The role of Statistics in Cancer Research

Daniel Sargent, PhD
ALLIANCE Group Statistician

May 2014

Objectives

After the presentation, participants will be able to:

- Restate the overall purpose of statistics in research.
- Discuss the advantages and limitations of randomization as it relates to subject enrollment, trial conduct and application of study results.
- Differentiate between various types and uses of analysis and their role in evaluating treatment efficacy and making trial conduct decisions.
- Compare the statistical advantages and disadvantages of restrictive vs broad eligibility criteria and the impact on overall study design.

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

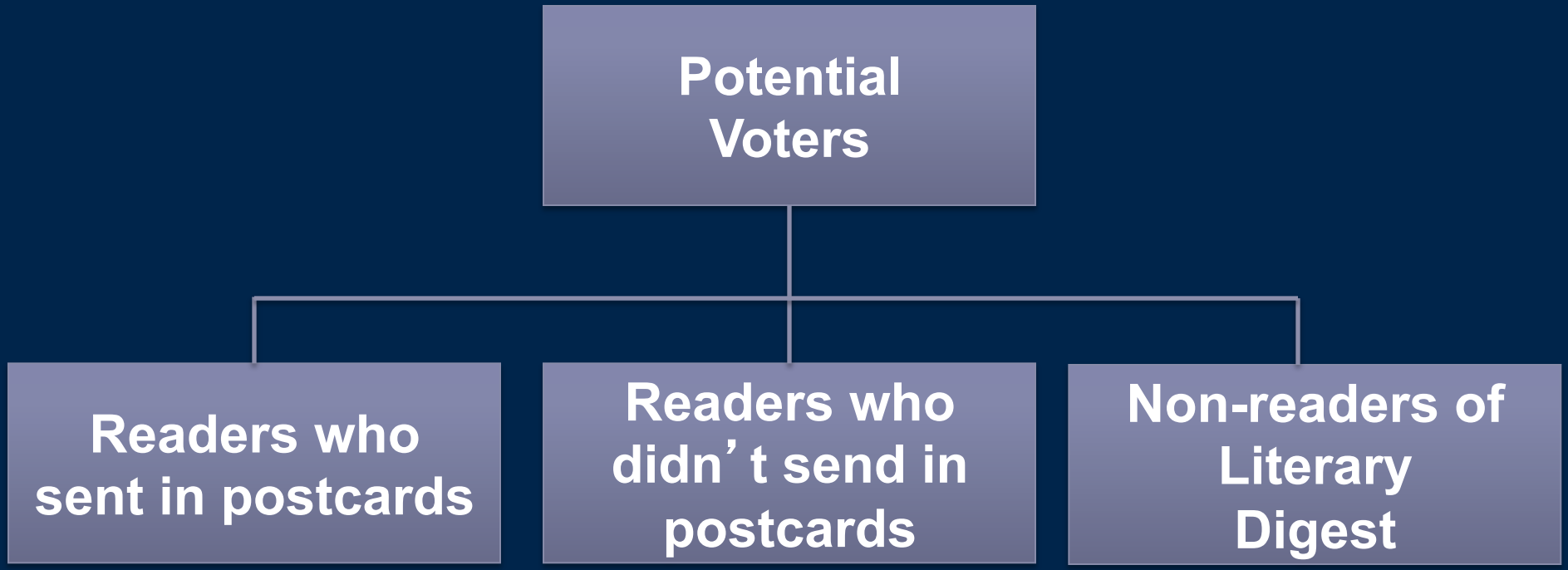
The Literary Digest predicted Alf Landon would win the presidency in 1936

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

1936 PRESIDENTIAL ELECTION RESULTS

	# electoral votes
• Roosevelt	523
• Landon	8

1936 Presidential election: Sampling



ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Outline

- What is statistics?
- Need for randomization
- Types of analysis
- Subgroup analysis
- Interim analyses and DSMBs
- Surrogate Endpoints
- Eligibility Criteria

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Statistics

- A foundation for scientific decision-making
- The ability to quantify errors
- The ability to generalize from those tested to a population

- These items are much more important than p-values

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Decisions in Clinical Trials

