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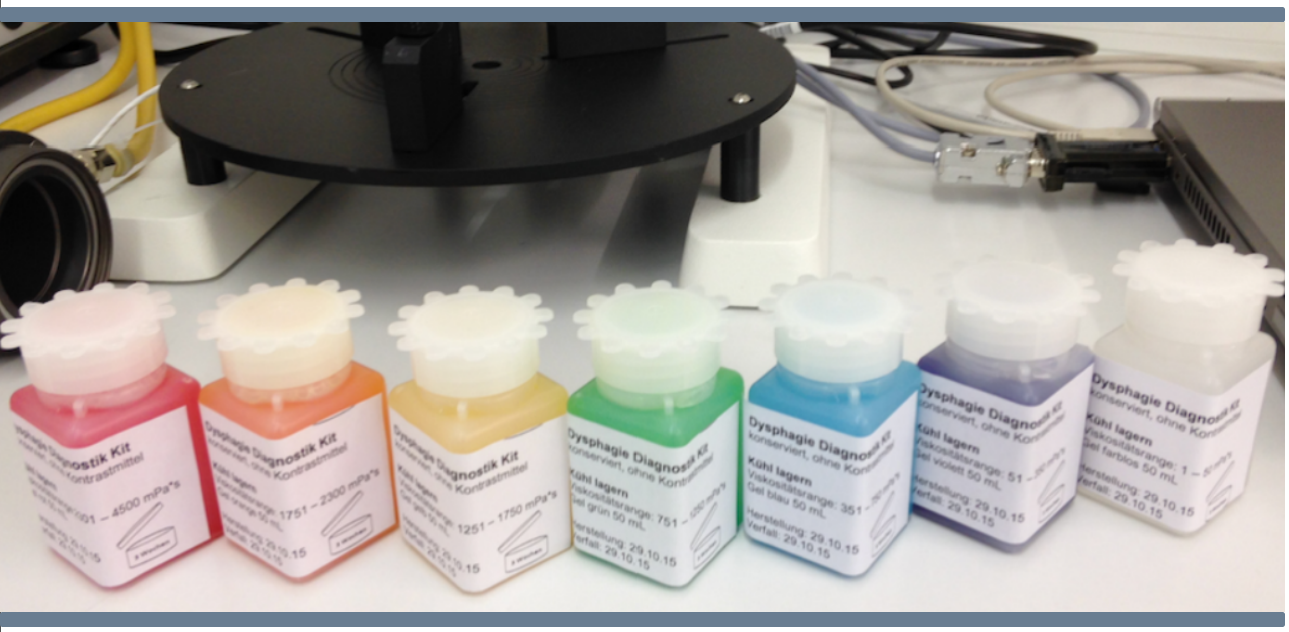
Haute école spécialisée bernoise
Bern University of Applied Sciences

Universität Zürich[UZH]

Psychiatrische Universitätsklinik Zürich

eahp
european association of hospital pharmacists



EAHP ACADEMY SEMINAR
30 September – 1 October 2017,
Vienna, Austria

Hospital Pharmacy Practice Research– Scientific Quality

Examples of research and development without patients involved

Derived from „non-clinical“ hospital pharmacy topics

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- University Hospital of Psychiatry PUK ZH, Internal Medicine Services, Hospital Pharmacy, CH-8008 Zürich, helena.jenzer@puk.zh.ch

Disclosure of conflicts of interest

- Nothing to declare
- My main interest is the patient's outcome (according to the Hippocratic Oath)
- No research fundings from private sources

Contents

- Research with or w/o persons, clinical or non-clinical, prospective or retrospective
  - Options and examples of research fields and activities out of wards
- Research by data aggregation
  - Literature Reviews
  - Meta-analysis
- Forecasting and Simulation
  - Linear
  - Non-linear systems dynamics approach

Evaluation of Learning Success

- Do Research Acts regulate only intervention studies with human study participants? (y/n)
- Does research with anonymised data need approval by an ethical committee's approval? (y/n)
- Can samples from biological material taken from previous diagnostic interventions be used freely for any research? (y/n)

Human Research – with or without patients involved?

Critical incidences in Clinical Trial Phase I (France 2015)

- Compound BIA 10-2474 (pain relief by acting on cannabinoid receptors)
- Rennes University Hospital Centre
  - 1 brain dead
  - 5 persons hospitalised with neurological symptoms
  - 90 healthy volunteers enrolled in trail
- Answers needed
  - Dosing? (oral)
  - Drug-induced symptomes or contamination-induced?
  - Dosed in parallel or sequentially
- Further incidence in Clinical Trials
  - Tegenero trial of TGN 1412 (London 2006)
  - six volunteers experienced cytokine storm after receiving a CD28-targeting superagonist

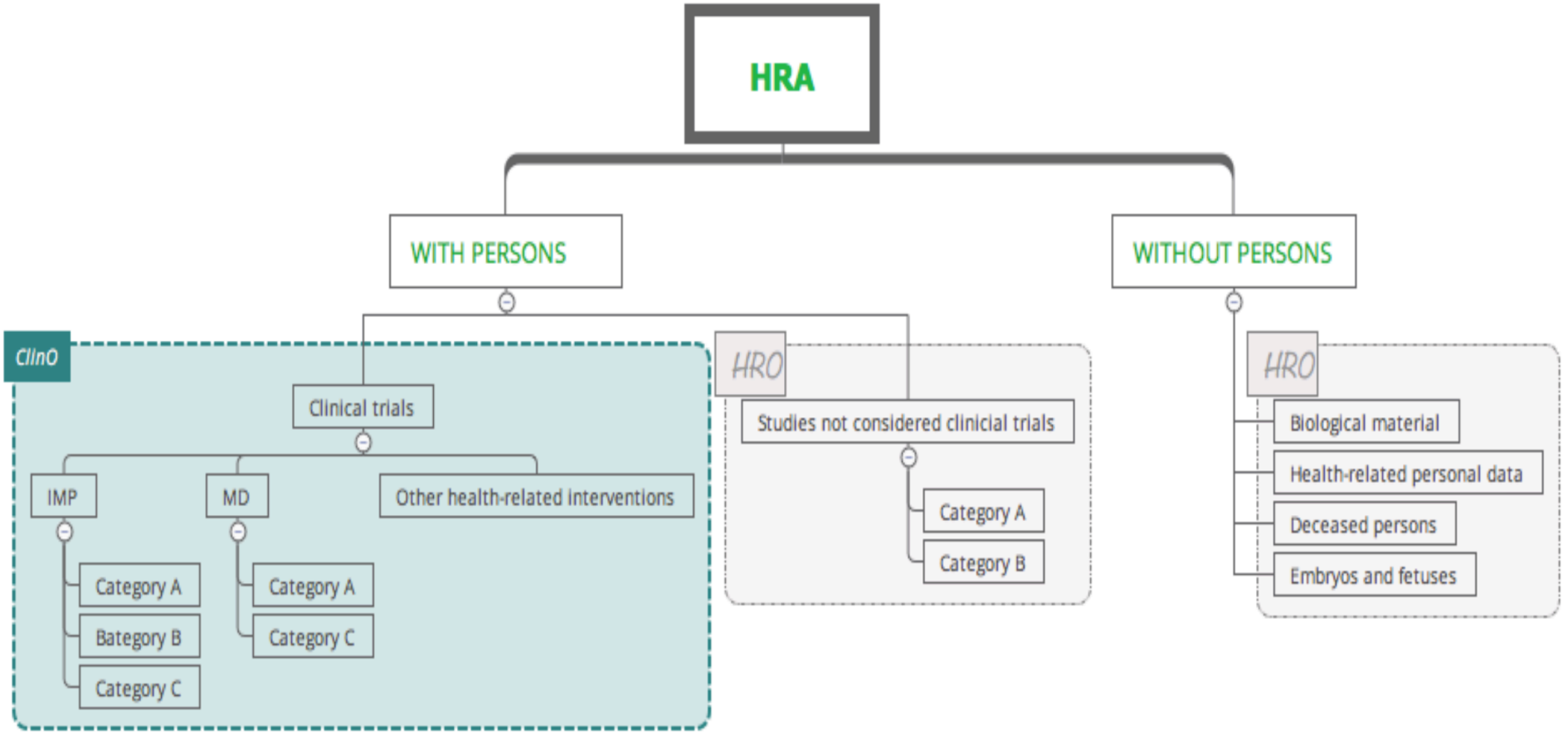
Basic question

- Would you include a member of your family in the study?
  - Compound BIA 10-2474 (pain relief by acting on cannabinoid receptors)
  - Tegenero trial of TGN 1412 (London 2006)
- Would you give consent for further research on biological material taken from one of your family members?
- Instead of you: an ethical committee will supervise the conformity to legal frames
- Criteria for approval
  - minimised risk
  - reasonable risk / benefit ratio
  - equitable subject selection
  - informed consent process
  - informed consent documented
  - data monitores for safety
  - confidentiality / privacy maintained
  - vulnerable populations protected (i.e. children, adolescents, mentally incapacitated or unconscious adults, prisoners, pregnant women, economically or educationally disadvantaged persons)
- Bern University Hospital Inselspital: Director of education and research asks patients by means of a leaflet to agree generally to the use of their biological material or health-related data for biomedical research.

