Erasmus MC
Universitair Medisch Centrum Rotterdam

Study design

Patricia van den Bemt, Erasmus MC

EAHP Seminar

September 29th 2017

Conflicts of interest

- No conflicts of interest related to content of presentation

Questions

- Is a randomized controlled trial (randomization of patients) suitable for an intervention with respect to prescribing skills?
  - Yes
  - No
- When analyzing the before-after study data which method is best?
  - Interrupted time series analysis
  - Comparing proportions
- The primary outcome determines the sample size
  - True
  - False

BMJ 2014;349:g7092 doi: 10.1136/bmj.g7092 (Published 16 December 2014)

RESEARCH

CHRISTMAS 2014: FOUND IN TRANSLATION

SearCh for humourIstic and Extravagant acroNyms and Thoroughly Inappropriate names For Important Clinical trials (SCIENTIFIC): qualitative and quantitative systematic study

The next step

- Research question
  - What is it I want to study (former presentation)
- Study design
  - What type of study do I need to answer my research question
    - In relation to possibilities and costs
- Study methods
  - How will I conduct the study
    - Definition of study population
    - Which outcome measures
    - How to measure patient characteristics and outcomes

Paragraphs of study protocol

- Title – research question
- Introduction/rationale
- Objective(s)
- Methods
  - Study design
  - Study population
  - Outcome measures
  - Study procedures
  - Data-analysis (incl. sample size)
- Ethical considerations
- Literature references

Paragraphs of study protocol

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Study design

- ??????
- Randomized Controlled Trial (RCT) or subtypes
  - Open, single/double-blind, assessor-blind
  - Cluster randomized
  - Cross-over
- Non-randomized intervention study
  - Before-after study
  - Historical control
- Observational
  - Cohort
  - Case-control
  - Prospective or retrospective

RCT

- Randomised, double-blind controlled trial
  - Randomisation takes care of comparable groups
  - Assignment by chance
  - In general well balanced groups
  - Double-blind: validity outcome measurement
- Gold standard
- Not always suitable:
  - Safety interventions – learning effect
  - Rare effects: not feasible; very high costs
  - Ethical issues

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

BMJ 2003;327:1459–61

Non-randomised intervention studies

- Before-after study
  - Very suitable for measuring effect of safety intervention
  - Be aware of other changes
    - Is effect due to the intervention?
    - Time series analysis
- Historical control group
  - Subtype of a before-after study
  - Difference: prospective datacollection
    - Before-after study: yes
    - Historical control group retrospectively (intervention group: prospectively)

Observational - cohort

- Compares two treatments/interventions
- Patients are not randomised
- Prospective or retrospective
- Bias:
  - Selection bias: disease status determines chance of allocation
    - E.g. selective drop-outs – incomplete follow-up
  - Information bias: chance of detection of outcome is higher in one group
    - E.g. cohort-study on association of oral contraceptive use with cervical cancer
      - OC-users higher frequency of screening
      - OC-users more temporal dysplasia due to infections
- You can’t adjust for bias!

Observational – cohort

- Confounding
  - Effect not due to intervention/treatment but due to another factor
  - Eliminate beforehand, but adjustment for confounding is possible
  - Before: ????
    - randomisation (ultimate), matching
  - A factor is a confounder when:
    - When measuring effect of E on Z and F is the possible confounder
    - F should have effect on Z independent of status of E
    - F should be associated with E
    - F may not be part of the causal chain leading from E to Z
- Effect modification
  - Effect of intervention/treatment differs per category of a third factor
    - E.g. different effect of aspirin in women compared to men

Observational – cohort

- Advantage:
  - Cause before consequence
  - Several outcome measures possible
  - Rare determinants are not a problem
- Disadvantage:
  - Relevant determinants need to be known beforehand
  - Not feasible for disease with low incidence or very long preclinical stage
  - No insight into selection due to earlier exposition (immunity)
  - Costs and length of study

