Strategies for Data Analysis: Randomized Controlled Trials

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Introduction

The strategy for data analysis depends on the study design

For experimental studies:

Design depending on method of randomization:

- Completely randomised
- Paired-matched
- Stratified

Design depending on unit of randomization:

- Individually randomised
- Cluster randomised

Introduction

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 (ITT)

All patients are included in the analysis in the group to which they were randomized, even if they did not receive the allocated treatment

Per protocol analysis

Randomised subjects who arenon-eligible are excluded

Trial profile: Analysis by ITT or per protocol?

Reasons subjects could be excluded from a trial:

Non-eligibility

Non-compliance

Had other illnesses

Did not attend all visits

Moved out

Dropped out

} Lost to follow-up

Trial profile: Analysis by ITT or per protocol?

Advantages of ITT

Inclusion of all randomized 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

Trial profile: Analysis by ITT or per protocol?

Construct a flow chart providing numbers of subjects:

registered or eligible

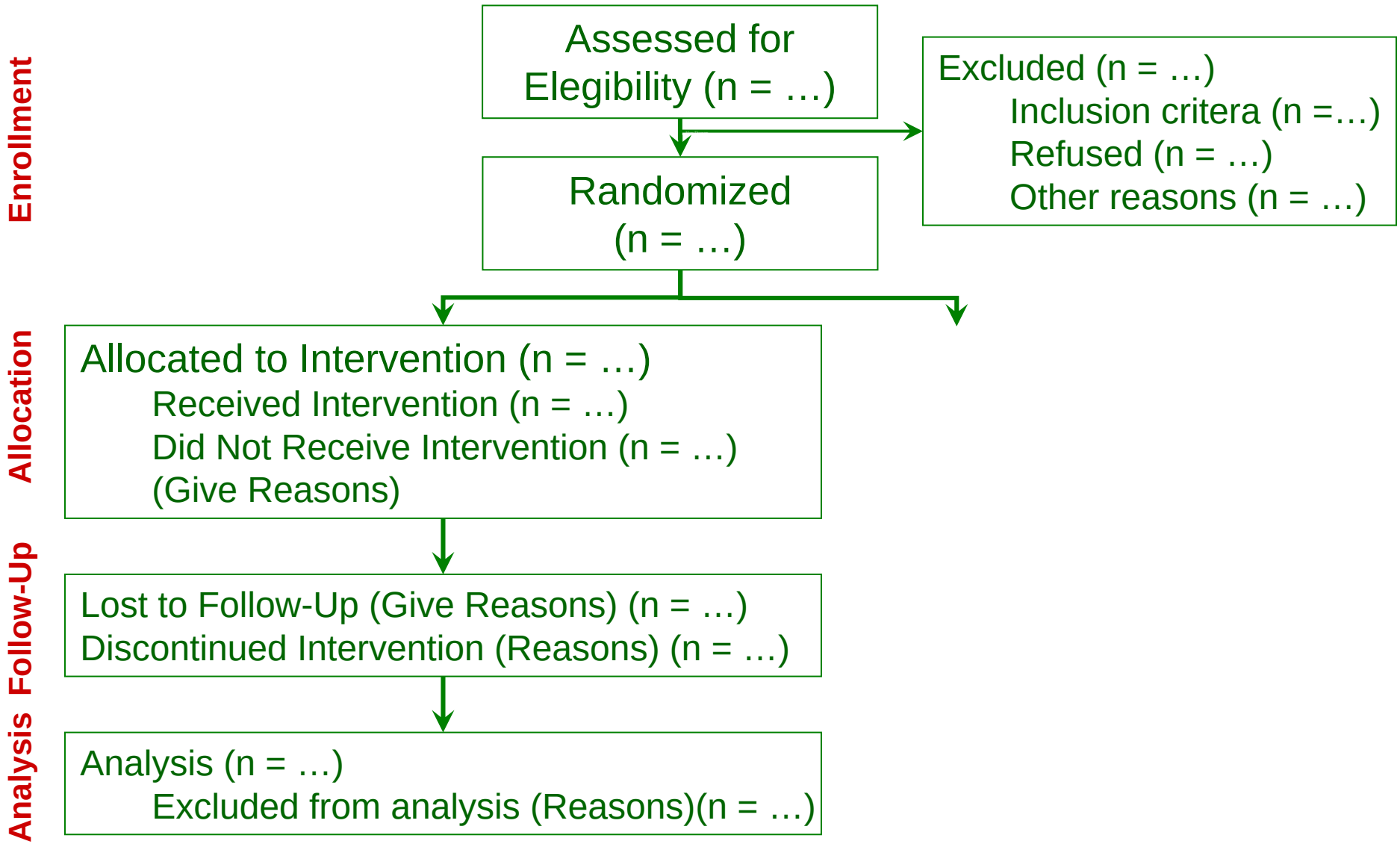
randomized

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- withdrawn (lost to follow-up and other reasons)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

Flow Diagram



The CREATE-ECLA Randomized Controlled Trial
(JAMA, Vol 293, 4, 437-446)

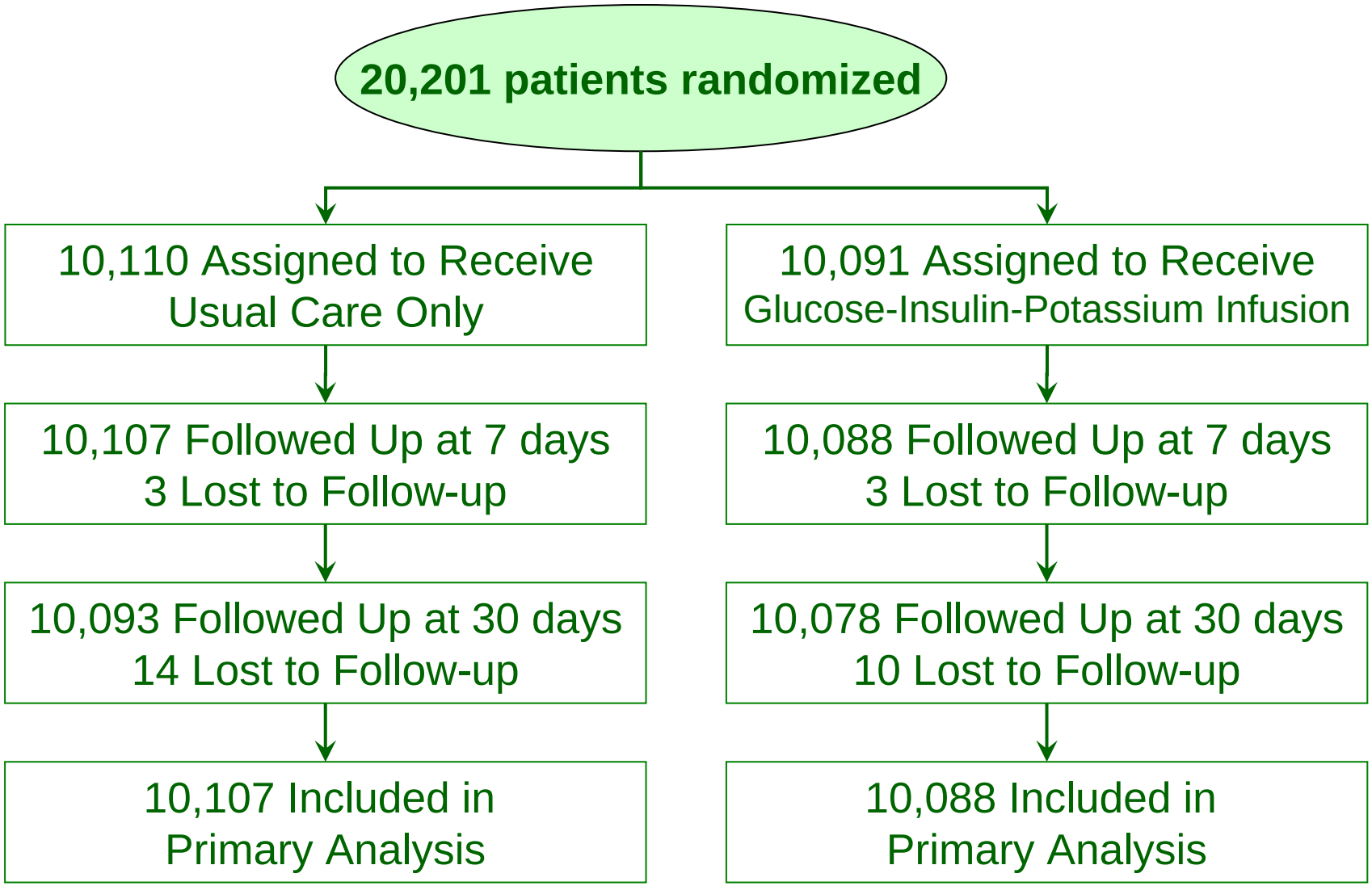
Context: Glucose-insulin-potassium (GIK) infusion is a widely applicable, low-cost therapy that has been postulated to improve mortality in patients with acute ST-segment elevation myocardial infarction (STEMI).

