Strategies for data analysis: RCTs & community intervention trials

Gilda Piaggio

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

Geneva, 12 March 2003
The strategy for data analysis depends on the study design

For experimental studies:

Design depending on method of randomisation:
- Completely randomised
- Paired-matched
- Stratified
- Cross-over

Design depending on unit of randomisation:
- Individually randomised
- Cluster randomised
Strategies for data analysis: RCTs

- 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:

All patients are included in the analysis in the group to which they were randomised, 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 were excluded from trials in the past:

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

Lost to follow-up or withdrawn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

‘...all eligible patients, regardless of compliance with protocol should be included in the analysis of results whenever possible’

‘The alternative ‘explanatory approach’ or ‘analysis of compliers only’ can distort treatment comparisons’

Pocock, 1983
Trial profile: analysis by ITT or per protocol?

Advantages of ITT:

• inclusion of all randomised 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 (caution: 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
- when eligibility criteria are clear and objective and when the trial is double-blind
Trial profile: analysis by ITT or per protocol?

Construct a flow chart providing numbers of subjects:

- registered or eligible
- randomised
- 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
The Yuzpe-levonorgestrel trial

Objectives:

• Confirm that two doses of 0.75mg of levonorgestrel given 12 hours apart for emergency contraception have
  • the same effectiveness but
  • fewer side effects than the Yuzpe regimen

• Assess regimens effectiveness if the delay between intercourse and the start of the treatment is extended
  (from 48 hours) to 72 hours.
The Yuzpe-levonorgestrel trial

Design:

- Randomised controlled trial
- Double-blind
- Multicenter (21 centres in 14 countries): stratified
- Equivalence trial
The Yuzpe-levonorgestrel trial

**Figure 1: Trial profile**

*To be treated with further emergency contraception.*
Strategies for data analysis: RCTs

- 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 groups

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 will produce very similar baseline statistics if the sample size is large
## The Yuzpe-levonorgestrel trial

### Characteristics of subjects

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Yuzpe (n=979)</th>
<th>LNG (n=976)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Age (years)</td>
<td>27.2</td>
<td>6.8</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>58.6</td>
<td>9.6</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>162.8</td>
<td>6.5</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.1</td>
<td>3.3</td>
</tr>
<tr>
<td>Cycle length (days)</td>
<td>28.8</td>
<td>2.5</td>
</tr>
<tr>
<td>Interval from estimated ovulation to intercourse (days)</td>
<td>-1.0</td>
<td>5.2</td>
</tr>
</tbody>
</table>
Strategies for data analysis: RCTs

- 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 Yuzpe-levonorgestrel trial

## Pregnancy rates

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of women</th>
<th>Observed pregnancies</th>
<th>Pregnancy rate (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yuzpe</td>
<td>979</td>
<td>31</td>
<td>3.2</td>
<td>(2.2 to 4.5)</td>
</tr>
<tr>
<td>LNG</td>
<td>976</td>
<td>11</td>
<td>1.1</td>
<td>(0.6 to 2.0)</td>
</tr>
</tbody>
</table>

Relative risk (RR) of pregnancy for LNG compared with Yuzpe:

<table>
<thead>
<tr>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.36</td>
<td>(0.18 to 0.70)</td>
</tr>
</tbody>
</table>
# The Yuzpe-levonorgestrel trial

## Incidence of side effects

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Yuzpe</th>
<th></th>
<th>LNG</th>
<th></th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Cases</td>
<td>Rate (%)</td>
<td>No. of Cases</td>
<td>Rate (%)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>494</td>
<td>50.5</td>
<td>226</td>
<td>23.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Vomiting</td>
<td>184</td>
<td>18.8</td>
<td>55</td>
<td>5.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Headache</td>
<td>198</td>
<td>20.2</td>
<td>164</td>
<td>16.8</td>
<td>0.06</td>
</tr>
<tr>
<td>Dizziness</td>
<td>163</td>
<td>16.7</td>
<td>109</td>
<td>11.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fatigue</td>
<td>279</td>
<td>28.5</td>
<td>165</td>
<td>16.9</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
Strategies for data analysis: RCTs

- 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
## The Yuzpe-levonorgestrel trial

**Efficacy: prevented fraction**

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of women</th>
<th>No. of pregnancies</th>
<th>Efficacy**</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed</td>
<td>Expected*</td>
<td>(%)</td>
<td></td>
</tr>
<tr>
<td>Yuzpe</td>
<td>979</td>
<td>31</td>
<td>74.2</td>
<td>58</td>
</tr>
<tr>
<td>LNG</td>
<td>976</td>
<td>11</td>
<td>76.3</td>
<td>86</td>
</tr>
</tbody>
</table>

* Using Dixon’s estimates of conception probabilities

** Prevented fraction

** Ratio of standardised pregnancy rates of LNG with respect to Yuzpe:

<table>
<thead>
<tr>
<th>Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.34</td>
<td>(0.16, 0.70)</td>
</tr>
</tbody>
</table>

*
Effect of treatment adjusted for possible confounders

• Determine possible confounders:
  • Variables with imbalance between groups
  • Variables related to outcome: examine association between different variables and the outcome
Effect of treatment adjusted for possible confounders

- 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
Strategies for data analysis: RCTs

- 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 analysis

- 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
The Yuzpe-levonorgestrel trial
Efficacy of Yuzpe by treatment delay

<table>
<thead>
<tr>
<th>Delay (hours)</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤24</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>25-48</td>
<td>2.1</td>
<td>(0.9, 4.7)</td>
</tr>
<tr>
<td>49-72</td>
<td>2.4</td>
<td>(0.9, 6.3)</td>
</tr>
</tbody>
</table>

