Strategies for data analysis: RCTs

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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

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

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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

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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Lost to follow-up or withdrawn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

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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 showing numbers of subjects:

- registered or eligible

- randomised

- assigned to each group

by 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
(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.

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?

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The Yuzpe-levonorgestrel trial

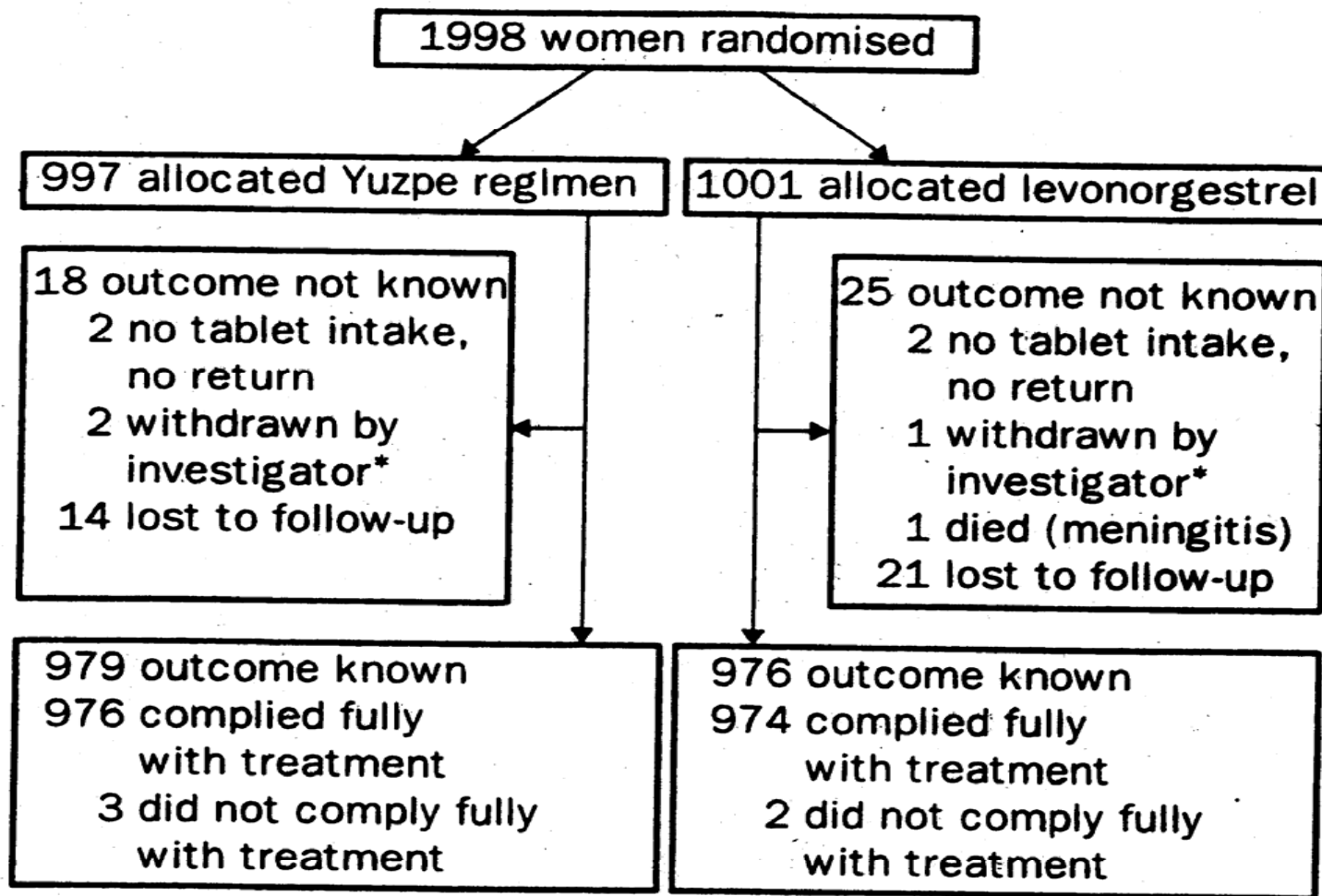Figure 1: **Trial profile**
*To be treated with further emergency contraception.

