Methodological designs of clinical implant trials and their power to answer a research question

Asbjørn Jokstad
University of Toronto

Clinical trial terminology - tower of Bable?

analytical study
case control study (89)
case serie
case study, case report
cause-effect study
clinical trial (79)
cohort study (89)
cohort study with historical controls
controlled clinical trial (95)
cross-sectional study (89)
descriptive study
diagnostic meta-analysis
diagnostic study
double blind randomized therapeutical trial with cross-over design
ecological study
etiological study
experimental study
explorative study
feasibility study (79)
follow-up study (67)
historical cohort study
incidence study
intervention study
longitudinal study (79)
N=1 trial
non-randomized trial with contemporaneous controls
non-randomized trial with historical controls
observational study
prospective cohort study
prospective follow-up study, observational or experimental
prospective study (67)
quasi-experimental study
randomized clinical trial, RTC
randomized controlled trial, RCT (89)
retrospective cohort study
retrospective follow-up study
retrospective study (67)
surveillance study
survey, descriptive survey
therapeutic meta-analysis
trohoc study

What is the significance of ”MESH –terms”

A: Never heard of this term before

B: Vaguely aware of this term

C: Know what the term “MESH” means

D: Familiar with, and apply “MESH” terms often

E: Don’t know the term and couldn’t care less

Clinical trial terminology - MESH terms 1967

case serie

case study, case report

follow-up study (67)

prospective study (67)

retrospective study (67)

Clinical trial terminology - MESH terms 1979

case serie		
case study, case report		prospective study (67)
	feasibility study (79)	
clinical trial (79)	follow-up study (67)	
	longitudinal study (79)	retrospective study (67)

Clinical trial terminology - MESH terms 1989

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- case study, case report
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- prospective study (67)
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- retrospective study (67)

Clinical trial terminology - MESH terms 1995

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Clinical trial terminology - tower of Bable → MESH terms

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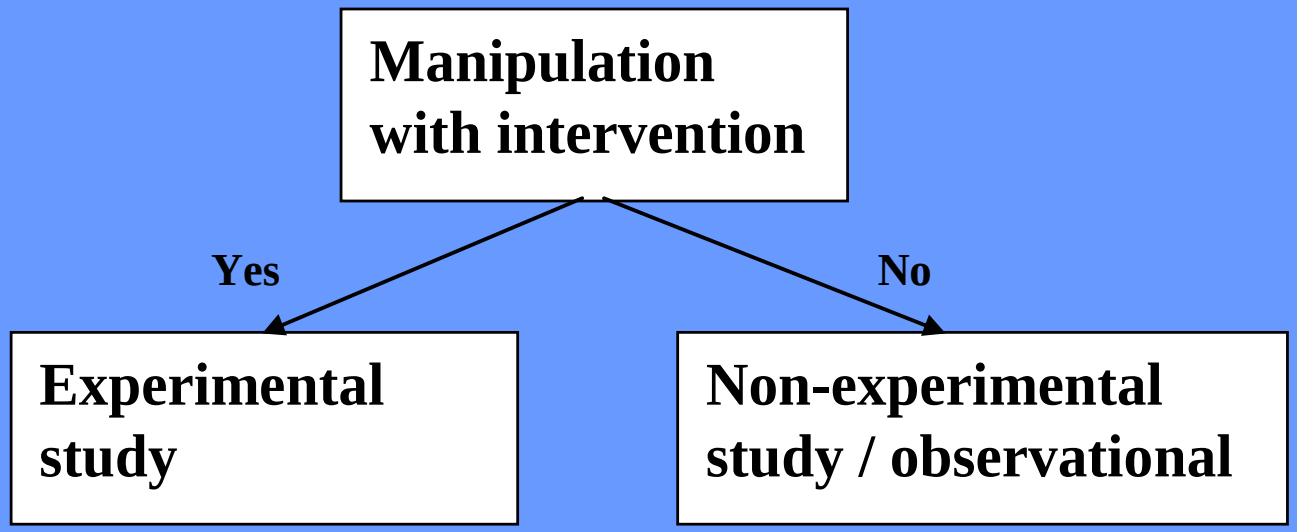
Clinical study designs (MESH terms):

1. Randomised Controlled Trial
2. Controlled Clinical Trial
3. Cohort Study
4. Case-Control Study
5. Cross-Sectional Survey
6. Case study/ case series



