Clinical Trial Ethics and Interim Trial Monitoring

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Epidemiology 205

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Basic ethical dilemma

- Everyone benefits from the information obtained from research studies
- Only study participants are exposed to direct risks from the research
- Goal of obtaining rigorous data from studies may conflict with the interests of participants
- Risk-to-benefit ratio may be greater in trials than other types of studies

Learning objectives

- Recognize special ethical concerns raised by interventional research
- Identify strategies for adapting interventional trial design to minimize participant risk
- Describe the purpose of and approaches to interim data and safety monitoring in interventional trials
- Identify approaches to making decisions about early termination of trials

General research ethics principles

- **Beneficence** (expected benefit should outweigh expected risk)
- **Respect for autonomy** (voluntary informed consent)
- **Justice** (equal access to benefits and risks of research)

Trial elements that raise ethical issues

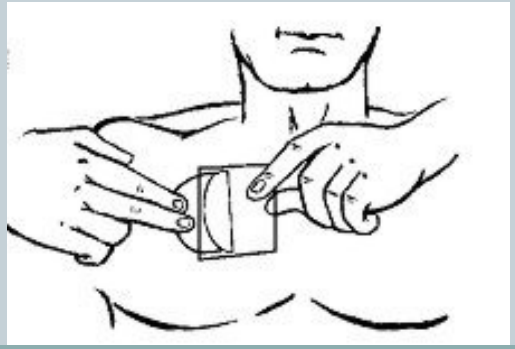
- Active experimental interventions
- Control or comparison interventions
- Random allocation to interventions
- Blinding of participants and providers
- Informed and voluntary consent

Is the “active” intervention acceptable?

- Is there a scientific rationale for anticipating a benefit (without definitive proof of benefit)?
- Are the adverse effects of the intervention likely to be acceptable in relation to the benefits?
- Can the intervention be administered in a way that will minimize risk to participants?

Ex: Transdermal nitroglycerin for hot flashes

- Goal: Assess if continuous use of a nitroglycerin skin patch can alleviate menopause-related hot flashes
- Participants: Perimenopausal or postmenopausal women who experience frequent hot flashes
- Interventions: Continuous use of transdermal NTG patches at 0.2-0.6 mg/hour vs. placebo patches for 12 weeks
- **Anticipated NTG side effects: headache, low or high blood pressure, dizziness or fainting, possible rebound chest pain or heart attack**



Protections against risks of continuous nitroglycerin?

Potential side effects	Possible protections
• Low blood pressure and/or lightheadedness • High blood pressure (after nitrate tolerance develops) • Headache (>1/3 of patients get headache with first use) • Possible rebound chest pain after discontinuation • Other unknown adverse effects?	• Exclusion of those with low or high blood pressure? • Frequent monitoring of interim blood pressure? • Exclusion of those with history of migraines? • Exclusion for heart disease or cardiac risk factors? • Frequent monitoring for chest pain on and after? • Screening ECGs to rule our past silent heart attack?

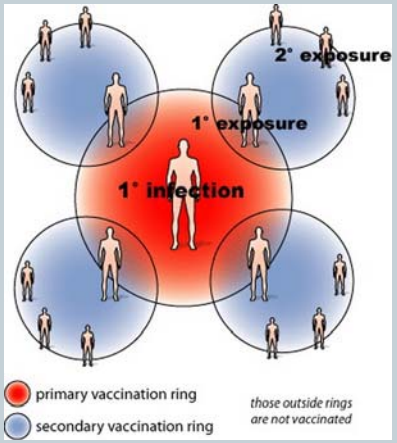
Is the control intervention acceptable?

Possible justifications for using a placebo or sham control:

- No other treatment yet been shown to be effective
- Participants have failed or cannot use established treatments
- No serious, irreversible effects of deferring active treatment

Ex: Delayed Ebola vaccination as an alternative to placebo in the Ebola ca Suffit trial?

- *Ebola ça Suffit* trial of novel and unproven Ebola virus vaccine in Guinea
- Launched in 2014 in the middle of the Ebola virus epidemic crisis



- Clusters of contacts randomly assigned to either immediate or delayed (21 days later) vaccination
- Designed to circumvent ethical issues raised by use of placebo vaccination for a potentially fatal disease

