Clinical Trial Ethics and Interim Monitoring

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Epidemiology 205

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Basic ethical dilemma

- Everyone benefits from the information obtained from clinical research studies
- But only study participants are put at direct risk from clinical research
- The need to obtain rigorous data may conflict with the interests of participants
- Risks may be greater in trials than other studies and may not be offset by benefit

Learning objectives

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

General research ethics principles

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

Ethical issues raised by trial components

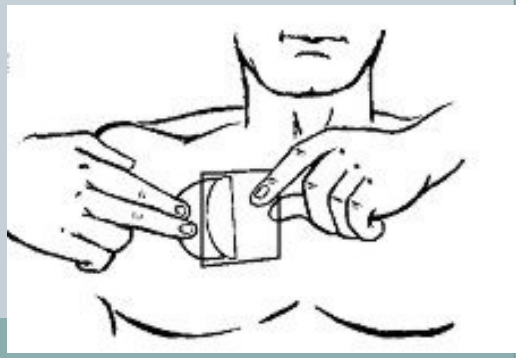
- Active experimental interventions
- Control or comparison interventions
- Random allocation to interventions
- Blinding of participants and providers
- Informed and voluntary consent

Is the “active” intervention acceptable?

- Is there a solid scientific rationale for anticipating a benefit?
- Has the effect of the intervention already been established?
- Are the adverse effects of the intervention likely to be acceptable in relation to benefits?
- Can the intervention be administered in a way that will minimize risk?

Ex: Transdermal nitroglycerin for hot flashes

- Goal: Assess whether continuous use of a nitroglycerin (NTG) skin patch can alleviate menopausal hot flashes
- Subjects: 140 perimenopausal or postmenopausal women with ≥ 7 hot flashes per day
- Interventions: Uninterrupted use of transdermal NTG patches at 0.2-0.6 mg/hour vs. placebo patches
- Prior experience: NTG already widely used to treat chest pain due to coronary artery disease and lower blood pressure



Prior work needed to support ethics of trial?

- Prior research showing that the proposed mechanism of action is reasonable?
- Prior pilot research providing preliminary evidence of symptomatic benefit of NTG for hot flashes?
- Prior research indicating that side effects of NTG in similar populations are acceptable?
- Prior work providing insight into differences in effects of different NTG dosages?

Reducing risk from trial interventions

- Selection criteria to exclude persons at high risk
- Procedures to monitor or manage known adverse effects
- Procedures to detect unanticipated harms
- Use of qualified staff to administer interventions

Protections against risks of transdermal NTG?

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 women with history of headache? • 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?

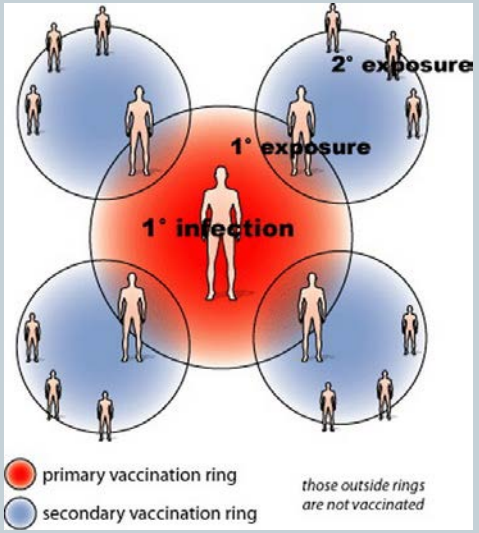
- Is placebo, sham procedure, standard of care, usual care – ethically acceptable?
  - Randomize adults with depression to a new medication vs. placebo?
  - Randomize adults with osteoarthritis to actual vs sham arthroscopy?
  - Randomize adults with Parkinson's disease to actual vs sham transplant of stem cells into brain?

