

ADAPTIVE DESIGNS IN CANCER TRIALS: CONSENSUS AND DEBATE

Susan S. Ellenberg, Ph.D.
Center for Clinical Epidemiology and
Biostatistics
U Penn School of Medicine

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ADAPTIVE DESIGNS IN CLINICAL TRIALS

- "Adaptive" simply means that one or more decision points are built into the trial design
 - Trial conduct following decision point depends on data observed to that point
 - Many different ways for trials to be adaptive

RATIONALE FOR ADAPTIVE DESIGNS

- Ethical
 - Need to modify or terminate a study when interim data suggest that patients are not being optimally treated
- Practical
 - Initial design parameters may be inaccurate
 - Without modification, high risk that study will be uninformative
 - Ability to terminate early for futility

EARLY ADAPTIVE DESIGN

- Gehan design for phase 2 cancer trials
 - Plan to study 25 patients
 - If no responses after 14 patients, terminate
 - If at least one response, continue to 25
 - Based on identifying drugs with response rate of 20% or more
- Standard phase 2 design for decades
- Many variations on this design
 - Different target response rates
 - More than 2 stages

PHASE 1 CANCER TRIALS

- Classic design (less aggressive) and newer designs (more aggressive) all include dose escalation schemes that are dependent on observed toxicity at each stage
- All designs are fundamentally adaptive

ADAPTIVE ALLOCATION

- This type of adaptation relates to treatment assignments
- Covariate-adaptive
 - Assign new subject to treatment that produces the best balance on all covariates of interest (Taves, 1974; Simon and Pocock, 1975)
- Response-adaptive
 - Increase probability of assigning treatment with better outcomes
 - "Play the Winner" (Zelen, 1969)

MULTI-STAGE DESIGNS

- Idea: let data from first stage influence design of second stage
- Examples
 - Fleming (1981): two-stage phase 2 trials
 - Thall, Simon, Ellenberg (1988,89): two-stage selection designs

SEQUENTIAL DESIGNS

- Sequential designs for comparative trials allow regular review of interim data with decisions regarding continuation or termination, while maintaining desired low probability of false positive conclusions
 - Continuous monitoring (Armitage, 1969)
 - Group sequential monitoring (Pocock, 1977)
 - Triangular testing (Whitehead, 1983)
 - Bayesian monitoring

CONSENSUS

- Adaptive approaches are appropriate in all phases of clinical research
- While not all proposed adaptive designs are uniformly favored, the concept of adaptation is universally accepted

DEBATE

WHAT IS NEW ABOUT ADAPTIVE DESIGNS?

- Increased use of Bayesian methods due to availability of computing power

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- Increased use of Bayesian methods due to availability of computing power
- Sample-size re-estimation in phase 3 trials based on interim comparison of study arms

SOME HISTORY

- Back in the "old days," clinical trials were sometimes TOO adaptive
- Investigators and sponsors (in many, not all, settings) reviewed data as they came in, made decisions about stopping, continuing or modifying a study based on emerging data
- Statisticians recognized some structure was needed to allow some mid-course changes but permit valid inference

CONCERNS ARISING FROM REVIEW OF INTERIM DATA

- Sponsors/investigators might change design to increase chance of "positive" results (e.g., change the primary endpoint)
- Investigators might change approach to entering, treating or evaluating patients
- Study might be inappropriately terminated early based on suggestive but not definitive data
- Such actions can increase chance of false positive conclusions

SOLUTION: KEEP INTERIM DATA CONFIDENTIAL

- Information on trends can affect
 - Willingness of investigators to continue to enroll patients
 - Management of patients enrolled
 - Evaluation of patient outcomes
 - Ability of sponsor to change protocol
- When changes are influenced by interim data, statistical tests lose meaning

EVOLUTION OF PROCEDURES FOR MAKING CHANGES IN ONGOING (PHASE 3) TRIALS

- Sequential designs focused on early termination, with type 1 error preserved by accounting for multiple looks
- Changes in sample size possible, based on overall event rate
- Changes in endpoints and other trial features generally acceptable when based only on data external to trial
- Emphasis on confidentiality of interim data

NEW APPROACHES

- Proschan and Hunsberger, 1995
 - Extending study based on conditional power
- Fisher, 1998: "Self-designing" trials
 - Sample size adjustment based on interim comparison, not aggregate data
- Many related proposals
 - Cui, Hung, Wang (1999)
 - Lehman and Wassmer (1999)
 - Schafer and Muller (2001)...etc.

