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Preparing high quality clinical trials

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Budapest

Preparing high quality clinical trials

http://photos1.blogger.com/blogger/2185/1871/1600/evidencepyramid1.jpg

What is a clinical trial?

- Prospective
- Observation or intervention
- Evaluation of health outcomes

http://www.who.int/topics/clinical_trials/en/

Altering events during study?

NO

OBSERVATIONAL STUDY

YES

INTERVENTIONAL STUDY

Preparing high quality clinical trials

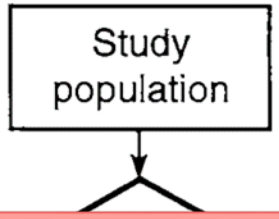
http://photos1.blogger.com/blogger/2185/1871/1600/evidencepyramid1.jpg

Steps to conduct a RCT

- **Simplify** protocols and outcomes assessed
- Enough **well-trained** proffesionals
- Regular **tranings** and retrainings : GCP and protocols
- Internal **audits**
- Data **managment**, **quality** assurance and data **analysis** plan
- Do **beta-tests**

Kleppinger,et al. *Clinical Infectious Diseases* 51.Supplement 1 (2010): S111-S116.

http://www.ucl.ac.uk/jro/biostatistics/RCT_nonCTIMP_protocol_guidelines.pdf



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SAMPLE SIZE CALCULATION

- sufficient statistical power to **detect differences** between groups
- based on **previous findings**
- **superiority**, **equality** or **non-inferiority** trials

Kadam P,. *International Journal of Ayurveda Research*, 2010

Why should we randomize?

- Trying to ensure that **ONLY ONE factor is different** between two or more groups
- Observe the **consequences**
- Attribute **causality**
- Eliminates **bias** in treatment assignments
- Facilitates **blinding** of the identity of treatments
- Permits the use of the **probability theory**

Vickers AJ. How to randomize. *Journal of the Society for Integrative Oncology*. 2006;4(4):194-198.

How can we randomize?

‚Almost'/'Quasi' random assignments:

Alphabet

Telephone number

Sequential

Bed number

Simple randomization

Flip a coin, roll a dice

Random assignment:

Computer generated list, table of random numbers

Richard Peto *et al.* (1976): "Physicians who are

Benjamin Freedman (1987):

Clinical equipoise exists when there is **genuine uncertainty** within the **professional community** as to which of the two treatment arms is superior

patients into a trial."

www.uab.edu/ethicscenter/weijer.ppt

Peto R, Baigent C. *BMJ : British Medical Journal*.1998;317(7167):1170-1171.

What is a clinical trial's greatest enemy?

- planning
- selection of participants

Systematic differences in the way participants are **accepted** or **rejected** for a trial, or in **how the intervention** is **assigned** to participants once they have been accepted

- results
- publication of reports

Steps to conduct a RCT

At night, residents were reluctant to call the consultant needed for the laparoscopic procedure but not the open

Allocation concealment

Procedure to protect the randomization process **before** the subject enters the trial

appendectomy group according to the passed-over envelope

(D. Wall, written communication, June 2000)

http://www.cebm.net/wp-content/uploads/2015/09/Teaching-RCTs.pdf

Schulz & Grimes. Lancet 2002

Masking of the treatments **after** randomization (once trial begins)

Double-Blinded **Single-Blinded**

STUDY PROTOCOL Open Access

Pancreatitis of biliary origin, optimal timing of cholecystectomy (PONCHO trial): study protocol for a randomized controlled trial

Stefan A Bouwense[1], Marc G Besselink[2,3,4], Sandra van Brunschot[1], Olaf J Bakker[2], Hjalmar C van Santvoort[2], Nicolien J Schepers[1], Marja A Boermeester[4], Thomas L Bollen[5], Koop Bosscha[6], Menno A Brink[7], Marco J Bruno[8], Esther C Consten[9], Cornelis H Dejong[10], Peter van Duijvendijk[11], Casper H van Eijck[12], Jos J Gerritsen[13], Harry van Goor[14], Joos Heisterkamp[15], Ignace H de Hingh[16], Philip M Kruyt[17], I Quintus Molenaar[2], Vincent B Nieuwenhuijs[18], Camiel Rosman[19], Alexander F Schaapherder[20], Joris J Scheepers[21], Marcel BW Spanier[22], Robin Timmer[23], Bas L Weusten[23], Ben J Witteman[24], Bert van Ramshorst[3], Hein G Gooszen[1], Djamila Boerma[3*] and for the Dutch Pancreatitis Study Group

Abstract

Background: After an initial attack of biliary pancreatitis, cholecystectomy minimizes the risk of recurrent biliary

Bouwense, Stefan A., et al. *Trials* 13.1 (2012)

To blind or not to blind?