	Truth: No Difference Between Regimens	Truth: Difference Between Regimens
Action: Conclude No Difference		
Action: Conclude a Difference		

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Decisions in Clinical Trials

	Truth: No Difference Between Regimens	Truth: Difference Between Regimens
Action: Conclude No Difference	True Negative	
Action: Conclude a Difference		True Positive

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Decisions in Clinical Trials

	Truth: No Difference Between Regimens	Truth: Difference Between Regimens
Action: Conclude No Difference	True Negative	**False Negative; Type II error**
Action: Conclude a Difference	**False Positive; Type I error**	True Positive

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Analogy

Jury Trial (criminal law)	Clinical Trial
• Presume innocent	• Assume the null hypothesis
• Goal: convict the guilty	• Goal: detect a true difference
• "Beyond reasonable doubt"	• "Level of significance"
• Requires: evidence (convincing testimony)	• Requires: evidence (adequate sample size)
• Mistake: convict innocent person	• Mistake: False positive (limit to 5%)
• Mistake: acquit guilty person	• Mistake: False negative (limit to 10%)

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

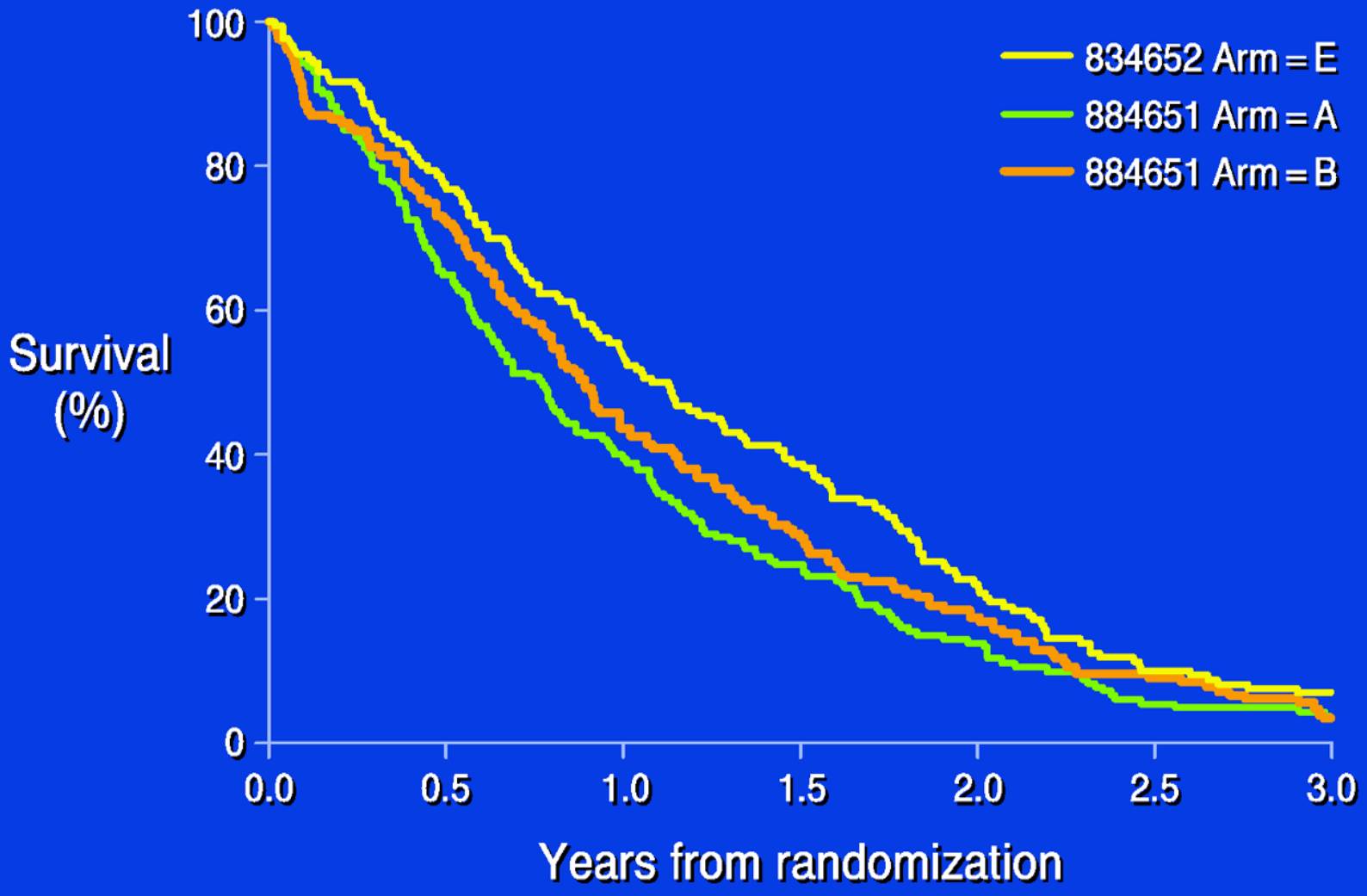
Randomized Clinical Trials

The randomized clinical trial (RCT): "a last resort for the evaluation of medical interventions. It is slow, ponderous, expensive, and often stifling of scientific imagination and creative change in ongoing protocols ..., however, no other method for studying the merits of clinical treatment regimens can approach the precision of estimating effects and the strength of inference permitted by sound RCTs."

Bailar, 1983

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Survival Curves for 3 Treatment Regimens



Randomization: Advantages

- Reduce Bias in trial enrollees
  - Patient selection by treating physician
  - Self-selection by patients

- Reduce Bias in trial conduct
  - Ineligibles
  - Refusals
  - Unknown confounding factors

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Randomization: Caveats

- Randomization does not ensure the study will include a representative sample of all patients with the disease

- Randomization does help ensure an unbiased evaluation of the relative merits of the two treatments for the types of patients entered

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Types of Analysis

- Intention to treat: All patients included in the group to which they were randomized irrespective of compliance, administrative errors, or other protocol deviations.