Observational – case-control

- Outcome/disease determines the groups
  - Group with disease compared to group without
  - Look back to exposition to determinant of interest
  - E.g. patient with and without lung cancer
    - Association with smoking behavior
- Bias:
  - Selection bias: higher risk than in cohort studies
  - Information bias: e.g. recall bias – people with disease remember better whether they used potentially causal agents
  - Confounding & effect-modification: as in cohort

Observational –case-control

- Advantages:
  - Limited length of study
  - Small sample size
- Disadvantages:
  - More validity issues than with cohort studies

- Observational hybrid designs
  - Nested case-control
  - Case-crossover

Other designs

- Diagnostic studies
  - specificity, sensitivity, PPV, NPV
  - E.g. comparing two tools to assess adherence
- Clinimetrics
  - Development of validated questionnaire
- Pharmacokinetic studies, PK/PD modelling
- Descriptive studies; aim to look into prevalence/incidence and type
  - Cross-sectional
  - Prospective
  - Retrospective

Characteristics to be measured: primary outcome

- Needs to correspond with primary objective
- Primary outcome will answer your study question
- Main table in your study report (but…..not table 1)
- Keep it simple……..select one primary outcome
- Primary outcome determines:
  - Choice of statistical test
  - Sample size


Glasgow 2009 Sameh Shehata


GET BACK
TO WORK,
MINION

Background:

Recent postmarketing trials produced conflicting results about the risk for hospitalized heart failure (hHF) associated with dipeptidyl peptidase-4 (DPP-4) inhibitors, creating uncertainty about the safety of these antihyperglycemic agents.

Objective:

To examine the associations of hHF with saxagliptin and sitagliptin.

Design:

Annals of Internal Medicine ORIGINAL RESEARCH

Risk for Hospitalized Heart Failure Among New Users of Saxagliptin, Sitagliptin, and Other Antihyperglycemic Drugs

A Retrospective Cohort Study

Background:
Prolonged sitting time has been associated with adverse health outcomes. Interventions at work may contribute to reduced sitting.

Objective:
To test if a multicomponent work-based intervention can reduce sitting time.

Design:

International Journal of Epidemiology, 2016, 1–13
doi: 10.1093/ije/dyw009
Original article

Original article

Take a Stand!–a multi-component intervention aimed at reducing sitting time among office workers–a cluster randomized trial

I.H. Danquah,[1] S. Kloster,[1] A. Holtermann,[2] M. Aadahl,[3,4] A. Bauman,[5] A.K. Ersbøll[1] and J.S. Tolstrup[1,*]

Background:
Previous studies have reported conflicting results as to whether an association exists between sedentary time and cardiovascular disease (CVD) risk among African Americans.

Objective:
To elucidate this relation, we investigated the associations of television (TV) viewing time and occupational sitting with carotid intima-media thickness (CIMT), a subclinical atherosclerosis measure, in a community-based sample of African Americans.

Diaz *et al. International Journal of Behavioral Nutrition and Physical Activity* (2016) 13:31
DOI 10.1186/s12966-016-0349-y

International Journal of Behavioral Nutrition and Physical Activity

Design:

RESEARCH Open Access

Sedentary behavior and subclinical atherosclerosis in African Americans: cross-sectional analysis of the Jackson heart study

Research question: outcome measures

Physician and Pharmacist Collaboration to Improve Blood Pressure Control

Arch Intern Med 2009;169:1996-2002

What would the primary outcome measure be?

Physician and Pharmacist Collaboration to Improve Blood Pressure Control

better guideline adherence, lower mean BP, and higher rates of BP control compared with a control group.[18,19]

Table 3. Clinic Blood Pressure (BP), 24-Hour BP, BP Control, and Guideline Adherence Scores[a]

