

Clinical Trial Ethics and Interim Monitoring



Alison Huang, MD, MAS, MPhil
Epidemiology 205
March, 2018

Basic ethical dilemma



- Everyone benefits from the information obtained from research studies
- But only study participants are put at direct risk from 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 trial research
- Identify strategies for adapting trial design to decrease risk to participants
- Describe the purpose of and approaches to interim data and safety monitoring in trials
- Assess 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 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?

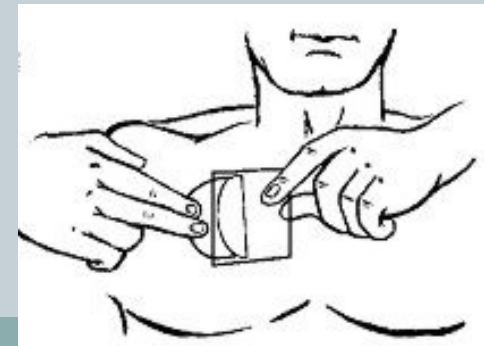


- Is there a solid scientific rationale for anticipating a benefit?
- Has the effect of the intervention already been established?
- Are the adverse effects of the intervention likely to be acceptable in relation to benefits?
- Can the intervention be administered in a way that will minimize risk?

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 NTG patches at 0.2-0.6 mg/hour vs. placebo patches for 12 weeks
- 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 risks associated with different NTG dosages or duration of use?

Reducing risk from trial interventions



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

Protections against risks of transdermal NTG?



Potential side effects

- 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?

Possible protections

- 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 out 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?

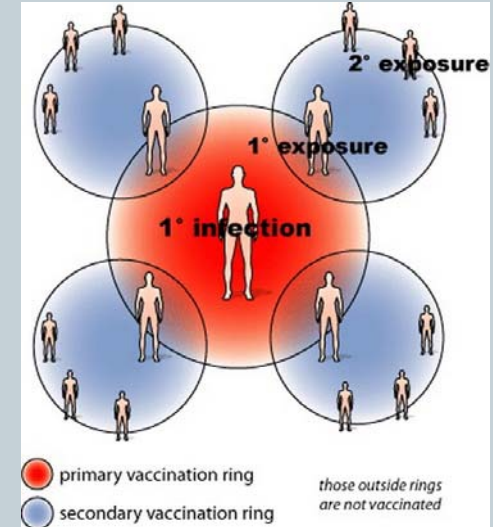
Justifications for placebo or sham control