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Types of Analysis

- Treatment received: Patients included in the group corresponding to treatment they actually received.

- Typically the intention to treat analysis answers the relevant clinical question.

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Multiple Comparisons

- Beware of Field of Dreams: ‘If you test it (enough times), it will come up significant’
- Example
  - 20 Markers, with prevalence from 10 - 50%, measured on 100 patients
  - None related whatsoever to response
  - Compare response rate in those with and without marker
  - Overall response rate 40%

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Multiple Comparisons

- Results
  - Response rates ranging from 22 - 75% in the marker (+) group
  - Difference in response rates between (+) and (-) ranged from 0.5 - 31%
  - 2 had $p < 0.05$ comparing response rate in (+) and (-) patients

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Subgroup Analyses

- Is it expected that the actual treatment effect may differ in a meaningful way between different subgroups?

- Apparent differences can result by chance alone
  - Increased risk of spurious results with greater number of subgroup analyses

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Beware of Subset Analysis (1)

5-FU and levamisole as adjuvant treatment for Dukes C colon cancer

1. Mayo Clinic Trial (Laurie et al, *J Clin Oncol* 1989)
   More effective for men, older patients
2. SWOG Trial (Moertel et al, *N Engl J Med*, 1990)
   More effective for women, younger patients
3. Meta Analysis (Gill et al *J Clin Oncol* 2004)
   No difference in by sex or age

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Beware of Subset Analysis (2)

- ISIS Cardiac Trial: 17,000 patients
  - Found aspirin > placebo at preventing vascular deaths
  - Subgroups: Didn't work in:
    - Non-diabetics
    - Systolic BP < 100 or > 175

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Beware of Subset Analysis (2)

- ISIS Cardiac Trial: 17,000 pts
  - To determine ‘significance’, compared these differences to difference in astrological signs
  - No patient characteristic separated patients by more than Gemini/Libra vs other
  - Concluded no real subgroup effects

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Monitoring Clinical Trials: Efficacy

- Patients enter sequentially over time, therefore information about the treatments increases as the trial progresses.
- How long is it ethical to continue enrollment in the face of mounting evidence?

