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GCP Refresher

Sven Trelle
CTU Bern
University of Bern

Tuesday, 7 June 2016, 9:00 – 12:00
Frauenklinik, Mehrzwekraum D 103

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The Swiss Human Research Act

The essentials regarding data

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English vs. German (incl. abbreviations)

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English

- Clinical Trials Ordinance (ClinO)
- Federal Office of Public Health (FOPH)
- Human Research Act (HRA)
- Human Research Ordinance (HRO)
- Swiss Ethics Committees on research involving humans (Swissethics)

German

- Verordnung über klinische Versuche (KlinV)
- Bundesamt für Gesundheit (BAG)
- Humanforschungsgesetz (HFG)
- Humanforschungs-verordnung (HFV)
- Schweizerische Ethik-kommissionen für die Forschung am Menschen

Terminology

- Trial == experimental study
  - Controlled conditions
  - Often randomized but necessarily (dose-finding studies, single-arm studies)
- Study == research project
  - Prospective or retrospective
  - General term including trials
  - Specific (research) question to be answered

Scope
(Art. 2 HRA)

Art. 2 Scope

[1] This Act applies to research concerning human diseases and concerning the structure and function of the human body, which involves:

a. persons;
b. deceased persons;
c. embryos and foetuses;
d. biological material;
e. health-related personal data.

[2] It does not apply to research which involves:

a. IVF embryos in accordance with the Stem Cell Research Act of 19 December 2003[1];
b. anonymised biological material;
c. anonymously collected or anonymised health-related data.

What research is (Art. 3 HRA)

Art. 3 Definitions

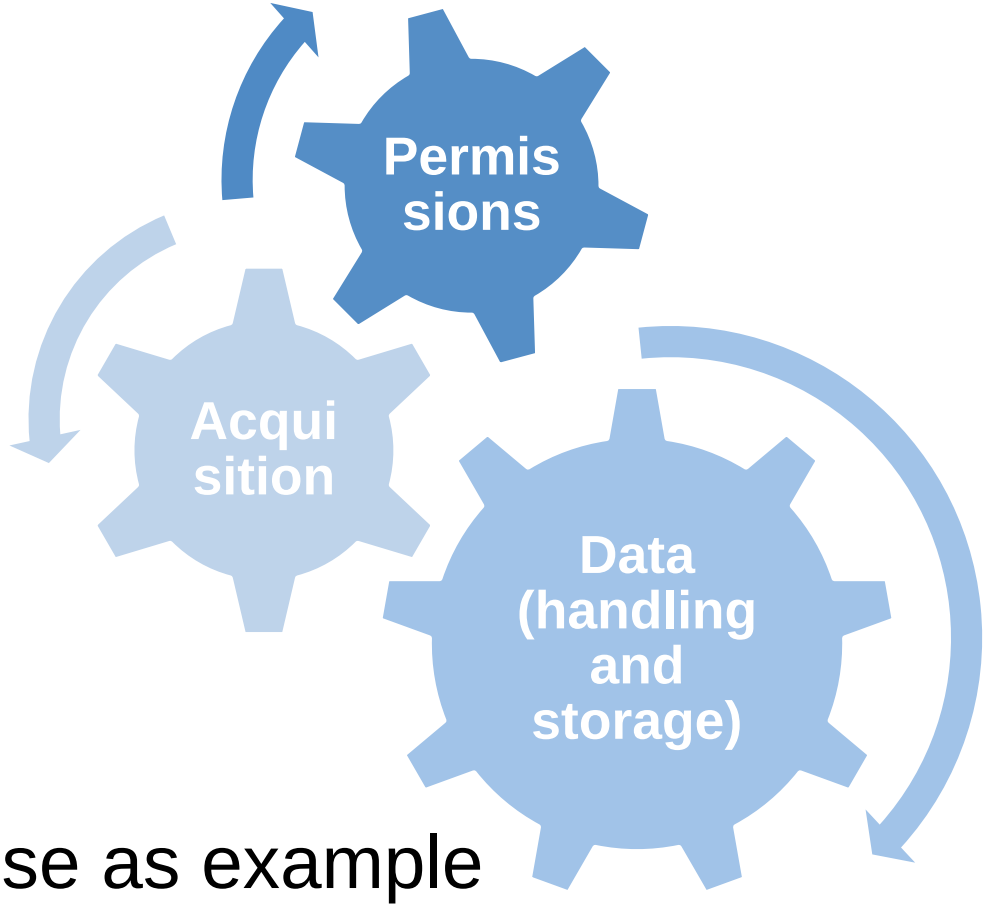
In this Act:

a. *Research* means method-driven search for generalisable knowledge;
b. *Research concerning diseases* means research on the causes, prevention, diagnosis, treatment and epidemiology of impairments of physical and mental health in human beings;
c. *Research concerning the structure and function of the human body* means basic research, in particular on human anatomy, physiology and genetics, and non-disease-related research concerning interventions and impacts on the human body;

- Research purpose
  - Data/sample collection without specific research question
- Research project (-question)
  - Specific research question (≈ outcome defined)