Justifications for placebo or sham control

- No treatment has yet been shown to be effective
- Participants have failed to respond to treatment
- Participants refuse to use established treatments
- No serious or irreversible risks are likely to occur
- Placebo or sham intervention poses limited risks

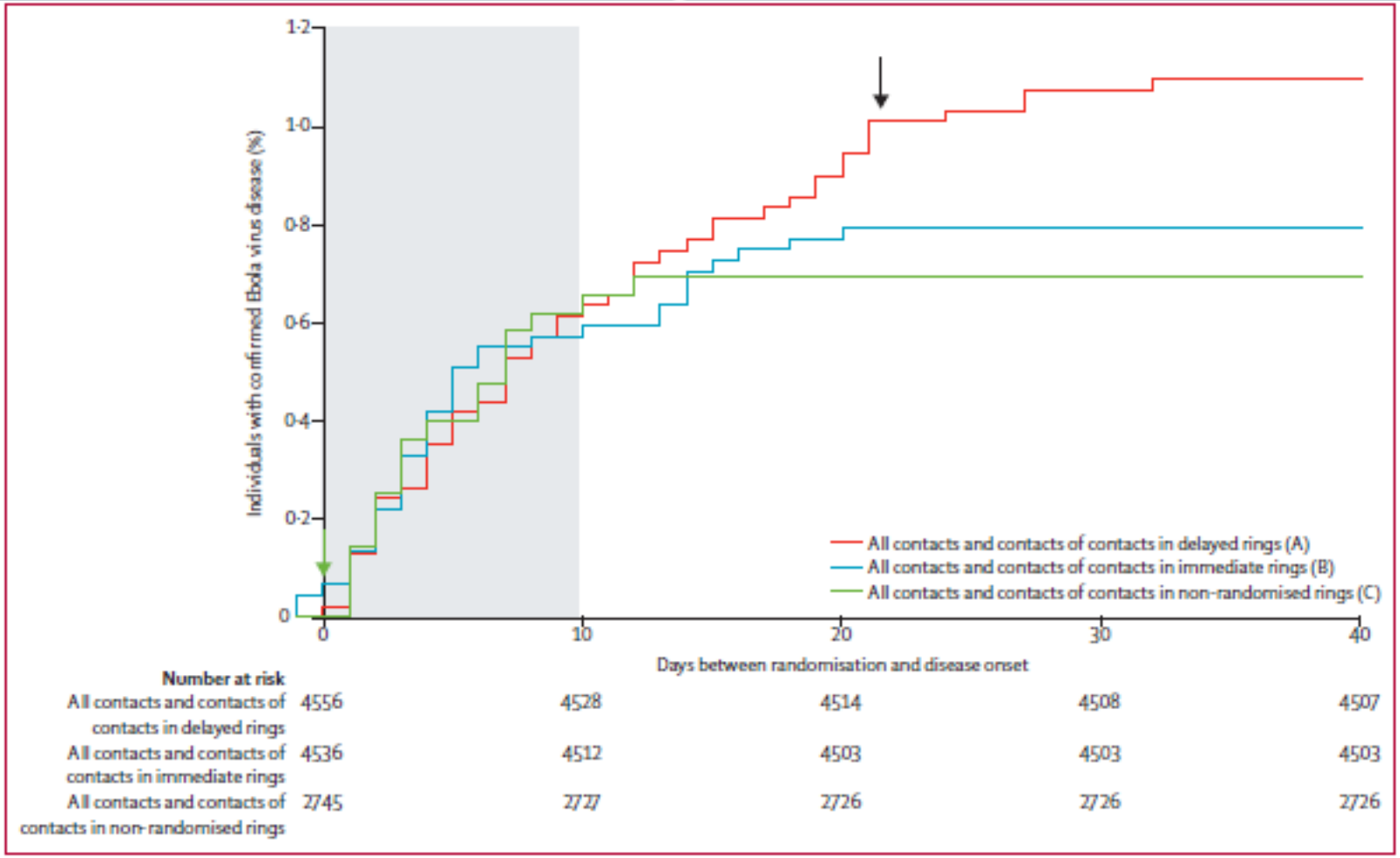
Ebola ça Suffit trial: ethical alternative to placebo vaccination

- *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

Ebola ça Suffit trial results



Number at risk					
All contacts and contacts of contacts in delayed rings	4556	4528	4514	4508	4507
All contacts and contacts of contacts in immediate rings	4536	4512	4503	4503	4503
All contacts and contacts of contacts in non-randomised rings	2745	2727	2726	2726	2726

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

Other aspects of Ebola ça Suffit design

- Vaccine was still investigational – claim to equipoise was greater since efficacy was unknown
- All participants received infection prevention advice and contact information for study team
- All participants monitored for symptoms of Ebola by daily home visits
- Participants given access to free medical checkups and care for any acute illness