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Interim analyses

- Definition - An analysis conducted prior to the planned final analysis
- Possible actions:
  - Continue as planned
  - Modify the trial
  - Stop
- Controlled by an independent DSMB

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Possible Reasons for Stopping Early

- One treatment convincingly superior or inferior
- Treatments convincingly not different
- Excessive toxicity
- Low accrual
- External evidence (e.g., other trials) leading to scientific irrelevance

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

DSMBs

- Independent panel of experts, including physician, statistician, lay people
- Have access to full data
- Report directly to study sponsor
- Strongly recommended by the FDA for all Phase III trials, becoming required by many IRBs

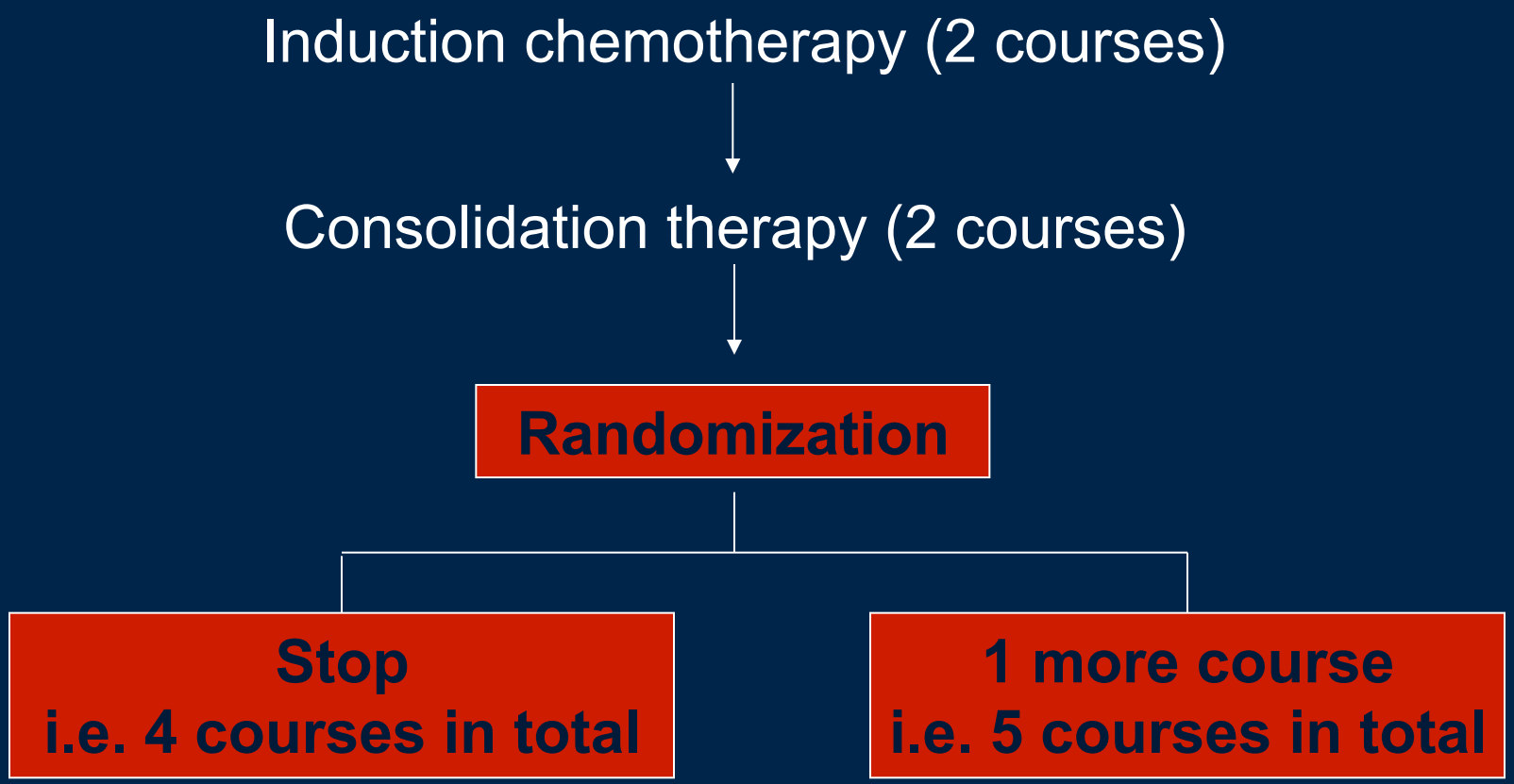
ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Potential Problems with Stopping Early