Ebola ça Suffit trial: new disease cases with immediate vs delayed vaccination

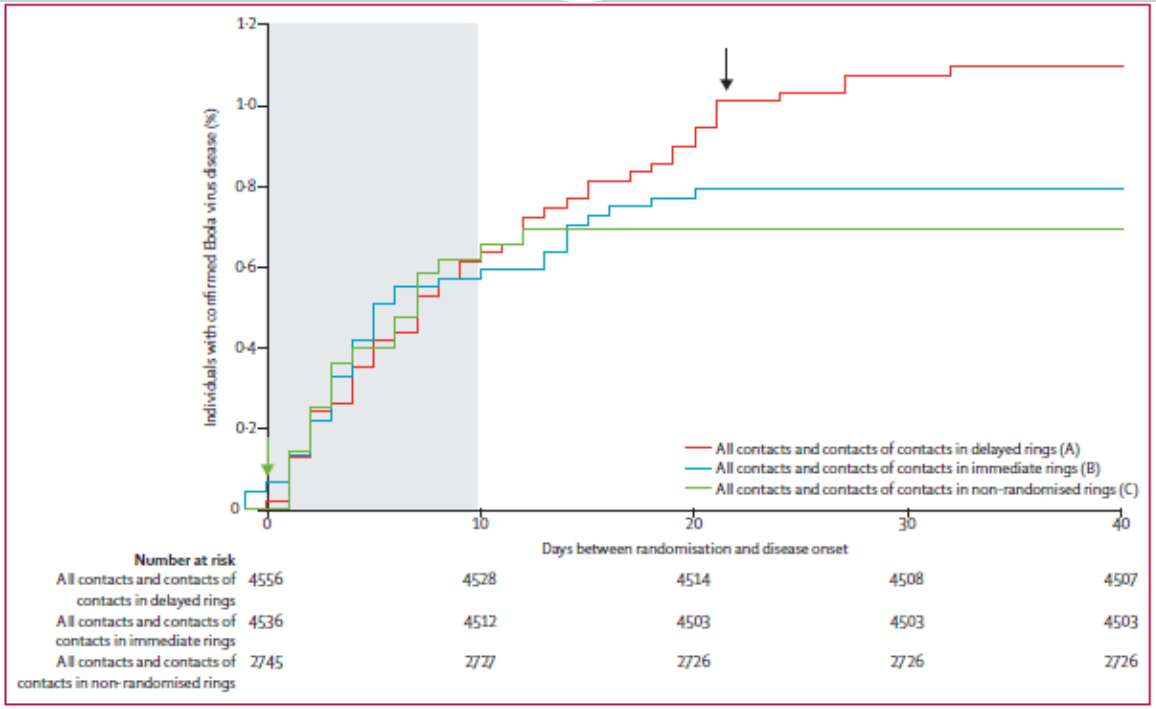


Figure 2: Kaplan-Meier plots for all confirmed cases of Ebola virus disease among all contacts and contacts of contacts in immediate, delayed, and non-randomised clusters

Ebola Ça Suffit trial group, 2016

Ethics of conducting trials in resource poor regions

- Does the proposed trial provide standard of care for the control group?
- Do the participants fully understand the risks of study participation?
- Does the research contribute to a public health priority in the host country?
- What is the effect on the wider medical or public health infrastructure?

Ex: Prevention of perinatal HIV transmission in Africa

- Standard care for HIV+ pregnant women in US
  - Zidovudine (AZT) orally before delivery
  - IV AZT during labor, then orally for newborns
  - RR .33 for new HIV infection in newborn
- Short-course for HIV+ pregnant women in Africa
  - randomized to oral AZT or placebo
  - most funded by US agencies

Rationale for short-course antiviral therapy in Africa

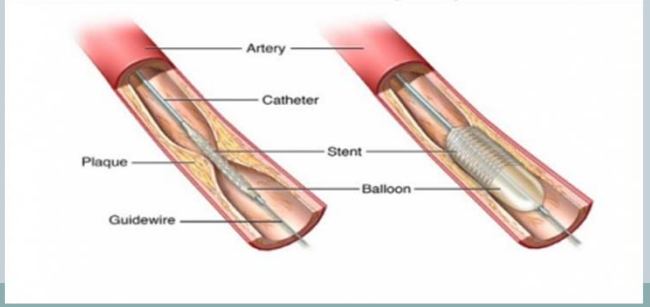
- Cons:
  - Effective drug regimen available in resource-rich countries
  - Promotes double standard of care in resource-poor countries
- Pros:
  - Placebo design addresses health priorities of the host country
  - No point in comparing short-course therapy to a regimen that is unfeasible to implement in Africa

What if the placebo or sham poses risks?

- Medication placebos– ex: skin reaction to placebo transdermal patch
- Sham invasive procedures– ex: sham arthroscopic debridement

Ex: Sham percutaneous coronary intervention in patients with stable coronary disease

- Percutaneous coronary intervention (PCI) used for decades in patients with coronary artery disease
- COURAGE trial (2007) failed to show that PCI reduced risk of heart attack, unstable angina, or cardiac death in stable coronary disease
- Trials comparing PCI to maximal medical therapy still reported potential benefits for control of angina (chest pain with exertion)
- Growing use of PCI in stable coronary disease in the absence of blinded trials using sham PCI



ORBITA trial of PCI versus sham PCI

- ORBITA trial (2018)– double-blinded trial of PCI versus sham PCI in 230 adults with severe single-vessel coronary stenosis
- Participants in sham PCI arm had cardiac catheterization, follow-up dual anti-platelet therapy
- No significant difference in primary endpoint of improvement in angina-free exercise time (mean diff. of 17 [-9, 42] seconds)
- Serious adverse events included 4 pressure-wire related complications and 3 major bleeding events in sham PCI group

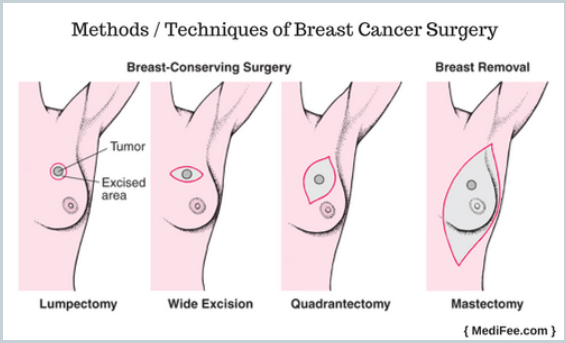
Ethical concerns raised by randomization in trials

- Assignment to intervention is based on chance rather than individualized judgment
- Concept of equipoise– no convincing evidence that one arm is superior to other
- True equipoise may not exist where researchers anticipate a differential effect

Population versus individual-level equipoise

- Anti-cholinergic versus selective beta agonist medication for older adults with overactive bladder

- Lumpectomy vs mastectomy +/- radiation therapy for ductal carcinoma in situ of the breast



Blinding or masking during trials

- Improves scientific rigor by minimizing bias in ascertainment of endpoints
- Can complicate evaluation of adverse events that may be related to study interventions
- May be unethical if other ongoing clinical care is contingent on knowledge of intervention

Unblinding of participants during trials

- Ethically necessary when knowledge of intervention is important to providing emergency care
- May not be necessary for events if knowledge would not influence management
- Ex: Randomized trial of one-time zoledronic acid vs placebo infusion, in which participant later develop chest pain

Informed consent: special challenges in clinical trials

Participants in trials may not understand that:

- Treatment delivered in a trial differs from standard care (‘therapeutic misconception’)
- Being randomized or assigned by chance to an intervention further alters risk
- Participation in an experimental trial may restrict their usual therapeutic options

Ethical challenges in informed consent for trials

- Vulnerable populations – Ex: enrollment of a patient into the antipsychotic CAFÉ study while committed for mental illness
- Incapacitated populations – Ex: patients with traumatic brain injury or severe cognitive impairment
- Emergency situations – Ex: randomization of patients with ST-elevation myocardial infarction without prospective consent in the HEAT-PPCI trial

Summary – ethical issues in clinical trials

- Multiple aspects of interventional trial design may raise special ethical issues
- Risk to participants may be posed by active and control interventions, randomization, blinding
- Challenge is to develop entry criteria, interventions, & procedures that minimize risk but yield useful data
- Consent processes for trials should encompass all aspects of trial that incur risk

Data and safety monitoring
(a.k.a. interim monitoring)

- Planned, ongoing process of reviewing data collected in a trial before recruitment is complete
- Primary goal: to monitor and protect the safety of the trial's participants
- Additional goal: to ensure the integrity and validity of the outcomes data
- Often required to satisfy requirements of study sponsors and/or regulatory bodies

What types of trials require a data and safety monitoring (DSM) plan?

