NTNU – Trondheim
Norwegian University of
Science and Technology

Study design in palliative care

Morten Thronæs, MD, PhD

Slides: Tora Skeidsvoll Solheim and Katrin Sigurdardottir

The goal of this lecture

- Basic knowledge of different study designs
  - some examples
- Touch upon some concepts
  - internal and external validity, bias, confounders

- Get some ideas and start the process- My research project
  - Possibilities and pitfalls

The goal of this lecture

- Basic knowledge of different study designs
  - some examples
- Touch upon some concepts
  - internal and external validity, bias, confounders

- Get some ideas and start the process- My research project
  - Possibilities and pitfalls

Your experiences in PC research?

Hierarchy of evidence

”Evidence-based medicine is the conscientious and explicit use of current best evidence in making decisions about the care of individual patients«

Sackett DL et al. (1996).

Evidence based medicine: what it is and what it isn't.

BMJ **312** (7023): 71–2

How to do excellent studies in palliative care?

- The most important prerequisite?
  - Ask a good research question!
    - This necessitates a good hypothesis and knowledge on existing evidence (and not to mention good ethics)

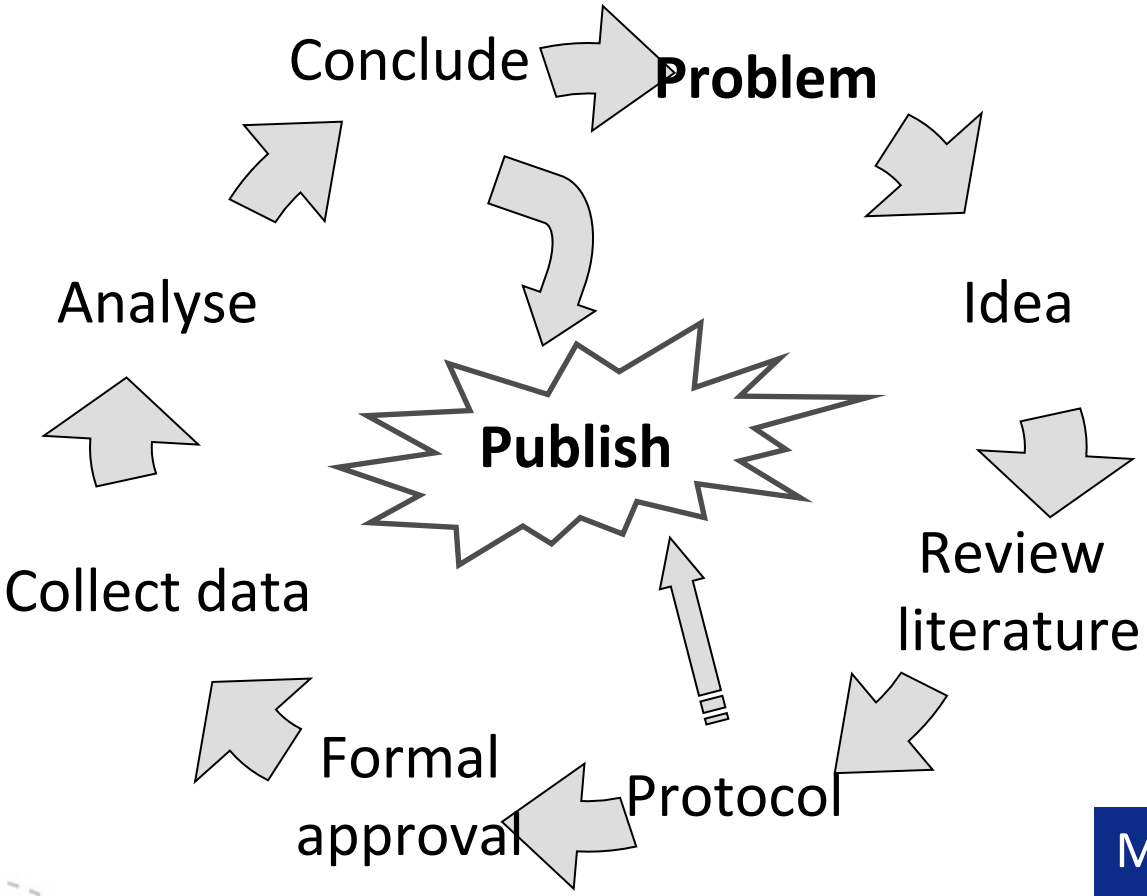
- The best study design?
  - Depends on the question asked..

Different study design

How many have particular symptom/problem?	Prevalence / incidence	**Cross-sectional study**
How can we determine if someone has ...?	Measuring instruments, tests and diagnostics	**Cross-sectional study with gold standard**
Why does someone get....?	Aetiology (causal relationships)	**Cohort study** **Case-control study** **Qualitative methods**
How does it go/develop ...?	Prognosis	**Cohort study**
How does it feel?	Experiences and attitude	**Qualitative methods**
What can we do ...? What is the effect of ...?	Impact of prevention, treatment	**Randomised controlled trials**

From Katrin R. Sigurdardottir

Circle of science



Motto: Make good a plan and stick to it!

From Ole Solheim 2009

You have a good RQ

- but are there practical limitations?
- example- NP

Control group? Blinding? Prospective? Patients (N)?