- 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

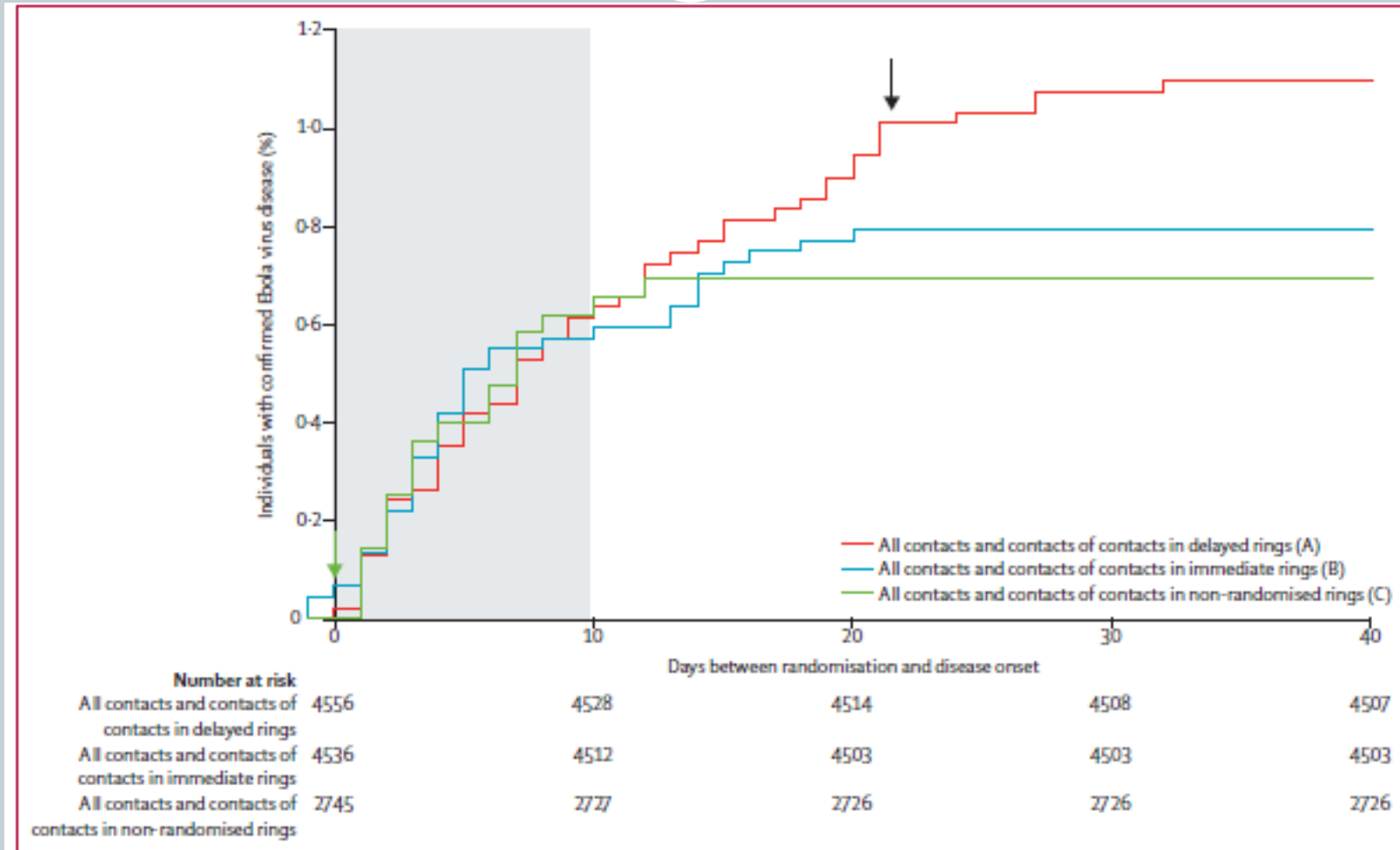


Figure 2: Kaplan-Meier plots for all confirmed cases of Ebola virus disease among all contacts and contacts of contacts in immediate, delayed, and non-randomised clusters

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

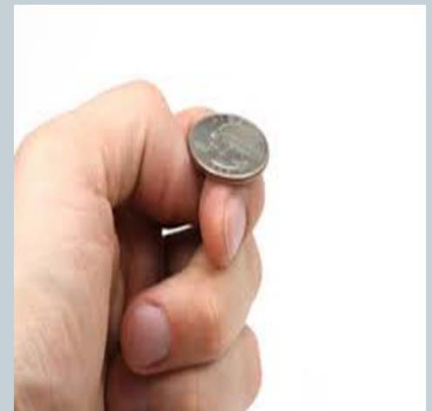


- Cons:
 - Effective drug regimen available in developed countries
 - Promotes double standard of care in developing countries
- Pros:
 - Placebo control design addresses health priorities of the host country
 - No point in comparing short-course therapy to a regimen that is unfeasible in Africa

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 may be related to the intervention
- Unethical when other ongoing aspects of care are contingent on knowledge of intervention 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 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 interventional 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 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