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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

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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)

*

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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The Yuzpe-levonorgestrel trial
Efficacy: prevented fraction

Group	No. of	No. of pregnancies		Efficacy**	
	women	Observed	Expected*	(%)	95% CI
Yuzpe	979	31	74.2	58	(41, 72)
LNG	976	11	76.3	86	(74, 93)

* Using Dixon's estimates of conception probabilities

** Prevented fraction

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

Ratio	95% CI
0.34	(0.16, 0.70)

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

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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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The Yuzpe-levonorgestrel trial
Efficacy of Yuzpe by treatment delay

Delay (hours)	RR	95% CI
≤24	1	-
25-48	2.1	(0.9, 4.7)
49-72	2.4	(0.9, 6.3)

Chi-square for trends: p=0.018

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The Yuzpe-levonorgestrel trial
ITT analysis and secondary analyses

Population	No. of women	No. of pregnancies	RR	95% CI
Efficacy ITT	1955	42	0.36	(0.18, 0.70)
Eligible	1855	31	0.34	(0.15, 0.76)
Perfect use	1157	16	0.46	(0.16, 1.32)

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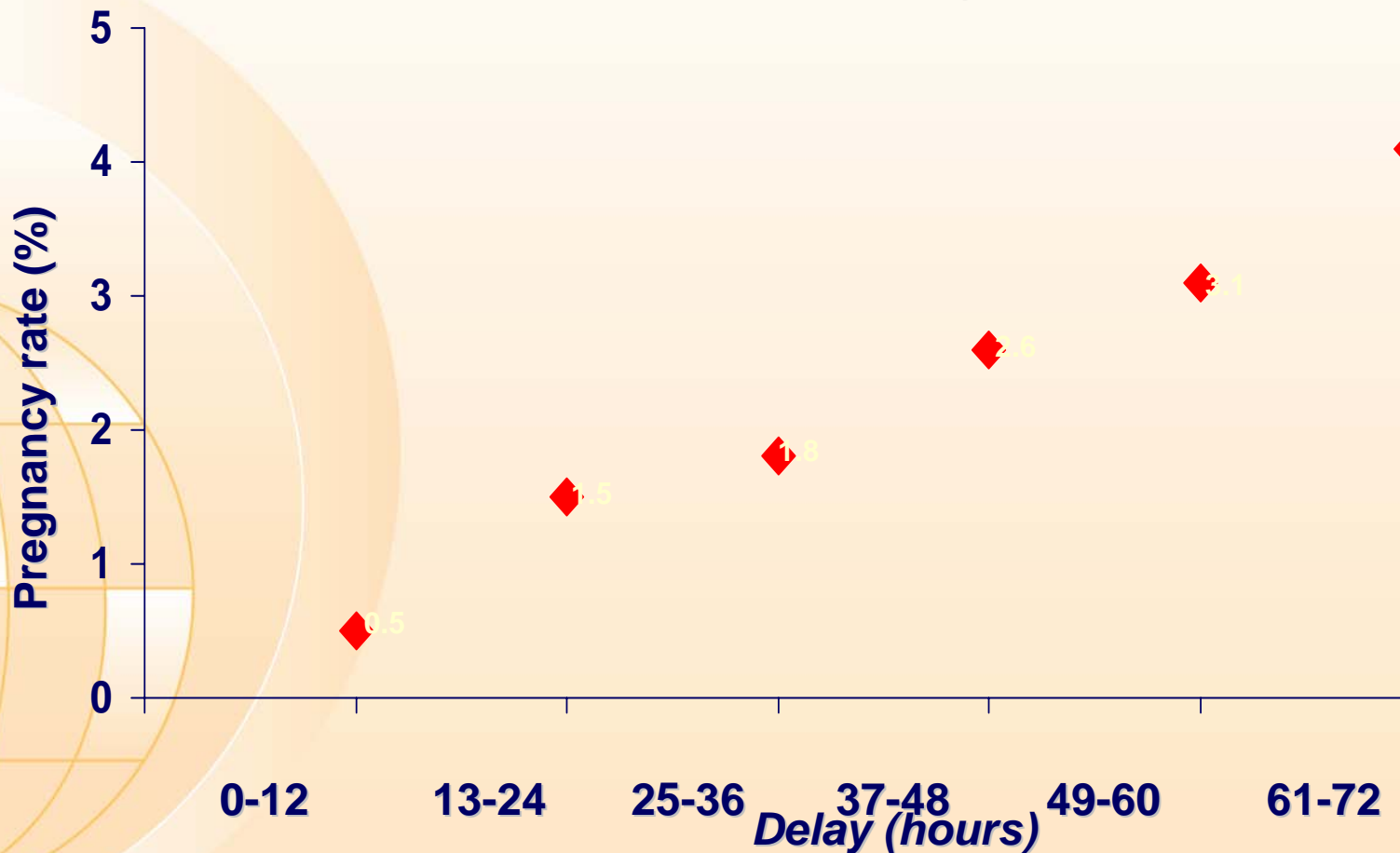Special Programme of Research, Development
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Interpretation

- State findings clearly

- Discuss internal validity: sources of bias and imprecision

- Discuss external validity

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The Yuzpe-levonorgestrel trial
Effect of delay on pregnancy rates

Pregnancy rate (%)

Delay (hours)

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

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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

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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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