Randomization? Time? Funding? Resources?

Valid outcome parameters? Ethics?

Challenges in design and interpretation of data

- Need to know if you can trust what you read?

- Some challenges are the same for several study designs
  - Always consider:
    - Validity
    - Bias
    - Confounder
    - Outcomes
    - Statistics
    - Correlation/causation

Challenges in design and interpretation of data

- Need to know if you can trust what you read?

- Some challenges are the same for several study designs
  - Always consider:
    - **Validity**
    - **Bias**
    - **Confounder**
    - **Outcomes**
    - Statistics
    - Correlation/causation

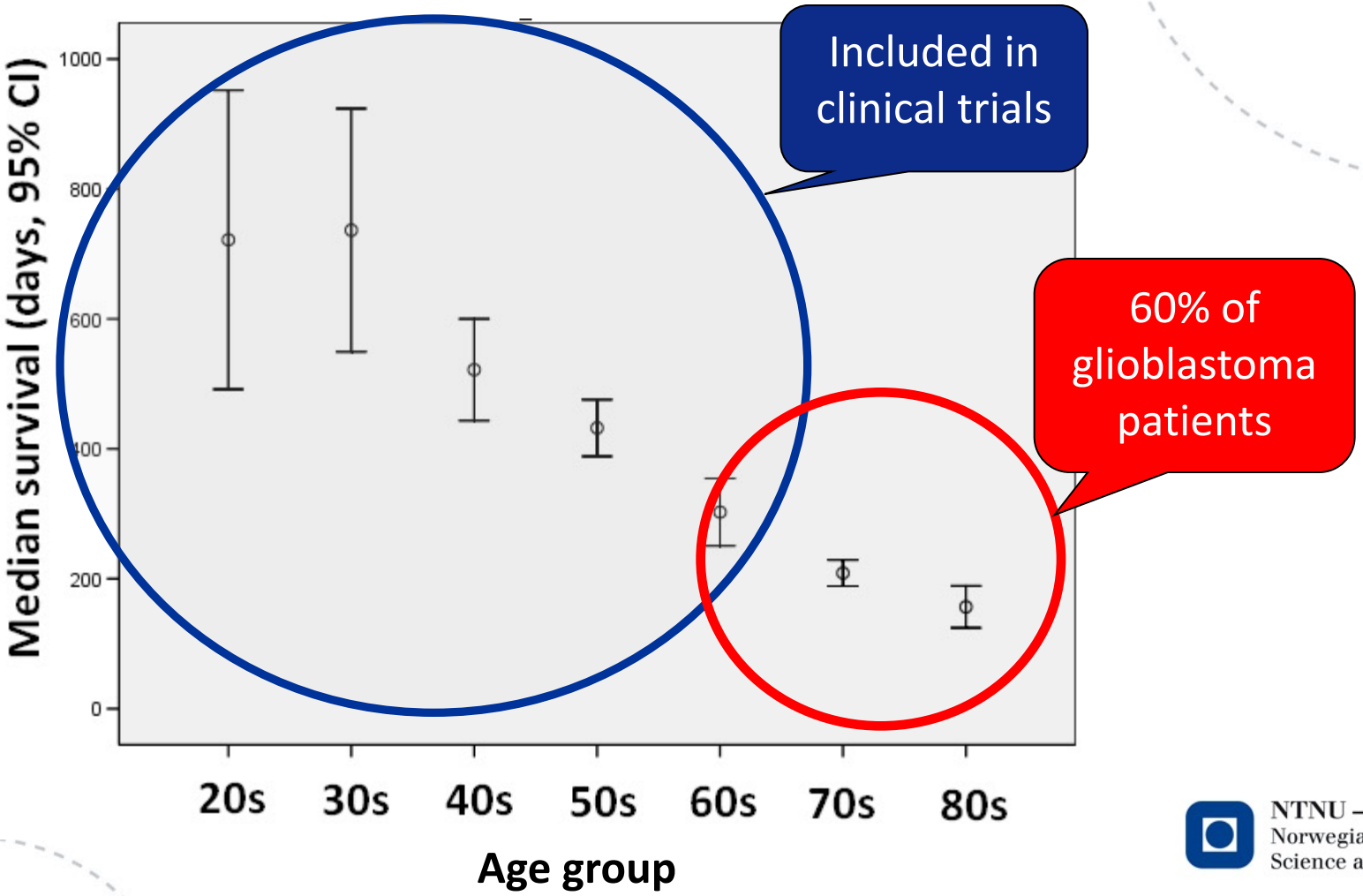
Challenge 1: Validity - is this true?

- External Validity:
  - Can I apply these conclusions to my patients?
  - Does it work in other settings than the studied?
- Internal Validity:
  - Can I rely on the conclusion of this study?
  - Was the research done right?