Objective: To determine the effect of high-dose GIK infusion on mortality in patients with STEMI.

Design: Randomized controlled trial conducted in 470 centers worldwide among 20,201 patients with STEMI who presented within 12 hours of sumptom onset.

Main Outcome Measure: Mortality, cardiac arrest, cardiogenic shock, and reinfarction at 30 days after randomization.

The CREATE-ECLA Randomized Controlled Trial



Strategies for Data Analysis: RCT

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Baseline Characteristics by Treatment Group

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 should produce very similar baseline statistics if the sample size is large

Baseline Characteristics by Treatment Group:
The CREATE-ECLA Randomized Controlled Trial

Selected Baseline Characteristics

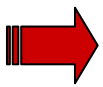
Characteristic	Usual Care Only (n = 10 107)	GIK Infusion (n = 10 088)
Age, mean (SD), y	58.6 (12.5)	58.6 (12.2)
Female gender	2267 (22.4)	2255 (22.4)
Type 2 Diabetes	1802 (17.8)	1780 (17.6)
Weight, mean (SD), kg	67.8 (12.8)	67.5 (12.8)
Systolic BP, mean (SD), mm Hg	128.8 (26.4)	129.1 (26.6)
Diastolic BP, mean (SD), mm Hg	81.5 (16.5)	81.6 (16.1)
Heart Rate, mean (SD), beats/min	79.7 (18.5)	79.5 (18.4)
Killip Class at Randomization		
I	8606 (85.1)	8490 (84.2)
II / III	1339 (13.2)	1435 (14.2)
IV	160 81.6)	157 (1.6)

* Data are expressed as No. (%) unless otherwise noted.

Strategies for Data Analysis: RCT

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 outcome measure can be of one of 3 types:

Categorical	Binary: Death (Yes-No) Multiple Levels: Improvement (Marked, Some, None)
Continuous	Cholesterol Level
Time to Event	Survival Type Measure: Time to Death

The statistical methods used to in the analysis will depend on the type of outcome measure.

Crude Effect of Treatment

The CREATE-ECLA Randomized Controlled Trial

Outcome	Usual Care Only (n = 10 107)	GIK Infusion (n = 10 088)	Relative Risk (RR, 95% CI)	P-value
30 Days				
Death	976 (9.7)	1004 (10.0)	1.03 (0.95 – 1.13)	0.45
Non Fatal Cardiac Arrest	151 (1.5)	139 (1.4)	0.93 (0.74 – 1.17)	0.51
Cardiogenic Shock	640 (6.3)	667 (6.6)	1.05 (0.94 – 1.17)	0.38
Reinfarction	246 (2.4)	236 (2.3)	0.98 (0.82 – 1.17)	0.81

* Data are expressed as No. (%) unless otherwise noted.

