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

Strategies for data analysis: RCTs

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

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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
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- Effect modifiers and stratified analyses
- Other analyses: secondary, sensitivity, subgroup

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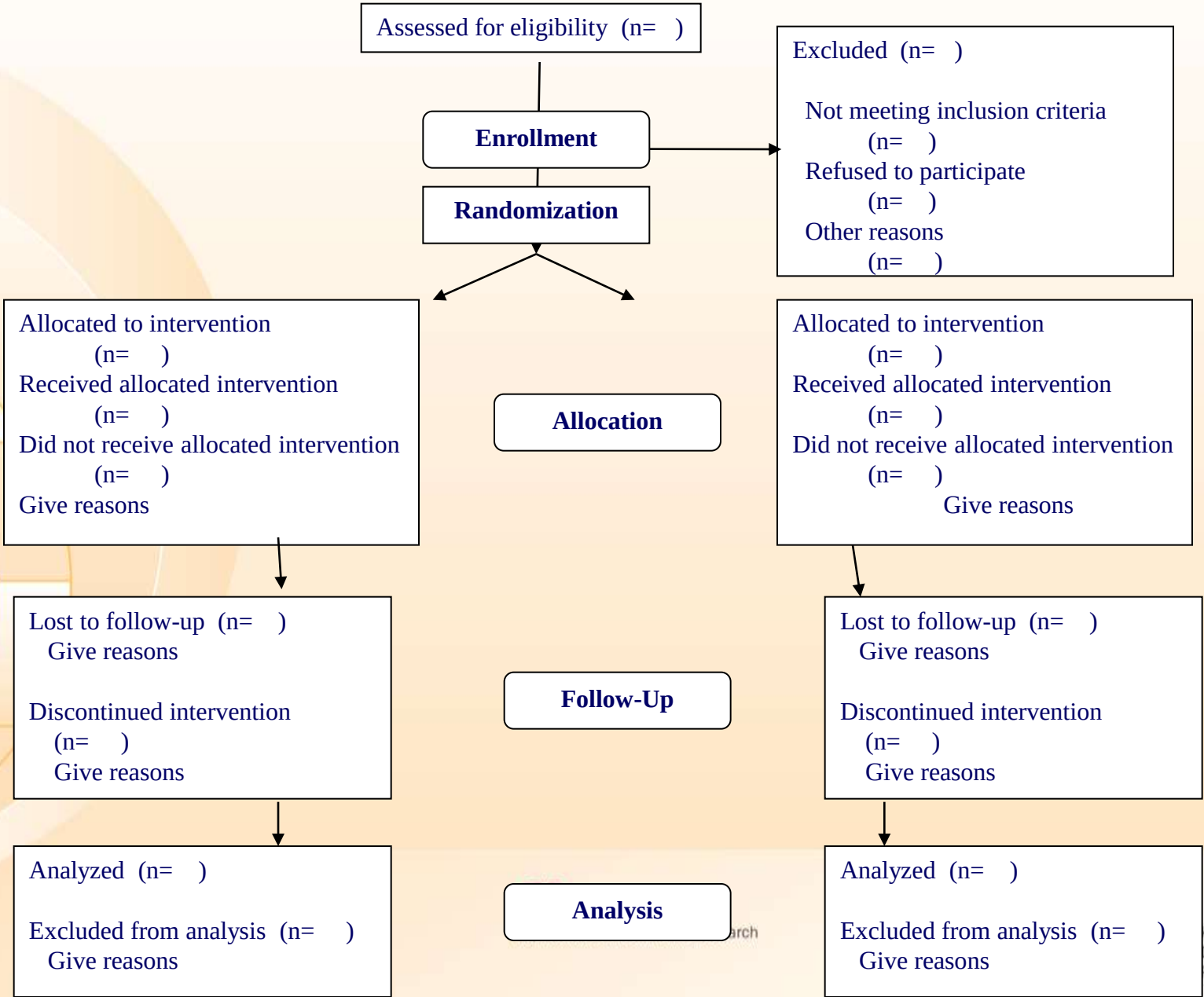
CONSORT flowchart

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

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Trial profile: analysis by ITT or per protocol?

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

} Lost to follow-up or withdrawn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?

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

by group:

- 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

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The Yuzpe-levonorgestrel trial
(Ref: Task Force on Postovulatory Methods of Fertility Regulation, Lancet 1998)

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.

