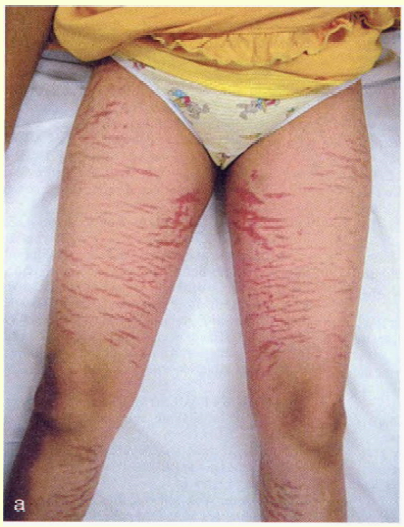
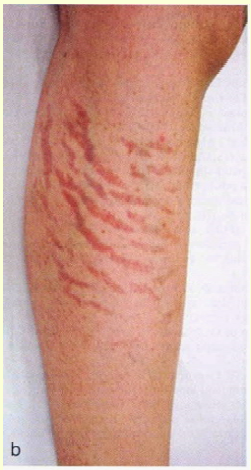
When the system fails: a girl with striae

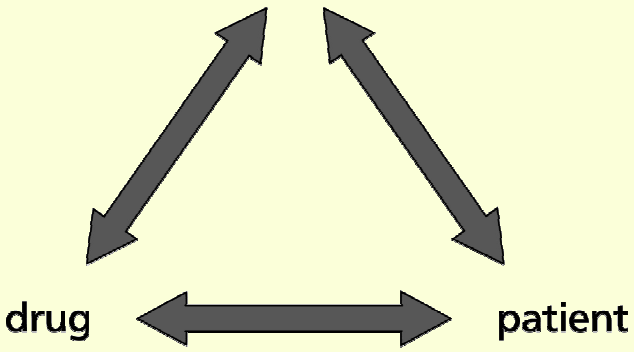




Intrinsic vs extrinsic (un)safety

medication errors

prescribing and use



type A / B adverse drug reactions

Today (9.00 – 16.00)

9-12

Essence of yesterday

Study designs, confounding

Next step in protocol + short presentation

13-16

Measures of (relative) risk

Assignment measures of risk

Measuring outcome / determinant

Misclassification

Epidemiology

Pr(outcome) = f(determinants)

Pharmacoepidemiology

- **drug = outcome (drug utilization)**
- **drug = determinant (usually)**

The occurrence relation: Pr(outcome) = f(determinant)

Determinant(s) ----------→ **outcome(s)**

characteristic / determinant	endpoint
exposure	disease (often)
drugs (often)	adverse effect
independent variable	dependent variable
The effect of….	on…..

Domain:

the population for which the occurrence relation is of potential relevance in….

Key message

Consistency of the essential items occurrence relation in:

- Title
- Objective
- Methods
- Primary graph / table

Many interesting research questions

Four will be worked out into a protocol
Presentations Friday after lunch

1. Effect of quinine (first trimester) on pregnancy outcomes

2. Effect of SRS vs IMP on ADR reports in hospitalized patients

3. Effect of influenza vaccination on myocardial infarction in patients with cardiovascular disease

4. Effect of ergotamine on amputations in patients using antiretroviral therapy

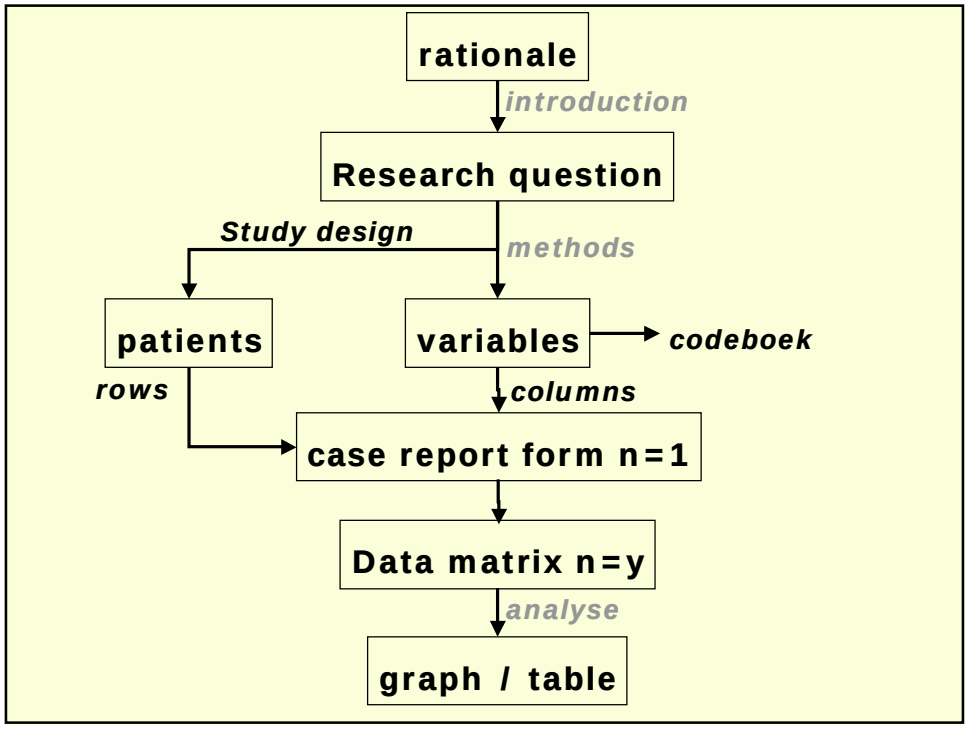
Operationalizing research question

From what I want to study and why (introduction)

To

How to study (methods)

- **study design (trial, follow-up, case control)**
- **study population: where (setting), who (in/ex) how many?**
- **measuring of determinant(s)**
- **measuring of the outcome(s)**



Study designs

Experiment:

Randomised Control Trial

Non-experiment (observational):

Non comparative (descriptive)

Case report / case series

Comparative (analytical)

Cross-sectional study

Follow-up study

Case control study

Case report / Case Series

Occurrence relation: Pr(outcome)=f(determinant)