Clinical trials in resource poor regions

- Does the trial provide standard of care for the control group?
- Do the participants understand the risks of 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 in Africa

- Standard care for HIV+ pregnant women in US
  - zidovudine orally before delivery
  - IV zidovudine 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 therapy in Africa

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

Ethical concerns about randomization

- Assignment to intervention is based on chance rather than individualized judgment
- Concept of equipoise– no convincing evidence that one arm is superior to other
- But true equipoise may not exist where researchers anticipate a differential effect
- Randomization can increase individual risk even when there is no clear evidence of differential effect on population level

Multiple levels of equipoise

- The scientific community – is there lack of conclusive evidence about the effect of the intervention(s)?
- The clinician or investigator – can the clinician refer participants in good faith?
- The individual participant – do all treatment arms offer similar risks to this specific individual?

Blinding or masking

- Improves scientific rigor by minimizing bias in ascertainment of trial endpoints
- Can be detrimental if a participant suffers an adverse event that might be related to the intervention
- Unethical when other ongoing aspects of care are contingent on knowledge of treatment assignment

Procedures for unblinding

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

Challenges in informed consent in trials

Participants in trials may not understand that:

- Treatment delivered in a trial differs from standard care (‘therapeutic misconception’)
- The active intervention used in a trial may not yet be known to be beneficial or safe
- Being randomized or assigned by chance further alters participant risk
- Participation in a clinical trial may restrict their usual therapeutic options

Special ethical challenges in trial consent

- Vulnerable populations – Ex: enrollment of a patient into the antipsychotic CAFÉ study while committed for mental illness
- Clinician as investigator – Ex: enrollment of a primary care patient seeking alternative treatment for urinary incontinence
- Emergency situations – Ex: randomization of patients with ST-elevation myocardial infarction without prospective consent in the HEAT-PPCI trial

Summary – ethical issues in trials

- Multiple aspects of clinical trial design may raise 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 clinical trial
- Primary purpose is to monitor and protect the safety of the participants
- Additional goal is to ensure the integrity and validity of the outcomes data
- Often required to satisfy the 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 potential risks and strategies to manage risks
2) Outline of procedures to protect data integrity and 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 diaries, questionnaires, or interviews?
- 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

Examples of potential risks
(for trial of vaginal estrogen ring in postmenopausal women)

Procedures	Risks/discomforts
Treatment with vaginal estrogen ring	→**Vaginal irritation, possible ↑ risk of endometrial cancer**
Endometrial biopsy to assess for hyperplasia	→**Bleeding, pelvic infection, puncture of uterine wall**
Questionnaires about sexual activity and 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 in postmenopausal women)

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?
- How will the investigative team maintain participant confidentiality during data collection?
- How will the investigative team protect the security of the study database?

