

# Clinical Trials III

## Case Studies

Nuno Sepúlveda

# Course content

1. Basic concepts related to CTs
2. Designing/Reporting CTs/Mendelian Randomisation/Survival Analysis
3. Reporting CTs (CONSORT guidelines)
4. Discussion on the controversial PACE trial
5. Project's Presentations/Course Summary

# CONSORT

## Consolidated Standard for Reporting Trials

1996

Begg C, Cho M, Eastwood S, et al. Improving the quality of reporting of randomized controlled trials. The CONSORT statement. *JAMA*. 1996;276(8):637-639.

2001

Moher D, Schulz KF, Altman DG; CONSORT. The CONSORT statement: revised recommendations for improving the quality of reports of parallel group randomized trials. *BMC Med Res Methodol*. 2001;1:2.

2010

Schulz KF, Altman DG, Moher D; CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010 340:c332.

To promote  
transparency, clarity,  
and completeness

# CONSORT 2010

Consolidated Standard for Reporting Trials



Checklist of 25 items

# CONSORT Checklist

CONSORT 2010 checklist of information to include when reporting a randomised trial\*

Section/Topic	Item No	Checklist item
<b>Title and abstract</b>		
	1a	Identification as a randomised trial in the title
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts [1, 2])
<b>Introduction</b>		
Background and objectives	2a	Scientific background and explanation of rationale
	2b	Specific objectives or hypotheses
<b>Methods</b>		
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons
Participants	4a	Eligibility criteria for participants
	4b	Settings and locations where the data were collected
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed
	6b	Any changes to trial outcomes after the trial commenced, with reasons
Sample size	7a	How sample size was determined
	7b	When applicable, explanation of any interim analyses and stopping guidelines
Randomisation:		
Sequence generation	8a	Method used to generate the random allocation sequence
	8b	Type of randomisation; details of any restriction (such as blocking and block size)
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how
	11b	If relevant, description of the similarity of interventions
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses
<b>Results</b>		

<https://www.equator-network.org/reporting-guidelines/consort/>



# CONSORT Checklist (continued)

Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome
	13b	For each group, losses and exclusions after randomisation, together with reasons
Recruitment	14a	Dates defining the periods of recruitment and follow-up
	14b	Why the trial ended or was stopped
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms <sup>2b</sup> )
<b>Discussion</b>		
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses
Generalisability	21	Generalisability (external validity, applicability) of the trial findings
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence
<b>Other information</b>		
Registration	23	Registration number and name of trial registry
Protocol	24	Where the full trial protocol can be accessed, if available
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders
<p>*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration [3] for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, [4] non-inferiority and equivalence trials [5], non-pharmacological treatments [6], herbal interventions [7], and pragmatic trials [8]. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see <a href="http://www.consort-statement.org">www.consort-statement.org</a>.</p>		

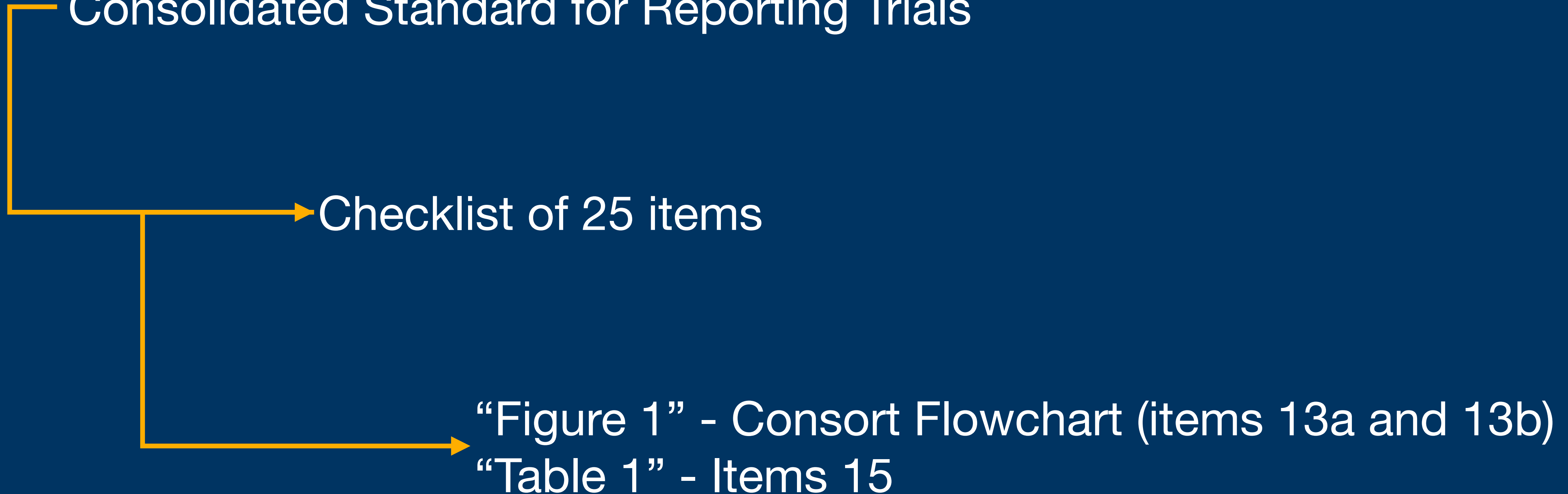
# CONSORT 2010

Consolidated Standard for Reporting Trials

Checklist of 25 items

“Figure 1” - Consort Flowchart (items 13a and 13b)

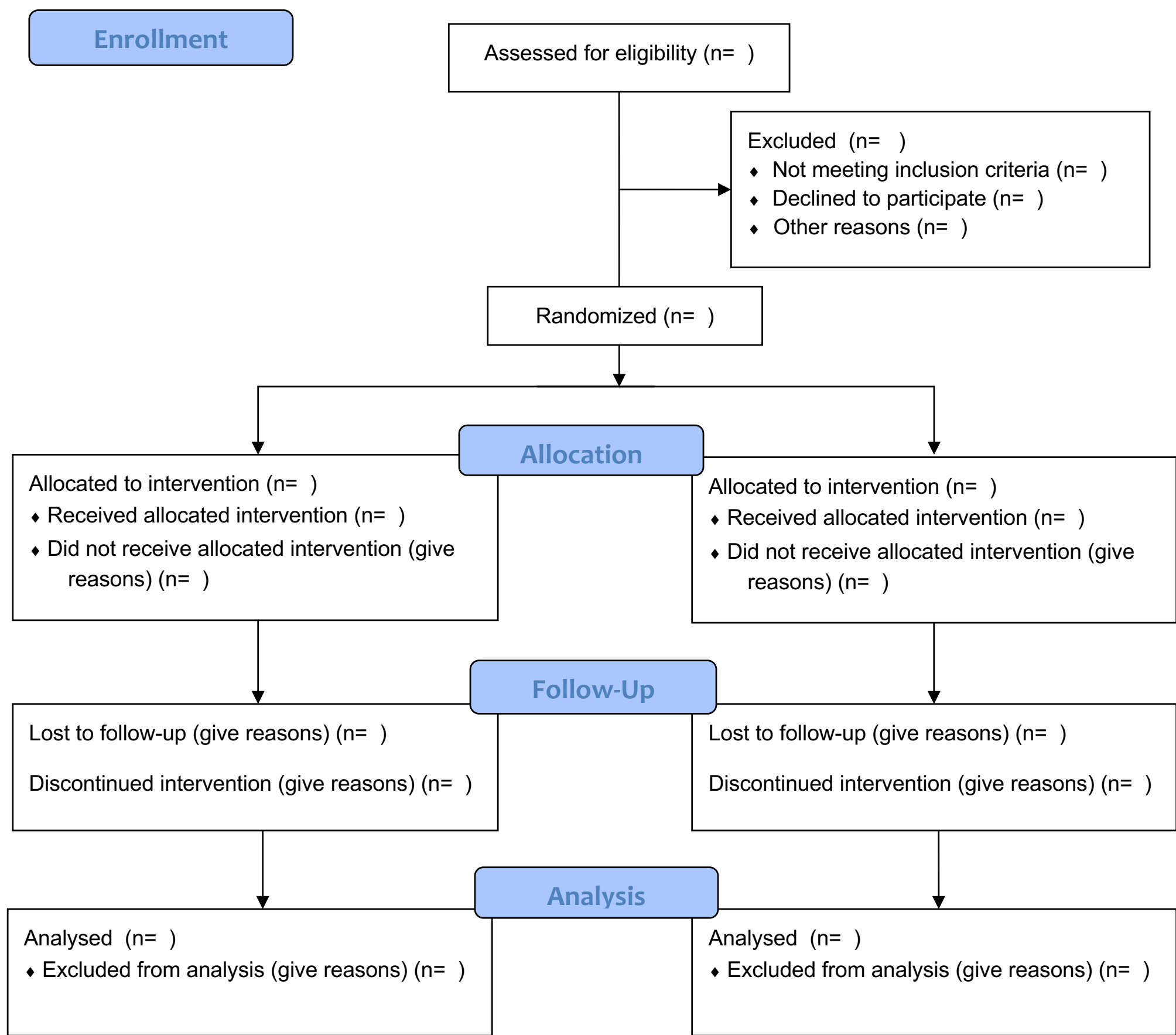
“Table 1” - Items 15



# CONSORT flowchart



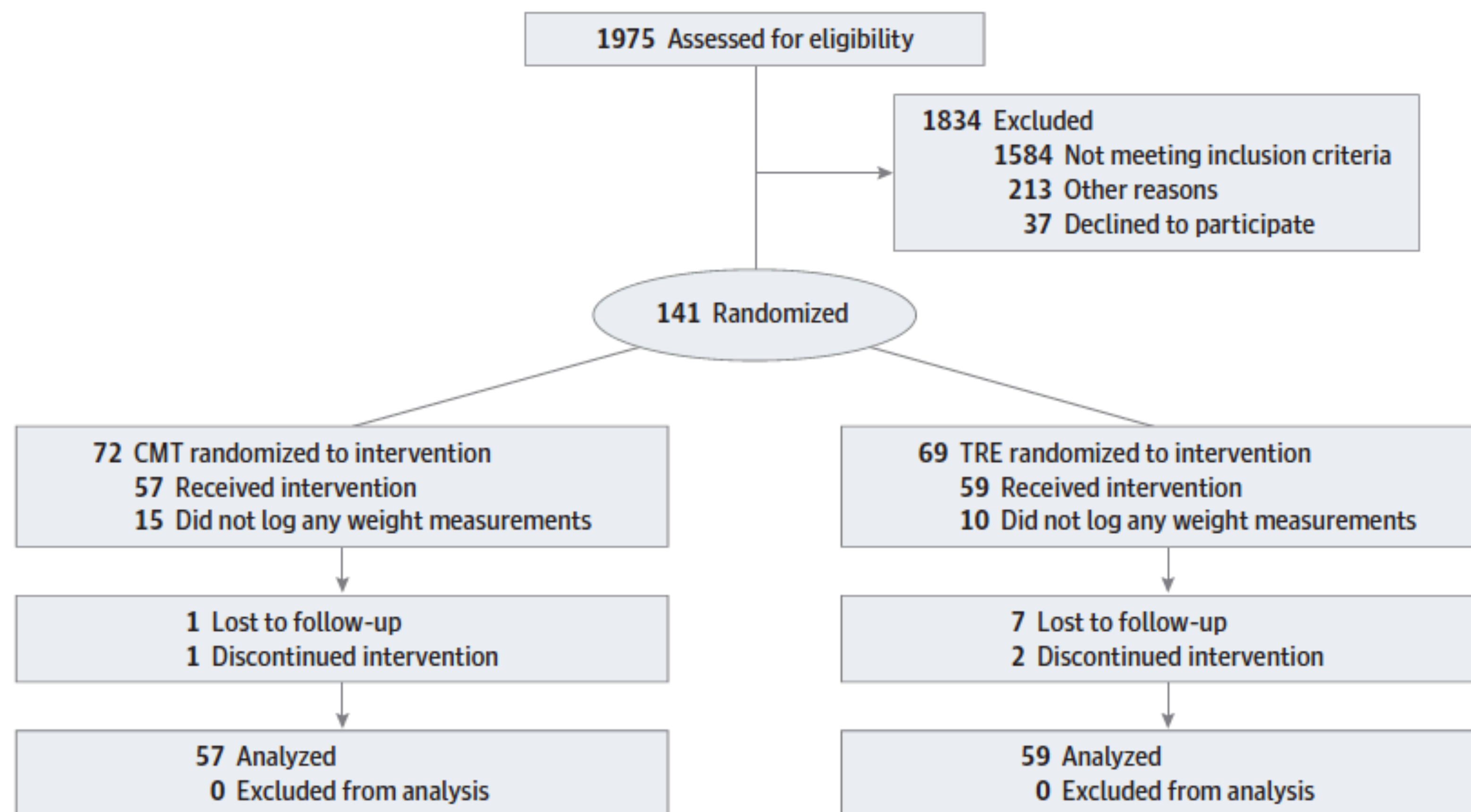
CONSORT 2010 Flow Diagram





# Effects of Time-Restricted Eating on Weight Loss and Other Metabolic Parameters in Women and Men With Overweight and Obesity The TREAT Randomized Clinical Trial