Clinical trial - definition

- *"Any research project that prospectively assigns human subjects to a health related intervention to determine its effects on health, structure or function of the human body"*
  (Federal Act on Research involving Human Beings, [Human Research Act HRA], CH, SR 810.30], of 30 September 2011, in force 1 January 2014)
- applies to research concerning
  - human diseases
  - structure and function of the human body
- and carried out
  - on persons (and deceased persons)
  - on embryos and fetuses
  - using biological material
  - using health-related personal data
- does not apply to
  - IVF embryos (in accordance with the stem cell research act)
  - anonymised biological material
  - anonymously collected or anonymised health-related data
- principles
  - informed consent
  - risk-benefit ratio must not be to the disadvantage of the person
  - mentally disabled persons might be included if results cannot be obtained with healthy persons
  - individual protection must be warranted

HRA (Swiss – Overview)



Clinical trials with medicinal products (ClinO Art 19, for IMP)

- Category A if MP is authorised in CH and use is
  - in accordance with prescribing information
  - indication or dosage different from specification in prescribing information
    - but within the same ICD group
    - but dosage is lower than specified
  - in accordance with internationally accepted quality criteria
- Category B if MP is authorised in CH and use is different from Category A
- Category C if MP is not authorised in CH

Clinical trials with medical devices (ClinO Art 20, for MD)

- Category A if MD
  - bears conformity marking and
  - is used in accordance with instructions
- Category C if MD
  - does not bear conformity marking
  - is not used in accordance with the intended purposes or
  - is prohibited in CH

Research closely related and derived from RCT (might be difficult to delimit)

- Compassionate use
- Parallel Trial / Early Access Program
- Experimental Therapy ("Heilversuche", off-label uses)
- No ethical approval needed if indicated for a single person or a defined group of special patients
- Ethical obligations (to fulfill also in non-clinical trials)
  - systematic use of prior evidence
  - adequate design and sample size
  - feasibility
  - complete, non-selective publication
  - timely reporting of serious adverse events to approval bodies ad review boards
- Example:
  Treatment of 10 autistic children with Calcium Levofolinate (mechanism: improve cerebral folate deficiency; effect on autism as a calcium channelopathy)

Example of a wound healing study

- Efficacy of honey for wound healing (shallow wounds, abrasions)
  - Focused research question (PICO)
    - 100 treated participants, 100 control, aged 18-35, acute, simple cases, lower legs, endpoint: length of time to granulation, exclusion: infection, necrosis, malnutrition, intermediate and complex wounds, compared to alginates
  - Prior evidence and relevance
    - old treatment against modern wound care
  - Appropriate study design
    - RCT, but not blinded
  - Outcome measures (primary, secondary; safety; what is assessed by whom, when and how?)
    - wound treated and assessed at renewal of dressing by wound care team, up to granulation maximum 4 days (secondary outcome: stagnation)
  - Setting (recruitment of participants, centers, etc)
    - Dermatology, out-patients
  - Does it fulfill the definition of a clinical trial?
    - Yes (RTC, but not blinded)

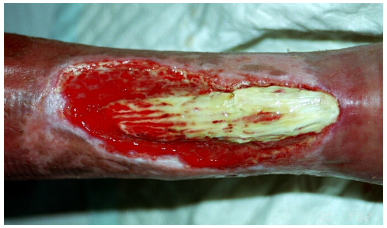
Example of a diagnostic urinary marker test

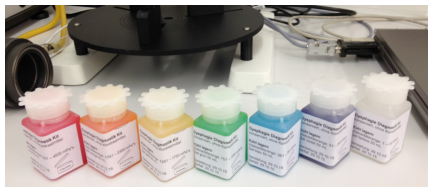
- Use of a biomoarker test in the own setting
  - Focused research question (PICO: Population, Index test, Comparator test, Outcome)
    - target condition: disease status to be defined
  - Outcome measures (primary, secondary outcome; safety; what is assessed by whom, when and how?)
  - Setting (recruitment of participants, centers, etc)
  - Does it fulfill the definition of a clinical trial?
    - no (observational study, no risk, runs under HRO)

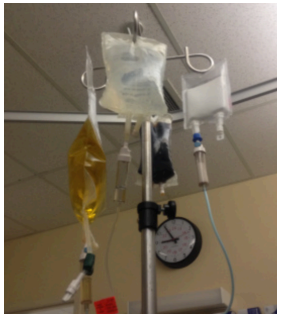
Hospital Pharmacy Research w/o patients involved as alternatives to Clinical Trials

Which aim: New knowledge or innovation?

- Basic research brings new knowledge (-> SNSF fundings)
- Applied research brings innovation (-> CTI fundings)



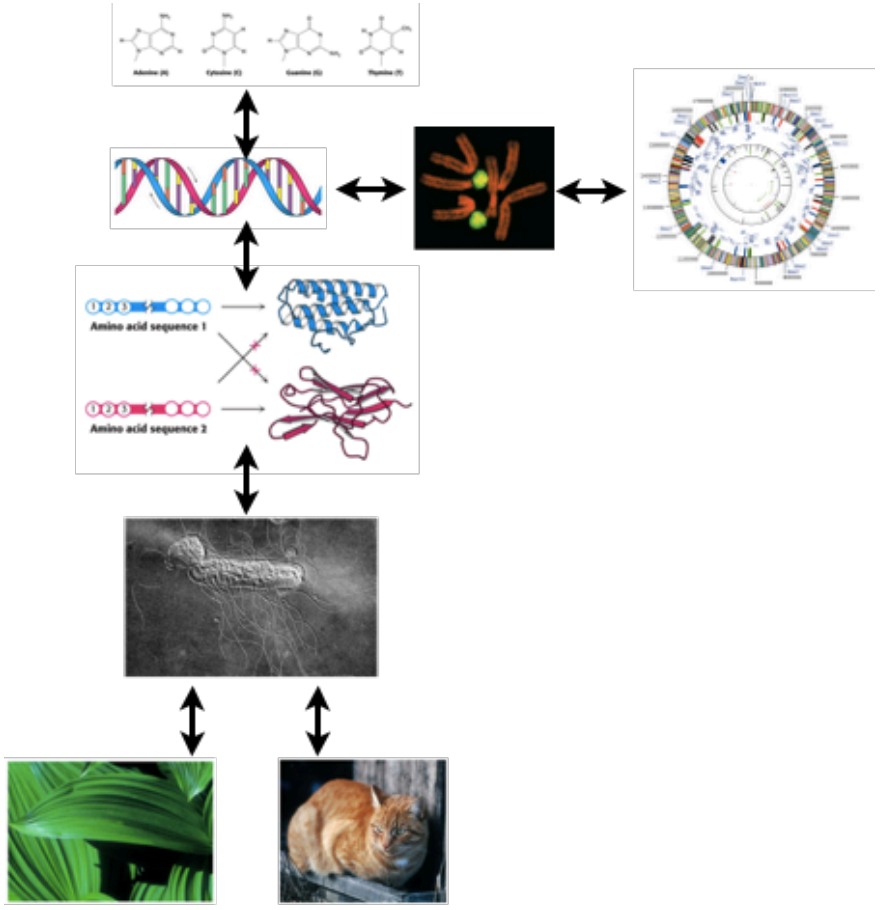




Methods and Objects - Natural Sciences versus „biological“ Methods (misuse of the patient as black box)

