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Study design in palliative care

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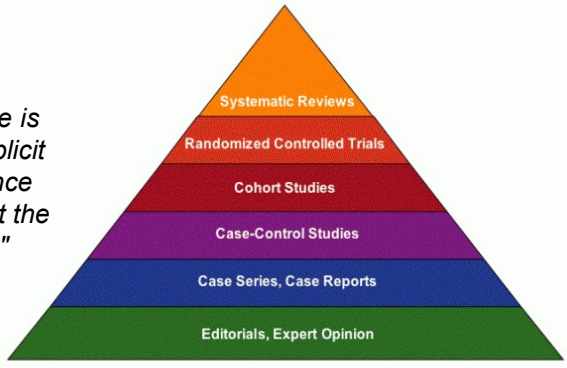
Hierarchy of evidence

"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

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First clinical trial

- *King Nebuchadnezzar II (605-562 BC) ordered a group of children to be fed a strict diet of meat and wine*
- *These were compared to Daniel and 3 other children who ate vegetables and water*
- *After 10 days, the king saw that those who ate vegetables and water seemed fitter than those who ate meat and wine*

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Source: Daniel 1: 1-16

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..

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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**

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You have a good RQ

- but are there practical limitations?




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

Randomization? Time? Funding? Resources?

Valid outcome parameters? Ethics?

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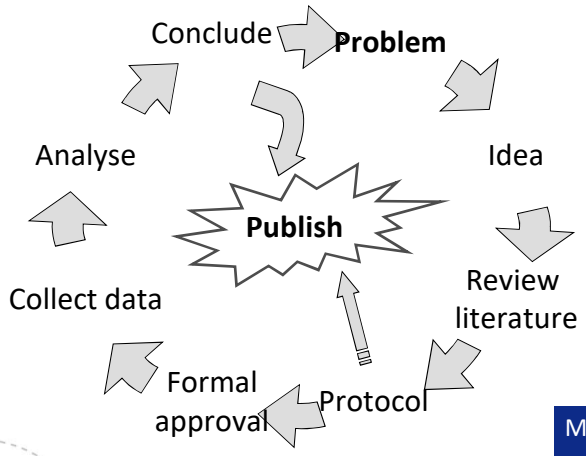
What can go wrong?

Circle of science



Motto: Make good a plan and stick to it!

From Ole Solheim 2009

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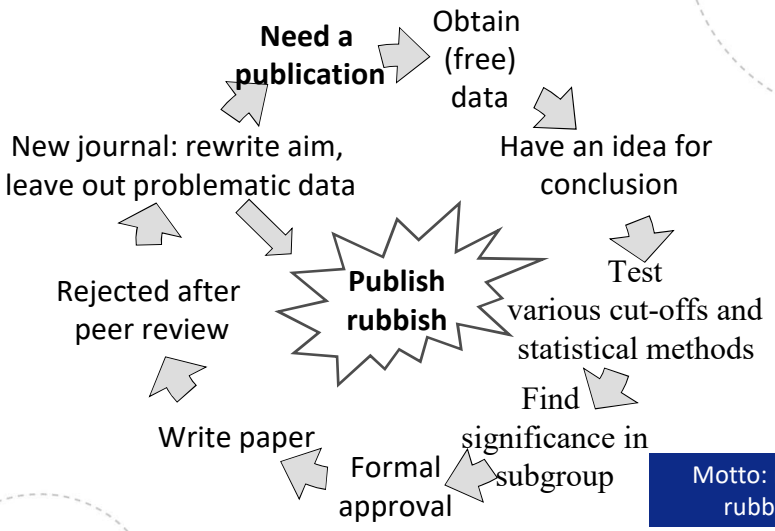
Circle of bias (How not to do it)



Motto: rubbish in, rubbish out!

From Ole Solheim 2009

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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

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TSS4
TSS13

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

TSS3

Challenges: Validity - is this true?