Dylan A. Lowe, PhD; Nancy Wu, MS; Linnea Rohdin-Bibby, BA; A. Holliston Moore, PhD; Nisa Kelly, MS; Yong En Liu, BS; Errol Philip, PhD; Eric Vittinghoff, PhD; Steven B. Heymsfield, MD; Jeffrey E. Olgin, MD; John A. Shepherd, PhD; Ethan J. Weiss, MD



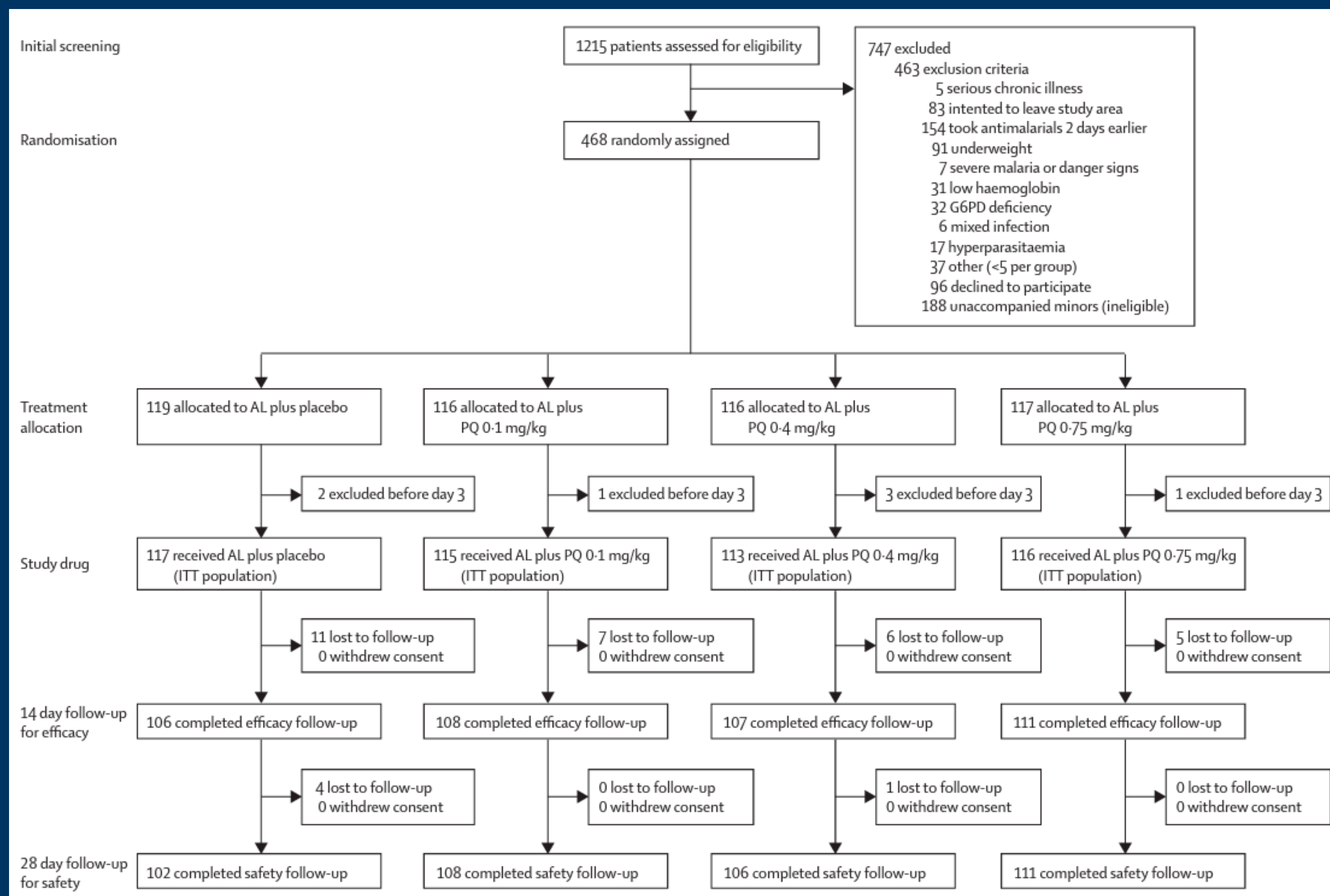
**What is important to show in the flowchart?**



# Single dose primaquine for clearance of *Plasmodium falciparum* gametocytes in children with uncomplicated malaria in Uganda: a randomised, controlled, double-blind, dose-ranging trial



Alice C Eziefula, Teun Bousema, Shunmay Yeung, Moses Kamya, Asiphas Owaraganise, Grace Gabagaya, John Bradley, Lynn Grignard, Kjerstin H W Lanke, Humphrey Wanzira, Arthur Mpimbaza, Samuel Nsoya, Nicholas J White, Emily L Webb, Sarah G Staedke, Chris Drakeley



## Table 1

**What elements should be reported?**



# Effects of Time-Restricted Eating on Weight Loss and Other Metabolic Parameters in Women and Men With Overweight and Obesity

## The TREAT Randomized Clinical Trial

Dylan A. Lowe, PhD; Nancy Wu, MS; Linnea Rohdin-Bibby, BA; A. Holliston Moore, PhD; Nisa Kelly, MS; Yong En Liu, BS; Errol Philip, PhD; Eric Vittinghoff, PhD; Steven B. Heymsfield, MD; Jeffrey E. Olgin, MD; John A. Shepherd, PhD; Ethan J. Weiss, MD

Table 1. Baseline Characteristics

Characteristic	No. (%)		
	Total	CMT	TRE
Total cohort			
No.	116	57	59
Age, mean (SD), y	46.5 (10.5)	46.1 (10.3)	46.8 (10.8)
Female	46 (39.7)	22 (38.6)	24 (40.7)
Male	70 (60.3)	35 (61.4)	35 (59.3)
Weight, mean (SD), kg	99.2 (16.0)	99.1 (15.1)	99.3 (16.9)
BMI, mean (SD)	32.7 (4.2)	32.6 (3.4)	32.9 (4.9)
In-person cohort			
No.	50	25	25
Age, mean (SD), y	43.8 (11.2)	44.4 (10.7)	43.3(11.8)
Female	22 (44.0)	10 (40.0)	12 (48.0)
Male	28 (56.0)	15 (60.0)	13 (52.0)
Black	2 (4.0)	0	2 (8.0)
White	25 (50)	16 (64.0)	9 (36.0)
Latinx	7 (14.0)	3 (12.9)	4 (16.0)
Asian	12 (24.0)	5 (20.0)	7 (28.0)
Other/multi	4 (8.0)	1 (4.0)	3 (12.0)
Weight, mean (SD), kg	92.8 (14.2)	93.0 (13.3)	92.6 (15.2)
BMI, mean (SD),	31.4 (4.0)	31.3 (3.5)	31.5 (4.5)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CMT, consistent meal timing group; TRE, time-restricted eating group.



# Single dose primaquine for clearance of *Plasmodium falciparum* gametocytes in children with uncomplicated malaria in Uganda: a randomised, controlled, double-blind, dose-ranging trial



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	Placebo (n=117)	Primaquine 0.1 mg/kg (n=115)	Primaquine 0.4 mg/kg (n=113)	Primaquine 0.75 mg/kg (n=116)
Boys	48.7% (57/117)	49.6% (57/115)	49.6% (56/113)	49.1% (57/116)
Age (years)	5.0 (3.0–7.5)	5.0 (3.3–7.0)	5.3 (3.2–7.0)	4.1 (3.0–7.0)
Bodyweight (kg)	16.0 (13.0–20.5)	16.0 (13.0–22.0)	17.0 (14.0–23.0)	15.0 (13.0–19.0)
Body temperature (°C)	38.0 (1.0)	38.3 (1.1)	38.0 (1.2)	38.2 (1.1)
Haemoglobin concentration (g/L)	113 (15)	109 (15)	112 (15)	112 (14)
Geometric mean sexual parasite density, parasites/mL (IQR)	17 661 (5260–65 130)	18 420 (4440–92 780)	16 457 (3260–81 240)	32 497 (10 880–151 180)
Gametocyte prevalence by microscopy	23.1% (27/117)	24.3% (28/115)	20.4% (23/113)	22.4% (26/116)
Gametocyte prevalence by QT-NASBA	79.8% (91/114)	86.7% (98/113)	78.7% (85/108)	82.0% (91/111)
Geometric mean gametocyte density (gametocytes/μL) by QT-NASBA (IQR)	15.2 (8.4–27.8)	14.5 (8.9–23.5)	19.4 (11.3–33.1)	24.6 (14.9–40.5)

Data are % (n/N), median (IQR), or mean (SD), unless otherwise indicated. QT-NASBA=quantitative real-time nucleic acid sequence-based analysis.

**Table 1: Baseline characteristics**

# Benefits of CONSORT 2010

Authors

Peer-reviewers/Editors

Readers

to assist  
reporting

to help in the revision  
process

to facilitate critical appraisal  
of the existing evidence



# Limitations of CONSORT 2010

Encourage some authors to report fictitiously suggested by the guidance than what was actually done.