FEATURES OF NEW DESIGNS

- Preservation of Type 1 error
- Ability to “start small” and enlarge only if effect size appears likely to be smaller than anticipated/hoped (but large enough to be worthwhile)
- Reverse of traditional approach: “start large” and stop early if big effect

CONVENTIONAL WISDOM DEFIED!

- Early stopping based on interim results well accepted, but not enlarging sample size
- Raised specter of "old days"
 - emerging results widely available
 - common to continue enrollment in hopes of nudging a suggestive p-value across the magic 0.05 boundary

CONTROVERSIES

- Do designs permitting sample size adjustment on the basis of interim comparative data really improve trial efficiency as compared to traditional sequential designs?
- Do these designs create potential for bias in trial conduct by providing information on emerging results?

EFFICIENCY

- Adaptive designs shown to be somewhat less efficient than group sequential designs
 - Tsiatis and Mehta (2003)
 - Jennison and Turnbull (2003)
- Adaptation may result in larger trial as well as smaller trial
- Careful upfront planning may achieve the desired flexibility more efficiently, using conventional group sequential designs

INFLUENCING TRIAL CONDUCT

- If an adaptive design is used, and at some point the sample size is increased, can this affect trial conduct?
 - Sponsor will know new sample size
 - Investigators will know new sample size
 - Basis for sample size changes will have to have been specified in protocol

FISHER, 1997

- Gave example: 2-stage trial
- Formula to calculate additional sample size after first stage, based on first stage sample size, observed effect, and desired error probabilities
- If new sample size is provided, straightforward to calculate back to interim observed effect

UNBLINDING

- Sample size increases will have to be made known to sponsor, others involved in trial
- If procedures are clearly pre-specified, sample size increases can be used to back-calculate interim estimate of treatment effect
- If procedures are not pre-specified, sponsor is essentially committing to open sequential design; seems impractical

IMPLICATIONS FOR TRIAL CONDUCT

- If interim results become known outside the DMC, all the concerns noted earlier will re-arise
- If interim results can become known by, say, investment firms, why shouldn't they be provided to potential new subjects in the informed consent?

WILL THE PUBLIC REALLY PAY ATTENTION TO IMPLICATIONS OF SAMPLE SIZE CHANGES?

- *Seattle Times*, August 2005
 - Investment firms interviewing physicians involved in clinical trials as investigators or DMC members
 - Firms have been able to glean sufficient knowledge to make highly accurate guesses about trial outcomes
 - Major effects on stock prices
 - Potential impact on ability to conduct and complete interpretable clinical trials

PROBLEM RECOGNIZED

- Schäfer and Müller: “[A]... problem is that knowledgeable observers can draw conclusions about the current observed treatment differences from the action determined.”
- Chen, DeMets, Lan: “Further research is still needed to investigate the impact...on the conduct of the trial and to find ways to protect the integrity of the study.”

WHAT INFORMATION IS PROVIDED BY KNOWING THAT A STUDY WITH A TRADITIONAL SEQUENTIAL DESIGN HAD AN INTERIM REVIEW BUT DIDN'T STOP?