    (Results will not be due to chance, bias or confounding factors)

Challenges example:

Glioblastoma : age vs prognosis



NTNU – Trondheim
Norwegian University of Science and Technology

Source: Norwegian Cancer Registry (1998 – 2009)

Challenge 2: Bias

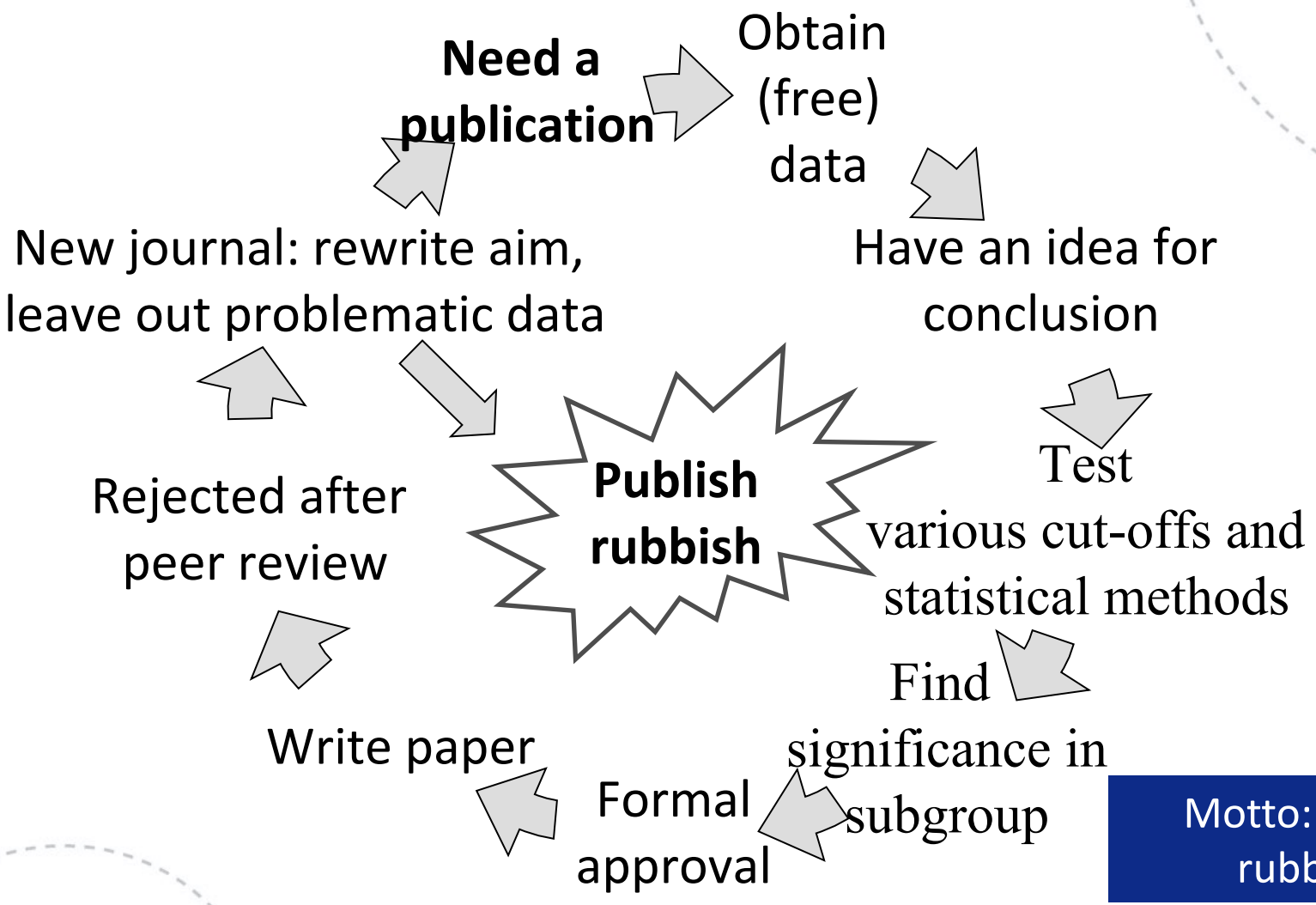
- Systematic error that shifts or influences results
- Can occur at any phase of research, including study design or data collection, as well as in the process of data analysis and publication

Measurement bias

Some types of bias

- Selection bias
- Recall bias
- Publication bias
  - Sackett; Bias in analytic research: 1979
  - J. Lambert; Statistics in Brief; How to assess Bias in Clinical Studies

Circle of bias (How not to do it)



Motto: rubbish in, rubbish out!

