Use of Screening Studies

Medical Studies as Diagnostic Tests

Clinical testing of a new treatment or preventive agent is analogous to using laboratory or clinical tests to diagnose a disease

Goal is to find a procedure that identifies truly beneficial interventions

Not surprisingly, the issues that arise when screening for disease apply to clinical trials

- Predictive value of a positive test is best when prevalence is high
- Use screening trials to increase prevalence of beneficial treatments

Medical Studies as Diagnostic Tests

Statistical hypothesis testing as a diagnostic test

P value: Probability of observing positive (statistically significant) test in absence of true treatment effect

- Level of significance is 1 - specificity
- Common choice of α=.05 means specificity is 95%

Medical Studies as Diagnostic Tests

Statistical hypothesis testing as a diagnostic test (cont.)

Statistical power: Probability of observing positive test in presence of true treatment effect

- Power is sensitivity
- Common choice of 80% sensitivity (not usually recommended by me)

Medical Studies as Diagnostic Tests

Statistical hypothesis testing as a diagnostic test (cont.)

Prevalence is the percentage of effective treatments among all tested treatments

Positive predictive value is the probability that a statistically significant trial indicates a truly useful treatment

Preliminary Studies in Screening

In cancer less than 5% of treatments studied in clinical trials are adopted

NCI drug development program 1970 - 1985

- 350,000 unique chemical structures studied
- 83 pass preclinical and phase I testing
- 24 pass phase II tests for biological activity

Preliminary Studies in Screening

Two possible approaches to studying new treatments

Study every treatment in a large definitive experiment

Perform small screening trials, with confirmatory trials of promising treatments passing early tests

We can explore our ability to identify beneficial treatments with limited resources

Preliminary Studies in Screening

Scenario 1: Only large trials

10% of drugs being investigated truly work

Level of significance .05

1000 subjects provide 97.5% power to detect clinically important treatment effect

1,000,000 subjects available for clinical trials

- Study 1,000 new treatments
- 100 effective treatments, 900 ineffective treatments

Preliminary Studies in Screening

Scenario 1: Only large trials (cont.)

Statistically significant results: 143 significant trials

- 97.5% of effective treatments: 98 studies significant
- 5% of ineffective treatments: 45 studies significant

Predictive value of a positive: 68%

- Only 68% of the 143 treatments identified truly work

Preliminary Studies in Screening

Scenario 2: Use of pilot studies

10% of drugs being investigated truly work

Level of significance .05

500 subjects provide 80% power to detect clinically important treatment effect

50 subjects provide 15% power to detect clinically important treatment effect

Preliminary Studies in Screening

Scenario 2: Use of pilot studies (cont.)

1,000,000 subjects available for clinical trials

- 625,000 subjects in pilot studies of 12,500 new treatments
- 374,500 subjects in confirmatory trials of 749 new treatments

Preliminary Studies in Screening

Scenario 2: Use of pilot studies (cont.)

Pilot Studies

- Investigate 12,500 new treatments in pilot studies (625,000 subjects)
- 1,250 effective treatments, 11,250 ineffective treatments

Preliminary Studies in Screening

Scenario 2: Use of pilot studies (cont.)

Statistically significant results: 749 significant pilot studies

- 15% of effective treatments: 187 studies significant
- 5% of ineffective treatments: 562 studies significant

- Predictive value of a positive: 25%
- 25% of treatments in significant pilot studies truly work

Preliminary Studies in Screening

Scenario 2: Use of pilot studies (cont.)}

Confirmatory Trials

- Investigate 749 new treatments (374,500 subjects)
- 187 effective treatments, 562 ineffective treatments

Preliminary Studies in Screening

Scenario 2: Use of pilot studies (cont.)}

Statistically significant results: 178 significant pilot studies

- 80% of effective treatments: 150 studies significant
- 5% of ineffective treatments: 28 studies significant

- Predictive value of a positive: 84%
- 84% of the 178 identified treatments truly work

Preliminary Studies in Screening

Comparison of scenarios

Scenario 1: Only large trials

- Use 1,000,000 subjects
- Screen 1,000 new treatments
- Adopt 98 effective treatments
- Adopt 45 ineffective treatments

Scenario 2: Use of pilot studies

- Use 999,500 subjects
- Screen 12,500 new treatments
- Adopt 150 effective treatments
- Adopt 28 ineffective treatments

Preliminary Studies in Screening

Bottom line

Pilot studies increase the predictive value of a positive study while using the same number of subjects. A greater number of effective treatments are identified due in part to the greater number of treatments screened.

- Phases of clinical trials

(Different choices for statistical power in screening and confirmatory trials can be used to optimize strategy for a particular setting)