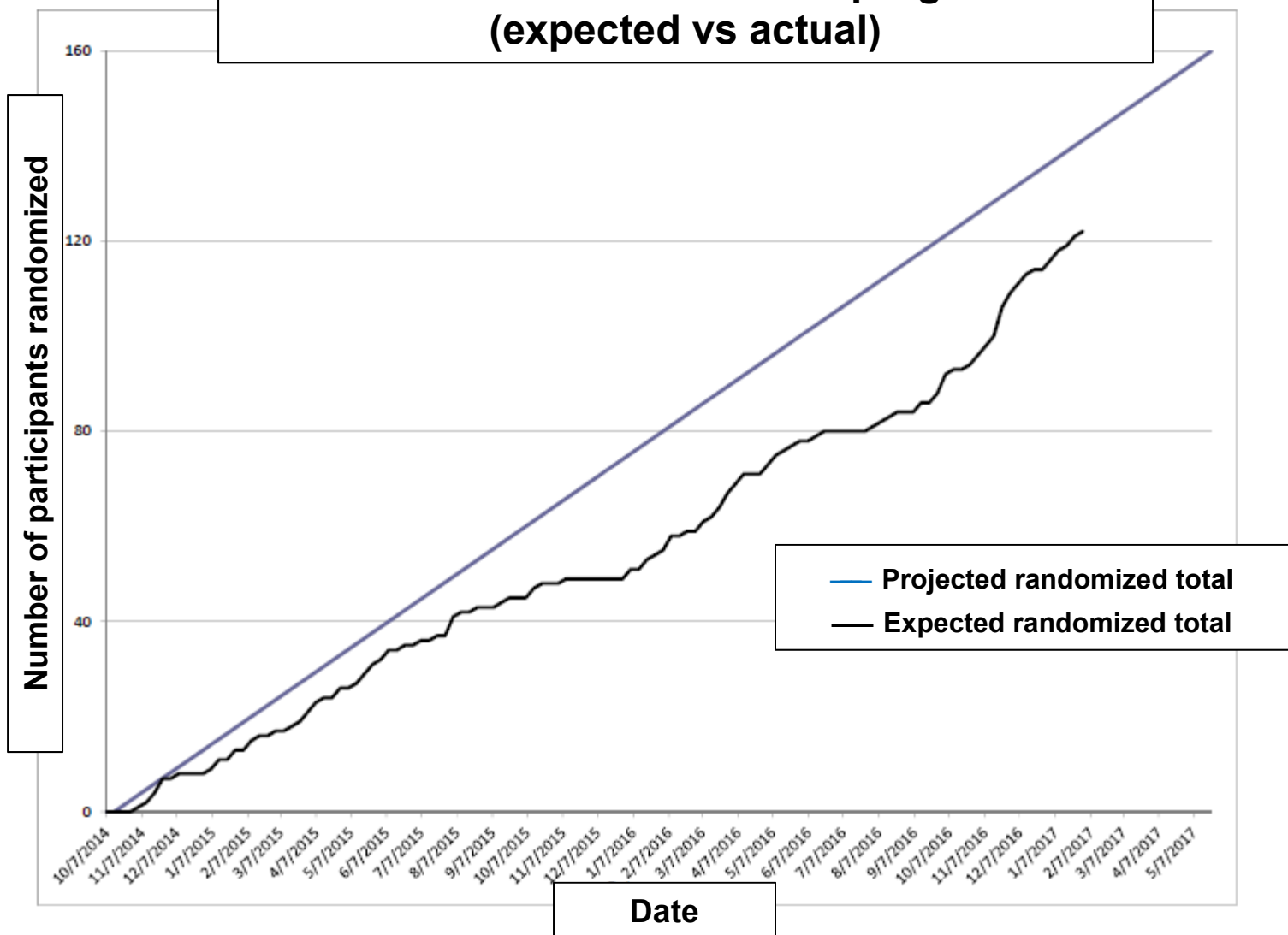
- Double data-entry procedures
- Verification of data by outside party
- Software with automatic checks for outliers
- Posting of queries for missing data values

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)



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 resection of a uterine polyp		X
Following resection, 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
- 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
for menopausal genitourinary symptoms)**

- 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, unblinded statistician
- Between-group findings
- Discussion regarding modifications

Summary – Data & Safety Monitoring Plans



- All interventional studies 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/cancer
- Early clear evidence of benefit
 - ❖ Reduction in genitourinary symptoms
- Not possible to determine 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 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
- Calculation of conditional power of trials to provide compelling evidence of benefit or harm
- Creation of global indices to capture overall benefit vs. harm in trials with multiple important outcomes