It does not include recommendations for designing and conducting a randomised trial



# Some useful R packages for reporting

“Figure 1”                      CONSORT 2010 flowchart

**visR (archived since last year)**

**ggconsort**

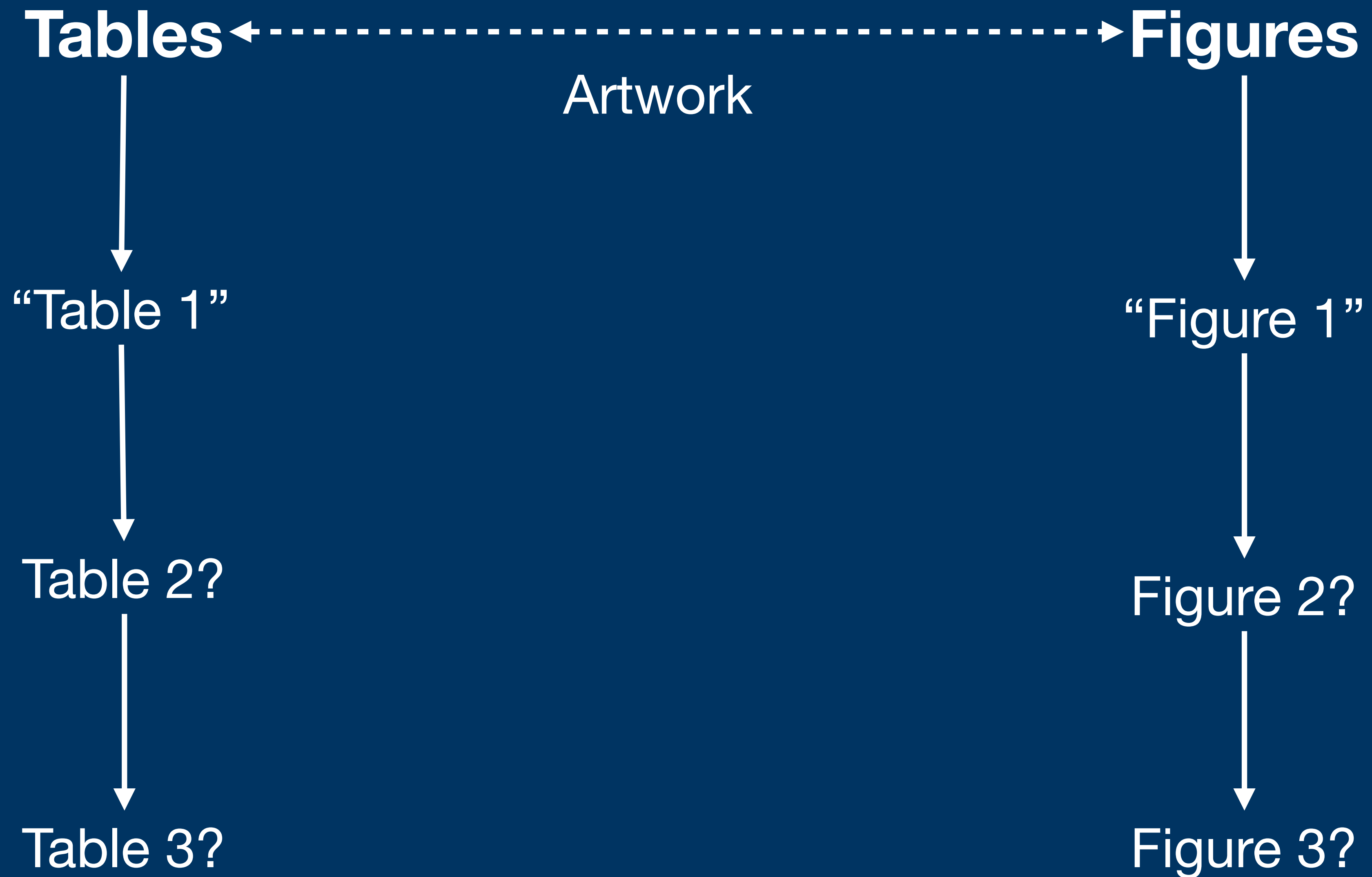
“Table 1”                      **(item 15 of CONSORT checklist)**

**visR**

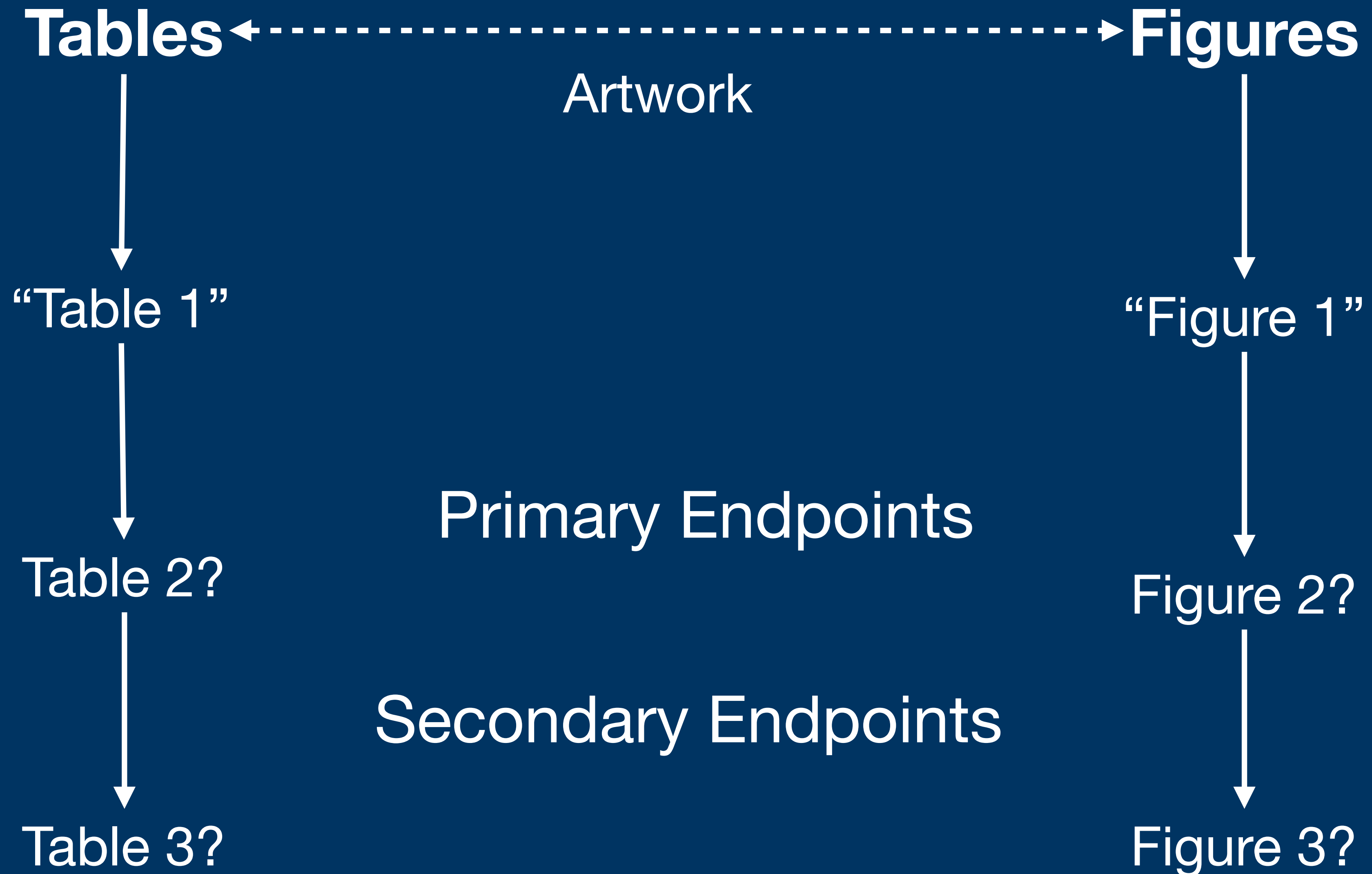
**Table1**

Baseline demographic and clinical characteristics of  
study participants

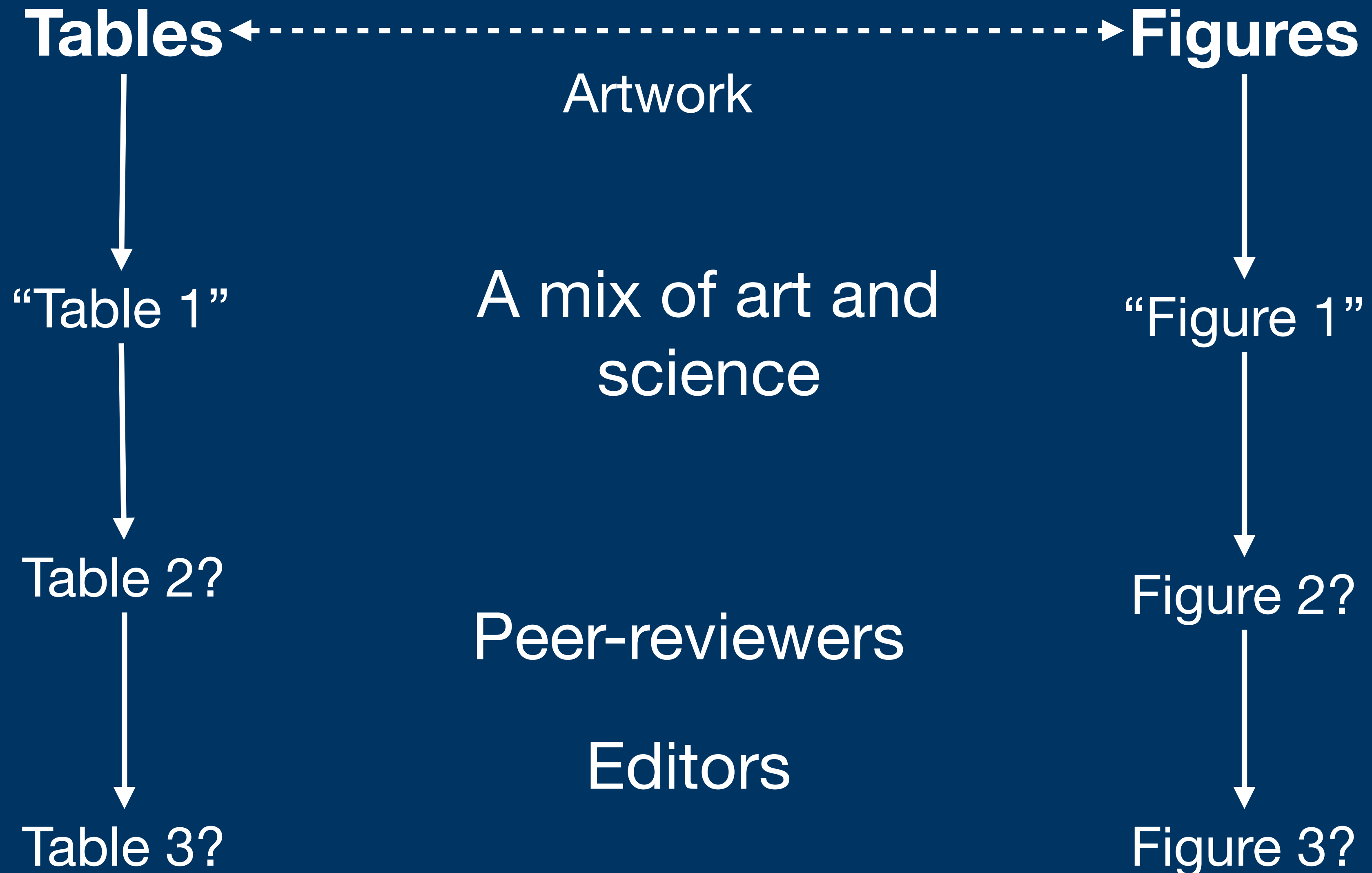
# Presenting the results



# Presenting the results



# Presenting the results





# Group discussion

**How many tables/figures?**

**When to use Tables?**

**Which Tables?**

**When to use Figures?**

**Which Figures?**

# Group discussion

How many tables/figures?

When to use Tables?

When to use Figures?

Which Tables?

Which Figures?