- External Validity:
  - Does it work in other settings than the studied?
- Internal Validity:
  - Was the research done right?
    (Results will not be due to chance, bias or confounding factors)

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Slide 11

TSS4 Outcome variables
Should answer the study question
Sensitive enough
Well defined
Unbiased
Measurable in all participants
Preferably stable and "validated"
Tora Skeidsvoll Solheim; 12.09.2016

TSS13 Statistics: obs subgroup analysis, regression to the mean, ceiling/floor effect, placebo
Tora Skeidsvoll Solheim; 15.09.2016

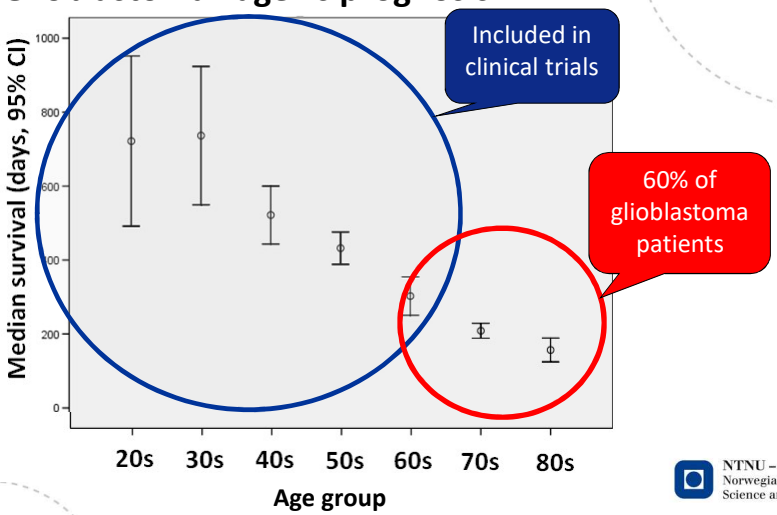
Slide 12

TSS3 "What works well at Sloan Kettering
may not work very well in Kettering
Tora Skeidsvoll Solheim; 12.09.2016

TSS5
TSS6

Challenges eksample:

Glioblastoma : age vs prognosis



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Source: Norwegian Cancer Registry (1998 – 2009)

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Challenges: 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

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TSS5 not only eksternal validity, but also an other improtant factor- what happens if the populations studied are and compared have different ages?
Tora Skeidsvoll Solheim; 12.09.2016

TSS6 Always check demographics
Tora Skeidsvoll Solheim; 12.09.2016

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Clinical Outcomes and Contributors to Weight Loss in a Cancer Cachexia Clinic

Egidio Del Fabbro, M.D., David Hui, M.D., Shalini Dalal, M.D., Rony Dev, M.D., Zohra Noorhuddin, M.D., and Eduardo Bruera, M.D.

Abstract

Background: Cancer cachexia is considered intractable, with few therapeutic options. Secondary nutrition impact symptoms (S-NIS) such as nausea may further contribute to weight loss by decreasing nutrient intake. In addition, treatable metabolic abnormalities such as hypogonadism, vitamin B12 deficiency, hypothyroidism, and hypoadrenalism could exacerbate anorexia and muscle wasting in patients with cancer cachexia. We determined the frequency and type of contributors to appetite and weight loss, and the effect of the cachexia clinic on clinical outcomes.

Methods: Review of 151 consecutive patients referred to a cachexia clinic. All received dietary counseling and exercise recommendations. Assessments included weight, body mass index (BMI), S-NIS, resting energy expenditure by indirect calorimetry, serum thyroid stimulating hormone (TSH), cortisol, total testosterone, and vitamin B12.

Results: Median weight loss in the 100 days before referral was 9% (4%–13%); median BMI at presentation was 20.8. Median number of S-NIS was 3 (2–4), most commonly treated by metoclopramide, laxatives, and antidepressants. Forty-one percent (24/59) of patients were hypermetabolic and 73% (52/71) of males hypogonadic, whereas hypoadrenalism (0/101, 0%), hypothyroidism (4/113, 4%), and low vitamin B12 (3/107, 3%) were uncommon. Poor appetite and weight loss before referral ($r = 0.18$, $p = 0.036$) were associated with increased S-NIS ($r = 0.22$, $p = 0.008$). Appetite improved ($p < 0.001$) and 31/92 (34%) of patients returning for a second visit gained weight.

