Intent-to-treat Analysis of Randomized Clinical Trials

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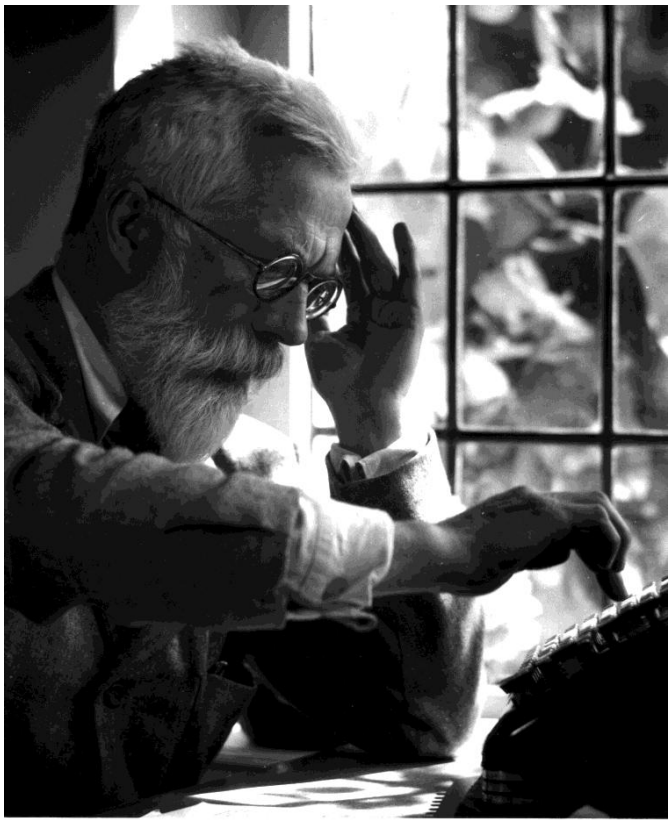
Outline

- Origin of Randomization
- Randomization in Clinical Trials
- Intention-to-Treat Analysis
- Pragmatic vs. Explanatory Analyses
- Compliance with Treatment
- Withdrawal from Trial
- Coronary Drug Project
- Actual Practice of ITT

Origin of Randomization



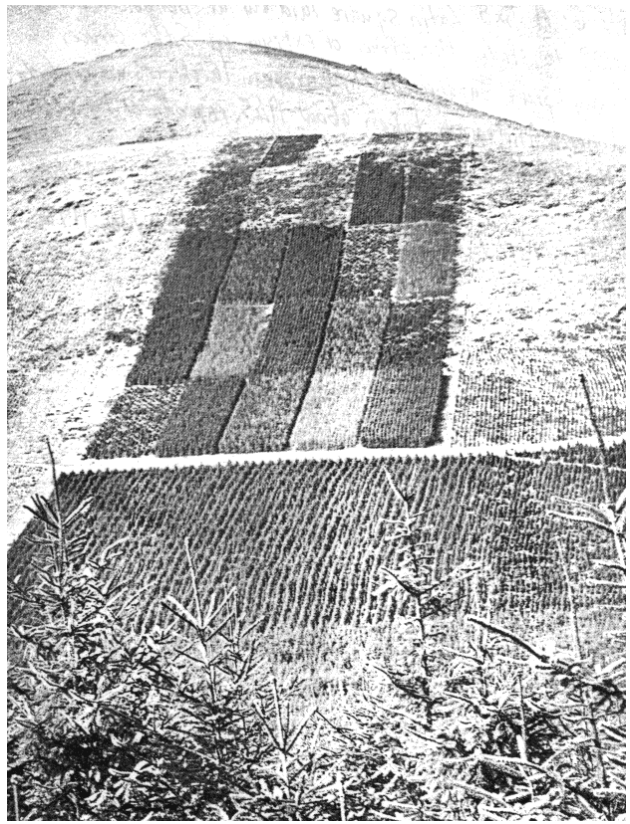
- Randomization for experimental studies was established by R.A. Fisher in 1923
- Statistician at the Rothamsted agricultural experimental station

Origin of Randomization

- The problem was to compare the effect of different fertilizers on potato yield
- Old method was
  - Apply each fertilizer to an entire field
  - Compare yields between fields
- But, some fields (and parts of each field) are more fertile than others

Origin of Randomization

- Fisher's method
  - Divide fields into small plots and rows within plots
  - Apply fertilizers by row within plots
  - **Randomly** assign fertilizers to rows



Origin of Randomization

- Randomization destroys any connection between soil fertility and treatment
- Randomization allows experimental results to be analyzed by permutation test
  - Treats outcomes as fixed
  - Treatment assignments are source of randomness in the analysis
  - Standard statistical tests (t-test, F-test, etc) approximate permutation test results