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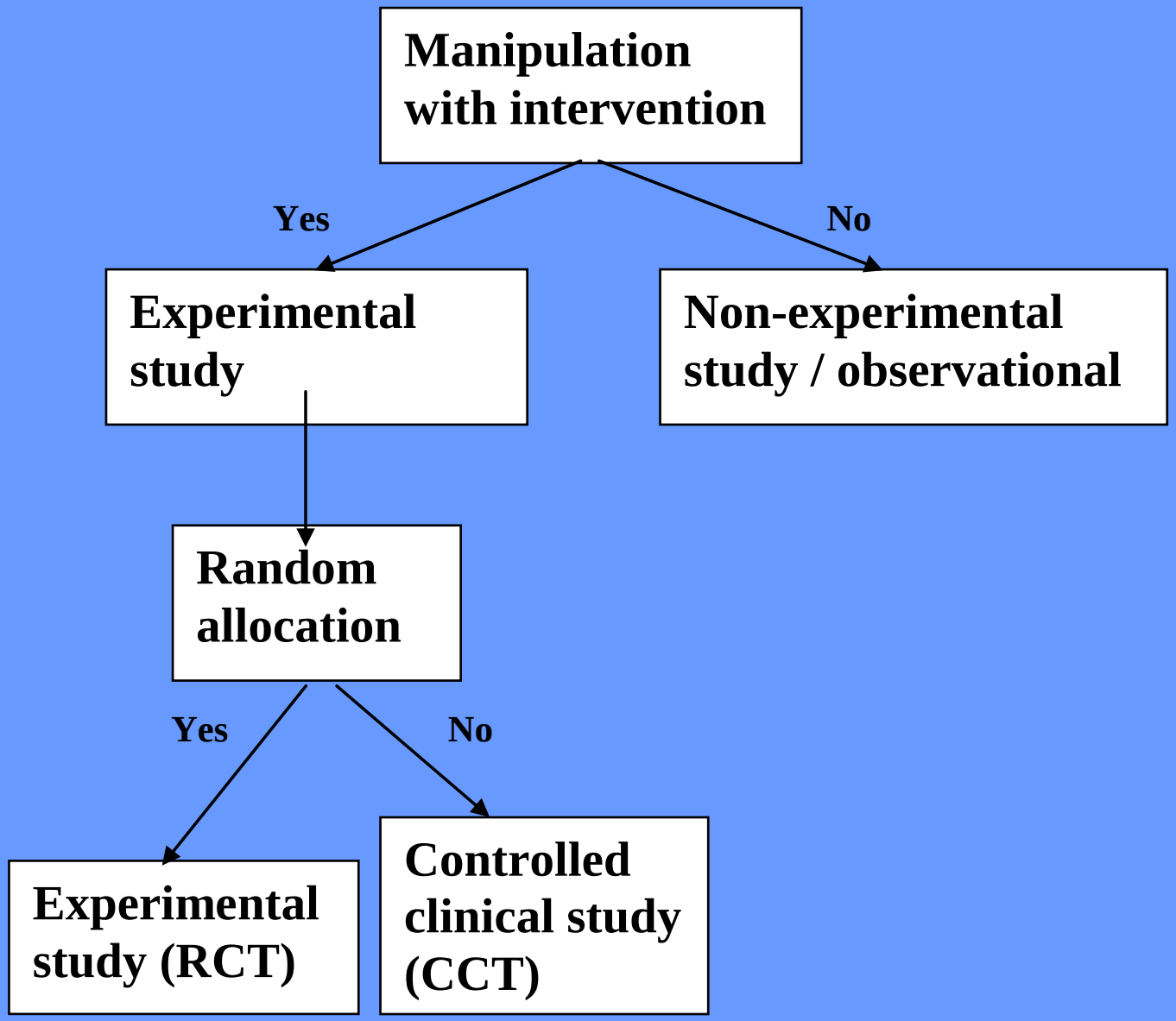

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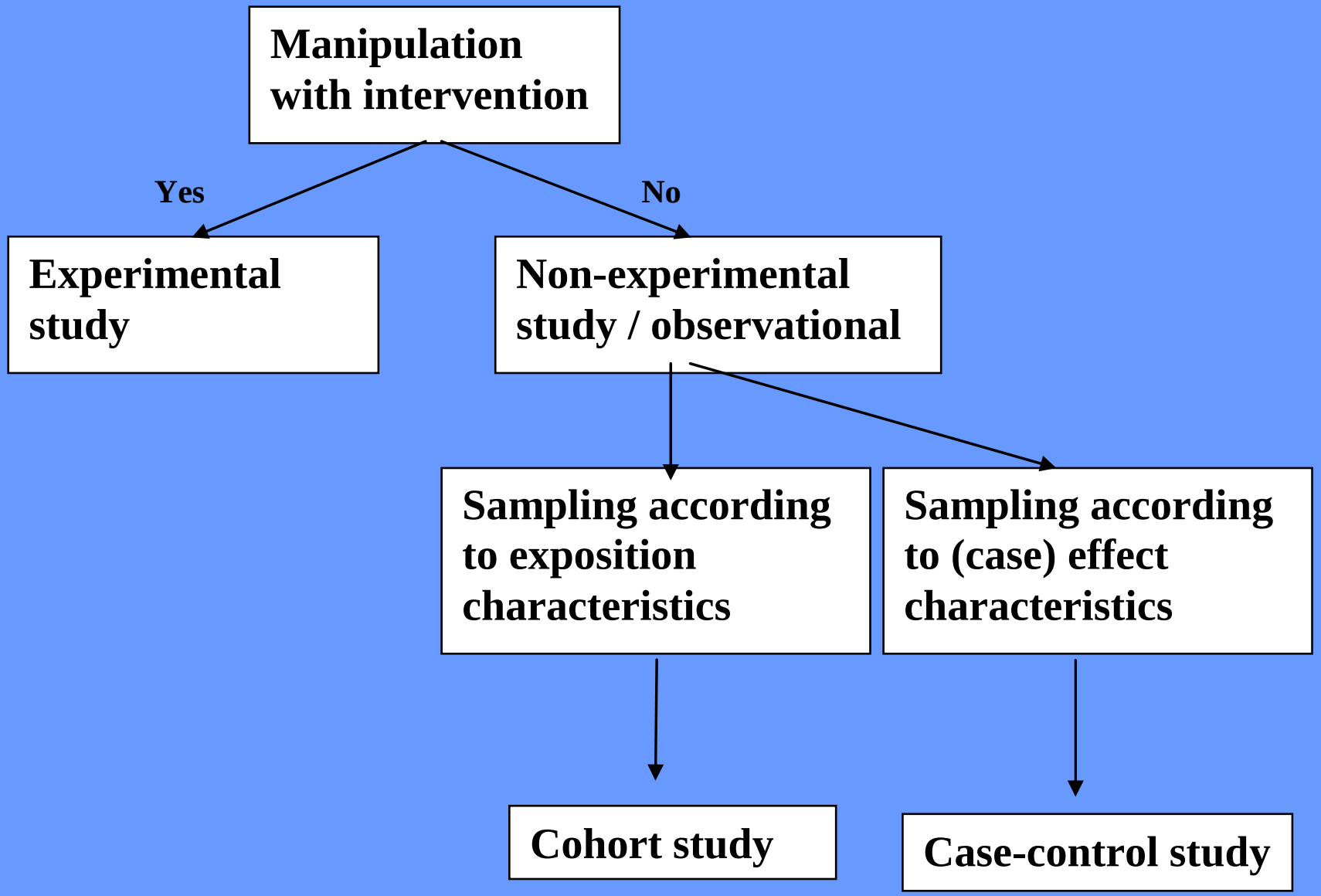