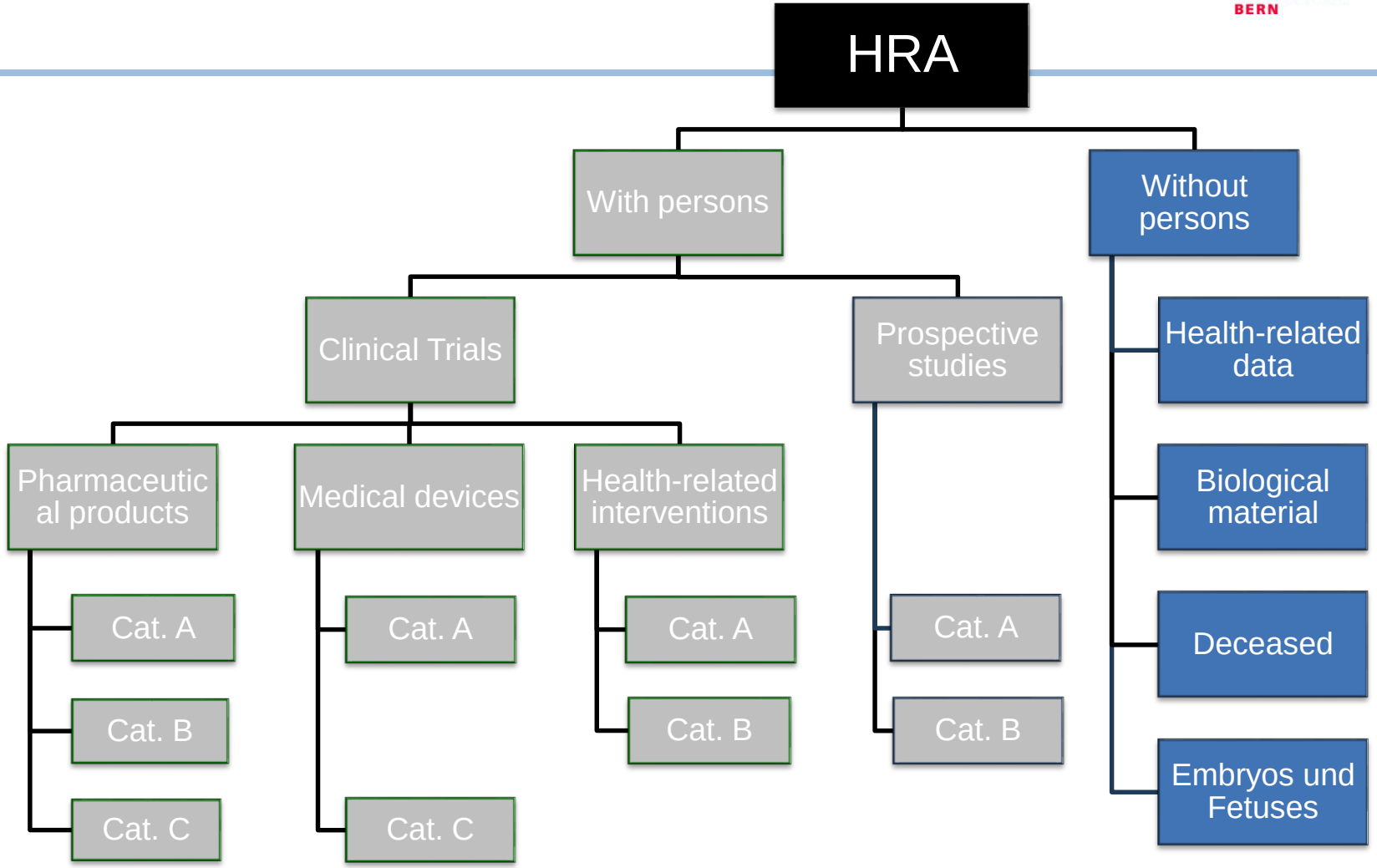
DATA UNDER THE HRA – THE CONCEPT

Framework



→ Further use as example

Overview


HRA
With persons
Without persons
Clinical Trials
Prospective studies
Health-related data
Pharmaceutical products
Medical devices
Health-related interventions
Biological material
Cat. A
Cat. A
Cat. A
Cat. A
Deceased
Cat. B
Cat. B
Cat. B
Embryos und Fetuses
Cat. C
Cat. C
ClinO
HRO

Further use
(Chapter 3, HRA)

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Art. 24 Further us

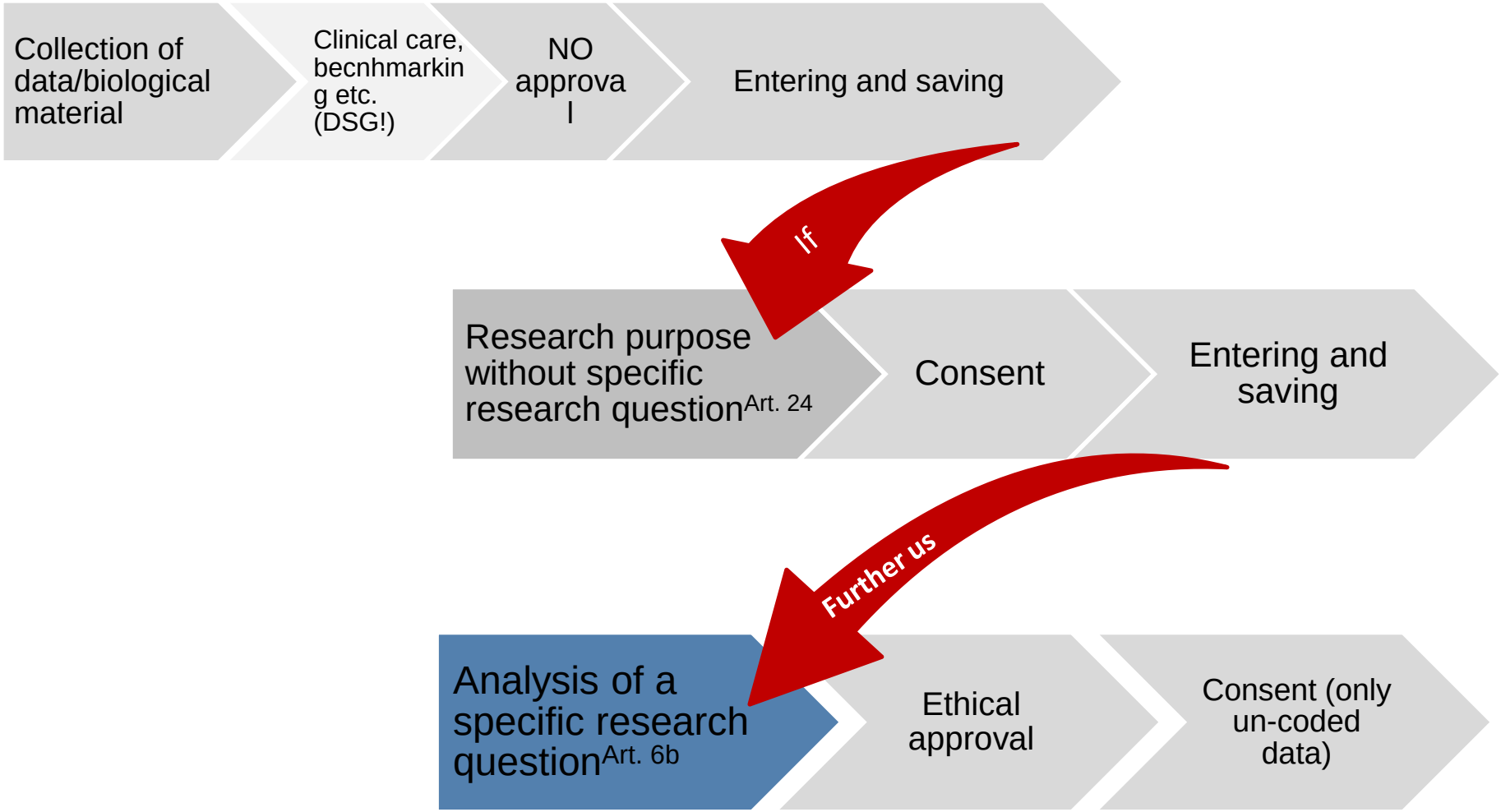
Further use of biological material and health-related personal data is defined as any handling, for research purposes, of biological material already sampled or data already collected, and in particular:

a. procuring, bringing together or collecting biological material or health-related personal data;
b. registration or cataloguing of biological material or health-related personal data;
c. storage or inclusion in biobanks or databases;
d. making accessible or available or transferring biological material or health-related personal data.

Research project (Chaper 3, HRA)

Art. 33 Research project
For the purposes of this Section, a research project is any project in which further use is made of biological material already sampled or health-related personal data already collected in order to answer a scientific question.

Consent and ethical approval



What are we doing when we perform a study?

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1. Definition of the data to be collected
2. Collect data (questions, assessments, examinations, …)
3. Record data from source data in a research database
4. Save data
5. (Data preparation)
6. (Save data)
7. Analyse data

> Start at 2: Research with persons
  — Ethical approval & informed consent
> Start at 3: Further use
  — Ethical approval & informed consent (for further use; often general consent; Art. 34 i.e. exemption possible!)
> Start at 3 and end at 6: Further use
  — Informed consent (for storage (& potential research questions)) (no ethical approval)
> Start at 5: Further use
  — Ethical approval & informed consent (for research question if not already done before; Art. 34 i.e. exemption possible!)

How do we get the already collected data?

- Look-up electronic health records, archive etc. and extraction
  - Patients primarily consented to the storage and use of their data **only** for health-care purposes **not** for any research purposes!
- → Requires explicit consent or general consent (earlier years: Generalbewilligung!)

How do we store and use data?

- With identifying information
  - Explicit consent
- Coded
  - No objection
- Anonymous
  - Outside the scope of the Human Research Act (HRA)

BUT!

Persons involved

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Usually

- Roles
  - Investigator
  - Study Nurse, Sub-Investigator
  - Statistiker
  - Zentrallabor
  - DSMB
  - Adjudication Committee
  - …

According to HRA

- Persons involved in the research project
- All others

Anonymous data

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Anonymous in the usual sense

- Identification of person impossible (or only with disproportionate efforts)
- For the person who uses the data

Anonymous according to the HRA

- Identification of person impossible (or only with disproportionate efforts)
- For the whole study team
  - Investigator
  - Study Nurse/Coordinator
  - Statistiker
  - …

Coded data

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Coding in the usual sense

- Data without identifying information («anonymous») but with ID e.g. consecutive number
- Key to decode ID separate e.g. patient-log

Coding according to the HRA

- Data without identifying information («anonymous») but with ID e.g. consecutive number
- Key to decode ID **not** controlled by **study team**
  - Trustee
  - Person not subjected to directions by members of study team

Reality

- Prospective studies always use identifying data (follow-up!), retrospective data very often
- Coded: extremely rare if at all
- Maybe anonymous

PROSPECTIVE STUDIES OTHER THAN CLINICAL TRIALS

Research with persons (Chapter 2, HRO)

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Art. 6 Research project

For the purposes of this Chapter, a research project is any project in which biological material is sampled or health-related personal data is collected from a person in order to:

a. answer a scientific question; or
b. make further use for research purposes of the biological material or the health-related personal data.