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The Yuzpe-levonorgestrel trial

Design:

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

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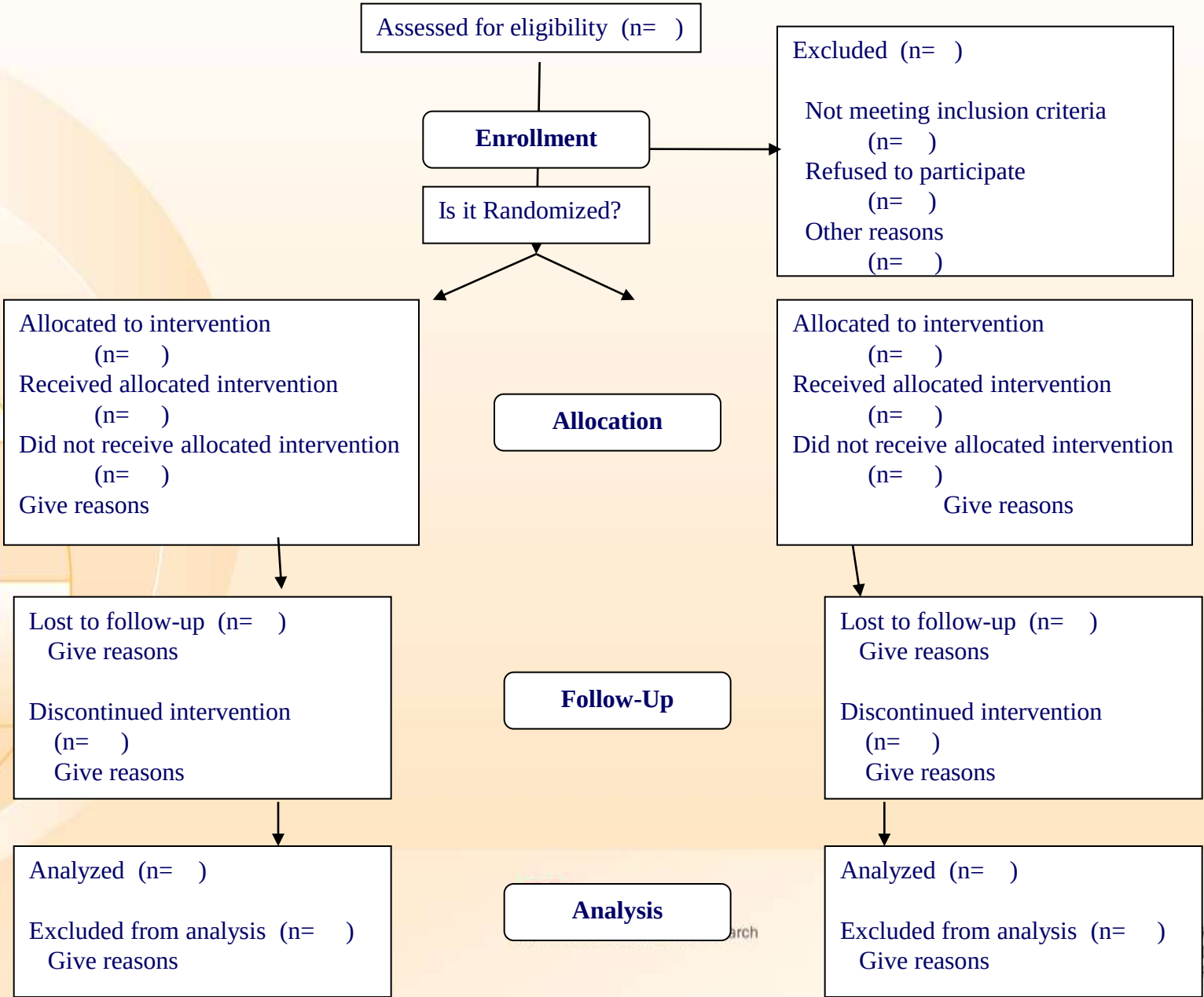

