

Conversion de données cliniques provenant d'universités et d'hôpitaux pour permettre l'interopérabilité et l'analyse à grande échelle

Frédéric Burdet & team, Vital-IT group, SIB Swiss Institute of Bioinformatics

24.06.2019, GUF CDISC, Paris



Swiss Institute of
Bioinformatics

Contents

- **Présentation du SIB et de Vital-IT**
- Pourquoi harmoniser et convertir les données? Présentation du système d'analyse fédéré
- Processus de conversion, notre utilisation de SDTM
- Exemple d'utilisation du système fédéré

SIB in brief

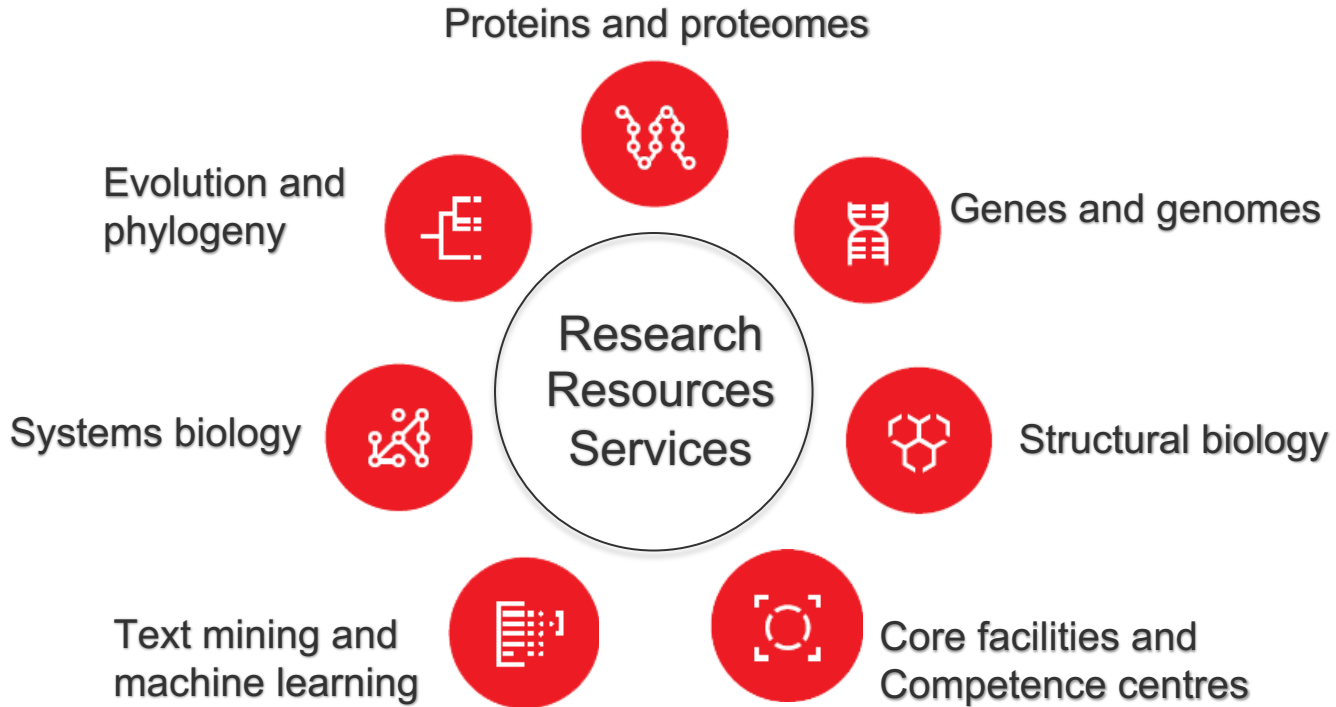
70 groups

800 scientists

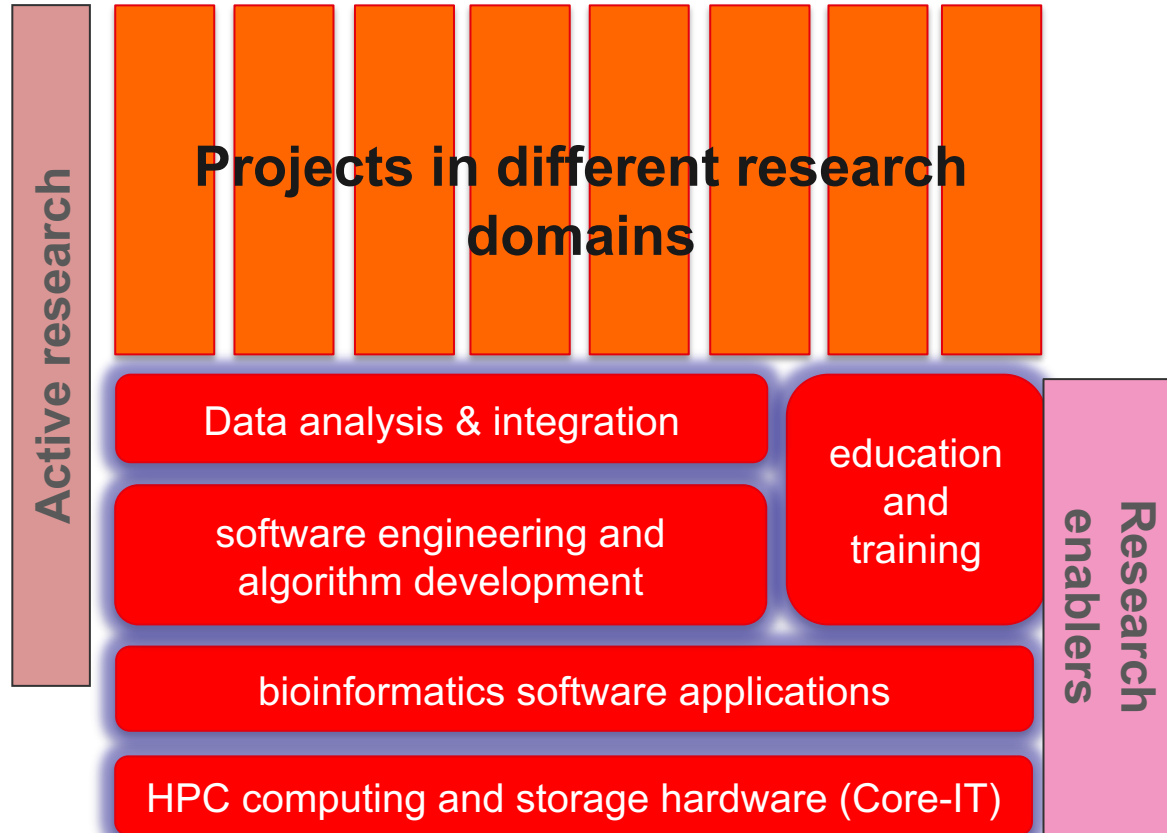
**20 partner
institutions**

**95 bioinformaticians
per million
inhabitants**

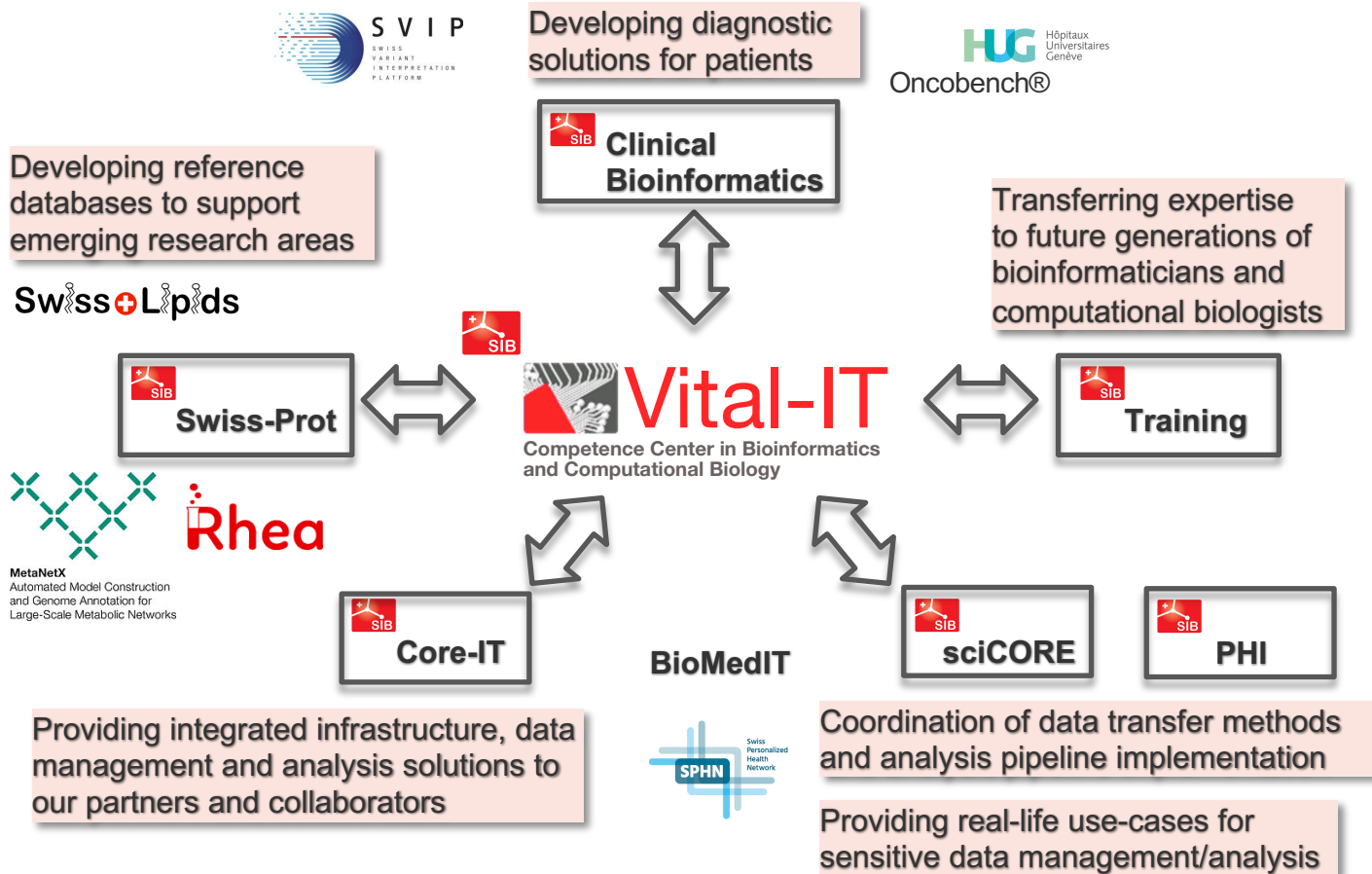
A complete and diverse activity scope



Vital-IT is an enabler and driver of life science research



Continued support of SIB-wide activities