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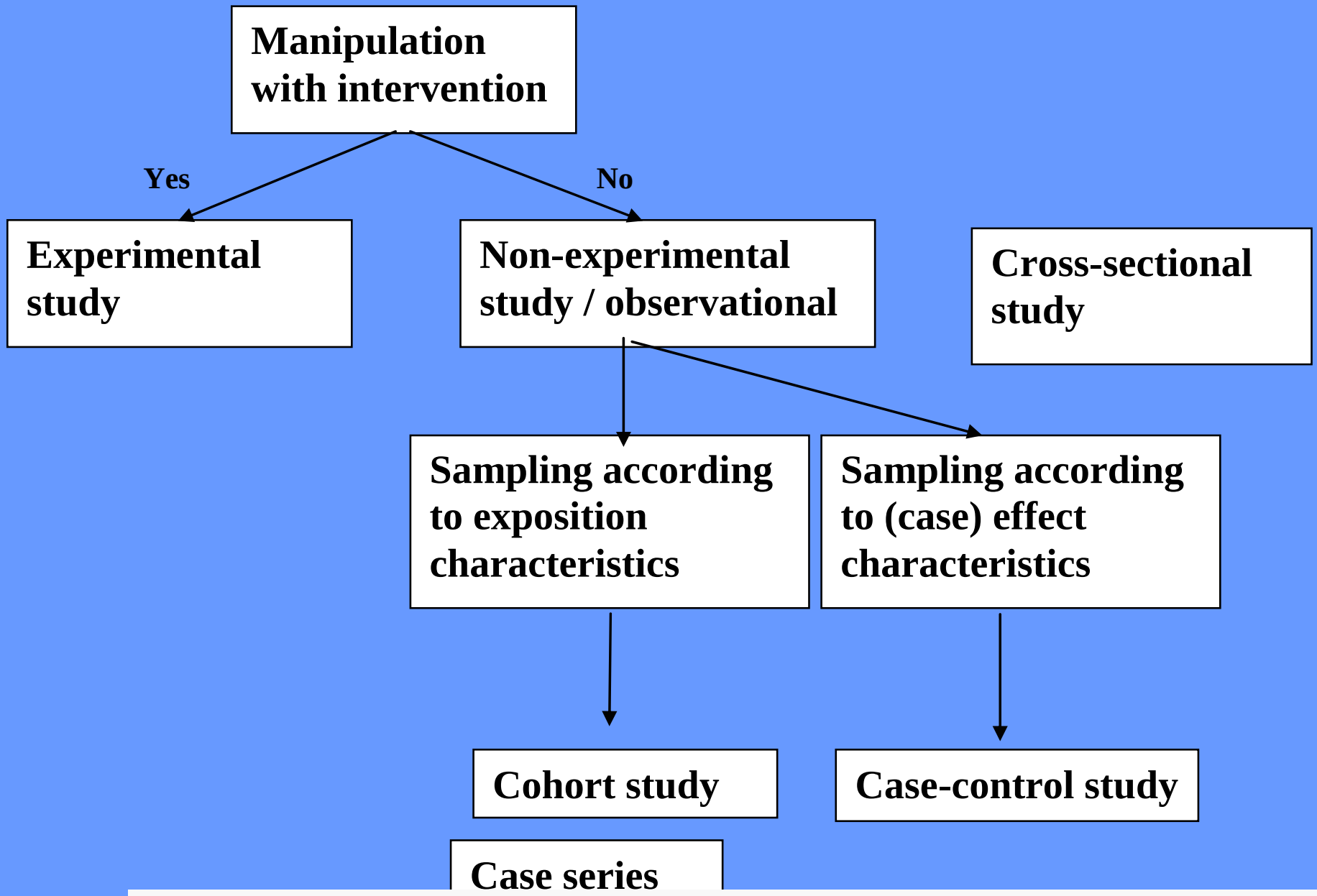