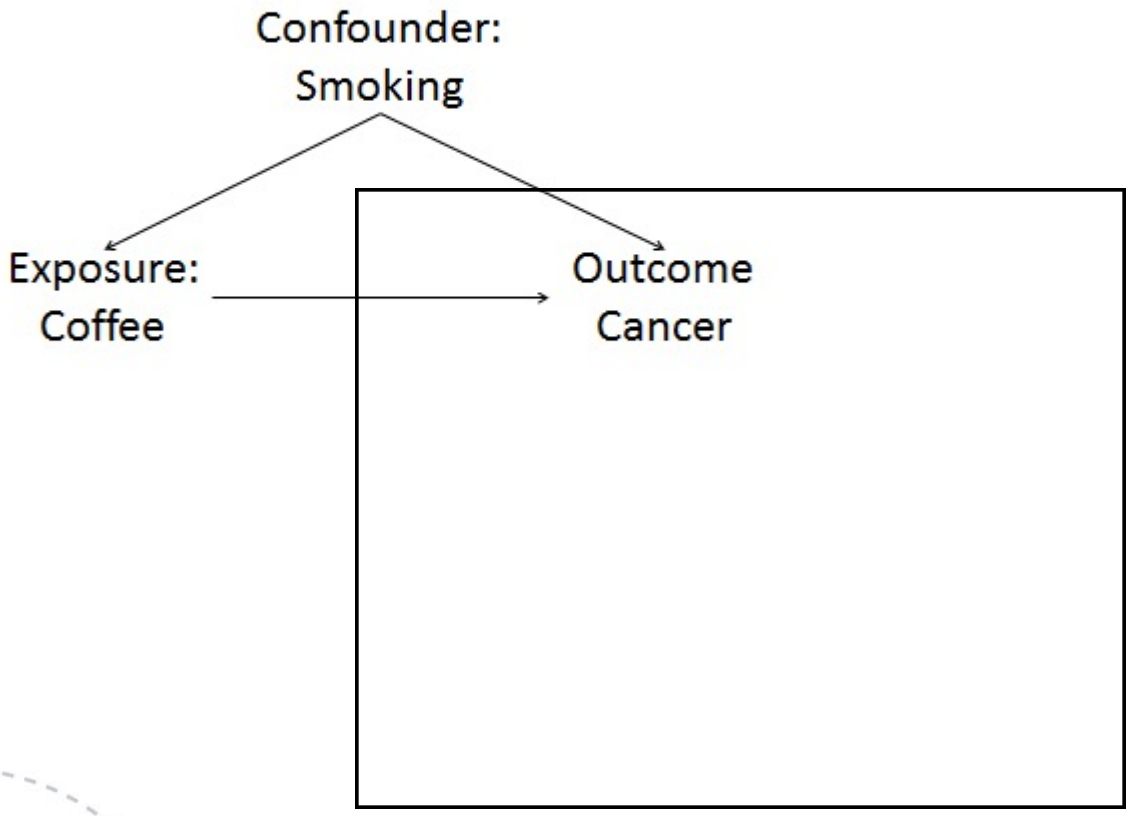
From Ole Solheim 2009

How to avoid the Circle of bias?

Publish protocols:

- Condition for publication of experimental trials in most medical journals (International Committee of Medical Journal Editors)
- To avoid post hoc aims, new outcomes and statistical fishing trips
- Review of protocols: In 40-62% of studies, at least one primary outcome measure was changed, introduced, or omitted

Challenge 3: Confounders



Confounders

- It might be your self/ colleagues/ unit

Challenge 4: Outcomes

- Outcome variables should answer the study question
  - Sensitive enough
  - Well defined
  - Unbiased
  - Measurable in all participants
  - Preferably stable and “validated”

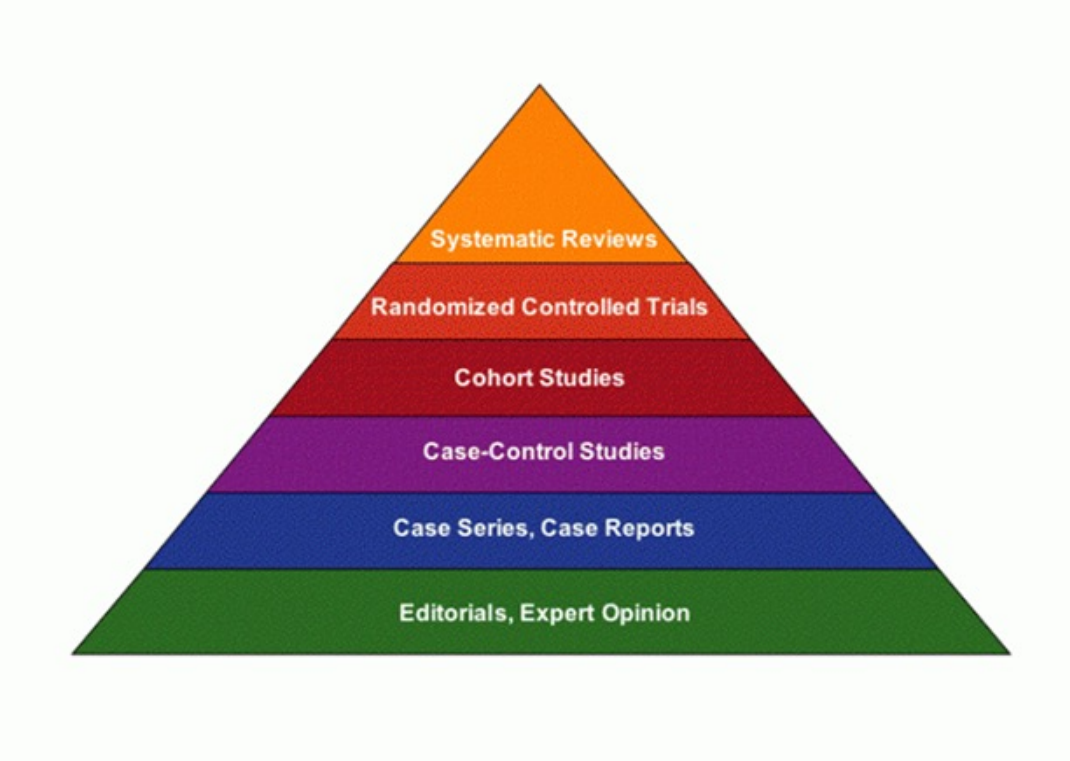
- Which outcomes should I use?
- Pain; Validated vs non-validated questionnaires
  - Example; BTP and NP
  - Definitions, assessment tools
  - Possibility to compare