Initial questions

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1. What is my data?
   - Biological material
   - Genetic data
   - Health-related data
2. What are my aims?
   - Answering a specific question (research project) i.e. outcome defined
     - Prospective study (most often observational study)
   - Collecting/storing already available data/samples for future studies
     - Register, observational study without study-specific procedures, linkage studies, …
3. What type is my data?
   - Uncoded
   - Coded
   - Anonymized

Study-related assessments/procedures

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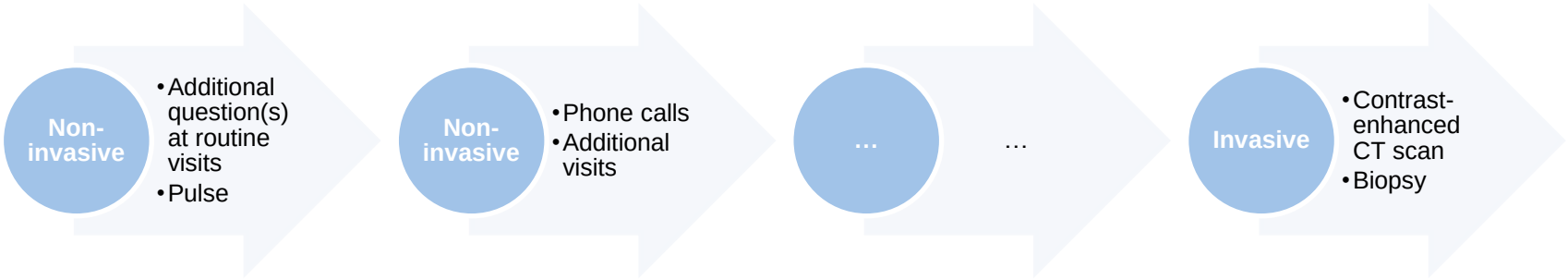
> **Anything** outside usual practice



Approval and consent («Bewilligung» and «Einwilligung»)

- (Independent) ethics committee
  - Assesses research project/question and **appropriateness** of study-related procedures (incl. qualification)
- Study participants
  - Approve (consent to) the usage of **their** data

→ No specific research question, no approval needed

→ BUT: Consent by study participants always needed (data sovereignty; it is their data!)

Feasibility & Costs

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Advanced GCP

Outline

- Feasibility
  - Recruitment
- Costs

Feasibility assessment domains

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- Intervention
  - Processes
  - Schedule
  - Availability
- Assessments
  - Deviations from standard of care
  - Availability (machines)
  - Schedule
  - Efforts, duration
- Eligibility and recruitment
  - Recruitment method
  - Informed consent procedure
  - Eligibility criteria (patient population)

Feasibility assessment items (examples)

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- Competing trials?
  - Enough patients
- Similarity to previous studies or completely new?
  - If similar, were these succesful?
- Integration in standard care?
- Visit schedule accepatable?
- Staff available?

- E.g. http://hub.ucsf.edu/sites/hub.ucsf.edu/files/FeasibilityChecklist_APRIL20132013.xls

Study design: intervention and assessments

- Threads for feasibility
  - Washout periods (tapering of current treatment)
  - Placebo control
  - Specialist equipment (intervention(s) or assessments)
  - Too many assessments or complex diary data
  - Invasive procedures especially in vulnerable populations
- Threads for approval
  - Not using the template
  - No explicit justification of study design
  - No detailed explanation of rescue intervention(s) and assessments
  - Protocol does not match to standard care
    - Assess for all (potential) centers practice for
      - Diagnosis
      - Treatment
      - Assessments
  - Invasive procedures in vulnerable populations

Discontinued (randomized) trials: Kasenda et al. JAMA 2014; 311: 1045

Research

Original Investigation

Prevalence, Characteristics, and Publication of Discontinued Randomized Trials

Benjamin Kasenda, MD; Erik von Elm, MD, MSc; John You, MD, MSc; Anette Blümle, PhD; Yuki Tomonaga, MSc; Ramon Saccilotto, MD, MSc; Alain Amstutz, BSc; Theresa Bengough, BSc; Joerg J. Meerpohl, MD; Mihaela Stegert, MD; Kari A. O. Tikkinen, MD, PhD; Ignacio Neumann, MD, MSc; Alonso Carrasco-Labra, MD, MSc; Markus Faulhaber, MD, MSc; Sohail M. Mulla, BSc; Dominik Mertz, MD, MSc; Elie A. Akl, MD, PhD, MPH; Dirk Bassler, MD, MSc; Jason W. Busse, DC, PhD; Ignacio Ferreira-González, MD, PhD; Francois Lamontagne, MD, MSc; Alain Nordmann, MD, MSc; Viktoria Gloy, PhD; Heike Raatz, MD, MSc; Lorenzo Moja, MD, MSc; Rachel Rosenthal, MD, MSc; Shanil Ebrahim, PhD; Stefan Schandelmaier, MD; Sun Xin, PhD; Per O. Vandvik, MD, PhD; Bradley C. Johnston, PhD; Martin A. Walter, MD; Bernard Burnand, MD, MSc; Matthias Schwenkglenks, PhD; Lars G. Hemkens, MD; Heiner C. Bucher, MD, MPH; Gordon H. Guyatt, MD, MSc; Matthias Briel, MD, MSc

IMPORTANCE The discontinuation of randomized clinical trials (RCTs) raises ethical concerns and often wastes scarce research resources. The epidemiology of discontinued RCTs, however, remains unclear.

OBJECTIVES To determine the prevalence, characteristics, and publication history of discontinued RCTs and to investigate factors associated with RCT discontinuation due to poor recruitment and with nonpublication.

DESIGN AND SETTING Retrospective cohort of RCTs based on archived protocols approved by

Editorial page 1019

Related articles pages 1063 and 1065

Supplemental content at jama.com

Kasenda et al.: prevalence and reasons

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- 1017 protocols of research ethics committees
  - Basel, Lucerne, Zurich, Freiburg i. Br./D, Hamilton/CA
- Prevalence: 25% (253/1017)

- Main reasons
  - Poor recruitment: 40%
  - Administrative e.g. strategy change (company), new regulatory requirements, move of PI: 15%
  - Futility including early-stopping: 15%
  - Harm: 9%
  - …
  - Lack of funding: 2%

Discontinued trials: Bernardez-Pereira et al. Am Heart J 2014; 168: 213

Cardiovascular Epidemiology

Prevalence, characteristics, and predictors of early termination of cardiovascular clinical trials due to low recruitment: Insights from the ClinicalTrials.gov registry

Sabrina Bernardez-Pereira, MD, MS,[a,b] Renato D. Lopes, MD, PhD,[c,d] Maria Julia Machline Carrion, MD, MS,[a] Eliana Vieira Santucci, MS,[a] Rafael Marques Soares, MS,[a] Matheus de Oliveira Abreu, MS,[a] Ligia Nasi Laranjeira, MS,[a] Dimas T. Ikeoka, MD, PhD,[a] Ana Denise Zazula, MD,[a] Frederico Rafael Moreira, MS,[a] Alexandre Biasi Cavalcanti, MD, PhD,[a] Evandro Tinoco Mesquita, MD, PhD,[b] Eric D. Peterson, MD, MPH,[c] Robert M. Califf, MD,[c] and Otavio Berwanger, MD, PhD[a], on behalf of the Methodological Evaluation of clinical TriAls (META) Study Group *Sao Paulo, Rio de Janeiro, Brazil; and Durham, NC*

Background Early termination of clinical trials due to low recruitment represents an understudied challenge for clinical research. We aimed to describe characteristics of cardiovascular trials terminated because of low recruitment and identify the major predictors of such early termination.