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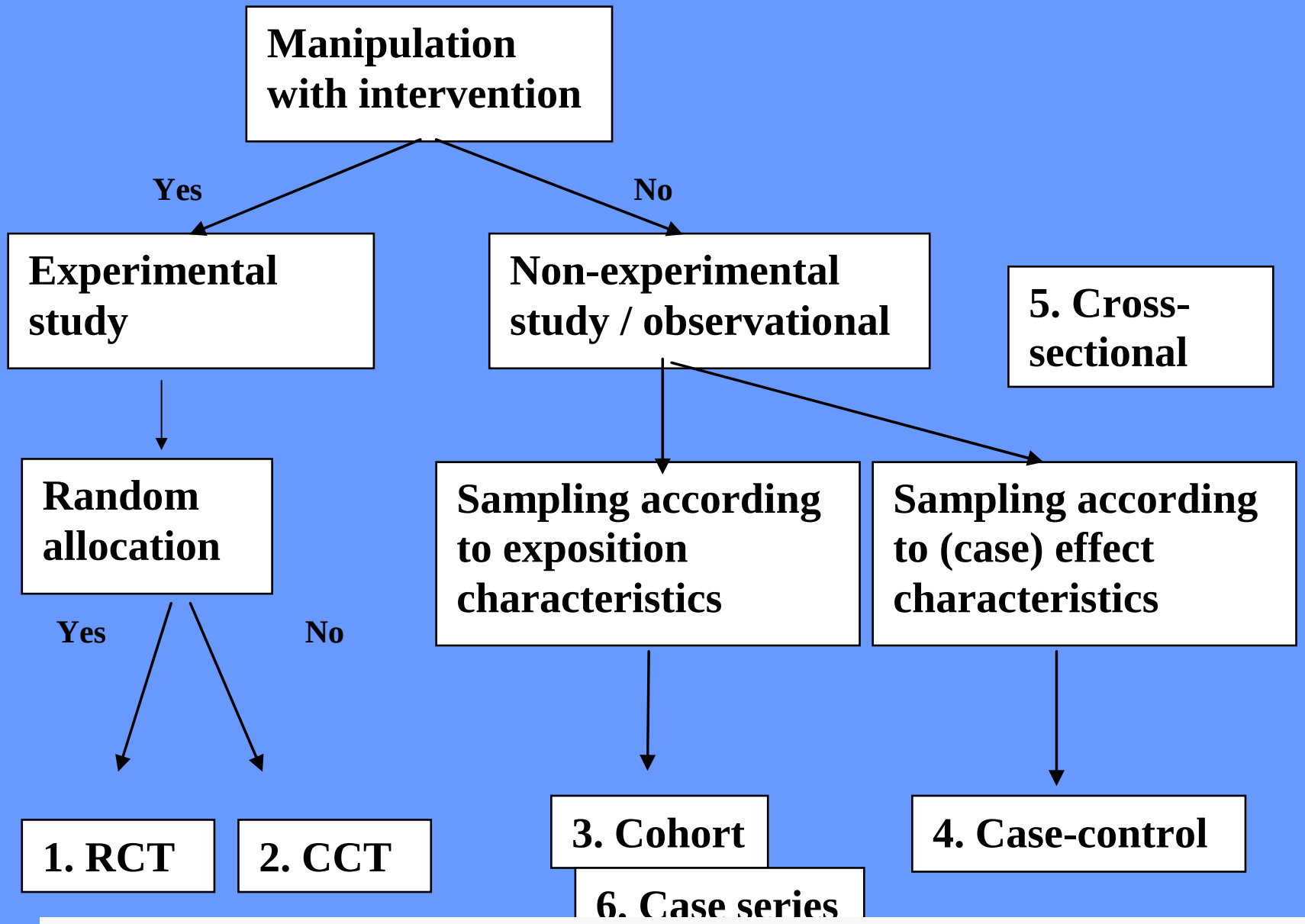


1. Randomised Controlled Trial, 2. Controlled Clinical Trial, 3. Cohort Study, 4. Case-Control Study, 5. Cross-Sectional Survey, 6. Case study/ case series

Clinical problems: - Examples

What is the value of RFA /Periotest /Periotest 2?
Which implant design / surgical technique /maintenance regime / education strategy is the best (or the most damaging)?
How does the implant “Fantisco” perform in the upper jaw?
How many patients are suitable for implant prosthetics?
How does implant protheses impact on the patient’s daily life?
How many patients have experienced fractured screws / implants?

Examples of Clinical problems

A question of.	
Diagnosis	**What is the value of RFA /Periotest /Periotest 2?**
	Which implant design / surgical technique /maintenance regime / education strategy is the best (or the most damaging)?

Examples of Clinical problems

Diagnosis	**What is the value of RFA /Periotest /Periotest 2?**
Therapy	**Which implant design / surgical technique /maintenance regime / education strategy is the best (or the most damaging)?**
	How does the implant “Fantisco” perform in the upper jaw?

Examples of Clinical problems

Diagnosis	**What is the value of RFA /Periotest /Periotest 2?**
Therapy	**Which implant design / surgical technique /maintenance regime / education strategy is the best (or the most damaging)?**
Prognosis	**How does the implant “Fantisco” perform in the upper jaw?**
	How many patients are suitable for implant prosthetics?

Examples of Clinical problems

Diagnosis	**What is the value of RFA /Periotest /Periotest 2?**
Therapy	**Which implant design / surgical technique /maintenance regime / education strategy is the best (or the most damaging)?**
Prognosis	**How does the implant “Fantisco” perform in the upper jaw?**
Screening	**How many patients are suitable for implant prosthetics?**
	How does implant prostheses impact on the patient’s daily life?

Examples of Clinical problems

Diagnosis	**What is the value of RFA /Periotest /Periotest 2?**
Therapy	**Which implant design / surgical technique /maintenance regime / education strategy is the best (or the most damaging)?**
Prognosis	**How does the implant “Fantisco” perform in the upper jaw?**
Screening	**How many patients are suitable for implant prosthetics?**
Views/beliefs perceptions	**How does implant prostheses impact on the patient’s daily life?**
	How many patients have experienced fractured screws / implants?

Examples of Clinical problems

Diagnosis	**What is the value of RFA /Periotest /Periotest 2?**
Therapy	**Which implant design / surgical technique /maintenance regime / education strategy is the best (or the most damaging)?**
Prognosis	**How does the implant “Fantisco” perform in the upper jaw?**
Screening	**How many patients are suitable for implant prosthetics?**
Views/beliefs perceptions	**How does implant protheses impact on the patient’s daily life?**
Prevalence/ hypothesis generation	**How many patients have experienced fractured screws / implants?**

Clinical problem & Appropriate Study Design

	Qualitative	Cross-Sectional	Case Control	Cohort	RCT
Diagnosis				☆	☆☆
Therapy				☆	☆☆
Prognosis				☆☆☆	
Screening			☆	☆	☆☆
Views/beliefs perceptions	☆☆☆				
Prevalence/ hypothesis generation	☆☆☆	☆☆☆			

Scientific studies can be graded according to the theoretical possibility of an incorrect conclusion.

