Randomised controlled trials

All who drink from this goblet shall recover quickly, except for those it does not cure, they shall die. Thus, we may conclude that it works, except for incurable cases.

Galenos (131 - ca. 200)

Advanced Epidemiology
Gondar University
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The English East India Company's experiences in 1605

Category	Number of crew members who received lemon juice	Did not receive lemon juice
Deaths	0	105
Survivors	202	117
Total	202	222

A taxonomy of interventions
Rows: Types of comparisons
Columns: Intervention

	Randomised	Internal	External	Observation
Individually controlled	Clinical trials			
Individually uncontrolled			Environmental changes	
Community controlled	Community trials	Community follow-up	Planned structural changes	
Community uncontrolled			Socio-political changes	Catastrophes

RCT

- Randomised
- Controlled
- Trial

Guidelines for RCT

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Guidelines and Guidance

CONSORT 2010 Statement: Updated Guidelines for Reporting Parallel Group Randomised Trials

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Introduction

Randomised controlled trials, when appropriately designed, conducted, and reported, represent the gold standard in evaluating healthcare interventions. However, randomised trials can yield biased results if they lack methodological rigour [1]. To assess a trial accurately, readers of a published report need complete, clear, and transparent information on its methodology and findings. Unfortunately, attempted assessments frequently fail because authors of many trial reports neglect to provide lucid and complete descriptions of that critical information [2,3,4].

That lack of adequate reporting fuelled the development of the original CONSORT (Consolidated Standards of Reporting Trials) statement in 1996 [5] and its revision five years later [6,7,8]. While those statements improved the reporting quality for some randomised controlled trials [9,10], many trial reports still remain inadequate [2]. Furthermore, new methodological evidence and additional experience has accumulated since the last revision in 2001. Consequently, we organised a CONSORT Group meeting to update the 2001 statement [6,7,8]. We introduce here the result of that process, CONSORT 2010.

Intent of CONSORT 2010

The CONSORT 2010 Statement is this paper including the 25 item checklist in the table (Table 1) and the flow diagram (Figure 1). It provides guidance for reporting all randomised controlled trials, but focuses on the most common design type—individually randomised, two group, parallel trials. Other trial designs, such as cluster randomised trials and non-inferiority trials, require varying amounts of additional information. CONSORT extensions for these designs, [11,12] and other CONSORT products, can be found through the CONSORT website (http://www.consort-statement.org). Along with the CONSORT statement, we have updated the explanation and elaboration article, [13] which explains the inclusion of each checklist item, provides methodological background, and gives published examples of transparent reporting.

Diligent adherence by authors to the checklist items facilitates clarity, completeness, and transparency of reporting. Explicit descriptions, not ambiguity or omission, best serve the interests of all readers. Note that the CONSORT 2010 Statement does not include recommendations for designing, conducting, and analysing trials. It solely addresses the reporting of what was done and what was found.

Nevertheless, CONSORT does indirectly affect design and conduct. Transparent reporting reveals deficiencies in research if they exist. Thus, investigators who conduct inadequate trials, but who must transparently report, should not be able to pass through the publication process without revelation of their trial's inadequacies. That emerging reality should provide impetus to improved trial design and conduct in the future, a secondary indirect goal of our work. Moreover, CONSORT can help researchers in designing their trial.

Background to CONSORT

Efforts to improve the reporting of randomised controlled trials accelerated in the mid-1990s, spurred partly by methodological research. Researchers had shown for many years that authors reported such trials poorly, and empirical evidence began to accumulate that some poorly conducted or poorly reported aspects of trials were associated with bias [14] Two initiatives aimed at developing reporting guidelines culminated in one of us (DM) and Drummond Rennie organising the first CONSORT statement in

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Randomisation

- Assigning to treatment groups
- Aims at obviating that effect is due to systematic difference between groups other than the treatment
- Analysis assumes that randomisation was used and was “successful”
- We should report a) sequence generation, b) allocation concealment, and c) implementation (CONSORT checklist)

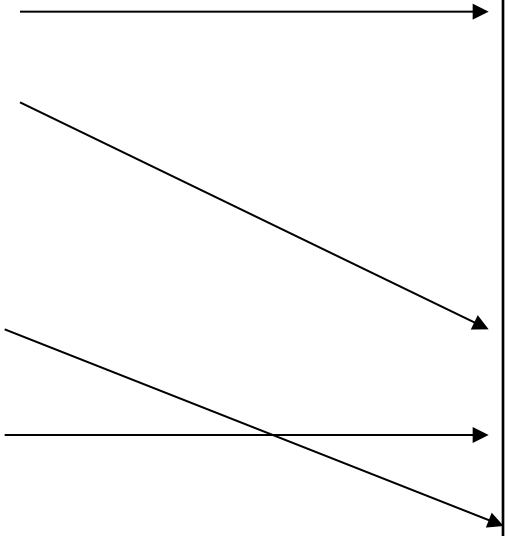
Sequence generation

Method used to generate the random allocation sequence

- *Simple randomisation*
  Sequence of random numbers from statistical textbook or computer
- *Permuted block randomisation*
  Especially for “small” trials to maintain a good balance

Permuted block method; block size of four with A = intervention and B= control

Random number sequence	Permuted blocks	Randomisation list
1 4 8 6 5	1. AABB 2. ABAB 3. ABBA 4. BBAA 5. BABA 6. BAAB	1. A A B B 4. B B A A



Concealment and implementation

Concealment and implementation

- Clarifying whether the allocation was concealed (“blinded”) until interventions were assigned
- Who generated the allocation sequence, who enrolled participants, who assigned participants to groups

Planning for sample size

- Confidence level? (0.05?)
- Power? (0.80?)
- Ratio intervention/control groups (1:1?)
- Expected frequency of disease in control group?
- Effect size you would like to show?

Epi Info (Statcalc for sample size estimation)

- http://www.cdc.gov/epiinfo/
- Free download
- Epidemiological software, a lot of possibilities, instruction material

Example, reporting on randomisation

Randomization

Randomization was planned and generated by an independent statistician, and was performed in blocks of 20. The pharmaceutical company marked the 4 different supplements with letter codes, blinded to researchers and participants. Information on group assignment was kept in a safe at the administrative offices of Gadjah Mada and Umeå Universities until after the intent-to-treat analysis. Participants were assigned to treatment groups by the recruitment field staff, who strictly followed the randomization list. The laboratory assessing the biochemical outcomes was not aware of the randomization groups.

Flow

Randomly allocated (n=1000)	
Allocated to intervention (n=500)	Allocated to placebo (n=500)
Lost to follow-up (n=60)	Lost to follow-up (n= 24)
No. with event at study end (n= 130); without (n=310)	No. with event at study end (n=170); without (n=306)

Sensitivity analysis of lost to follow-up

- Evaluating “worst case” scenario or most likely scenario
- Concluding what should have been the effect had those lost to follow-up in the different treatment groups had a certain frequency of events

Baseline data

- Demographic characteristics
- Potential confounders
- Factors that predict or alter adverse reactions
- Stratification factors
- Pre-specified subgroups

Example; baseline data

TABLE 1
Baseline characteristics of the study participants according to treatment regimen

Baseline characteristic	Zinc group ($n = 200$)	Placebo group ($n = 200$)	P^1
Week of gestation at first visit (wk)	23.0 ± 3.5[2]	22.5 ± 3.5	0.12
Age (y)	26.7 ± 4.9	27.0 ± 5.0	0.45
No. of previous pregnancies	1.6 ± 1.5	1.8 ± 1.8	0.46
Midupper arm circumference (cm)	26.0 ± 2.9	26.3 ± 3.2	0.38
Weight (kg)	58.9 ± 9.5	60.6 ± 10.6	0.09
Lacks formal education [% (*n*)]	6.6 ± 13	6.0 ± 12	0.82
Has secondary education [% (*n*)]	19.2 ± 38	16.5 ± 33	0.48
Is housewife [% (*n*)]	67.0 ± 132	68.0 ± 136	0.83
Has male partner [% (*n*)]	86.4 ± 171	84.0 ± 168	0.51
Has her own income [% (*n*)]	33.3 ± 66	32.5 ± 65	0.86
Has had miscarriage [% (*n*)]	21.9 ± 43	25.1 ± 50	0.46
Has had stillbirths [% (*n*)]	4.6 ± 9	4.0 ± 8	0.78
Primiparous [% (*n*)]	25.5 ± 50	23.6 ± 47	0.66

[1] Wilcoxon's rank-sum and chi-square tests for continuous and categorical characteristics, respectively.
[2] $\bar{x}$ ± SD (all such values).

Intention-to-treat analysis

- For ideal ITT analysis:
  - Full compliance with randomised treatment
  - No missing responses
  - Follow-up of all participants

Example; intention-to-treat analysis

TABLE 3
Effect of zinc supplements on low birth weight and prematurity

Outcome[1]	Zinc group[2]	Placebo group[2]	Relative risk (95% CI)[3]	P^4
	%	%		
Preterm < 37 wk	17.2 [31/180]	15.6 [29/186]	1.11 (0.63, 2.04)	0.78
Low birth weight, < 2500 g	10.9 [19/174]	10.3 [19/184]	1.06 (0.47, 2.38)	0.87
Small-for-gestational age[5]	14.4 [25/176]	18.5 [34/184]	0.78 (0.41, 1.38)	0.32

[1] For twin pregnancies, the outcome was positive when at least one of the twins had it.
[2] Values in brackets represent the number of infants at risk out of the total number of infants.
[3] 95% CI based on the exact binomial distribution.
[4] Fisher's exact test.
[5] <10th Percentile of weight for gestational age according to Brenner's reference

Outcomes and estimation

Example

	Diarrhoea incidence (n=197 049)		Impetigo incidence (n=200 156)		
	Mean incidence*	Difference *vs* control (95% CI)	Mean incidence*	Difference *vs* control neighbourhoods (95% CI)	Difference *vs* plain-soap households (95% CI)†
Antibacterial soap	2·02	−50% (−64% to −37%)	0·61	−36% (−53% to −18%)	−2% (−24% to 20%)
Plain soap	1·91	−53% (−65% to −41%)	0·62	−34% (−52% to −16%)	..
Control	4·06	..	0·94	..	..

*Mean incidence (episodes per 100 person-weeks) calculated with mean of neighbourhood rates weighted by person-weeks at risk from every neighbourhood. †Accounts for clustering by household.

***Table 3*: Primary diarrhoea and impetigo outcomes in children younger than 15 years by intervention group**

Which treatment would seem reasonable to introduce?

A. 91.8% in the group allocated to the active treatment survived, compared with 88.5% in the placebo group
B. Patients allocated to the active treatment had a 30% reduction in the risk of death
C. Mortality was reduced by 3.3% in the group allocated to the active treatment
D. One death was avoided for every 30 patients treated

Subgroup analysis

	Individuals aged less than 1 year (n=7679)		Individuals aged 1–2 years (n=9238)		Individuals aged 2–5 years (n=41 675)	
	Pneumonia incidence*	Difference vs control (95% CI)	Pneumonia incidence*	Difference vs control (95% CI)	Pneumonia incidence*	Difference vs control (95% CI)
Antibacterial soap	2·65	−24% (−80% to 32%)	5·93	−45% (−69% to −21%)	1·55	−51% (−70% to −33%)
Plain soap	2·46	−29% (−78% to 20%)	5·04	−54% (−74% to −33%)	1·56	−51% (−68% to −34%)
Control	3·48	..	10·86	..	3·17	..

*Incidence (episodes per 100 person-weeks) calculated with mean incidence of every cluster weighted by person-weeks at risk for that cluster.

Table 4: **Mean pneumonia incidence by age and intervention group**

Probability of at least one significant result at the 5% significance level given no true differences

1 test	0.05
2 tests	0.10
3 tests	0.14
5 tests	0.23
10 tests	0.40
20 tests	0.64

Example; reporting on adverse events

Table 1. Frequency of reported symptoms (possible side-effects) after one month of antenatal iron supplementation in daily (n=86) and weekly (n=86) supplementation groups

Symptom	Reported frequency (%) in daily supplementation	Reported frequency (%) in weekly supplementation	p value
Heartburn	11.5	13.6	0.658
Nausea	14.4	17.5	0.551
Vomiting	9.6	21.4	0.019
Diarrhoea	10.6	14.6	0.389
Constipation	59.6	61.2	0.821
Any of the five	61.5	62.1	0.93

CLUSTER-RANDOMISED TRIALS, A FEW COMMENTS

Why using clusters (and what is that)?

- Started with studies at schools: groups of children. Hospital-ward patients, women at antenatal clinics etc. Even single person with teeth!
- Measurements within cluster may be (are often) correlated
- Few clusters = problems
- Unit for randomisation: cluster (loss of statistical power)
- Intracluster correlation coefficient (ICC, proportion of total variance that can be explained by the variation between clusters)
- Analysis should be adjusted for ICC

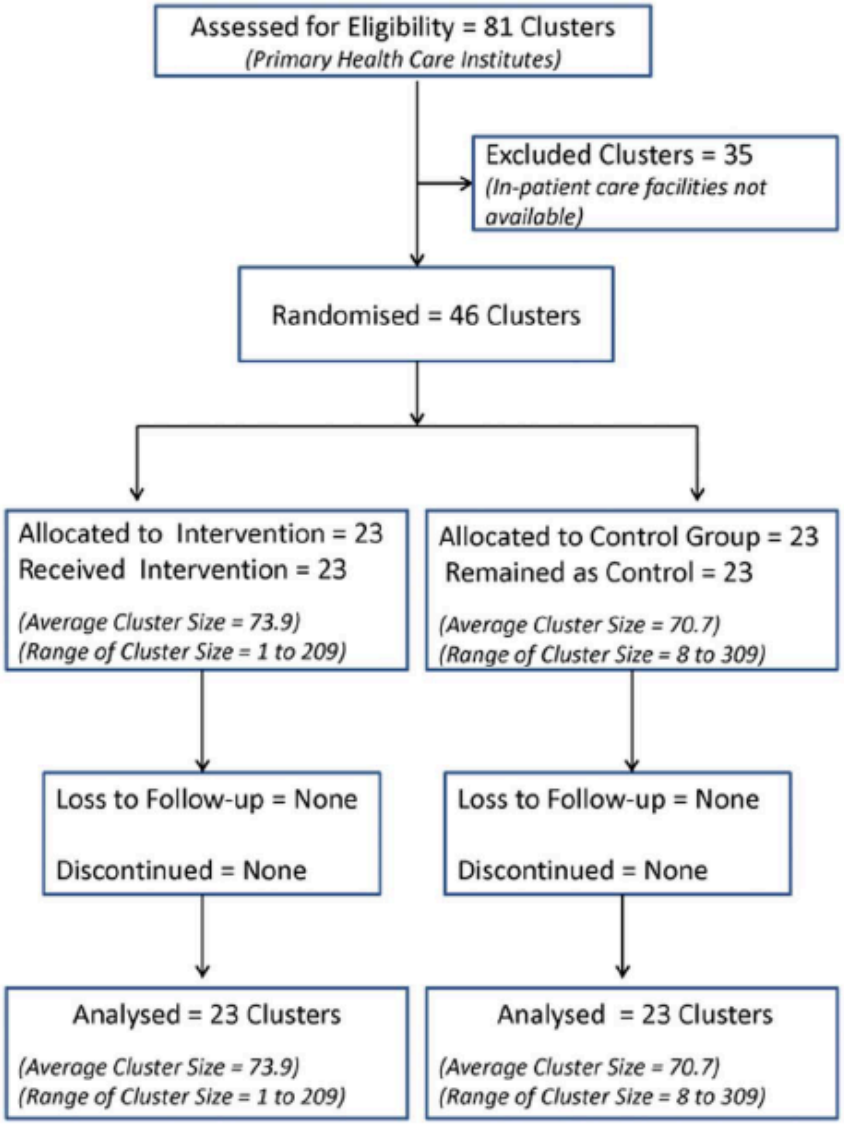


Figure 2. Participant flow chart.
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