Different study design

How many have particular symptom/problem?	Prevalence / incidence	**Cross-sectional study**
How can we determine if someone has ...?	Measuring instruments, tests and diagnostics	**Cross-sectional study with gold standard**
Why does someone get....?	Aetiology (causal relationships)	**Cohort study** **Case-control study** **Qualitative methods**
How does it go/develop ...?	Prognosis	**Cohort study**
How does it feel?	Experiences and attitude	**Qualitative methods**
What can we do ...? What is the effect of ...?	Impact of prevention, treatment	**Randomised controlled trials**

From Katrin R. Sigurdardottir

Different study design



Expert opinions and case-reports

- Don’t trust it –think for your self
  - It might be true though…
- Starting points for good research questions?
- Expert opinions and palliative care
  - Ex: WHO pain ladder, Steroids, Ketamine

Example PC: case report study

- Tolerability of Dexmedetomidine for in-patients at an APCU
  - Indications, doses, days on dexmedetomidine, change in opioid dose, tolerability, (effect)

Types of observational studies

Observational studies

- Cohort studies
- Case-control studies
- Cross sectional studies

Characteristics of observational studies

- Study individuals in their natural environment
- Lower cost, low risk
  - Cross sectional/case control also quick..
- Often high external validity
- Cohort studies may answer the question: Does it work (in regular practice)?
- Cross sectional studies can show the impact of a risk factor or prevalence of a symptom

Characteristics of observational studies

- But:
  - No control over study units/Individuals
    - Recall bias? Selection bias? Valid control groups?
  - Possibility of confounders

Cross-sectional study

- A **cross-sectional study** is an observational study in which exposure and disease are determined at the same point in time in a given population

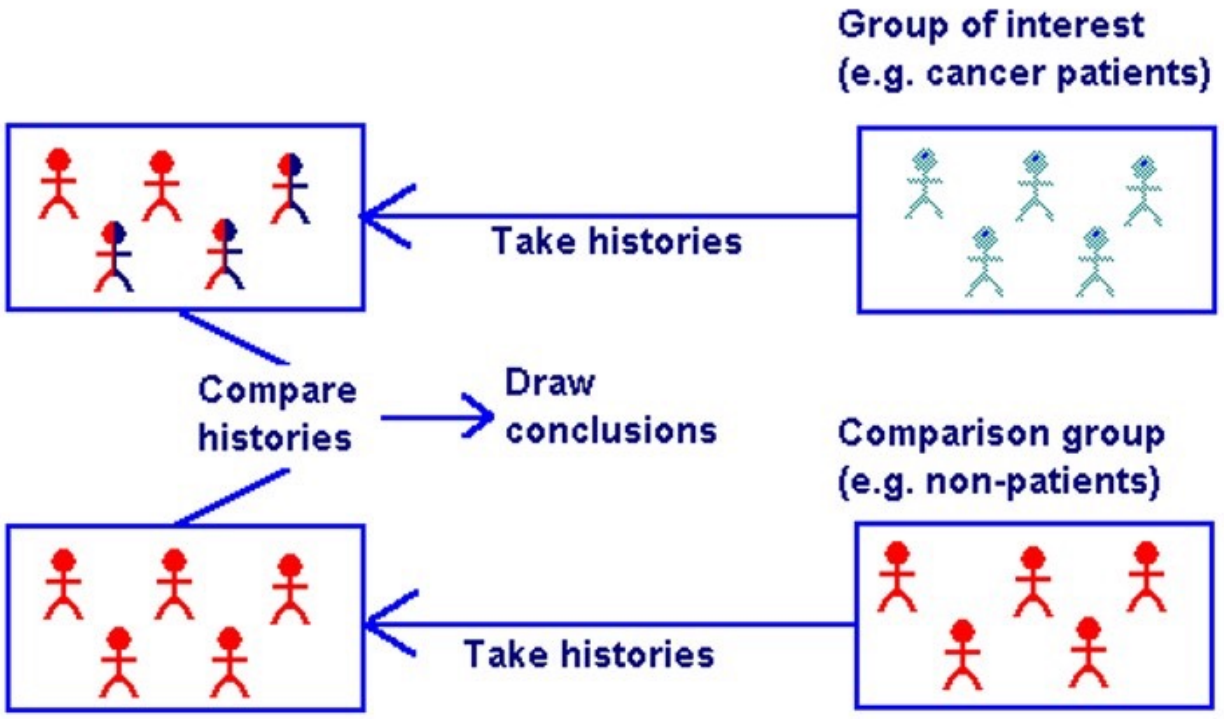
- The temporal relationship between exposure and disease cannot be determined – it only raises questions on hypothesis..