- Inflation of error rates: false positive or false negative
- Biased estimates of treatment effects
- Decreased precision from original plan
- Inability to investigate secondary objectives
- Conclusions may change with further follow-up
- Lack of credibility - failure to influence medical practice

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

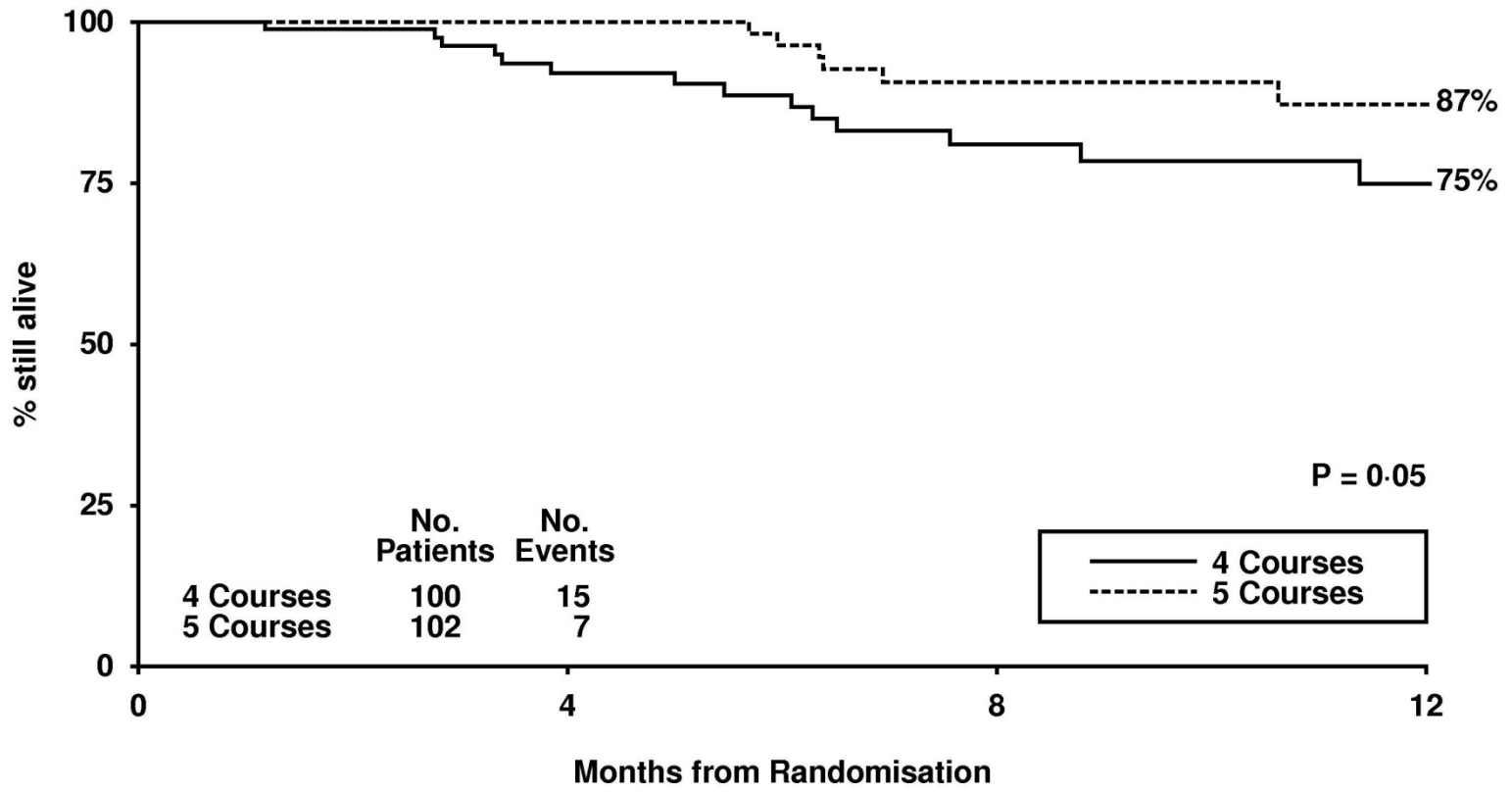
MRC AML12 – Design