Storytelling/Understanding data

# Little quiz - what is the best plot?

Response/Non-Response

Disease score

Endpoint

Quantitative biomarker

Time-to-event

# Effects of Time-Restricted Eating on Weight Loss and Other Metabolic Parameters in Women and Men With Overweight and Obesity

## The TREAT Randomized Clinical Trial

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**Primary endpoint:**  
change in weight loss

**Secondary endpoints:**  
blood pressure, heart rate, total cholesterol, LDLc, HDLc, triglycerides, fasting glucose, fasting Insulin, C-Reactive Protein, Homocysteine



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### 3 Figures

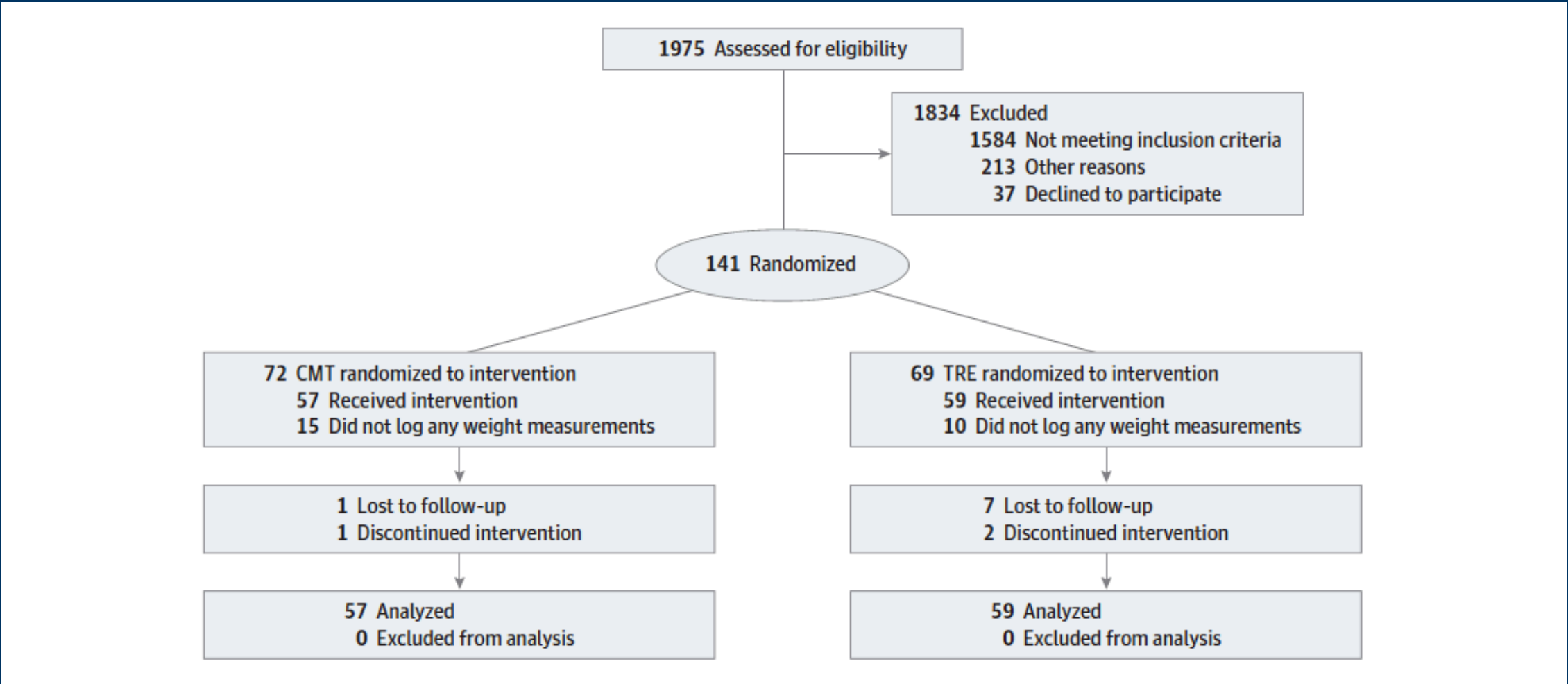


Figure 2. Prescribed vs Actual Energy Intake in the Alternate-Day Fasting and Daily Calorie Restriction Groups

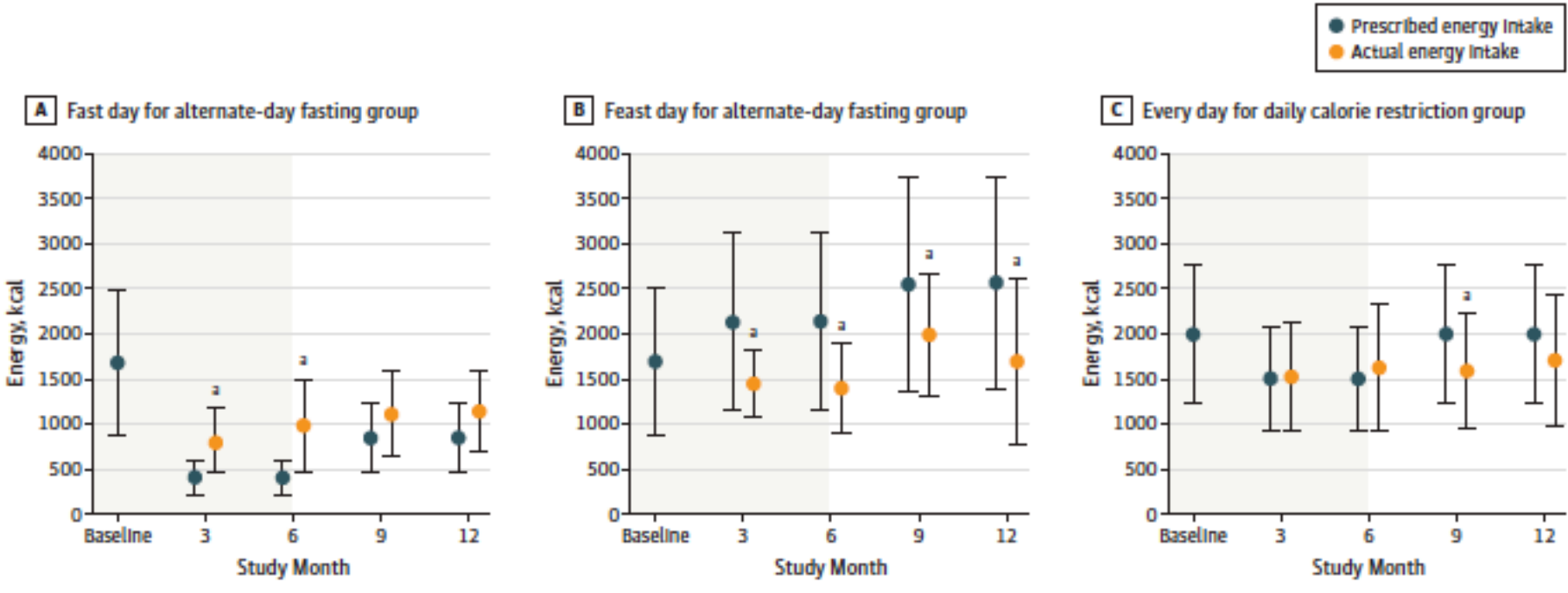
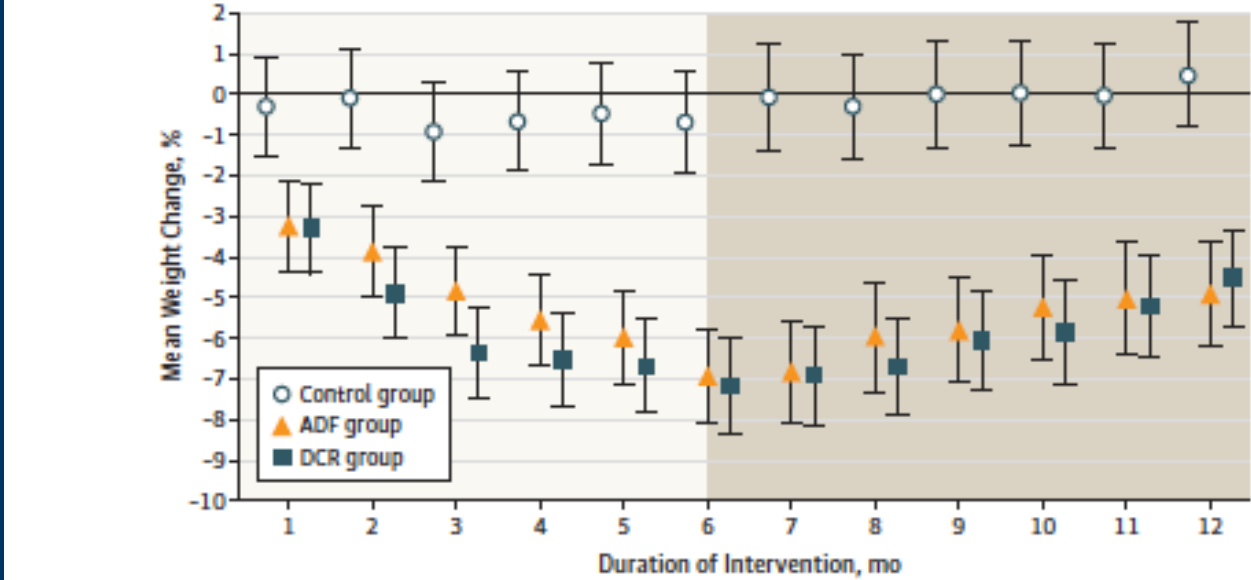


Figure 3. Weight Loss by Diet Group Relative to Baseline



Data were included for 100 participants; mean (SD) values were estimated using an intention-to-treat analysis with a linear mixed model. Error bars indicate 95% CIs for weight change from baseline by diet group at each time point (1-12 months). ADF indicates alternate-day fasting; DCR, daily calorie restriction.

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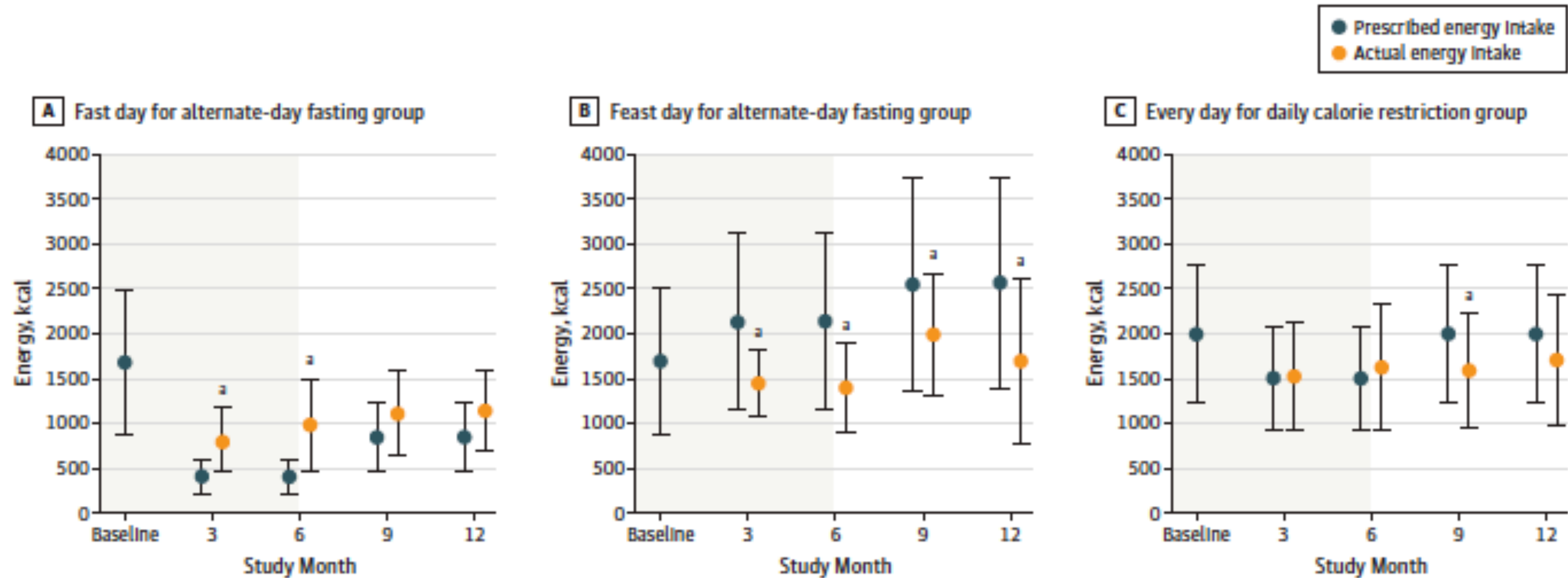
Table 2. Pairwise Effects Estimates of Diet on Mean Changes From Baseline in Body Weight and Risk Indicators for Cardiovascular Disease<sup>a</sup>