Multicenter randomized trial of a new surgical vs sham procedure?

Single-center trial of a low-risk diet and exercise program?

Phase 1 pilot of an established drug for a new indication?

Approaches to data and safety monitoring

	Written DSM plan	Multi-person DSMB	Interim data review	Formal stopping rules
Multisite randomized trial of new surgical vs sham procedure	✓	✓	✓	✓
Single-center trial of diet and lifestyle change program	✓	?	✓	?
Pilot feasibility trial of established drug for new indication	✓	?	?	?

Common components of a DSM plan

1) Summary of risks and strategies to manage risks
2) Outline of procedures to protect data integrity or security
3) Plans for monitoring recruitment and adherence
4) Plan for monitoring adverse events or alarm findings
5) Designation of person(s) overseeing safety
6) Description of approach to interim monitoring

1) Potential risks of study procedures

- What are the possible side effects of the study interventions?
- What risks or discomforts may result from study measurements?
- What is the burden of completing study self-report measures?
- Any there any special risks associated with loss of privacy?

Possible steps to minimize risks

- Exclusion of populations at greatest risk
- Special training or qualifications of staff
- Surveillance systems to detect early harm
- Special procedures to protect privacy

Ex: Vaginal estrogen ring for postmenopausal women with urgency-type incontinence

Procedures	Potential risks/discomforts
Treatment with high-dose vaginal estrogen ring	→**Increased risk of endometrial or other estrogen-sensitive cancer**
Endometrial biopsy to assess for hyperplasia	→**Bleeding, pelvic infection, puncture of uterine wall**
Questionnaires about sexual activity/function	→**Embarrassment related to answering sensitive questions**
Questions about sexually transmitted infections	→**Risks to reputation in setting of loss of confidentiality**

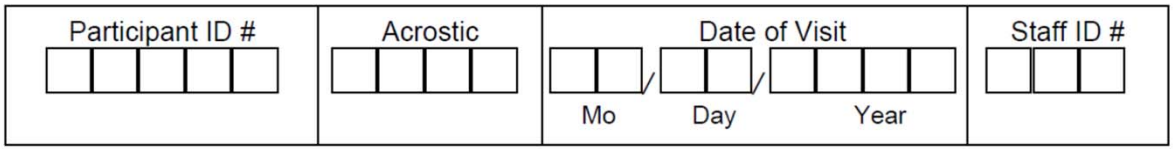
Examples of steps to minimize risks

(for trial of vaginal estrogen ring for urgency incontinence)

Procedures	Risks/discomforts
Possible ↑ risk of endometrial cancer	→Exclusion of women with known endometrial hyperplasia
Risk of puncture during endometrial biopsy	→Certification of healthcare personnel performing biopsy
Embarrassment from sensitive questionnaires	→Use of sealed envelopes for return of questionnaires
Risks to reputation from loss of confidentiality	→Use of study ID numbers on data forms, database security

2) Protection of data integrity and security

- What systems will be used to enter and manage participant data (e.g., electronic data capture systems)?
- How will the investigative team maintain participant confidentiality (e.g., use of study ID numbers rather than personal idenfiers)?
- How will the investigative team protect the security of the study data (e.g., secure database platforms, plan for destroying identifiers)?