Input

Output

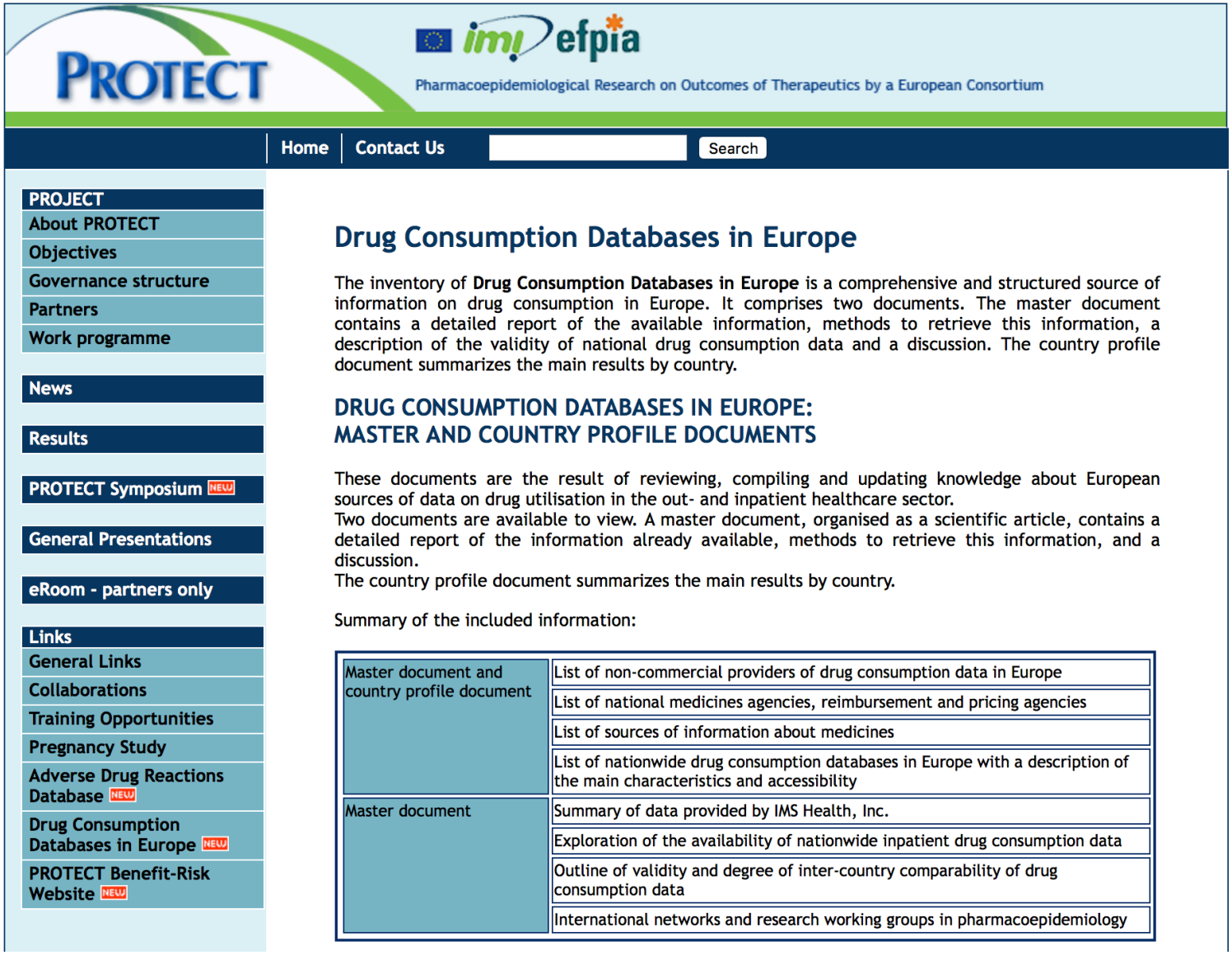


Bildquelle:
Berg, Biochemistry, 2002

Retrospective non-clinical trial
(HRA does not apply, in general no ethical approval needed)

- applies to research concerning
  - human diseases
  - structure and function of the human body
- and is carried out
  - on persons (and deceased persons)
  - on embryos and fetuses
  - using biological material
  - using health-related personal data
- but is
  - anonymised biological material
  - anonymously collected or anonymised health-related data
- Example
  - The use of open access databases is suitable for research in Pharmacoeconomics and Pharmacoepidemiology
    - Drug use (e.g. benzodiazepines, statins)
    - Non-communicable diseases prevalence and rates (e.g. hip fracture)
    - Combinations to estimate relative risk reduction

Drug Consumption Database in Europe - http://www.imi-protect.eu/drugConsumption.shtml



PROTECT

imi efpia

Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

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Pregnancy Study
Adverse Drug Reactions Database NEW
Drug Consumption Databases in Europe NEW
PROTECT Benefit-Risk Website NEW

Drug Consumption Databases in Europe

The inventory of **Drug Consumption Databases in Europe** is a comprehensive and structured source of information on drug consumption in Europe. It comprises two documents. The master document contains a detailed report of the available information, methods to retrieve this information, a description of the validity of national drug consumption data and a discussion. The country profile document summarizes the main results by country.

DRUG CONSUMPTION DATABASES IN EUROPE: MASTER AND COUNTRY PROFILE DOCUMENTS

These documents are the result of reviewing, compiling and updating knowledge about European sources of data on drug utilisation in the out- and inpatient healthcare sector.
Two documents are available to view. A master document, organised as a scientific article, contains a detailed report of the information already available, methods to retrieve this information, and a discussion.
The country profile document summarizes the main results by country.

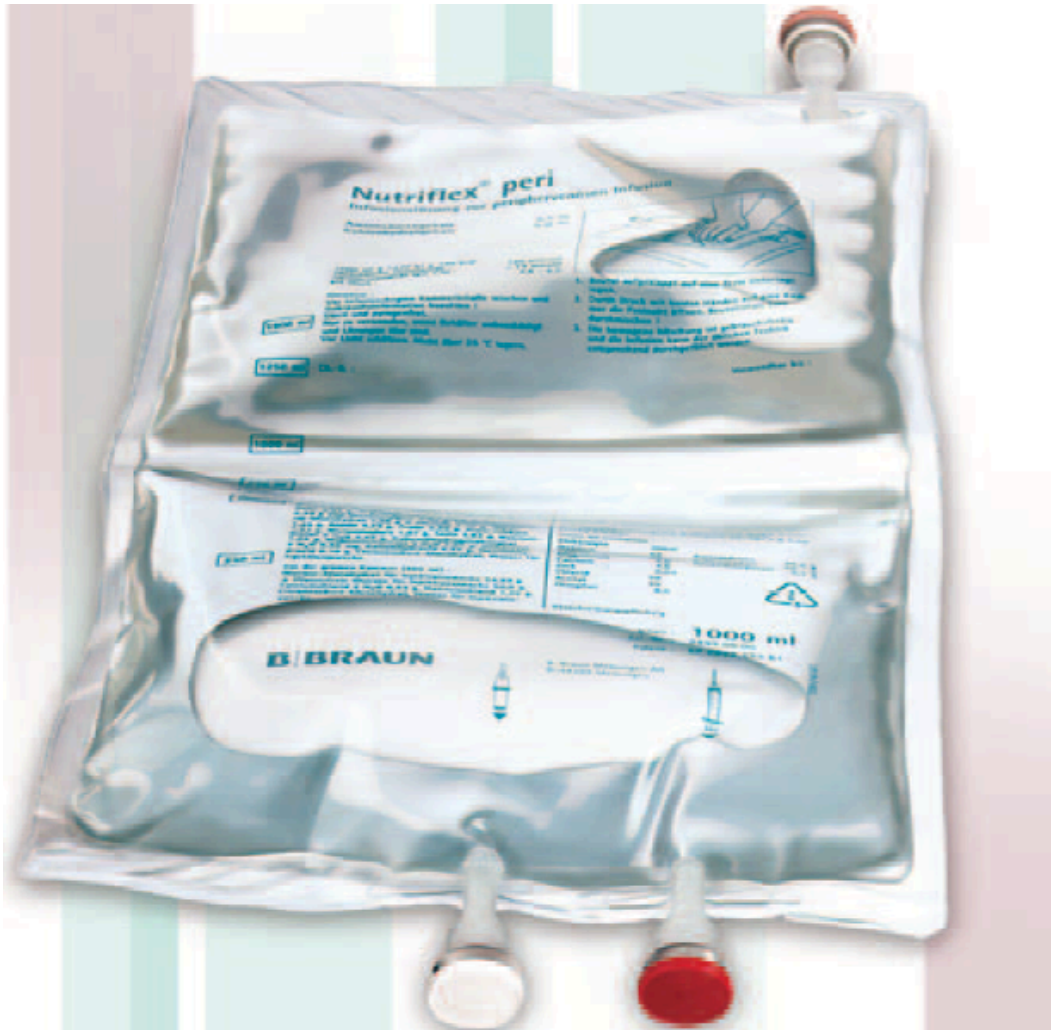
Summary of the included information:

Master document and country profile document	List of non-commercial providers of drug consumption data in Europe
	List of national medicines agencies, reimbursement and pricing agencies
	List of sources of information about medicines
	List of nationwide drug consumption databases in Europe with a description of the main characteristics and accessibility
Master document	Summary of data provided by IMS Health, Inc.
	Exploration of the availability of nationwide inpatient drug consumption data
	Outline of validity and degree of inter-country comparability of drug consumption data
	International networks and research working groups in pharmacoepidemiology

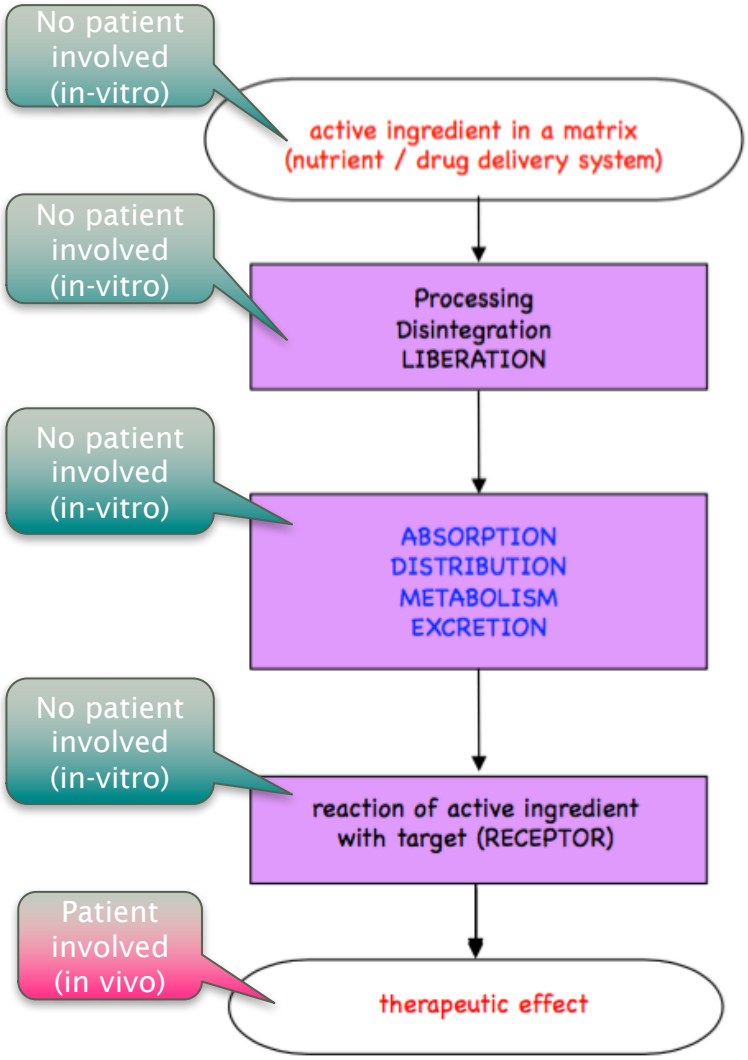
How to identify suitable Hospital Pharmacy research fields without patients involved

Identify your **special interest** (e.g. in Parenteral Nutrition) and join SI and Research Groups

- "You'll never walk alone"



Identify topic from a general pharmacology view



INCOMPATIBILITY

Pharmaceutic Phase (pharmaceutical availability)

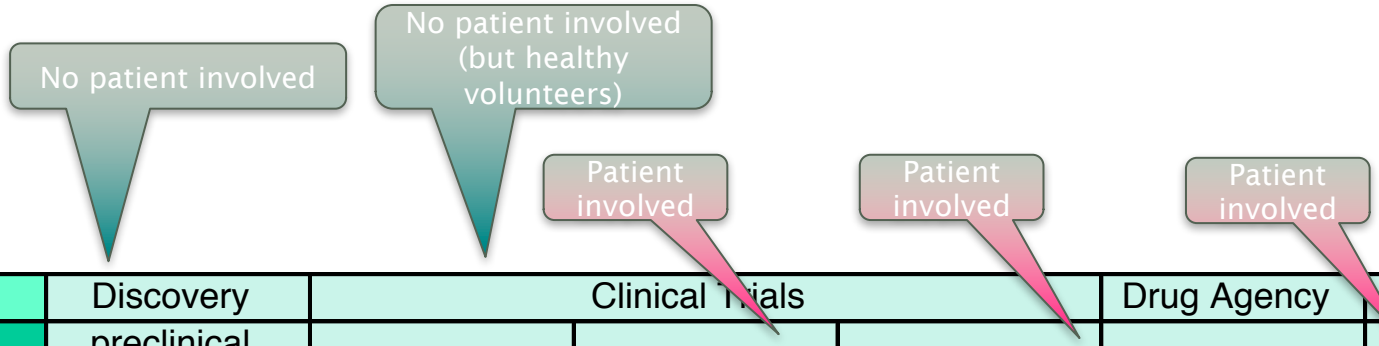
Pharmacokinetic Phase (biological availability)

INTERACTION

Pharmacodynamic Phase

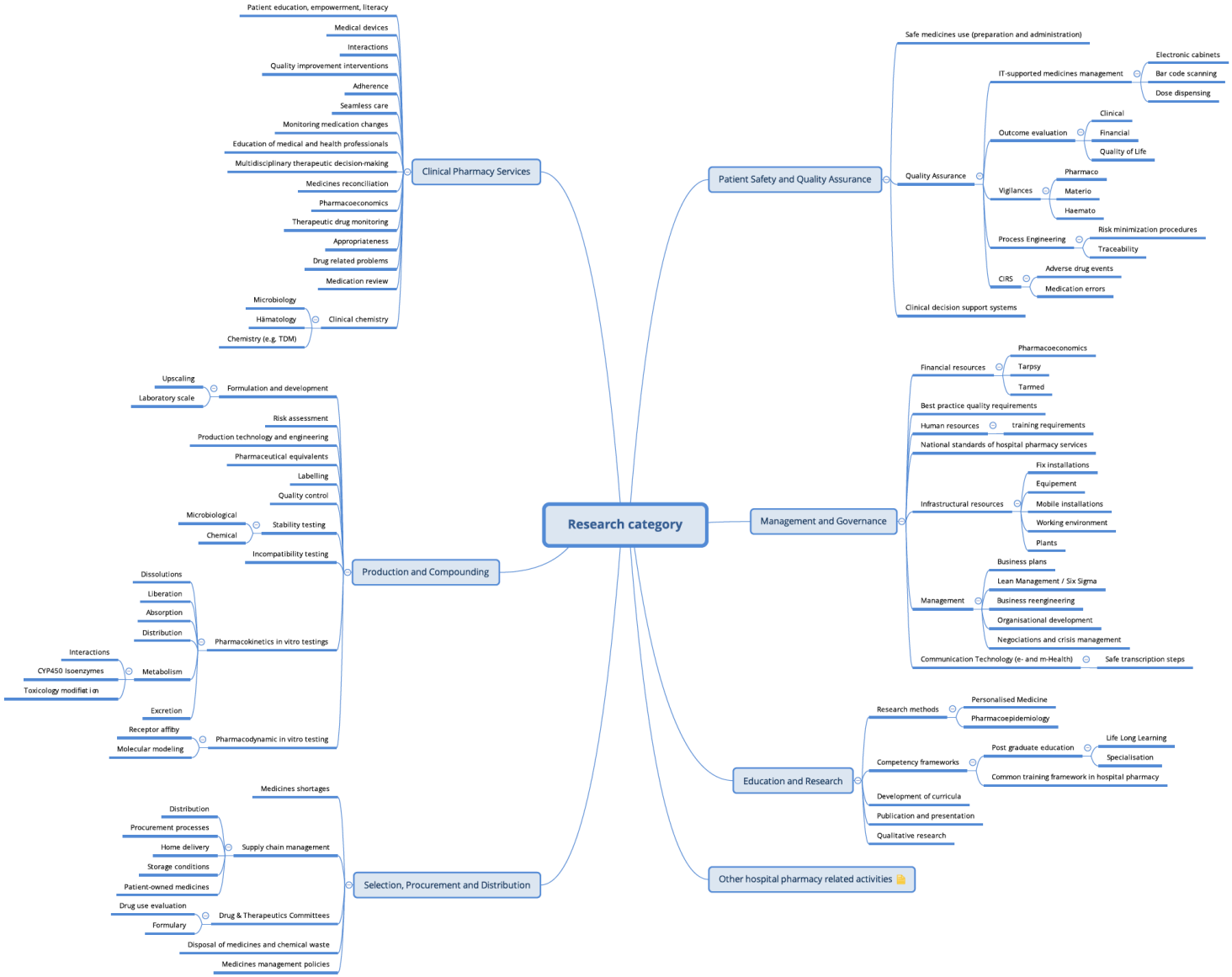
Extract data from NCE* and medicines development

