Clinical Trials III

Case Studies

Nuno Sepúlveda

Recap

Power

Study design

Definition population

Primaquine example

Type of analysis

Rituximab example

Sample size

Primary endpoint

Outcome

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	Reported on page No
Title and abstract			
	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])	
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	
	2b	Specific objectives or hypotheses	
Methods			
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	
Results			

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[28])
Discussion		
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
Other information		
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

*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 www.consort-statement.org.

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

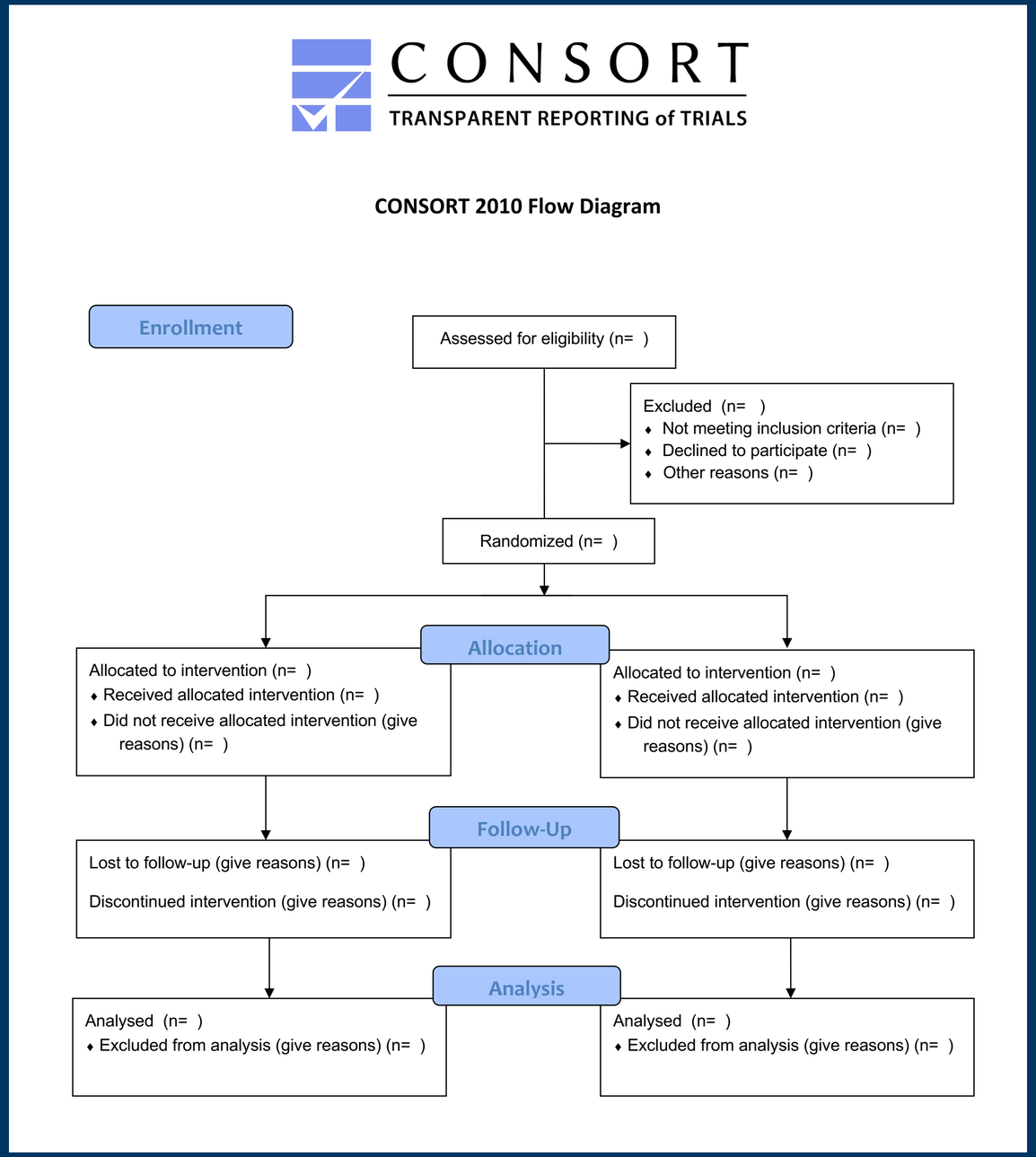
CONSORT 2010

Consolidated Standard for Reporting Trials

Checklist of 25 items

“Figure 1” - Consort Flowchart (items 13a and 13b)
“Table 1” - Items 15

CONSORT flowchart



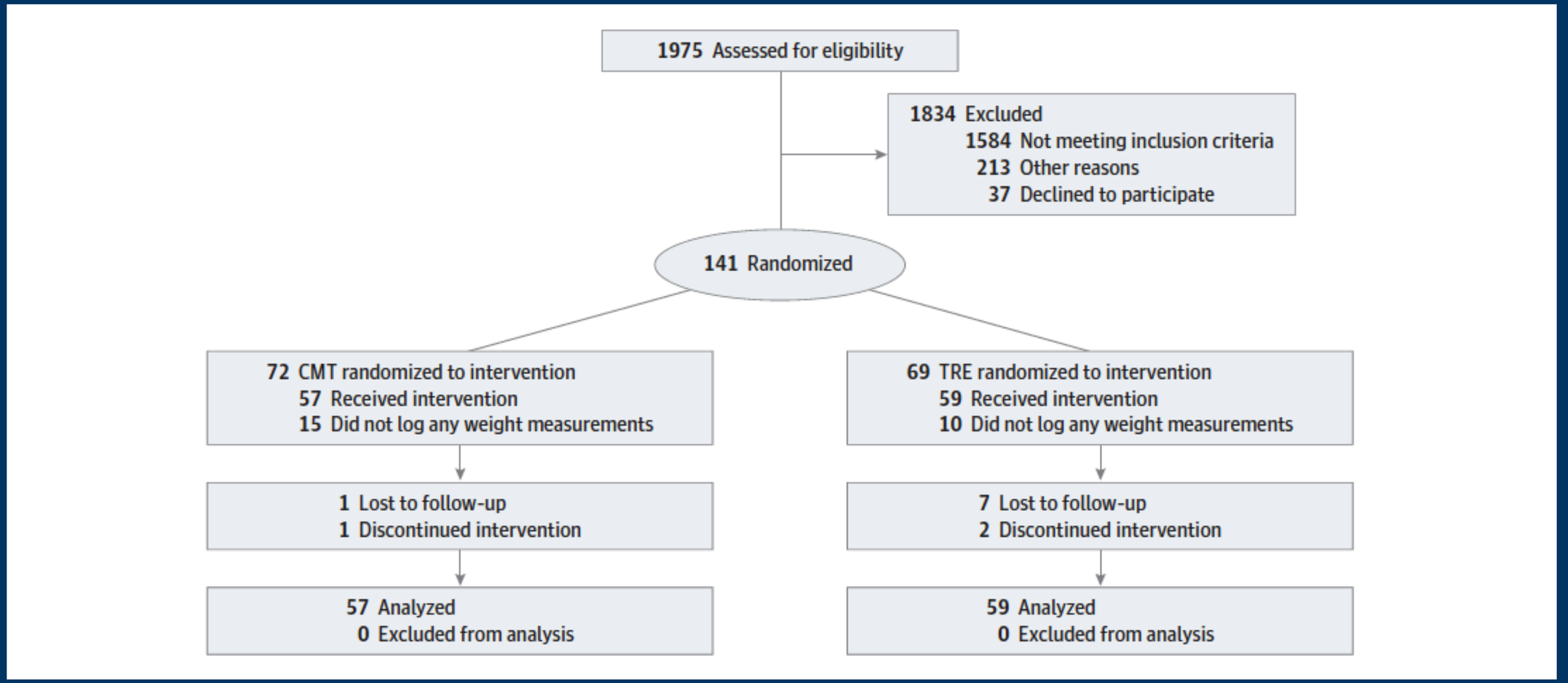
https://www.equator-network.org/reporting-guidelines/consort/