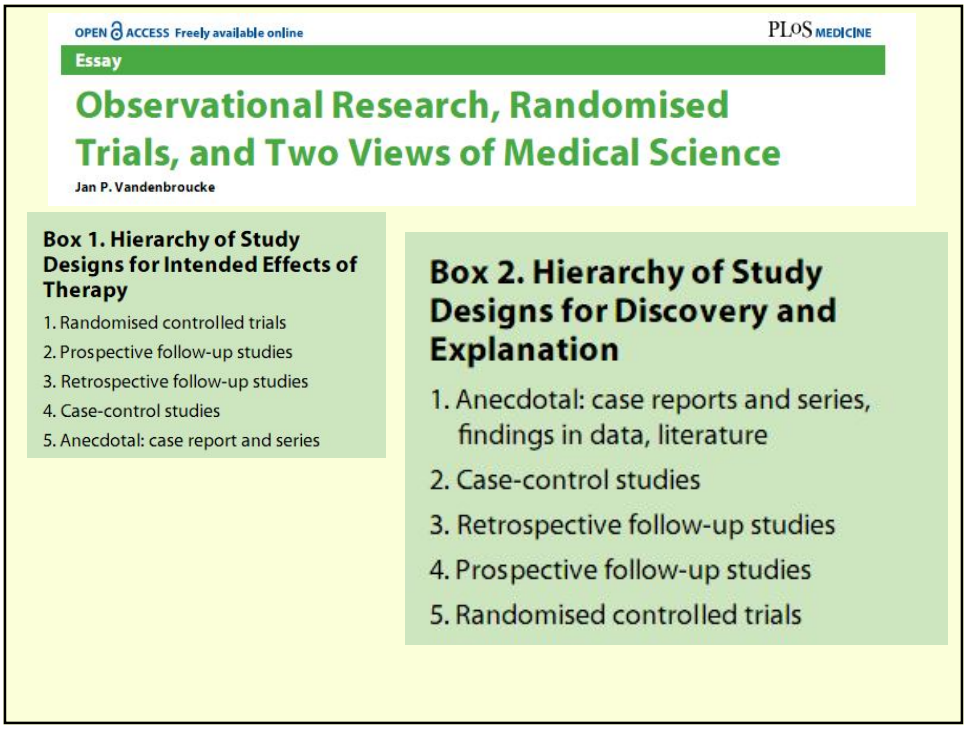
in one or a few patients

Hypothesis generating (signal detection)

Early warning

Awareness, education

Relatively cheap and easy



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Essay

Observational Research, Randomised Trials, and Two Views of Medical Science

Jan P. Vandenbroucke

Box 1. Hierarchy of Study Designs for Intended Effects of Therapy

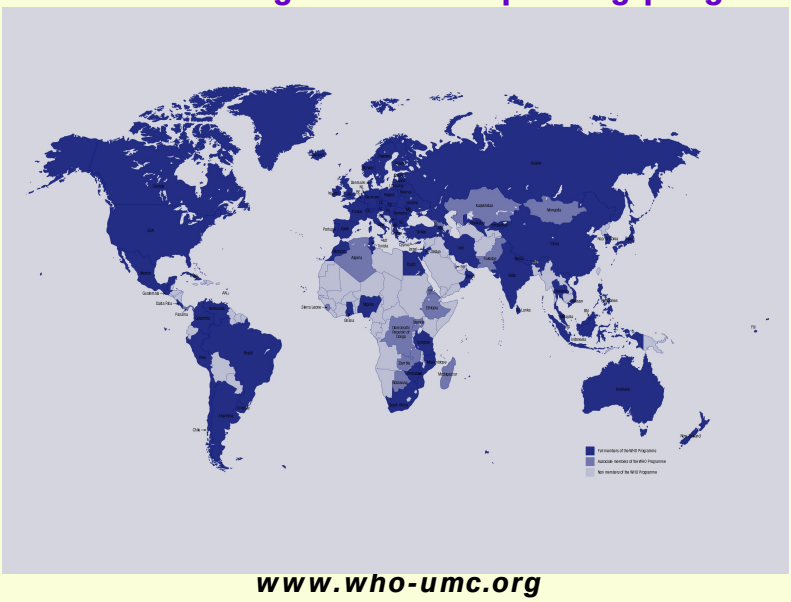
1. Randomised controlled trials
2. Prospective follow-up studies
3. Retrospective follow-up studies
4. Case-control studies
5. Anecdotal: case report and series

Box 2. Hierarchy of Study Designs for Discovery and Explanation

1. Anecdotal: case reports and series, findings in data, literature
2. Case-control studies
3. Retrospective follow-up studies
4. Prospective follow-up studies
5. Randomised controlled trials

System for case reports

WHO adverse drug reaction reporting programme



www.who-umc.org

Study designs

Experiment:

Randomised Control Trial

Non-experiment (observational):

Non comparative (descriptive)

Case report / case series

Comparative (analytical)

Cross-sectional study

Follow-up study

Case control study

Epidemiology: comparative

Pr(outcome) = f(determinants)

Determinant A ---------→ Pr(Outcome)
Determinant B ---------→ Pr(Outcome)

Drug (group) A ---------→ Pr(Outcome)
Drug (group) B ---------→ Pr(Outcome)

TIME

Experiment: randomised controlled trial

Pr(outcome) = f(determinants)

Drug (group) A ---------→ Pr(Outcome)
Drug (group) B ---------→ Pr(Outcome)

TIME

Random allocation of the determinant!!

