Erasmus MC
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European database networking models

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Disclosure

- MS is/has been projectleader of a variety of projects that are funded (unrestricted grants) by the pharmaceutical industry: Merck, Pfizer, AstraZeneca

- The experiences here represents knowledge generated in the TEDDY, ALERT and SOS consortium that have many partners, amongst which many ENCePP centers

What is our experience with databases and linking across EU?

- Databases
  - IPCI database: electronic medical record database > 10 years
  - PHARMO RLS alliance (> 1 year)

- Current EU activities:
  - EC funded public calls:
    - TEDDY-NoE (FP 6) (18 partners)
    - ALERT (FP-7) (18 partners)
    - SOS (FP-7) (11 partners)
    - @NEURIST (FP-6) (37 partners)
    - EUDRAGENE-follow-up (FP-5)

- Commercially funded research: dopamine agonists and valvular disorders (4 databases)

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Legal basis for combining data

- Directive 95/46/EC regulates the processing of personal data and the free movement of personal data (including health care) -> implemented in all countries.
- Principle: personal data may not be processed
  - Scientific purposes are an exception
  - However transparency is required (except when this is impossible)
    - Use of coded data in large databases is possible
- Each country may have different implementation of directive
  - Needs to be explored
  - Processing rules depend on country where the data are (also after they have been sent across borders)

- Each database has own ethical framework and procedures for processing data, these need to be satisfied as well

EU safety studies

- Philosophy: local (database) persons know best how to handle and interpret the data and should be fully involved

- EU Projects currently conducted through distributed database network:
  - Company studies: Coordinating center and local collaborating centers

  - EU funded studies: several models




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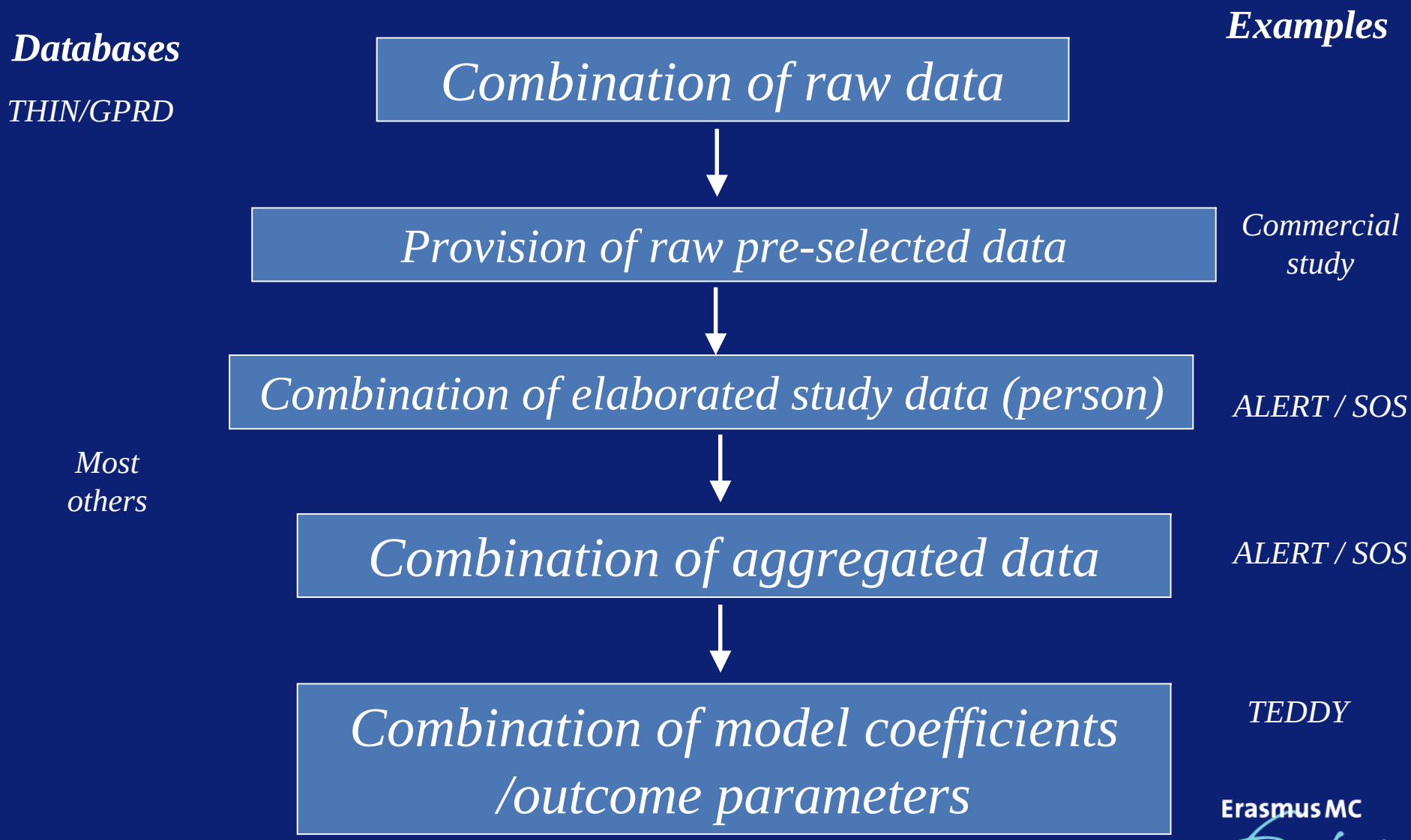
Working models for combining data