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Effect of treatment adjusting for possible confounders

Determine possible confounders:

Variables with imbalance between groups

Variables related to outcome: examine association between different variables and the outcome

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

Effect of treatment adjusting for possible confounders

The CREATE-ECLA Randomized Controlled Trial

Suposse that there was a baseline imbalance for the variable Killip Class at Randomization which is known to be associated with mortality after myocardial infarction.

If one of the two groups has more patients with Killip Class > I, then the observed difference (or lack of) could be attributed to the imbalance.

Solution: Produce "adjusted" measures of the association between treatment and outcome.

In experimental design generally is not necessary to perform this type of adjustment since randomization tends to eliminate all imbalances.

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Effect modifiers and stratified analyses

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: RCT

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Secondary Analysis: analysis (or analyses) that are of secondary importance in a study.

Examples:

- 7 day death in the GIK trial
- Combined events
- Safety Outcomes

Outcome	Usual Care Only (n = 10 107)	GIK Infusion (n = 10 088)	Relative Risk (RR, 95% CI)	P-value
Significant Phebitis	17 (0.2)	339 (3.4)	20.0 (12.3 – 32.5)	< 0.001
Hypoglycemia	11 (0.1)	34 (0.4)	3.10 (1.57 – 6.11)	< 0.001

Other analyses: secondary, sensitivity, subgroup

Sensitivity Analysis: secondary analyses carried out by varying the assumptions that are made about the data and models used, including or excluding unsual data points (outliers), etc. The purpose of such analyses is to see if the results and conclusions from a study are robust.

Subgroup Analysis: analysis of the results of a study just in certain subgroups.

Subgroup analysis should be specified in advance, not seeing the data. They should be included in the protocol.

Subgroup Analysis

The CREATE-ECLA Randomized Controlled Trial

Group	Usual Care Only	GIK Infusion	P-value
Thrombolytic Therapy	676 / 7503 (9.0)	703 / 7454 (9.4)	0.373
Time to Randomization (Less than 4 hours)	350 / 4218 (8.3)	366 / 4124 (8.9)	0.347
Killip Class (II-IV)	368 / 1499 (24.5)	399 / 1592 (25.1)	0.741

Discussion

Strengths and weakness of trial results results, based on design and analysis

Consistency with data from outside the trial

Consistency with other biological knowledge

Implications for clinical practice

Implications for researcg

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

Presentation
The CREATE-ECLA Randomized Controlled Trial

"In conclusion, the CREATE-ECLA randomized trial has reliably established that high-dose GIK infusion in patients with STEMI has no impact on mortality, cardiac arrest, or cardiogenic shock and is unlikely to be of any material value in patients with STEMI"

Strategies for data analysis: community intervention trials (cluster randomized trials)

Standard approaches for statistical analysis tend to bias p-values downwards and give spurious statistical significance