The Yuzpe-levonorgestrel trial

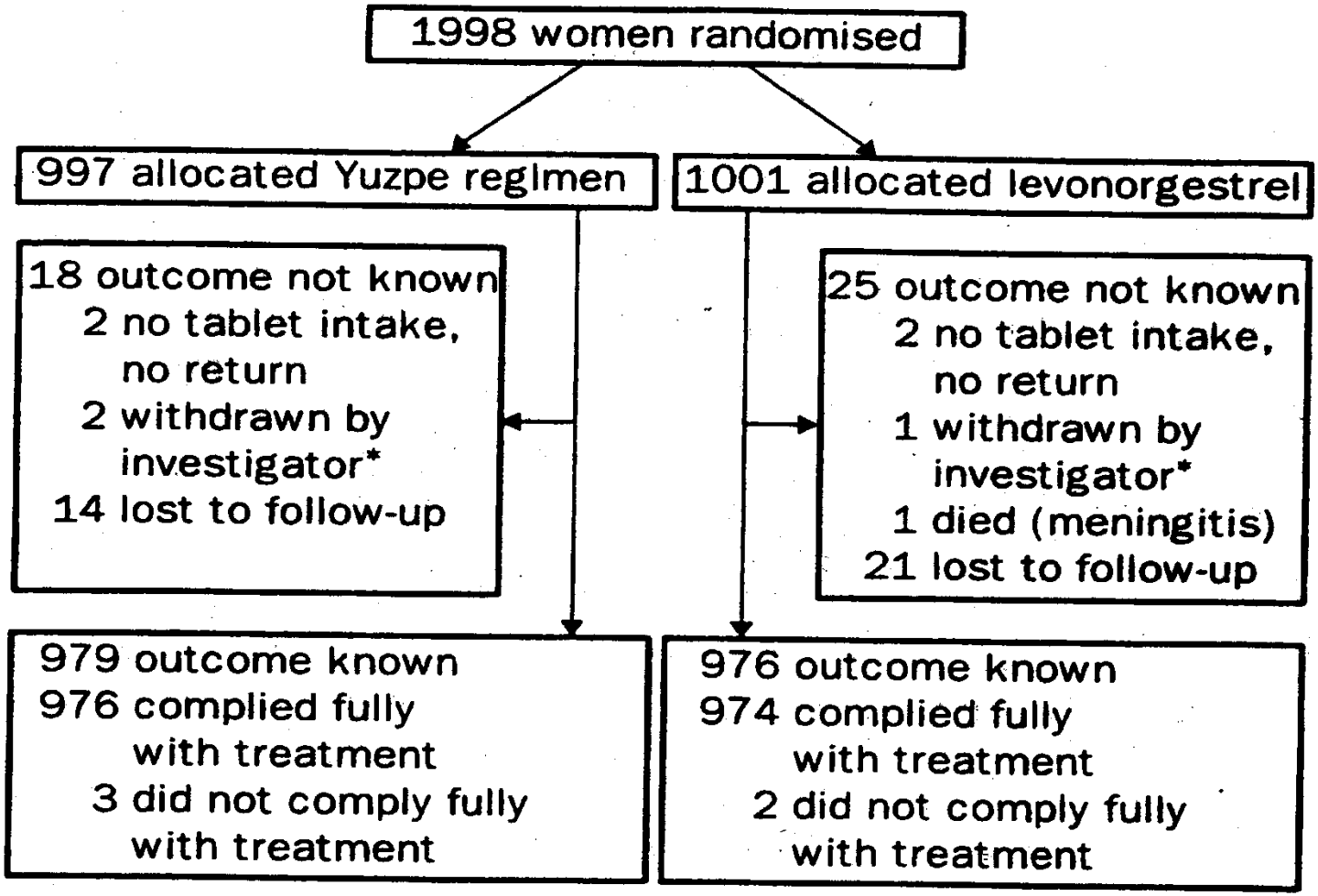

Figure 1: **Trial profile**

*To be treated with further emergency contraception.

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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

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The Yuzpe-levonorgestrel trial

Characteristics of subjects

Treatment group	Yuzpe (n=979)		LNG (n=976)	
Variable	**Mean**	**SD**	**Mean**	**SD**
Age (years)	27.2	6.8	27.3	7.0
Weight (kg)	58.6	9.6	58.4	10.4
Height (cm)	162.8	6.5	162.9	6.4
BMI (kg/m^2)	22.1	3.3	22.0	3.6
Cycle length (days)	28.8	2.5	28.9	2.4
Interval from estimated ovulation to intercourse (days)	-1.0	5.2	-0.9	5.0

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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

	Pregnant	Not pregnant	Risk
Yuzpe	a	b	a/(a+b)
LNG	c	d	c/(c+d)

Risk difference=a/(a+b) - c/(c+d)

Relative risk (RR)

	Pregnant	Not pregnant	Risk
Yuzpe	a	b	a/(a+b)
LNG	c	d	c/(c+d)

RR=a/(a+b)/c/(c+d)

Odds ratio (OR)

	Pregnant	Not pregnant	Odds
Yuzpe	a	b	a/b
LNG	c	d	c/d

$$OR = a/b / c/d = ad/bc$$

Relative risk (RR)

	Pregnant	Not pregnant	All	Risk
Yuzpe	31	948	979	31/979=0.032
LNG	11	965	976	11/976=0.011

RR=11/976/31/979 = 0.36

The Yuzpe-levonorgestrel trial

Pregnancy rates

Group	Number of women	Observed pregnancies	Pregnancy rate (%)	95% CI
Yuzpe	979	31	3.2	(2.2 to 4.5)
LNG	976	11	1.1	(0.6 to 2.0)

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

RR	95% CI
0.36	(0.18 to 0.70)

*

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The Yuzpe-levonorgestrel trial

Incidence of side effects

Side effect	Yuzpe		LNG		p-value
	No. of Cases	Rate (%)	No. of Cases	Rate (%)	
Nausea	494	50.5	226	23.1	<0.01
Vomiting	184	18.8	55	5.6	<0.01
Headache	198	20.2	164	16.8	0.06
Dizziness	163	16.7	109	11.2	<0.01
Fatigue	279	28.5	165	16.9	<0.01

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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

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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

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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.