(NCE = new chemical entity)



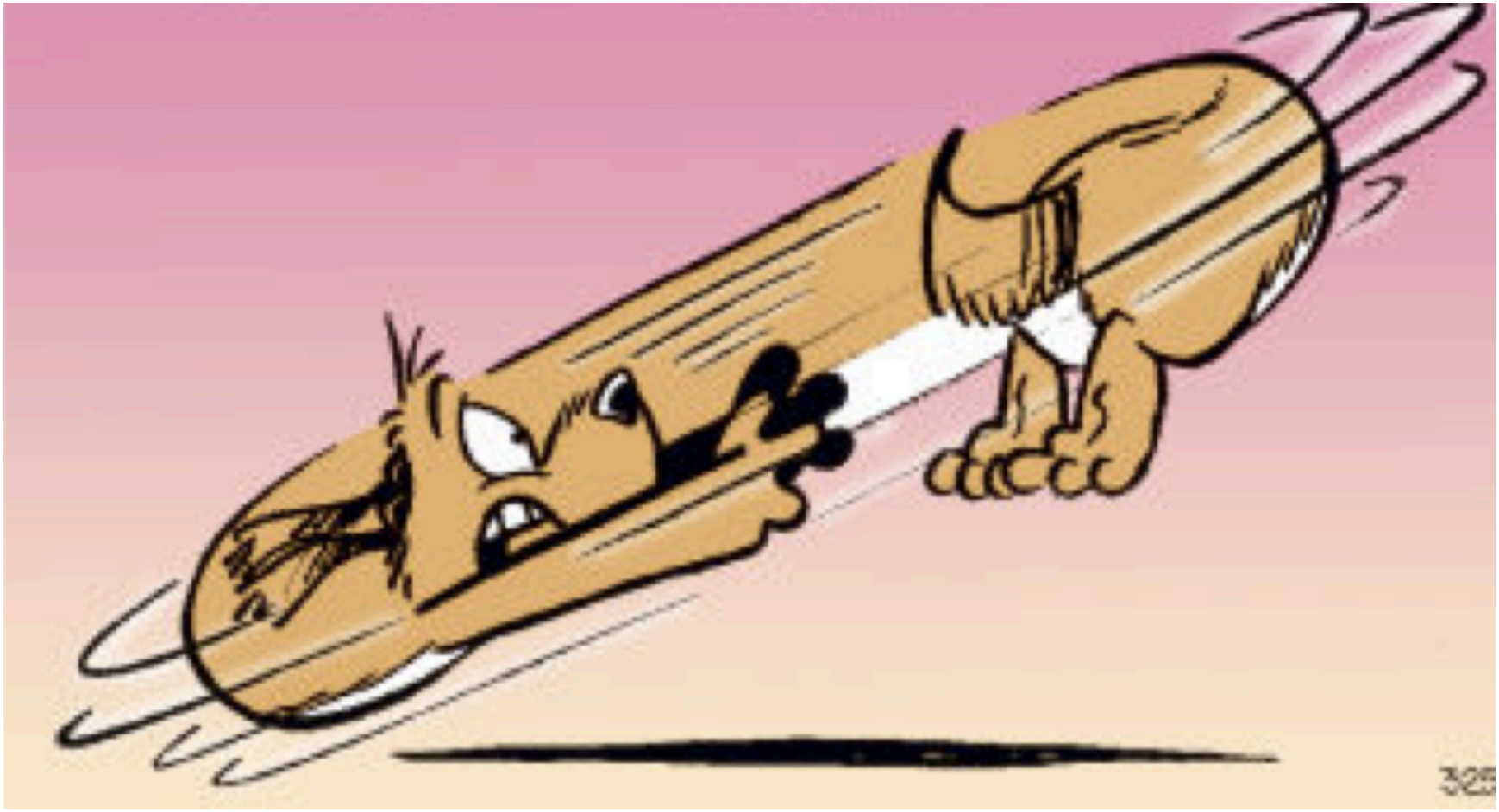
	Discovery	Clinical Trials			Drug Agency	Launching
	preclinical testing	phase I	phase II	phase III	-	phase IV
Years approximately	6.5	1.5	2	3.5	1.5	
Test population	laboratory and animal studies	20 to 100 healthy volunteers	100 to 500 patient volunteers	1000-5000 patient volunteers	review process, approval	Additional post-marketing testing
Purpose	assess safety, biological activity and formulations	determine safety and dosage	evaluate effectiveness, look for side effects	confirm effectiveness, monitor adverse reactions from long-term use		
Yield	5'000 compounds evaluated		5 enter trials		1 approved	

Find research question according to the **European Hospital Pharmacy Statements**



Example: Observation of prices for social insurances and reimbursement -> The dog hunts for its tail...

- Pharmacoeconimcs: Global price leveling
  - CH observes NL, F, D....
  - NL, F, D observe ....



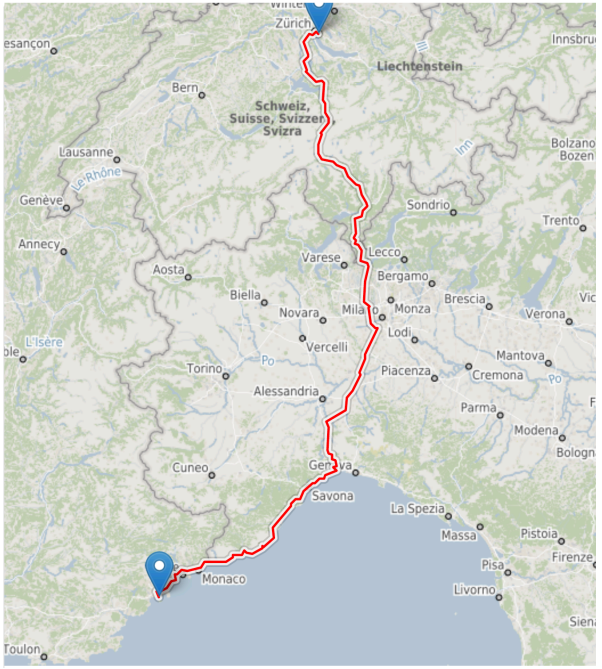
Research by data aggregation

- Reviews
- MetaAnalysis
- Cooperational Research (e.g. COST Actons)

Methods of Literature Reviews

- **Classic, traditional (narrative) review**
  - Expert invited -> subjective -> cave bias and confounding
  - Summary judgement of selection of studies
  - Emphasis on authority
  - Transparency? -> you only get the information the expert is willing to give!
- **Systematic review**
  - Based on a concrete, well-defined research question
  - Formulation of an explicit, reproducible search strategy and inclusion / exclusion criteria
  - Assessment of methodological quality: Bias? Confounding?
- **Statistical pooling -> Meta-analysis**
  (computer-aided by RevMan5® for Cochrane reviews)
  https://www.youtube.com/watch?v=oKfEh8Xoof4