Example PC: Cross-sectional study

- Prevalence of pain and BTP in 2008 and 2014

- All cancer pts at the hospital
- Filled in a crf and a questionnaire
- Pain Y/N
- Pain intensity, BTP

Case-control study



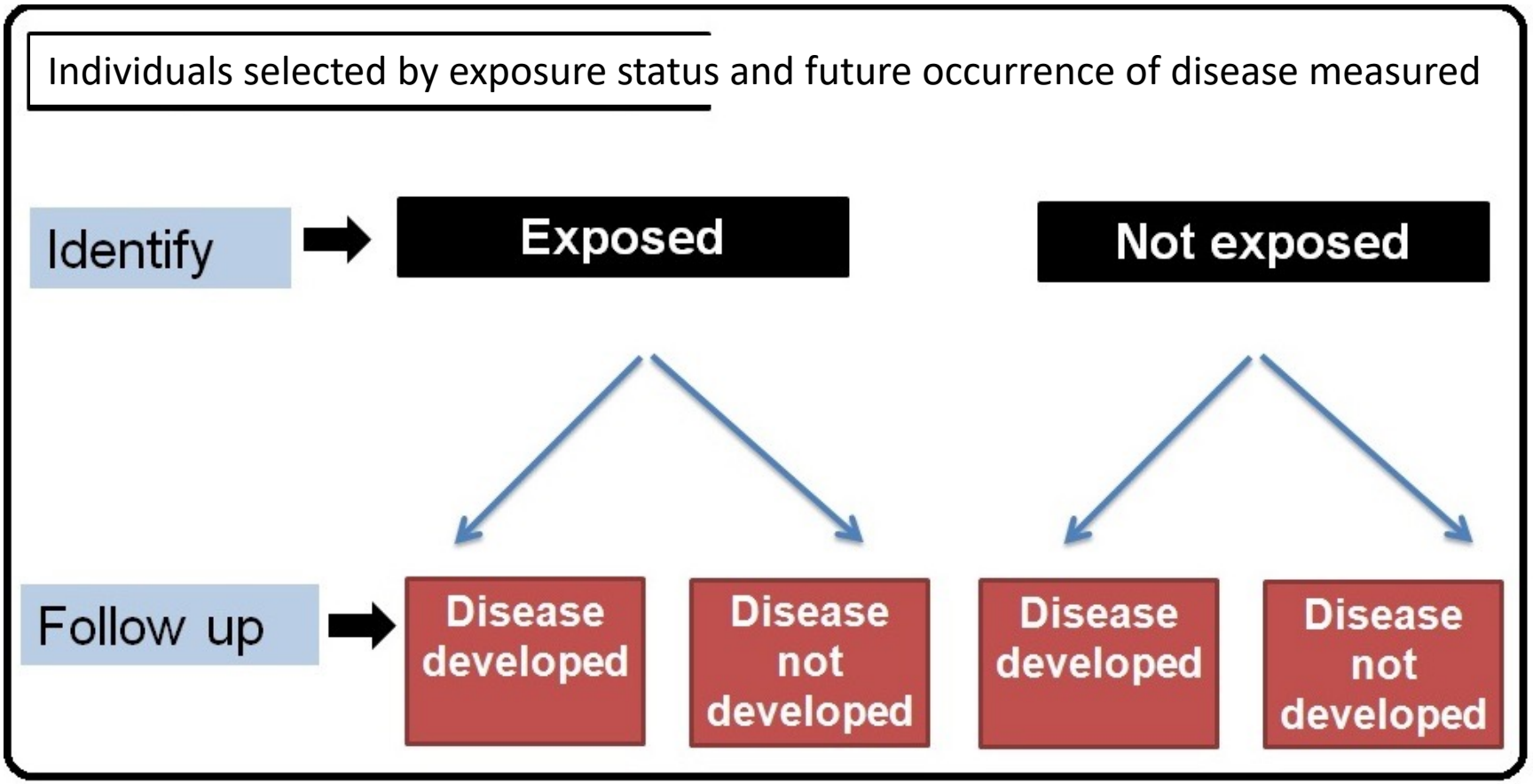
- Diseased and non-diseased individuals are selected first
- Then past exposure status is retrieved, retrospectively

- Good for rare diseases

Case control example

- Lung cancer- not lung cancer
- Exposure during life

Cohort studies



Cohort studies

- Time consuming and expensive
- Loss to follow-up & unavailability of data
- Potential confounding factors
- Inefficient for rare diseases

- Can look at multiple exposures
- Demonstrate direction of causality
- Can measure incidence and prevalence