Protecting data security

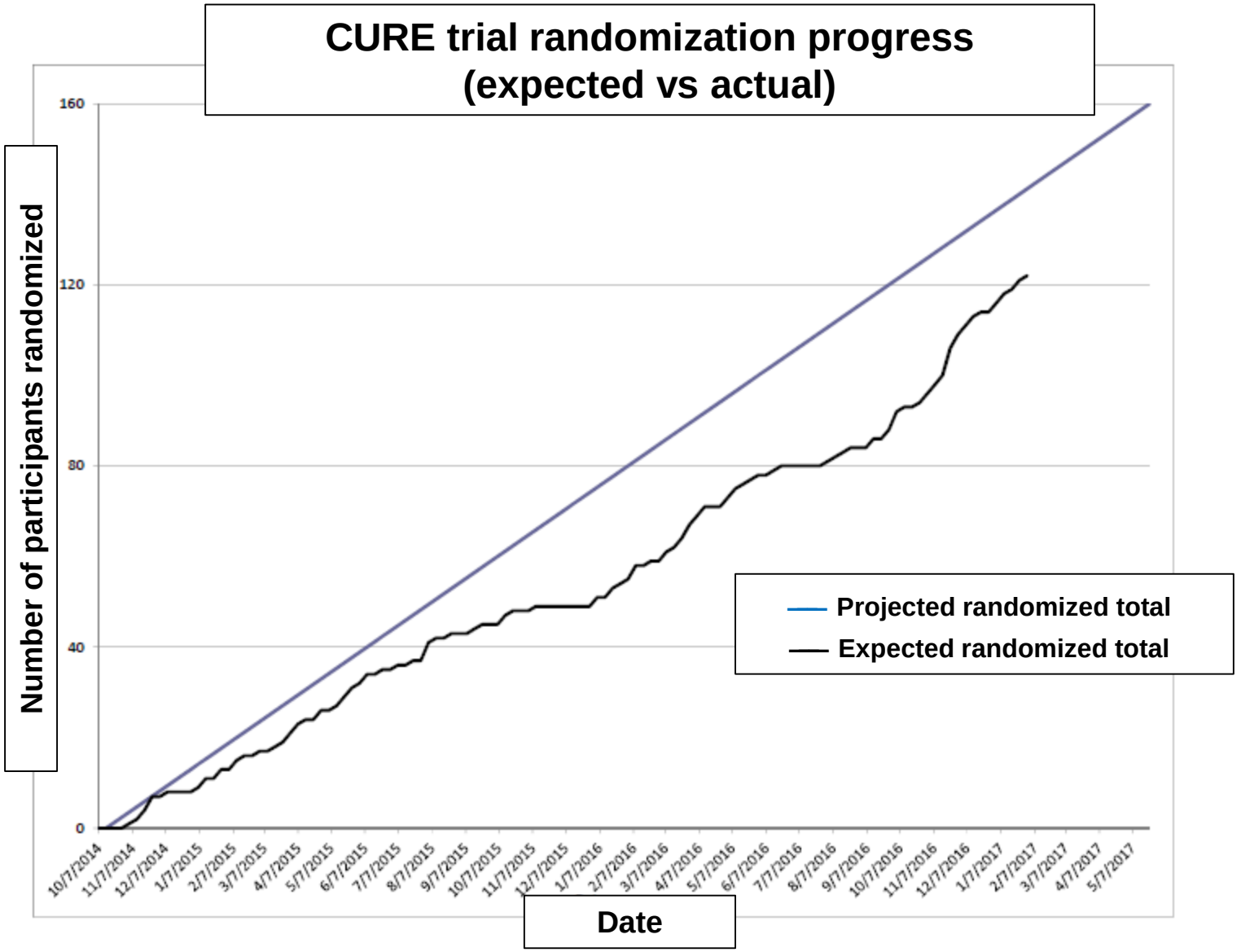
- Storage of data on password-protected servers
- Use of data encryption software on computer tablets
- Use of study ID numbers or acrostics on data forms
- Plan for protecting, then destroying identifiers

Protecting data accuracy

- Double data-entry procedures
- Verification of data by outside party
- Software with automatic checks for outliers
- Posting of queries for missing data values

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
10/7/2014
11/7/2014
12/7/2014
1/7/2015
2/7/2015
3/7/2015
4/7/2015
5/7/2015
6/7/2015
7/7/2015
8/7/2015
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3/7/2016
4/7/2016
5/7/2016
6/7/2016
7/7/2016
8/7/2016
9/7/2016
10/7/2016
11/7/2016
12/7/2016
1/7/2017
2/7/2017
3/7/2017
4/7/2017
5/7/2017
Date
Projected randomized total
Expected randomized total

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 adverse event definitions

- **Adverse event (AE)** = any negative change in health occurring while participants are on treatment, regardless of apparent relationship to treatment

- **Serious adverse event (SAE)** = death, disability, or unexpected hospitalization or prolongation of hospitalization while on treatment

Which of the following are reportable serious adverse events?

	Yes	No
A participant is struck by a bolt of lightening and suffers a cardiac arrest	X	
A participant undergoes a previously scheduled myomectomy (fibroid resection) procedure		X
Following myomectomy, a participant is unable to urinate and is kept overnight in the hospital	X	
A participant has a seizure but refuses to go to the emergency room or get medical attention	X	

Common AE assessment procedures

- Systematic assessment for AEs at follow-up visits
- Standardized questions to screen for AEs
- Proactive questioning about specific important AEs
- Assessment of timing/duration and severity of AEs
- Possible attribution of AEs to study treatments
- Reporting of AEs/SAEs to IRBs, DSMs, sponsors

Referral for follow-up care of AEs

(Ex: trial of transdermal nitroglycerin for menopausal hot flashes)

- How will you notify participants or healthcare providers about abnormal electrocardiogram (ECG) findings?
- What time frame of referral or follow-up is appropriate for different types of ECG abnormalities?
- How will you preserve the distinction between research findings and clinical care?