Not the normal treatment decision

Randomised: why?

Control group: why?

Double blind: why?

Effect size: probability of outcome

	drug	placebo
Natural history	effectNH	effectNH
Placebo effect	effectPL	effectPL
Assessor effect	effectAS	effectAS
Pharmacological effect	effectPE	----

Example RCT

Pr(agranulocytosis) = f(clozapine)

Clozapine -------6 months----→ agranulocytosis
N=3000 n=6 (0.2%)

Olanzapine -----6 months----→ agranulocytosis
N=6000 n=3 (0.05%)

The 2 x 2 table

		outcome yes	no	Pr(outcome
Clozapine (n=3000)	6	2994		6/3000 = 0.2%
Olanzapine (n=6000)	3	5997		3/6000 = 0.05%

Relative risk = 0.2% / 0.05% = 4.0 (95%CI, p-value)

Number needed to harm = 100 / (0.2-0.05) = 666 patients

Randomised controlled trial

Gold standard for treatment effects

Expensive, taks time (only prospective)

Impractible/costly for rare outcomes, long latency

Ethical problems

High internal validity

Low external validity

Counting Adverse Drug Reactions in RCTs

301 Multiple Sclerosis patients followed for approx. 2 years

Side effects	Placebo (n=143)	Interferon-ß (n=158)
Headache	57%	67%
Symptoms of influenza	40%	61%
Fever	13%	23%

Jacobs JD et al. Ann Neurol 1996;39:285-94

Follow-up study / cohort

Non-random equivalent of the trial

Pr(outcome) = f(determinants)

Drug (group) A ---------→ Pr(Outcome)

Drug (group) B ---------→ Pr(Outcome)

TIME

Non-Random allocation of the determinant!!

Treatment decision of the physician

Example follow-up study

Pr (GI-bleed) = f(NSAID use)

Example large database (eg GPRD)

NSAID users -----1 year---→ GI-bleed

N=40.000 n=200 (0.5%)

COX2 users -----1 year---→ GI bleed

N=20.000 n=160 (0.8%)

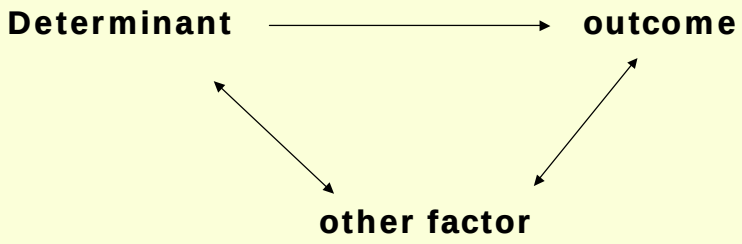
The 2 x 2 table

	outcome yes	no	Pr(outcome)
NSAIDs (n=40.000)	200	39.800	200/40000 = 0.5%
COX2 (n=20.000)	160	19.840	160/20.000 = 0.8%

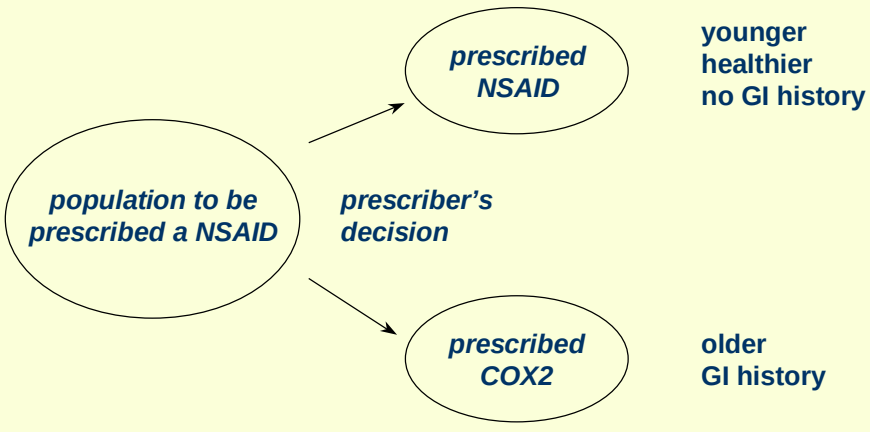
Relative risk = 0.8% / 0.5% = 1.6 (95%CI, p-value)