JAMA Internal Medicine | Original Investigation

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 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 Nsobya, Nicholas J White, Emily L Webb, Sarah G Staedke, Chris Drakeley

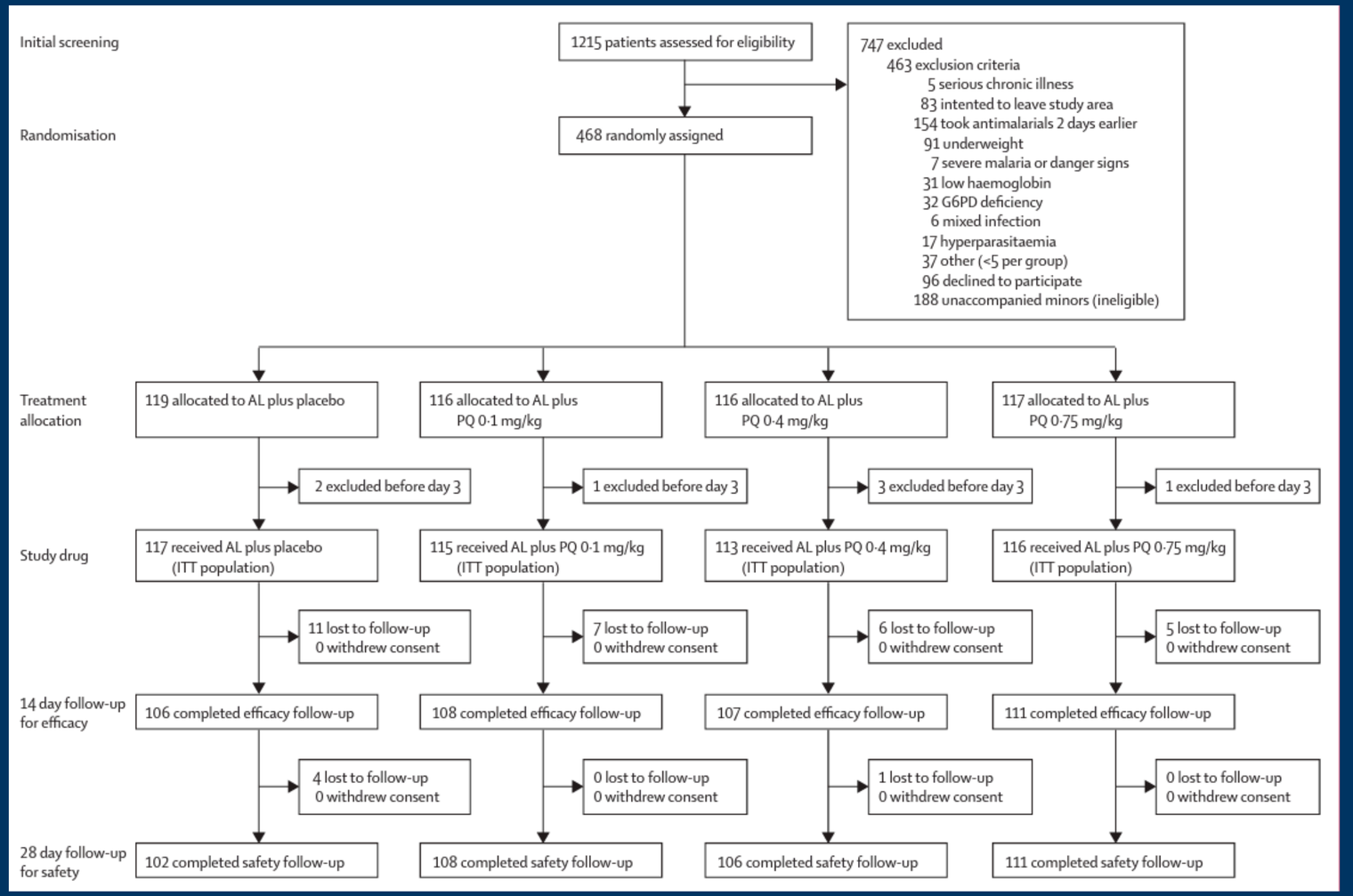


Table 1

What elements should be reported?

JAMA Internal Medicine | Original Investigation

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

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 Nsobya, Nicholas J White, Emily L Webb, Sarah G Staedke, Chris Drakeley