Methods We reviewed all cardiovascular clinical trials (7,042 studies) registered in ClinicalTrials.gov from February 29, 2000, to January 17, 2013, and assessed information about trials that were completed and those that were terminated early. Logistic regression models were developed to identify independent predictors of early termination due to low recruitment.

Results Our search strategy identified 6,279 cardiovascular clinical trials, of which 684 (10.9%) were terminated prematurely. Of these halted trials, the main reason for termination was lower than expected recruitment (278 trials; 53.6%)

Bernardez-Pereira et al.: prevalence and reasons

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- 6279 cardiovascular trials registered at clinicaltrials.gov 2000-2013
- Prevalence: 11% (684/6279)

- Main reasons
  - Poor recruitment: 41%
  - Administrative e.g. strategy change (company), new regulatory requirements, move of PI
  - Futility including early-stopping
  - Harm
  - Lack of funding
  - …

Risk factors for low recruitment

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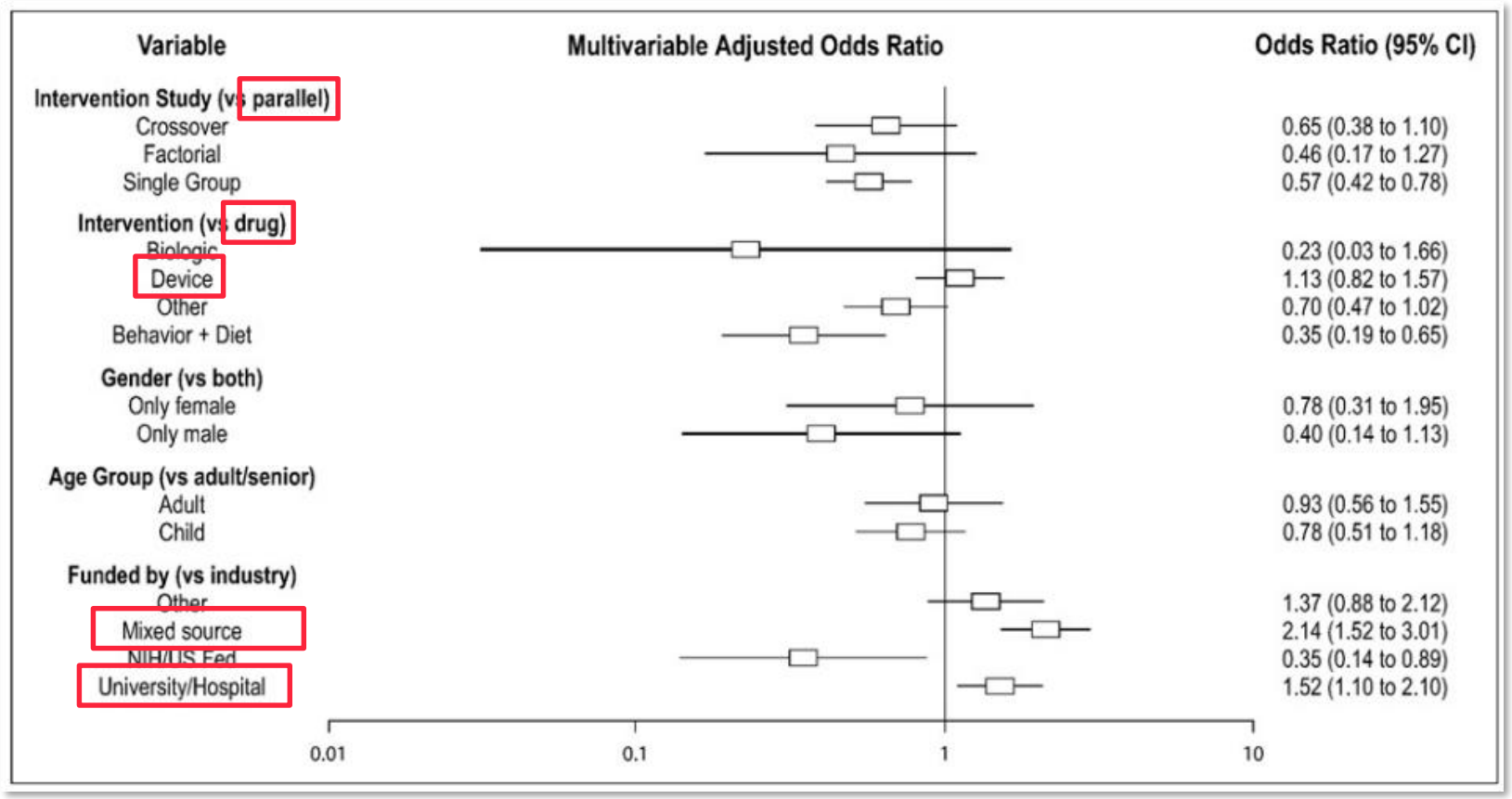
> Bernardez-Pereira et al.: discontinued due to low recruitment



Site-specific factors for recruitment

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- Levett et al. Clin Trials 2014; 11: 584. Above-average recruitment in a perinatal clinical trial
  - Implementation of a clearly defined 'system' of recruitment
  - Engagement of other staff
  - Time from ethics approval to first recruit
  - Provision of a dedicated trial coordinator
- Page et al. BMC Medical Research Methodology 2011; 11: 35. GP cluster randomised trial
  - Time constraints
  - Few eligible patients
  - Forgot to recruit patients
  - Confusion about recruitment strategies
  - Lack of patient interest and lack of patient incentives

Eligibility criteria

- Try to reduce number to an absolute minimum
- To ensure safety of participants and validity of the study
- Avoid trial-specific assessments and invasive procedures

Predicting recruitment during trial conduct

Barnard *et al. BMC Medical Research Methodology* 2010, **10**:63
http://www.biomedcentral.com/1471-2288/10/63

BMC
Medical Research Methodology

RESEARCH ARTICLE Open Access

A systematic review of models to predict recruitment to multicentre clinical trials

