Strategies for Data Analysis: Randomized Controlled Trials

Daniel Wojdyla

UNDP / UNFPA / WHO / World Bank Special Programme of Research, Development and Research Training in Human Reproduction
World Health Organization

2005
Introduction

The strategy for data analysis depends on the study design

For experimental studies:

Design depending on method of randomization:

- Completely randomised
- Paired-matched
- Stratified

Design depending on unit of randomization:

- Individually randomised
- Cluster randomised
Introduction

Trial profile: analysis by ITT or per protocol?

Baseline characteristics by treatment groups

Crude effect of treatment

Effect of treatment adjusting for possible confounders

Effect modifiers and stratified analyses

Other analyses: secondary, sensitivity, subgroup
Trial profile: Analysis by ITT or per protocol?

**Intention-to-treat principle (ITT)**

All patients are included in the analysis in the group to which they were randomized, even if they did not receive the allocated treatment.

**Per protocol analysis**

Randomised subjects who are non-eligible are excluded.
Trial profile: Analysis by ITT or per protocol?

Reasons subjects could be excluded from a trial:

- Non-eligibility
- Non-compliance
- Had other illnesses
- Did not attend all visits
- Moved out
- Dropped out

Lost to follow-up
Trial profile: Analysis by ITT or per protocol?

Advantages of ITT

Inclusion of all randomized subjects guards against any bias incurred by subjective choice of ineligible subjects.

Inclusion better if the trial’s findings are to be extrapolated to future clinical practice in which eligibility for a given treatment is less-strictly defined.
Trial profile: Analysis by ITT or per protocol?

Intention to treat is not possible or can be relaxed:

When outcome is not known (for example, in withdrawals)

When a subject withdraws before treatment starts
(cautions: check if numbers and reasons are similar between groups)

In Phase I and Phase II clinical trials, which explore properties of treatment in idealized conditions
Trial profile: Analysis by ITT or per protocol?

Construct a flow chart providing numbers of subjects:

- registered or eligible
- randomized
- assigned to each group
- withdrawn (lost to follow-up and other reasons)
- completing the trial (with outcome known)
- not receiving / complying with treatment as allocated
**Flow Diagram**

**Enrollment**
- Assessed for Elegibility *(n = …)*
- Randomized *(n = …)*
  - Excluded *(n = …)*
    - Inclusion criteria *(n = …)*
    - Refused *(n = …)*
    - Other reasons *(n = …)*

**Allocation**
- Allocated to Intervention *(n = …)*
  - Received Intervention *(n = …)*
  - Did Not Receive Intervention *(n = …)*
    - (Give Reasons)

**Follow-Up**
- Lost to Follow-Up *(Give Reasons) (n = …)*
- Discontinued Intervention *(Reasons) (n = …)*

**Analysis**
- Analysis *(n = …)*
  - Excluded from analysis *(Reasons) (n = …)*
The CREATE-ECLA Randomized Controlled Trial
(JAMA, Vol 293, 4, 437-446)

**Context:** Glucose-insulin-potassium (GIK) infusion is a widely applicable, low-cost therapy that has been postulated to improve mortality in patients with acute ST-segment elevation myocardial infarction (STEMI).

**Objective:** To determine the effect of high-dose GIK infusion on mortality in patients with STEMI.

**Design:** Randomized controlled trial conducted in 470 centers worldwide among 20,201 patients with STEMI who presented within 12 hours of symptom onset.

**Main Outcome Measure:** Mortality, cardiac arrest, cardiogenic shock, and reinfarction at 30 days after randomization.
The CREATE-ECLA Randomized Controlled Trial

20,201 patients randomized

10,110 Assigned to Receive Usual Care Only
10,091 Assigned to Receive Glucose-Insulin-Potassium Infusion

10,107 Followed Up at 7 days
  3 Lost to Follow-up

10,093 Followed Up at 30 days
  14 Lost to Follow-up

10,107 Included in Primary Analysis

10,088 Followed Up at 7 days
  3 Lost to Follow-up

10,088 Followed Up at 30 days
  10 Lost to Follow-up

10,088 Included in Primary Analysis
Strategies for Data Analysis: RCT

Trial profile: analysis by ITT or per protocol?

Baseline characteristics by treatment groups

Crude effect of treatment

Effect of treatment adjusting for possible confounders

Effect modifiers and stratified analyses

Other analyses: secondary, sensitivity, subgroup
Baseline Characteristics by Treatment Group

Comparison is made by assessing the prognostic relevance of the difference observed, **not using tests of hypothesis**:

Compute sample statistics (means and standard deviations or medians and quartiles or percentages) by treatment group.