Projets IMI pour lesquels nous avons converti des données en CDISC

- **IMI** : Innovative Medicines Initiative, **EU public-private** partnership funding health research and innovation
- **RHAPSODY**: Assessing risk and progression of pre-diabetes and type 2 diabetes to enable disease modification
 - **10 cohortes**
- **BEAt-DKD**: Biomarker Enterprise to Attack Diabetic Kidney Disease
 - **5 cohortes**

Contenu

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BOTNIA

ANDIS

GoDARTS

MDC

ADDITION-DK

ADDITION-PRO

DCS

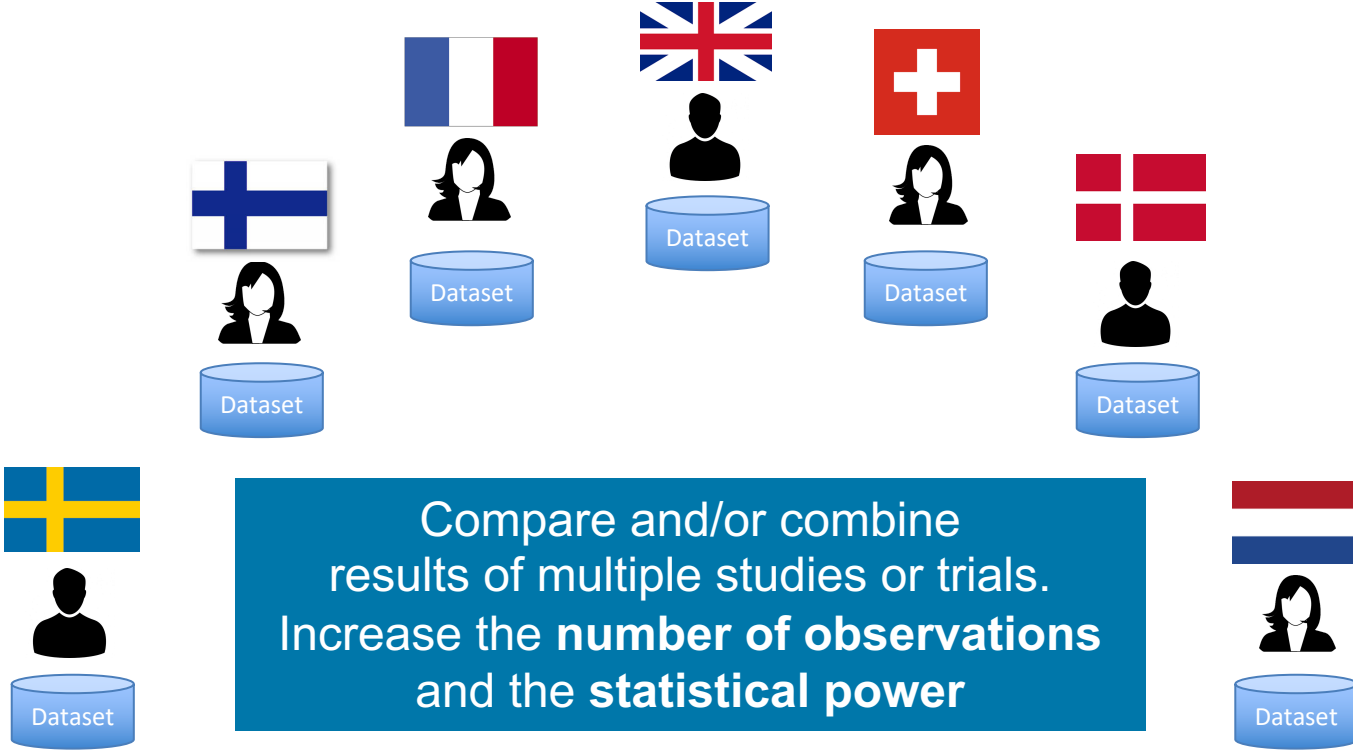
DESIR

ABOS

CoLaus



Meta-analysis is necessary to gain analysis power



Ethical and/or **legal/governance** constraints on clinical cohort data mean that often sensitive individual-level (patient) data **cannot be shared** or **copied** and **cannot be analysed together in a centralized way**