5) Designation of a data & safety monitor

- Is independent data and safety monitoring needed for this study?
- 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?

Functions of a DSM or DSMB

1) Evaluate adequacy and timeliness of recruitment and adherence to protocol
2) Monitor participant safety including trends in adverse events during the trial
3) Consider external factors when they may have an impact on safety
4) Evaluate the quality and integrity of data management and security
5) 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)

- Clinicians experienced in menopausal or genitourinary 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 decisions 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
- Summary and recommendations made by DSM Chair

Confidentiality of DSM review

- **Open session**
  - DSMB, sponsor, investigators, NIH, FDA
  - Recruitment, retention, data quality
  - Overall (non group-specific) findings
- **Closed session**
  - DSMB members, ± statistician
  - Between-group findings
  - Discussion regarding modifications

Summary – Data & Safety Monitoring Plans

- All interventional studies may benefit from a 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
- Early clear evidence of benefit
  - Reduction in genitourinary symptoms
- Not possible to demonstrate benefit
  - Poor enrollment or poor rates of adherence
- Question answered by another study
  - Ex: Canadian Atrial Fibrillation Anticoagulation (CAFA)

Factors to consider in stopping decisions

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

Statistical analyses to guide early termination

- Need for corrections to minimize chance differences emerging from repeated comparisons
- Calculation of conditional power to provide compelling evidence of benefit or harm
- Creation of global indices to capture overall benefit vs. harm in trials with multiple important outcomes

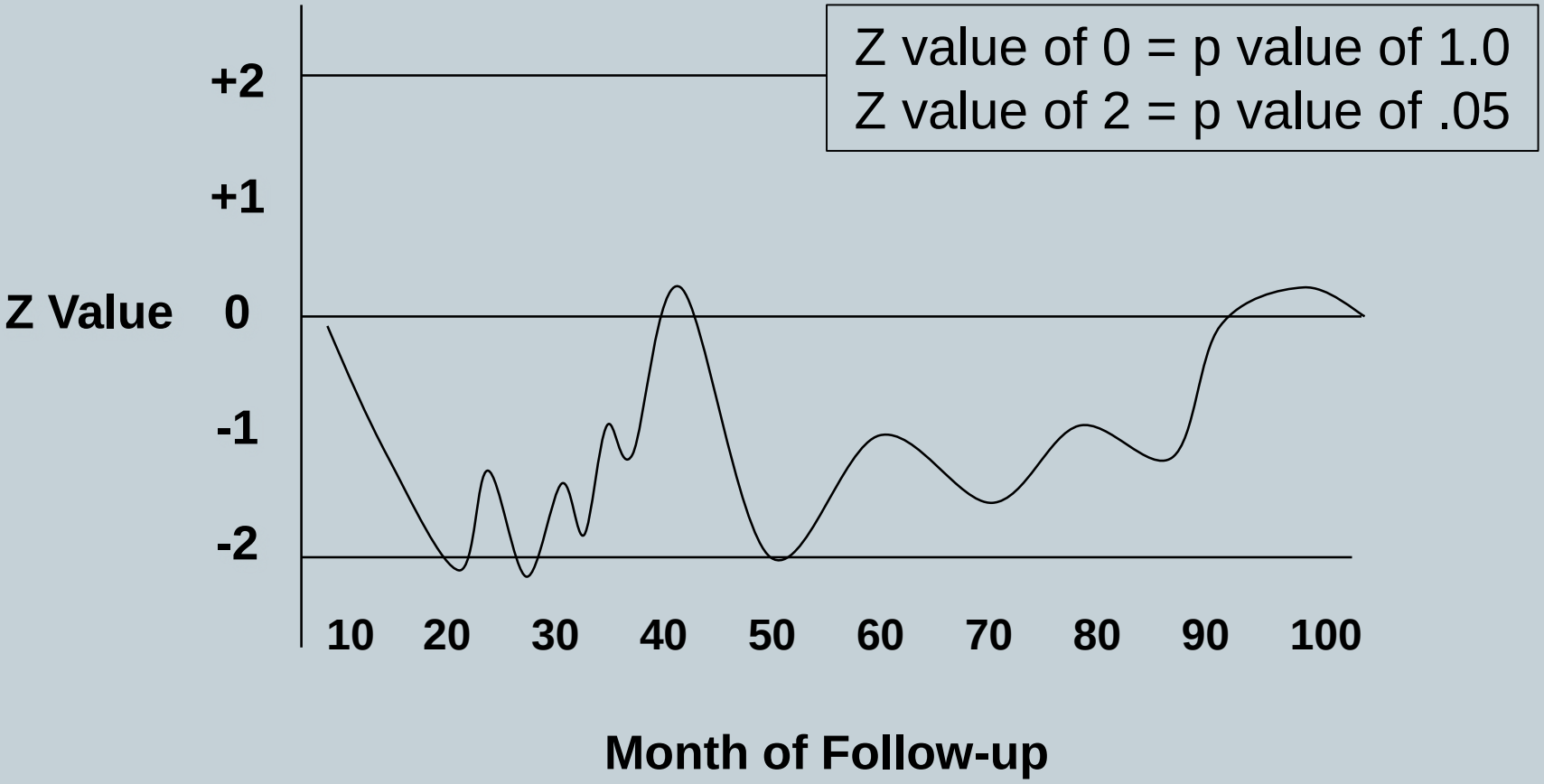
Simplistic approach to assessing early harm or benefit