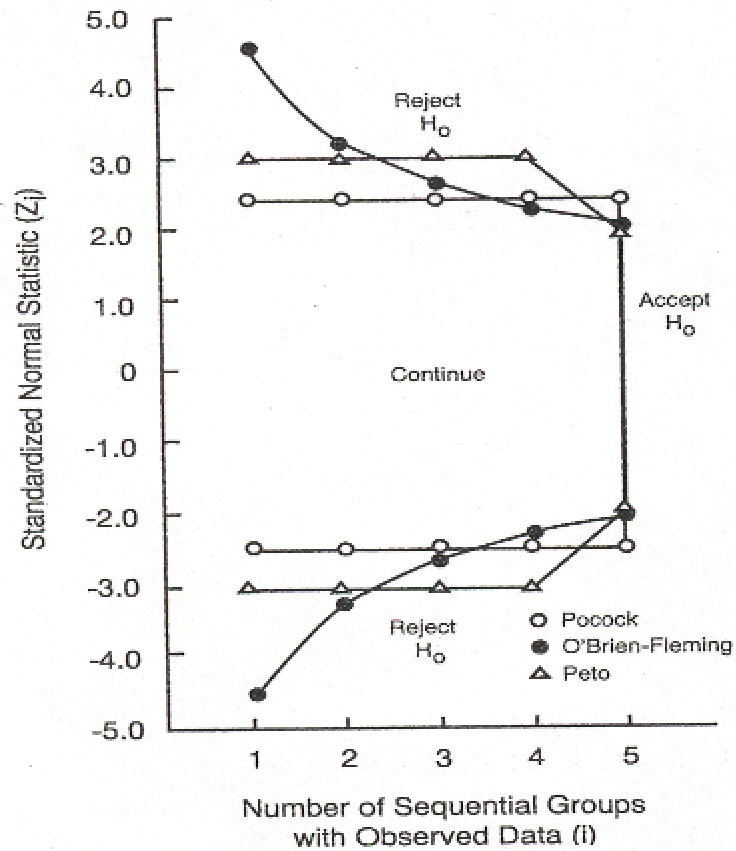
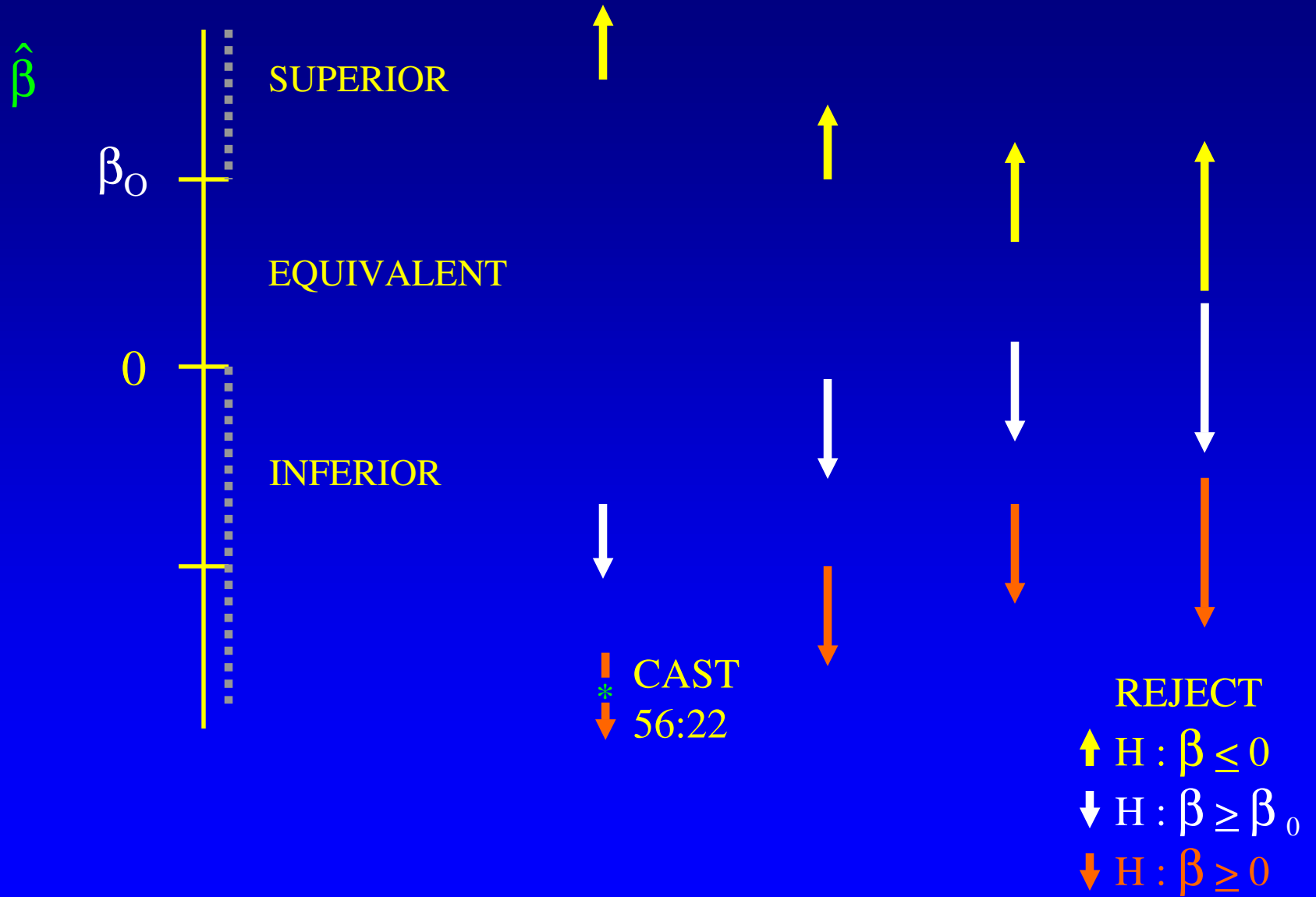


Fig. 15-4 Three group sequential stopping boundaries for the standardized normal statistic (Z_i) for up to five sequential groups with two-sided significance level of 0.05.

WHAT IF FUTILITY BOUNDARIES ARE ADDED?

- If futility boundaries are pre-specified, a DMC recommendation to continue a study is more informative
- Continuing trial conveys that treatment effect is neither hugely positive (such that early stopping would be recommended) nor hopelessly close to zero or in the wrong direction
- Cannot back-calculate to interim estimate of treatment effect; bounds on size of effect still fairly wide

- Symmetric Group Sequential Boundaries



CONCLUDING REMARKS

- Actions following interim review inevitably reveal something about the accumulating data
- Continuation of a study being monitored by traditional group sequential design narrows range of possible interim differences, but range remains wide, even when futility boundaries are added
- Concerns about study integrity should be addressed before adaptive designs become more widely used to change sample size

CONCLUDING REMARKS

- Increase in sample sizes when based only on overall estimate of outcome (pooled over both groups) provides limited information about treatment difference
- Increase in sample size when based on interim comparison may reveal interim treatment effect
- Concerns about study integrity should be addressed before adaptive designs using sample size re-estimation become more widely used in phase 3 trials



CHANGES TO PROTOCOL

- Long-standing concern about sponsors with knowledge of interim data making changes to protocol that might bias toward a favorable result
- Extreme example: sponsor sees that hypothesis test on interim data produces a nominal p-value of 0.04, terminates study and declares victory (this used to happen a lot before the FDA got wise)

SEQUENTIAL DESIGNS

- Sequential designs were developed for clinical trials to deal with the recognized need to monitor accumulating data
 - No major safety issue requiring protocol change or suspension
 - Data not yet definitive—appropriate and ethical to continue trial

MAINTAINING CONFIDENTIALITY WITH GROUP SEQUENTIAL DESIGNS

- Establish an independent data monitoring committee that would review accumulating data at regular intervals and make recommendations to trial sponsor/steering committee
- DMC would be only body with access to interim data
- Trial protected from unquantifiable increases in type 1 error

MAKING PROTOCOL CHANGES

- DMC may recommend changes such as
 - Stopping the trial
 - Modifying the dose for safety reasons
 - Modifying the informed consent
 - Anything else related to safety
- Protocol team (with no access to interim comparisons) may
 - Increase the sample size (eg, due to low event rate)
 - Change concomitant medication strategy
 - Anything else based on non-confidential interim results and/or external information

WHAT DO PROTOCOL CHANGES TELL YOU ABOUT INTERIM RESULTS?

- If study is stopped early—a lot, but irrelevant to credibility of study
- If study is modified to mitigate a safety issue, no information about efficacy other than that given by study continuing
- If sample size increased, information that overall event rate is low
 - Some may view this as indication that treatment is working, but often not the case

NOTE

- Further discussion focuses on superiority trials—trials designed to show efficacy of new drug, or superiority of one treatment regimen over another.
- Equivalence/noninferiority trials raise other issues beyond scope of current discussion
- Bayesian designs are also of interest for adaptive approaches, but are not considered here

ADAPTIVE DESIGNS

- Much interest over past 10 years
- Motivated by desire for increased flexibility in conducting trials
 - Ability to adjust design if initial assumptions on which study design was based seem to have been off the mark
 - Many possible ways to adjust design; today will focus on sample size changes

ADAPTIVE STRATEGIES

- Bauer and Kohne, 1994
- Proschan and Hunsberger, 1995
- Lloyd Fisher, 1997
- Lehmacher and Wassmer, 1999
- Schäfer and Müller, 2001
- Li, Shih, Xie and Lu, 2002
- Chen, DeMets, Lan, 2004

JOURNAL SPECIAL ISSUES

- Journal of Biopharmaceutical Statistics
 - Special Issue on Adaptive Designs in Clinical Research, 2005
- Statistics in Medicine
 - Proceedings of workshop on adaptive designs jointly sponsored by FDA and the Harvard-MIT Division of Health Sciences & Technology, 2006

TYPES OF ADAPTIVE DESIGNS

- Multiple strategies proposed
- Level of flexibility varies
 - Two-stage plans
 - Multi-stage plans
 - Open designs allowing reconsideration of sample size at any time