Conclusions: Patients had a high frequency of multiple S-NIS, hypogonadism, and hypermetabolism. A combination of simple pharmacological and nonpharmacological interventions improved appetite significantly, and increased weight in one third of patients who were able to return for follow-up. Cachexia clinics are feasible and effective for many patients with advanced cancer.

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TABLE 4. PATIENTS NOT RETURNING FOR A SECOND VISIT

Causes	*Number of patients*	*Percentage*
Died <30 days of referral	7	11.9
Unable to follow up (residence out of state)	7	11.9
Hospice <30 days of referral	10	16.9
Decline to follow up or Noncompliant	17	29.8
Developed other intractable symptoms (e.g., pain/delirium)	18	29.8
Total	59/151	

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Sources of bias

- Patient selection
- Treatments assignment
- Evaluation of outcomes
- Dropouts, crossover
- Losses to follow up
- Missing data
  - RCT, double blind, intention to treat

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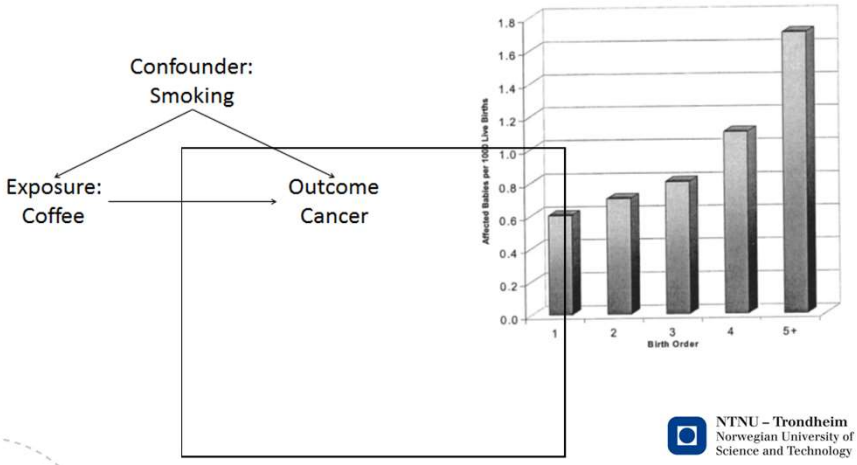
Confounder



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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**

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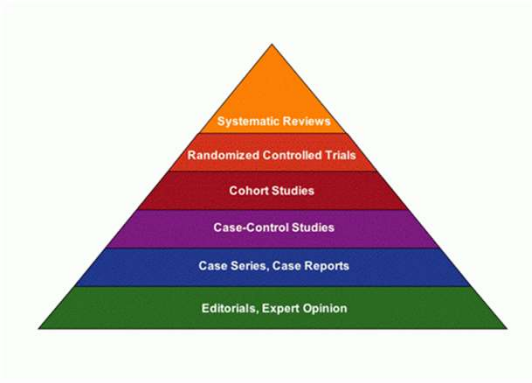
Different study designs



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Expert opinions, case-reports

- Don't trust it –think for your self
  - It might be true though…
- Starting points for good research questions?

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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

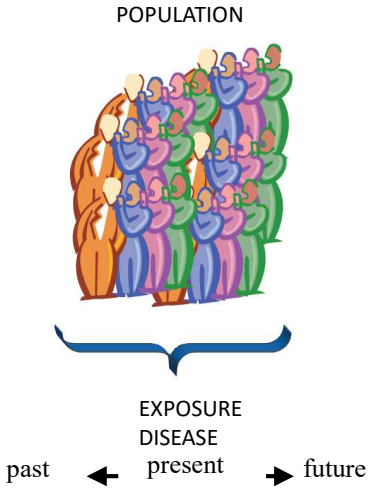
Katrin Sigurdardottir 2015 (+Solheim)

