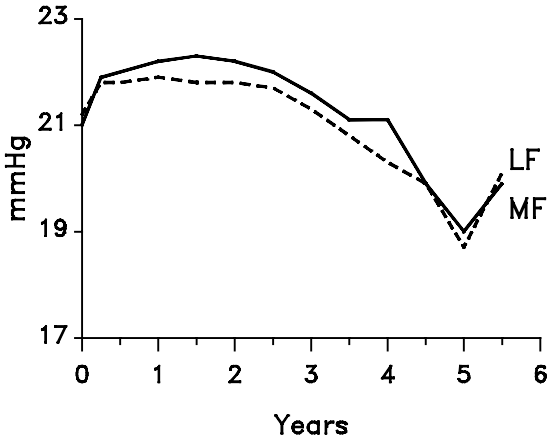


34 Glaucoma Laser Trial

Mean intra ocular pressure



Visual field mean Db



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Acronym glossary

ACAS	Asymptomatic Carotid Atherosclerosis Study
ADAMHA	Alcohol, Drug Abuse and Mental Health Administration
AGIS	Advanced Glaucoma Intervention Study
AMIS	Aspirin Myocardial Infarction Study
AREDS	Age-related Eye Diseases Study
ART	Anturane Reinfarction Trial
BHAT	Beta Blocker Heart Attack Trial
BL	baseline
BMI	body mass index
BTCG	Brain Tumor Cooperative Group
BVOT	Branch Vein Occlusion Trial
CALGB	Cancer and Acute Leukemia Group B
CAMP	Childhood Asthma Management Program
CASS	Coronary Artery Surgery Study
CC	coordinating center
CCMP	Coordinating Center Models Project
CCSG	Children's Cancer Study Group
CCTS	Collaborative Corneal Transplantation Study
CCU	Coronary Care Unit
CDC	Centers for Disease Control
CDP	Coronary Drug Project
CDPA	Coronary Drug Project Aspirin Study
CFR	Code of Federal Regulations
COMS	Collaborative Ocular Melanemia Study
CPT	Cerebral Palsy Trial
CVOS	Central Vein Occlusion Study
DBW	desirable body weight
DHHS	Department of Health and Human Services
DRS	Diabetic Retinopathy Study
EC	executive committee
ECOG	Eastern Cooperative Oncology Group
ETDRS	Early Treatment of Diabetic Retinopathy Study
EVS	Endophthalmitis Vitrectomy Study
FDA	Food and Drug Administration
FFSS	Fluorouracil Filtering Surgery Study
FGRT	Foscarnet Ganciclovir Retinitis Trial
FOIA	Freedom of Information Act
FTE	Full-time equivalent
FU	followup

FY	fiscal year
GLT	Glaucoma Laser Trial
GLTFS	Glaucoma Laser Trial Followup Study
GOG	Gynecological Oncology Group
GTT	glucose tolerance test
HCFA	Health Care Financing Administration
HDFP	Hypertension Detection and Followup Program
HEDS	Herpetic Eye Diseases Study
HPT	Hypertension Prevention Trial
IDC	indirect cost
IDE	Investigational Device Exemption
IHDP	Infant Health and Development Program
IND	Investigational New Drug
INDA	Investigational New Drug Application
IOP	Intraocular pressure
IRB	Institutional Review Board
IRS	Intergroup Rhabdomyosarcoma Study
IRSC	International Reflux Study in Children
LRC	Lipid Research Clinics
MEDLARS	Medical Literature Analysis Retrieval System
MEDLINE	Medical Literature Analysis Retrieval System On Line
MeSH	Medical Subject Heading
MILIS	Multicenter Investigation for Limiting Infarct Size
MorVitAT	Morbidity Vitamin A Trial
MPS	Macular Photocoagulation Studies
MPS:SMD	Macular Photocoagulation Study: Senile Macular Degeneration
MPS:IN	Macular Photocoagulation Study: Idiopathic Neovascularization
MPS:OH	Macular Photocoagulation Study: Ocular Histoplasmosis
MRFIT	Multiple Risk Factor Intervention Trial
NCCTG	North Central Cancer Treatment Group
NCGS	National Cooperative Gallstone Study
NETT	National Emphysema Treatment Trial
NDI	National Death Index
NEI	National Eye Institute
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
NLM	National Library of Medicine
NSABP	National Surgical Adjuvant Breast and Bowel Project

NTIS	National Technical Information Service
NWTS	National Wilms' Tumor Study
OMB	Office of Management and Budget
ONTT	Optic Neuritis Treatment Trial
PARIS	Persantine Aspirin Reinfarction Study
PDR	Physician's Desk Reference
PEPI	Postmenopausal Estrogen/Progestin Interventions
PERK	Prospective Evaluation of Radial Keratotomy
PHS	Physician's Health Study
PIRAT	Peripheral Ischemia Regional Anesthesia Trial
PMA	Pre-market Approval
POG	Pediatric Oncology Group
POSCH	Program on the Surgical Control of the Hyperlipidemias
PPBT	Project on Publication Bias in Trials
RAI	research award index
RBO	relative betting odds
RFA	Request for application
RFP	Request for proposal
RTOG	Radiation Therapy Oncology Group
SC	steering committee
SCI	Science Citation Index
SCT	Society for Clinical Trials
SurPT	Surfactant Prophylaxis Trial
SurTT	Surfactant Treatment Trial
SOCA	Studies of Ocular Complications of AIDS
SWOG	Southwest Oncology Group
TEMAC	Treatment Effects Monitoring and Analysis Committee
TEMC	treatment effects monitoring committee
ToHP	Trials of Hypertension
UGDP	University Group Diabetes Program
USPHS	United States Public Health Service
VA	Veterans Administration
VA43	Veterans Administration Study 43
VACSP	Veterans Administration Cooperative Studies Program
WHO	World Health Organization

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