Chi-square for trends: p=0.018
Strategies for data analysis: RCTs

- 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
The Yuzpe-levonorgestrel trial
ITT analysis and secondary analyses

<table>
<thead>
<tr>
<th>Population</th>
<th>No. of women</th>
<th>No. of pregnancies</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy ITT</td>
<td>1955</td>
<td>42</td>
<td>0.36</td>
<td>(0.18, 0.70)</td>
</tr>
<tr>
<td>Eligible</td>
<td>1855</td>
<td>31</td>
<td>0.34</td>
<td>(0.15, 0.76)</td>
</tr>
<tr>
<td>Perfect use</td>
<td>1157</td>
<td>16</td>
<td>0.46</td>
<td>(0.16, 1.32)</td>
</tr>
</tbody>
</table>

*
Interpretation

• State findings clearly
• Discuss internal validity: sources of bias and imprecision
• Discuss external validity
The Yuzpe-levonorgestrel trial

Effect of delay on pregnancy rates

Pregnancy rate (%) vs. Delay (hours):

- 0-12 hours: 0.5%
- 13-24 hours: 1.5%
- 25-36 hours: 1.8%
- 37-48 hours: 2.6%
- 49-60 hours: 2.6%
- 61-72 hours: 3.1%

(n=386) (n=522) (n=326) (n=379) (n=191) (n=146)
Presentation

• 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
The Yuzpe-levonorgestrel trial

Conclusions

- The LNG regimen is more effective than the Yuzpe regimen.
- It is better tolerated.
- With both regimens, earlier treatment is more effective.
Strategies for data analysis: community intervention trials (cluster randomised trials)

- Standard approaches for statistical analysis tend to bias p-values downwards and give spurious statistical significance.
- Need special 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
Study Design and Women’s Flow Chart

53 eligible clinics

26 Control clinics

Do not seek consent

Standard ANC

Seek consent

Yes

New ANC model
CLASSIFICATION form

Special care

No

164 women (1.3%) did not agree to participate

Basic Programme

Standard ANC

27 Intervention clinics
The Antenatal Care Trial: trial profile

24678 women enrolled in 53 ANC clinics

- 152 women not pregnant

24526 pregnant women

- 12568 pregnant women in 27 New ANC Model clinics (100%)
  - 253 lost to follow-up (2.0%)
  - 537 abortions (4.3%)
  - 11778 births (93.7%)
    - 11672 single births

- 11958 pregnant women in 26 Std ANC Model clinics (100%)
  - 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></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
control
## Primary outcomes

<table>
<thead>
<tr>
<th></th>
<th>ANC MODEL</th>
<th>Women No.</th>
<th>%</th>
<th>Stratified OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low birth weight (&lt;2500g)</strong></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><strong>Preeclampsia/eclampsia</strong></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><strong>Postpartum anaemia</strong></td>
<td>New</td>
<td>10720</td>
<td>7.67</td>
<td>1.02</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Standard</td>
<td>10050</td>
<td>8.72</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Treated urinary tract infection</strong></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>
The Antenatal Care Trial
Primary outcomes

<table>
<thead>
<tr>
<th>Condition</th>
<th>Standard Model</th>
<th>New ANC Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Birth Weight</td>
<td>1.10 (0.95 - 1.27)</td>
<td>1.02 (0.95 - 1.27)</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>1.22 (0.92 - 1.60)</td>
<td>0.90 (0.56 - 1.45)</td>
</tr>
<tr>
<td>PP Anemia</td>
<td>1.02 (0.92 - 1.60)</td>
<td>0.90 (0.56 - 1.45)</td>
</tr>
<tr>
<td>Treated UTI</td>
<td>1.10 (0.95 - 1.27)</td>
<td>1.02 (0.95 - 1.27)</td>
</tr>
</tbody>
</table>
### 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(^{nd}) trimester</td>
<td>0.8</td>
<td>0.5</td>
</tr>
<tr>
<td>Vaginal bleeding 3(^{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>
## The Antenatal Care Trial
### Secondary outcomes

<table>
<thead>
<tr>
<th></th>
<th>New ANC Model N=11672</th>
<th>Standard ANC Model N=11121</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal death</td>
<td>1.4</td>
<td>1.1</td>
</tr>
<tr>
<td>Neonatal Mort. (&lt;1&lt;sup&gt;st&lt;/sup&gt; day)</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Neonatal Mort. (&gt;1&lt;sup&gt;st&lt;/sup&gt;-discharge)</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Perinatal Mortality</td>
<td>2.0</td>
<td>1.7</td>
</tr>
</tbody>
</table>
### The Antenatal Care Trial

Stratified analysis according to baseline ANC visits: 12 or more ANC visits

<table>
<thead>
<tr>
<th></th>
<th><strong>New ANC Model</strong></th>
<th><strong>Standard ANC Model</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>N=2852 (6 clinics)</strong></td>
<td><strong>N=2721 (6 clinics)</strong></td>
</tr>
<tr>
<td><strong>%</strong></td>
<td><strong>%</strong></td>
<td><strong>%</strong></td>
</tr>
<tr>
<td>LBW (&lt;2500g)</td>
<td>7.2</td>
<td>6.7</td>
</tr>
<tr>
<td>Preeclampsia/eclampsia</td>
<td>2.0</td>
<td>1.6</td>
</tr>
<tr>
<td>Postpartum anaemia</td>
<td>9.4</td>
<td>10.3</td>
</tr>
<tr>
<td>Treated UTI</td>
<td>7.2</td>
<td>9.3</td>
</tr>
</tbody>
</table>

*(median ANC visits 6) (median ANC visits 13)*
The Antenatal Care Trial
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