This is reflected by the design of the study.

…we will never know exact answers in science….

Assumption of internal and external validity

- Internal validity: extent to which systematic error (bias) is minimised in clinical trials

Internal validity - systematic bias, e.g.

- Selection bias: biased allocation to comparison groups
- Performance bias: unequal provision of care apart from treatment under evaluation
- Detection bias: biased assessment of outcome
- Attrition bias: biased occurrence and handling of deviations from protocol and loss to follow up

Assumption of internal and external validity

Internal validity: extent to which systematic error (bias) is minimised in clinical trials

External validity: extent to which results of trials provide a correct basis for generalisation to other circumstances

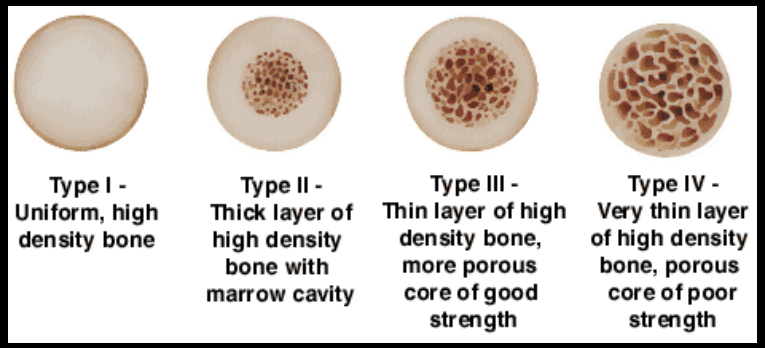
External validity, focus on e.g.

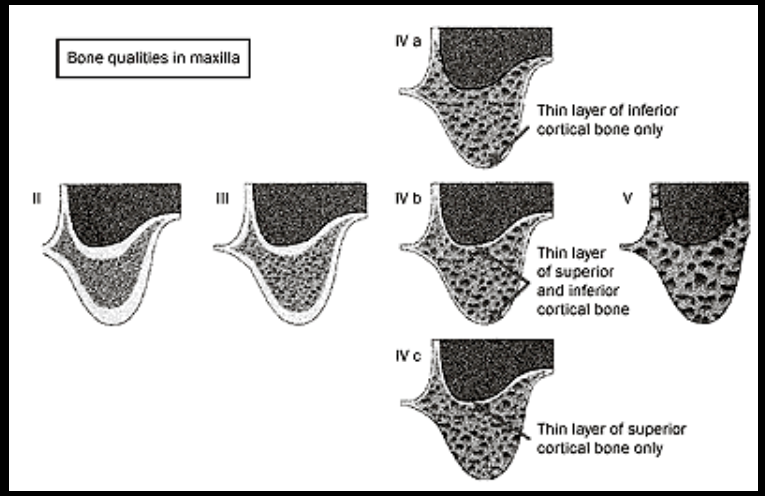
- Patients: age, gender, severity of disease/situation and risk factors, co-morbidity
- Treatment regimens: type of treatment within a class of treatments, concomitant treatments
- Settings: level of care (primary to tertiary) and experience and specialisation of care provider
- Modalities of outcomes: type or definition of outcomes and duration of follow up

Study questions

Diagnostic tests

- Does the use of RFA or the Periotest have any merits?
- What is the validity of the Zarb and Lekholm bone quality classification?





Diagnostic tests, Differential diagnosis

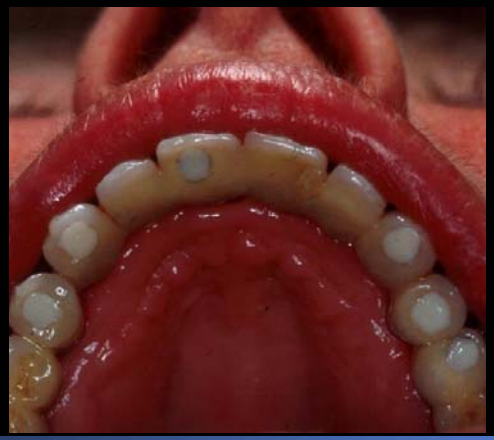
	Qualitative	Cross-Sectional	Case Control	Cohort	RCT
Diagnosis				☆	☆☆
Therapy				☆	☆☆
Prognosis				☆☆☆	
Screening			☆	☆	☆☆
Views/beliefs perceptions	☆☆☆				
Prevalence/ hypothesis generation	☆☆☆	☆☆☆			

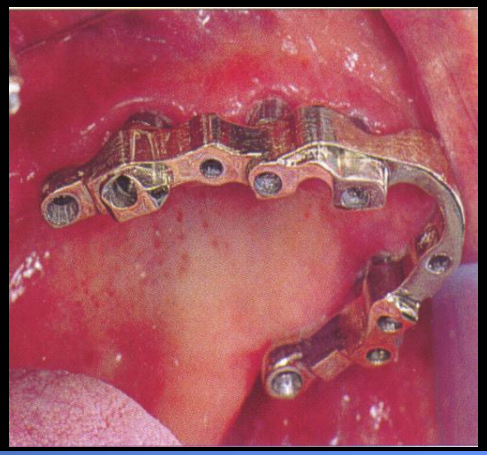
- Clearly identified comparison groups, at least one of which is free of the target disorder
- Either an objective diagnostic standard/contemporary clinical diagnostic standard with reproducible criteria for any objectively interpreted component
- Interpretation of the test without knowledge of the diagnostic standard result
- Interpretation of the diagnostic standard without knowledge of the test result
- A statistical analysis consistent with study design

Therapy /Prevention /Education

- Which implant design / surgical technique /maintenance regime / education strategy provides the *best result**?