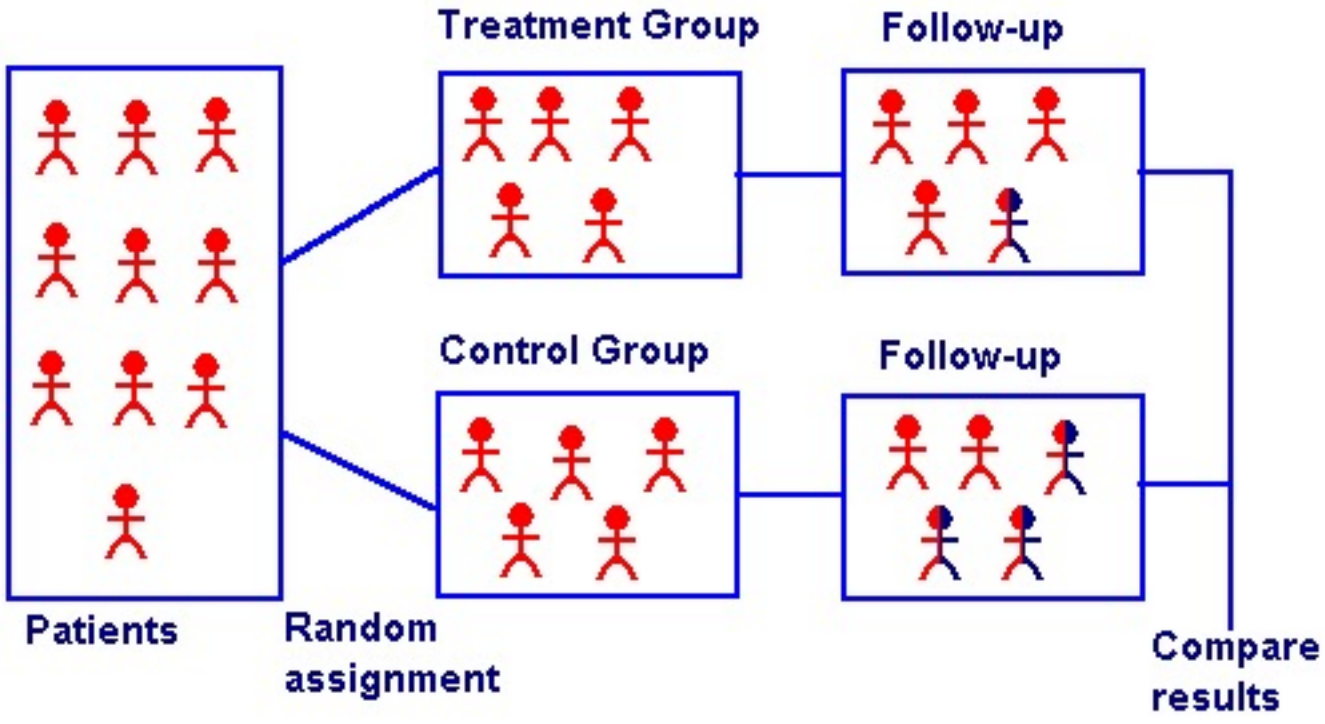
Other types of observational studies

Experimental studies

- Randomised Controlled trials:
  - Parallel design
  - Cross over design
  - Cluster randomised design

- Non-Randomised Controlled trials/Quasi-experimental studies

Randomised Controlled Trial



Randomised control trial

- Get an assessment of the relative effects of interventions
- Reduces risk of bias
  - Minimizing differences in patient characteristics and confounders
  - But be aware: quality!
    - Blinding
    - Allocation bias
    - Funding bias, responder bias etc

Example PC: Parastop

- Cancer pts with pain, on opioids and paracetamol
- Randomized to paracetamol or placebo
- Followed for one week
- Difference in pain

Example PC:
Cluster randomized controlled trial

- Pallion- palliative care integrated in oncology
- 12 departements were randomized
- Intervention vs regular practice
- Electronic symptom assessment, educational program, implementation of patient-centered care pathways (early referrals to PC)