Variable	Baseline	3 Months	6 Months
Control (n=210)			
BP, mean (SD), mm Hg			
Systolic	150.6 (14.1)[b]	146.1 (19.6)	143.8 (20.5)[b]
Diastolic	83.6 (12.3)	81.5 (14.0)	79.1 (14.3)
BP control, %	0	25.4	29.9[c]
24-h BP, mean (SD), mm Hg			
Systolic	137.9 (15.8)	. . .	131.5 (17.7)
Diastolic	77.2 (10.7)	. . .	73.7 (10.7)
Total guideline adherence score, % criteria met, mean (SD)	49.4 (19.3)	. . .	53.4 (18.1)[d]
Intervention (n=192)			
BP, mean (SD), mm Hg			
Systolic	153.6 (12.8)[b]	134.8 (14.6)	132.9 (15.5)[b]
Diastolic	87.4 (11.9)	79.9 (11.3)	77.7 (11.2)
BP control, %	0	49.7	63.9[c]
24-h BP, mean (SD), mm Hg			
Systolic	136.2 (14.6)	. . .	121.1 (13.7)
Diastolic	78.5 (11.7)	. . .	70.2 (8.7)
Total guideline adherence score, % criteria met, mean (SD)	40.4 (22.6)	. . .	62.8 (13.5)[d]

[a] *P* values are based on between-group differences adjusted for baseline age, sex, race/ethnicity, educational degree, insurance status, annual household income, marital status, smoking status, alcohol intake, body mass index, number of coexisting conditions, number of antihypertensive medications, and medication adherence. Blood pressure control is defined as less than 130/80 mm Hg for patients with diabetes or chronic kidney disease and as less than 140/90 mm Hg for patients without diabetes or chronic kidney disease.
[b] $P < .05$.
[c] $P < .001$.
[d] $P = .04$ (unadjusted) and $P = .09$ (adjusted).

Arch Intern Med 2009;169:1996-2002

More measurements…..

Besides primary outcome:

- Secondary outcome measures
  - Selection – nice to know vs needed to know
  - Analysis: as for primary outcome
  - However: not important for sample size
- Population characteristics
  - ……this is table 1
  - Also statistical analysis
    - Why?

Description of study population

- Internal validity
  - Are study groups comparable with respect to all determinants except the determinant of interest?
    - What is the best way to achieve this?
- External validity
  - Can the study population be translated to real life patients?
  - A good description of the study population (in- and exclusion criteria) is necessary to assess this

Physician and Pharmacist Collaboration to Improve Blood Pressure Control

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Table 2. Patient Demographics at Baseline

Demographic	Control Office (n=210)	Intervention Office (n=192)	*P* Value for Difference
Sex[a]			.19
Female	117 (55.7)	120 (62.5)	
Male	93 (44.3)	72 (37.5)	
Race/ethnicity[a]			.04
White	163 (77.6)	165 (85.9)	
Hispanic	0	8 (4.2)	
African American	41 (19.5)	13 (6.8)	
American Indian	2 (1.0)	1 (0.5)	
Mixed or other	4 (1.9)	5 (2.6)	
Age, mean (SD), y	59.2 (13.8)	57.3 (14.3)	.19
Married[a]	91 (43.3)	130 (67.7)	<.001
Education beyond high school[a]	76 (36.2)	65 (33.9)	.75
Annual household income <$25 000[a]	109 (51.9)	41 (21.4)	<.001
Insurance status[a]			<.001
Individual or group plan	68 (32.4)	108 (56.3)	
Medicare or Medicaid	85 (40.5)	71 (37.0)	
Self-pay or other	57 (27.1)	13 (6.8)	
Body mass index, mean (SD)[b]	34.2 (8.7)	32.1 (6.8)	.01
Smoker, within past 15 y[a]	86 (41.0)	65 (33.9)	.15
≥2 Alcoholic drinks per wk[a]	8 (3.8)	5 (2.6)	.58
History of coexisting conditions[a]			
Family history of premature cardiovascular event	50 (23.8)	37 (19.3)	.28
Diabetes mellitus	80 (38.1)	38 (19.8)	<.001
Stroke or transient ischemic attack	16 (7.6)	12 (6.3)	.70
Myocardial infarction	13 (6.2)	0	.002
Coronary artery bypass grafting	5 (2.4)	3 (1.6)	.73
Heart failure	4 (1.9)	1 (0.5)	.37
Angina	12 (5.7)	1 (0.5)	.003
Peripheral arterial disease	4 (1.9)	4 (2.1)	>.99
Chronic kidney disease	16 (7.6)	11 (5.7)	.55
Left ventricular hypertrophy	3 (1.4)	3 (1.6)	>.99
No. of coexisting conditions			
≥1[a]	200 (95.2)	173 (90.1)	.05
Mean (SD)	3.6 (2.2)	2.8 (1.8)	<.001
No. of antihypertensive medications			
≥1[a]	192 (91.4)	127 (66.1)	<.001
Mean (SD)	1.9 (1.0)	1.3 (1.2)	<.001
Low self-reported medication adherence, score ≥3[a]	19 (9.0)	17 (8.9)	>.99