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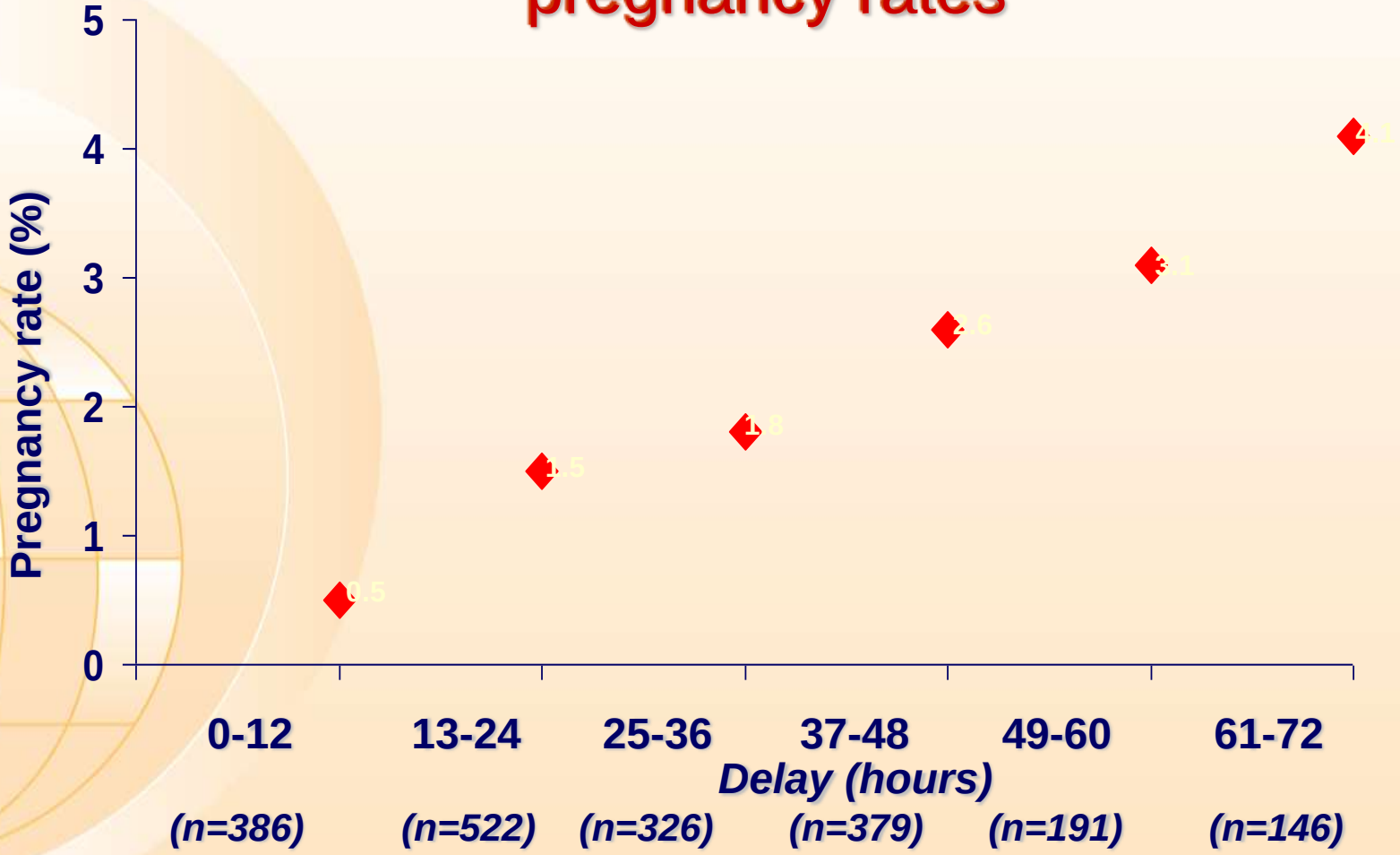
The Yuzpe-levonorgestrel trial

Secondary analyses: the effect of delay on pregnancy rates



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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

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