Compare baseline characteristics between treatment groups to discover possible confounders: randomisation should produce very similar baseline statistics if the sample size is large.
### Baseline Characteristics by Treatment Group: The CREATE-ECLA Randomized Controlled Trial

#### Selected Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Usual Care Only (n = 10,107)</th>
<th>GIK Infusion (n = 10,088)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>58.6 (12.5)</td>
<td>58.6 (12.2)</td>
</tr>
<tr>
<td>Female gender</td>
<td>2267 (22.4)</td>
<td>2255 (22.4)</td>
</tr>
<tr>
<td>Type 2 Diabetes</td>
<td>1802 (17.8)</td>
<td>1780 (17.6)</td>
</tr>
<tr>
<td>Weight, mean (SD), kg</td>
<td>67.8 (12.8)</td>
<td>67.5 (12.8)</td>
</tr>
<tr>
<td>Systolic BP, mean (SD), mm Hg</td>
<td>128.8 (26.4)</td>
<td>129.1 (26.6)</td>
</tr>
<tr>
<td>Diastolic BP, mean (SD), mm Hg</td>
<td>81.5 (16.5)</td>
<td>81.6 (16.1)</td>
</tr>
<tr>
<td>Heart Rate, mean (SD), beats/min</td>
<td>79.7 (18.5)</td>
<td>79.5 (18.4)</td>
</tr>
<tr>
<td>Killip Class at Randomization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>8606 (85.1)</td>
<td>8490 (84.2)</td>
</tr>
<tr>
<td>II / III</td>
<td>1339 (13.2)</td>
<td>1435 (14.2)</td>
</tr>
<tr>
<td>IV</td>
<td>160 (1.6)</td>
<td>157 (1.6)</td>
</tr>
</tbody>
</table>

* Data are expressed as No. (%) unless otherwise noted.
Strategies for Data Analysis: RCT

- Trial profile: analysis by ITT or per protocol?
- Baseline characteristics by treatment groups
- Crude effect of treatment
- Effect of treatment adjusting for possible confounders
- Effect modifiers and stratified analyses
- Other analyses: secondary, sensitivity, subgroup
Crude Effect of Treatment

Estimate the magnitude of the effect on the outcome measure and compute a confidence interval.

A p-value can also be provided.

The outcome measure can be of one of 3 types:

<table>
<thead>
<tr>
<th>Categorical</th>
<th>Binary: Death (Yes-No) Multiple Levels: Improvement (Marked, Some, None)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous</td>
<td>Cholesterol Level</td>
</tr>
<tr>
<td>Time to Event</td>
<td>Survival Type Measure: Time to Death</td>
</tr>
</tbody>
</table>

The statistical methods used to in the analysis will depend on the type of outcome measure.
# Crude Effect of Treatment

The CREATE-ECLA Randomized Controlled Trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Usual Care Only (n = 10 107)</th>
<th>GIK Infusion (n = 10 088)</th>
<th>Relative Risk (RR, 95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>30 Days</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>976 (9.7)</td>
<td>1004 (10.0)</td>
<td>1.03 (0.95 – 1.13)</td>
<td>0.45</td>
</tr>
<tr>
<td>Non Fatal Cardiac Arrest</td>
<td>151 (1.5)</td>
<td>139 (1.4)</td>
<td>0.93 (0.74 – 1.17)</td>
<td>0.51</td>
</tr>
<tr>
<td>Cardiogenic Shock</td>
<td>640 (6.3)</td>
<td>667 (6.6)</td>
<td>1.05 (0.94 – 1.17)</td>
<td>0.38</td>
</tr>
<tr>
<td>Reinfarction</td>
<td>246 (2.4)</td>
<td>236 (2.3)</td>
<td>0.98 (0.82 – 1.17)</td>
<td>0.81</td>
</tr>
</tbody>
</table>

* Data are expressed as No. (%) unless otherwise noted.
Strategies for Data Analysis: RCT

Trial profile: analysis by ITT or per protocol?

Baseline characteristics by treatment groups

Crude effect of treatment

Effect of treatment adjusting for possible confounders

Effect modifiers and stratified analyses

Other analyses: secondary, sensitivity, subgroup
Effect of treatment adjusting for possible confounders

Determine possible confounders:

- Variables with imbalance between groups
- Variables related to outcome: examine association between different variables and the outcome

Adjust for confounders:

- Include confounders in a multivariate model
- Account for collinearity between variables in the model
- Confounding is not as important as in observational studies because randomisation will produce balance between treatment groups
Effect of treatment adjusting for possible confounders
The CREATE-ECLA Randomized Controlled Trial

Suposse that there was a baseline imbalance for the variable Killip Class at Randomization which is known to be associated with mortality after myocardial infarction.