[a] Data are given as number (percentage).
[b] Calculated as weight in kilograms divided by height in meters squared.

Arch Intern Med
2009;169:1996-2002

HOW am I going to answer the study question

- Translate determinant(s) and outcome(s) into variables
  - Primary outcome
  - Secondary outcome(s)
  - Population characteristics
- Study procedures: how to measure your outcomes
- Data collection

Measurement of variables
Example: blood pressure

- *analogous*
- *electronic*

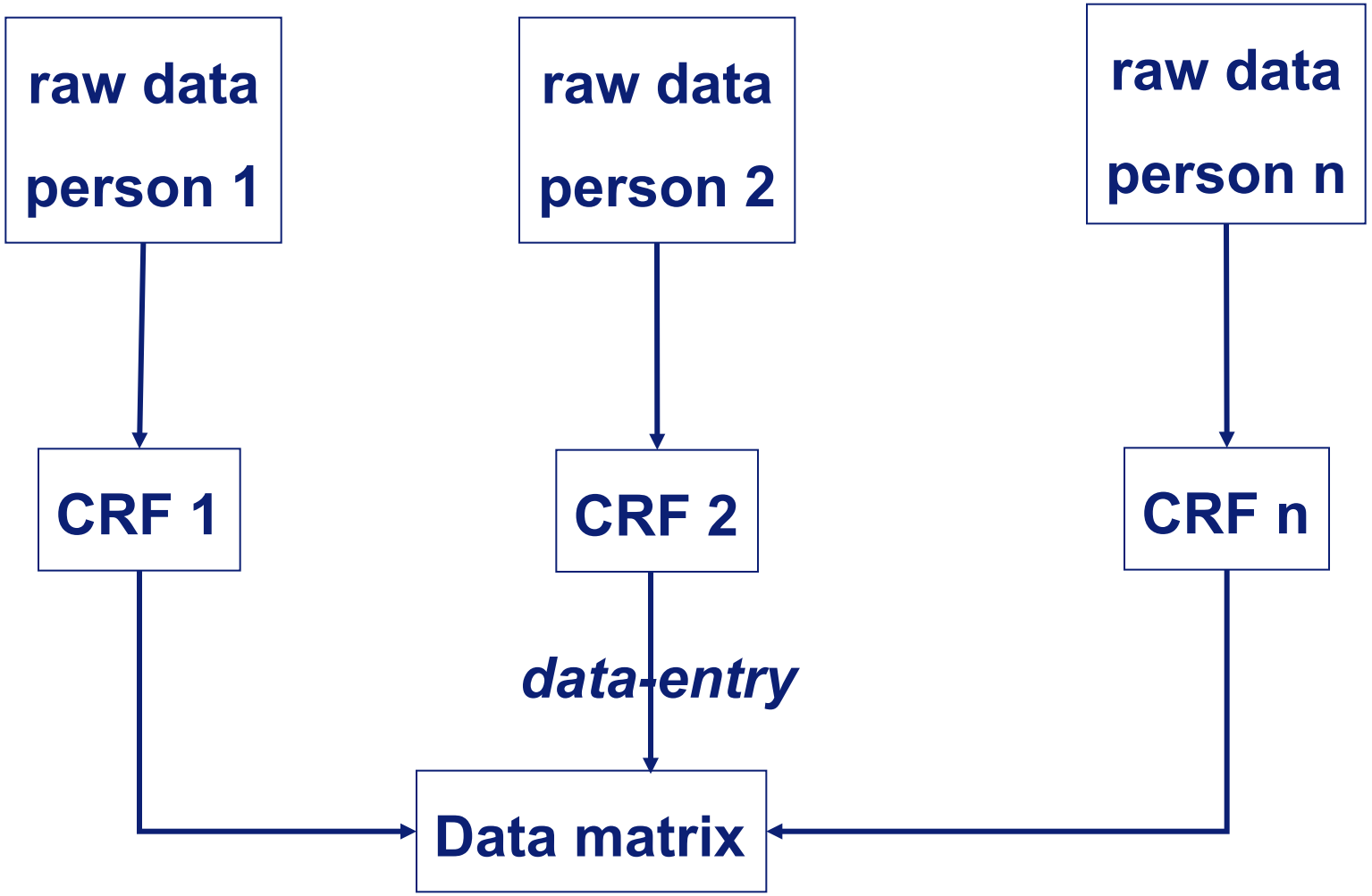
} *how often?* / *by whom?*

- *24-hour holter*
- *systolic – diastolic*
- *MAP (ICU)*

Population characteristics

- Often from (electronic) medical patient records
- Questionnaires
  - e.g. living situation, degree of education, etc.
- Outpatient data
  - General practitioner
  - Community pharmacy

Flow of study data



Data matrix

patientnr	intervention	age	sex	BP diast
11	0	85	0	82
12	1	49	0	97
13	0	57	0	102
14	1	63	1	99

Data matrix in SPSS

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bloeddruk.sav [DataSet2] - SPSS Data Editor

File Edit View Data Transform Analyze Graphs Utilities Window Help

8 : BP_dias_t6

	patnr	age	sex	BP_sys_t0	BP_dias_t0	BP_sys_t3	BP_dias_t3	BP_sys_t6	BP_dias_t6	interventie	var	var	var	var
1	11,00	85,00	,00	140,00	92,00	135,00	90,00	130,00	85,00	1,00				
2	12,00	49,00	,00	130,00	97,00	132,00	96,00	135,00	97,00	,00				
3	13,00	57,00	,00	150,00	102,00	140,00	101,00	145,00	99,00	,00				
4	14,00	63,00	1,00	145,00	99,00	120,00	80,00	125,00	85,00	1,00				
5	15,00	65,00	1,00	180,00	110,00	170,00	100,00	160,00	95,00	1,00				
6	16,00	72,00	,00	175,00	108,00	160,00	100,00	150,00	99,00	,00				
7	17,00	85,00	1,00	160,00	105,00	150,00	100,00	140,00	95,00	1,00				
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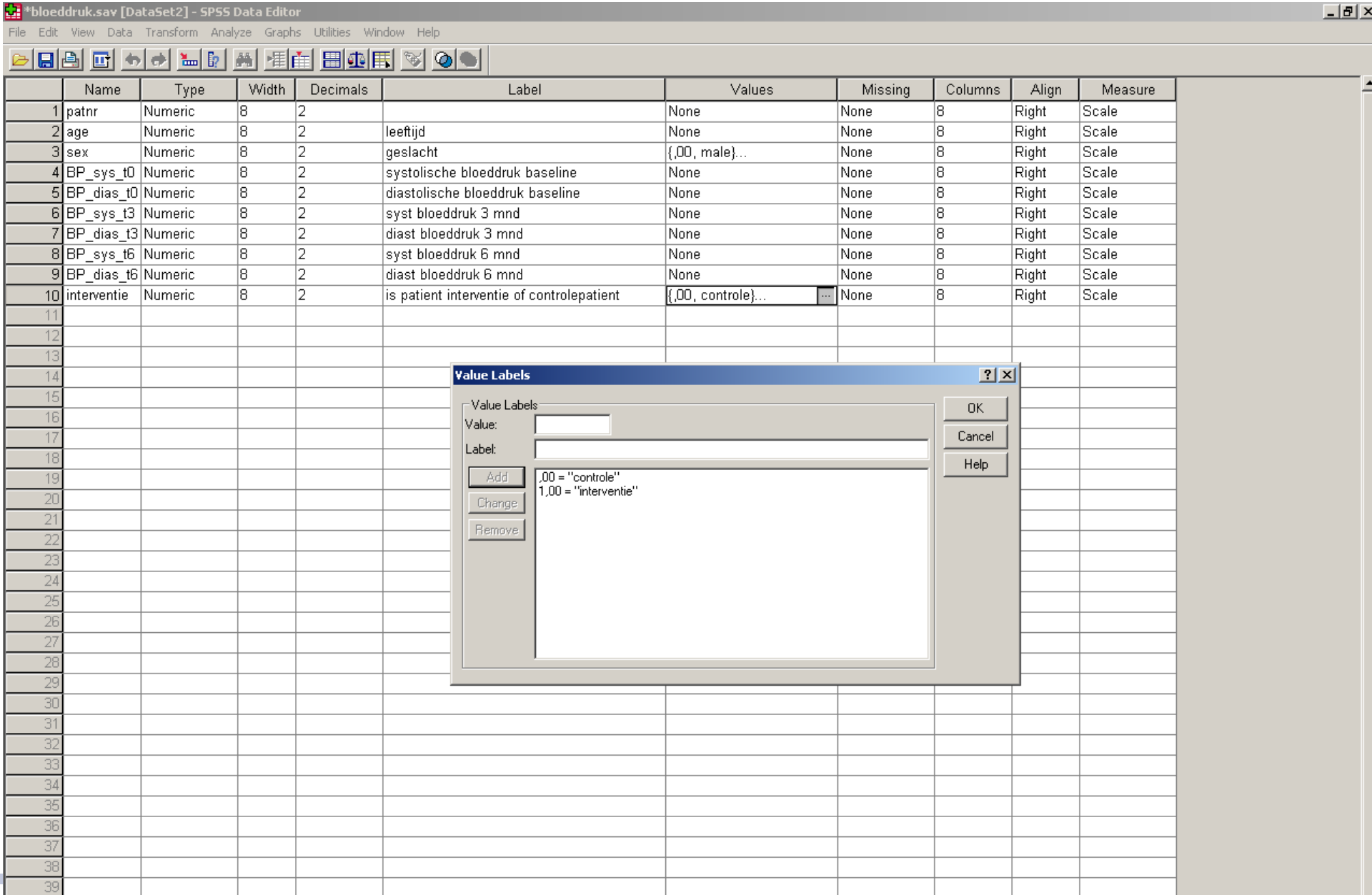
Data View Variable View

