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
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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

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} Lost to follow-up or withdrawn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

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

The Yuzpe-levonorgestrel trial

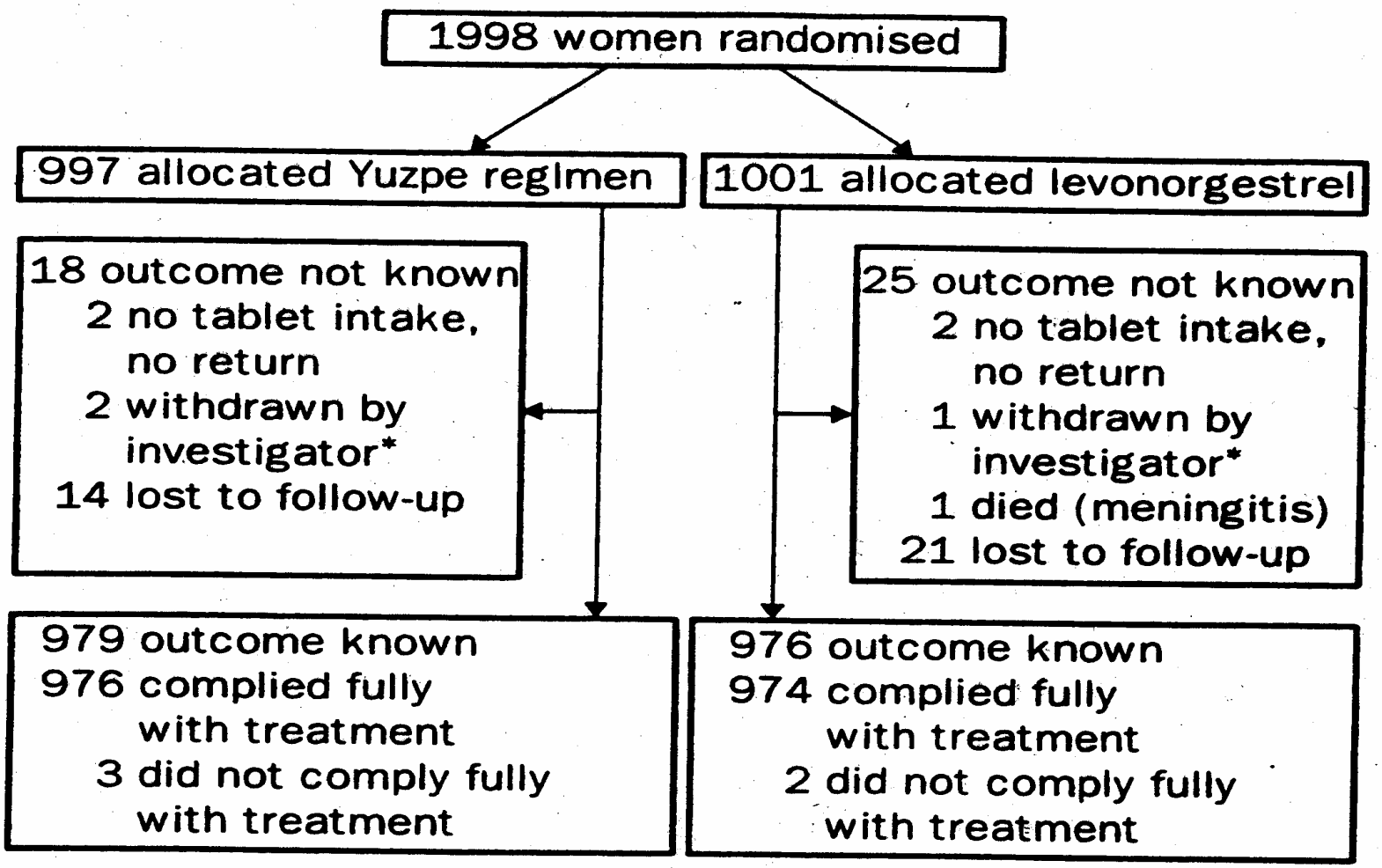

Figure 1: **Trial profile**

*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

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 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

	Yuzpe		LNG		
Side effect	**No. of Cases**	**Rate (%)**	**No. of Cases**	**Rate (%)**	**p-value**
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 women	No. of pregnancies		Efficacy**	
		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

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

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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

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)

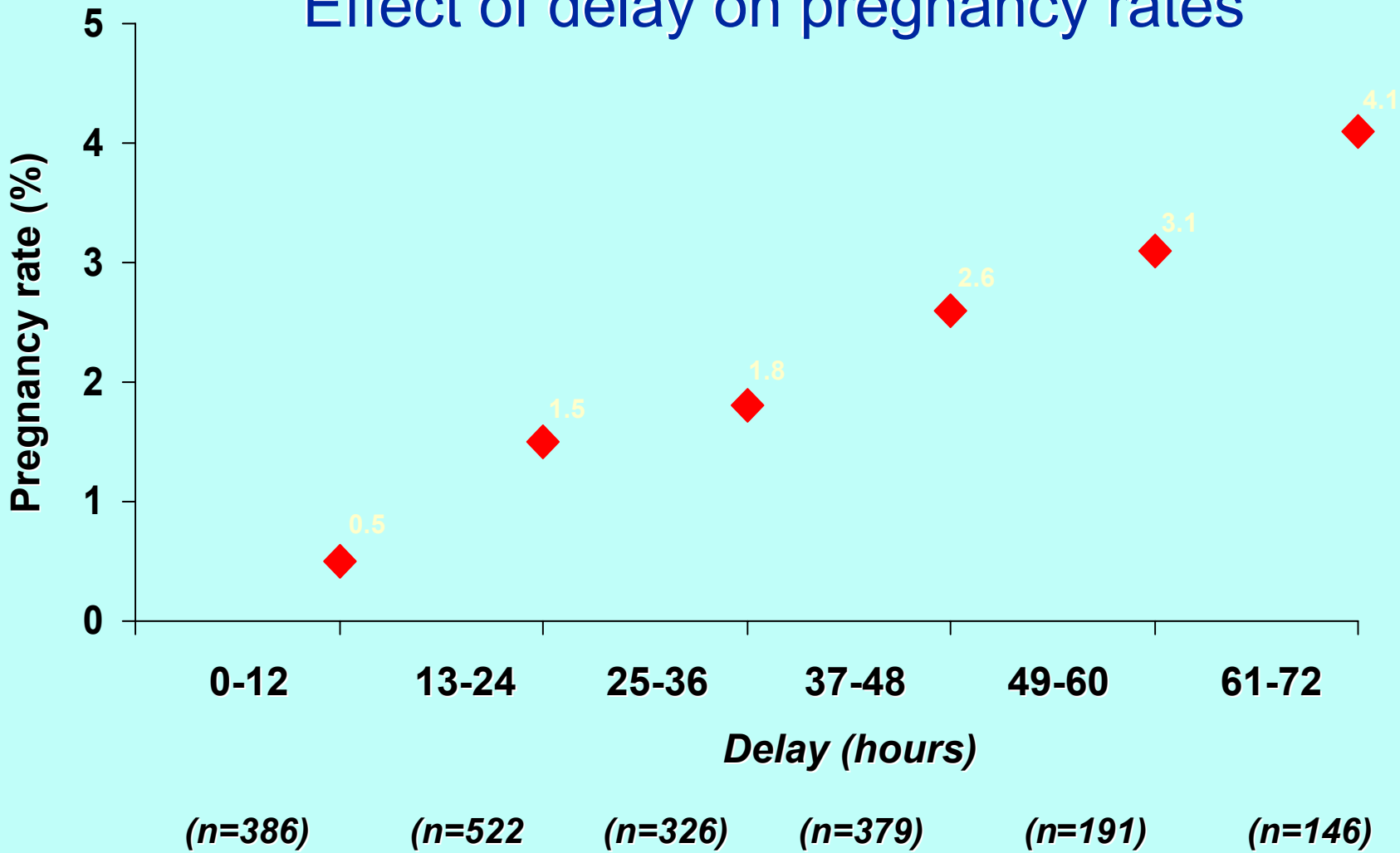
*

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



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

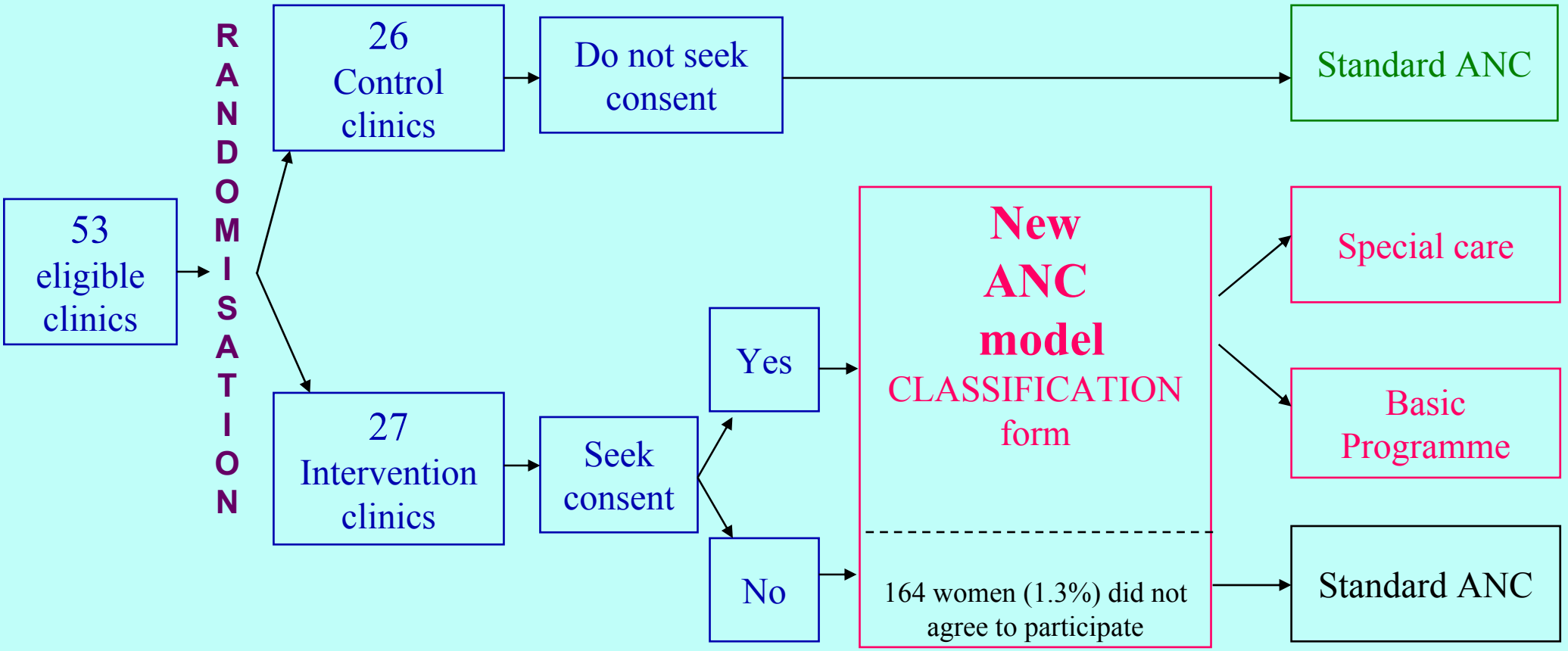
Hypothesis:

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

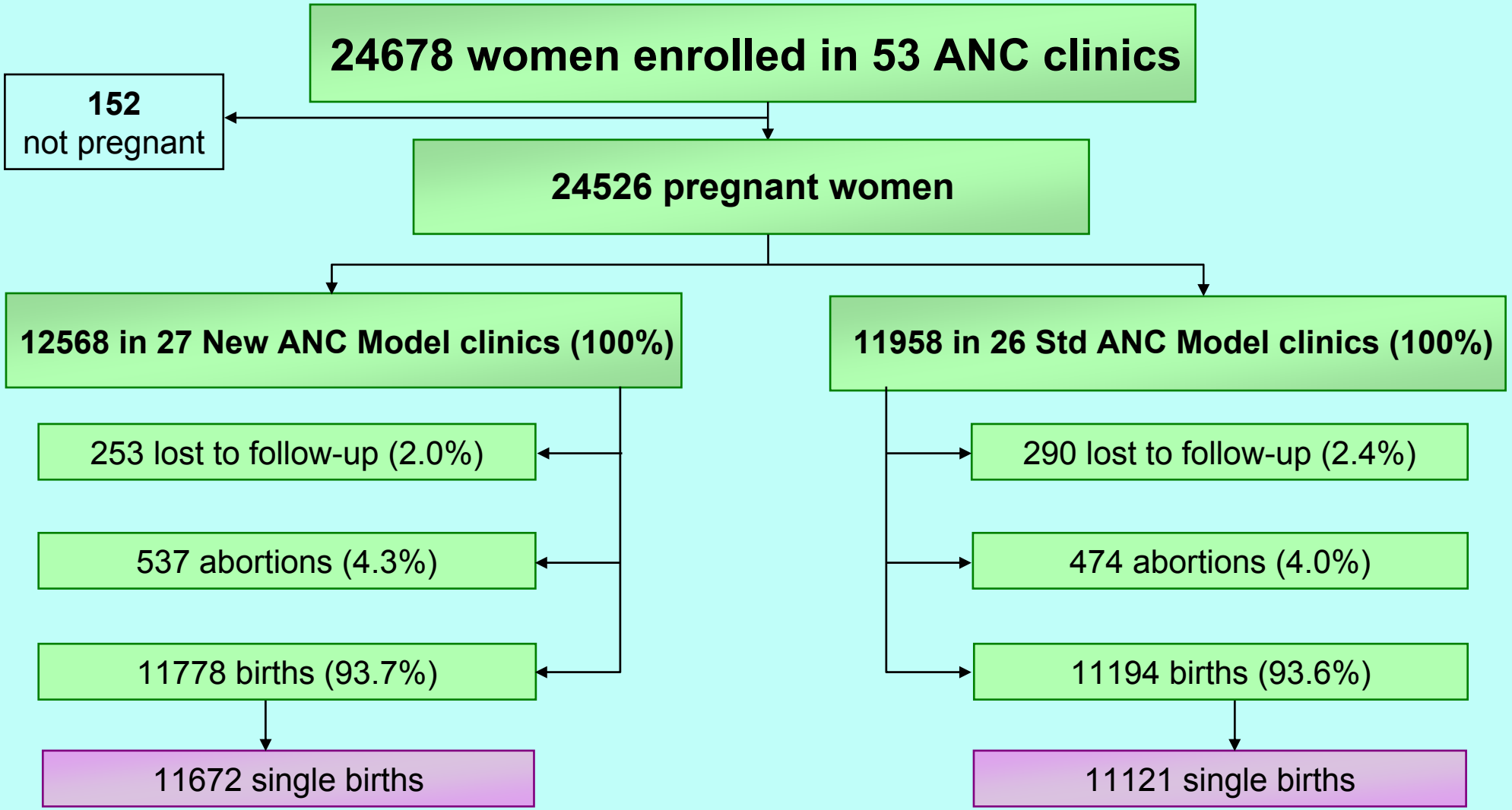
- low birth weight
- maternal morbidity

is not more expensive and
is acceptable by women and provider

Study Design and Women's Flow Chart



The Antenatal Care Trial: trial profile



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

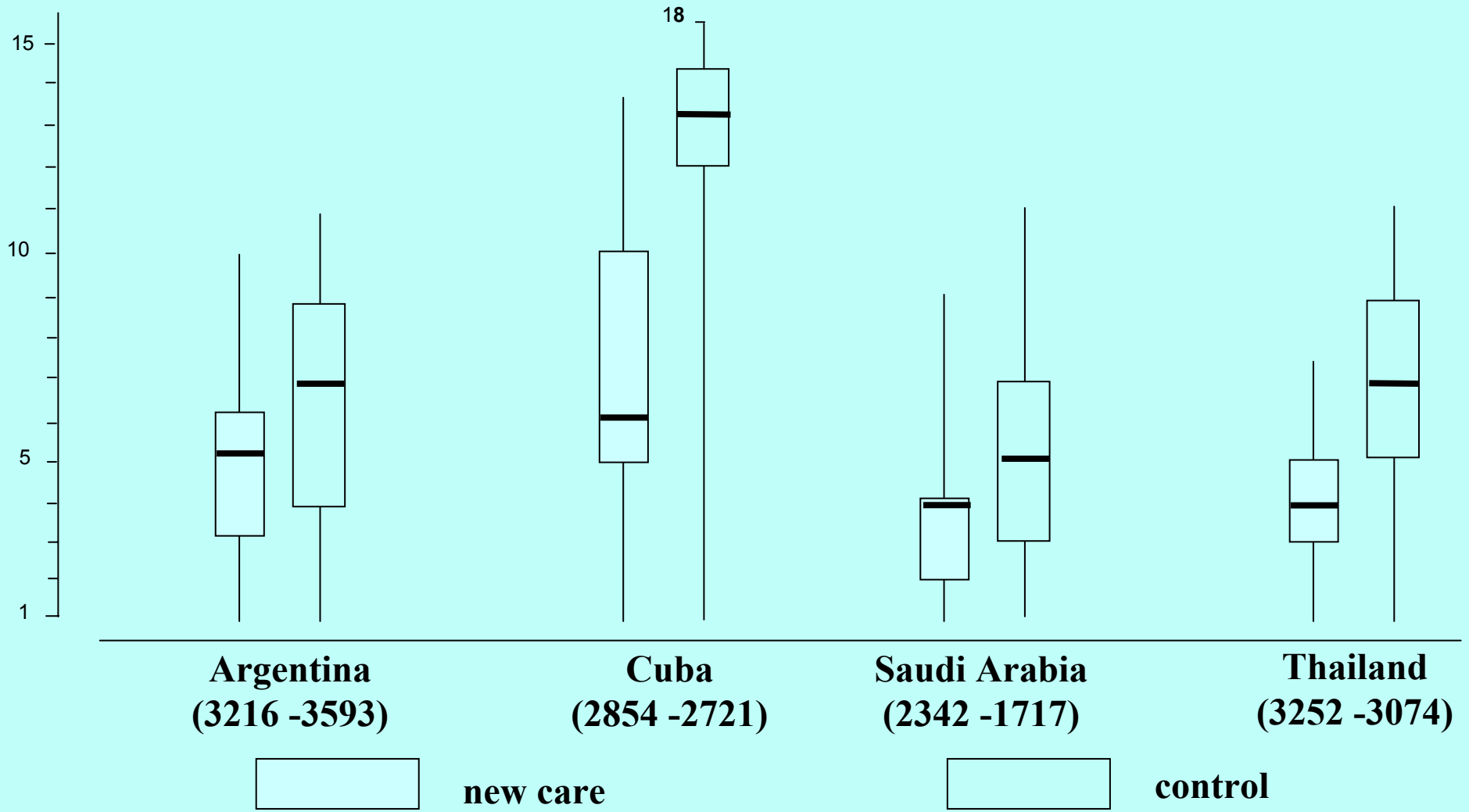
Baseline characteristics

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

	New Model %	Standard Model %
Specialist in Obst.Gynecol	61.7	57.1
General practitioner	18.9	19.0
Midwife	19.1	18.8

The Antenatal Care Trial

Number of visits



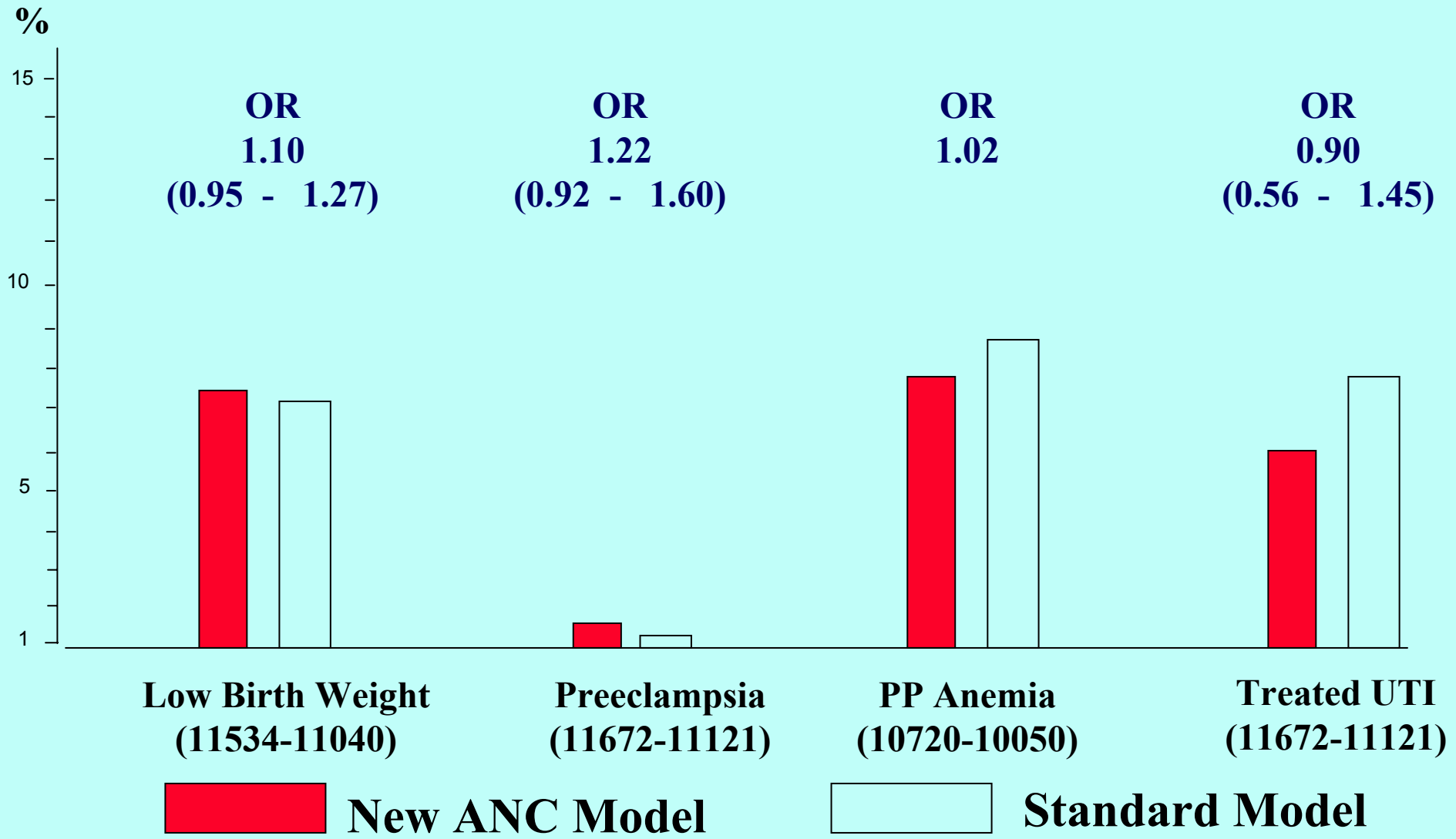
The Antenatal Care Trial

Primary outcomes

	ANC MODEL	Women No.	%	Stratified OR	95% CI
Low birth weight (<2500g)	New	11534	7.68	1.10	(0.95 to 1.27)
	Standard	11040	7.14		
Preeclampsia/eclampsia	New	11672	1.69	1.22	(0.92 to 1.60)
	Standard	11121	1.38		
Postpartum anaemia	New	10720	7.67	1.02	-
	Standard	10050	8.72		
Treated urinary tract infection	New	11672	5.95	0.90	(0.56 to 1.45)
	Standard	11121	7.41		

The Antenatal Care Trial

Primary outcomes



The Antenatal Care Trial

Secondary outcomes

	New ANC Model N=11672 %	Standard ANC Model N=11121 %
Pregnancy-induced hypertension	3.4	5.0
Preeclampsia	1.6	1.3
Preeclampsia hospital admission	0.4	0.3
Eclampsia	0.07	0.08
Severe anaemia pregnancy	4.4	3.9
Hypertension with referral/treatment	2.3	3.9
Hypertension without referral/treatment	1.1	1.0
Vaginal bleeding 2nd trimester	0.8	0.5
Vaginal bleeding 3rd trimester	0.7	0.6
Any vaginal bleeding	3.2	2.2

The Antenatal Care Trial

Secondary outcomes

	New ANC Model N=11672 %	Standard ANC Model N=11121 %
Fetal death	1.4	1.1
Neonatal Mort. (<1st day)	0.3	0.3
Neonatal Mort. (>1st-discharge)	0.4	0.4
Perinatal Mortality	2.0	1.7

The Antenatal Care Trial

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

	New ANC Model	Standard ANC Model
	N=2852 (6 clinics) %	N=2721 (6 clinics) %
	(median ANC visits 6)	(median ANC visits 13)
LBW (<2500g)	7.2	6.7
Preeclampsia/eclampsia	2.0	1.6
Postpartum anaemia	9.4	10.3
Treated UTI	7.2	9.3

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