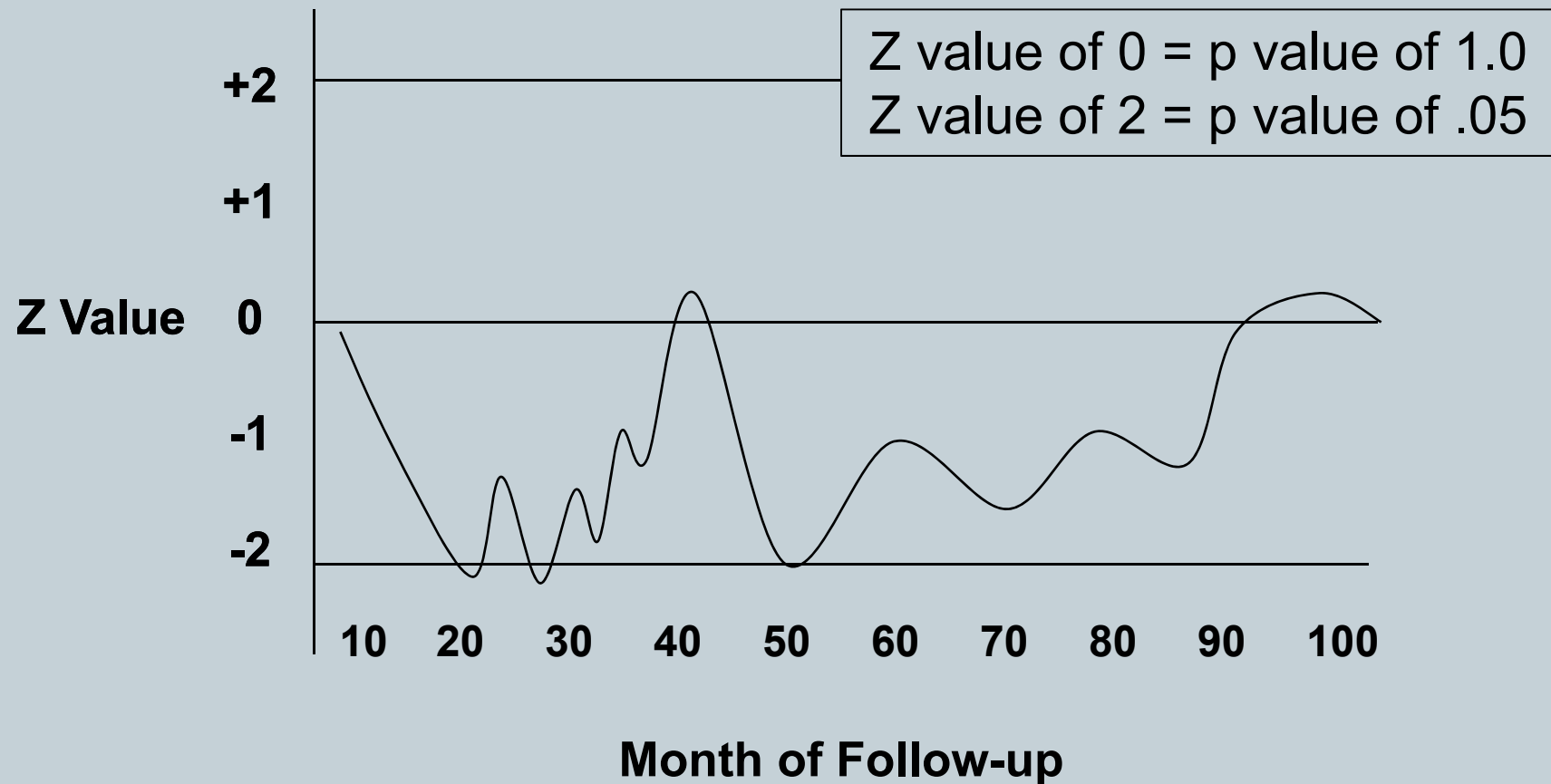
Simplistic approach to assessing early harm or benefit



- Perform tests of significance and stop the trial if any $p < .05$
- Straightforward, but flawed approach

<u>total tests</u>	<u>overall alpha</u>
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