Outcome Variable	Change In ADF – Change In DCR (95% CI)		Change In ADF – Change In Control (95% CI)		Change In DCR – Change In Control (95% CI)	
	At 6 mo	At 12 mo	At 6 mo	At 12 mo	At 6 mo	At 12 mo
Body weight, % change	0.0 (–2.2 to 2.2)	–0.7 (–3.1 to 1.6)	–6.8 (–9.1 to –4.5)	–6.0 (–8.5 to –3.6)	–6.8 (–9.1 to –4.6)	–5.3 (–7.6 to –3.0)
Fat mass, kg	0.9 (–1.3 to 3.1)	0.0 (–2.4 to 2.4)	–4.2 (–6.6 to –1.8)	–2.0 (–4.4 to 0.5)	–5.1 (–7.5 to –2.7)	–2.0 (–4.4 to 0.4)
Lean mass, kg	0.6 (–1.0 to 2.2)	0.5 (–1.2 to 2.2)	–1.5 (–3.2 to 0.2)	–0.9 (–2.7 to 0.9)	–2.1 (–3.8 to 0.4)	–1.4 (–3.1 to 0.3)
Visceral fat mass, kg	0.2 (–0.1 to 0.5)	0.1 (–0.2 to 0.5)	–0.4 (–0.7 to –0.1)	–0.4 (–0.7 to –0.1)	–0.6 (–0.9 to –0.2)	–0.5 (–0.8 to –0.2)
Blood pressure, mm Hg						
Systolic	0.8 (–7.1 to 8.7)	–1.1 (–9.5 to 7.4)	–3.1 (–11.3 to 5.2)	–2.3 (–11.0 to 6.4)	–3.9 (–12.1 to 4.4)	–1.24 (–9.7 to 7.2)
Diastolic	–0.3 (–5.9 to 5.4)	–3.0 (–9.0 to 3.0)	–1.5 (–7.4 to 4.4)	–0.1 (–6.3 to 6.1)	–1.2 (–7.1 to 4.6)	2.9 (–3.1 to 8.9)
Heart rate, beats/min	–4.9 (–10.1 to 0.4)	–2.0 (–7.7 to 3.8)	–5.8 (–11.3 to –0.3)	–1.2 (–7.1 to 4.7)	–0.9 (–6.4 to 4.5)	0.8 (–4.8 to 6.4)
Cholesterol, mg/dL						
Total	3.4 (–7.2 to 13.9)	9.7 (–2.2 to 21.7)	–4.3 (–15.4 to 6.9)	4.2 (–8.2 to 16.5)	–7.6 (–18.8 to 3.6)	–5.6 (–17.6 to 6.4)
HDL	6.2 (0.1 to 12.4)	1.0 (–5.9 to 7.8)	8.4 (1.9 to 14.7)	2.9 (–4.2 to 10.0)	2.2 (–4.3 to 8.7)	1.9 (–5.1 to 8.9)
LDL	2.5 (–6.0 to 10.9)	11.5 (1.9 to 21.1)	–2.6 (–11.5 to 6.4)	1.2 (–8.7 to 11.2)	–5.0 (–14.0 to 3.9)	–10.3 (–19.9 to –0.6)
Triglycerides, mg/dL	–10.5 (–26.7 to 5.8)	–9.9 (–28.3 to 8.6)	–19.1 (–36.3 to –1.8)	–24.4 (–43.5 to –5.3)	–8.6 (–25.9 to 8.7)	–14.5 (–33.1 to 4.0)
Glucose, mg/dL	–1.4 (–8.0 to 5.2)	5.7 (–1.6 to 13.0)	–6.3 (–13.3 to 0.7)	–3.9 (–11.5 to 3.6)	–4.9 (–12.0 to 2.1)	–9.6 (–17.1 to –2.2)
Insulin, μIU/mL	–0.4 (–5.5 to 4.7)	–1.3 (–6.9 to 4.3)	–7.5 (–12.9 to –2.0)	–5.9 (–11.7 to –0.1)	–7.0 (–12.5 to –1.6)	–4.6 (–10.4 to 1.2)
HOMA-IR <sup>2</sup>	0.07 (–1.56 to 1.70)	0.02 (–1.78 to 1.81)	–2.49 (–4.22 to –0.76)	–1.86 (–3.73 to 0.01)	–2.56 (–4.30 to –0.82)	–1.88 (–3.72 to –0.03)
HS CRP, mg/dL	–0.04 (–0.19 to 0.11)	0.00 (–0.16 to 0.17)	–0.07 (–0.23 to 0.08)	–0.07 (–0.24 to 0.11)	–0.04 (–0.19 to 0.12)	–0.07 (–0.24 to 0.10)
Homocysteine, mg/L	0.03 (–0.10 to 0.17)	0.03 (–0.12 to 0.18)	0.10 (–0.04 to 0.24)	0.02 (–0.13 to 0.18)	0.06 (–0.08 to 0.20)	–0.01 (–0.16 to 0.14)



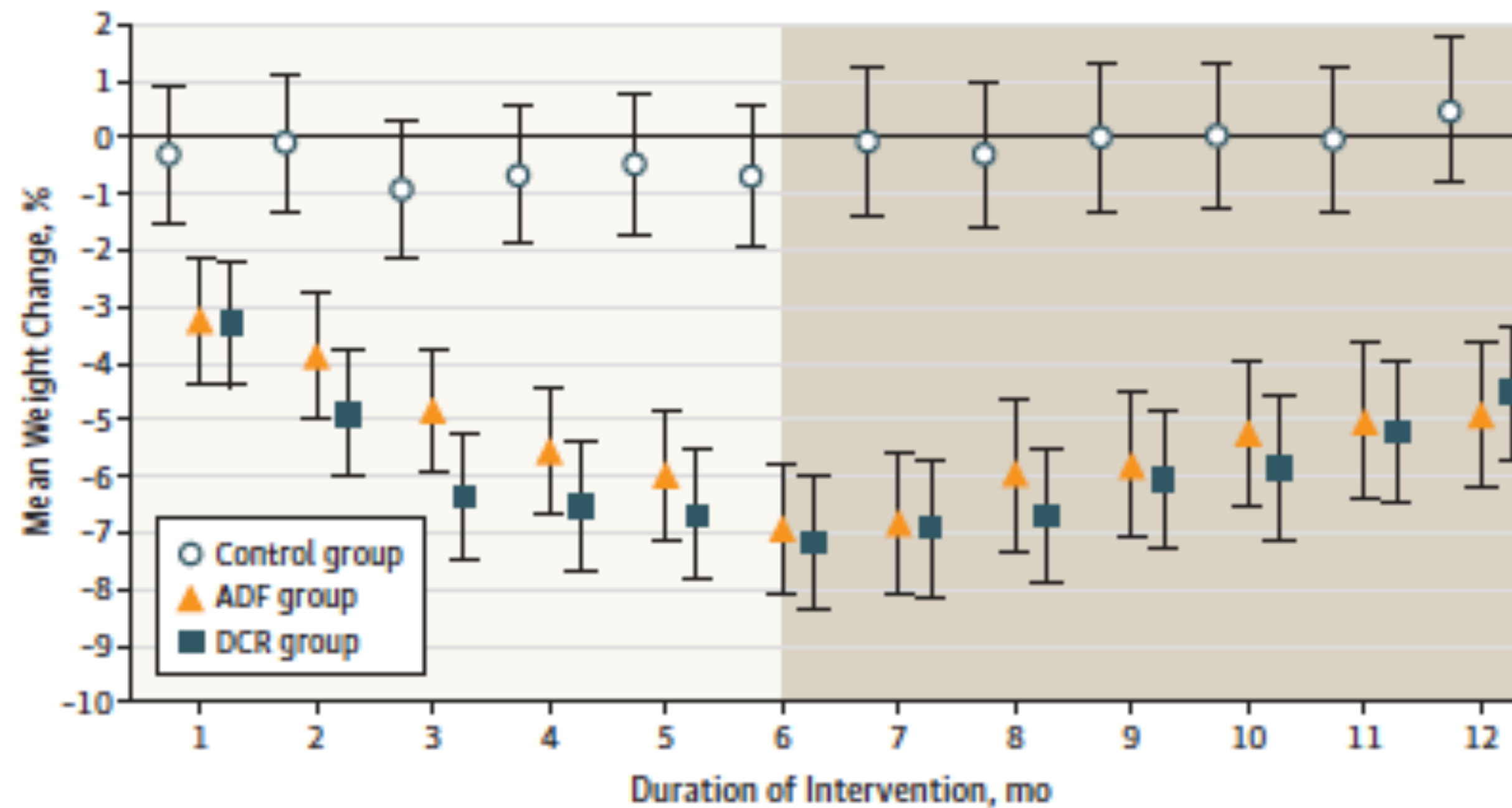
# What does this figure tell us?

Figure 2. Prescribed vs Actual Energy Intake in the Alternate-Day Fasting and Daily Calorie Restriction Groups



# What does this figure tell us?

Figure 3. Weight Loss by Diet Group Relative to Baseline



Data were included for 100 participants; mean (SD) values were estimated using an intention-to-treat analysis with a linear mixed model. Error bars indicate 95% CIs for weight change from baseline by diet group at each time point (1-12 months). ADF indicates alternate-day fasting; DCR, daily calorie restriction.



# What does this table tell us?

Table 2. Pairwise Effects Estimates of Diet on Mean Changes From Baseline in Body Weight and Risk Indicators for Cardiovascular Disease<sup>a</sup>