If one of the two groups has more patients with Killip Class > I, then the observed difference (or lack of ) could be attributed to the imbalance.

Solution: Produce "adjusted" measures of the association between treatment and outcome.

In experimental design generally is not necessary to perform this type of adjustment since randomization tends to eliminate all imbalances.
Strategies for Data Analysis: RCT

- Trial profile: analysis by ITT or per protocol?
- Baseline characteristics by treatment groups
- Crude effect of treatment
- Effect of treatment adjusting for possible confounders
- Effect modifiers and stratified analyses
- Other analyses: secondary, sensitivity, subgroup
Effect modifiers and stratified analyses

Stratify by centre

Test homogeneity of effect across centres (interaction of treatment by centre)

If there is homogeneity between centres, pool the effect over centres (adjust effect for centres)

Consider other effect modifiers
Strategies for Data Analysis: RCT

- Trial profile: analysis by ITT or per protocol?
- Baseline characteristics by treatment groups
- Crude effect of treatment
- Effect of treatment adjusting for possible confounders
- Effect modifiers and stratified analyses
- Other analyses: secondary, sensitivity, subgroup
**Other analyses: secondary, sensitivity, subgroup**

**Secondary Analysis**: analysis (or analyses) that are of secondary importance in a study.

**Examples:**
- 7 day death in the GIK trial
- Combined events
- Safety Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Usual Care Only (n = 10 107)</th>
<th>GIK Infusion (n = 10 088)</th>
<th>Relative Risk (RR, 95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Significant Phlebitis</td>
<td>17 (0.2)</td>
<td>339 (3.4)</td>
<td>20.0 (12.3 – 32.5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>11 (0.1)</td>
<td>34 (0.4)</td>
<td>3.10 (1.57 – 6.11)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
Other analyses: secondary, sensitivity, subgroup

**Sensitivity Analysis**: secondary analyses carried out by varying the assumptions that are made about the data and models used, including or excluding unusual data points (outliers), etc. The purpose of such analyses is to see if the results and conclusions from a study are robust.

**Subgroup Analysis**: analysis of the results of a study just in certain subgroups.

Subgroup analysis should be specified in advance, not seeing the data. They should be included in the protocol.
## Subgroup Analysis
The CREATE-ECLA Randomized Controlled Trial

<table>
<thead>
<tr>
<th>Group</th>
<th>Usual Care Only</th>
<th>GIK Infusion</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombolytic Therapy</td>
<td>676 / 7503 (9.0)</td>
<td>703 / 7454 (9.4)</td>
<td>0.373</td>
</tr>
<tr>
<td>Time to Randomization (Less than 4 hours)</td>
<td>350 / 4218 (8.3)</td>
<td>366 / 4124 (8.9)</td>
<td>0.347</td>
</tr>
<tr>
<td>Killip Class (II-IV)</td>
<td>368 / 1499 (24.5)</td>
<td>399 / 1592 (25.1)</td>
<td>0.741</td>
</tr>
</tbody>
</table>
Discussion

Strengths and weakness of trial results, based on design and analysis

Consistency with data from outside the trial

Consistency with other biological knowledge

Implications for clinical practice

Implications for research
Describe protocol deviations from the study as planned, together with the reasons (for ineligibility, non-compliance, withdrawal)

Percentages: state results in absolute numbers (10/20, not only 50%)

Present statistics in sufficient detail to permit alternative analyses and replication
"In conclusion, the CREATE-ECLA randomized trial has reliably established that high-dose GIK infusion in patients with STEMI has no impact on mortality, cardiac arrest, or cardiogenic shock and is unlikely to be of any material value in patients with STEMI"
Strategies for data analysis: community intervention trials (cluster randomized trials)

Standard approaches for statistical analysis tend to bias p-values downwards and give spurious statistical significance

Need special statistical analysis techniques

Basic difference in analysis is to consider a variance inflation factor or design effect

\[ DE = 1 + \rho (m - 1) \]
The Antenatal Care Trial
(Ref: Villar et al, Lancet 2001)

**Purpose**: to compare the standard model of antenatal care with a new model that emphasises actions known to be effective in improving maternal or neonatal outcomes and has fewer clinic visits

**Design**: stratified cluster randomised (strata based on countries and clinic characteristics)

**Unit of randomisation**: clinics (463 women recruited by clinic, on average)
The Antenatal Care Trial

Hypothesis:

A New ANC Model based on components shown to improve maternal, perinatal and neonatal outcomes is as effective as the Standard ANC model with regard to