Origin of Randomization

- Randomization plays 2 key roles
  - Produces groups that are not systematically different with regard to known and *unknown* prognostic factors
  - Permits a valid analysis
    - Permutation test is justified by randomization
    - Standard analyses are valid approximations of the correct permutation test

Randomization in Clinical Trials

- Fisher's method is the foundation of randomized controlled trials
- However, unlike rows of plants, people sometimes
  - Fail to comply with randomly assigned therapies
  - Do not complete the trial

Randomization in Clinical Trials

- Randomization provides a time point when the two groups start to diverge in ways that might be unpredictable

Randomization in Clinical Trials

- Any difference between groups that arises after randomization could be due to consequences of the randomized treatment assignment
- Adjusting the analysis of treatment effect by post-randomization group differences could introduce bias

Intention-to-Treat Analysis

Includes all randomized patients in the groups to which they were randomly assigned, regardless of their adherence with the entry criteria, regardless of the treatment they actually received, and regardless of subsequent withdrawal from treatment or deviation from the protocol

(Lloyd) Fisher et al., 1990

Intention-to-Treat Analysis

- Key points
  - Use every subject who was randomized according to randomized treatment assignment
  - Ignore noncompliance, protocol deviations, withdrawal, and anything that happens after randomization
- ***As randomized, so analyzed***

Intention-to-Treat Analysis

- The ITT analysis holds the randomization as of paramount importance
- Deviation from the original randomized groups can contaminate the treatment comparison

Pragmatic vs. Explanatory Analyses

- Some authors categorize hypotheses from clinical trials as being either
  - Pragmatic – identify the utility of a treatment for clinical practice
  - Explanatory – isolate and identify the biologic effects of treatment
- Both types of hypotheses are important and relevant
- Both types of hypotheses cannot always be addressed in the same trial

Pragmatic vs. Explanatory Analyses

- The hypothesis that an ITT analysis addresses is pragmatic – the effectiveness of therapy when used in autonomous individuals
- Analyses that focus on the biologic effects of therapy are addressing explanatory hypotheses
  - This is often done by excluding noncompliant subjects from analysis

Compliance with Treatment

- Some subjects do not comply with their assigned treatment
- For explanatory analyses these subjects might not be used
  - No biologic effect if no treatment taken
- For ITT analysis they would be used
  - Why?

Compliance with Treatment

- Why include noncompliant subjects in ITT analysis? The statistical reasons are
  - Compliance or noncompliance occurs **after** randomization
  - Attempting to account for noncompliance by excluding noncompliant subjects can bias the treatment evaluation

Compliance with Treatment

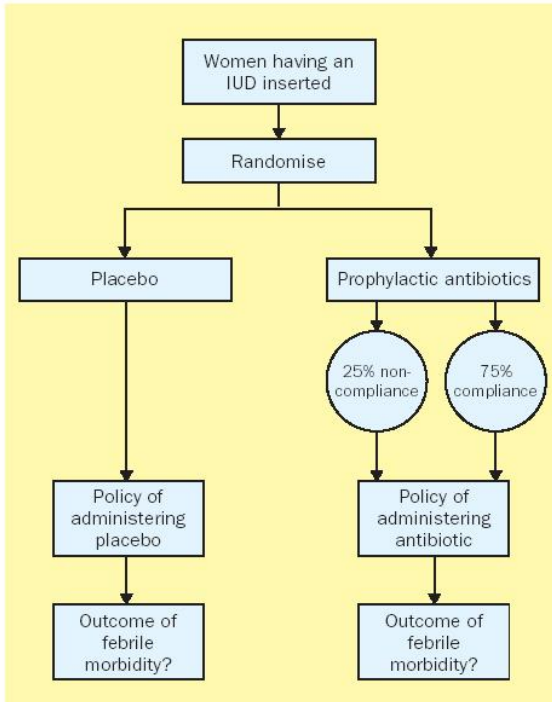
- Why include noncompliant subjects in ITT analysis? Other considerations are
  - In clinical practice, some patients are not fully compliant
  - Compliant subjects usually have better outcomes than noncompliant subjects, regardless of treatment

Compliance with Treatment

- Does this mean explanatory analyses shouldn't be done?
  - No!
  - But they need to be done with an eye to possible biases due to compliance
    - Sensitivity analysis to address impact of bias

Compliance with Treatment

- Trial report should include detailed description of compliance (chart from Schultz and Grimes)
- This should be done for both ITT and explanatory analyses



Schematic of randomised IUD patients, accounting for their compliance with treatment during the trial
IUD=intrauterine device.