Katharine D Barnard*, Louise Dent, Andrew Cook

Abstract

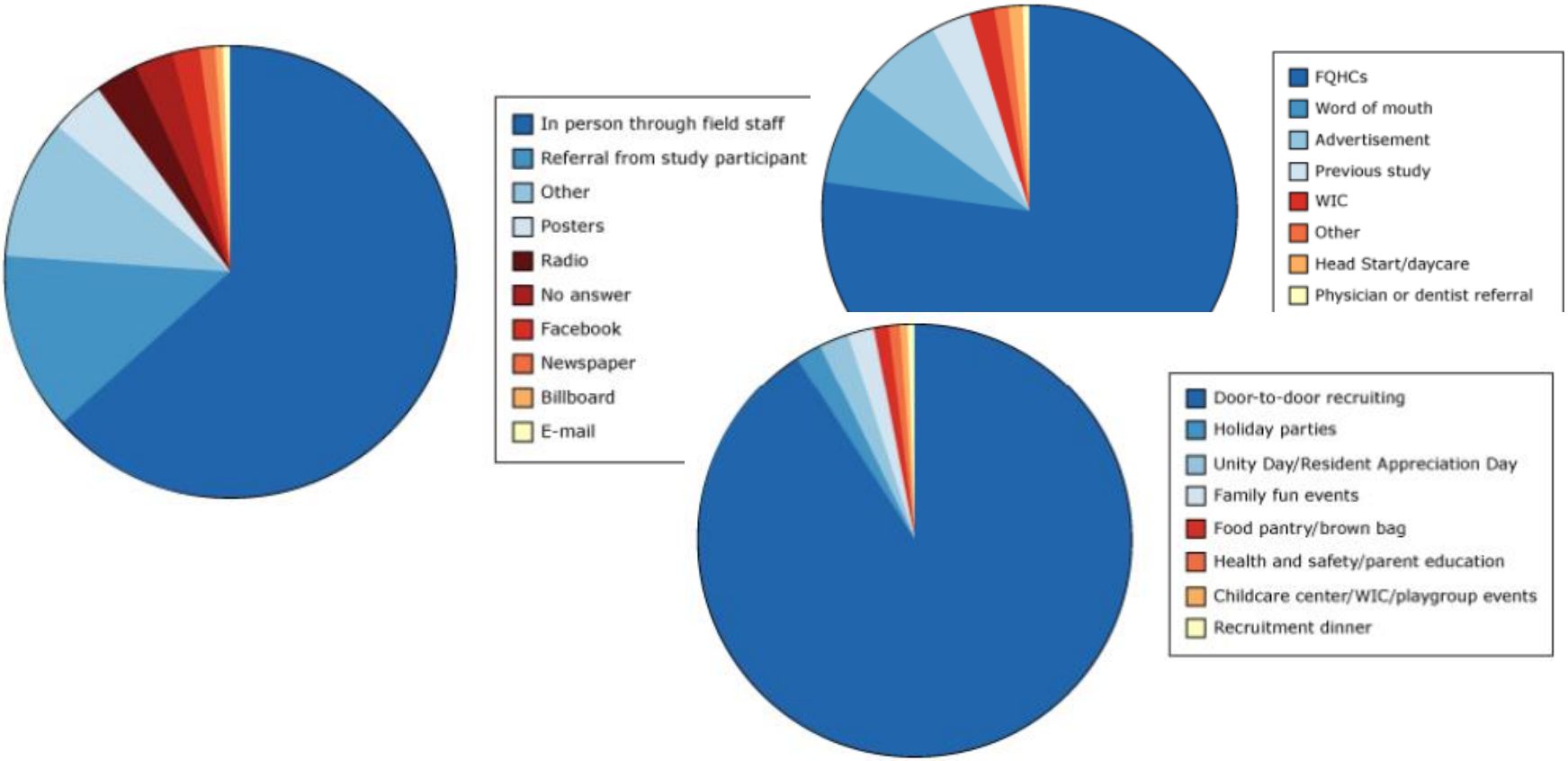
Background: Less than one third of publicly funded trials managed to recruit according to their original plan often resulting in request for additional funding and/or time extensions. The aim was to identify models which might be useful to a major public funder of randomised controlled trials when estimating likely time requirements for recruiting trial participants. The requirements of a useful model were identified as usability, based on experience, able to reflect time trends, accounting for centre recruitment and contribution to a commissioning decision.

Methods: A systematic review of English language articles using MEDLINE and EMBASE. Search terms included: randomised controlled trial, patient, accrual, predict, enrol, models, statistical; Bayes Theorem; Decision Theory; Monte Carlo Method and Poisson. Only studies discussing prediction of recruitment to trials using a modelling approach were included. Information was extracted from articles by one author, and checked by a second, using a pre-defined form.

Results: Out of 326 identified abstracts, only 8 met all the inclusion criteria. Of these 8 studies examined, there are

Special settings: challenges and approaches to enhance recruitment

- Community studies, preventive trials …
- Tiwari et al. Prev Chronic Dis 2014; 11: 140.



Costs

Budgeting a study project

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- Chronic disease randomized mega-trial
  - 20’000 patients
  - 1’000 study sites
  - 2 arms: drug A vs. B
  - Study length 48 months (first patient – last patient out)
- Congestive heart failure double-blind, randomized trial
  - 14’500 patients
  - 800 study sites
  - 3 arms: drug A vs. B vs. A+B
  - Outcomes: myocardial infarction, death, cardiovascular death, and nonfatal cardiovascular events (30% to be adjudicated by independent experts)
  - Study population comparable to previous mega-trials

Small group work

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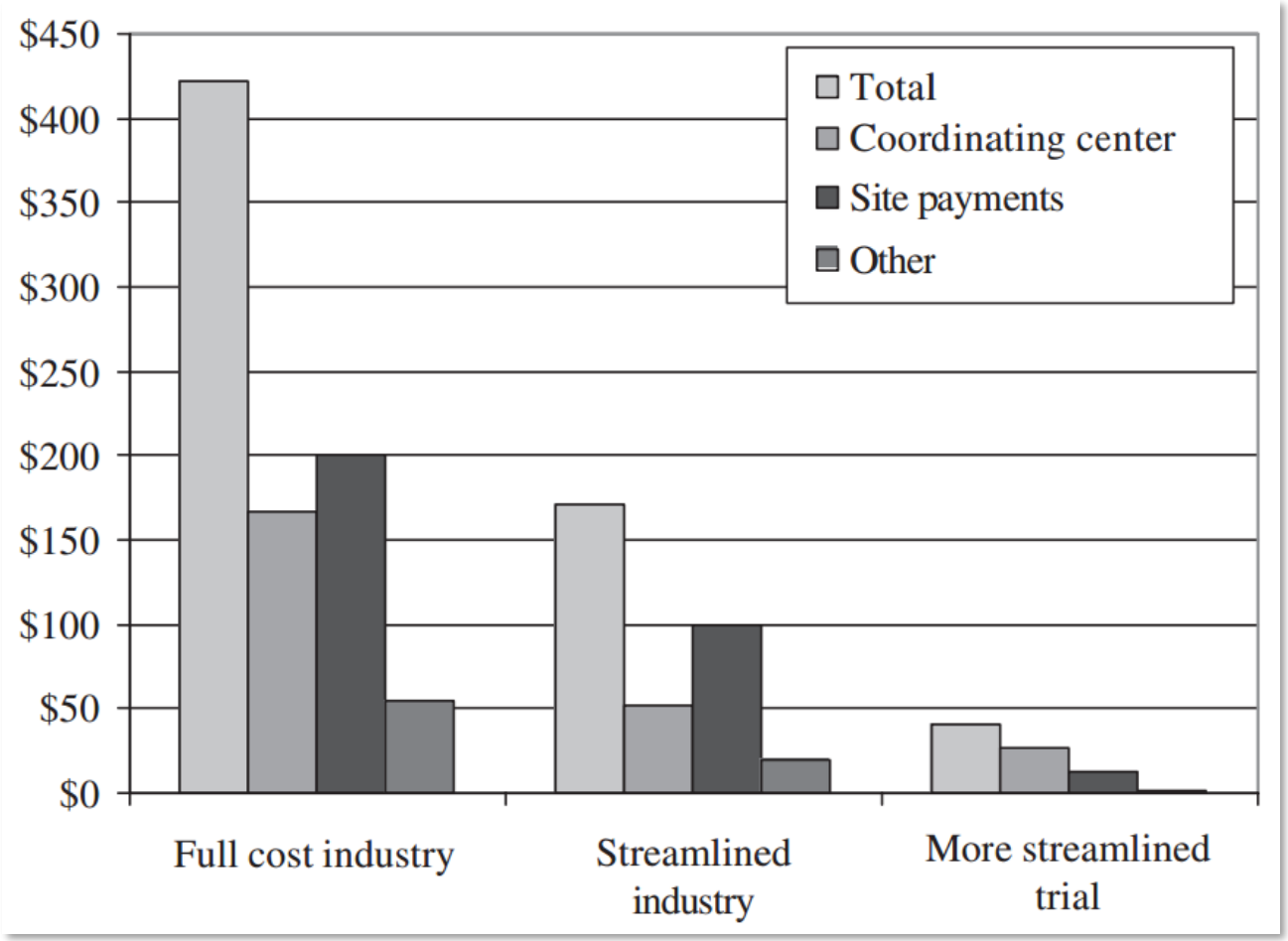
- With your neighbour
- Quickly discuss budget of one of these trials
- Consider the different cost domains
- 5-10 minutes

- Eyeballing!