Characteristics of observational studies

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

Katrin Sigurdardottir 2015

Cross-sectional study

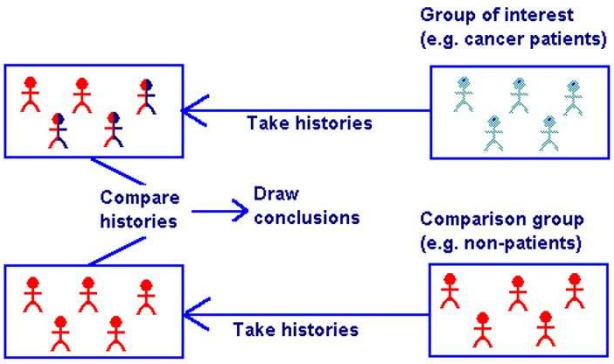


- A **cross-sectional study** is an observational study in which exposure and disease are determined at the same point in time in a given population
- The temporal relationship between exposure and disease cannot be determined – it only raises questions on hypothesis..

Prevalence study example

TSS7
TSS9

Case-control study



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

Case control example

- Lung cancer- not lung cancer
- Exposure during life

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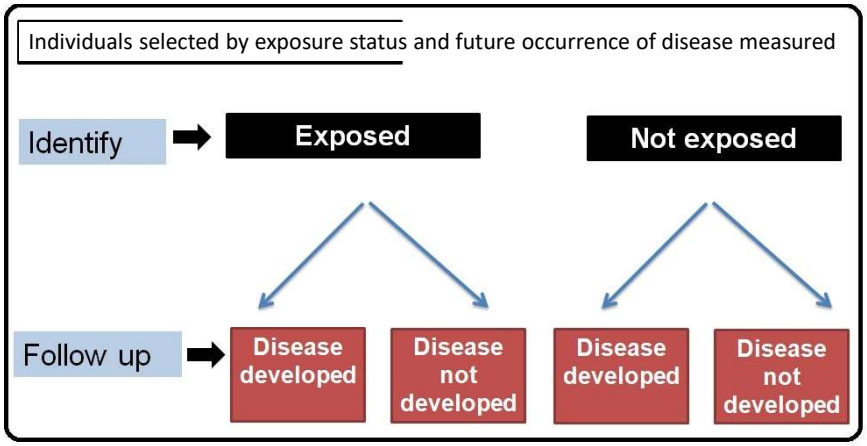
TSS7 Unable to estimate incidence rates of disease (unless study is population based).
Poor choice for the study of rare exposures.
The temporal sequence between exposure and disease may be difficult to determine.
Tora Skeidsvoll Solheim; 13.09.2016

TSS9 Good for rare diseases
Tora Skeidsvoll Solheim; 13.09.2016

TSS8
TS TSS11
TSS12

Cohort studies



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Types of observational studies

Experimental studies

- Randomised Controlled trials:
  - Parallel design
  - Cross over design
  - Cluster randomised design
- Non-Randomised Controlled trials/Quasi-experimental studies

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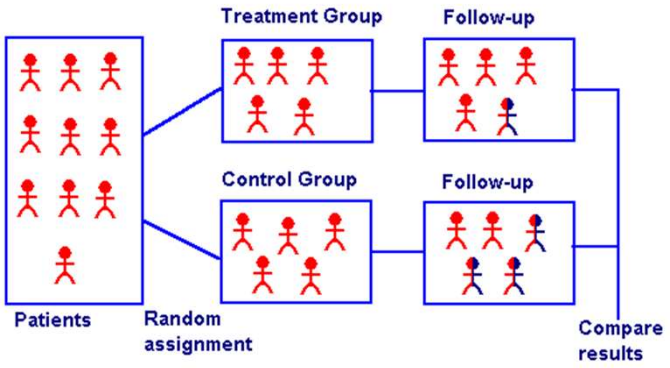
TSS8 HARKING bias? (Hypothesizing After Results Are Known)
Tora Skeidsvoll Solheim; 13.09.2016

TSS10 Follow up bias
Tora Skeidsvoll Solheim; 13.09.2016

TSS11 Can look at multiple exposures.
Good for measuring rare exposures, for example among different occupations.
Demonstrate direction of causality.
Can measure incidence and prevalence
Tora Skeidsvoll Solheim; 13.09.2016