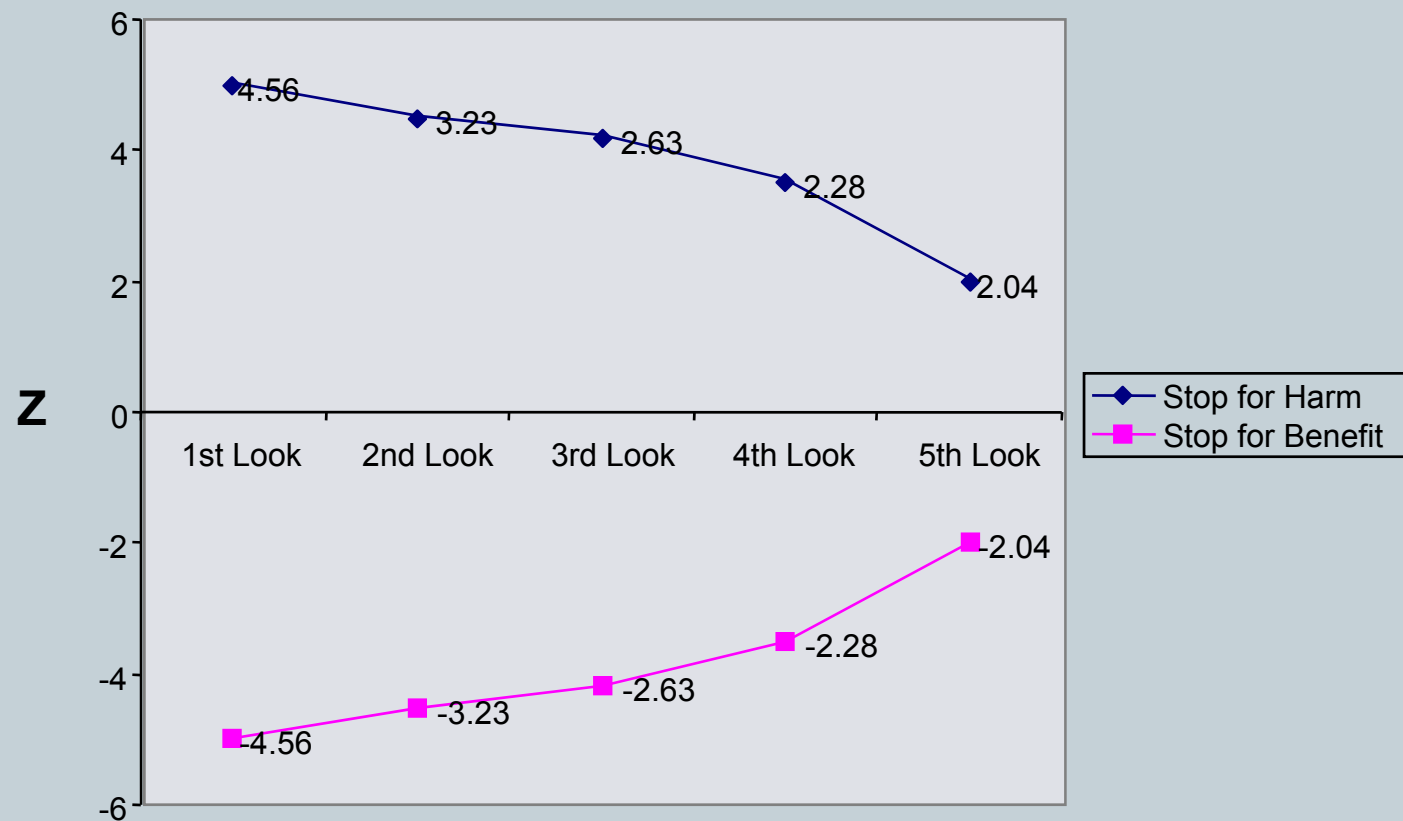
- O' Brien - Fleming small α_i for early interim tests
gradually increasing α_i over time
such that α_f close to final
- Lan-DeMets specifies an α spending function
defined by N previous “looks”
proportion of data/time between

O' Brien-Fleming alpha spending function



<u>Look</u>	<u>Z-value</u>	<u>P-value</u>
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_0 given data so far)

Deterministic Curtailed Sampling

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

Stochastic Curtailed Sampling

- ✦ assume H_0 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%)
- Outcome – myocardial infarction, stroke, death from cardiovascular disease
- Follow-up – 3.5 of planned 5.6 years before trial termination

Accord Study Group, NEJM, 2008

ACCORD trial interim results



Outcome	Percent with outcome		Relative risk	P value
	Intensive therapy	Standard therapy		
Cardiovascular events	6.9	7.2	0.9	.20
Death (any cause)	5.0	4.0	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: 5157 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