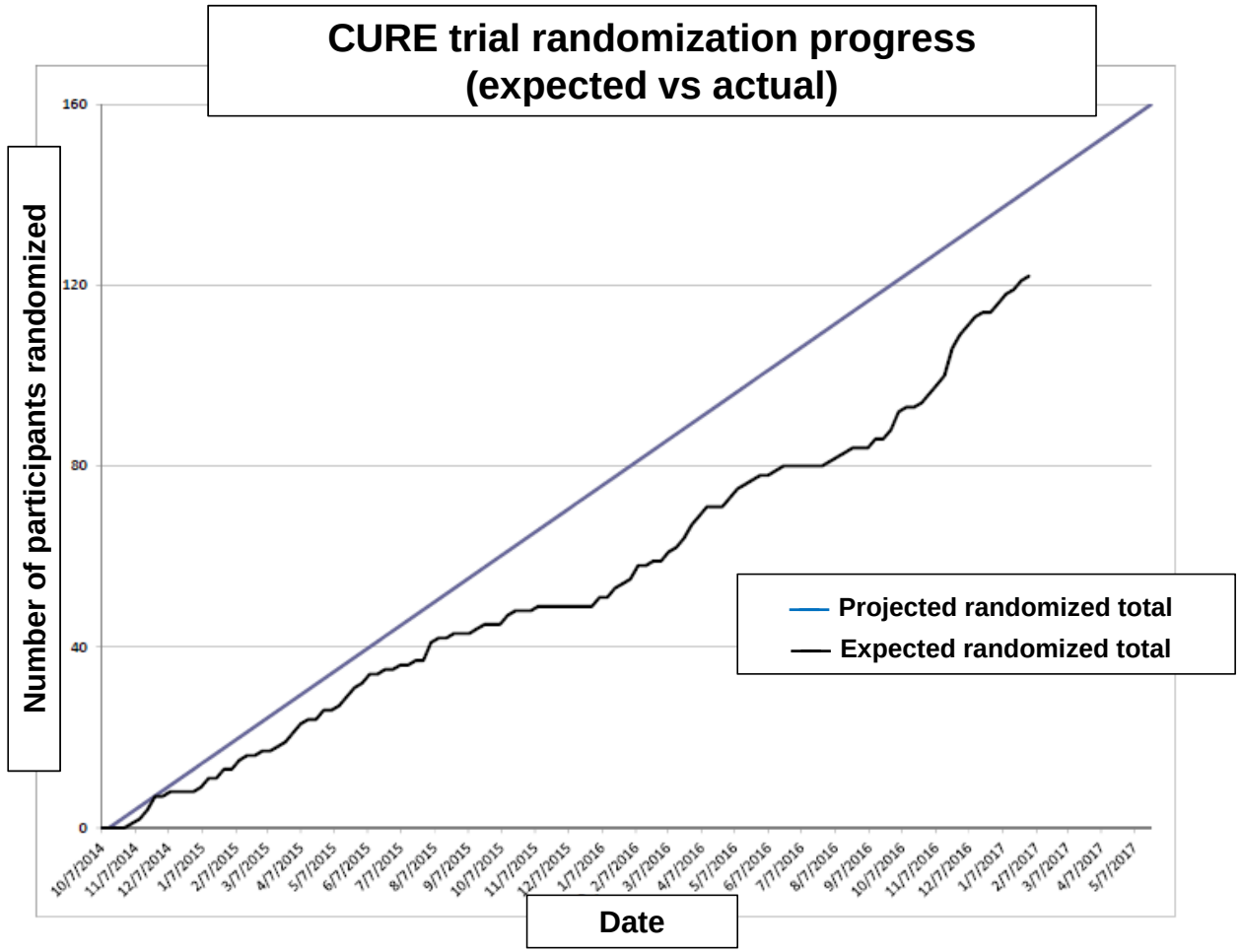


Promoting data accuracy/completeness

- Double/duplicate data-entry procedures
- Verification of data by an outside party
- Programmed/automatic checks for data outliers
- Posting of queries for missing or incomplete data

3) Plans for monitoring recruitment & adherence

- If recruitment is too slow or loss to follow-up is too great, then the trial may never achieve its goals
- Poor adherence to interventions may also compromise ability to answer study question
- Detailed DSM plan may specific rates of optimal, adequate, and acceptable follow-up or adherence


CURE trial randomization progress
(expected vs actual)
Number of participants randomized
160
120
80
40
0
Projected randomized total
Expected randomized total
10/7/2014
11/7/2014
12/7/2014
1/7/2015
2/7/2015
3/7/2015
4/7/2015
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4/7/2017
5/7/2017
Date

4) Plan for monitoring adverse events

- **HOW** will you define adverse events (AEs)?
- **WHEN** or how often will AEs be assessed?
- **WHAT** procedures will be used to detect AEs?
- **WHO** will be notified about AEs as they occur?

Common AE assessment procedures

- Definitions and categories of AEs to be assessed
- Standardized procedures to screen for AEs
- Assessment of timing/duration and severity of AEs
- Possible attribution of AEs to study treatments
- Reporting of AEs/SAEs to IRBs, DSMs, sponsors

5) Designation of an independent data & safety monitor

- Is independent data and safety monitoring needed for this clinical trial?
- If independent monitoring is needed, is one DSM or a multi-person DSMB indicated?
- What qualifications or experience should the DSM or DSMB members have?
- Is the DSM or DSMB acting in an advisory capacity to the investigators versus the sponsor

Functions of a DSM or DSMB

- Evaluate adequacy and timeliness of recruitment and adherence to protocol
- Monitor participant safety including trends in adverse events during the trial
- Consider external factors when they may have an impact on the safety of participants
- Make recommendations on continuation, termination, or other modifications to the trial

Who should serve as a DSM?

NOT:

- Investigators with a direct stake in the research
- Sponsors or sponsor representatives
- Direct collaborators of the study investigators
- Individuals at the same institution at the study team

Who should serve as a DSM?

(Ex: clinical trial of a vaginal estrogen ring in women with breast cancer)

- Clinicians experienced in menopausal or breast health?
- PhD-trained statistician or other statistical expert?
- Experts in clinical trial design or research bioethics?
- Patient representatives or members of advocacy groups?
- Representatives of sponsors as non-voting members?

6) Interim monitoring plans

- When should the DSM or DSMB review the data?
- What issues should be reviewed at each time point?
- What procedures will be followed during review?
- How should recommendations about stopping early be made?

When and what issues to monitor?

Early issues:

- Problems with trial design
- Success of recruitment
- Success of adherence
- Loss to follow-up
- Data quality and timeliness
- Data from other studies

Later issues:

- Early evidence of clear benefit
- Early evidence of clear harm
- Lack of conditional power to meet goals
- Subgroup analyses

Developing a monitoring schedule

- **Prior to start of recruitment:** review and suggest modifications to the study protocol and DSM plan
- **Soon after start of recruitment:** review progress of recruitment and rates of adherence and follow-up; examine data completeness and quality
- **Periodically throughout trial:** re-review recruitment, adherence, follow-up, and assess efficacy and harm

Procedures for DSM or DSMB review

- Circulation of data tables prior to DSM review
- “Closed” vs “open” meetings to preserve blinding
- “Voting” vs “non-voting” DSMB members
- Possible “executive session” at the end of review
- Summary and recommendations made by DSM Chair

Summary – Data & Safety Monitoring Plans

- All interventional studies benefit from a written data and safety monitoring plan
- Plans should describe protections against risk and procedures to ensure accurate data
- Safety monitors should not have a vested interest in the study outcomes
- Detailed and thoughtful interim review plans are needed for larger or more complex trials

Why stop a clinical trial early?
(Ex: clinical trial of vaginal estrogen ring)

- Early clear evidence of harm
  - Increased risk of endometrial hyperplasia/cancer
- Early clear evidence of benefit
  - Reduction in urgency incontinence episodes
- Not possible to determine benefit
  - Poor enrollment or poor rates of adherence
- Question answered by another study

Factors to consider in stopping decisions

- Does the evidence of benefit or harm appear to strengthen over time?
- Is the impact on primary outcomes also correlated by secondary outcomes?
- Do the observed trends in benefit or harm seem biologically plausible?
- Are overall trends toward benefit or harm also observed in subgroups?