Eisenstein et al. Clin Trials 2008; 5: 75: Chronic disease mega-trial



Potential for cost reductions

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Table 1 Economic simulations

	Full cost industry model	Trial components						Streamlined industry model	
		Planning	Enrollment	CRF length	Number of sites	EDC	Site management	$10,000 per Patient Site Payment	$5,000 Per Patient Site Payment
		6 > 4 months	24 > 18 months	60 > 20 pages	1000 > 750				
Total costs	$421.5*	$419.8	$414.8	$406.8	$385.9	$380.2	$332.5	$272.4	$171.4
Cost reduction		$1.7	$6.7	$14.7	$35.6	$41.3	$89.0	$149.1	$250.1
Percent cost reduction		0.4%	1.6%	3.5%	8.4%	9.8%	21.1%	35.4%	59.3%
After site payment Percent cost reduction		0.8%	3.0%	6.7%	16.2%	18.8%	40.6%	67.9%	67.9%

*$ in US 2007 Millions.

Eisenstein et al. Am Heart J 2005; 149: 482: Congestive heart failure trial

- 6 industry experts
- Short-Form Clinical Trials Cost Estimation Model by Duke Clinical Research Institute (DCRI)

Survey question	CHF trial
Months required for the entire study (planning through manuscript submission)	58 ± 12.5
Months sites would be active (enrollment, follow-up, closeout)	45 ± 11.6
Number sites*	800
Number pages in the case report form	78 ± 55.9
Number monitoring visits per site	12 ± 6.1
Number calls/ meetings for the Data and Safety Monitoring Board requiring honoraria	8 ± 3.6
Number drug kits produced	22,085 ± 11,420
U.S. site payment	$4733 ± $2380
Percent cases to Clinical Events Committee*	30%

Data listed are numbers, means with SD, or percentages.
*These amounts were fixed as part of the case scenarios.

Eisenstein et al. Am Heart J 2005; 149: 482: Congestive heart failure trial

Cost center	CHF trial	
	Costs	Percentage
Site payments	$68,633,333 ± $34,516,904	48%
Site management	$42,159,167 ± $11,846,592	30%
Data management and statistics	$16,162,917 ± $5,126,069	11%
Pharmacy	$6,658,375 ± $3,140,483	5%
Safety and Clinical Events Committee	$4,688,333 ± $4,693,896	3%
Project planning	$3,920,333 ± $671,209	3%
Publications*	$40,000	0%
Total costs	$142,262,458 ± 40,937,930	100%

All costs expressed in 2001 $U.S., as means with SD.
*Cost fixed in case scenario.

Site-specific costs/coverage analysis I

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Start Up | Close Out | Invoicables | Per Patient

Categories of tasks

- Protocol-related tasks
- Budget-related tasks
- IEC Docs
- Training
- Pharmacy communication
- Communications w/Sponsor

FEES

- Advertisement
- Office supplies
- Pharmacy start-up, inventory
- Translation of Informed Consent

Tasks

- Complete Feasibility Questionnaire from Sponsor
- Review protocol & study flow
- (Review by Scientific Review Committee)
- Preparation and return of Sponsor/Site documents
- Pre-Study Site Selection visit, prepare for & attend
- Prepare, distribute, collect and copy financial disclosures
- Obtain and copy CV's
- Preparatory Research
- CMS determination

Site-specific costs/coverage analysis II

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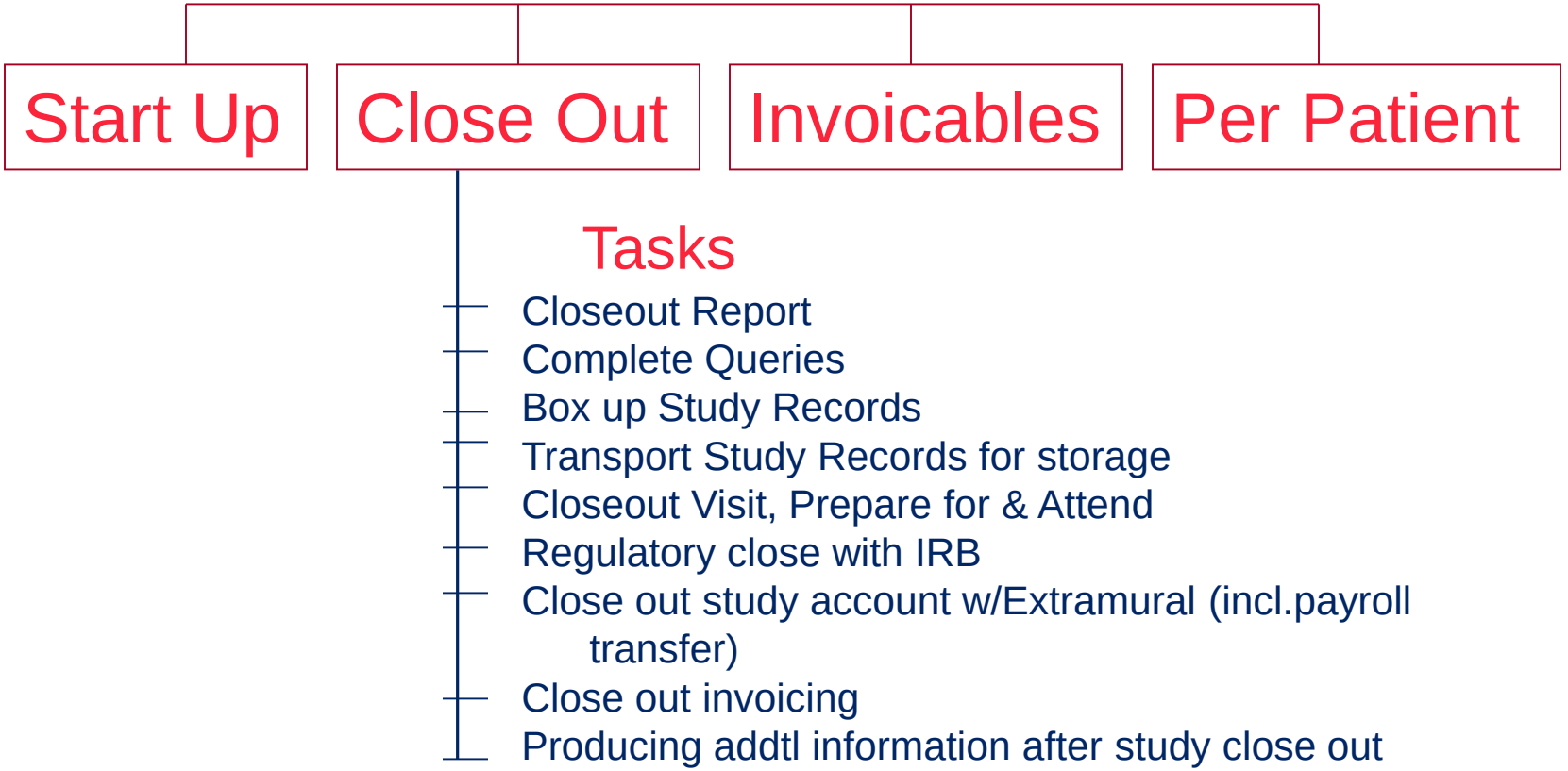
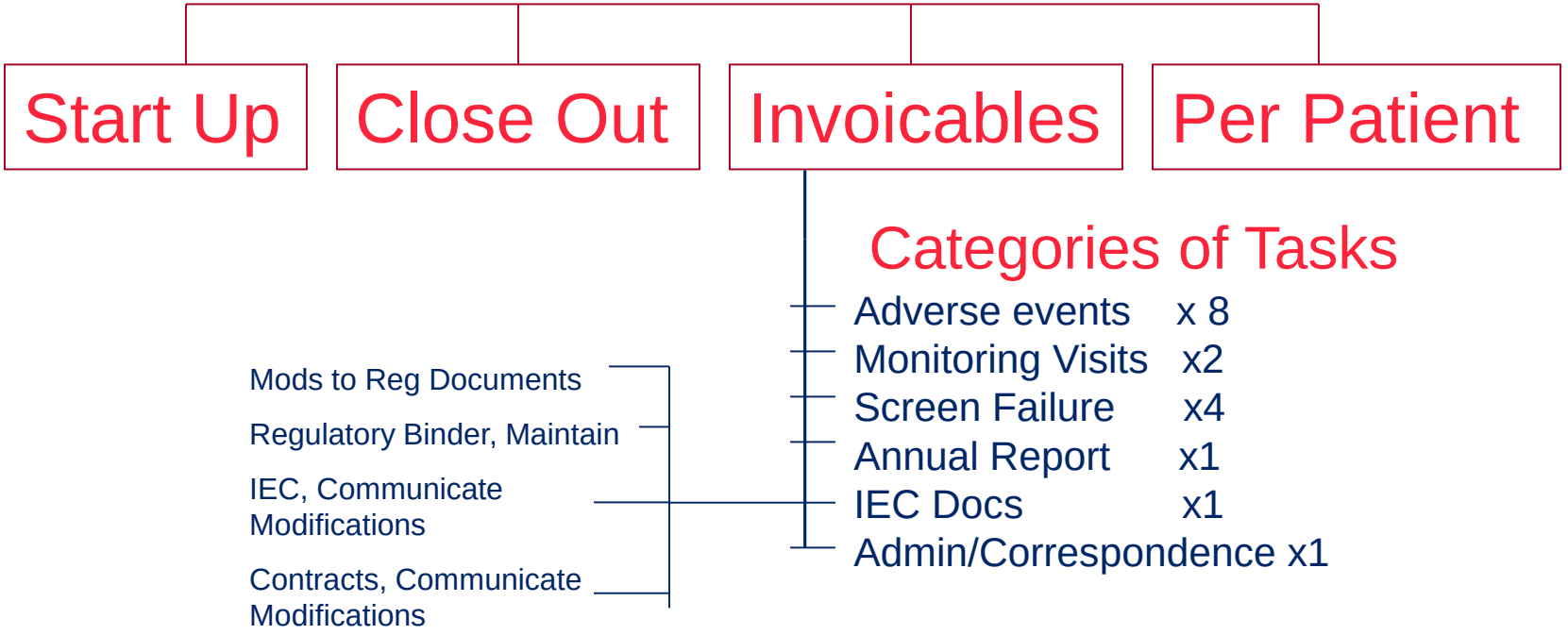