Withdrawal from Trial

- Issues raised by withdrawals from the trial
  - Some subjects chose to end participation before the end of the trial
  - For both explanatory and ITT analyses these subjects are problematic
    - Outcome information is usually not available
    - Results in exclusion from analyses unless an analytic approach such as last-observation carried forward is used to impute the outcome values

Withdrawal from Trial

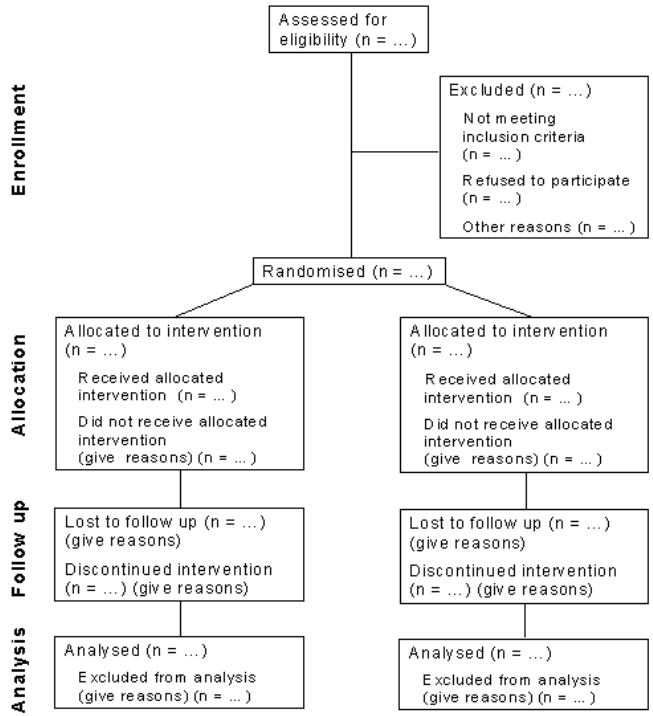
- Why should we try to include withdrawals in ITT analysis?
  - Withdrawal occurs after randomization and might be treatment-related
  - Excluding subjects who withdraw could bias results
- Often outcome information cannot be obtained on subjects who withdraw
- Experts encourage proactive steps to minimize withdrawal from trials

Withdrawal from Trial

- How can we deal with withdrawals in an ITT analysis?
  - Design trial to minimize withdrawal
  - Use alternative source of outcome information when possible (e.g. death registries)
  - Analytic approaches (last-observation-carried-forward, multiple imputation) can be used to reduce, but not remove the effect of withdrawal

Withdrawal from Trial

- Large withdrawal percentage indicates more uncertainty in results than indicated by standard p-values and confidence bounds
- This makes it important to accurately report withdrawal (as in CONSORT flow chart)



Coronary Drug Project

- Randomized, multi-center, double-blind, placebo-controlled trial of clofibrate for treatment for coronary heart disease
  - 1103 men on clofibrate
  - 2789 men on placebo
- ITT analysis of 5-year mortality on clofibrate was 20.0%, 20.9% on placebo (p=0.55)

Coronary Drug Project

- There was speculation that good compliers would show the clofibrate benefit and poor compliers would have mortality similar to placebo subjects
- Good compliance defined as 80% of protocol prescribed treatment taken

Coronary Drug Project

- In **clofibrate** subjects, mortality rates at 5 years were
  - Compliant: 15.0%
  - Non-compliant: 24.6%
- Subjects compliant with clofibrate had significantly lower mortality (p=0.0001)!
- Explanatory analysis – compare compliant clofibrate subjects to subjects without adequate clofibrate intake (clofibrate noncompliers and placebo subjects) – **significant**!

Coronary Drug Project

- But, in **placebo** subjects, mortality rates at 5 years were
  - Compliant: 15.1%
  - Non-compliant: 28.2%
- Subjects compliant with placebo had significantly lower mortality ($p < 0.0001$)!
- The explanatory analysis would miss this effect of compliance

Coronary Drug Project

- Clofibrate wasn’t more beneficial than placebo
- Compliance with assigned treatment was beneficial
- The decrease in mortality of subjects complying with clofibrate shouldn’t be attributed to clofibrate as would be done in an explanatory analysis
- The ITT result of non-significant clofibrate effect is correct

Actual Practice of ITT

- Survey of randomized controlled trials published in 1997 in BMJ, Lancet, JAMA, and NEJM (Hollis & Campbell)
- Out of 249 trials, 119 (48%) explicitly stated that an ITT analysis was performed
  - 15 (13%) clearly did not analyze as randomized
  - 65 (55%) appeared to analyze as randomized, but without enough detail for the readers to verify
  - No consistent method for handling withdrawal

Summary

- Randomization is of central importance in clinical trials
- ITT analyses try to preserve the randomized groups and address pragmatic hypotheses about the clinical utility of treatment
- Explanatory analyses address interesting hypotheses about the biological effect of treatment, but are more prone to bias

Summary

- ITT analyses should be the primary analysis for most clinical trials
- Explanatory analyses should carefully consider the effect of compliance
- Clinical trial reports should document compliance and withdrawal in detail

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