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

- Straightforward, but flawed approach

total tests	overall alpha
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
  - Bonferroni correction?
  - Classical sequential methods?
  - Group sequential methods
    - Pocock
    - Haybittle and Peto
    - O'Brien and Flemming
    - Lan and DeMets

Group sequential methods

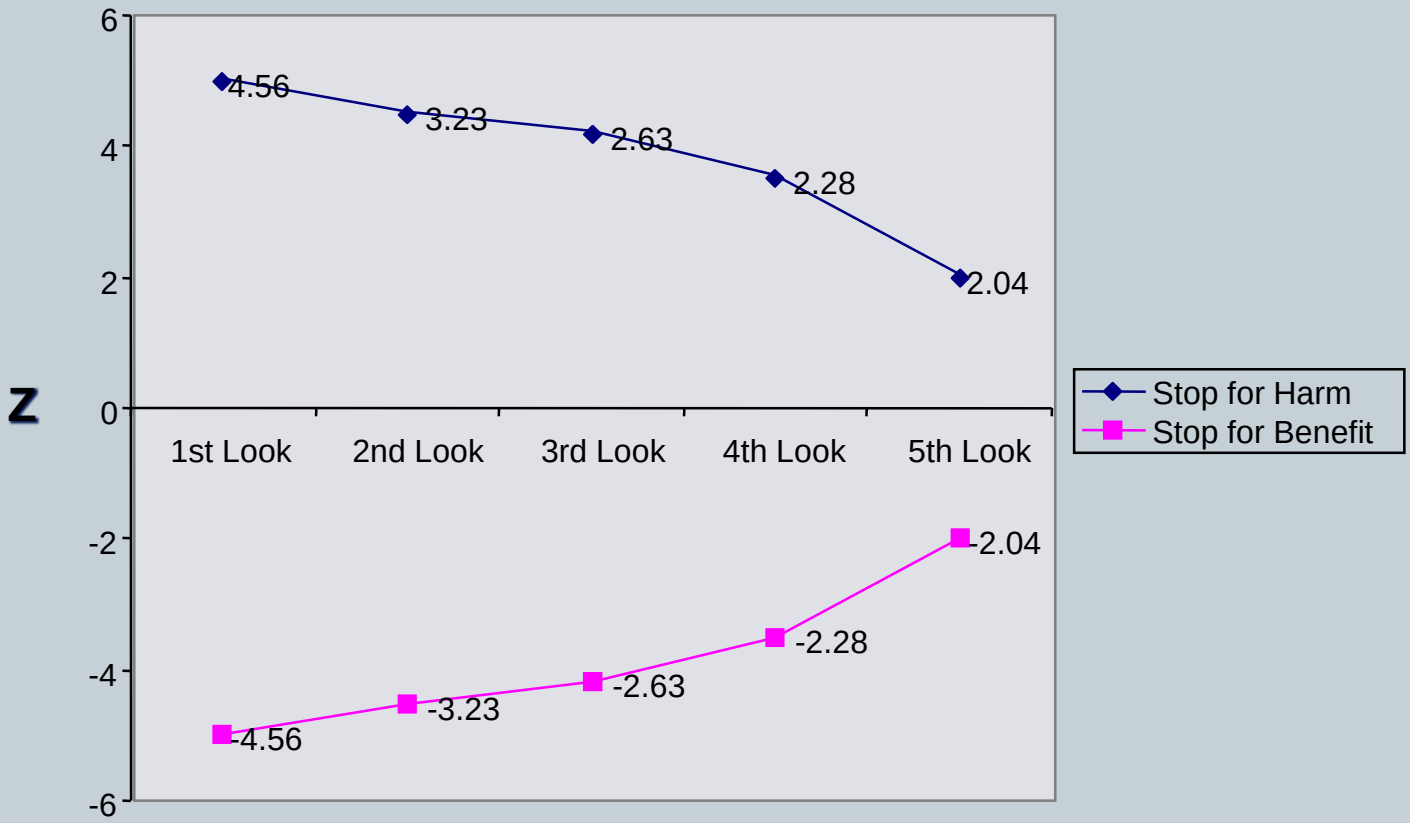
- O'Brien - Fleming — small α_i for early interim tests gradually increasing α_l over time such that α_f close to final