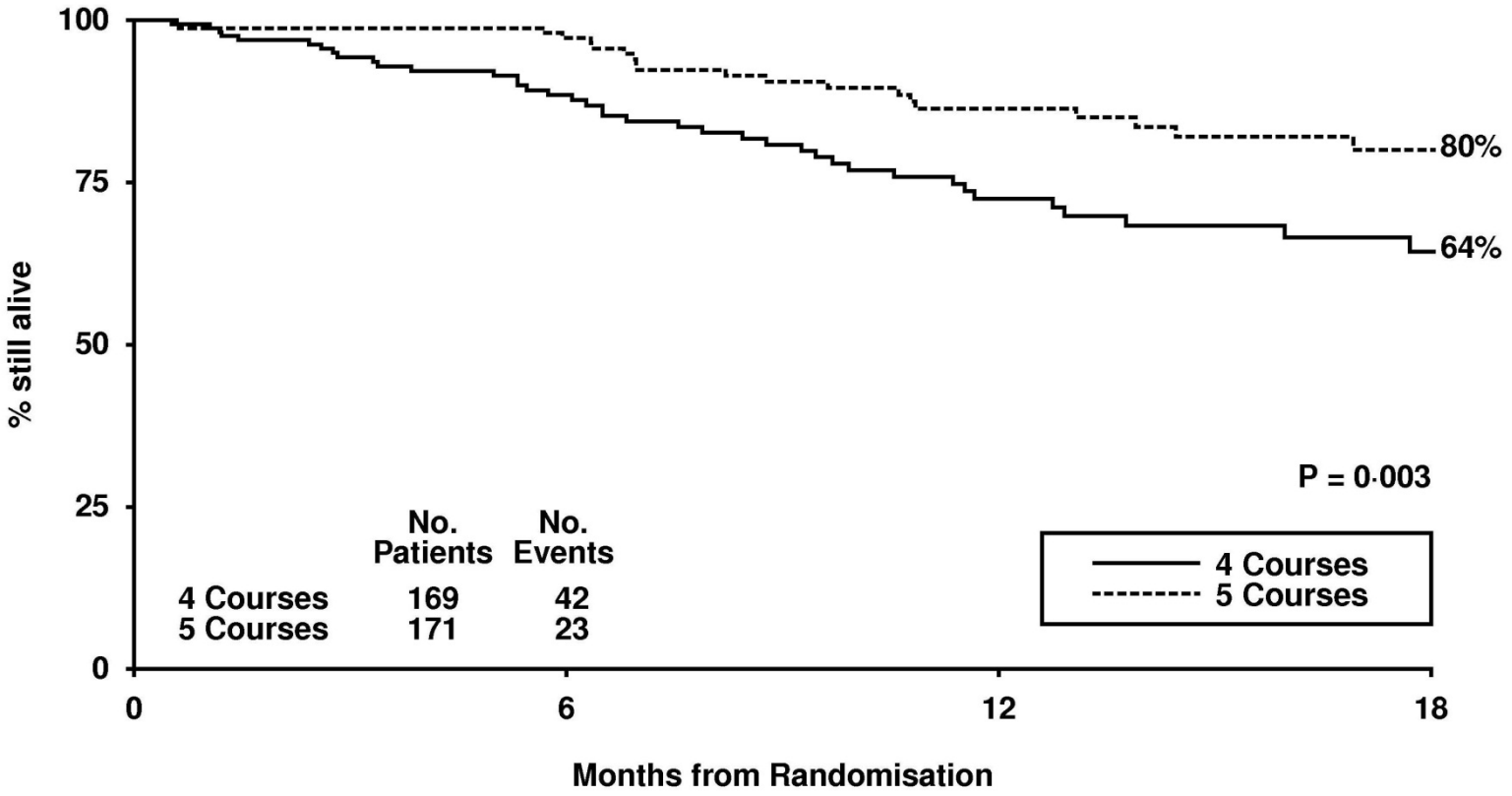
Goal: 1000 Patients

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

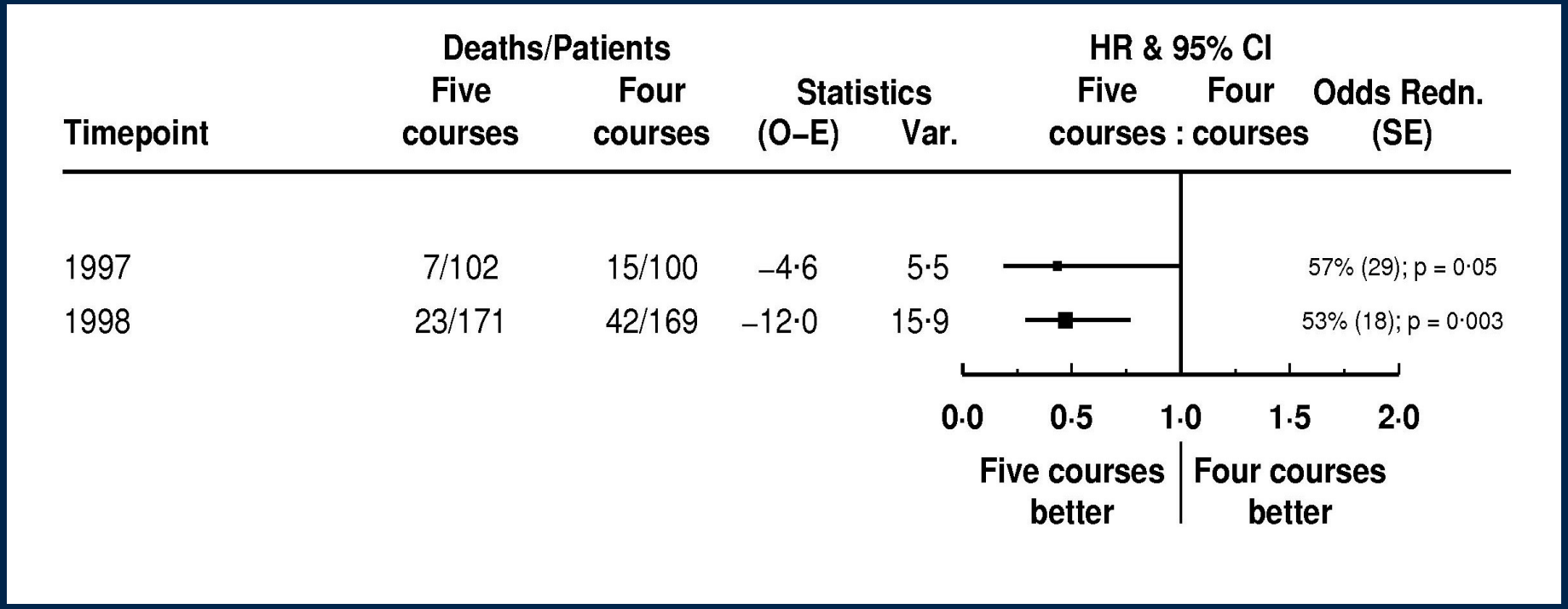
AML12 – First DMC review (1997)



AML12 – Second DMC review (1998)