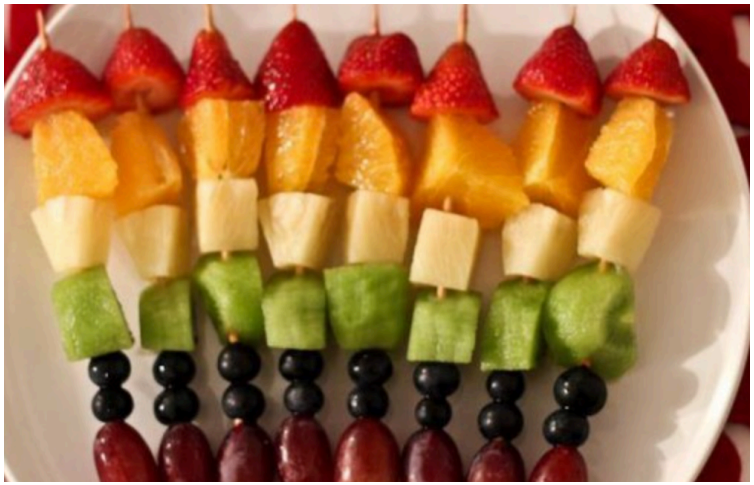
Steps Systematic Review

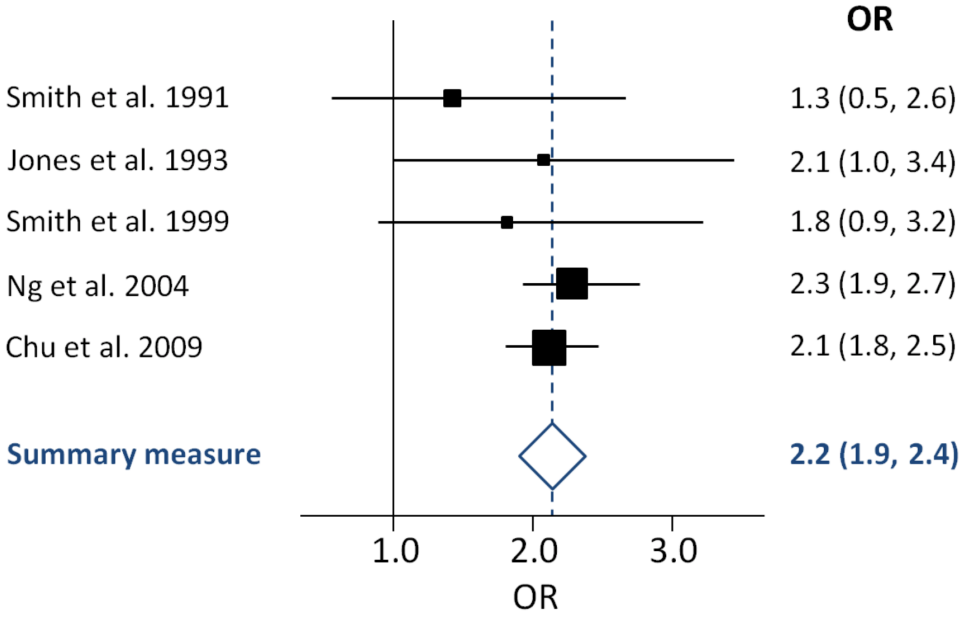


- Define <u>research question</u>
- Define <u>inclusion and exclusion</u> criteria
- Critically identify components (2 reviewers)
  - Exhaustive and reproducible?
  - Sensitive but not specific? doubtful records also selected?
  - Reference tracking, expert inquiry, hand search, unpublished research?
- Extraction of design characteristics (2 reviewers)
- Extraction of study results (2 reviewers)
- Check for <u>publication bias</u>
- Assessment of <u>heterogeneity</u>
- Statistical analysis/pooling
- <u>Interpretation (confounding: alternative explanation of results?)</u>

Review vs Meta Analysis (Pooling)

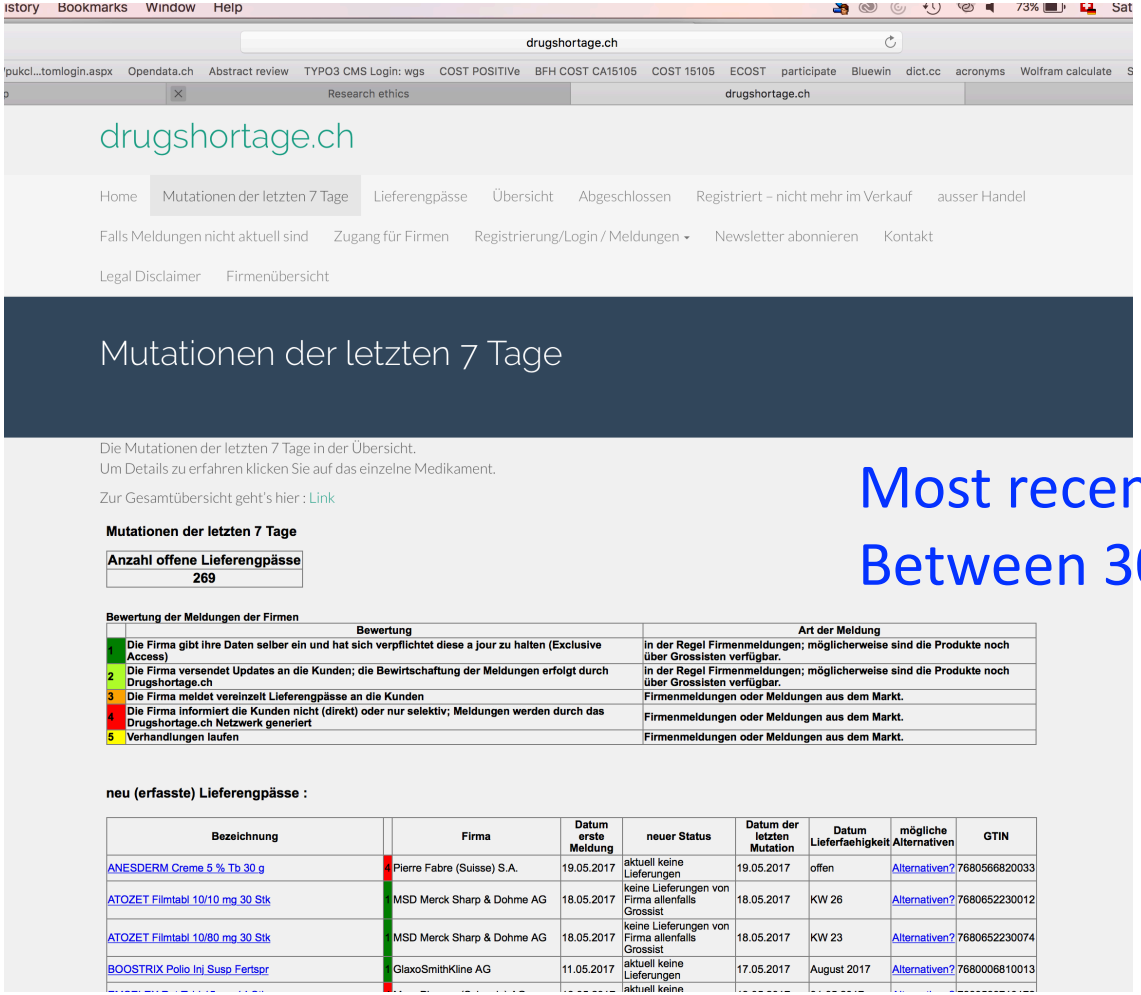
- Review
  - Statistical analysis aimed to critically appraise former research and publications within one topic
- Meta Analysis = Analysis of a set of single analyses
  - Produce an estimate of a treatment effect
  - Pooling
    - Only suitable if samples are taken from the same population -> test of heterogeneity as second step after aggregation
  - Advantage: more power
  - Do not spoil the pooled data





COST* Action CA15105: Medicines shortages

We do not need to create more databases. We need solutions!



drugshortage.ch

Home | Mutationen der letzten 7 Tage | Lieferengpässe | Übersicht | Abgeschlossen | Registriert – nicht mehr im Verkauf | ausser Handel

Falls Meldungen nicht aktuell sind | Zugang für Firmen | Registrierung/Login / Meldungen | Newsletter abonnieren | Kontakt

Legal Disclaimer | Firmenübersicht

Mutationen der letzten 7 Tage

Die Mutationen der letzten 7 Tage in der Übersicht.
Um Details zu erfahren klicken Sie auf das einzelne Medikament.