Number needed to harm = 100 / (0.8-0.5) = 333 patients

Confounding



e.g. history of GI bleed, age

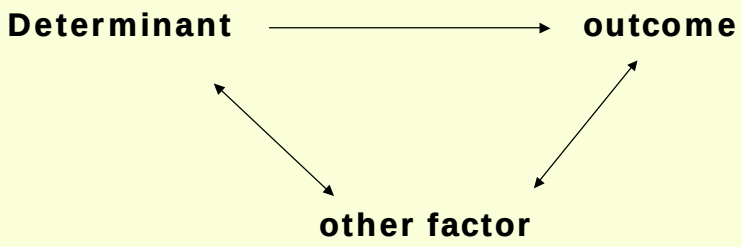


Selective prescribing of newer drugs

	` COX2 n=5000	NSAID n=5000
recent use NSAIDs	49.8%	7.9%
recent use H2 blockers	12.4%	4.0%
recent use proton-pump inh.	11.1%	4.0%
history of dyspepsia	38.4%	20.3%
history of peptic ulcer	6.1%	3.1%

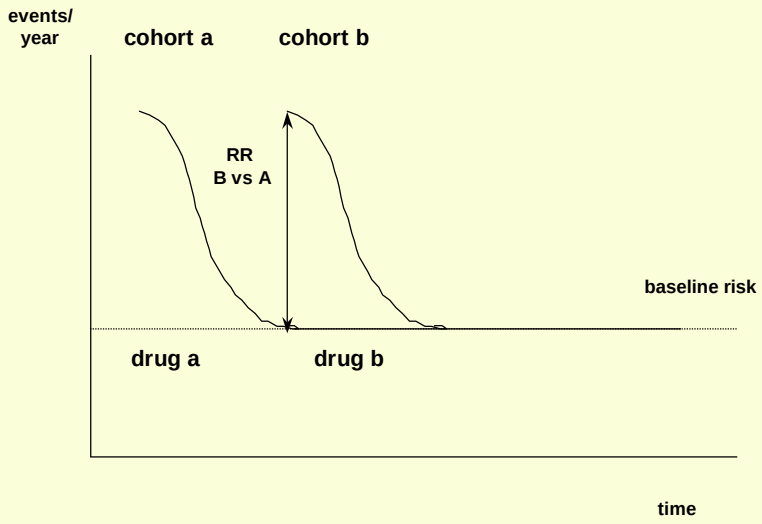
Lanes et al. Pharmacoepidemiol & Drug Saf 2000;9:113-7

Confounding



e.g. history of GI bleed, age

Attrition / Depletion of Susceptibles



Selective prescribing = channeling

Did the drug bring the problem to the patient?

Versus

Did the patient bring the problem to the drug?

