From Research to Practice: Training in Sexual and Reproductive Health Research

Strategies for data analysis: RCTs

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The strategy for data analysis depends on the study design

Design options:

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

Design depending on unit of randomisation:
- Individually randomised
- Cluster randomised
Strategy 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
CONSORT flowchart

Enrollment

Assessed for eligibility  (n=  )
Excluded  (n=  )
Not meeting inclusion criteria  (n=  )
Refused to participate  (n=  )
Other reasons  (n=  )

Allocation

Allocated to intervention  (n=  )
Received allocated intervention  (n=  )
Did not receive allocated intervention  (n=  )
Give reasons

Lost to follow-up  (n=  )
Give reasons
Discontinued intervention  (n=  )
Give reasons

Analysis

Allocated to intervention  (n=  )
Received allocated intervention  (n=  )
Did not receive allocated intervention  (n=  )
Give reasons

Lost to follow-up  (n=  )
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Discontinued intervention  (n=  )
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Follow-Up

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Give reasons

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Discontinued intervention  (n=  )
Give reasons

http://www.consort-statement.org/
Trial profile: analysis by ITT or per protocol?

**Intention-to-treat (ITT) 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.
Reasons why investigators have excluded subjects from analysis in a per protocol analysis:

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

\[\text{Lost to follow-up or withdrawn}\]
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
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
Trial profile: analysis by ITT or per protocol?

Construct a flow chart showing 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
Strategies for data analysis: RCTs

- Trial profile: analysis by ITT or per protocol?
- Baseline characteristics by treatment groups
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- Other analyses: secondary, sensitivity, subgroup
CONSORT flowchart

Assessed for eligibility (n =)

Excluded (n =)
- Not meeting inclusion criteria (n =)
- Refused to participate (n =)
- Other reasons (n =)

Is it Randomized?

Allocated to intervention (n =)
Received allocated intervention (n =)
Did not receive allocated intervention (n =)
Give reasons

Analysis

Analyzed (n =)
Excluded from analysis (n =)
Give reasons

Follow-Up

Lost to follow-up (n =)
Give reasons

Discontinued intervention (n =)
Give reasons

Allocation

Allocated to intervention (n =)
Received allocated intervention (n =)
Did not receive allocated intervention (n =)
Give reasons

Lost to follow-up (n =)
Give reasons

Discontinued intervention (n =)
Give reasons

Enrollment

http://www.consort-statement.org/
The Yuzpe-levonorgestrel trial

1998 women randomised

997 allocated Yuzpe regimen

- 18 outcome not known
  - 2 no tablet intake, no return
  - 2 withdrawn by investigator*
  - 14 lost to follow-up

1001 allocated levonorgestrel

- 25 outcome not known
  - 2 no tablet intake, no return
  - 1 withdrawn by investigator*
  - 1 died (meningitis)
  - 21 lost to follow-up

979 outcome known

- 976 complied fully with treatment
- 3 did not comply fully with treatment

976 outcome known

- 974 complied fully with treatment
- 2 did not comply fully with treatment

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
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• 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
## Characteristics of subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Yuzpe (n=979)</th>
<th>LNG (n=976)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>27.2 6.8</td>
<td>27.3 7.0</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>58.6 9.6</td>
<td>58.4 10.4</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>162.8 6.5</td>
<td>162.9 6.4</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>22.1 3.3</td>
<td>22.0 3.6</td>
</tr>
<tr>
<td>Cycle length (days)</td>
<td>28.8 2.5</td>
<td>28.9 2.4</td>
</tr>
<tr>
<td>Interval from estimated ovulation to intercourse (days)</td>
<td>-1.0 5.2</td>
<td>-0.9 5.0</td>
</tr>
</tbody>
</table>
Strategies for data analysis: RCTs

- Trial profile: analysis by ITT or per protocol?
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**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 three type:
  - Categorical: binary (death, disease, pregnancy) or multiple levels (severe, moderate, mild, none)
  - Continuous: cholesterol levels
  - Time-to-event: time to death or to disease
Crude effect of treatment

• Measures of the magnitude of the effect for binary outcomes:
  - Absolute measures: risk difference
  - Relative measures: relative risk and odds ratio

• Measures of the magnitude of the effect for continuous outcomes:
  - Difference between means
Risk difference

<table>
<thead>
<tr>
<th></th>
<th>Pregnant</th>
<th>Not pregnant</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yuzpe</td>
<td>a</td>
<td>b</td>
<td>a/(a+b)</td>
</tr>
<tr>
<td>LNG</td>
<td>c</td>
<td>d</td>
<td>c/(c+d)</td>
</tr>
</tbody>
</table>

Risk difference = \( \frac{a}{a+b} - \frac{c}{c+d} \)
Relative risk (RR)

<table>
<thead>
<tr>
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<th>Pregnant</th>
<th>Not pregnant</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yuzpe</td>
<td>a</td>
<td>b</td>
<td>(a/(a+b))</td>
</tr>
<tr>
<td>LNG</td>
<td>c</td>
<td>d</td>
<td>(c/(c+d))</td>
</tr>
</tbody>
</table>

\[RR = \frac{a}{a+b} / \frac{c}{c+d}\]
Odds ratio (OR)

<table>
<thead>
<tr>
<th>Pregnant</th>
<th>Not pregnant</th>
<th>Odds</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>b</td>
<td>a/b</td>
</tr>
<tr>
<td>c</td>
<td>d</td>
<td>c/d</td>
</tr>
</tbody>
</table>

OR = \( \frac{a}{b} \div \frac{c}{d} = \frac{ad}{bc} \)
### Relative risk (RR)

<table>
<thead>
<tr>
<th></th>
<th>Pregnant</th>
<th>Not pregnant</th>
<th>All</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yuzpe</td>
<td>31</td>
<td>948</td>
<td>979</td>
<td>31/979 = 0.032</td>
</tr>
<tr>
<td>LNG</td>
<td>11</td>
<td>965</td>
<td>976</td>
<td>11/976 = 0.011</td>
</tr>
</tbody>
</table>

RR = \frac{11}{976} / \frac{31}{979} = 0.36
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 No. of Cases</th>
<th>Yuzpe Rate (%)</th>
<th>LNG No. of Cases</th>
<th>LNG Rate (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<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>
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Strategies for data analysis: RCTs

• Trial profile: analysis by ITT or per protocol?
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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 (contd.)

- 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

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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
Strategies for data analysis: RCTs

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Strategies for data analysis: RCTs

- Sensitivity analysis: secondary analysis including or excluding unusual data points (non-ITT). The purpose is to assess whether results and conclusions are robust.

- Subgroup analysis: analysis of a part of the participating subjects. They should be specified in advance, in the protocol, before seeing the data.
The Yuzpe-levonorgestrel trial
Secondary analyses: the effect of delay on pregnancy rates

Pregnancy rate (%)

Delay (hours)
0-12 (n=386)  13-24 (n=522)  25-36 (n=326)  37-48 (n=379)  49-60 (n=191)  61-72 (n=146)
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