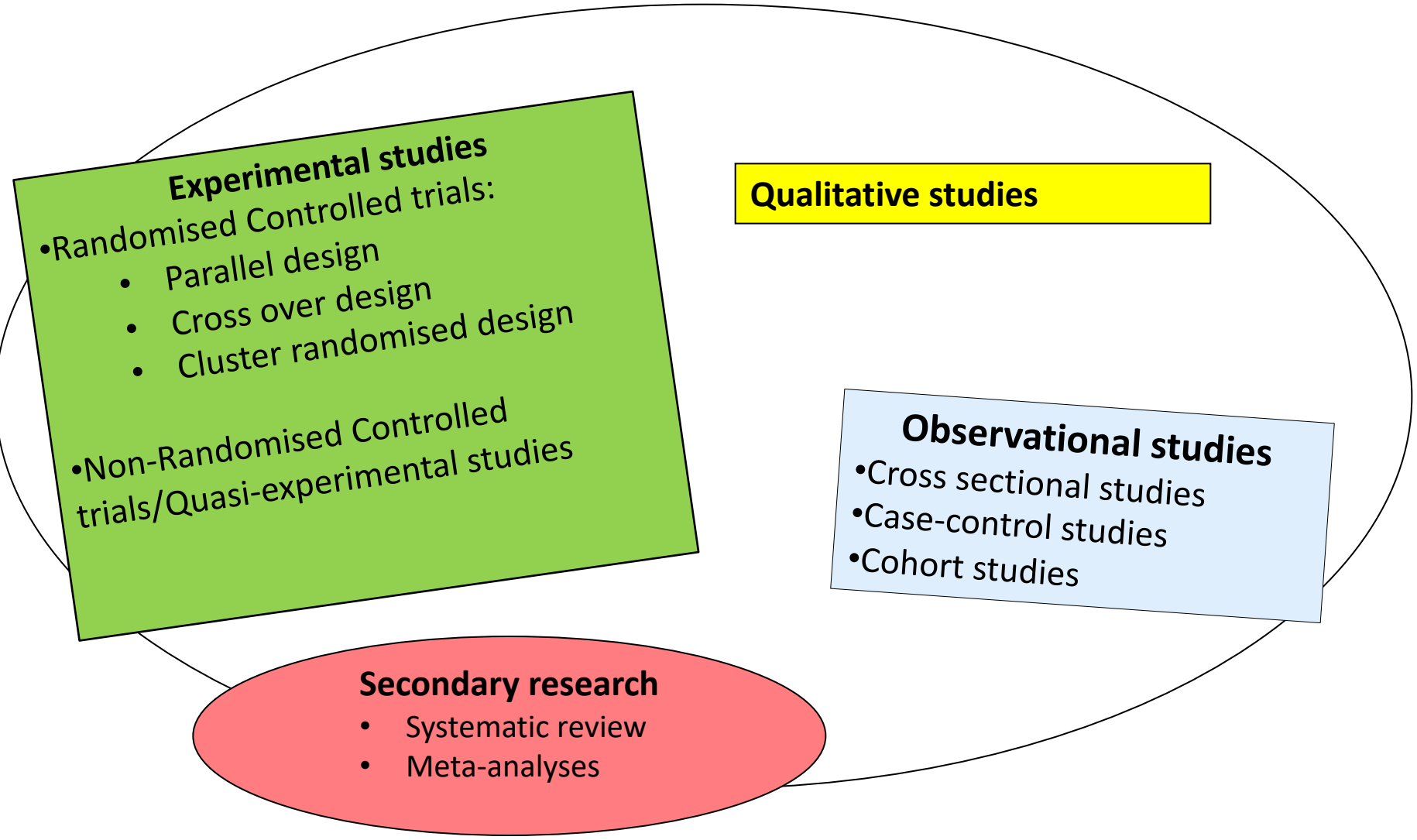
Different study designs

Secondary research
- Systematic review
- Meta-analyses

Systematic reviews
Meta analysis

- Secondary research, summarises other research
- Be aware: - apples and pears
  - systematic reviews of bad research do not lead to good answers
  - one well-performed RCT is higher on the evidence hierarchy than one metaanalysis of bad research

Different study design:



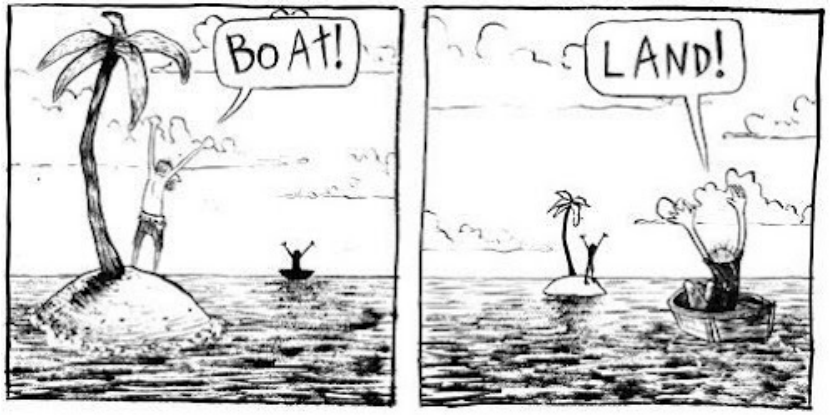
Qualitative Methods

- Participant observation
  - Collecting data on naturally occurring behaviors in their usual contexts
- In-depth interviews
  - For collecting data on individuals personal histories, perspectives, and experiences, particuarly when sensitive topcs are being explored
- Focus groups
  - Are effective in elicitating data on the cultural norms of a group and in generating broad overviews issues of concern to the cultural group or subgroup represented

Qualitative studies

Be aware:

- Research quality dependent on researcher skills
  - and more easily influenced by personal biases and idiosyncrasies
- Researcher's presence during data gathering (often unavoidable in qualitative research) can affect the subjects' responses
- Data collected from a few cases or individuals so findings cannot be generalized to a larger population



Ex PC Qualitative study

- Silent voices: Family caregivers' narratives of involvement in palliative care
  - Tarberg et al

Some challenges in palliative care research

- Recruitment
  - Not able to give informed consent , Too sick
- Dropouts, missing data
- Variable description of populations
- Lack of consensus on definitions
- Lack of consensus on outcomes
  - Subjective outcomes
- Lack of culture for research
  - Try to «protect» patients, no awarness of what research can do

The levels of recommendation

Levels of evidence	Criteria	Recommendation
1a	Systematic review of RCTs	A
1b	RCT with narrow confidence interval	
		B
2a	Systematic reviews of cohort studies	
2b	Cohort study or low quality RCT	
3a	Systematic reviews of case-control studies	C
3b	Case-control study	
4	Case series, poor quality cohort or case-control studies	
5	Expert opinions	D

Source: Oxford Centre for Evidence Based Medicine

Palliative care?

Table 4 Types of research methodologies

Classification	Number of articles	% of total articles ($n = 215$)
Qualitative/descriptive studies	136	63
Quantitative methods	31	14
Mixed methods	16	7
Measurement/methodology	12	5.5
Systematic reviews	12	5.5
Secondary analysis	5	2
Unclassifiable	2	1
Randomised controlled trials	1	0.4
Total	215	

Closing remarks:

How can we improve?

1. Have a good question!
2. Plan ahead! (Detailed, realistic protocols) and follow the protocols
3. Consider to publish the protocols, also in observational trials?
4. Beware of bias and confounders
5. Beware of barriers (also your own)
6. Better (sensitive, reliable and unbiased) outcome parameters
7. Always report negative results
8. More well-designed multicenter RCTs on key topics
9. More cooperation between centers