- Lan-DeMets — specifies an α spending function defined by N previous "looks" proportion of data/time between

O’Brien-Fleming alpha spending function

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

Symmetric stopping boundaries for Z-values



Assessment of conditional power

Compute p (reject H_o given data so far)

Deterministic Curtailed Sampling

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

Stochastic Curtailed Sampling

- assume H_o true
- assume H_a true

Consider terminating trial for futility

How can a trial be altered after initiation?

Early alterations	Later alterations
• Change eligibility criteria • Increase/decrease sample size • Change primary outcome • Adjust delivery of interventions	• Increase duration of the 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
- Implications for medical practice and public policy

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

- Subjects – 10,251 persons with type II diabetes and cardiovascular disease or risk factors
- Intervention – intensive vs standard glycemic control (HbA1c lowering <6% versus 7-7.9%)
- Follow-up –3.5 of planned 5.6 years before trial termination
- Outcome – myocardial infarction, stroke, death from cardiovascular disease

Accord Study Group, NEJM, 2008

ACCORD trial interim results

Outcome	Percent with outcome		Relative risk	P value
	Intensive therapy	Standard therapy		
Cardiac events	6.9	7.2	0.9	.20
Death (any cause)	4.0	5.0	1.2	.02
Hypoglycemia	10.5	3.5	3.0	<.001

Accord Study Group, NEJM, 2008

Letrozole after Tamoxifen for Breast Cancer - stopped for benefit

- Subjects: Postmenopausal women with hormone receptor+ breast tumors after 5 years of tamoxifen
- Interventions: Letrozole (oral aromatase inhibitor therapy) versus placebo
- Follow-up: completed 2.4 out of 5 planned years before early termination
- Outcome: Local or metastatic recurrences of breast cancer or new cancers in contralateral breast