* *Clinical, patient centred, surrogate or economic*





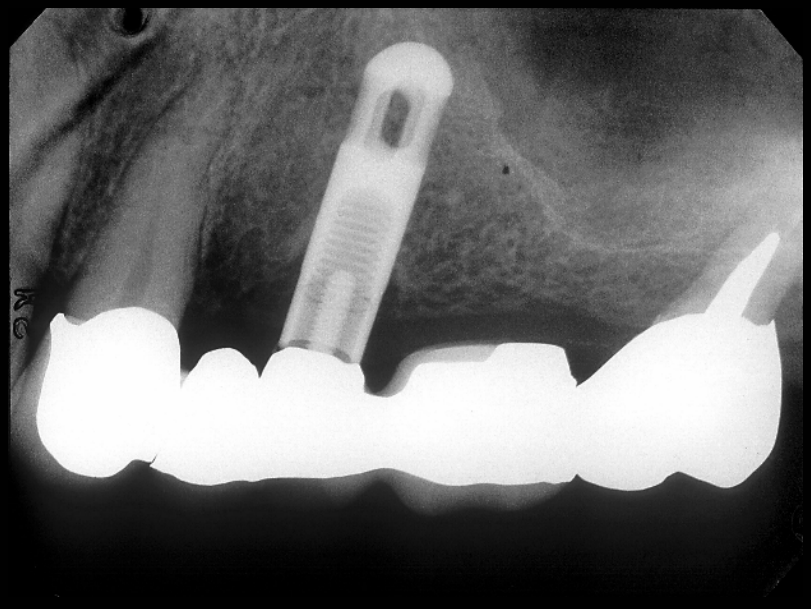
Therapy / Prevention / Education

	Qualitative	Cross-Sectional	Case Control	Cohort	RCT
Diagnosis				☆	☆☆
Therapy				☆	☆☆
Prognosis				☆☆☆	
Screening			☆	☆	☆☆
Views/beliefs perceptions	☆☆☆				
Prevalence/ hypothesis generation	☆☆☆	☆☆☆			

- Random allocation of the participants to the different interventions
- Outcome measures of known or probably clinical importance for at least 80 per cent of participants who entered the investigation
- A statistical analysis consistent with the study design

Prognosis

- How predictable is the performance of the implant “Fantisco” in the upper posterior jaw?



Prognosis

	Qualitative	Cross-Sectional	Case Control	Cohort	RCT
Diagnosis				☆	☆☆
Therapy				☆	☆☆
Prognosis				☆☆☆	
Screening			☆	☆	☆☆
Views/beliefs perceptions	☆☆☆				
Prevalence/ hypothesis generation	☆☆☆	☆☆☆			

- An inception cohort of persons, all initially free of the outcome of interest
- Follow-up of at least 80 per cent of patients until the occurrence of either a major study criteria or the end of the study
- A statistical analysis consistent with the study design.

Views /beliefs /perceptions

- How does implant prostheses impact on the patient's daily life?
- Why are colleagues hesitant to implement implant prosthetics in their practices?

Qualitative research

	Qualitative	Cross-Sectional	Case Control	Cohort	RCT
Diagnosis				☆	☆☆
Therapy				☆	☆☆
Prognosis				☆☆☆	
Screening			☆	☆	☆☆
Views/beliefs perceptions	☆☆☆				
Prevalence/ hypothesis generation	☆☆☆	☆☆☆			

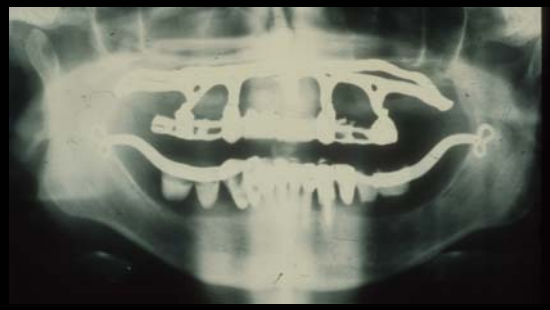
- Aim to make sense of, or interpret, phenomena in terms of the meanings people bring to them
- May define preliminary questions which can then be addressed in quantitative studies
- Address a clinical problem through a clearly formulated question and using more than one research method (triangulation)
- Analysis of qualitative data can and should be done using explicit, systematic, and reproducible methods

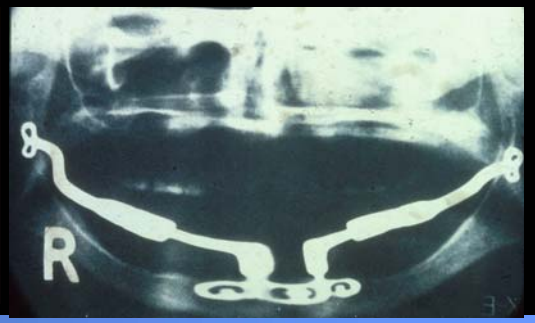
Implementation of a new implant concept and appropriate study design

	Qualitative research	Survey	Case Control	Cohort	RCT	Non-exper	Systematic review
Effectiveness Does it work?				☆	☆☆	☆	☆☆☆
Process of intervention delivery How does it work?	☆☆	☆				☆	☆☆☆
Salience Does it matter?	☆☆	☆☆					☆☆☆
Safety Will it do more good than harm?	☆		☆	☆	☆☆	☆	☆☆☆
Acceptability Will the patient accept the intervention?	☆☆	☆			☆	☆	☆☆☆
Cost effectiveness Is it worth paying for the intervention?					☆☆		☆☆☆
Appropriateness Is this the right intervention for this patient?	☆☆	☆☆					☆☆
Satisfaction with the intervention Are users, providers and other stakeholders satisfied?	☆☆	☆☆	☆	☆			☆

Can implants be harmful?