Panel 1: **Potential benefits accruing dependent on those individuals successfully blinded**

Individuals blinded	Potential benefits
Participants	Less likely to have biased psychological or physical responses to intervention More likely to comply with trial regimens Less likely to seek additional adjunct interventions Less likely to leave trial without providing outcome data, leading to lost to follow-up
Trial investigators	Less likely to transfer their inclinations or attitudes to participants Less likely to differentially administer co-interventions Less likely to differentially adjust dose Less likely to differentially withdraw participants Less likely to differentially encourage or discourage participants to continue trial
Assessors	Less likely to have biases affect their outcome assessments, especially with subjective outcomes of interest

Schulz KF, Grimes DA, Lancet. 2002

administering intervention/ inve

outcomes

- **TRIPLE BLIND:** +data analyst(s)

Steps to conduct a RCT

1. The protocol
2. Selecting reference/control and experimental populations, determining sample size
3. Randomization
4. **Intervention**
5. Follow up
6. Assessment

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Table 1. **Steps in the Publishing Process Where Publication Bias May Intrude**

Phases of research publication	Actions contributing to and/or resulting in publication bias
Preliminary and pilot studies	Small studies, more likely to be negative (discarded failed hypotheses), are unpublished—some under "industrial secret."
Trial design, organization, and funding	Proposal selectively cites positive studies.
Institutional/ethics review board approval	No registries are kept of approved trials.
Study completion	Interim analysis shows that study is likely to be negative and project is dropped.
Report completion	Authors decide reporting a negative study is worthless and uninteresting, and no time or effort is assigned.
Report submission	Authors decide to forgo the submission of the negative study.
Journal selection	Authors decide to submit the report to a nonindexed, non–English-language, limited-circulation journal.
Editorial consideration	Editor decides that the negative study is not worth peer review process and rejects manuscript. If editor decides it is worth reviewing, manuscript goes to lower priority list.
Peer review	Reviewers conclude that the negative study does not contribute to the field and recommend rejection of the manuscript.
Author revision and resubmission	Author of rejected manuscript decides to forgo the submission of the negative study or to do it again at a later time to another journal (see "Journal selection").
Report publication	Journal delays publication of the negative study.
Lay press report	The negative study is not considered newsworthy.
Electronic database indexing	Medline, EMBASE, Best Evidence do not scan or index articles in the journal/language of publication of the negative study.
Decision-maker retrieval	Health managers and policymakers do not retrieve the negative study to dictate policy.
Further trial evidence	New trial reports discuss their findings but do not cite the findings of the negative study.
Narrative review	Experts draft a review, but the negative study is never cited.
Systematic review	Reviewer goes to extremes to identify negative reports but misses the negative study. Industry-associated reviewer uses arbitrarily selected unpublished data "on file"; this further discredits incorporation of unpublished reports in systematic reviews.
Systematic review submission	Journal editors reject a meta-analysis because it included unpublished reports not exposed to the rigor of peer review. Review then follows the same path described here for the negative study.
Practice guidelines	Evidence-based guidelines are produced based on a systematic review that missed the negative study.
Funding opportunities	Further funding opportunities are identified without consideration of the negative study.

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Montori et al. Mayo Clin Proc 2000

Bias in RCTs

Can occur at all phases!

- Selection bias
- Information bias
- Bias due to competing interests

The PLoS Medicine Editors. Making Sense of Non-Financial Competing Interests. PLoS Medicine.2008

Bias in RCTs

Can occur at all phases!

- Selection bias
- Information bias
- Bias due to competing interests
- Inappropriate handling of withdrawals, drop outs, and protocol violations

Thank you for your attention!

The Hungarian Pancreatic Study Group is committed to improving the lives of patients suffering from pancreatic diseases.

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