Letrozole after tamoxifen interim results

	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	132

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

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

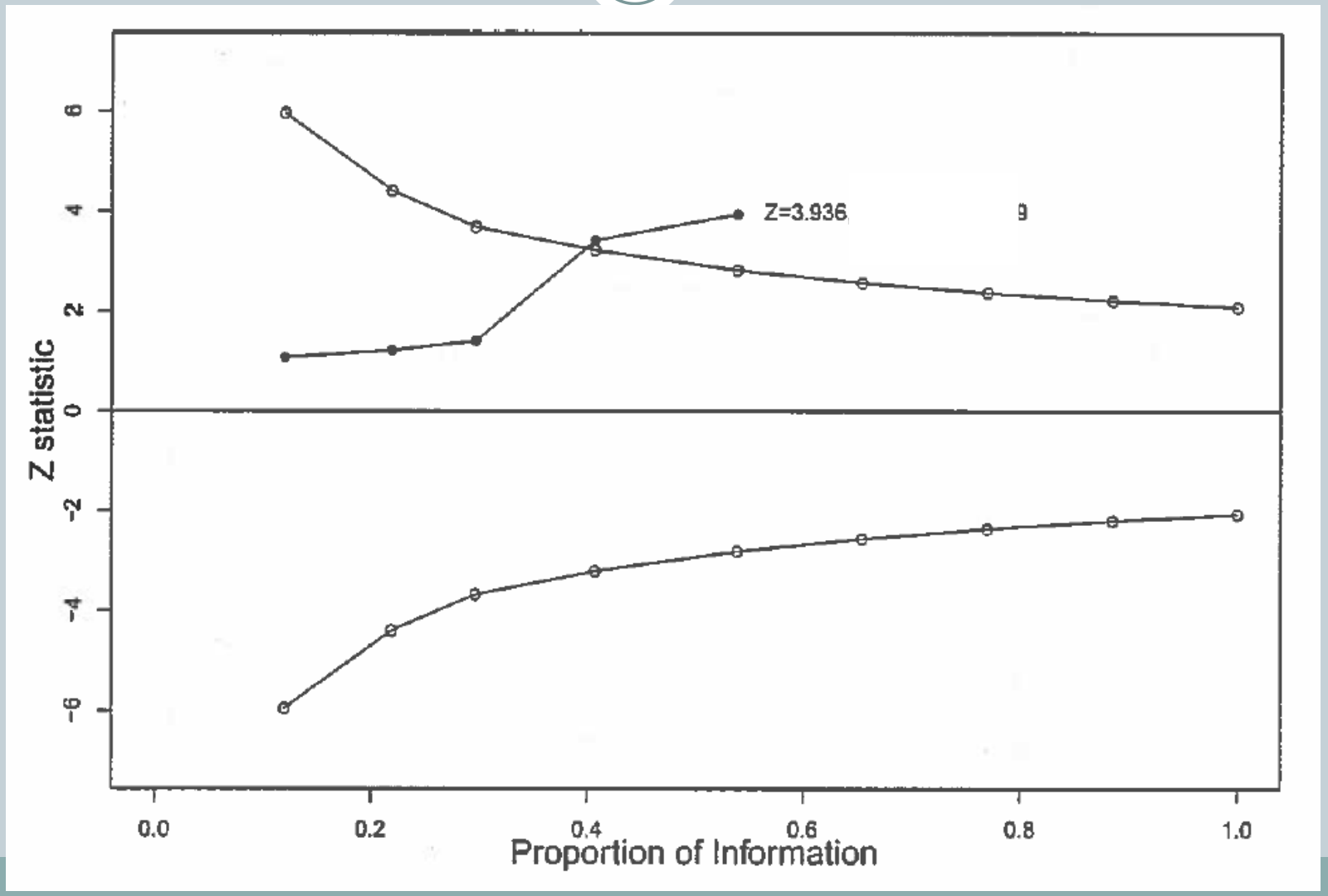
SPRINT Study Group, NEJM, 20015

SPRINT interim results

Outcome	Percent with outcome		Relative risk	P value
	Intensive therapy	Standard therapy		
Cardiovascular events	5.2	6.8	.75	<.001
Death (from any cause)	3.3	4.5	.73	.003
Decline in renal function (≥30% decrease in GFR)	3.8	1.1	3.5	<.001

Accord Study Group, NEJM, 2008

SPRINT stopping rules



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

Liability of interim trial monitors

- Adenomatous Polyp Prevention on Vioxx (APPROVe) trial evaluating rofecoxib for prevention of colon cancer
- DSMB recommended early termination because of evidence of ↑ cardiovascular risk by 18 months
- Lawsuits later filed by patients with cardiovascular events after taking Vioxx for arthritis pain
- DSMB members were required to provide depositions and court testimony

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?

Summary – Early Termination

- Trials may be stopped early for compelling evidence of harm or benefit or for futility
- Any decision to terminate a trial should be carefully considered
- 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 of DSM plans

- **Guidelines and examples**
  - **NIH Toolbox:**
    - **https://www.nia.nih.gov/research/dgcg/clinical-research-study-investigators-toolbox**
  - **CTSI DSM Protocol Library**
    - **https://accelerate.ucsf.edu/research/dsmb**

Questions?