Statistical analyses to guide early termination

- Need for corrections to minimize chance differences emerging from repeated interim comparisons
- Recognition that early interim data may provide less reliable information than later data
- Calculation of conditional power of trials to provide compelling evidence of benefit or harm

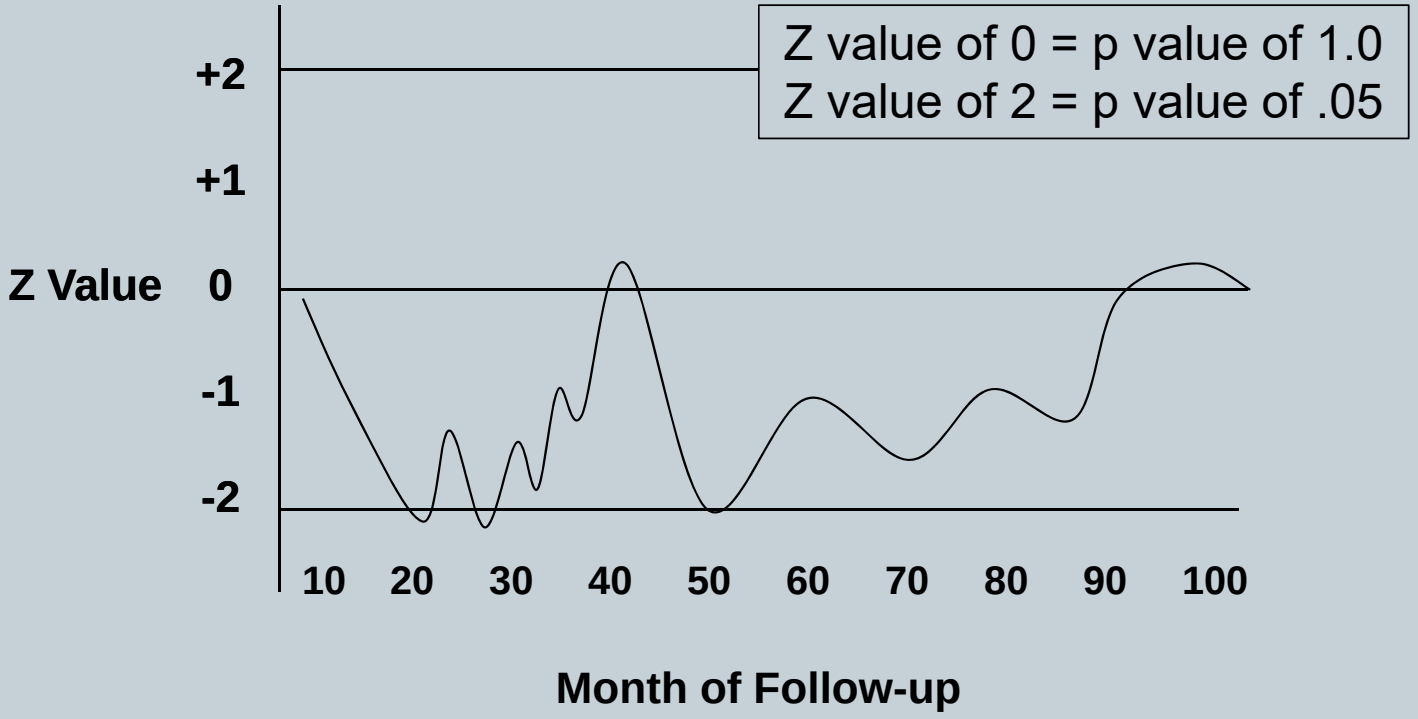
Simplistic approach to assessing early harm or benefit

Perform repeated tests of significance and stop the trial if any p<.05

Straightforward, but ultimately flawed approach:

total tests	overall alpha level
1	.05
2	.08
5	.14
10	.20
20	.35

Interim analyses for clofibrate vs. placebo in the Coronary Drug Project



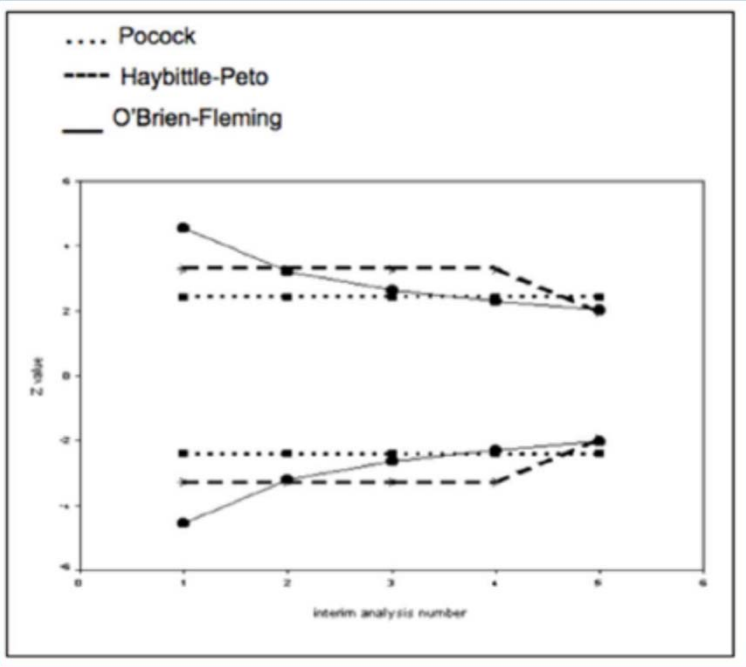
Possible approaches to correcting for multiple comparisons

Perform tests of significance and adjust test-wise α (type 1 error)

- Bonferroni correction
- Classical sequential methods
- Group sequential methods

Early group sequential methods: Pocock, Haybittle-Peto, O'Brien-Fleming

Defining specific boundaries for alpha level to allow multiple analyses while protecting the cumulative alpha level by the end of the trial