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	At 6 mo	At 12 mo	At 6 mo	At 12 mo	At 6 mo	At 12 mo
Body weight, % change	0.0 (-2.2 to 2.2)	-0.7 (-3.1 to 1.6)	-6.8 (-9.1 to -4.5)	-6.0 (-8.5 to -3.6)	-6.8 (-9.1 to -4.6)	-5.3 (-7.6 to -3.0)
Fat mass, kg	0.9 (-1.3 to 3.1)	0.0 (-2.4 to 2.4)	-4.2 (-6.6 to -1.8)	-2.0 (-4.4 to 0.5)	-5.1 (-7.5 to -2.7)	-2.0 (-4.4 to 0.4)
Lean mass, kg	0.6 (-1.0 to 2.2)	0.5 (-1.2 to 2.2)	-1.5 (-3.2 to 0.2)	-0.9 (-2.7 to 0.9)	-2.1 (-3.8 to 0.4)	-1.4 (-3.1 to 0.3)
Visceral fat mass, kg	0.2 (-0.1 to 0.5)	0.1 (-0.2 to 0.5)	-0.4 (-0.7 to -0.1)	-0.4 (-0.7 to -0.1)	-0.6 (-0.9 to -0.2)	-0.5 (-0.8 to -0.2)
Blood pressure, mm Hg						
Systolic	0.8 (-7.1 to 8.7)	-1.1 (-9.5 to 7.4)	-3.1 (-11.3 to 5.2)	-2.3 (-11.0 to 6.4)	-3.9 (-12.1 to 4.4)	-1.24 (-9.7 to 7.2)
Diastolic	-0.3 (-5.9 to 5.4)	-3.0 (-9.0 to 3.0)	-1.5 (-7.4 to 4.4)	-0.1 (-6.3 to 6.1)	-1.2 (-7.1 to 4.6)	2.9 (-3.1 to 8.9)
Heart rate, beats/min	-4.9 (-10.1 to 0.4)	-2.0 (-7.7 to 3.8)	-5.8 (-11.3 to -0.3)	-1.2 (-7.1 to 4.7)	-0.9 (-6.4 to 4.5)	0.8 (-4.8 to 6.4)
Cholesterol, mg/dL						
Total	3.4 (-7.2 to 13.9)	9.7 (-2.2 to 21.7)	-4.3 (-15.4 to 6.9)	4.2 (-8.2 to 16.5)	-7.6 (-18.8 to 3.6)	-5.6 (-17.6 to 6.4)
HDL	6.2 (0.1 to 12.4)	1.0 (-5.9 to 7.8)	8.4 (1.9 to 14.7)	2.9 (-4.2 to 10.0)	2.2 (-4.3 to 8.7)	1.9 (-5.1 to 8.9)
LDL	2.5 (-6.0 to 10.9)	11.5 (1.9 to 21.1)	-2.6 (-11.5 to 6.4)	1.2 (-8.7 to 11.2)	-5.0 (-14.0 to 3.9)	-10.3 (-19.9 to -0.6)
Triglycerides, mg/dL	-10.5 (-26.7 to 5.8)	-9.9 (-28.3 to 8.6)	-19.1 (-36.3 to -1.8)	-24.4 (-43.5 to -5.3)	-8.6 (-25.9 to 8.7)	-14.5 (-33.1 to 4.0)
Glucose, mg/dL	-1.4 (-8.0 to 5.2)	5.7 (-1.6 to 13.0)	-6.3 (-13.3 to 0.7)	-3.9 (-11.5 to 3.6)	-4.9 (-12.0 to 2.1)	-9.6 (-17.1 to -2.2)
Insulin, $\mu$ U/mL	-0.4 (-5.5 to 4.7)	-1.3 (-6.9 to 4.3)	-7.5 (-12.9 to -2.0)	-5.9 (-11.7 to -0.1)	-7.0 (-12.5 to -1.6)	-4.6 (-10.4 to 1.2)
HOMA-IR <sup>a</sup>	0.07 (-1.56 to 1.70)	0.02 (-1.78 to 1.81)	-2.49 (-4.22 to -0.76)	-1.86 (-3.73 to 0.01)	-2.56 (-4.30 to -0.82)	-1.88 (-3.72 to -0.03)
HS CRP, mg/dL	-0.04 (-0.19 to 0.11)	0.00 (-0.16 to 0.17)	-0.07 (-0.23 to 0.08)	-0.07 (-0.24 to 0.11)	-0.04 (-0.19 to 0.12)	-0.07 (-0.24 to 0.10)
Homocysteine, mg/L	0.03 (-0.10 to 0.17)	0.03 (-0.12 to 0.18)	0.10 (-0.04 to 0.24)	0.02 (-0.13 to 0.18)	0.06 (-0.08 to 0.20)	-0.01 (-0.16 to 0.14)



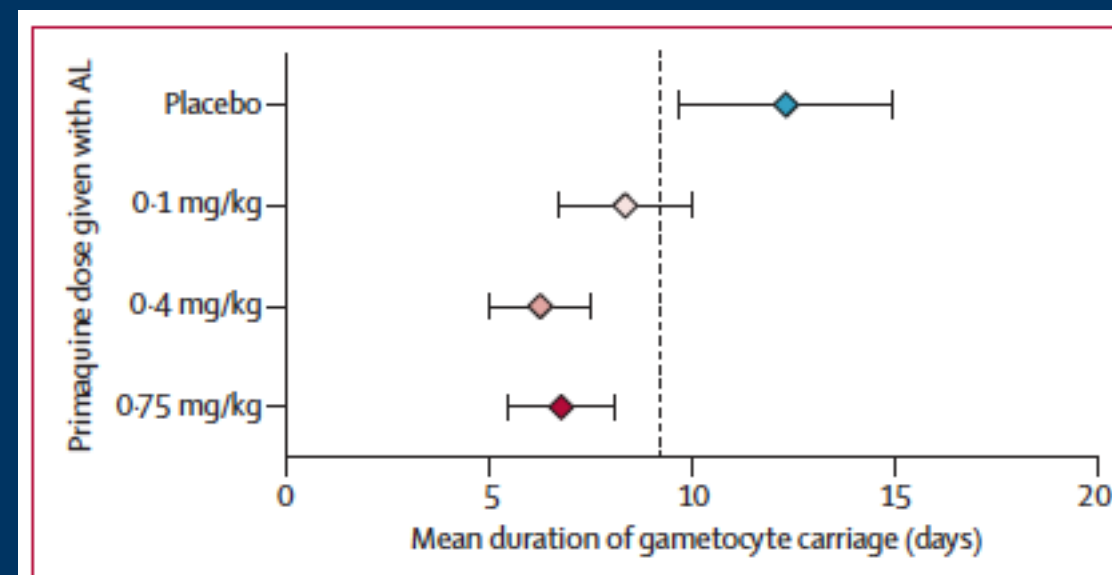
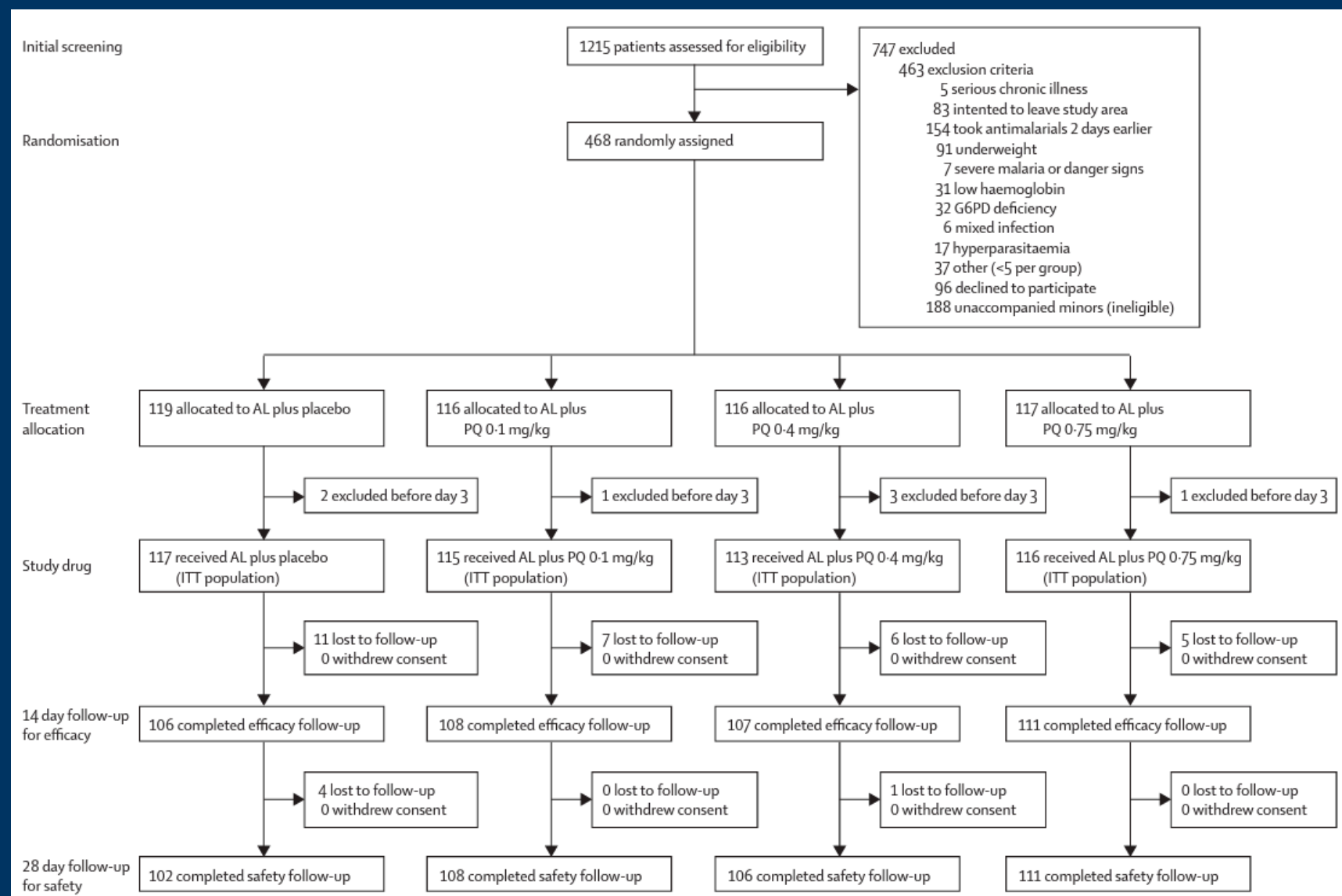


# Single dose primaquine for clearance of *Plasmodium falciparum* gametocytes in children with uncomplicated malaria in Uganda: a randomised, controlled, double-blind, dose-ranging trial

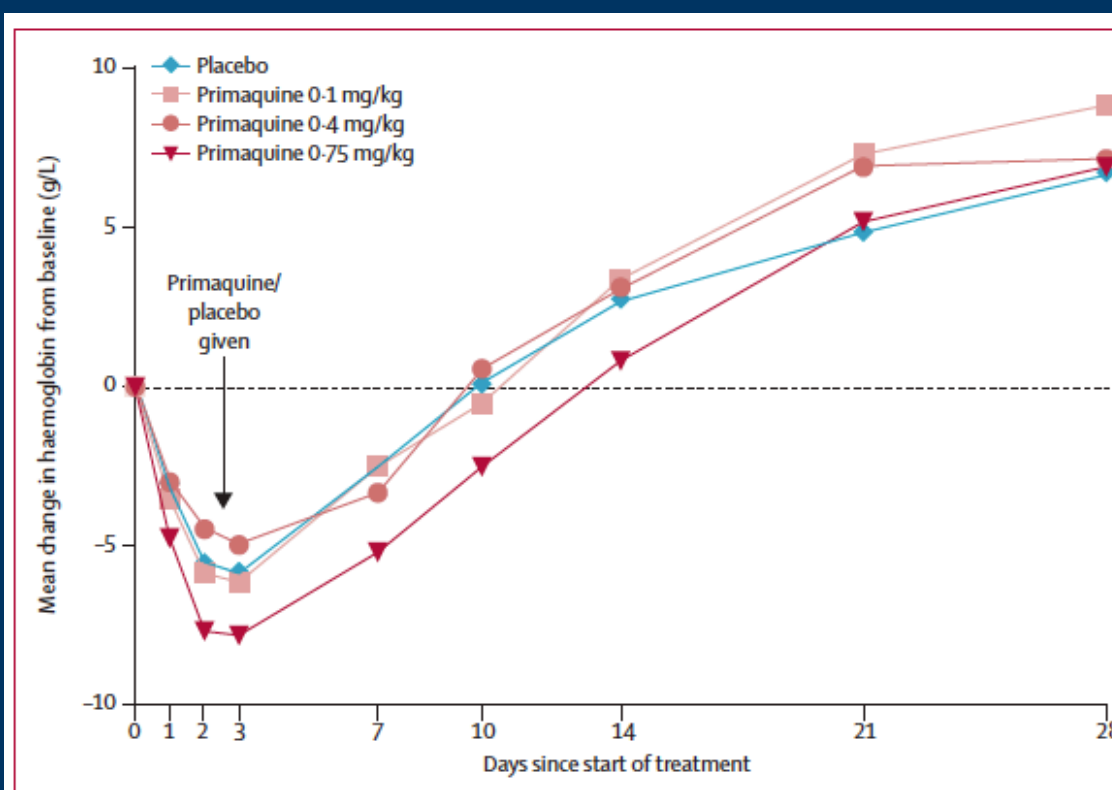


Alice C Eziefula, Teun Bousema, Shunmay Yeung, Moses Kamya, Asiphaw Owaraganise, Grace Gabagaya, John Bradley, Lynn Grignard, Kjerstin H W Lanke, Humphrey Wanzira, Arthur Mpimbaza, Samuel Nsohya, Nicholas J White, Emily L Webb, Sarah G Staedke, Chris Drakeley