Zur Gesamtübersicht geht's hier : Link

Mutationen der letzten 7 Tage

Anzahl offene Lieferengpässe
269

Bewertung der Meldungen der Firmen

	Bewertung	Art der Meldung
1	Die Firma gibt ihre Daten selber ein und hat sich verpflichtet diese a jour zu halten (Exclusive Access)	in der Regel Firmenmeldungen; möglicherweise sind die Produkte noch über Grossisten verfügbar.
2	Die Firma versendet Updates an die Kunden; die Bewirtschaftung der Meldungen erfolgt durch Drugshortage.ch	in der Regel Firmenmeldungen; möglicherweise sind die Produkte noch über Grossisten verfügbar.
3	Die Firma meldet vereinzelt Lieferengpässe an die Kunden	Firmenmeldungen oder Meldungen aus dem Markt.
4	Die Firma informiert die Kunden nicht (direkt) oder nur selektiv; Meldungen werden durch das Drugshortage.ch Netzwerk generiert	Firmenmeldungen oder Meldungen aus dem Markt.
5	Verhandlungen laufen	Firmenmeldungen oder Meldungen aus dem Markt.

neu (erfasste) Lieferengpässe :

Bezeichnung		Firma	Datum erste Meldung	neuer Status	Datum der letzten Mutation	Datum Lieferfaehigkeit	mögliche Alternativen	GTIN
ANESDERM Creme 5 % Tb 30 g	4	Pierre Fabre (Suisse) S.A.	19.05.2017	aktuell keine Lieferungen	19.05.2017	offen	Alternativen?	7680566820033
ATOZET Filmtabl 10/10 mg 30 Stk	3	MSD Merck Sharp & Dohme AG	18.05.2017	keine Lieferungen von Firma allenfalls Grossist	18.05.2017	KW 26	Alternativen?	7680652230012
ATOZET Filmtabl 10/80 mg 30 Stk	3	MSD Merck Sharp & Dohme AG	18.05.2017	keine Lieferungen von Firma allenfalls Grossist	18.05.2017	KW 23	Alternativen?	7680652230074
BOOSTRIX Polio Inj Susp Fertspr	3	GlaxoSmithKline AG	11.05.2017	aktuell keine Lieferungen	17.05.2017	August 2017	Alternativen?	7680006810013

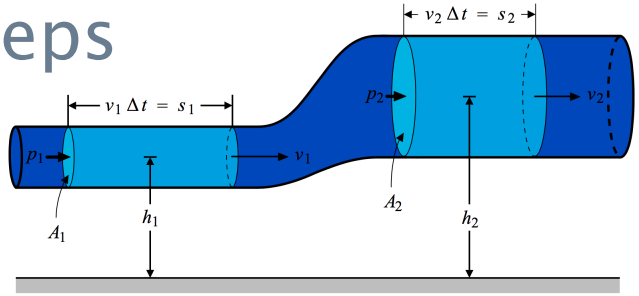
Most recent weeks:
Between 300 and 330

* COST is the cooperation in science and technology

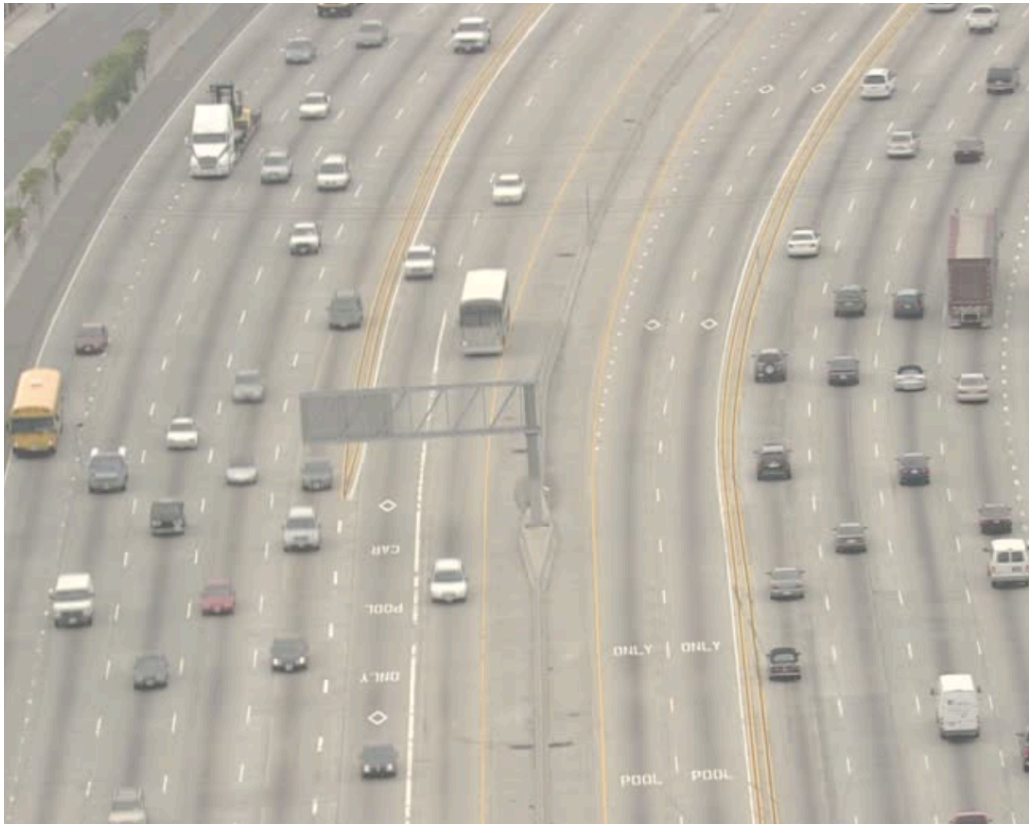
http://www.cost.eu/COST_Actions/ca/CA15105