Follow-up studies

Retrospective / prospective

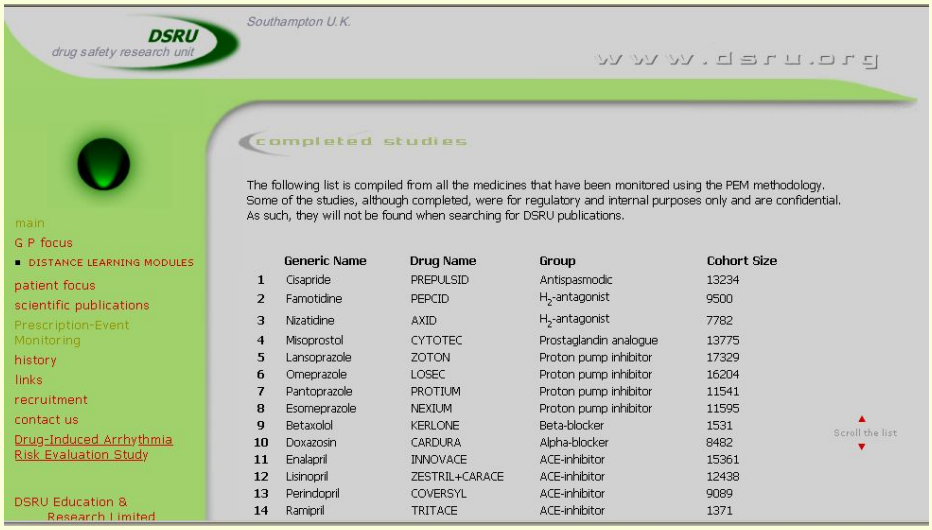
Can study multiple outcomes

Can calculate absolute frequency measures

Can be inefficient when additonal data are needed

System for follow-up of drug users

e.g. PEM = prescription event monitoring



	Generic Name	Drug Name	Group	Cohort Size
1	Cisapride	PREPULSID	Antispasmodic	13234
2	Famotidine	PEPCID	H_2-antagonist	9500
3	Nizatidine	AXID	H_2-antagonist	7782
4	Misoprostol	CYTOTEC	Prostaglandin analogue	13775
5	Lansoprazole	ZOTON	Proton pump inhibitor	17329
6	Omeprazole	LOSEC	Proton pump inhibitor	16204
7	Pantoprazole	PROTIUM	Proton pump inhibitor	11541
8	Esomeprazole	NEXIUM	Proton pump inhibitor	11595
9	Betaxolol	KERLONE	Beta-blocker	1531
10	Doxazosin	CARDURA	Alpha-blocker	8482
11	Enalapril	INNOVACE	ACE-inhibitor	15361
12	Lisinopril	ZESTRIL+CARACE	ACE-inhibitor	12438
13	Perindopril	COVERSYL	ACE-inhibitor	9089
14	Ramipril	TRITACE	ACE-inhibitor	1371

www.dsru.org

Case control study

As researcher you start with the outcome

NSAID use <-------- GI bleed

Collect patients with GI bleed (cases)
Collect patients without GI bleed (controls)

Measure frequency of determinant in both groups

Example case control study

Pr (GI-bleed) = f(NSAID use)
Collect cases for example from hospital

NSAID users <-------- GI-bleed
N=? n=200

COX2 users <-------- GI bleed
N=? n=200

The 2 x 2 table

		outcome yes	outcome no	Pr(outcome)
NSAIDs (n=?)	40	20		200/? =
COX2 (n=?)	20	15		200/? =
		200	200	

Relative risk = approximate by odds ratio
= exposure odds
= (40/20) / (20/15) = 2 / 1.3 = 1.5

SSRIs, NSAIDs and GI-bleeds

	cases GI-bleed n=1651	controls no GI-bleed n=10000	odds ratio
non-use	1115 (67.5%)	8180 (81.8%)	1 (ref)
current use			
NSAID	295 (17.9%)	652 (6.5%)	3.7
SSRI	38 (2.3%)	93 (0.9%)	2.6
NSAID+SSRI	16 (1.0%)	9 (0.1%)	15.6

Albajo et al. BMJ 1999;319:1106-9

Case control

Retrospective (and prospective)

Efficient with rare outcomes

Can study multiple determinants

Comparative designs

Follow-up:

Determinant ----------→ outcome

experimental variant = RCT

Case control:

Determinant ←---------- outcome

Assignment

Sharpen the research question, provide rationale

Draw most important graph / table

How:

- **Design**
- **Where / how study population**
- **How to measure determinant(s)**
- **How to measure outcome(s)**
- **Potential confounders?**

Report max 2 sheets