	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

ggconsort

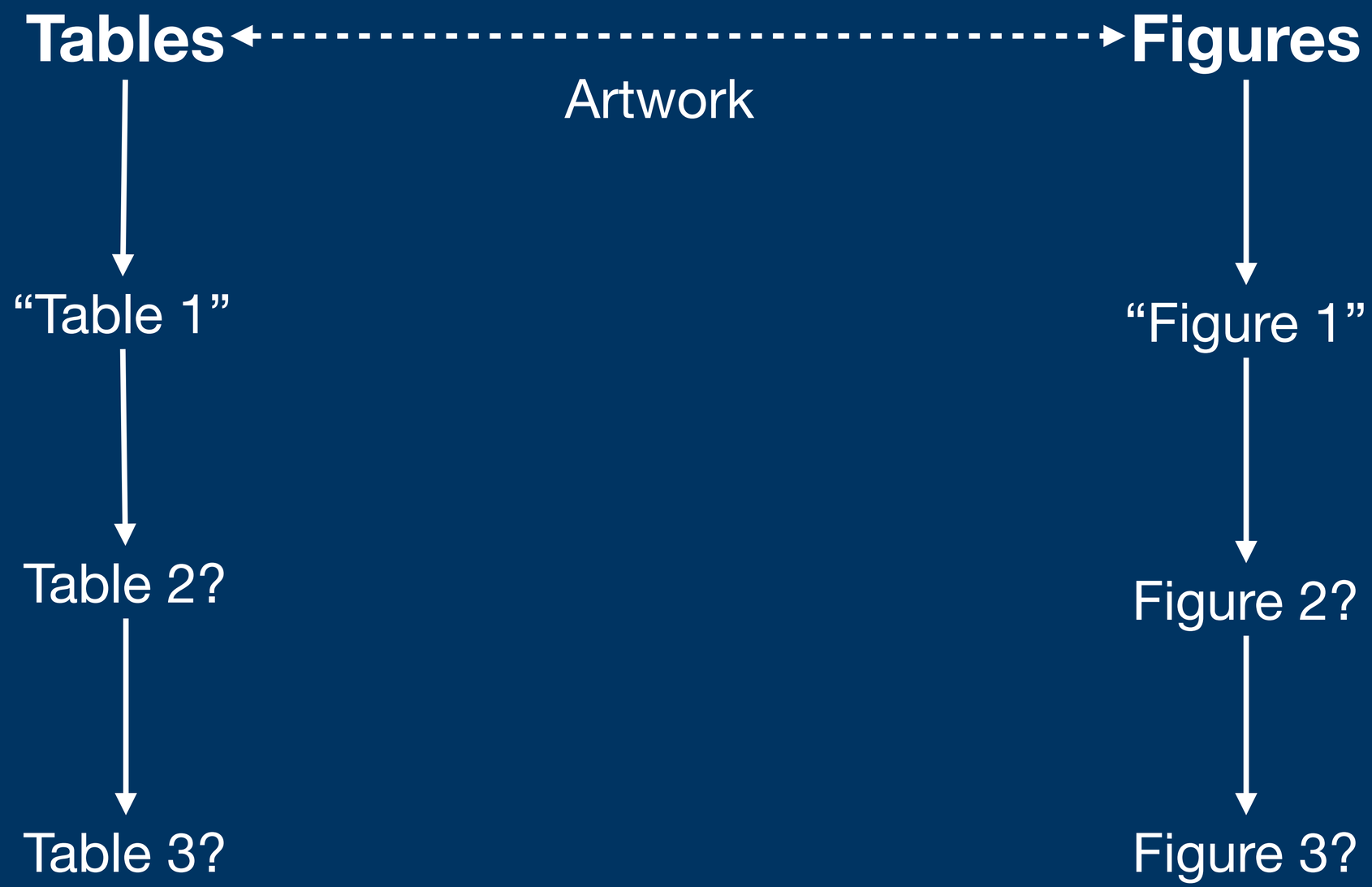
"Table 1" **(item 15 of CONSORT checklist)**

visR

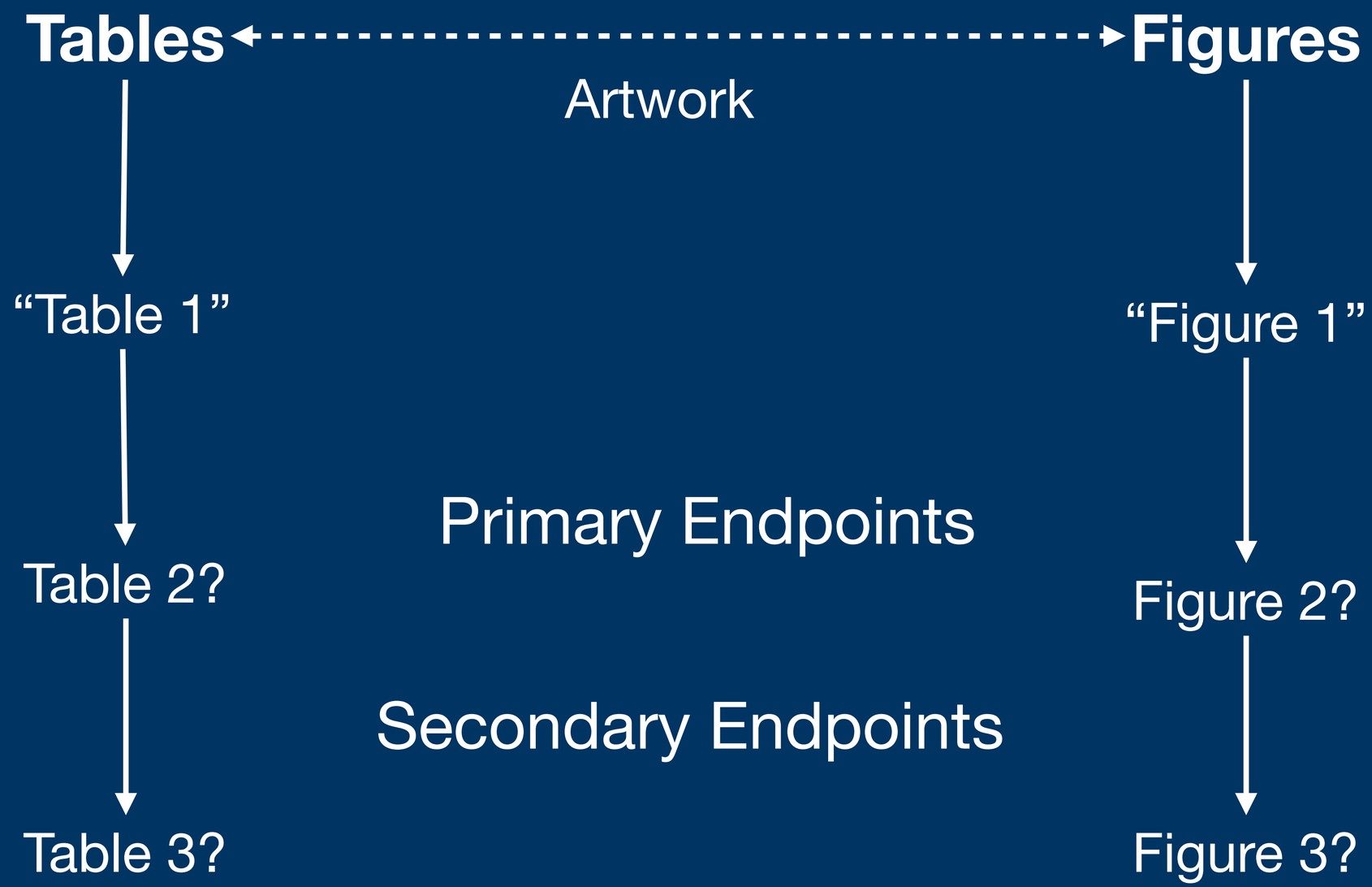
Table1

Baseline demographic and clinical characteristics of study participants

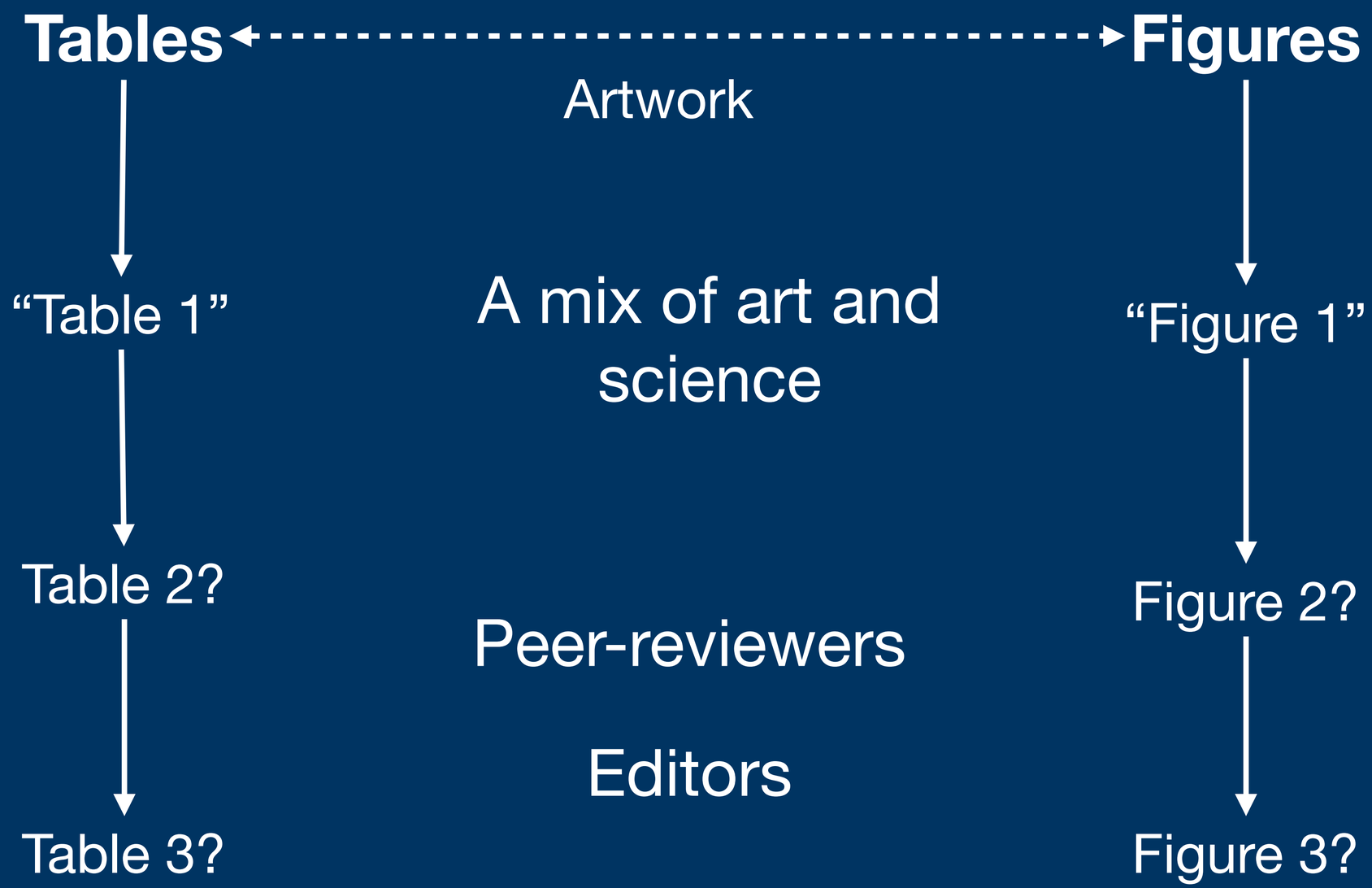
Presenting the results



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?

Which Tables?

When to use Figures?

Which Figures?

Storytelling/Understanding dara

Little quiz - what is the best plot?

Endpoint

Response/Non-Response

Disease score

Quantitative biomarker

Time-to-event

JAMA Internal Medicine | Original Investigation

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

Primary endpoint:

change in weight loss

Secondary endpoints:

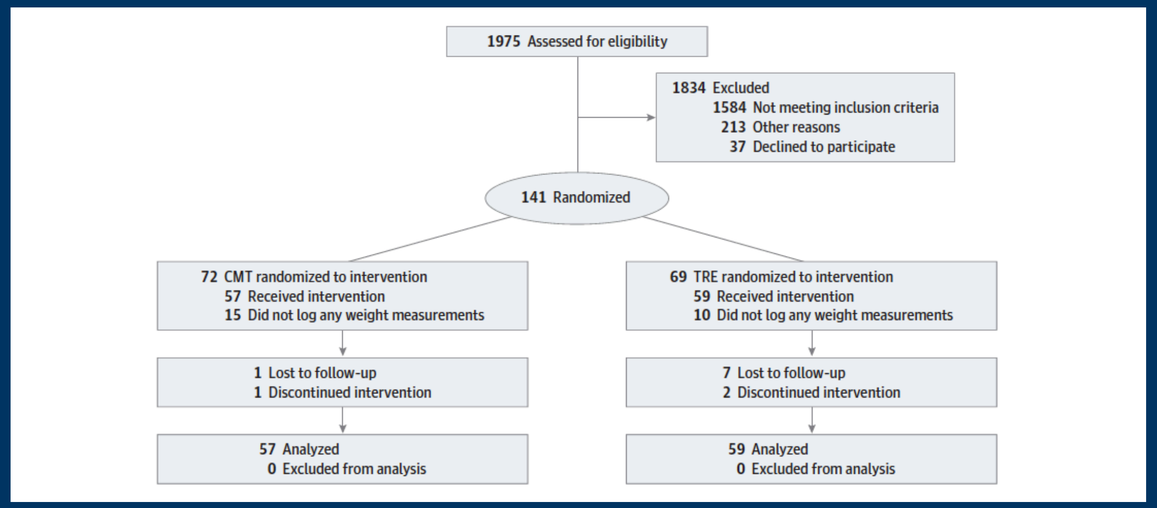
blood pressure, heart rate, total cholesterol, LDLc, HDLc, triglycerides, fasting glucose, fasting Insulin, C-Reactive Protein, Homocysteine

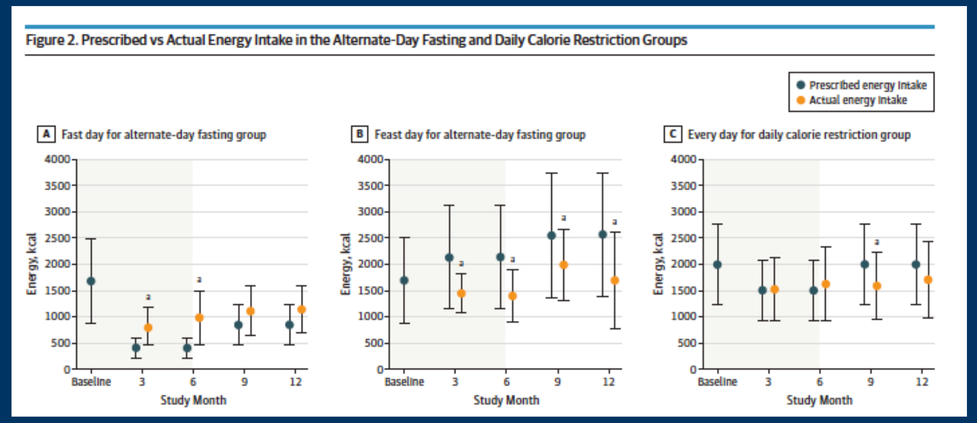
JAMA Internal Medicine | Original Investigation

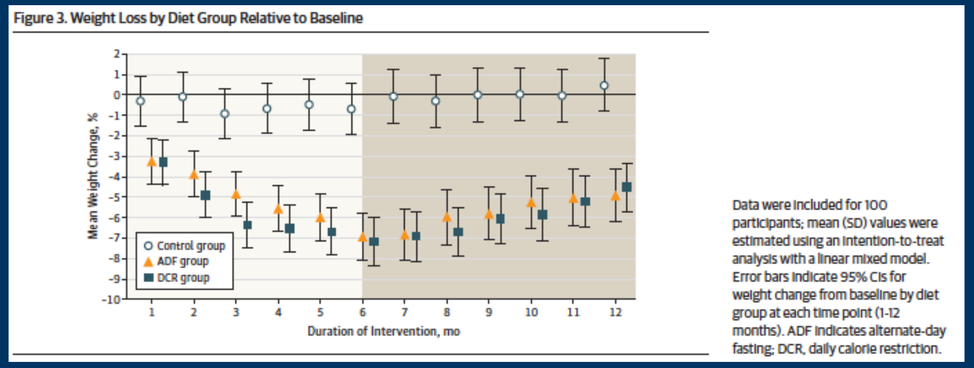
Effects of Time-Restricted Eating on Weight Loss and Other Metabolic Parameters in Women and Men With Overweight and Obesity
The TREAT Randomized Clinical Trial

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

3 Figures







JAMA Internal Medicine | Original Investigation

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

2 Tables

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)

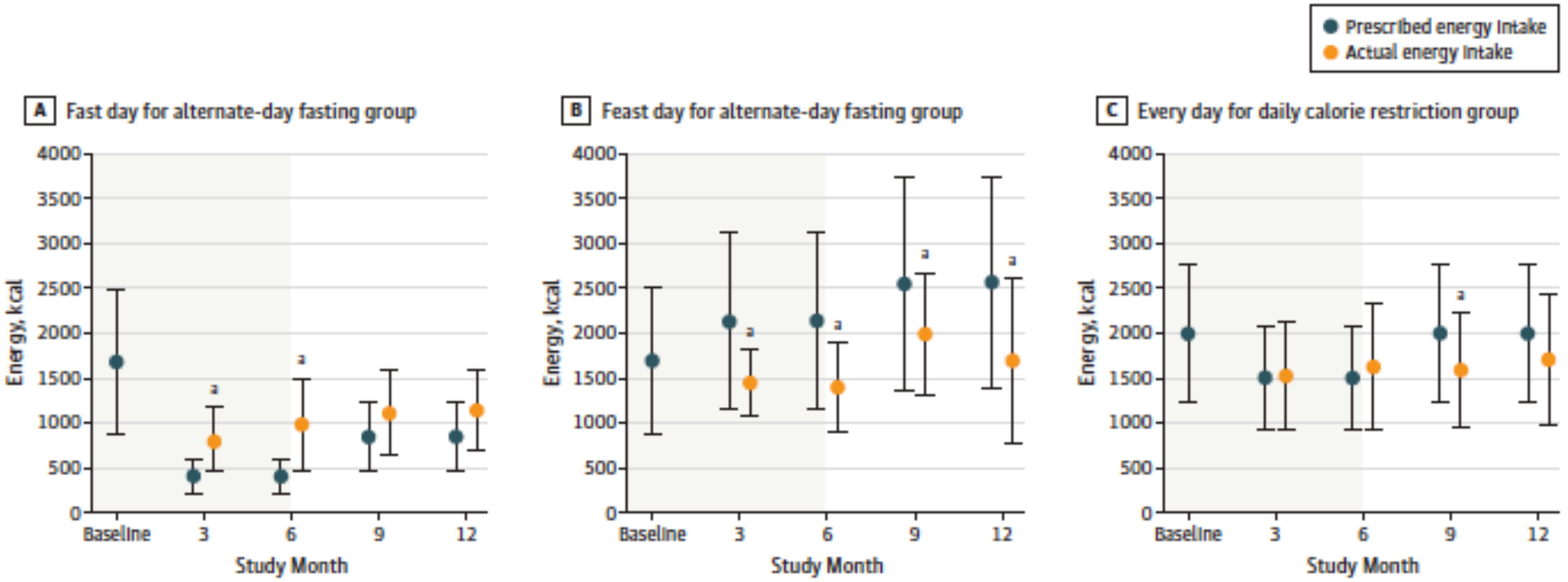
Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CMT, consistent meal timing group; TRE, time-restricted eating group.

Table 2. Pairwise Effects Estimates of Diet on Mean Changes From Baseline in Body Weight and Risk Indicators for Cardiovascular Disease[a]

Outcome Variable	Change in ADF − Change in DCR (95% CI) At 6 mo	Change in ADF − Change in DCR (95% CI) At 12 mo	Change in ADF − Change in Control (95% CI) At 6 mo	Change in ADF − Change in Control (95% CI) At 12 mo	Change in DCR − Change in Control (95% CI) At 6 mo	Change in DCR − Change in Control (95% CI) 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[a]	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)

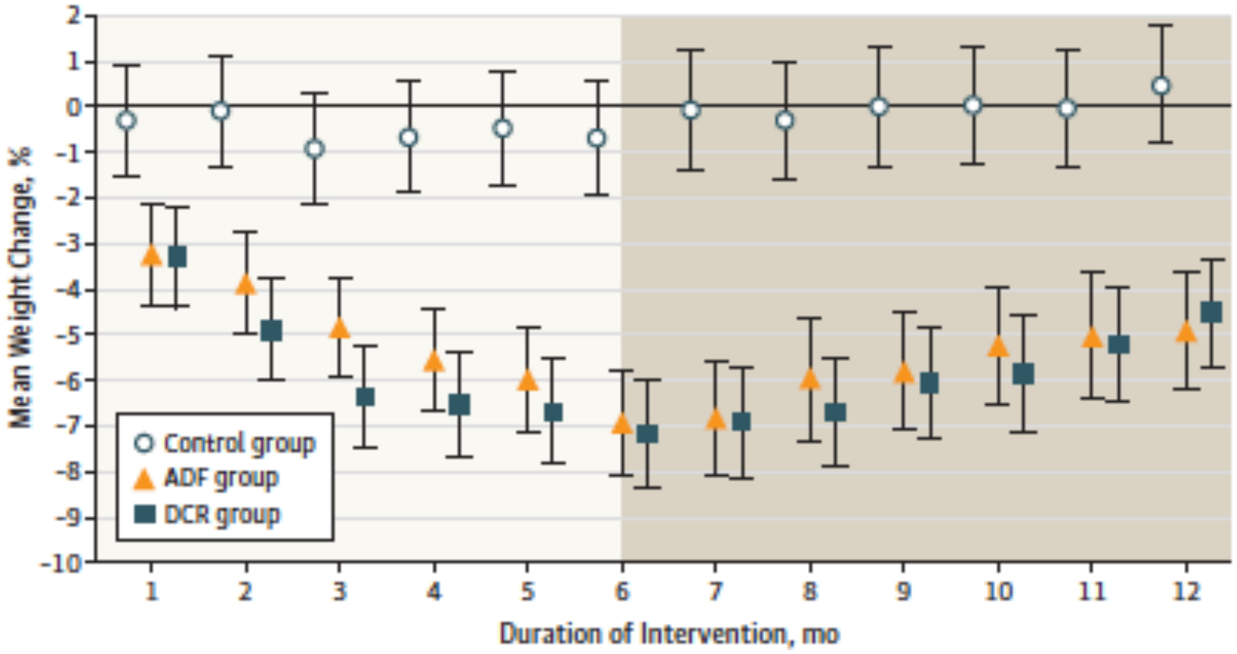
What does this figure tell us?

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?

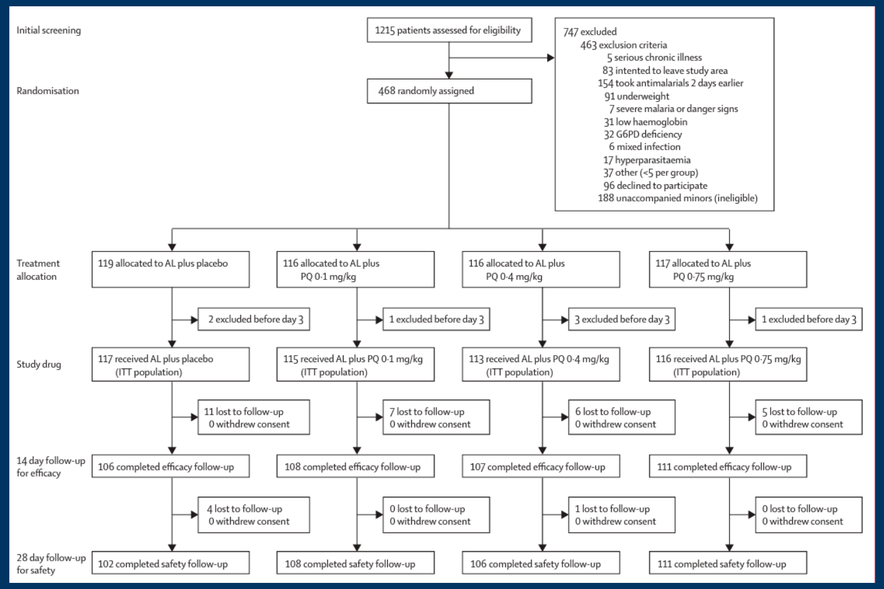
Table 2. Pairwise Effects Estimates of Diet on Mean Changes From Baseline in Body Weight and Risk Indicators for Cardiovascular Disease[a]

	Change in ADF − Change in DCR (95% CI)		Change in ADF − Change in Control (95% CI)		Change in DCR − Change in Control (95% CI)	
Outcome Variable	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[a]	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, Asiphas Owaraganise, Grace Gabagaya, John Bradley, Lynn Grignard, Kjerstin H W Lanke, Humphrey Wanzira, Arthur Mpimbaza, Samuel Nsobya, Nicholas J White, Emily L Webb, Sarah G Staedke, Chris Drakeley

4 Figures



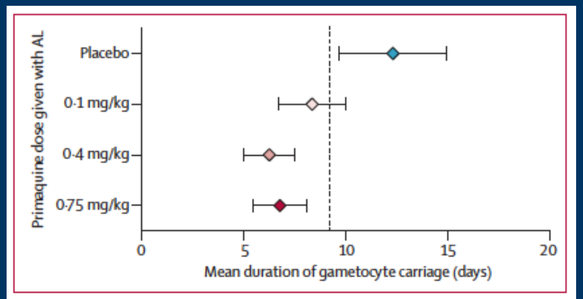


Figure 2: **Mean duration of gametocyte carriage by treatment regimen**
The duration of gametocyte carriage was estimated by fitting of a straightforward deterministic compartmental mathematical model to repeated *Pfs25* quantitative real-time nucleic acid sequence-based analysis gametocyte prevalence 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.

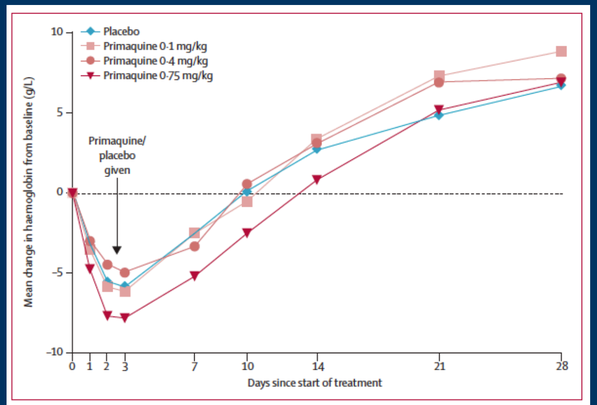


Figure 4: **Mean change in haemoglobin measurements by treatment regimen during 28 day follow-up**
Haemoglobin concentrations (g/L) during follow-up are expressed relative to that at enrolment for each treatment group.

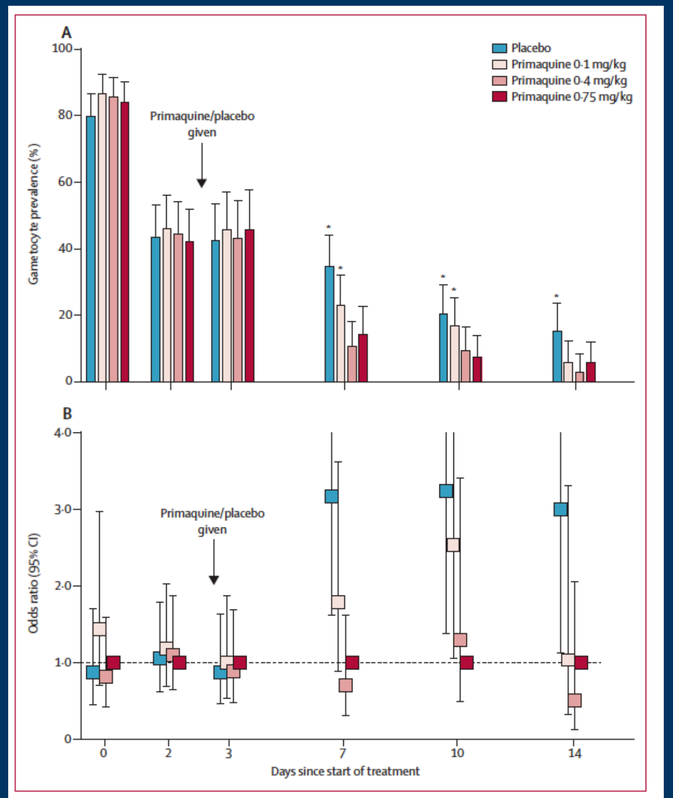


Figure 3: **Gametocyte prevalence and prevalence ratio for each treatment regimen during 14 day follow-up**
(A) Gametocyte prevalence during follow-up, as measured by *Pfs25* quantitative real-time nucleic acid sequence-based analysis. Error bars indicate the upper limit of the 95% CI. (B) Odds ratio 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.

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 Nsobya, Nicholas J White, Emily L Webb, Sarah G Staedke, Chris Drakeley

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

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 Nsobya, Nicholas J White, Emily L Webb, Sarah G Staedke, Chris Drakeley

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 hemoglobulin 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

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 Nsobya, Nicholas J White, Emily L Webb, Sarah G Staedke, Chris Drakeley

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.[26] *p values are for comparison with placebo, with χ^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?

	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.[26] *p values are for comparison with placebo, with χ^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**

What does this table tell us?

	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?

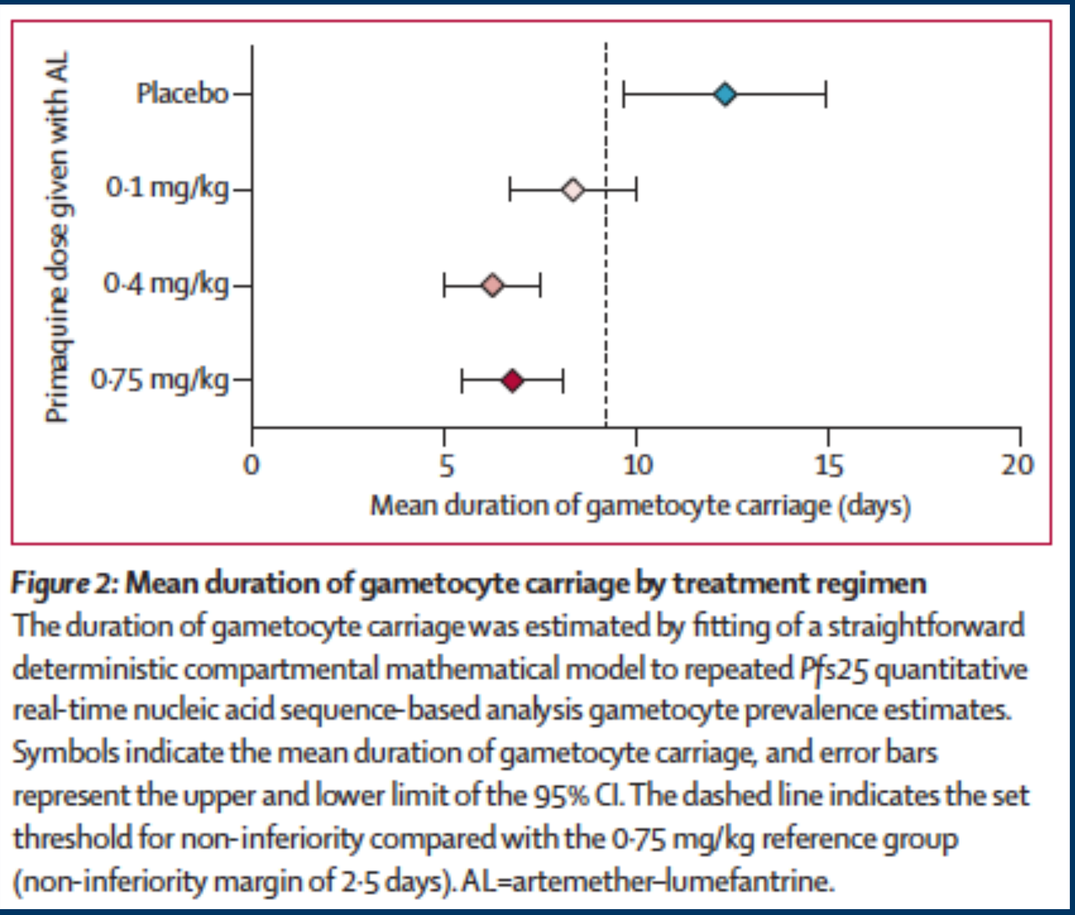


Figure 2: **Mean duration of gametocyte carriage by treatment regimen**
The duration of gametocyte carriage was estimated by fitting of a straightforward deterministic compartmental mathematical model to repeated *Pfs25* quantitative real-time nucleic acid sequence-based analysis gametocyte prevalence 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?

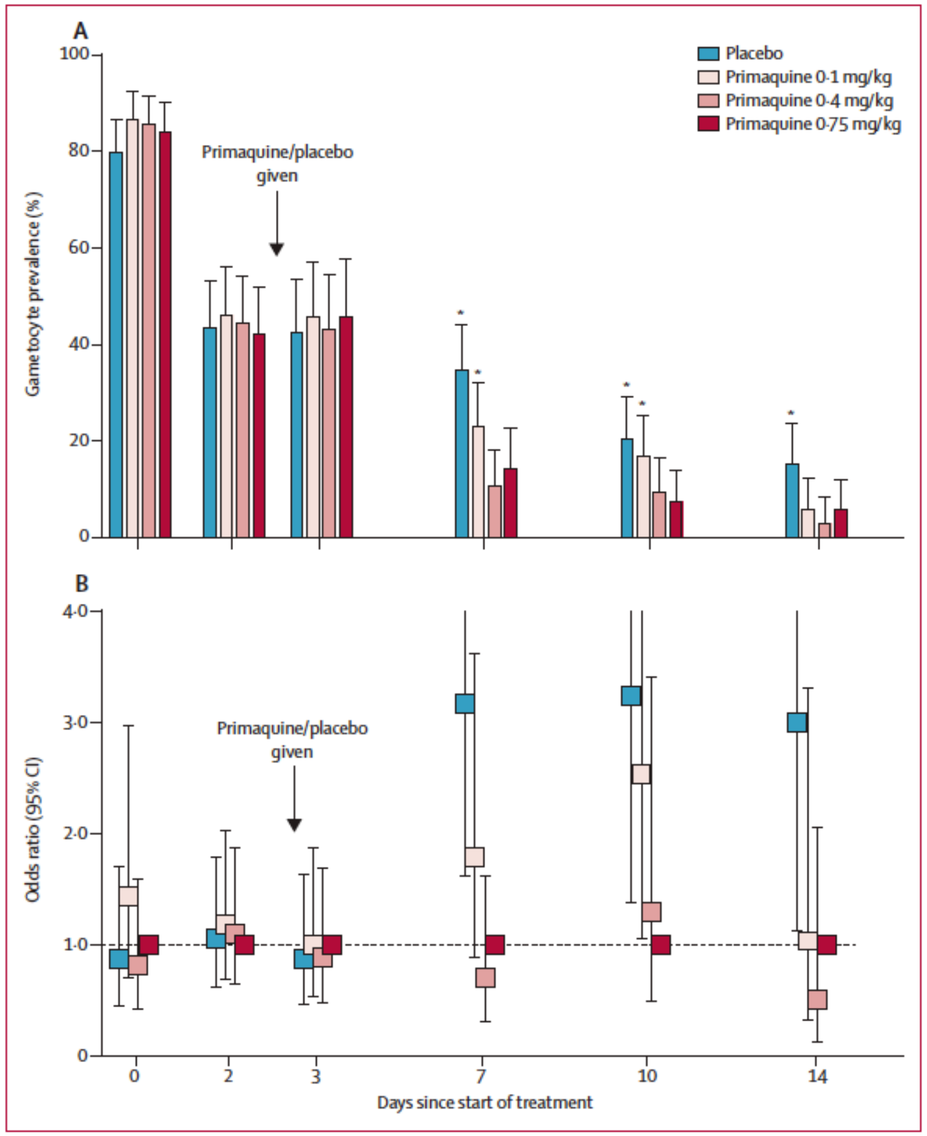


***Figure 3*: Gametocyte prevalence and prevalence ratio for each treatment regimen during 14 day follow-up**
(A) Gametocyte prevalence during follow-up, as measured by *Pfs25* quantitative real-time nucleic acid sequence-based analysis. Error bars indicate the upper limit of the 95% CI. (B) Odds ratio 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.

What does this figure tell us?

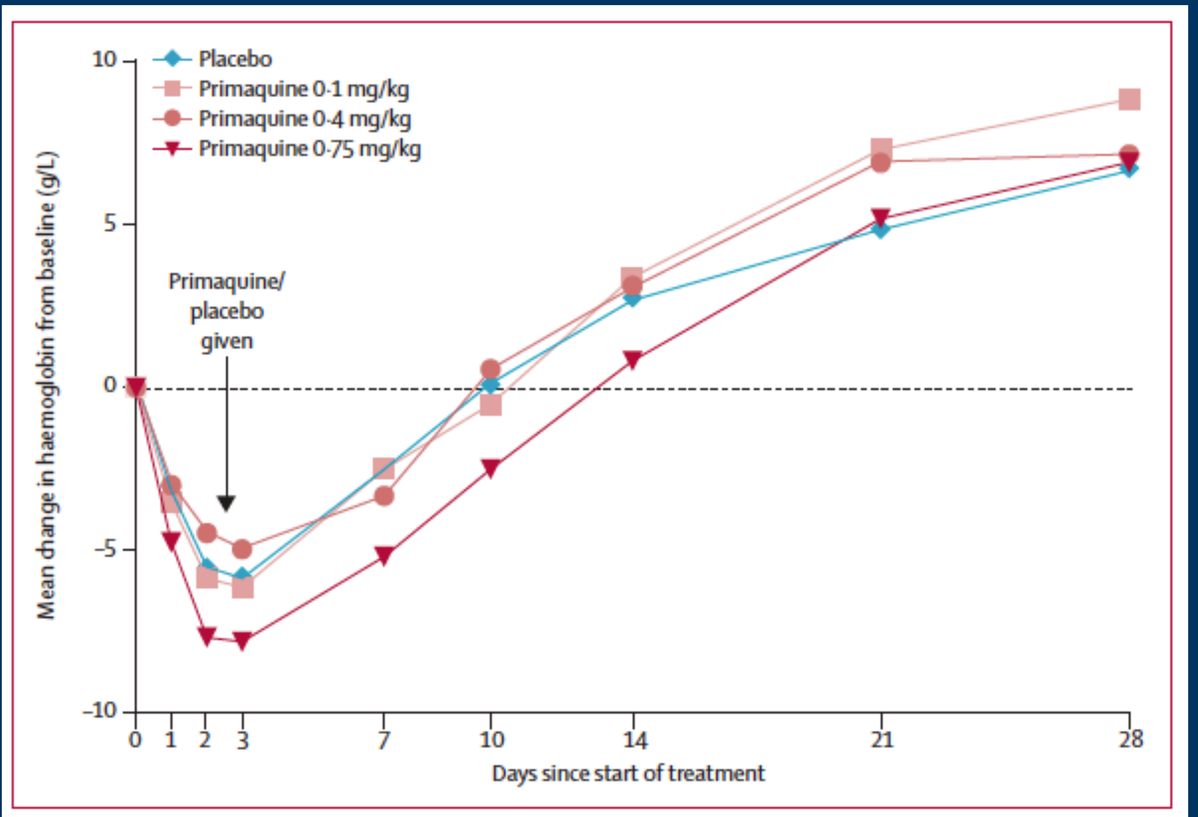


Figure 4: **Mean change in haemoglobin measurements by treatment regimen during 28 day follow-up**
Haemoglobin concentrations (g/L) during follow-up are expressed relative to that at enrolment for each treatment group.