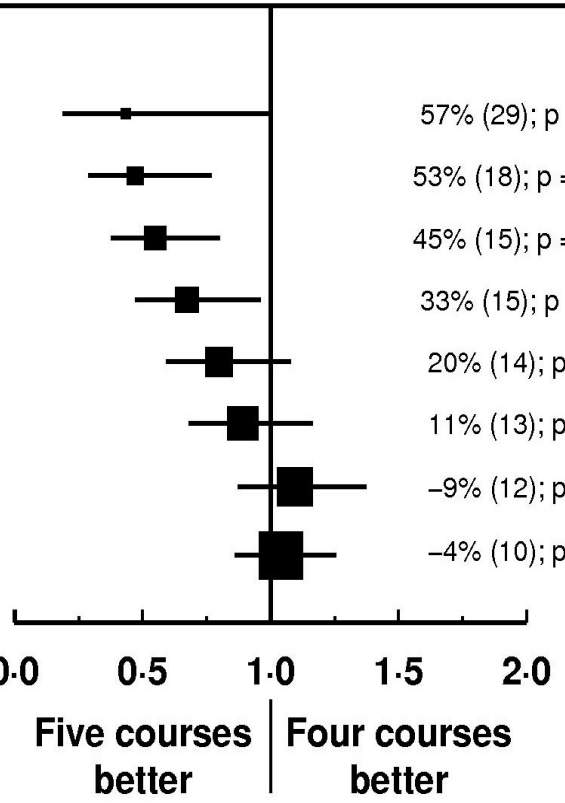


AML12 – Hazard ratio plot



AML12 – Subsequent results

Timepoint	Deaths/Patients Five courses	Four courses	Statistics (O–E)	Var.	HR & 95% CI Five courses : Four courses	Odds Redn. (SE)
1997	7/102	15/100	–4·6	5·5		57% (29); p = 0·05
1998 (1)	23/171	42/169	–12·0	15·9		53% (18); p = 0·003
1998 (2)	41/240	66/240	–16·0	26·7		45% (15); p = 0·002
1999	51/312	69/309	–11·9	30·0		33% (15); p = 0·03
2000	79/349	91/345	–9·5	42·4		20% (14); p = 0·1
2001	106/431	113/432	–6·2	53·7		11% (13); p = 0·4
2002	157/537	140/541	6·7	74·0		–9% (12); p = 0·4
2003	220/615	215/619	4·3	108·6		–4% (10); p = 0·7



ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

AML12 - Summary

- DMC's decision supported by subsequent results
- Main reason for not stopping was that treatment effect "too good to be true" – 50% reduction in mortality with just 25% more therapy
- Had trial been stopped, patients would now be recommended 5 courses (toxic, 3-4 weeks in hospital, ~ 3% die)

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Eligibility Criteria

- Eligibility criteria determine the study population, frequently a subset of the target population.
- Trade off - Restrictive vs. Broad

  Restrictive: Advantages

  1. Homogeneous patients
  2. Smaller sample sizes

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Eligibility Criteria (continued)

Trade off - Restrictive vs. Broad

Restrictive: Disadvantages

1. Results may not be generalizable
2. Fewer patients eligible implies longer study duration
3. Patients treated off study with some treatments anyway
4. Patient access to therapy

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Toward More Liberal Entry Criteria

- "Uncertainty principle": any patient for whom the effect of treatment is uncertain should be included.
- Eligibility criteria should be loosened as trials become larger.

	Sample Size	Eligibility Criteria
Phase I	Small	Restrictive
Phase II	↓	↓
Phase III	Large	Liberal

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Endpoints

- Must be
    a. Sensitive to the effect of treatment
    b. Clinically relevant
- Sensitive in what way?
    a. Biologic activity - short term
    b. Clinical efficacy - long term
- Question: When can a short term endpoint be substituted for a long term endpoint? That is, when can we use a surrogate endpoint?

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Surrogate endpoint example: AIDS

- HIV Infection associated with progressive depletion of CD4+.
- Multiple studies show CD4+ level predicts onset of AIDS.
- Zidovudine (ZDV) a potent inhibitor of HIV replication in vitro.
- Two large studies (BW 02: 281 pts, and ACTG 016: 351 pts) demonstrated large beneficial effect of ZDV on CD4+
- 1990 US: Placebo controlled trial (ZDV vs. placebo) with survival endpoint cannot be done.

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Surrogate endpoint example: AIDS

- 1993 Concorde Study: 1749 patients in Europe:
  - Result 1: Immediate ZDV maintained higher CD4+ count than deferred ZDV.
  - Result 2: Immediate ZDV: 95 deaths
    Deferred ZDV: 76 deaths
- Conclusion: "Results do not encourage early use of ZDV in symptom free HIV infected adults."

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Summary

- Much of statistics, when you really think about it, is common sense
- Computers can calculate numbers, people need to make decisions
- Proper statistical thought provides the data to inform these decisions

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY