Beginning With the End in Mind: CONSORT

Cape Town 2007

Kenneth F. Schulz, PhD, MBA
RCTs and CONSORT: My Agenda for Today

- Examples of poor reporting
- An example of the import of methodological quality
- Examples of trials with poor methodological quality display the need for transparent reporting
- Discuss research showing the widespread problems with reporting in medical research
- Led to the CONSORT guidelines for reporting
- You will have to report according to CONSORT

- Hence, “Beginning with the end in mind”
EFFECT OF THE ANGIOTENSIN-CONVERTING-ENZYME INHIBITOR BENAZEPRIL ON THE PROGRESSION OF CHRONIC RENAL INSUFFICIENCY

Abstract Background. Drugs that inhibit angiotensin-converting enzyme slow the progression of renal insufficiency in patients with diabetic nephropathy. Whether these drugs have a similar action in patients with other renal diseases is not known. We conducted a study to determine the effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of renal insufficiency in patients with various underlying renal diseases.

The patients in each group were then randomly assigned to receive 10 mg of benazepril or placebo once daily. Randomization was balanced for disease severity at each center.

NEJM 1996;334:939-41
Double-blind trial of aspirin in primary prevention of myocardial infarction in patients with stable chronic angina pectoris

Clinical trials have demonstrated a prophylactic role for aspirin in myocardial infarction and in unstable angina pectoris. The Swedish Angina Pectoris Aspirin Trial (SAPAT) is the first prospective study of aspirin in stable angina.

“After showing good tolerance of sotalol for at least three weeks the patients were randomised double blind to aspirin 75 mg daily (n=1009) or placebo (n=1026).”

Abstract  Background. In patients with human immunodeficiency virus (HIV) infection, combined treatment with several agents may increase the effectiveness of antiviral therapy. We studied the safety and efficacy of saquinavir, an HIV-protease inhibitor, given with one or two nucleoside antiretroviral agents as compared with the safety and efficacy of a combination of two nucleosides alone.

“The study (AIDS Clinical Trials Group protocol 229) was a randomized, double-blind, phase 2 trial of three treatment regimens”

NEJM 1996;334:1011-17
Bacterial Vaginosis: Treatment with Topical Intravaginal Clindamycin Phosphate

We tested topical intravaginal clindamycin phosphate at concentrations of 0.1, 1.0, and 2.0% in the treatment of 62 women with symptomatic bacterial vaginosis in a prospective, randomized, double-blind, placebo-controlled trial. practitioners use systemic metronidazole and alternative therapy, particularly for pregnant women, is highly effective. This study examined the safety and efficacy of topical clindamycin phosphate.

"... prospective, randomized, double-blind, placebo-controlled trial."

Randomized Controlled Trial of Antenatal Social Support to Prevent Preterm Birth

Abstract

Objective--To test the effect of a programme of additional antenatal social support on the occurrence of preterm birth (a birth from 20 to 36 weeks gestation) in women at risk of preterm birth.

Design--A prospective randomized controlled trial. The design was one of randomization before consent for a new treatment.

“Design - A prospective randomized, controlled trial.”

EFFECT OF THE ANGIOTENSIN-CONVERTING-ENZYME INHIBITOR BENAZEPRIL ON THE PROGRESSION OF CHRONIC RENAL INSUFFICIENCY

Abstract

Background. Drugs that inhibit angiotensin-converting enzyme slow the progression of renal insufficiency in patients with diabetic nephropathy. Whether these drugs have a similar action in patients with other renal diseases is not known. We conducted a study to determine the effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of renal insufficiency in patients with various underlying renal diseases.

Methods. In a three-year trial involving 583 patients with renal insufficiency caused by various disorders, 300 received benazepril and 283 received placebo. We conducted a prospective, double-blind, randomized study involving 49 European hospitals.

We conducted a prospective, double-blind, randomized study involving 49 European hospitals.

NEJM 1996;334:939-41
(Patho)physiological Implications of Chronic Dietary Sodium Restriction During Pregnancy; a longitudinal prospective randomized study

Abstract: **Objective**--To study the possible pathophysiological implications of long continued dietary sodium restriction in pregnancy

**Design**--Longitudinal prospective randomized study of the effects of a low sodium diet compared with unrestricted sodium intake in pregnancy.

**Setting**--Academic Department of Obstetrics and Gynaecology, Nijmegen, The Netherlands.

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The Term Prospective Trial Is a “Pleonasm”

- “Trial” used increasingly in combination with “prospective”
- “A PubMed search ‘prospective trial’ yielded 507 hits for the period 1999-2001. However, ‘prospective’ is a pleonasm (superfluous)”
- “Because all trials are prospective by definition; the only way to do a retrospective trial is for the investigator to travel back in time with a box of pills.”

  - Letter in The Lancet, Sept 2002 by Martijn B Katan, Netherlands
Randomization

• **Sequence generation**
  - Method used to generate the allocation sequence, including any details about restriction
    - What does restriction mean?

• **Allocation concealment**
  - Method used to implement the random allocation sequence

• **Implementation**
  - Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups
Allocation concealment

- A technique used to prevent selection bias by concealing the allocation sequence from those assigning participants to intervention groups, until the moment of assignment.

- Allocation concealment prevents researchers from (unconsciously or otherwise) influencing which participants are assigned to a given intervention group.
Importance of allocation conceallment

• Unclearly concealed and inadequately concealed trials, compared to adequately concealed trials, exaggerated the estimates of an intervention’s effectiveness by 30% to 40%, on average.

Ignorance Is Not Bliss

“Most physicians are not trained in basic scientific principles, let alone clinical trials”
- Stephen George, Duke University, chair of the statistics committee for NCI, NIH Cancer Clinical Cooperative Groups

“I fantasize that in the future (training) will become a requirement for running clinical trials”
- John Gallin, director of NIH’s clinical center
A Controlled Trial of Povidone-Iodine as Prophylaxis Against Ophthalmia Neonatorum

Abstract  Background. Neonatal conjunctivitis (ophthalmia neonatorum) continues to cause blindness, because the agents used prophylactically to prevent this condition are not completely effective and are not widely available in many parts of the world. Povidone--iodine ophthalmic solution is an effective antibacterial agent with broad activity to which no bacteria are known to be resistant.

“Randomization was achieved by rotating the three medications after each was used for a week.”

NEJM 1995;332:562-6
Stopping Smoking in Pregnancy: Effect of a Self-help manual in Controlled Trial

Summary. For medical reasons, encouraging women to stop smoking during pregnancy and post partum has high priority. Many smokers want to stop smoking but decline clinical treatment when it is offered. The aim of this study was to find a method which was accepted by a large number of smokers and had a high success rate.

“Women were randomized . . . born on days 1-10 of every month formed the control group (n=231), and those born on days 11-31 formed the treatment group (n=492).”

Nifedipine in the Treatment of Severe Preeclampsia

We conducted a randomized clinical trial in which patients with severe preeclampsia between 26-36 weeks of gestation receive either nifedipine (10-30 mg sublingually, then 40-120 mg/day orally; N= 24) or hydralazine (6.25-12.5 mg intravenously, then 80-120 mg/day orally; N= 25).

"We conducted a randomized controlled trial..."

"Subjects were assigned to the nifedipine or hydralazine group according to the week of the month."

Obstet Gynecol 1991; 77:331-7
The use of Histoacryl for Episiotomy Repair

Summary. Histoacryl-tissue adhesive (B. Braun Melsungen AG W. Germany) was used in place of skin sutures (2/0 chromic catgut, Ethicon Ltd, Edinburgh, Scotland) for episiotomy repair in a group of 20 women. This group was compared with two groups of women undergoing first and repeat episiotomy. Variables analysed included pain in the episiotomy site, pain while walking, sitting, sleeping, lying down, breast-feeding, micturating and defaecating. The Histoacryl group was superior with regard to all the variables.

“Groups 1 and 3 (first episiotomy repair) were selected randomly, by registration number; group 1 odd and group 3 even numbers.”

Biocompatible membranes in acute renal failure: prospective case-controlled study.

Schiffl H, Lang SM, Konig A, Strasser T, Haider MC, Held E.

“The mortality of critically ill patients with acute renal failure has been halved through intervention by haemodialysis. However, several reports suggest that the course of the disorder may be prolonged by this procedure. Our prospective randomised study was done . . .”

Effectiveness of antibiotic prophylaxis in preventing bacteriuria after multichannel urodynamic investigations: A blind, randomized study in 124 female patients

Am J Obstet Gynecol;1991;165:679-81
On completion of the procedures, the patients were randomly assigned to prophylaxis or nonprophylaxis groups according to hospital number. Both the physician and the nurse technician were blind as to which assignment the patient received. Patients in group A received nitrofurantoin 50 mg four times and phenazopyridine hydrochloride 200 mg three times for 1 day. Patients in group B received phenazopyridine hydrochloride only. The code was broken at the completion of the study.
## Table I. Patient demographics

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<th>Group A</th>
<th>Group B</th>
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<td>No. of patients</td>
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<td>Age (yr)</td>
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<td>Mean</td>
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<td>58.58</td>
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<td>Patients with infections on follow-up</td>
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<td>%</td>
<td>8.2</td>
<td>18.9</td>
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Reviewed 2000 randomized trials of all treatments for schizophrenia

Only 4% (n=80) of the trials clearly described the methods of allocation

Reporting of method of randomization

- Review of 122 RCTs of selective serotonin uptake inhibitors in patients with depression (Hotopf et al 1997)
  - Only 1 trial report included details of the method of randomization

# Method of allocation of treatment in 208 controlled trials in head injury

Dickinson K, et al., BMJ 2000;320:1308-1311

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<th>Method of allocation</th>
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<tr>
<td>Centralised randomisation by telephone</td>
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<td>Numbered/coded identical containers administered sequentially</td>
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<td>Randomisation scheme controlled by pharmacy</td>
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<td>Sequentially numbered, sealed, opaque envelopes</td>
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<td>Alternation</td>
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<td><strong>Not stated</strong></td>
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## Randomization Process

<table>
<thead>
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<th>Proper Approach</th>
<th>4 Major General Medical Journals</th>
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<tr>
<td>Generation of Allocation Sequence</td>
<td>49%</td>
</tr>
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<td>Allocation Concealment</td>
<td>26%</td>
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<td>Both</td>
<td>15%</td>
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[Lancet 1990; 335: 149-153.]
History of CONSORT  *(Consolidated Standards of Reporting Trials)*

- Started with the standards of Reporting Trials (SORT) meeting in 1993, in Ottawa
  - Clinical researchers and biomedical editors
- Evidence-based, whenever possible
  - Not reporting the item, compared to reporting it, was associated with bias
    - e.g., Allocation concealment
The CONSORT Statement: Revised Recommendations for Improving the Quality of Reports for Parallel-Group Randomized Trials

David Moher, MSc
Kenneth F. Schulz, PhD, MBA
Douglas Altman, DSc
for the CONSORT Group

JAMA, April 18, 2001—Vol 285, No. 15  1987
Moher D, Schulz KF, Altman DG, for the CONSORT group. The CONSORT statement: revised recommendations for improving the quality of reports of parallel group randomized trials.

Annals of Internal Medicine 2001;134:657-662
The Lancet 2001;357:1191-1194
BioMedCentral Medical Research Methodology 2001, 1:2 (20 April 2001)
Dissemination

• Major general & internal medicine journals endorsed CONSORT
  ➢ Required authors to submit RCT reports using template

• Editorial groups that have endorsed CONSORT
  ➢ World Association of Medical Editors (WAME)
  ➢ Council of Science Editors (CSE)
  ➢ International Committee of Medical Journal Editors (ICMJE or Vancouver Group)
Development of the Explanation and Elaboration manuscript

• To enhance the use and dissemination of CONSORT

• Format
  ➢ Checklist item
  ➢ Examples
  ➢ Explanation
    ▪ Patterned after the ICMJE’s “Uniform requirements for manuscripts submitted to biomedical journals”
The Revised CONSORT Statement for Reporting Randomized Trials: Explanation and Elaboration

Douglas G. Altman, DSc; Kenneth F. Schulz, PhD; David Moher, MSc; Matthias Egger, MD; Frank Davidoff, MD; Diana Elbourne, PhD; Peter C. Gøtzsche, MD; and Thomas Lang, MA, for the CONSORT Group

17 April 2001   Annals of Internal Medicine   Volume 134   Number 8   663
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**Checklist of items to include when reporting a randomised trial**

1. **Title and abstract**
   - How participants were allocated to interventions (e.g., "random allocation", "randomised", or "randomly assigned").

2. **Introduction**
   - Background
   - Eligibility criteria for participants and the settings and locations where the data were collected.

3. **Methods**
   - Participants
   - Inclusion criteria
   - Exclusion criteria
   - Interventions
   - Description of intervention(s)
   - Objectives
   - Primary and secondary outcomes
   - Outcomes
   - Overall description of outcomes measured
   - Sample size
   - Methodology
   - Randomisation
   - Allocation concealment
   - Sequence generation
   - Allocation concealment
   - Blinding (masking)
   - Blinding of participants
   - Blinding of personnel
   - Blinding of outcome assessment
   - Statistical methods
   - Methodology
   - Analysis plan
   - Sample size calculation
   - Power and sample size
   - Randomisation
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Table. Checklist of Items To Include When Reporting a Randomized Trial

<table>
<thead>
<tr>
<th>Paper Section and Topic</th>
<th>Item Number</th>
<th>Descriptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title and abstract</td>
<td>1</td>
<td>How participants were allocated to interventions (e.g. “randomized,” or “randomly assigned”).</td>
</tr>
<tr>
<td>Introduction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Background</td>
<td>2</td>
<td>Scientific background and explanation of rationale.</td>
</tr>
<tr>
<td>Methods</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants</td>
<td>3</td>
<td>Eligibility criteria for participants and the settings and collected.</td>
</tr>
<tr>
<td>Interventions</td>
<td>4</td>
<td>Precise details of the interventions intended for each were actually administered.</td>
</tr>
<tr>
<td>Objectives</td>
<td>5</td>
<td>Specific objectives and hypotheses.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>6</td>
<td>Clearly defined primary and secondary outcome measurement methods used to enhance the quality of measurement training of assessors.</td>
</tr>
<tr>
<td>Sample size</td>
<td>7</td>
<td>How sample size was determined and, when applicable, analyses and stopping rules.</td>
</tr>
<tr>
<td>Randomization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sequence generation</td>
<td>8</td>
<td>Method used to generate the random allocation sequence restriction (e.g., blocking, stratification).</td>
</tr>
<tr>
<td>Method Used to Implement the Random Allocation Sequence (e.g., personal or central telephone), clarifying whether the sequence of interventions were assigned.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Who generated the allocation sequence, who enrolled participants to their groups.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whether or not participants, those administering the intervention, or the outcomes were blinded to group assignment. If blinding was evaluated.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statistical methods used to compare groups for primary and additional analyses, such as subgroup analyses and multiplicity adjustments.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Results

<table>
<thead>
<tr>
<th>Flow of participants through each stage (a diagram is helpful). Specifically, for each group report the numbers of participants receiving intended treatment, completing the study, and those lost to follow-up. Describe protocol deviations from the original protocol and any other changes in the conduct or setting of the study.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dates defining the periods of recruitment and follow-up.</td>
</tr>
<tr>
<td>Baseline demographic and clinical characteristics of each group.</td>
</tr>
<tr>
<td>Number of participants (denominator) in each group.</td>
</tr>
<tr>
<td>Whether the analysis was by “intention to treat.”</td>
</tr>
<tr>
<td>For each primary and secondary outcome, a summary estimate of the effect size and its precision (e.g., 95% confidence interval) and its statistical significance.</td>
</tr>
<tr>
<td>Address multiplicity by reporting any other analyses performed.</td>
</tr>
<tr>
<td>Results</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>Participant flow</td>
</tr>
<tr>
<td>Recruitment</td>
</tr>
<tr>
<td>Baseline data</td>
</tr>
<tr>
<td>Numbers analyzed</td>
</tr>
<tr>
<td>Outcomes and estimation</td>
</tr>
<tr>
<td>Ancillary analyses</td>
</tr>
<tr>
<td>Adverse events</td>
</tr>
</tbody>
</table>

| Discussion |  |
| Interpretation | 20 | Interpretation of the results, taking into account study limitations, bias or imprecision, and the dangers associated with generalizing outcomes. |
| Generalizability | 21 | Generalizability (external validity) of the trial findings. |
| Overall evidence | 22 | General interpretation of the results in the context of the evidence. |
Participant flow through a randomized trial . . . important?
Figure 4. Flow diagram of a trial of the topoisomerase I inhibitor irinotecan in patients with metastatic colorectal cancer in whom fluorouracil chemotherapy had failed.

279 patients randomly allocated (2:1)

189 allocated to receive irinotecan, 300–350 mg/m², and supportive care
   183 received allocated intervention
   6 did not receive allocated intervention

90 allocated to receive supportive care alone
   90 received allocated intervention

5 lost to follow-up

184 in analysis
   123 died
   61 alive
   5 excluded (lost to follow-up)

85 in analysis
   71 died
   14 alive
   5 excluded (lost to follow-up)

The diagram includes the results for the main outcome (overall survival).
Revamped web site
(www.consort-statement.org)

• Reprints of statement and E & E document (copyright is in the public domain)

• Data bank of “good” and “not so good” examples of trial reporting

• Reference citations of new evidence
Does the CONSORT checklist work? Methods

- 4 “general & internal medicine” journals
  - 3 endorsed CONSORT (BMJ, JAMA, Lancet)
  - 1 did not (NEJM)
- Hand searched all 4 journals for 1994 and 1998 (January to June), respectively
- Used number of CONSORT items, Jadad score and adequacy of allocation concealment
  - Trained 2 assessors
Does CONSORT work?  
More results

<table>
<thead>
<tr>
<th>Journal</th>
<th>1994 N</th>
<th>1998 N</th>
<th>Pre Mean (SD)</th>
<th>change (CI)</th>
<th>Pre Mean</th>
<th>Change (CI)</th>
</tr>
</thead>
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<tr>
<td>BMJ</td>
<td>14</td>
<td>20</td>
<td>2.07 (0.92)</td>
<td>0.43 (-0.34, .20)</td>
<td>79</td>
<td>-29 (-62, 4)</td>
</tr>
<tr>
<td>JAMA</td>
<td>29</td>
<td>20</td>
<td>3.00 (1.04)</td>
<td>0.35 (-0.29, .99)</td>
<td>59</td>
<td>-14 (-43, 16)</td>
</tr>
<tr>
<td>Lancet</td>
<td>28</td>
<td>37</td>
<td>2.75 (0.89)</td>
<td>0.68 (0.14, .22)</td>
<td>54</td>
<td>-24 (-48, 1)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>71</strong></td>
<td><strong>77</strong></td>
<td><strong>2.72 (1.00)</strong></td>
<td><strong>0.45 (0.08, .82)</strong></td>
<td><strong>61</strong></td>
<td><strong>-22 (-38, -6)</strong></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>26</strong></td>
<td><strong>37</strong></td>
<td><strong>3.12 (1.03)</strong></td>
<td><strong>-0.01 (-0.55,0.54)</strong></td>
<td><strong>69</strong></td>
<td><strong>-8 (-33, 17)</strong></td>
</tr>
</tbody>
</table>

Conclusion

• Without proper reporting of a trial
  • Journals may reject
  • If published, readers may question results
  • Trial not included in meta-analyses
• Begin with the end in mind
• Proper protocol development: the critical process
• Remember: registration of all trials at clinicaltrials.gov