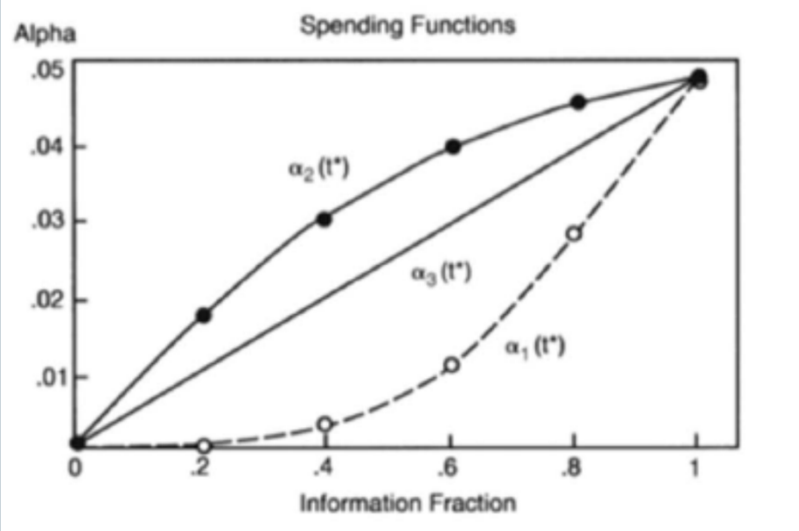


For O'Brien-Fleming:

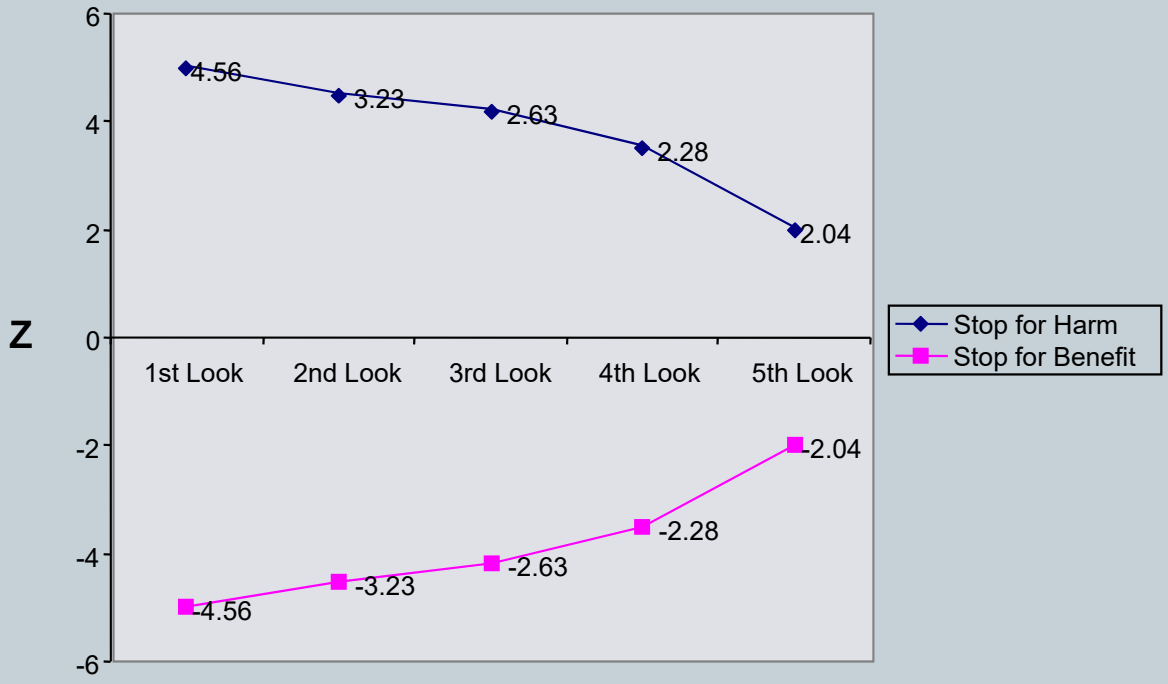
Look	Z-value	P-value
1	4.56	.00001
2	3.23	.0001
3	2.63	.009
4	2.28	.023
5	2.04	.041

Later approaches: alpha-spending function curves

Lan-DeMets: specifies a smoother α spending function defined by N previous “looks”proportion of data/time between



Symmetric stopping boundaries for Z-values



Stopping a trial for futility

- What if early trends in outcomes data suggest that a trial won't be able to prove its hypothesis?
- Poor recruitment, retention, adherence, or data quality can lead to futility
- Original sample size or power calculations may also have used incorrect assumptions
- Conditional power- the probability of rejecting the null hypothesis (H_0) at the end of the study

Approaches to assessing conditional power

Compute p (reject Ho given data so far)

Deterministic Curtailment Sampling

- assume all future outcomes in treated
- assume all future outcomes in placebo

Stochastic Curtailment Sampling

- assume H_o true
- assume H_a true

Consider terminating trial for futility

Alternate approach: beta spending function

How can a trial be altered after initiation?

Early alterations	Later alterations
• Change eligibility criteria • Add extra screening measures • Change primary outcome • Adjust delivery of interventions	• Increase duration or size of trial • Stop one arm of the intervention • Terminate high risk groups • Add additional safety measures

Other issues to be weighed by DSMs

- Outcome events still in the “pipeline”
- Possible baseline differences between groups
- Possible bias in assessment of outcomes
- Impact of missing or incomplete data
- Differential rates of adherence or co-interventions
- Consistency of findings across subgroups

Action to Control Cardiovascular Risk in Diabetes (ACCORD) – stopped for harm

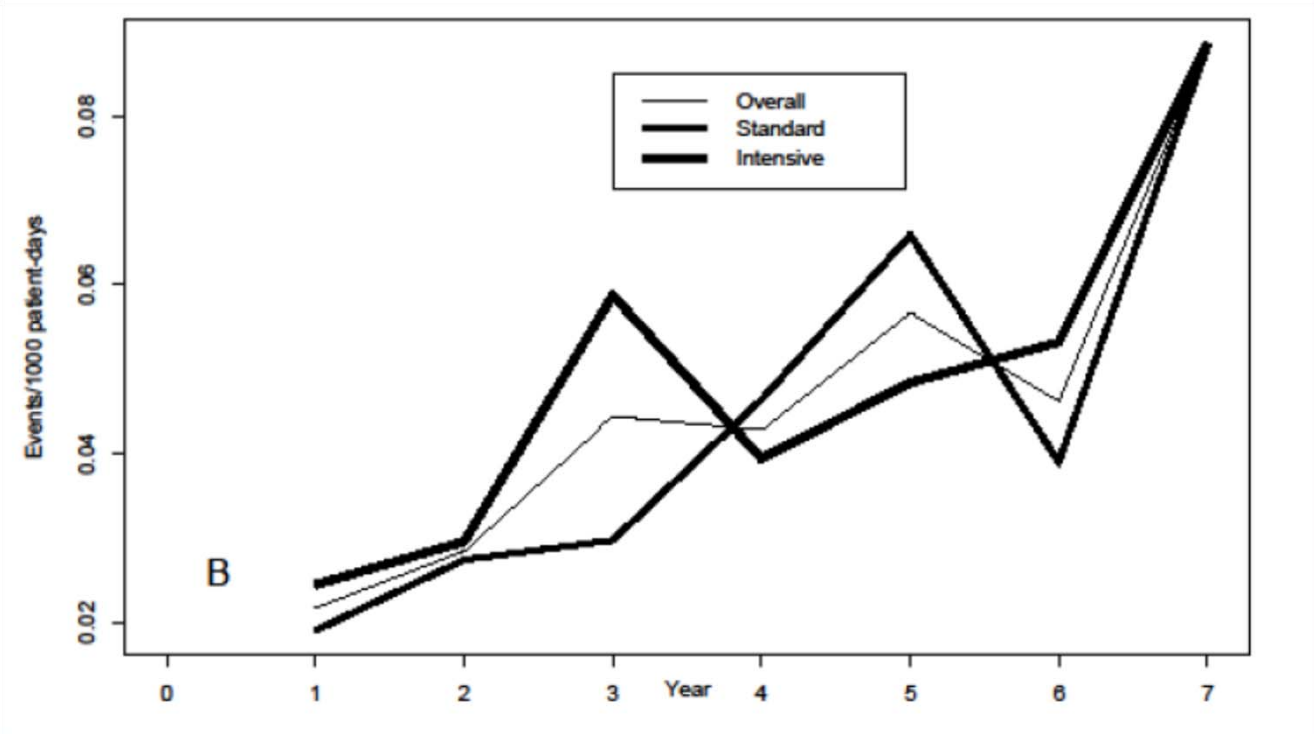
- Design – double factorial trial comparing intensive vs. standard blood sugar control and blood pressure control in type 2 diabetes
- Participants – 10,251 persons with type 2 diabetes and cardiovascular disease or risk factors
- Primary outcome – composite of myocardial infarction, stroke, death from cardiovascular disease
- Follow-up –3.5 of planned 5.6 years before early trial termination for harm associated with intensive blood sugar control (HbA1c <6%)

ACCORD interim results for blood sugar control

Outcome	N (%) with outcome		Hazard ratio	P
	Intensive therapy N = 5128	Standard therapy N = 5123		
Cardiovascular events (primary)	352 (6.9%)	371 (7.2%)	0.9	.20
All-cause mortality	257 (5.0%)	203 (4.0%)	1.2	.02
Hypoglycemia requiring intervention	538 (10.5%)	179 (3.5%)	3.0	<.001

Accord Study Group, NEJM, 2008

All-cause mortality in ACCORD by timepoint



Combination Antibiotics for Methicillin Resistant *Staphylococcus aureus* (CAMERA2) trial – stopped for harm

- Design: Multicenter trial of combining antistaphylococcal beta-lactam antibiotic with daptomycin versus vancomycin for MRSA bacteremia
- Participants: 352 hospitalized patients from Australia, Singapore, New Zealand, Israel
- Primary outcome: 90-day composite of mortality, persistent bacteremia at day 5, microbiologic relapse or treatment failure
- Secondary outcomes: 90-day mortality, persistent bacteremia at day 2 and 5, acute kidney injury, microbiologic relapse and treatment failure

CAMERA2 trial interim results

Outcome	Number (%) with outcome		Relative risk	P value
	Combination therapy (N = 174)	Standard therapy (N=178)		
Primary outcome	59 (35%)	68 (39%)	-4.2	.42
Mortality at 90 days	35 (23%)	28 (16%)	4.5	.28
Bacteremia at day 5	19 (11%)	35 (20%)	-9.9	.02
Acute kidney injury	34 (23%)	9 (6%)	17.2	<.001

CAMERA2 Study Group, JAMA, 2020

Letrozole after Tamoxifen for Breast Cancer - stopped for benefit

- Design: Multicenter randomized trial of treatment with letrozole therapy (vs placebo) after five years of tamoxifen therapy
- Participants: 5157 postmenopausal women with hormone receptor+ breast tumors after 5 years of tamoxifen
- Primary outcome: disease-free survival (until local or metastatic recurrences of breast cancer or new cancers in contralateral breast)
- Follow-up: completed 2.4 out of 5 planned years before early termination for benefit

Letrozole after tamoxifen interim results (median 2.4 years follow-up)

	N (%) with events)	
	Letrozole group N=2575	Placebo group N=2582
Recurrent breast cancer	61 (2.4%)	106 (4.1%)
New primary contralateral tumor	14 (0.5%)	26 (1.0%)
Total of recurrence + new primary	75 (2.9%)	132 (5.1%)