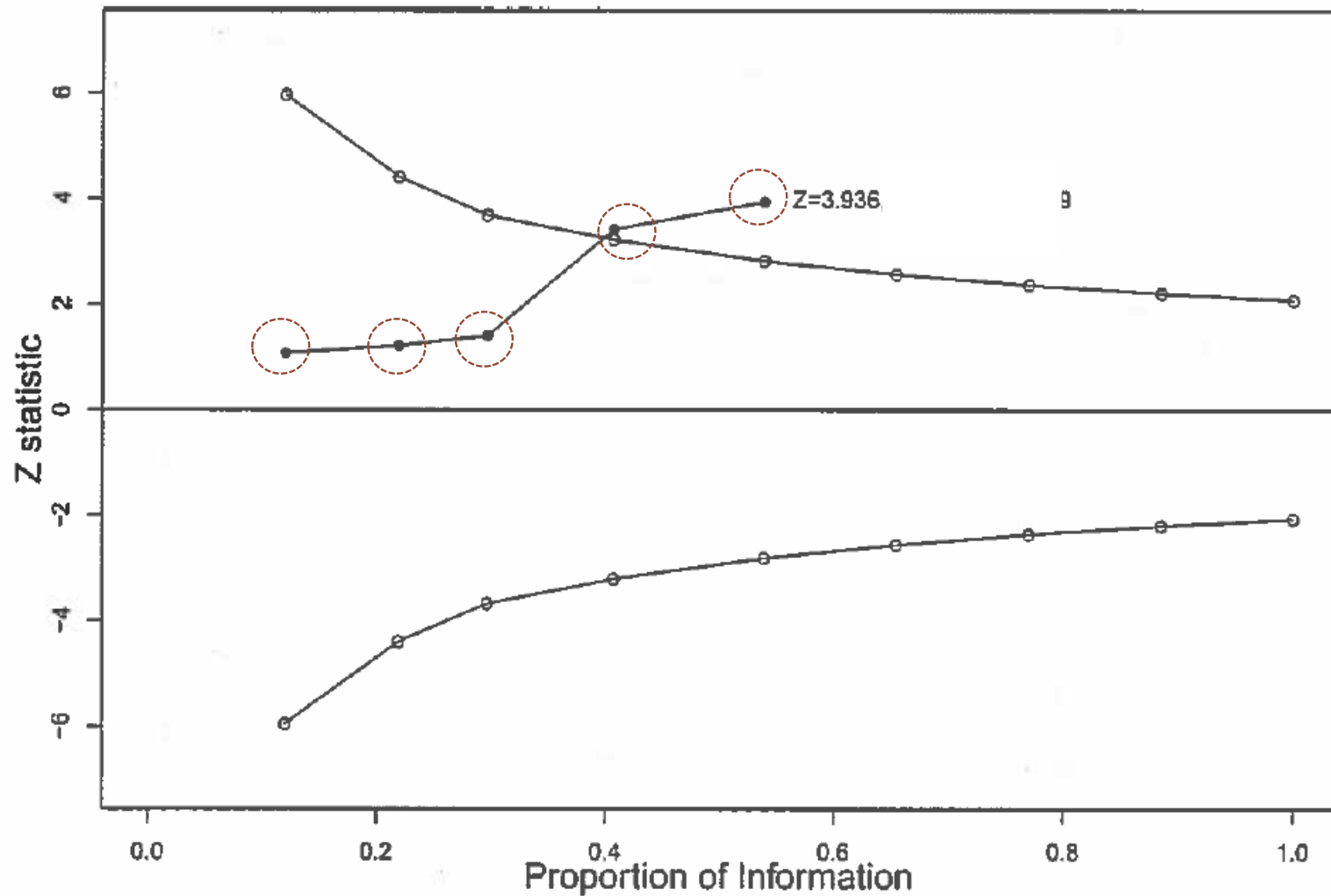
SPRINT interim results



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 ($\geq 30\%$ 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

- | | <i>% Change in Risk</i> |
|-----------------|-------------------------|
| • 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 for DSM plans



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

Questions?