Analyst 1

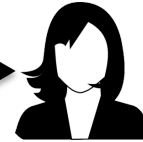


Performs analysis
on dataset 1



Generates
hypothesis

Collaboration



Analyst
2



Performs analysis
on dataset 2

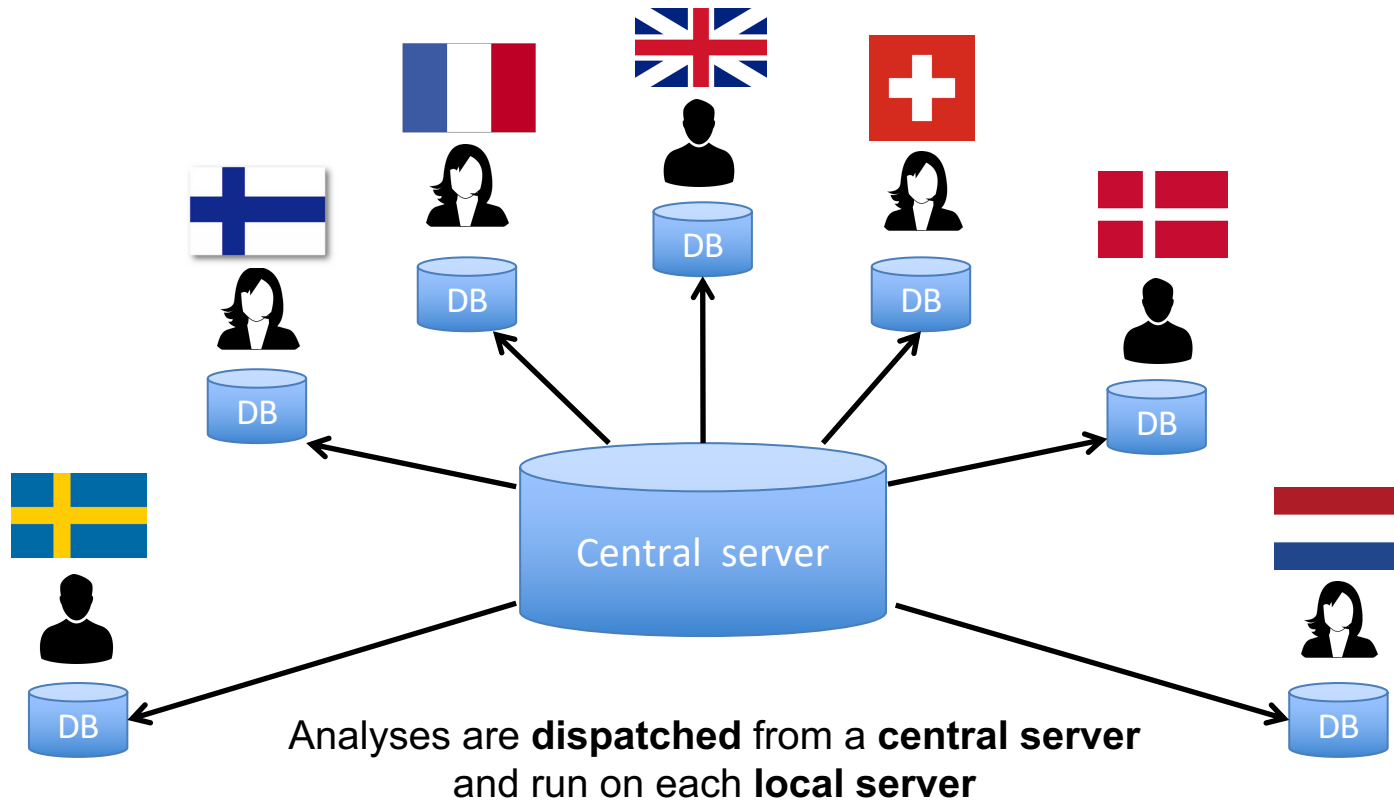


Confirms (or not)
hypothesis

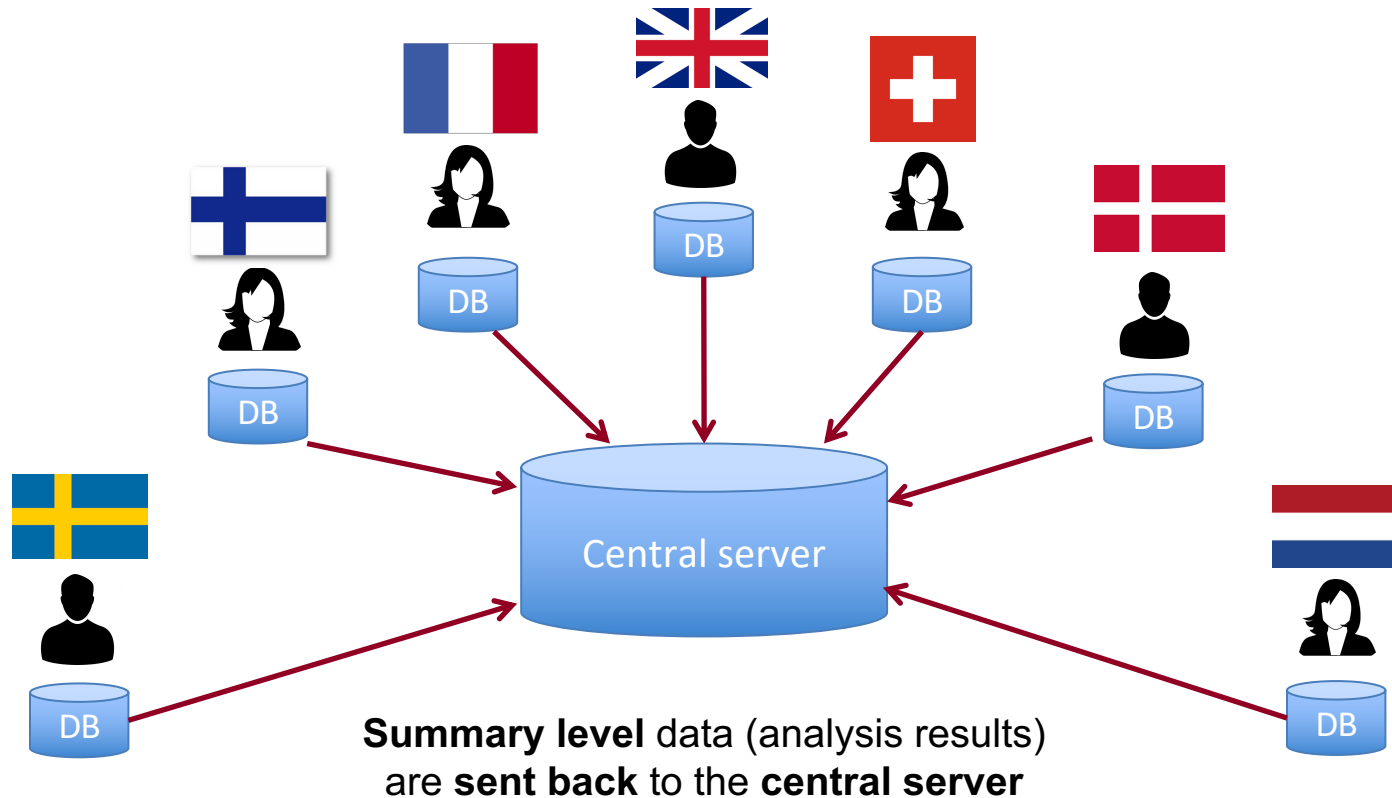
Problèmes de cette méthode ...

- Les noms de variables et la structure de donnée sont différents, on doit donc faire des analyses séparées
- Les mesures dans chaque set de donnée ne sont pas forcément similaires ou équivalentes
- Il est donc difficile de comparer les analyses, donc d'évaluer si les résultats sont comparables

Federated analysis is a possible solution



Federated analysis is a possible solution



Avantages du système d'analyse fédéré

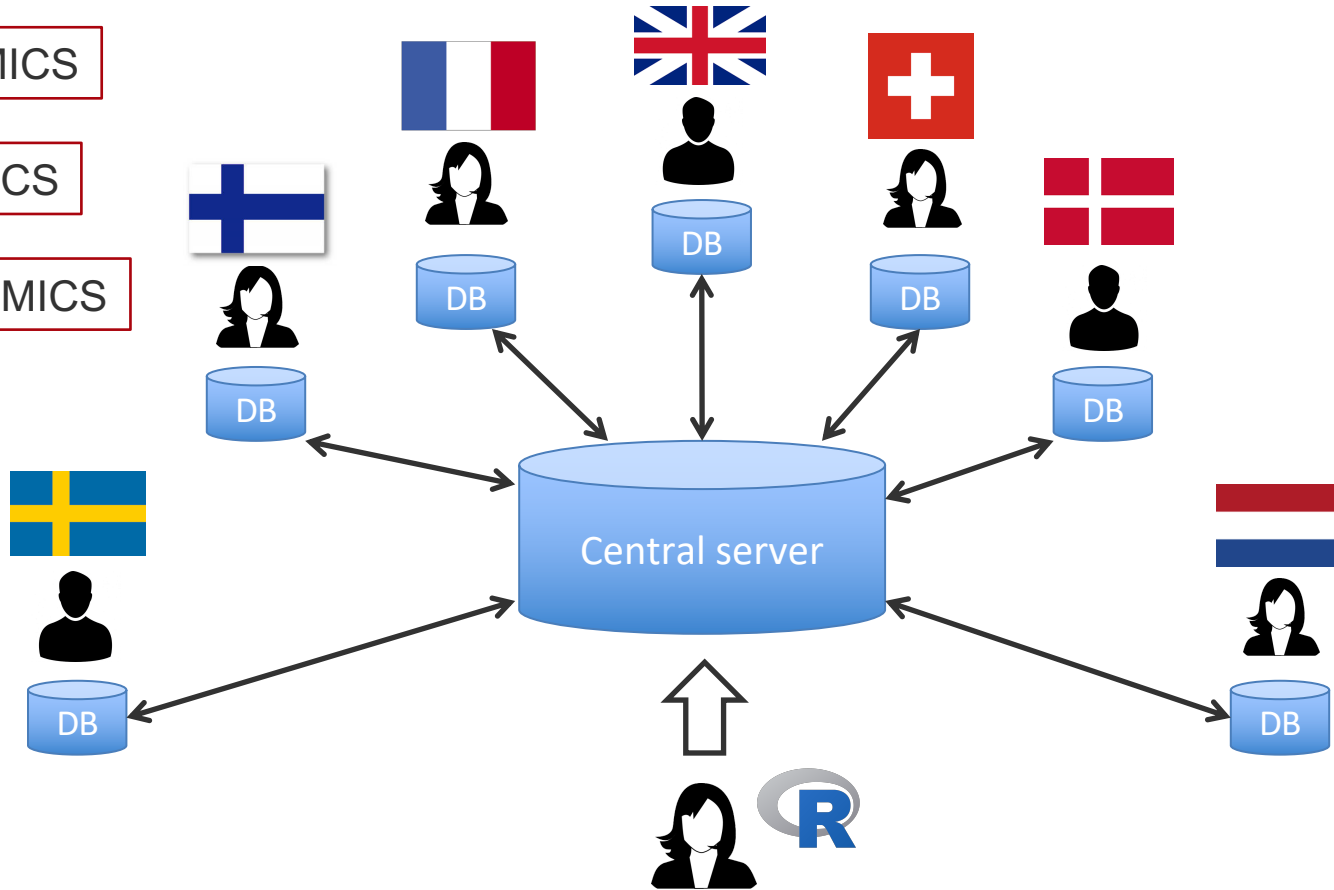
- L'analyse peut être effectuée **sans copier les données** sur un autre serveur, évitant d'éventuels problèmes éthiques ou de régulation
- Les data managers et administrateurs système locaux **gardent le contrôle** sur l'utilisation de leurs données
- Les analyses statistiques peuvent être **standardisées à travers les études / cohortes** (p.ex. les méthodes d'analyse, la gestion des variables continues, des time points, ...)
- **Accès à l'ensemble des variables**, contrairement à un sous-ensemble lors d'un transfert => plus flexible

New data can be added and accessed

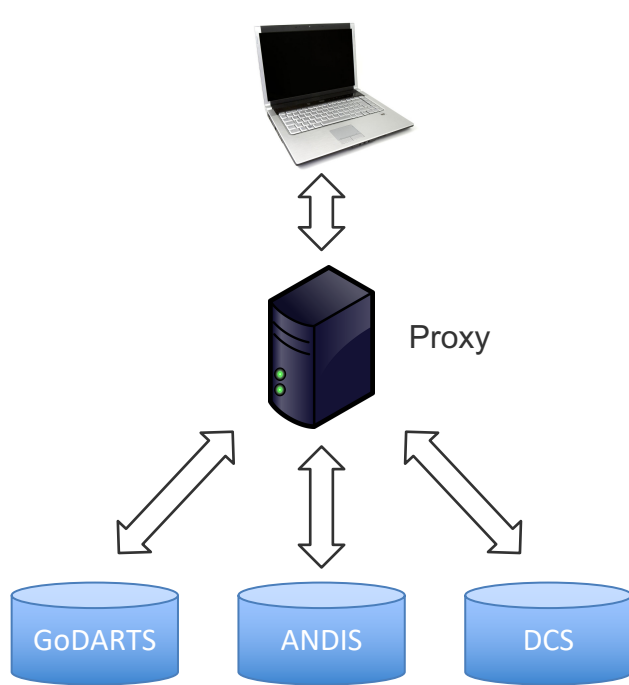
PROTEOMICS

LIPIDOMICS

METABOLOMICS

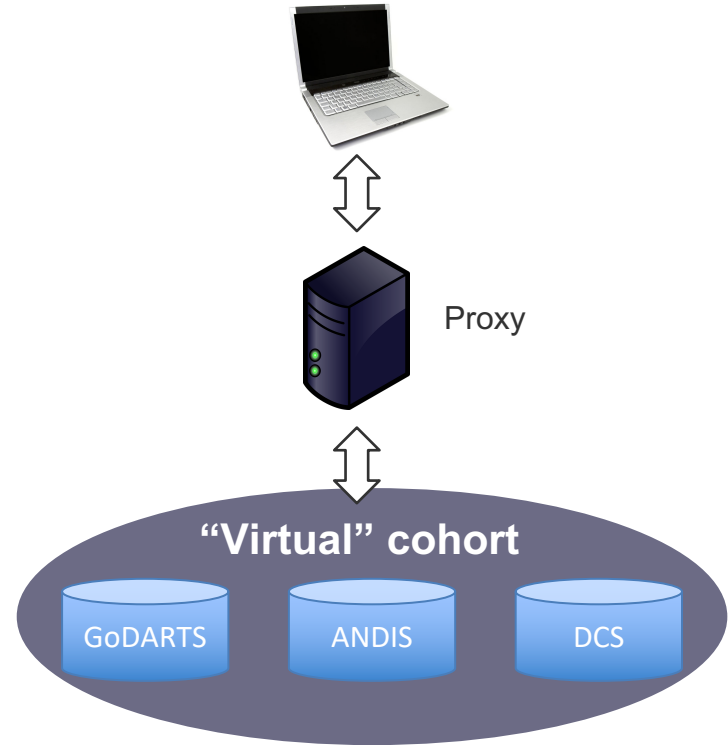


Two modes of federated analysis are possible



REPLICATION MODE:

The same analysis is performed on each cohort



VIRTUAL COHORT MODE:

The analysis is performed as if there is a single cohort

Contenu

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Pourquoi harmoniser les données?

- Pour s'assurer que les mesures entre cohortes peuvent être **comparées** et **analysées**, avec un format commun
- CDISC – SDTM semblait la meilleure option
 - Obligatoire pour les nouvelles études
 - Recommandé par l'IMI
 - Possibilité d'intégrer facilement des cohortes originellement capturées en SDTM par la suite

Three main steps for setting up the federated database

1. Cohort data harmonization in SDTM
 1. Mapping
 2. Conversion
 3. Vérification
2. Set up of remote IT infrastructure and loading of harmonised data on each node
3. Development of software for accessing the data and performing remote analysis

Challenges techniques

- Pour des raisons de privacité des données, nous ne recevons généralement des données que pour 10 ou 20 patients
- Les personnes sur les sites universitaires / hopitaux
 - Ne sont pas data manager
 - N'ont souvent pas beaucoup de temps à consacrer à la conversion
- Les données sont souvent dans une seule table, à assigner dans les domaines SDTM
- Les métadonnées sont à “collecter”

Harmonisation “Jamborees”



Données reçues

- Liste des variables

variable clinical	Variable description	Unit
patid	patient number	1-2519 (UKR), 6001-6521 (UMM)
Gendercode	sex	1=male 2=female
clientID	center ID	3=Regensburg 25=Mannheim
visitDate_char_V1	date of inclusion into study	ddmmmyyyy
diabetes_char	date of diagnosis of type 2 diabetes	ddmmmyyyy
diabetesfirstdiag_char_V1	date of first receipt of glucose lowering therapy	ddmmmyyyy
hypertfirstdiag_char_V1	date of first receipt of antihypertensive therapy	ddmmmyyyy
smoke_ever_V1	ever smoker	1=yes, 2=no
Med_RAS_V1	ACE inhibitor and/or angiotensin receptors blockers and/or renin inhibitor	1=yes, 0=no
Med_AD_V1	glucose lowering therapy	1=yes, 0=no
Med_RAS_V2	ACE inhibitor and/or angiotensin receptors blockers and/or renin inhibitor	1=yes, 0=no
Med_AD_V2	glucose lowering therapy	1=yes, 0=no
BMI_V1	body mass index	weight in kg/height in m ²
RRsys_mean_V1	mean systolic blood pressure from two measurements	mmHg
RRdia_mean_V1	diastolic blood pressure from two measurements	mmHg
BMI_V2	body mass index	weight in kg/height in m ²

- "Dummy" data: souvent en format excel, format large

Pseudo-code pour le mapping

- Peut-être facilement utilisé par les curateurs
- Peut-être importé en R ou autre langage de programmation pour la conversion
- Intègre le code de mapping et les méta-données en plus de la CDISC Variable Name:
 - **CDISC Variable Mapping:** p. ex “1=Y,2=N,NA=NA”
 - **Associated CDISC Variables:** p.ex
“LBTESTCD=GLUC;LBSPEC=PLASMA;VISIT=BASELINE”

Mapping

variable clinical	Variable description	Unit	CDISC Variable Name	CDISC Variable Mapping	Associated CDISC Variables	CDISC table
patid	patient number	1-2519 (UKR), 6001-6521 (UMM)	USUBJID	NA	NA	ALL
Gendercode	sex	1=male 2=female	SEX	1=M,2=F,NA=NA	NA	DM
clientID	center ID	3=Regensburg 25=Mannheim	SITEID	38=Regensburg,39=Mannheim	NA	DM
visitDate_char_V1	date of inclusion into study	ddmmyyyy	DMDTC	NA	VISIT=BASELINE	DM
diabetes_char	date of diagnosis of type 2 diabetes	ddmmyyyy	MHDTC	NA	MHTERM=TYPE 2 DIABETES	MH
diabetesfirstdiag_char_V1	date of first receipt of glucose lowering therapy	ddmmyyyy	MHDTC	NA		
hypertfirstdiag_char_V1	date of first receipt of antihypertensive therapy	ddmmyyyy	MHDTC	NA	MHTERM=HYPERTENSION	MH
smoke_ever_V1	ever smoker	1=yes, 2=no	SUCAT::SUOCCUR	1&2&NA=TOBACCO_FOR MER::1=Y,2=N,NA=NA 0&1&NA=AGENTS ACTING	VISIT=BASELINE	SU
Med_RAS_V1	ACE inhibitor and/or angiotensin receptors blockers and/or renin inhibitor	1=yes, 0=no	CMCAT::CMOCCUR	ON THE RENIN- ANGIOTENSIN SYSTEM::0=N,1=Y,NA=NA 0&1&NA=BLOOD	VISIT=BASELINE	CM
Med_AD_V1	glucose lowering therapy	1=yes, 0=no	CMCAT::CMOCCUR	GLUCOSE LOWERING DRUGS::0=N,1=Y,NA=NA 0&1&NA=AGENTS ACTING	VISIT=BASELINE	CM
Med_RAS_V2	ACE inhibitor and/or angiotensin receptors blockers and/or renin inhibitor	1=yes, 0=no	CMCAT::CMOCCUR	ON THE RENIN- ANGIOTENSIN SYSTEM::0=N,1=Y,NA=NA 0&1&NA=BLOOD	VISIT=1	CM
Med_AD_V2	glucose lowering therapy	1=yes, 0=no	CMCAT::CMOCCUR	GLUCOSE LOWERING DRUGS::0=N,1=Y,NA=NA	VISIT=1	CM
BMI_V1	body mass index	weight in kg/height in m2	VSORRES	NA	VSTESTCD=BMI;VISIT=BASELINE	VS
RRsys_mean_V1	mean systolic blood pressure from two measurements	mmHg	VSORRES	NA	VSTESTCD=SYSBP;VISIT=BASELINE	VS
RRdia_mean_V1	diastolic blood pressure from two measurements	mmHg	VSORRES	NA	VSTESTCD=DIABP;VISIT=BASELINE	VS
BMI_V2	body mass index	weight in kg/height in m2	VSORRES	NA	VSTESTCD=BMI;VISIT=VISIT1	VS

Explications du mapping + pseudocode

Original variable	Description	Values	SDTM variable	SDTM mapping	Associated SDTM	Domain
smoke_ever_V1	ever smoker	1=yes, 2=no	SUCAT::SUOCCUR	1&2&NA=TOBACCO_FORMER::1=Y,2=N,NA=NA	VISIT=BASELINE	SU
Med_AD_V1	glucose lowering therapy	1=yes, 0=no	CMCAT::CMOCCUR	0&1&NA=BLOOD GLUCOSE LOWERING DRUGS::0=N,1=Y,NA=NA	VISIT=BASELINE	CM
BMI_V1	body mass index	weight in kg/height in m ²	VSORRES	NA	VSTESTCD=BMI;VISIT=BASELINE	VS
BMI_V2	body mass index	weight in kg/height in m ²	VSORRES	NA	VSTESTCD=BMI;VISIT=VISIT1	VS

Tables SDTM utilisées

SDTM Tables

DM: demographics

LB: laboratory test results

CM: concomitant medication (i.e. treatments)

MH: medical history (i.e. conditions & diseases)

VS: vital signs (e.g. weight, height, BMI)

SU: substance use (e.g. tobacco)

APMH: associated person medical history

Conversion en R, exemples

- Utilisation de listes pour ajouter les métadonnées

```
"genderCode": {  
  "SEX": {  
    "1": ["M"],  
    "2": ["F"],  
    "NA": ["NA"]  
  }  
},  
"clientId": {  
  "SITEID": {  
    "38": ["Regensburg"],  
    "39": ["Mannheim"]  
  }  
}
```

- Utilisation de “merge” (par exemple pour les dates / codes de visites), de “melt” pour passer de données en large à en long

Melt

patNr	glukosekorr_V 1	glukosekorr_V 2	glukosekorr_V 3	HbA1c_percent_V 1	HbA1c_percent_V 2	HbA1c_percent_V 3	CRP_V1	CHOL_V1
1	156	159.07	250	8.00598	8.00598	9.103976	0.76	228.46
2	165	214	138	7.91448	11.025469	6.907983	5.77	270.87
3	142	150.26	NA	7.639981	8.00598	NA	2.81	192.21
...	100	103.42	NA	5.992987	5.901487	NA	3.28	217.74
...	118	105.49	NA	6.999483	6.907983	NA	0.74	201.24
...	146	NA	NA	7.182482	NA	NA	2.34	284.32



patNr	variable	value
1	glukosekorr_V1	156
1	glukosekorr_V2	159.07
1	glukosekorr_V3	250
1	HbA1c_percent_V1	8.00598
1	HbA1c_percent_V2	8.00598
1	HbA1c_percent_V3	9.103976
1	CRP_V1	0.76
1	CHOL_V1	228.46

Ajouter les méta-données en utilisant la liste de mapping

patNr	variable	value	LBORRES	LBTESTCD	LBSPEC	VISIT
1	glukosekorr_V1	156	156	GLUC	PLASMA	BASELINE
1	glukosekorr_V2	159.07	159.07	GLUC	PLASMA	VISIT1
1	glukosekorr_V3	250	250	GLUC	PLASMA	VISIT2
1	HbA1c_percent_V1	8.00598	8.00598	HBA1C	BLOOD	BASELINE
1	HbA1c_percent_V2	8.00598	8.00598	HBA1C	BLOOD	VISIT1
1	HbA1c_percent_V3	9.103976	9.103976	HBA1C	BLOOD	VISIT2
1	CRP_V1	0.76	0.76	CRP	SERUM	BASELINE
1	CHOL_V1	228.46	228.46	CHOL	SERUM	BASELINE

Puis merger avec la table des dates :

visitOrig	patNr	date	LBDC	VISIT
visitDate_char_V1	1	03-Feb-10	2010-02-03	BASELINE
visitDate_char_V1	2	04-Feb-10	2010-02-04	BASELINE
visitDate_char_V1	3	18-Feb-10	2010-02-18	BASELINE
visitDate_char_V1	4	18-Feb-10	2010-02-18	BASELINE
visitDate_char_V1	5	19-Feb-10	2010-02-19	BASELINE
visitDate_char_V1	7	22-Feb-10	2010-02-22	BASELINE

Vérification de la conversion

Diagnostic
script

LBTESTCD	min(LBORRES)	max(LBORRES)	avg(LBORRES)	median(LBORRES)
CHOL	1.70	24.30	4.961617	4.80
CPEPTIDE	0.30	103.00	1.287961	1.15
CREAT	12.00	1282.00	89.176106	78.00
GAD	1.00	49.00	1.727868	1.00
GLU	1.00	88.00	10.370918	8.10

20 random patients
double coded

LBTESTCD	LBTEST	LBORRESU
CHOL	Cholesterol	mmol/l
CPEPTIDE	C-peptide	mmol/l
CREAT	Creatinine	µmol/l
GAD	Glutamic Acid Decarboxylase 1	U/ml
GLU	Glucose	mmol/l
HBA1C	Glycated Haemoglobin (A1c)	%
HBA1C	Glycated Haemoglobin (A1c)	mmol/mol

Number of patients:

DM 7354
CM 7271
LB 7354
MH 7352
VS 7351
SU 7354

Patients not in

CM 83
LB 0
MH 2
VS 3
SU 0

Number of lines in the tables:

DM 7354
CM 798470
LB 1300750
MH 29408
VS 959138
SU 7354

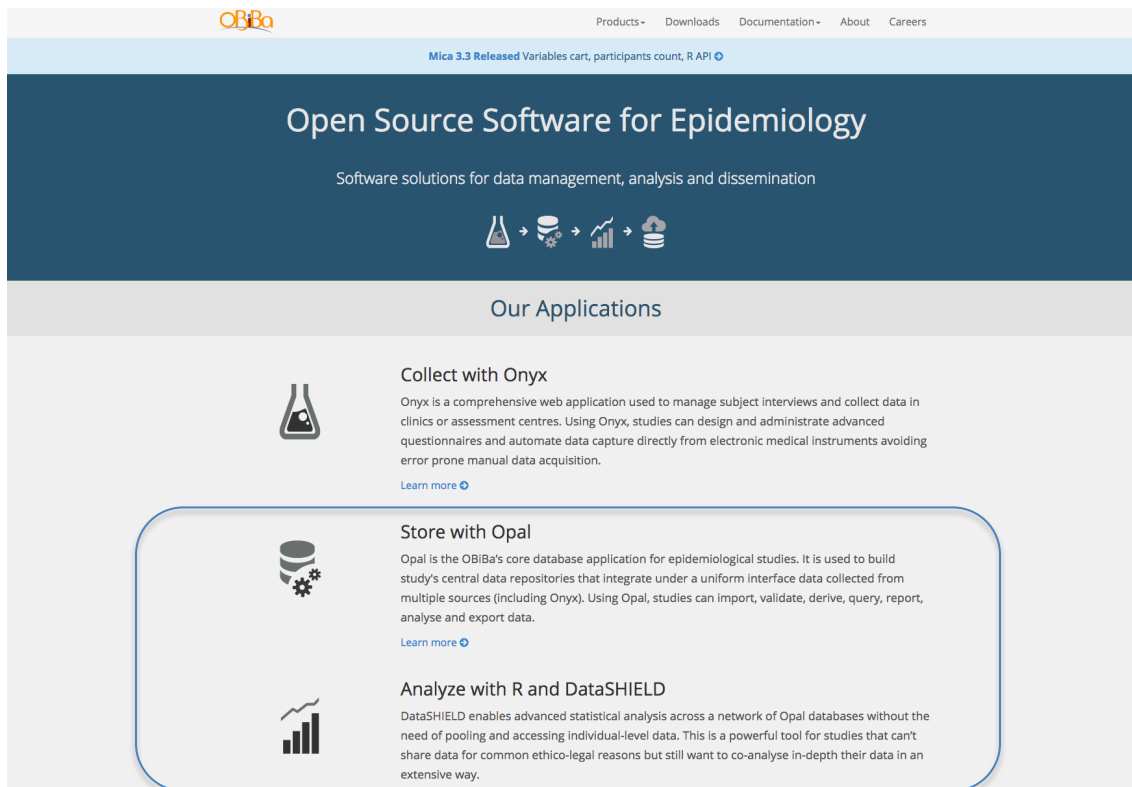


Manually
checked by Anne

Quelques remarques

- Nous avons parfois pris quelques libertés avec le format SDTM, le but était plus d'harmoniser que de coller parfaitement au standard (pas de soumission de donnée prévue)
- Plus généralement, ces cohortes sont très différentes de patients recrutés pour une étude clinique (ici pas treatment arm, exposure, adverse events, ...)

Infrastructure: Introducing OBiBa software



The screenshot shows the OBiBa website homepage. At the top, there is a navigation bar with the OBiBa logo on the left and links for Products, Downloads, Documentation, About, and Careers on the right. Below the navigation bar, a light blue banner displays the text "Mica 3.3 Released Variables cart, participants count, R API". The main content area has a dark blue background with the heading "Open Source Software for Epidemiology" and the subtitle "Software solutions for data management, analysis and dissemination". A central graphic shows a sequence of icons: a flask, a database cylinder, a bar chart, and a cloud storage icon. Below this is a section titled "Our Applications" with three items: "Collect with Onyx" (with a flask icon), "Store with Opal" (with a database icon), and "Analyze with R and DataSHIELD" (with a bar chart icon). Each item includes a brief description and a "Learn more" link. The entire content area is enclosed in a rounded rectangle with a blue border.


OBiBa

Products - Downloads Documentation - About Careers

Mica 3.3 Released Variables cart, participants count, R API

Open Source Software for Epidemiology

Software solutions for data management, analysis and dissemination



Our Applications

Collect with Onyx

Onyx is a comprehensive web application used to manage subject interviews and collect data in clinics or assessment centres. Using Onyx, studies can design and administrate advanced questionnaires and automate data capture directly from electronic medical instruments avoiding error prone manual data acquisition.

[Learn more](#)

Store with Opal

Opal is the OBiBa's core database application for epidemiological studies. It is used to build study's central data repositories that integrate under a uniform interface data collected from multiple sources (including Onyx). Using Opal, studies can import, validate, derive, query, report, analyse and export data.

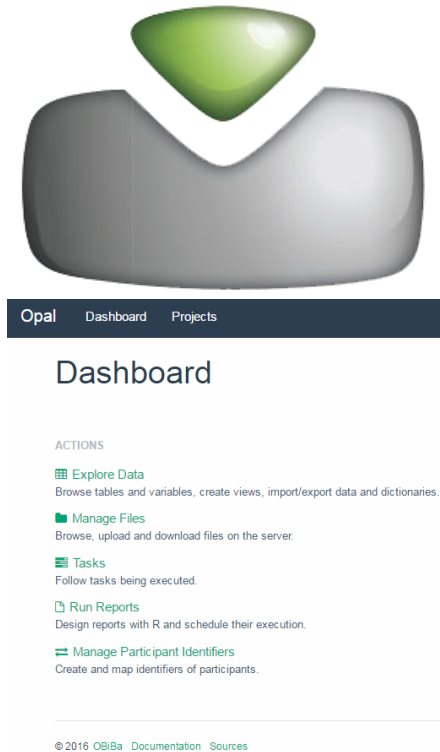
[Learn more](#)

Analyze with R and DataSHIELD

DataSHIELD enables advanced statistical analysis across a network of Opal databases without the need of pooling and accessing individual-level data. This is a powerful tool for studies that can't share data for common ethico-legal reasons but still want to co-analyse in-depth their data in an extensive way.

www.obiba.org

Infrastructure: Virtual machine with complete set of software to run a RHAPSODY node



- Oracle VirtualBox platform 5.0.20
 - Runs on Linux, Solaris, Windows, Mac OS
- Oracle Enterprise Linux 7 as guest OS
- BioShare Opal 2.5.1 (the latest available)
 - MySQL 5.7.12
 - R 3.2.3
 - Opal-rserver
 - R studio
 - DataShield
 - Python API utilities
- Ready to be distributed (4GB)
- Repository and workbench for harmonized RHAPSODY data
- Only 15 GB disk space – needs additional volume(s) to be mounted, direct or NFS
- Needs node-specific analysis R script(s)

Lists of analyses that are possible using the federated database (programmées en R)

Already Implemented:

- Quantiles, summaries, *glm* (DataSHIELD)
- *PCA*
- *Kmeans* clustering
- Fast linear regression
- Gaussian mixtures
- Random forests (*not fully tested*)

- *KNN* imputation (*vim*)
- Cox proportional hazards (*coxph*)
- Conditional logistic regression (*clogit*)
- Linear mixed models (*nlme*)

Possible to run in
“*Virtual cohort*” mode

Possible to run in
Replication mode only

Work in progress:

- Similarity Network Fusion (*SNF*)

In RHAPSODY we have built a **federated database** comprising **10 clinical cohorts**

Available data in federated databases can be browsed on web interface

Federated nodes status (live) ● ANDIS ● DIACORE ● German-CKD ● GoDARTS ● PROVALID

Cohort status [Show status history](#)

Cohorts [A andis](#) [O godarts](#) [P provalid](#) [Filter cohort](#) [show cohort filters](#)

Visualization

[Histogram](#)

[Smooth scatterplot](#)

7 variables present in at least 3 cohorts n=3 cohorts

3

Variables CHOL (mmol/L) [A](#) [O](#) [P](#) [X](#)

Actions [Show histogram](#) [advanced parameters](#) [reset](#)

Slider for shared cohort variables

andis ● recruitment

godarts ● recruitment

provalid ● baseline

Histograms and smooth scatterplots

Deep clinical phenotypes for ~50K individuals harmonised and federated in RHAPSODY

Cohort	Cohort type	No. Individuals
GoDARTS	Progression	9081
ANDIS	Progression	11549
DCS	Progression	5560
BOTNIA	Pre-diabetes	3354
MDC	Pre-diabetes	3008
DESIR	Pre-diabetes	5212
COLAUS	Pre-diabetes	6187
ABOS	Gastric bypass	249
ADDITION-DK	Progression	1533
ADDITION-PRO	Pre-diabetes	2093
Total		47826

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- **Exemple d'utilisation du système fédéré**

Diabetes is actually five separate diseases, research suggests

By James Gallagher
Health and science correspondent, BBC News

🕒 2 March 2018 | 📄 231

f 🐦 💬 ✉️ 🌐 Share



Scientists say diabetes is five separate diseases, and treatment could be tailored to each form.

<http://www.bbc.com/news/health-43246261>

Can we replicate the clusters using the federated database?

Perform *kmeans* clustering using 5 clinical variables
(HBA1c, Cpeptide, BMI, Age, HDL) on
ANDIS, **DCS** and **GoDARTS** cohorts through the
RHAPSODY federated database