Goss et al, NEJM, 2003

Systolic Blood Pressure Intervention Trial (SPRINT) - stopped for benefit

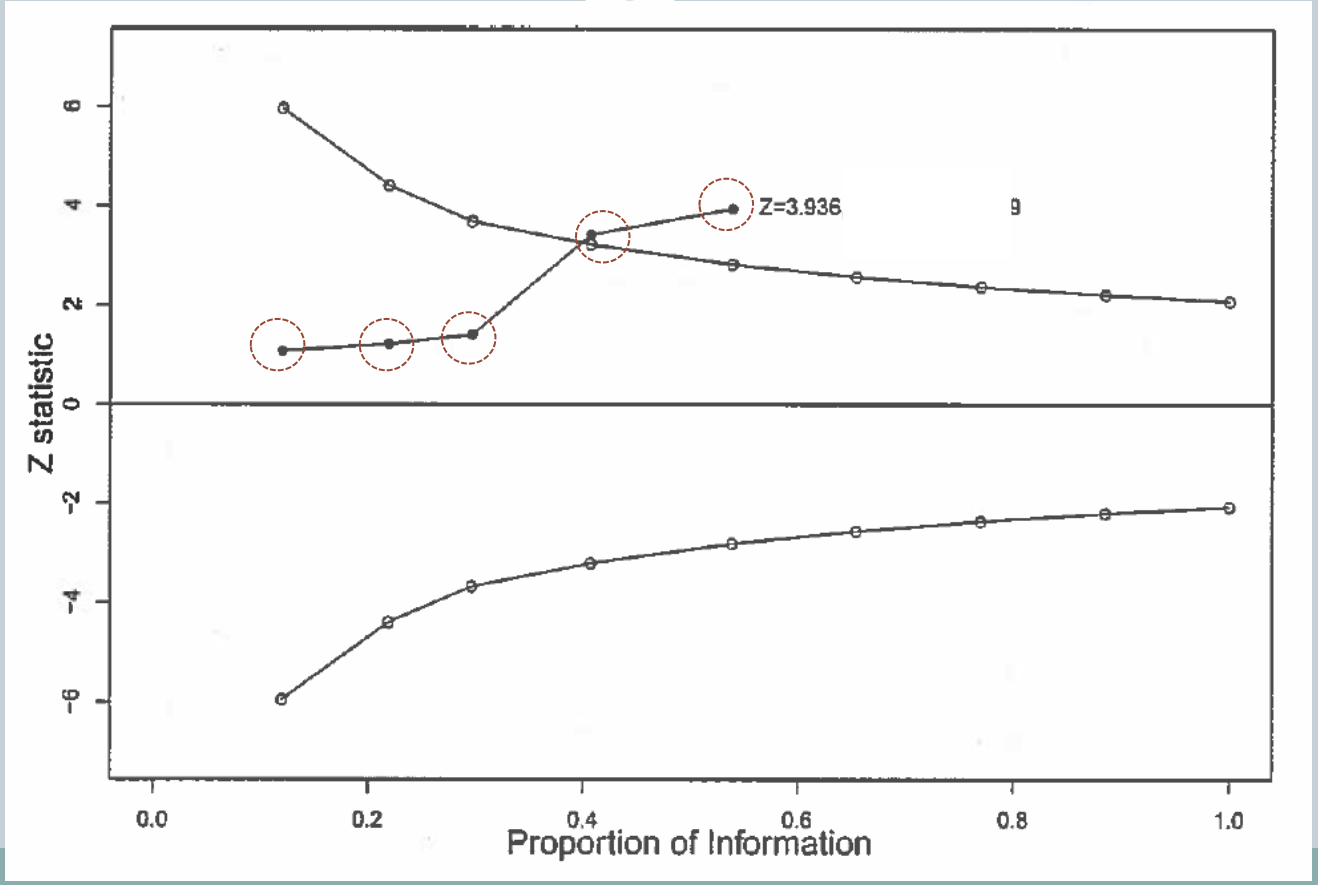
- Design – multicenter randomized trial of intensive systolic blood pressure lowering (<120 mmHg) or standard (<140 mmHg)
- Participants – 9361 persons with systolic blood pressure >130, cardiovascular risk factors, no diabetes
- Outcome – composite of myocardial infarction, acute coronary syndrome, stroke, heart failure, or death from cardiovascular disease
- Follow-up – completed 3.3 of planned 5 years before early termination

SPRINT interim results

Outcome	N (%) with outcome		Relative risk	P value
	Intensive therapy (N = 4678)	Standard therapy (N = 4683)		
Cardiovascular events	243 (5.2%)	319 (6.8%)	.75	<.001
All-cause mortality	155 (3.3%)	210 (4.5%)	.73	.003
Decline in renal function (≥30% decrease in GFR)	127 (3.8%)	37 (1.1%)	3.5	<.001

SPRINT Study Group, NEJM, 2015

SPRINT stopping rules



Consequences of stopping a trial early

- Trials stopped early (especially for benefit) may be outliers that are susceptible to overestimation of effects
- In many cases, additional trials addressing the same question continue to be launched
- Early terminated trials may seem more “newsworthy” and result in rapid dissemination
- Ex: 1999 trial of bisoprolol (a beta-blocker medication) in patients with vascular disease having non-cardiac surgery

Different rules for stopping for harm vs benefit?

- "Liberal" rules to stop for harm to protect participants in the trial
- More stringent rules for benefit to answer important questions
  - Does benefit strengthen over time?
  - Does treatment reduce mortality?
  - Were side effects underestimated?
  - What is the impact on secondary outcomes?
  - What is the effect within subgroups?

Look AHEAD trial: modified rather than terminated early

- Trial of intensive lifestyle intervention on obese adults with diabetes
  - Initially designed to have 90% power to detect an 18% reduction in cardiovascular event rate in intensive lifestyle group
  - Lower than expected early rate of cardiovascular events in control group involving diabetes education in the first 2 years
  - Interim modification– expand the definition of the primary endpoint of the study to capture more events, extend follow-up of participants

Complex Trials: Women's Health Initiative

Harm	*% Change in Risk*
• CHD	+29%
• Stroke	+41%
• Breast cancer	+26%
• Pulm. embolus	+2.1X
Benefit	
• **Hip fracture**	**-34%**
• **Colorectal cancer**	**-37%**

Global Index

Summary – Early Termination

- Trials may be stopped early for compelling evidence of harm or benefit or for futility
- Stopping rules can help guide decisions, but other factors may influence termination
- Early termination may affect the clinical or public health impact of a trial

Resources for DSM plans

- **Guidelines and examples**
  - **NIH Toolbox:**
    - https://www.nia.nih.gov/research/dgcg/clinical-research-study-investigators-toolbox/data-and-safety-monitoring
  - **CTSI DSM Protocol Library**
    - https://hub.ucsf.edu/dsm-examples

Questions?