Besides data matrix….



	Name	Type	Width	Decimals	Label	Values	Missing	Columns	Align	Measure
1	patnr	Numeric	8	2		None	None	8	Right	Scale
2	age	Numeric	8	2	leeftijd	None	None	8	Right	Scale
3	sex	Numeric	8	2	geslacht	{,00, male}...	None	8	Right	Scale
4	BP_sys_t0	Numeric	8	2	systolische bloeddruk baseline	None	None	8	Right	Scale
5	BP_dias_t0	Numeric	8	2	diastolische bloeddruk baseline	None	None	8	Right	Scale
6	BP_sys_t3	Numeric	8	2	syst bloeddruk 3 mnd	None	None	8	Right	Scale
7	BP_dias_t3	Numeric	8	2	diast bloeddruk 3 mnd	None	None	8	Right	Scale
8	BP_sys_t6	Numeric	8	2	syst bloeddruk 6 mnd	None	None	8	Right	Scale
9	BP_dias_t6	Numeric	8	2	diast bloeddruk 6 mnd	None	None	8	Right	Scale
10	interventie	Numeric	8	2	is patient interventie of controlepatient	{,00, controle}...	None	8	Right	Scale

Workshop assignment

- Chose study design most appropriate for your study question
- Translate study question into:
  - Primary outcome
  - Secondary outcome(s)
  - Population characteristics
- Make data matrix including definition of labels and values of labels
  - Maximum of 10 variables (artificial selection)
- How to measure the 10 variables?

Questions

- Is a randomized controlled trial (randomization of patients) suitable for an intervention with respect to prescribing skills?
  - Yes
  - No
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