Comparison Shortages and Traffic – Committed and rate-determining steps

Mergers of multiple supply chains to one leads sooner or later to a congestion



What we need

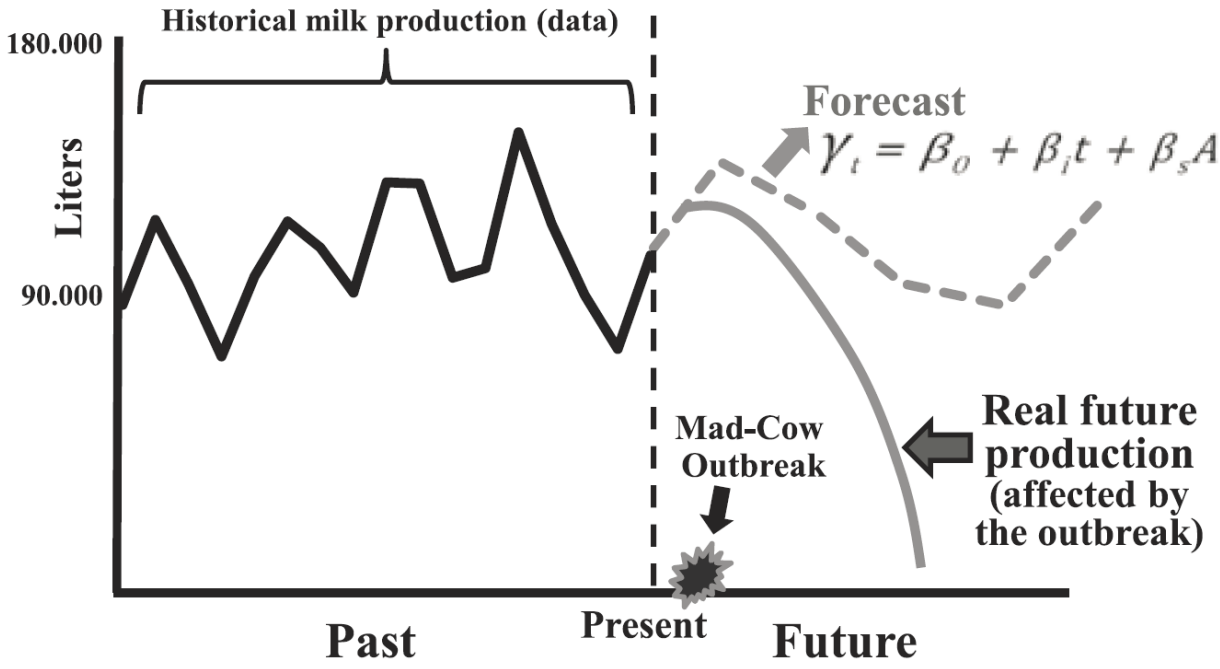


Large tubular cross-sections

What is done

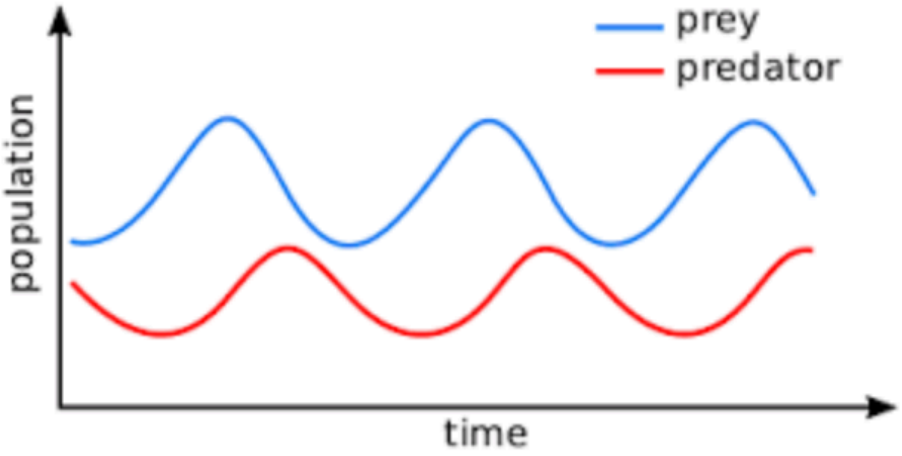
rather than supply-chain bottlenecks

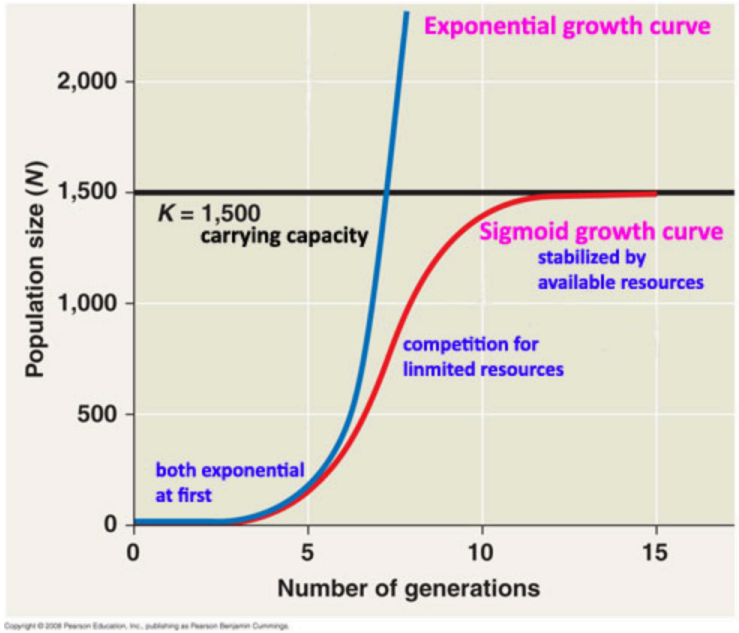
Shortages foresight: „gouverner c'est prévoir" – What did we miss? Variables?

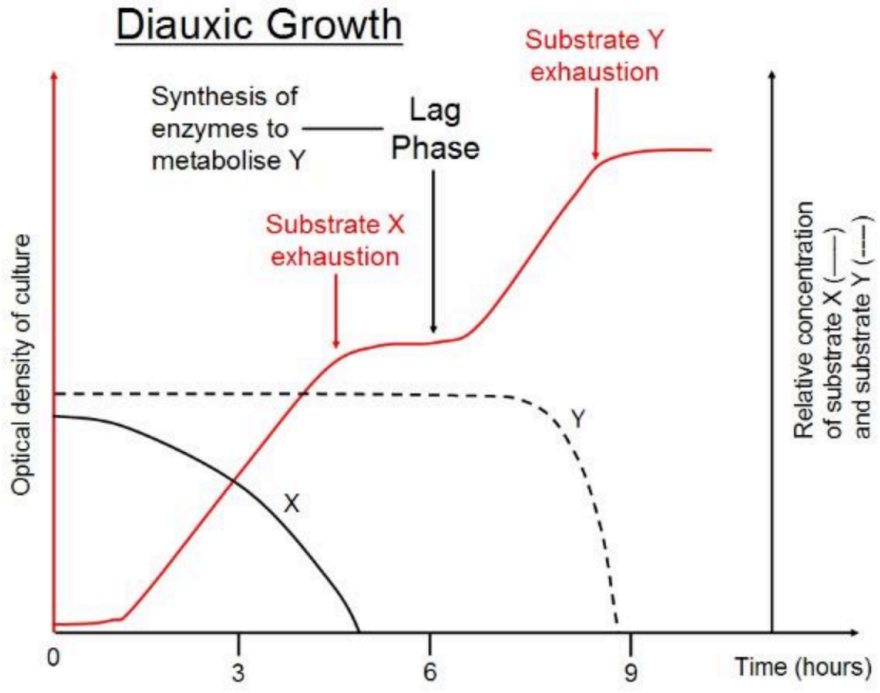


Forecasts

Would biological growth calculations be more suitable?
-> linear growth will not do
-> exponential growth



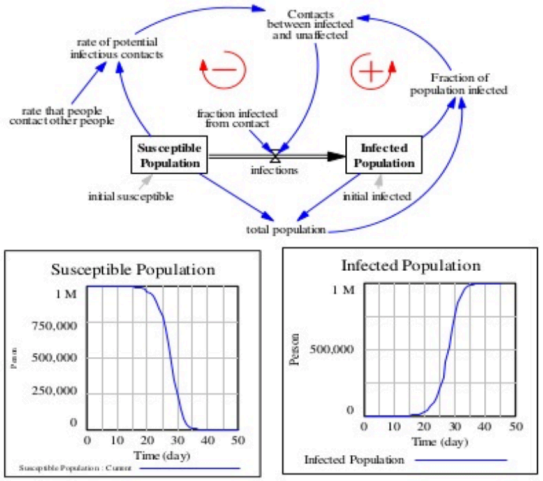


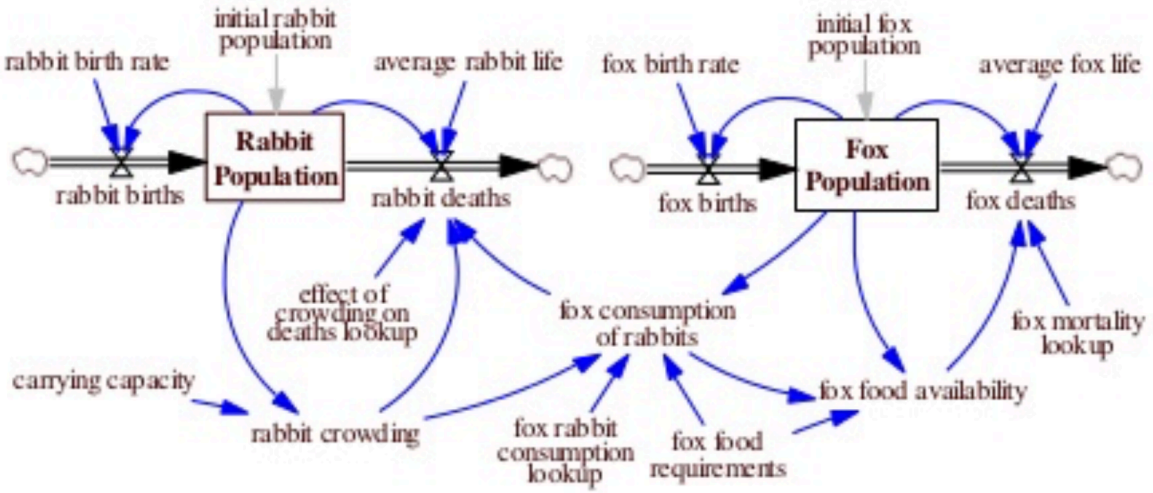


Systems dynamics and simulation

- Computer-aided approach to policy analysis
- Complex social, managerial, economic, and ecological systems
- Interdependence, mutual interaction, circular causality

Simple epidemic model





http://vensim.com/data-science-bottom-line/
http://vensim.com/causal-tracing-in-vensim/
http://vensim.com/building-a-simple-vensim-model/

Summary

Summary

- Research with or w/o persons, clinical or non-clinical, prospective or retrospective
- Options and examples of research fields and activities out of wards
- Research by data aggregation
  - Literature Reviews
  - Meta-analysis
- Forecasting and Simulation
  - Linear
  - Non-linear systems dynamics approach

Evaluation of Learning Success

Evaluation of Learning Success

- Do Research Acts regulate only intervention studies with human study participants? (y/n)
  - No (slide HRA overview)
- Does research with anonymised data need approval by an ethical committee's approval? (y/n)
  - In general not, but we cannot be fully sure: Ask the Ethical Committee for a declaration of non-cognizance
- Can samples from biological material taken from previous diagnostic interventions be used freely for any research? (y/n)
  - No, only if the hospital asks patients for a general consent including the use of samples for further research

That's all folks – questions or coffee break?