Site-specific costs/coverage analysis III



Invoicables may or may not happen
Each category multiplied by the number of occurrences
Must include to come up with the total budget

Site-specific costs/coverage analysis IV

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Start Up | Close Out | Invoicables | Per Patient

Schedule of Study Assessments *

Procedure	Screening ≤ 28 days from Baseline (First day of drug administration)	Cycle 1,2				Cycles 3,4,5,6		Discontinuation From Protocol Therapy	Follow-Up Phase
		Day 1	Day 8	Day 15	Day 22	Day 1	Day 14		Every 6 months
Informed Consent	X								
Record prior medications, treatments	X								
History, physical examination, vital signs, weight	X	X[9]				X	X	X	
ECOG performance status	X	X[9]				X	X	X	
Chest x-ray[1], Urinalysis	X								
ECG	X							X	
Hematology	X	X[9]		X		X	X	X	
Serum chemistry, LFTs[4]	X	X[9]		X		X[4]	X[4]	X	
Pregnancy testing[5]	X[6]	X	X	X	X	X[6]	X[6]	X[6]	

Overall study budget

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Fixed and up-front costs

> Are needed for study conduct and incurred whether or not a subject is enrolled

Per-participant costs

> Related to participant visits (assessment, personnel, consumables, …)

Dissecting the protocol

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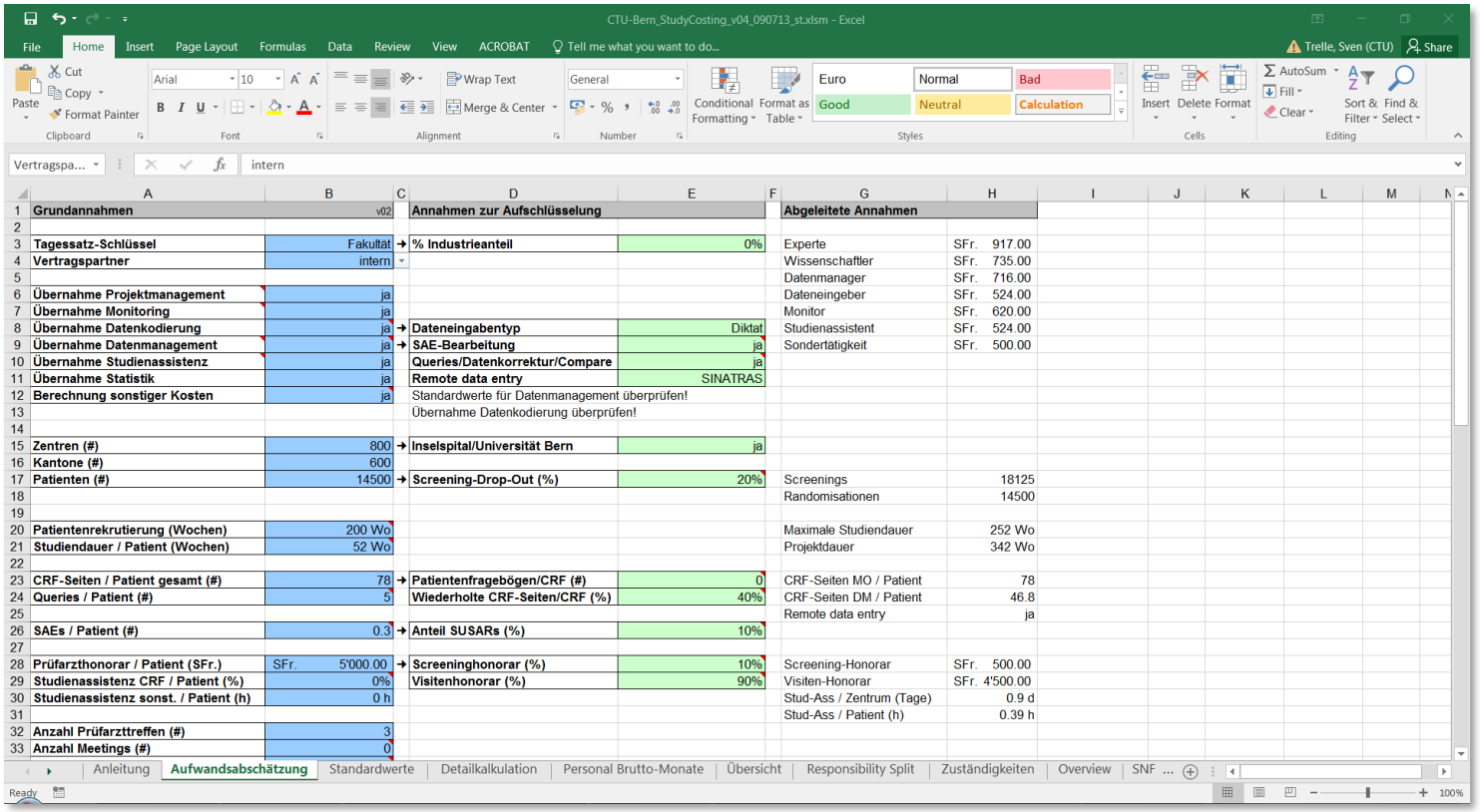
- Visit schedule
  - Identify all items that will generate expenses for the site
  - Number and complexity of participant visits
- Laboratory assessments
- …
- Hidden study costs
  - Delayed start
  - Informed consent process
  - Increased salaries & operating costs over time
  - Travel to clinics or offsite locations, overnight stays, meals
  - Unscheduled visits
  - Audits
  - Pharmacy
  - Amendments
  - Queries
  - …