Commercial EU studies: organization

Role coordinating center:

- Identification of appropriate databases in EU to address research question (size, exposure, outcome, availability) negotiations
- (Sub)contracting
- Communication with pharmaceutical industry
- Coordination of centers
- Mapping of codes /protocol development
- Analysis and reporting

Role of local centers

- Feedback on protocol
- Assist in ethical review issues
- May decide on type active /passive research participation
- Supply of pre-selected data
- Fully participate in the publications
- Local evaluation of narratives

Example: cardiovascular safety of dopamine agonists

- Coordinating center: Erasmus MC
- Local centers: EPIC, PHARMO, SIMG

- Choice of databases based on required sample size, expertise, cost and possibility to validate the diagnosis against original records

- Subcontracting: each center separate subcontract
  - EPIC
  - SIMG
  - PHARMO
- Ethical review: each database own procedure
- Mapping of codes for integration and local validation most important scientific issue (READ, ICD-9, ICPC)

Activities in Europe: EC-funded projects

Examples:

- **FP-6/7: TEDDY**

- **FP-7: ALERT**

  SOS

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Examples of workmodels in EC-funded studies

- TEDDY-NoE: Drug utilization /safety in children

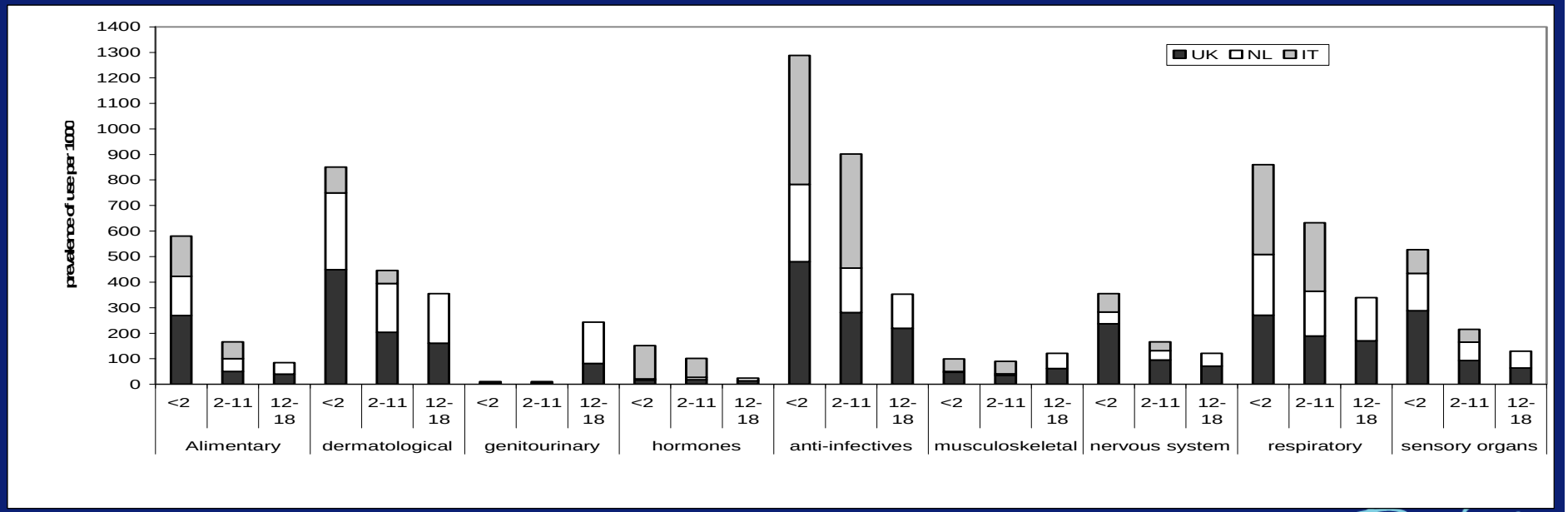
  Databases: IMS (UK) School of Pharmacy London

  IPCI (NL), Erasmus MC

  PEDIANET (IT), SoSeTe

  > 600,000 children electronic medical records

  Workmodel: Combination of parameters (prevalence)



DRUG UTILISATION IN CHILDREN -A cohort study in three European countries-BMJ November 2008

Examples of workmodels in EC-funded studies SOS

SOS:	Safety of NSAIDs (FP-7 Health 4.2.2**)**
Databases:	PHARMO, IPCI, QRESEARCH, BIPS, Regional ISSR, OSSIFF, Pedianet (NL, UK, DE, IT)
	> 35 million persons
Workmodel:	Combination of data that are pre-elaborated in each center

EU funded project: ALERT (FP7-ICT: 215847)

- ***ALERT:*** Early detection of Adverse Drug events by Integrative Mining of Clinical records and Biomedical Knowledge

- **Objective:**

  To design, develop and validate a computerized system that exploits data from electronic healthcare records and biomedical databases for the early detection of adverse drug reactions

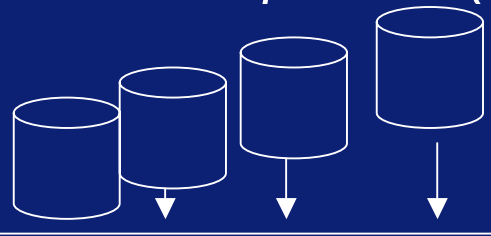
  Started: 1 February 2008

ALERT Partners

- Erasmus Universitair Medisch Centrum Rotterdam, Coordinator
- Fundació IMIM (FIMIM), ES
- Universitat Pompeu Fabra (UPF), ES
- Universidade de Aveiro (UAVR), PO
- IRCCS Centro Neurolesi Bonino Pulejo (NEUROLESI), IT
- Université Victor Segalen – Bordeaux 2 (UB2), FR
- London School of Hygiene and Tropical Medicine (LSHTM), UK
- Aarhus Universitetshospital, Aarhus Sygehus (AUH-AS), DK
- Astrazeneca AB (AZ), SW
- The University of Nottingham (UNOTT), UK
- Università di Milano – Bicocca (UNIMIB), IT
- Agenzia regionale di sanità della Toscana (ARS), IT
- Pharmo Coöperation U.A. (PHARMO), NL
- Società' Servizi Telematici SRL (PEDIANET), IT
- Universidade de Santiago de Compostela (USC), ES
- Tel-Aviv University (TAU), ISR
- Imperial College London (ICL), UK
- Società Italiana di Medicina Generale (SIMG), IT

ALERT concept

Medical databases: 30 Million persons (IT, NL, UK, DK)



Data mining

- *Data extraction: periodic*
- *Signal generation*
- *Signal substantiation*
- *Retrospective and prospective signal validation*

- *Mapping of events and drugs*
- *Development of extraction tools*
- *Literature*
- *Known side effects*
- *Pathway analysis*
- *In-silico simulation*

www.alert-project.org

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- **Link a total of 30 million electronic patient records** from 4 member states (UK, Denmark, Netherlands, Italy (HSD, PEDIANET, ISSR Lombardia, ISSR Toscana)

- **Signal generation on selected events with newly developed methods (Jerboa software)**

- **Signal substantiation** to avoid false positive signals

Type of databases

Electronic medical

- IPCI (NL)
- QRESEARCH (UK)
- PEDIANET (IT)
- HSD (IT)

Administrative

- PHARMO (NL)
- Aarhus (DK)
- ARS (IT)
- UNIMIB (IT)

ALERT concept

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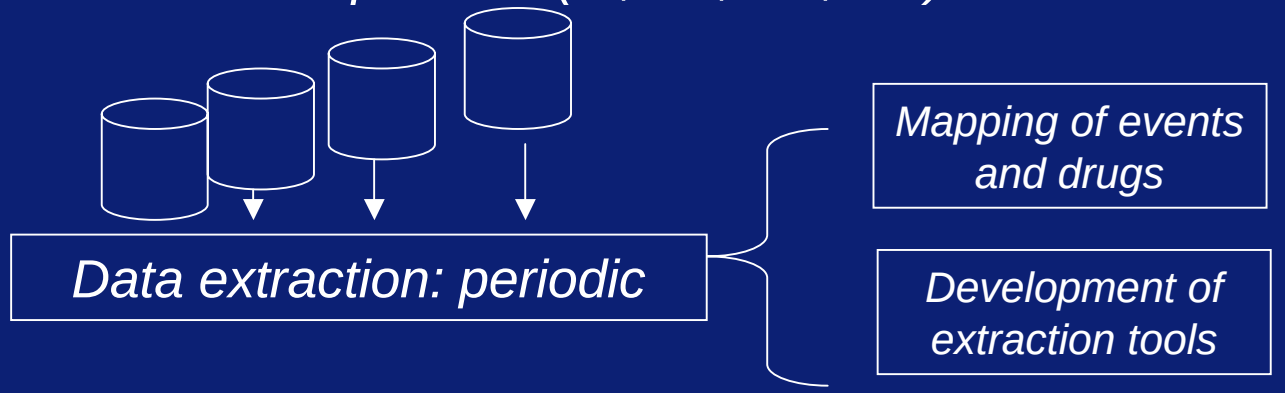

Due to differences in privacy regulations and the idea that database provider knows best what the data mean, DBs are kept local and are linked through a virtual network

Linking databases and data extraction in ALERT

- Step 1: Mapping of codes (disease, drugs, language):
- Step 2: Definitions of follow-up time, population
- Step 3: Application of purpose built (open source) software to extract data locally
- Step 4: Comparison and bench marking of rates
- Step 5: Assessment of drug-event associations

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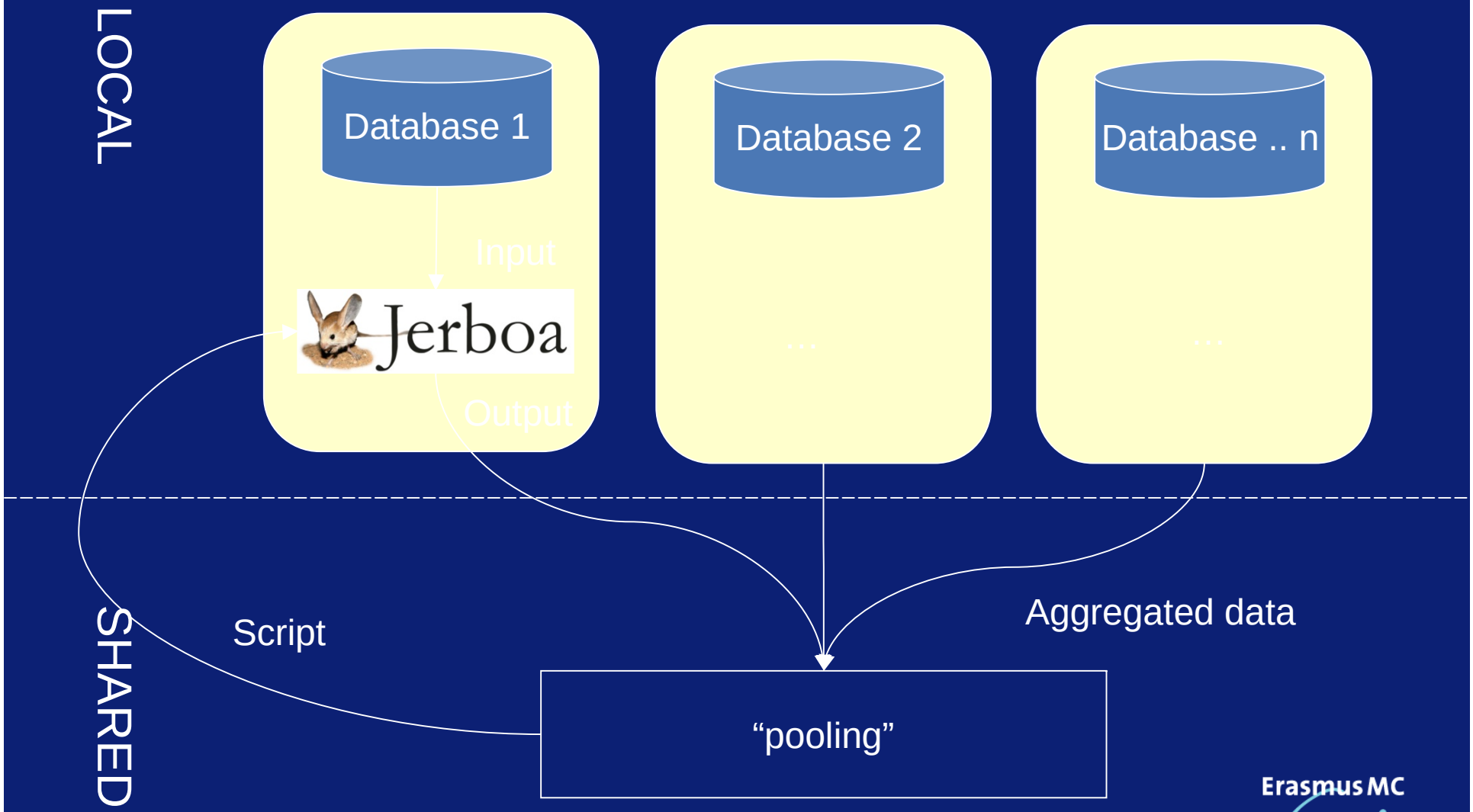
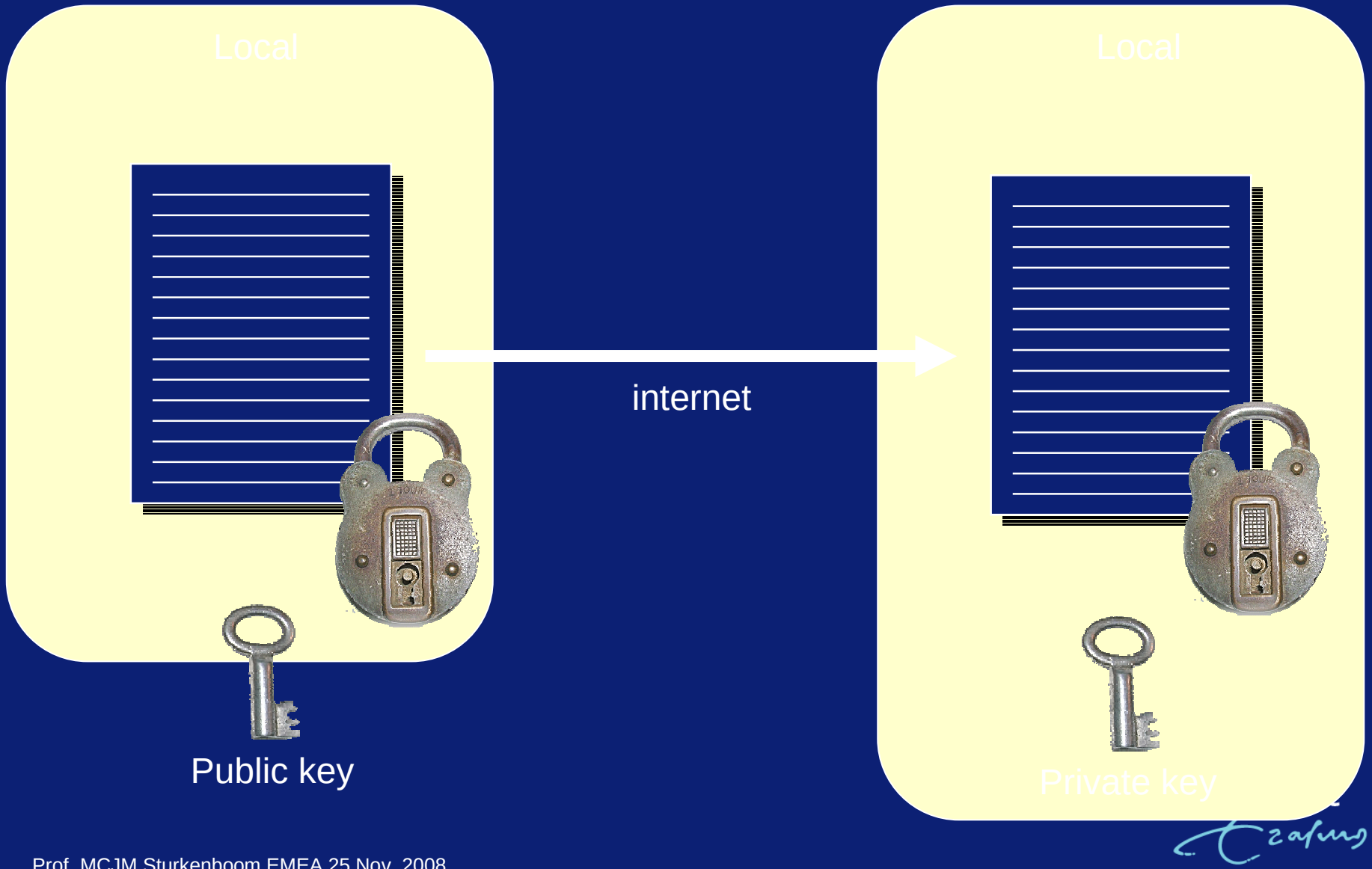
Step 2/3: Software for linking databases



Step 2/3: Software for linking databases
Encryption



Conclusion

- Experience on combining data is being built up across countries, especially around concrete projects
- Best model seems a distributed network in which DB centers maintain important role
- Major work is in mapping codes for drugs and diseases and verifying validity of each database