Need special statistical 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

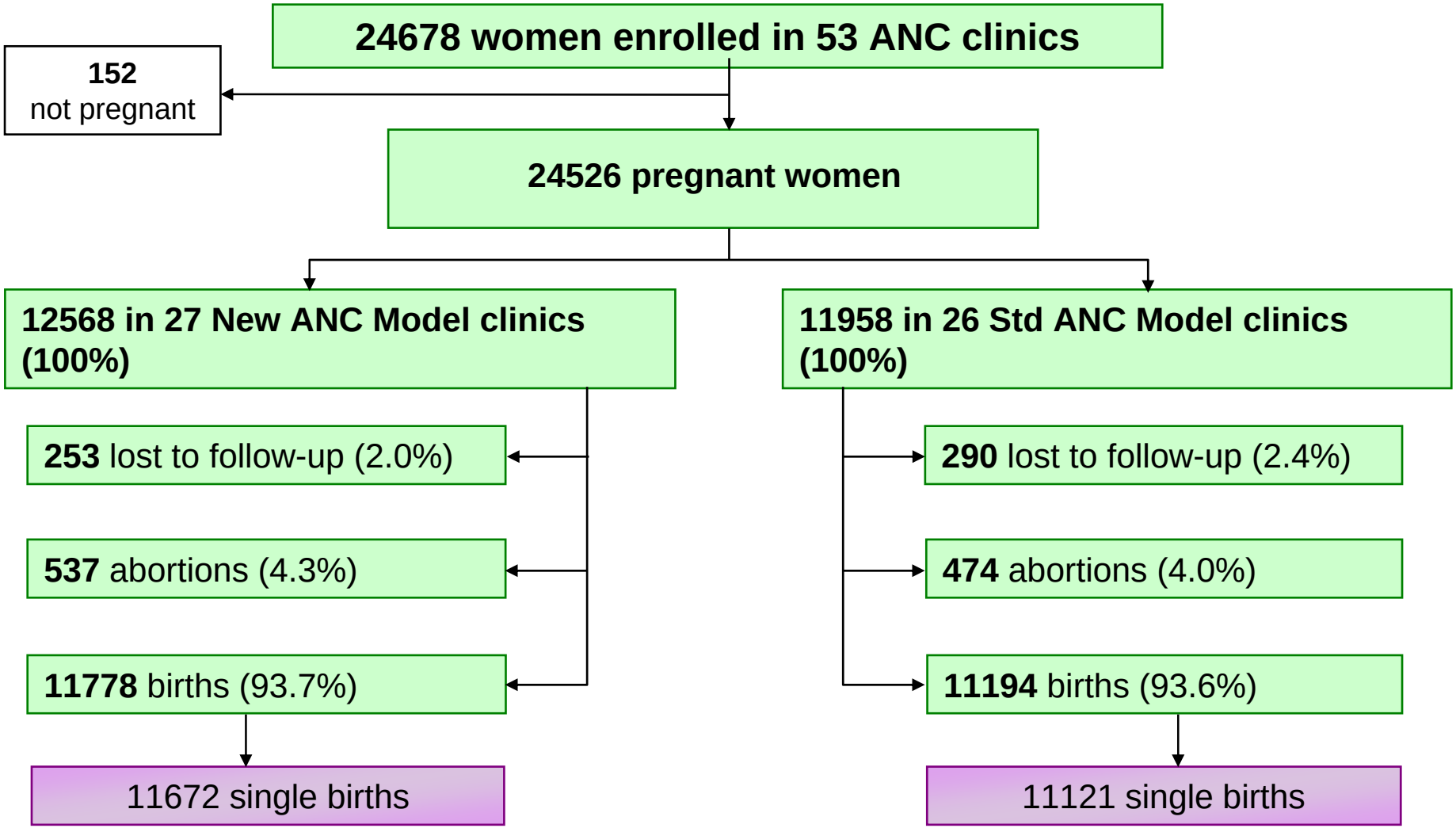
Hypothesis:

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

The Antenatal Care Trial
Study Design Flow chart



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:

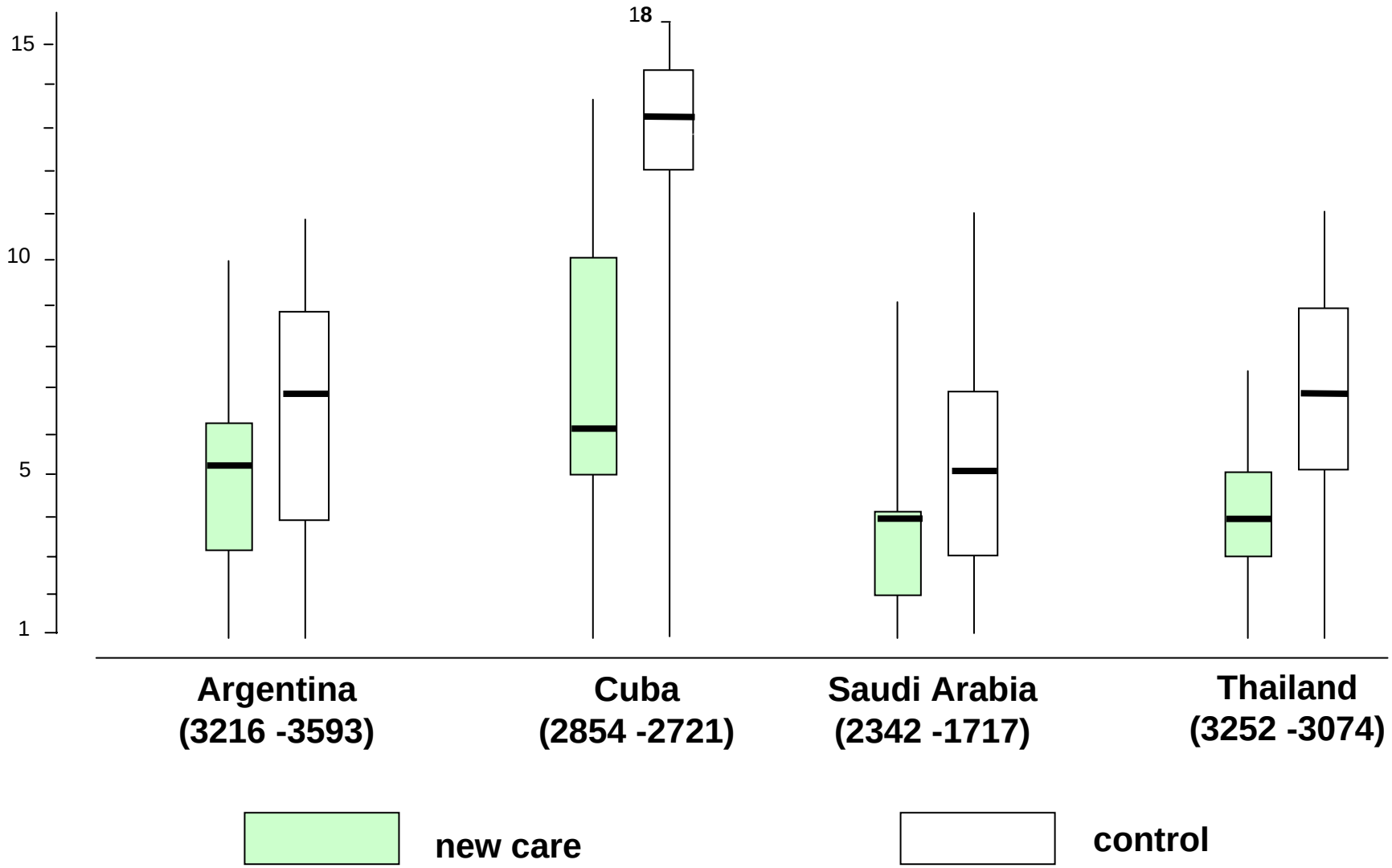
New ANC Model:	**16.5 ± 8.4 weeks**
Standard ANC:	**16.0 ± 8.0 weeks**