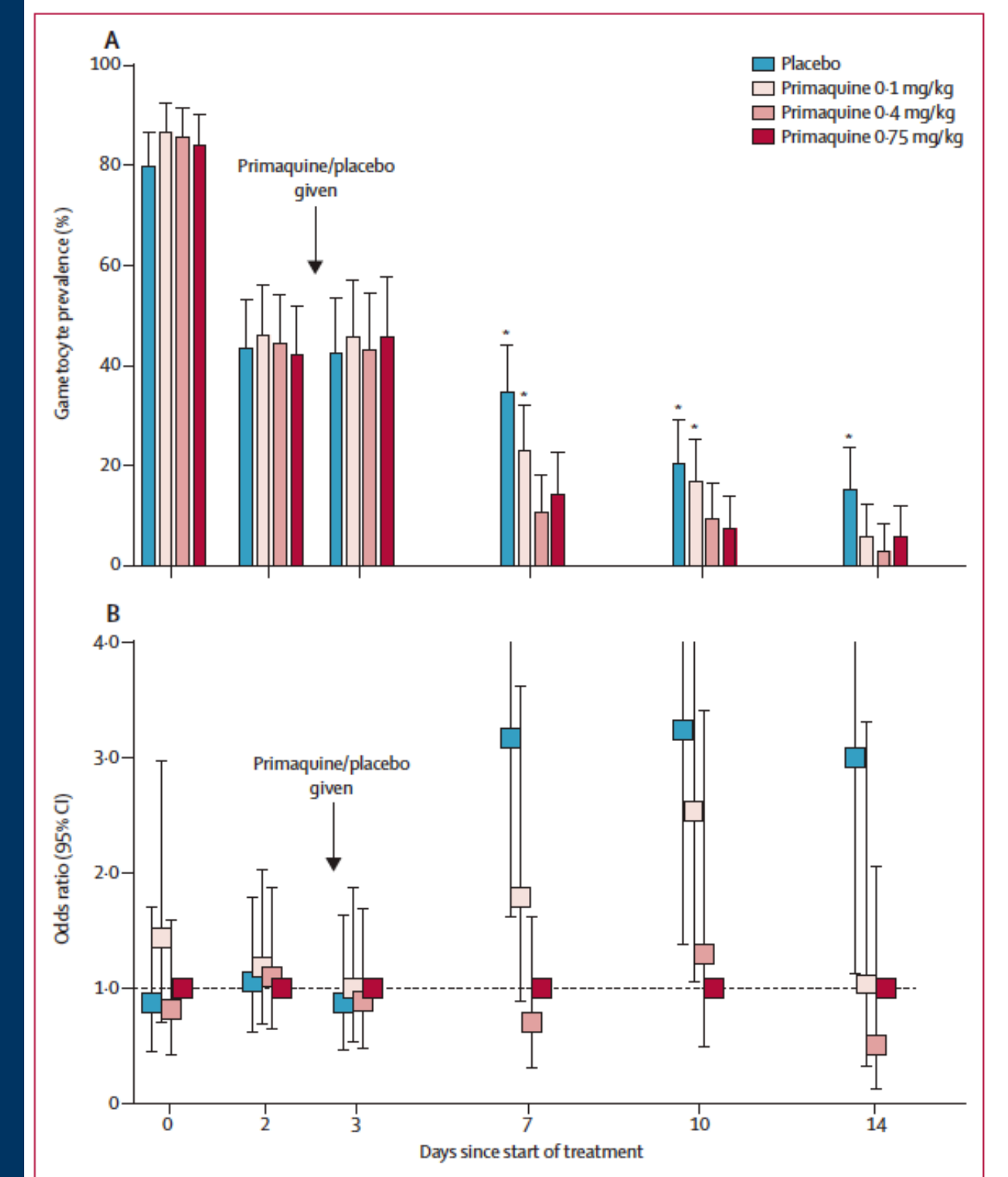
## 4 Figures



**Figure 2: Mean duration of gametocyte carriage by treatment regimen**  
The duration of gametocyte carriage was estimated by fitting of a straightforward deterministic compartmental mathematical model to repeated Pfs25 quantitative real-time nucleic acid sequence-based analysis gametocyte prevalence estimates. Symbols indicate the mean duration of gametocyte carriage, and error bars represent the upper and lower limit of the 95% CI. The dashed line indicates the set threshold for non-inferiority compared with the 0.75 mg/kg reference group (non-inferiority margin of 2.5 days). AL=artemether-lumefantrine.



**Figure 4: Mean change in haemoglobin measurements by treatment regimen during 28 day follow-up**  
Haemoglobin concentrations (g/L) during follow-up are expressed relative to that at enrolment for each treatment group.



**Figure 3: Gametocyte prevalence and prevalence ratio for each treatment regimen during 14 day follow-up**  
(A) Gametocyte prevalence during follow-up, as measured by Pfs25 quantitative real-time nucleic acid sequence-based analysis. Error bars indicate the upper limit of the 95% CI. (B) Odds ratio of gametocyte prevalence on each of the days of follow-up compared with the reference 0.75 mg/kg group after adjustment for baseline gametocyte density. Error bars indicate the upper and lower limits of the 95% CI. \*Indicates a statistically significant difference compared with the reference 0.75 mg/kg group.





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## Primary endpoint (efficacy):

Non-inferiority of the mean duration of gametocyte carriage in the test doses compared with the reference group (PQ 0.75 mg/kg)

## Secondary endpoints (efficacy):

Point prevalence of gametocytes at days 7, 10, 14

Gametocyte circulation time

AUC of gametocyte density after PQ administration



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## Primary endpoint (safety):

Superiority of arithmetic mean maximum decrease in Hb from enrolment to day 28 in PQ treated groups comparing to placebo

## Secondary endpoints (safety):

Superior assessment of day of hemoglobin nadir

The maximum percentage of Hb decrease

% of participants with Hb <5 g/dl

Requirement of blood transfusion

Evidence of black urine

Frequency of adverse events





# Single dose primaquine for clearance of *Plasmodium falciparum* gametocytes in children with uncomplicated malaria in Uganda: a randomised, controlled, double-blind, dose-ranging trial



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## 3 Tables

	Placebo (n=117)	Primaquine 0.1 mg/kg (n=115)	Primaquine 0.4 mg/kg (n=113)	Primaquine 0.75 mg/kg (n=116)
Boys	48.7% (57/117)	49.6% (57/115)	49.6% (56/113)	49.1% (57/116)
Age (years)	5.0 (3.0–7.5)	5.0 (3.3–7.0)	5.3 (3.2–7.0)	4.1 (3.0–7.0)
Bodyweight (kg)	16.0 (13.0–20.5)	16.0 (13.0–22.0)	17.0 (14.0–23.0)	15.0 (13.0–19.0)
Body temperature (°C)	38.0 (1.0)	38.3 (1.1)	38.0 (1.2)	38.2 (1.1)
Haemoglobin concentration (g/L)	113 (15)	109 (15)	112 (15)	112 (14)
Geometric mean sexual parasite density, parasites/mL (IQR)	17 661 (5260–65 130)	18 420 (4440–92 780)	16 457 (3260–81 240)	32 497 (10 880–151 180)
Gametocyte prevalence by microscopy	23.1% (27/117)	24.3% (28/115)	20.4% (23/113)	22.4% (26/116)
Gametocyte prevalence by QT-NASBA	79.8% (91/114)	86.7% (98/113)	78.7% (85/108)	82.0% (91/111)
Geometric mean gametocyte density (gametocytes/μL) by QT-NASBA (IQR)	15.2 (8.4–27.8)	14.5 (8.9–23.5)	19.4 (11.3–33.1)	24.6 (14.9–40.5)

Data are % (n/N), median (IQR), or mean (SD), unless otherwise indicated. QT-NASBA=quantitative real-time nucleic acid sequence-based analysis.

**Table 1: Baseline characteristics**

	Placebo	Primaquine 0.1 mg/kg	p value*	Primaquine 0.4 mg/kg	p value*	Primaquine 0.75 mg/kg	p value*
Number evaluated	117	115	..	113	..	116	..
Excluded from ITT analysis							
Withdrawal unrelated to study drug or malaria	0	0	..	2/113 (1.8%)	0.245	0	..
Lost to follow-up	15/117 (12.8%)	7/115 (6.1%)	0.080	7/113 (6.2%)	0.088	5/116 (4.3%)	0.033
ACPR on day 28	98/102 (96.1%)	101/108 (93.5%)	0.41	106/106 (100%)	0.12	106/111 (95.5%)	0.83
Treatment failures							
Early (day 3)	0	0	..	0	..	0	..
Late (day 28)	4/102 (3.9%)	7/108 (6.5%)	0.41	0	0.12	5/111 (4.5%)	0.83

Data are n/N (%), unless otherwise indicated. ITT=intention to treat. ACPR=adequate clinical and parasitological response. Definitions of ACPR, early treatment failure, and late treatment failure are according to WHO Methods for Surveillance of Antimalarial Drug Efficacy 2009.<sup>26</sup> \*p values are for comparison with placebo, with  $\chi^2$  or Fisher's exact tests. Outcomes are unadjusted by PCR.

**Table 2: Treatment outcomes for the different regimens on day 28 after start of treatment**

	Placebo	p value*	Primaquine 0.1 mg/kg	p value*	Primaquine 0.4 mg/kg	p value*	Primaquine 0.75 mg/kg
Duration of gametocyte carriage (days)†	12.4 (9.9–15.0)	<0.0001	8.0 (6.6–9.4)	0.14	6.3 (5.1–7.5)	0.74	6.6 (5.3–7.8)
Circulation time per gametocyte (days)	1.97 (1.64–2.31)	<0.0001	1.47 (1.22–1.73)	0.0012	0.95 (0.77–1.13)	0.80	0.98 (0.78–1.18)
Gametocyte prevalence on day 7	40/115 (34.8%)	0.001	25/108 (23.1%)	0.044	11/104 (10.6%)	0.47	15/104 (14.4%)
Gametocyte prevalence on day 10	23/112 (20.5%)	0.008	18/107 (16.8%)	0.020	10/107 (9.3%)	0.46	8/108 (7.4%)
Gametocyte prevalence on day 14	16/105 (15.2%)	0.017	6/103 (5.8%)	0.72	3/103 (2.9%)	0.51	6/106 (5.7%)

Data are mean (95% CI) or n/N (%). Except for the duration of gametocyte carriage, all estimates were adjusted for gametocyte density at enrolment. \*p values are for comparison with reference 0.75 mg/kg treatment group. †Calculated for all children who had gametocytes on the day of primaquine or placebo administration.