Tools

- Commercial software
- Extensive Excel sheets (Google)



CTU-Bern_StudyCosting_v04_090713_st.xlsm - Excel

	A	B	C	D	E	F	G	H
1	**Grundannahmen**	v02		**Annahmen zur Aufschlüsselung**			**Abgeleitete Annahmen**	
2								
3	**Tagessatz-Schlüssel**	Fakultät	→	**% Industrieanteil**	0%		Experte	SFr. 917.00
4	**Vertragspartner**	intern					Wissenschaftler	SFr. 735.00
5							Datenmanager	SFr. 716.00
6	**Übernahme Projektmanagement**	ja					Dateneingeber	SFr. 524.00
7	**Übernahme Monitoring**	ja					Monitor	SFr. 620.00
8	**Übernahme Datenkodierung**	ja	→	**Dateneingabentyp**	Diktat		Studienassistent	SFr. 524.00
9	**Übernahme Datenmanagement**	ja	→	**SAE-Bearbeitung**	ja		Sondertätigkeit	SFr. 500.00
10	**Übernahme Studienassistenz**	ja		**Queries/Datenkorrektur/Compare**	ja			
11	**Übernahme Statistik**	ja		**Remote data entry**	SINATRAS			
12	**Berechnung sonstiger Kosten**	ja		Standardwerte für Datenmanagement überprüfen!				
13				Übernahme Datenkodierung überprüfen!				
14								
15	**Zentren (#)**	800	→	**Inselspital/Universität Bern**	ja			
16	**Kantone (#)**	600						
17	**Patienten (#)**	14500	→	**Screening-Drop-Out (%)**	20%		Screenings	18125
18							Randomisationen	14500
19								
20	**Patientenrekrutierung (Wochen)**	200 Wo					Maximale Studiendauer	252 Wo
21	**Studiendauer / Patient (Wochen)**	52 Wo					Projektdauer	342 Wo
22								
23	**CRF-Seiten / Patient gesamt (#)**	78	→	**Patientenfragebögen/CRF (#)**	0		CRF-Seiten MO / Patient	78
24	**Queries / Patient (#)**	5		**Wiederholte CRF-Seiten/CRF (%)**	40%		CRF-Seiten DM / Patient	46.8
25							Remote data entry	ja
26	**SAEs / Patient (#)**	0.3	→	**Anteil SUSARs (%)**	10%			
27								
28	**Prüfarzthonorar / Patient (SFr.)**	SFr. 5'000.00	→	**Screeninghonorar (%)**	10%		Screening-Honorar	SFr. 500.00
29	**Studienassistenz CRF / Patient (%)**	0%		**Visitenhonorar (%)**	90%		Visiten-Honorar	SFr. 4'500.00
30	**Studienassistenz sonst. / Patient (h)**	0 h					Stud-Ass / Zentrum (Tage)	0.9 d
31							Stud-Ass / Patient (h)	0.39 h
32	**Anzahl Prüfarzttreffen (#)**	3						
33	**Anzahl Meetings (#)**	0						

Anleitung | Aufwandsabschätzung | Standardwerte | Detailkalkulation | Personal Brutto-Monate | Übersicht | Responsibility Split | Zuständigkeiten | Overview | SNF

Development costs for a drug

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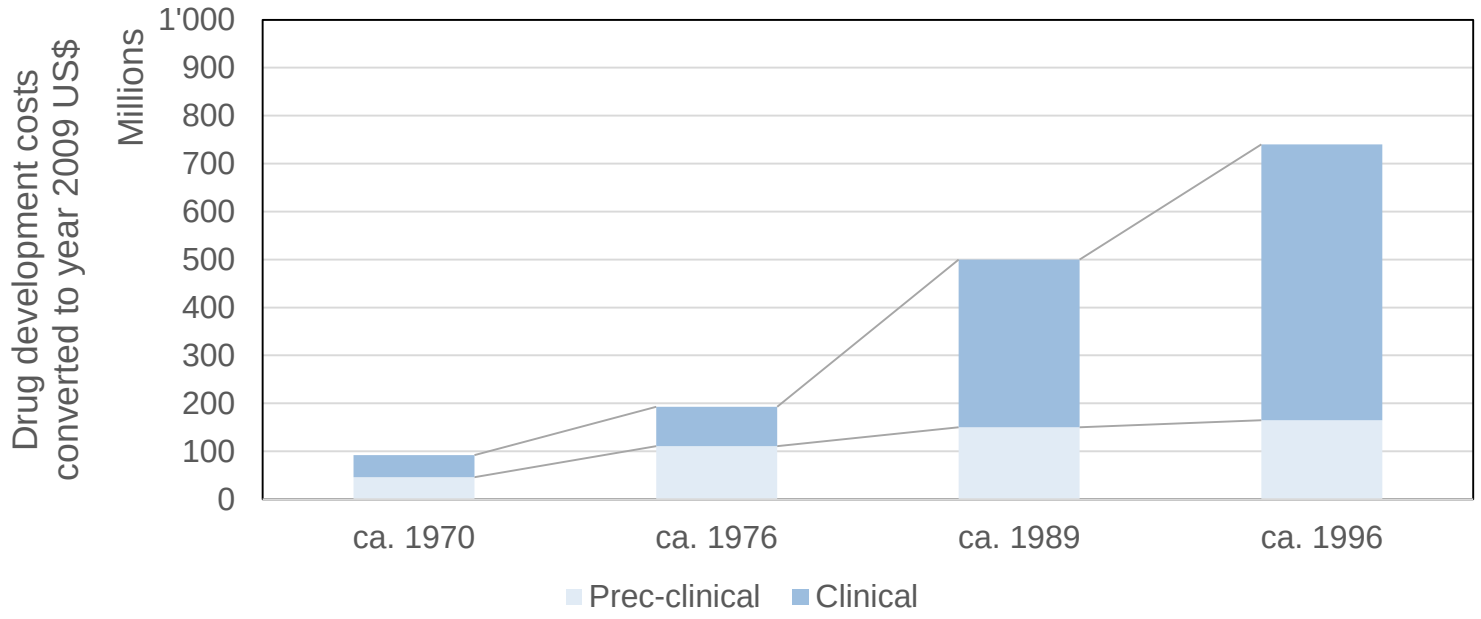
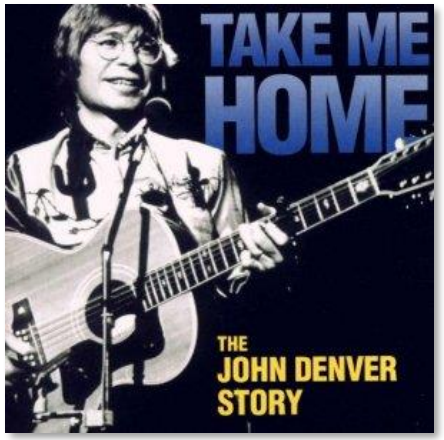
- DiMasi et al. J of Health Econ 2003; 22: 151.
  - Ca. 800 Mio. US$
- Adams and Brantner. Health Aff 2006; 25: 420.
  - Ca. 870 Mio. US$ (500 to 2000 Mio. US$)



Morgan et al. Health Policy 2011; 100: 4-17

Take home message



- Feasibility
  - Eligibility criteria
  - Time
  - Dedicated study staff
  - Integrated into daily practice
- Overall study budget
  - Difficult (even experts usually underestimate overall study budget by at least 10% often more than 15%)
  - Dissect protocol
  - Eyeballing
    CHF 500/participant == very (too) cheap
    CHF 1000/participant == (still too) cheap
    CHF 10’000/participant == not necessarily exaggerated