- How many patients have experienced fractured screws / implants?
- Does trace elements from implants cause adverse general effects?
- Has a certain batch of implants been contaminated during the production process?





Etiology - Harm - Causation

- Evidence levels: Randomised clinical trial > clinical trial > case -control > cross-sectional > single case
- Clearly identified comparison group for those at risk for, or having, the outcome of interest
- Observers of outcomes masked to exposures
- Observers of exposures masked to outcomes for case-control studies and individuals masked to exposure for all other study designs
- A statistical analysis consistent with the study design.

Study Designs

	Qualitative	Cross-Sectional	Case Control	Cohort	RCT
Diagnosis				☆	☆☆
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Screening			☆	☆	☆☆
Views/beliefs perceptions	☆☆☆				
Prevalence/ hypothesis generation	☆☆☆	☆☆☆			

Cross-Sectional Survey

<u>Advantages</u>

1. Cheap and simple
2. Ethically safe

<u>Disadvantages</u>

1. Establishes association at most, not causality
2. Recall bias susceptibility
3. Confounders may be unequally distributed
4. Group sizes may be unequal

	Qualitative	Cross-Sectional	Case Control	Cohort	RCT
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Views/beliefs perceptions	☆☆☆				
Prevalence/ hypothesis generation	☆☆☆	☆☆☆			

Case-Control Study

Advantages:

1. Quick and cheap
2. Only feasible method for very rare clinical situations or those with long lag between exposure and outcome
3. Fewer individuals needed than cross-sectional studies

Disadvantages:

1. Rely on recall or records to determine exposure status
2. Confounders
3. selection of control groups is difficult
4. Potential bias: recall, selection

	Qualitative	Cross-Sectional	Case Control	Cohort	RCT
Diagnosis				☆	☆☆
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Views/beliefs perceptions	☆☆☆				
Prevalence/ hypothesis generation	☆☆☆	☆☆☆			

Questions to ask:

- How were cases defined and selected?
- How were controls defined and selected?
- Does the study adequately control for demographic characteristics and important potential confounders in the design or analysis?
- Was measurement of exposure to the factor of interest (eg the new intervention) adequate and kept blinded to case/control status?
- Were all selected subjects included in the analysis?

	Qualitative	Cross-Sectional	Case Control	Cohort	RCT
Diagnosis				☆	☆☆
Therapy				☆	☆☆
Prognosis				☆☆☆	
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Views/beliefs perceptions	☆☆☆				
Prevalence/ hypothesis generation	☆☆☆	☆☆☆			

Characteristics of a poor case-control study:

Fail to:

- clearly define comparison groups
- and/or fail to measure exposures and outcomes in the same (preferably blinded), objective way in both cases and controls
- and/or fail to identify or appropriately control known confounders.

	Qualitative	Cross-Sectional	Case Control	Cohort	RCT
Diagnosis				☆	☆☆
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Views/beliefs perceptions	☆☆☆				
Prevalence/ hypothesis generation	☆☆☆	☆☆☆			

Cohort Study

Advantages:

1. Ethically safe
2. individuals can be matched
3. Can establish timing and directionality of events
4. Eligibility criteria and outcome assessments can be standardised
5. Administratively easier and cheaper than RCT

Disadvantages:

1. Controls may be difficult to identify
2. Exposure may be linked to a hidden confounder
3. Blinding is difficult
4. Randomisation not present
5. For rare disease, large sample sizes or long follow-up necessary

	Qualitative	Cross-Sectional	Case Control	Cohort	RCT
Diagnosis				☆	☆☆
Therapy				☆	☆☆
Prognosis				☆☆☆	
Screening			☆	☆	☆☆
Views/beliefs perceptions	☆☆☆				
Prevalence/ hypothesis generation	☆☆☆	☆☆☆			

Questions to ask:

- How were subjects selected for the cohort?
- How were subjects selected for the comparison or control group?
- Does the study adequately control for demographic characteristics, clinical features and other potential confounding variables in the design or analysis?
- Was the measurement of outcomes unbiased (ie blinded and comparable across groups)?
- Was follow-up long enough for outcomes to occur?
- Was follow-up complete and were there exclusions from the analysis?

Characteristics of a poor cohort study:

	Qualitative	Cross-Sectional	Case Control	Cohort	RCT
Diagnosis				☆	☆☆
Therapy				☆	☆☆
Prognosis				☆☆☆	
Screening			☆	☆	☆☆
Views/beliefs perceptions	☆☆☆				
Prevalence/ hypothesis generation	☆☆☆	☆☆☆			

Fail to :

- clearly define comparison groups and/or
- measure exposures and outcomes in the same (preferably blinded), objective way in both exposed and non-exposed individuals and/or
- identify or appropriately control known confounders and/or
- carry out a sufficiently long and complete follow-up of patients.

	Qualitative	Cross-Sectional	Case Control	Cohort	RCT
Diagnosis				☆	☆☆
Therapy				☆	☆☆
Prognosis				☆☆☆	
Screening			☆	☆	☆☆
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Prevalence/ hypothesis generation	☆☆☆	☆☆☆			

Randomised Controlled Trial - RCT

Advantages

1. Unbiased distribution of confounders
2. Blinding more likely
3. Randomisation facilitates statistical analysis

Disadvantages

1. Size, time and money - Expensive!
2. Volunteer bias
3. Ethically problematic at times

	Qualitative	Cross-Sectional	Case Control	Cohort	RCT
Diagnosis				☆	☆☆
Therapy				☆	☆☆
Prognosis				☆☆☆	
Screening			☆	☆	☆☆
Views/beliefs perceptions	☆☆☆				
Prevalence/ hypothesis generation	☆☆☆	☆☆☆			

Questions to ask:

- Was the study double blinded?
- Was allocation to treatment groups concealed from those responsible for recruiting the subjects?
- Were all randomised participants included in the analysis?