**Table 3: Gametocyte carriage during follow-up for the different treatment regimens**

# What does this table tell us?

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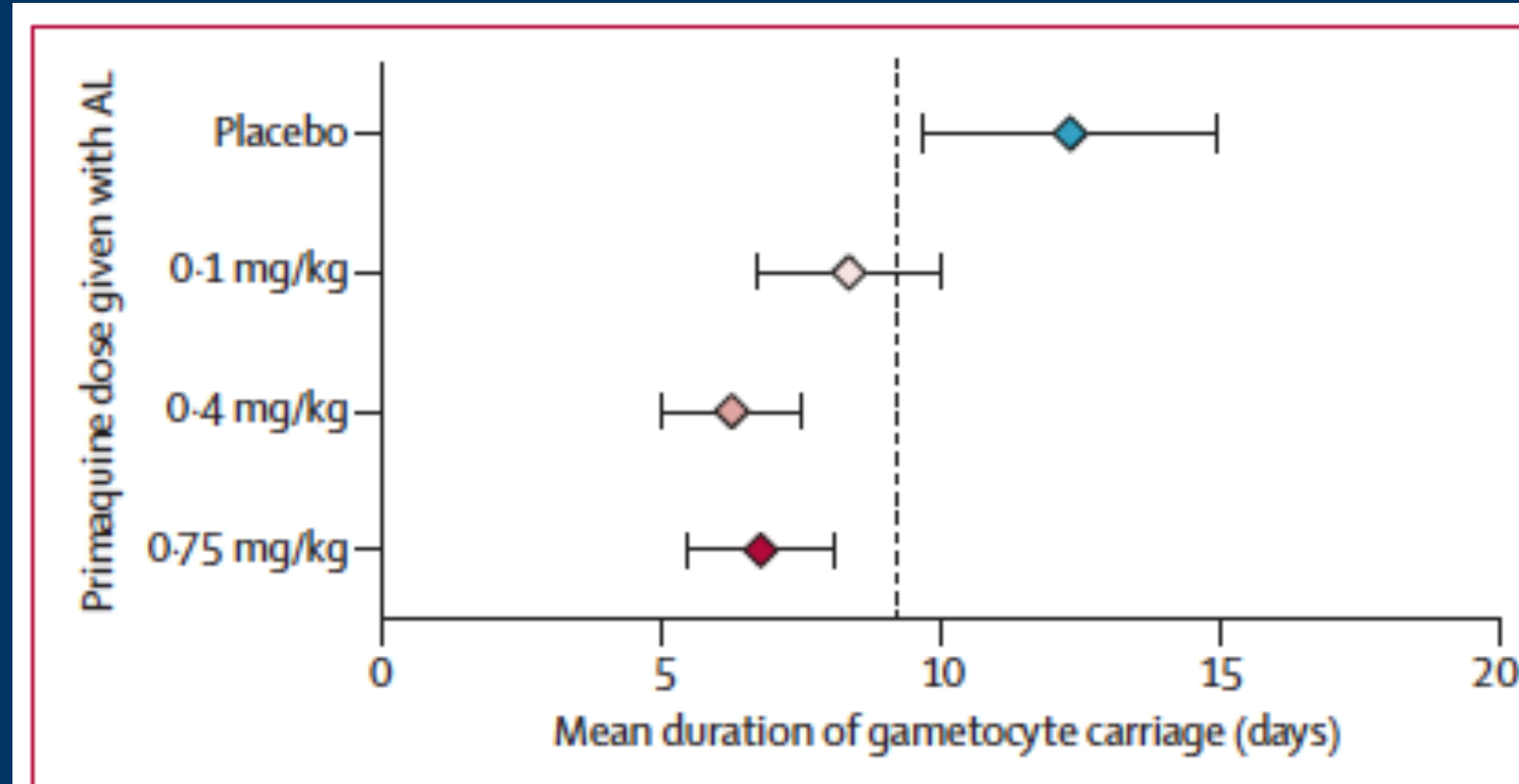
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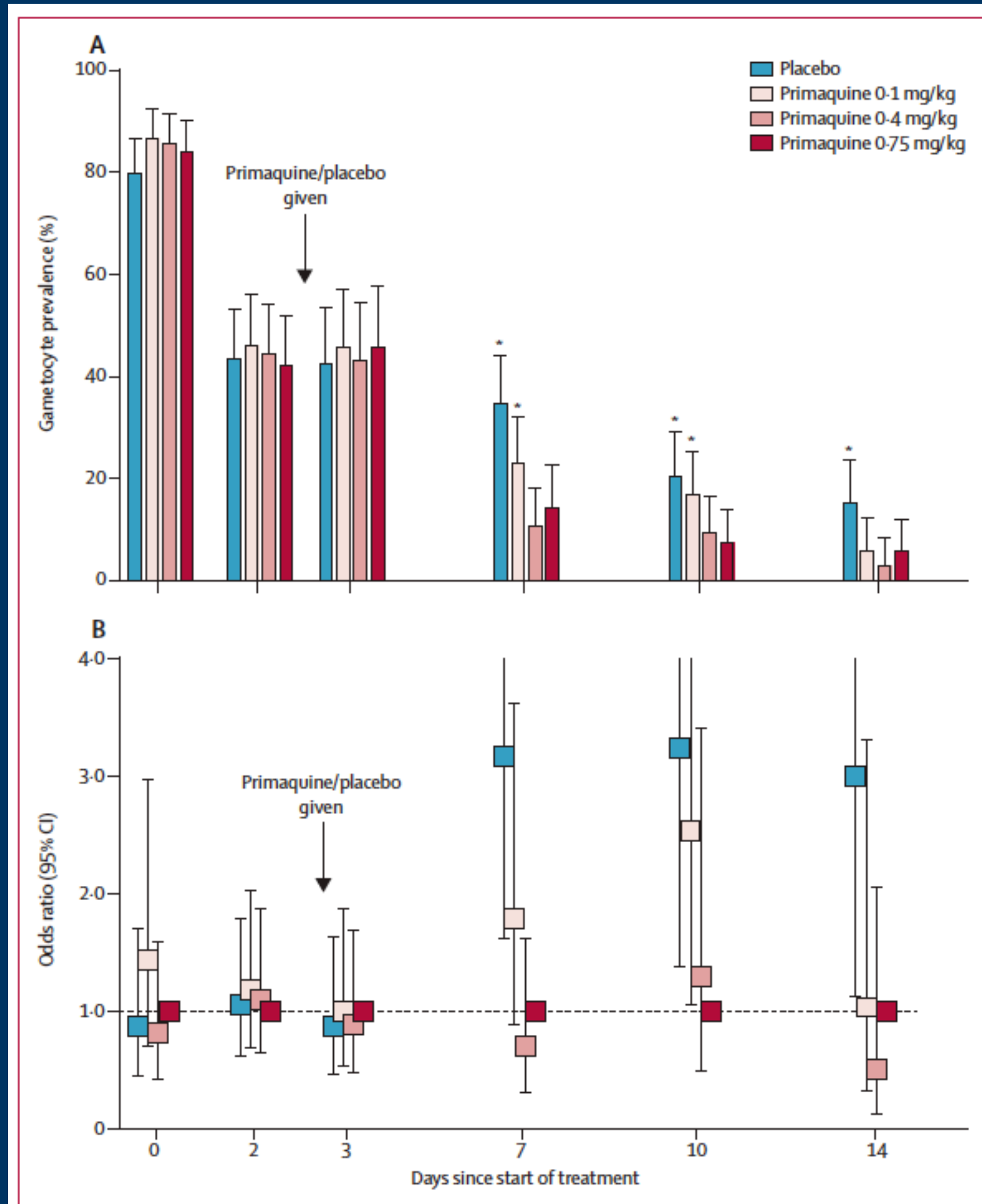


**Figure 2: Mean duration of gametocyte carriage by treatment regimen**

The duration of gametocyte carriage was estimated by fitting of a straightforward deterministic compartmental mathematical model to repeated *Pfs25* quantitative real-time nucleic acid sequence-based analysis gametocyte prevalence estimates. Symbols indicate the mean duration of gametocyte carriage, and error bars represent the upper and lower limit of the 95% CI. The dashed line indicates the set threshold for non-inferiority compared with the 0.75 mg/kg reference group (non-inferiority margin of 2.5 days). AL=artemether-lumefantrine.

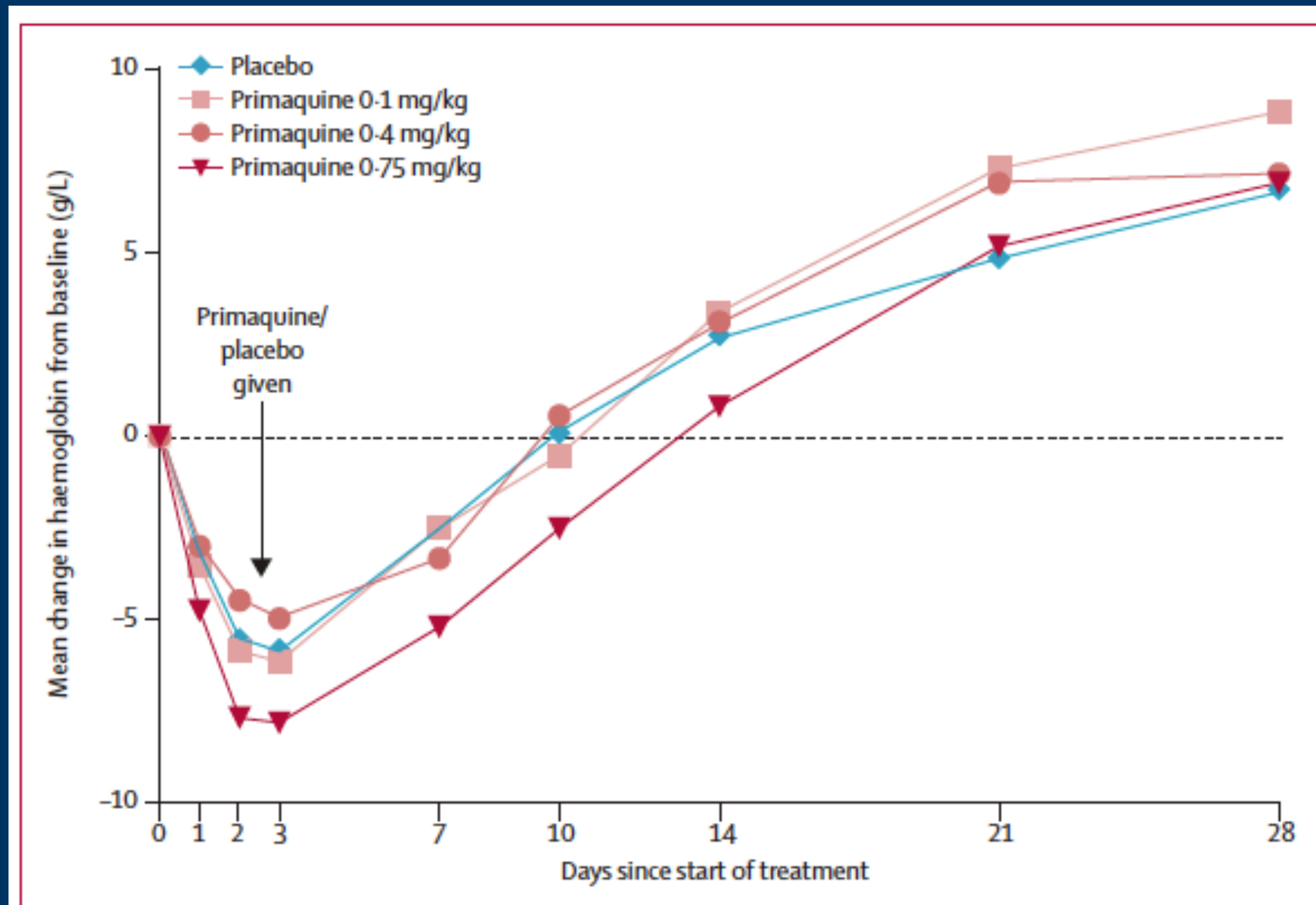


# What does this figure tell us?



**Figure 3: Gametocyte prevalence and prevalence ratio for each treatment regimen during 14 day follow-up**  
(A) Gametocyte prevalence during follow-up, as measured by *Pfs25* quantitative real-time nucleic acid sequence-based analysis. Error bars indicate the upper limit of the 95% CI. (B) Odds ratio of gametocyte prevalence on each of the days of follow-up compared with the reference 0.75 mg/kg group after adjustment for baseline gametocyte density. Error bars indicate the upper and lower limits of the 95% CI. \*Indicates a statistically significant difference compared with the reference 0.75 mg/kg group.

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