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

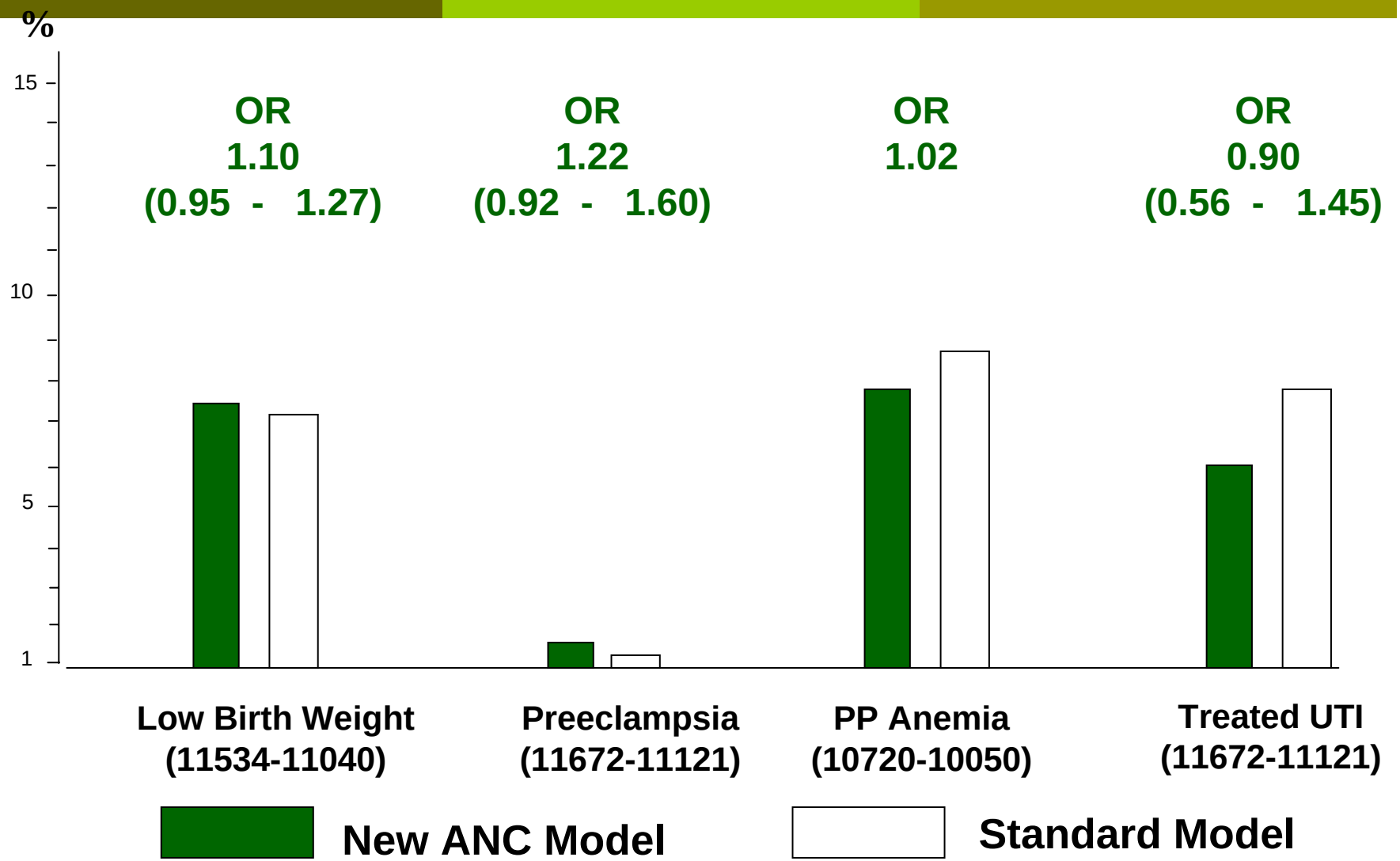


The Antenatal Care Trial
Primary Outcomes

Outcome	Group	Women	%	OR	95% CI
Low Birth Weight (< 2500 g)	New	11534	7.68	1.10	0.95 to 1.27
	Standard	11040	7.14		
Pre-eclampsia / Eclampsia	New	11672	1.69	1.22	0.92 to 1.60
	Standard	11121	1.38		
Postpartum anaemia	New	10720	7.59	1.02*	
	Standard	10050	8.67		
Treated urinary-tract infection	New	11672	5.95	0.90	0.56 to 1.45
	Standard	11121	7.41		

* Effect was heterogeneous across sites and strata, therefore pooled estimates may hide site-specific effects

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
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