- Low birth weight
- Maternal morbidity

is not more expensive and is acceptable by women and provider
The Antenatal Care Trial
Study Design Flow chart

24678 women enrolled in 53 ANC clinics

24526 pregnant women

152 not pregnant

12568 in 27 New ANC Model clinics (100%)

11958 in 26 Std ANC Model clinics (100%)

253 lost to follow-up (2.0%)

537 abortions (4.3%)

11778 births (93.7%)

11672 single births

290 lost to follow-up (2.4%)

474 abortions (4.0%)

11194 births (93.6%)

11121 single births
The Antenatal Care Trial
Baseline Characteristics

Clinic characteristics: location, new patients, resources

Enrolled women: demographic, obstetric-gynecologic history, present pregnancy status

Gestational age at entry to the trial:

New ANC Model: 16.5 ± 8.4 weeks
Standard ANC: 16.0 ± 8.0 weeks
### The Antenatal Care Trial

#### Baseline Characteristics

Who was the principal provider of ANC?
(Percentages of women)

<table>
<thead>
<tr>
<th>Provider</th>
<th>New Model %</th>
<th>Standard Model %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specialist in Obst.Gynecol</td>
<td>61.7</td>
<td>57.1</td>
</tr>
<tr>
<td>General practitioner</td>
<td>18.9</td>
<td>19.0</td>
</tr>
<tr>
<td>Midwife</td>
<td>19.1</td>
<td>18.8</td>
</tr>
</tbody>
</table>
The Antenatal Care Trial
Number of Visits

- Argentina: (3216 - 3593)
- Cuba: (2854 - 2721)
- Saudi Arabia: (2342 - 1717)
- Thailand: (3252 - 3074)

New care vs. control
### The Antenatal Care Trial

**Primary Outcomes**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Group</th>
<th>Women</th>
<th>%</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Birth Weight (&lt; 2500 g)</td>
<td>New</td>
<td>11534</td>
<td>7.68</td>
<td>1.10</td>
<td>0.95 to 1.27</td>
</tr>
<tr>
<td></td>
<td>Standard</td>
<td>11040</td>
<td>7.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-eclampsia / Eclampsia</td>
<td>New</td>
<td>11672</td>
<td>1.69</td>
<td>1.22</td>
<td>0.92 to 1.60</td>
</tr>
<tr>
<td></td>
<td>Standard</td>
<td>11121</td>
<td>1.38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postpartum anaemia</td>
<td>New</td>
<td>10720</td>
<td>7.59</td>
<td>1.02*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Standard</td>
<td>10050</td>
<td>8.67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated urinary-tract infection</td>
<td>New</td>
<td>11672</td>
<td>5.95</td>
<td>0.90</td>
<td>0.56 to 1.45</td>
</tr>
<tr>
<td></td>
<td>Standard</td>
<td>11121</td>
<td>7.41</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Effect was heterogeneous across sites and strata, therefore pooled estimates may hide site-specific effects.
The Antenatal Care Trial
Primary Outcomes

- **Low Birth Weight**: OR 1.10 (0.95 - 1.27)
- **Preeclampsia**: OR 1.22 (0.92 - 1.60)
- **PP Anemia**: OR 1.02
- **Treated UTI**: OR 0.90 (0.56 - 1.45)

**Graph:**
- New ANC Model vs. Standard Model
- Comparison of outcomes between models for different health conditions.
## The Antenatal Care Trial

### Secondary Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>New ANC Model N=11672</th>
<th>Standard ANC Model N=11121</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy-induced hypertension</td>
<td>3.4%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>1.6%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Preeclampsia hospital admission</td>
<td>0.4%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Eclampsia</td>
<td>0.07%</td>
<td>0.08%</td>
</tr>
<tr>
<td>Severe anaemia pregnancy</td>
<td>4.4%</td>
<td>3.9%</td>
</tr>
<tr>
<td>Hypertension with referral/treatment</td>
<td>2.3%</td>
<td>3.9%</td>
</tr>
<tr>
<td>Hypertension without referral/treatment</td>
<td>1.1%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Vaginal bleeding 2\textsuperscript{nd} trimester</td>
<td>0.8%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Vaginal bleeding 3\textsuperscript{rd} trimester</td>
<td>0.7%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Any vaginal bleeding</td>
<td>3.2%</td>
<td>2.2%</td>
</tr>
</tbody>
</table>
Conclusions

The New ANC Model is as effective as the Standard Model.

The New ANC Model is in general well accepted by women and providers, although some women will be concerned about the spacing between visits.

The New ANC Model costs less to women and services.