TSS12 time consuming and expensive
loss to follow-up & unavailability of data
potential confounding factors
inefficient for rare diseases
Knowledge of exposure may bias classification of the outcome
Being in the study may alter patient's behaviour
Tora Skeidsvoll Solheim; 13.09.2016

Randomised Controlled Trial



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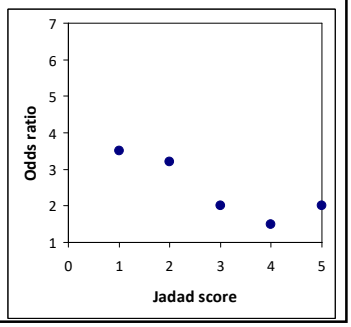
Randomised control trial

- 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
    - Cross over
    - Funding bias, responder bias etc



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- Custer-randomized- ex
- Cross-over design- ex

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Different study designs

Secondary research
- Systematic review
- Meta-analyses

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Systematic reviews
Meta analysis

- Secondary research, summarises other research
- More elsewhere
- 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

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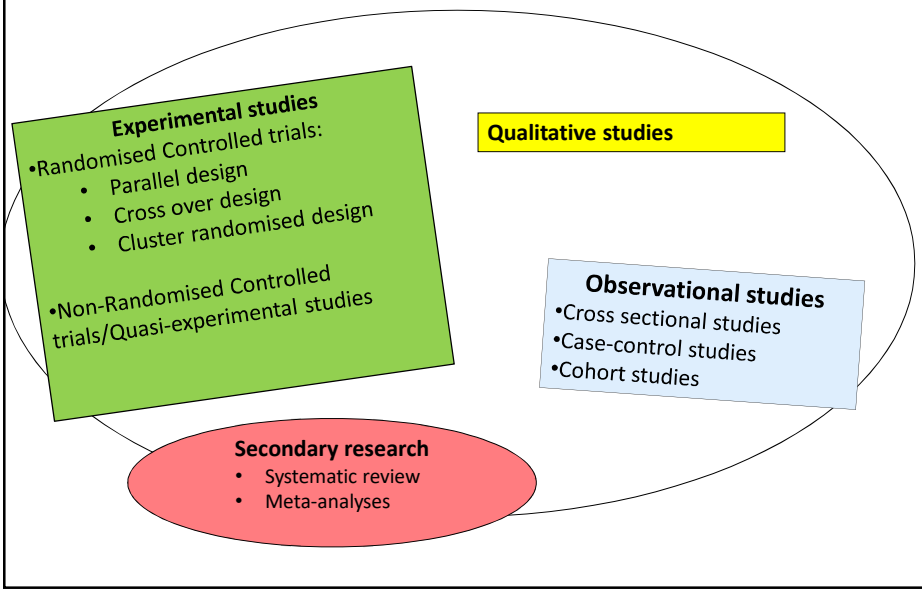
Different study design:



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

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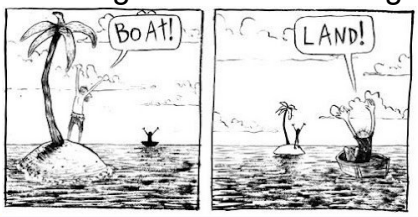
Qualitative studies

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



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Some challenges in palliative care research design?

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

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The levels of recommendation

Levels of evidence	Criteria	Recommendation
1a	Systematic review of RCTs	A
1b	RCT with narrow confidence interval	
1c	All or none-studies	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

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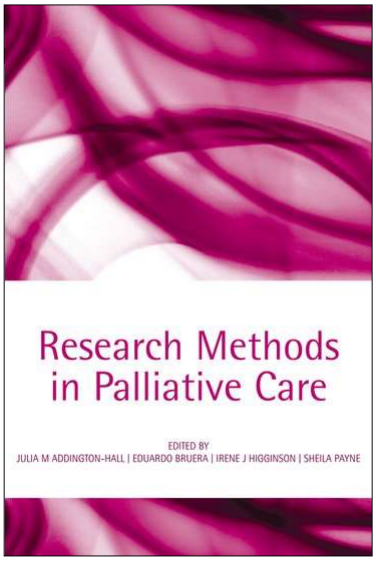
Palliative care?

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