CONSORT STATEMENT

strength in science, sound ethics

Improving the Quality of Reporting of Randomized Controlled Trials

Colin Begg, PhD; Mildred Cho, PhD; Susan Eastwood, ELS(D); Richard Horton, MB; David Moher, MSc; Ingram Olkin, PhD; Roy Pitkin, MD; Drummond Rennie, MD; Kenneth F. Schulz, PhD; David Simel, MD; Donna F. Stroup, PhD

TRANSLATIONS AND PDF FORMATS

View or Download the ADOBE PDF Version of the Entire Document (51 K)

- The Statement Text Section (13K)
- The Statement Checklist (8 K)
- The Statement Flowchart (6 K)
- The Statement Comments Section(10 K)
- The Statement References List (14 K)

Visit the Adobe web site to download the free Acrobat Reader

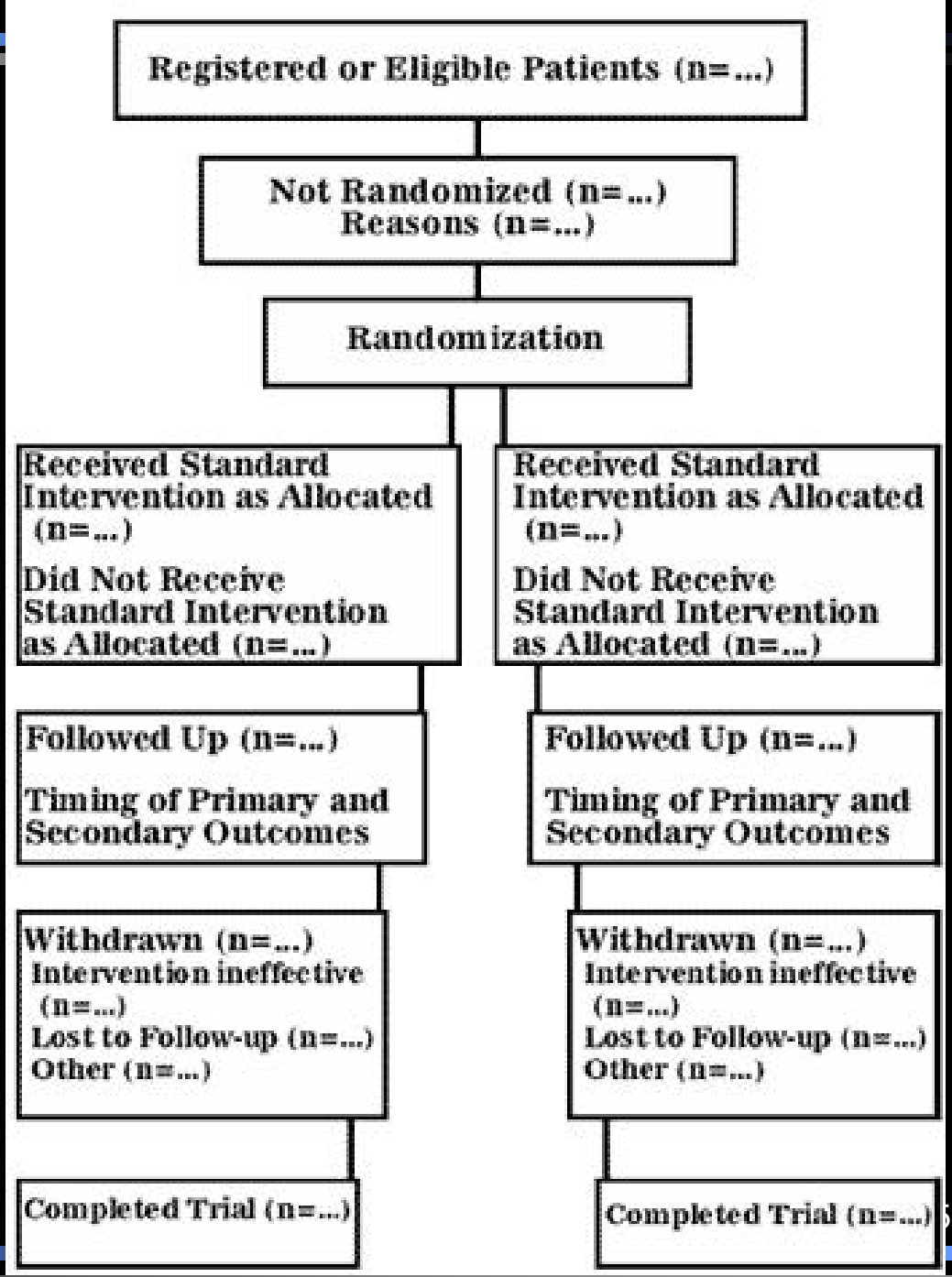
Foreign Language Translations of CONSORT:

- FRENCH
- GERMAN
- SPANISH
- JAPANESE (This site requires a browser configured for Japanese text)
- For hard copy versions of the CONSORT Statement in Dutch please contact us.

INTRODUCTION

Reporting:

CONSORT



The scientific merits of any clinical study is improved when it is:

- Large
- Multicentered
- Multidimensional

SO:

START COOPERATING WITH OTHER CENTRES WHEN PLANNING YOUR NEXT CLINICAL TRIAL!