GoDARTS

BOTNIA

ANDIS

MDC

ADDITION-DK

ADDITION-PRO

DCS

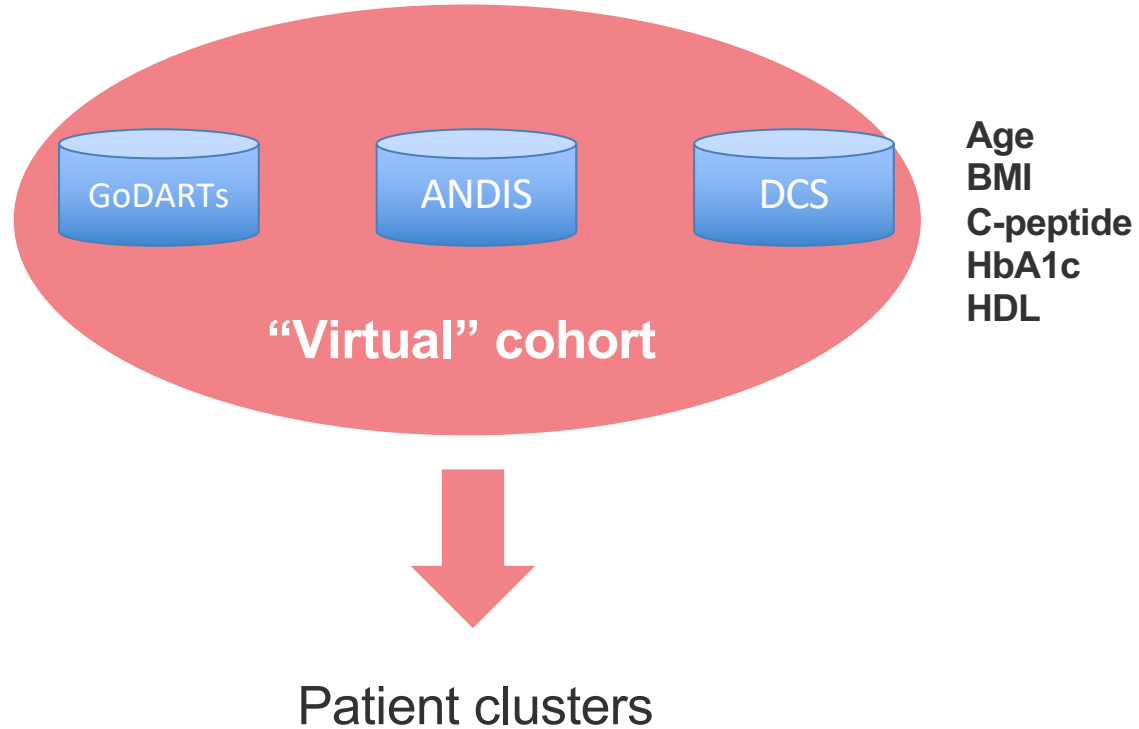
DESIR

ABOS

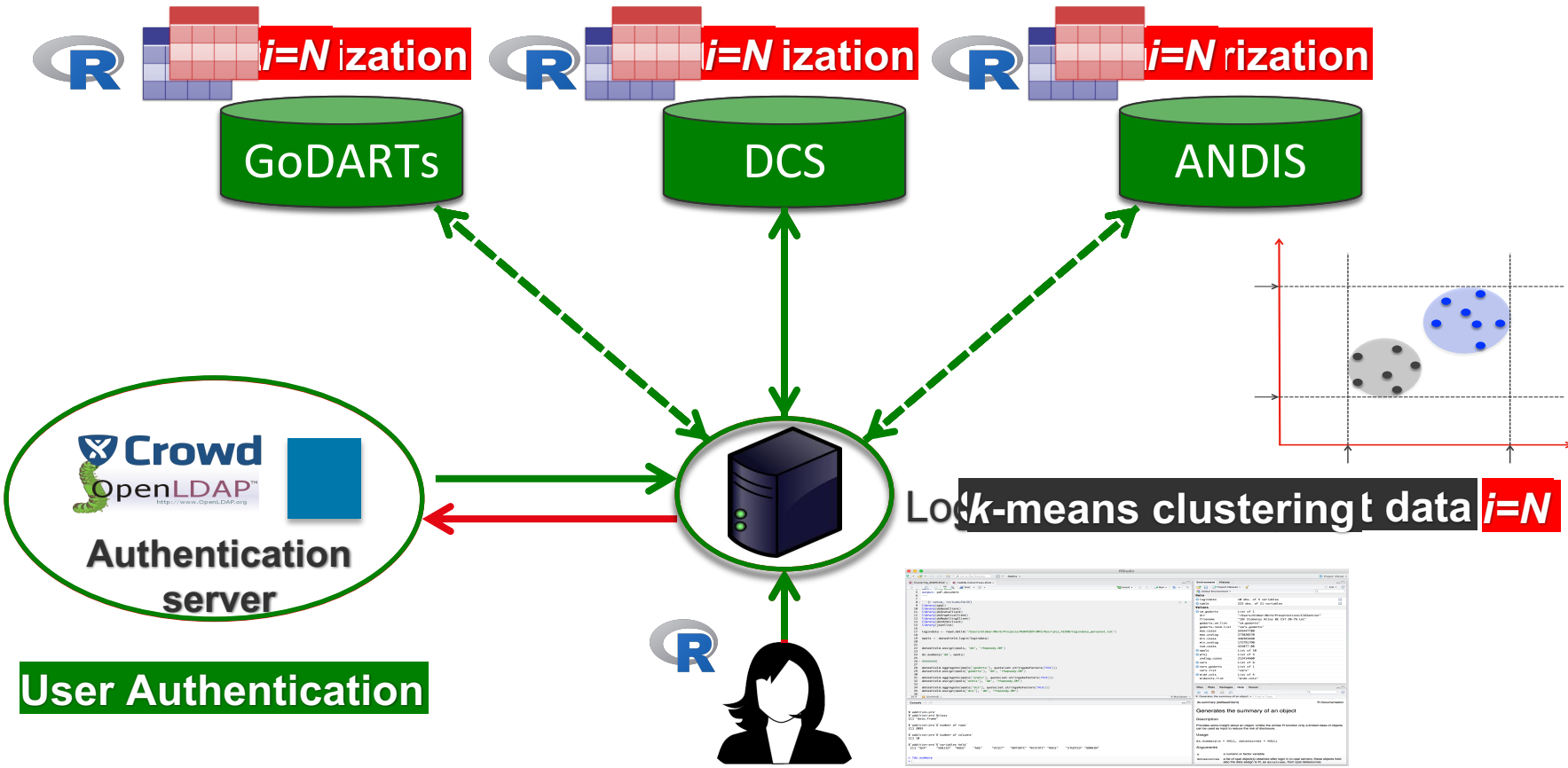
CoLaus



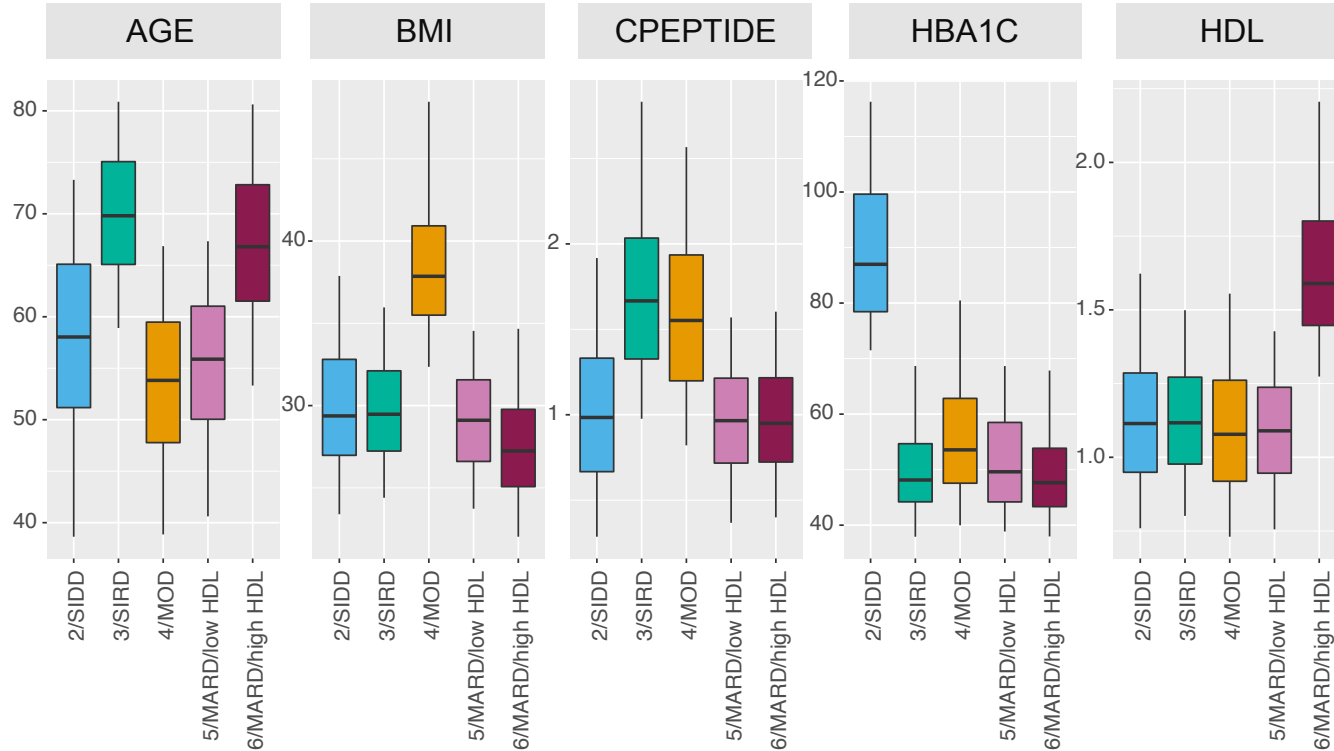
Federated k -means clustering using 5 variables



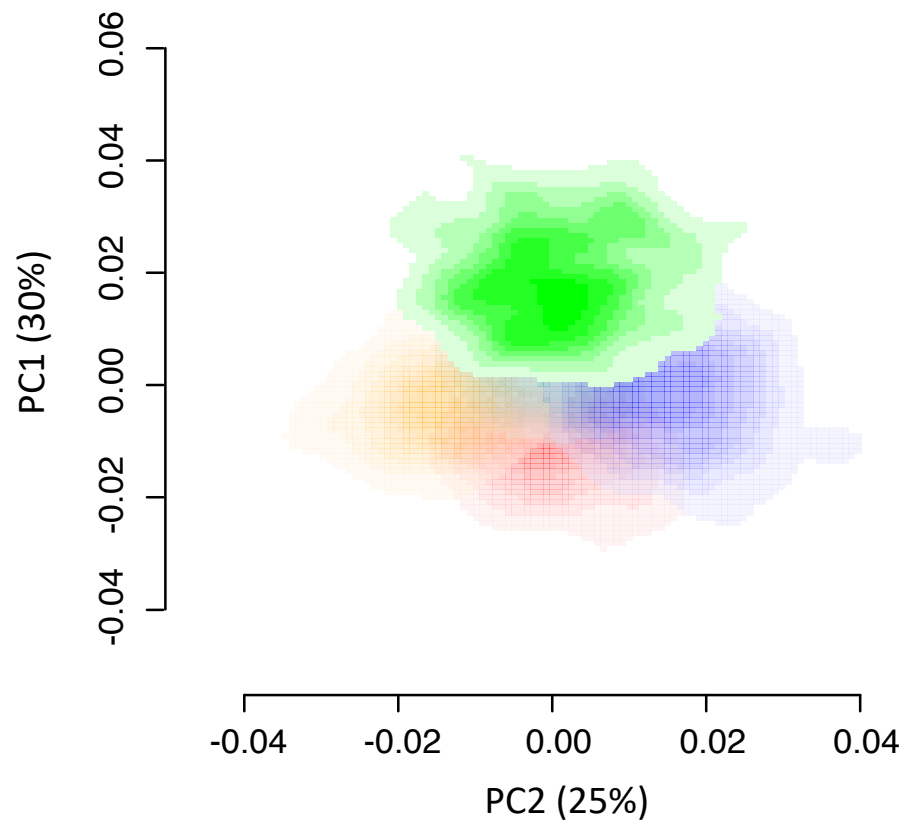
How it works ..



Clustering reproduced on a “virtual” cohort comprising ANDIS, DCS and GoDARTS cohorts



Federated PCA on “virtual” cohort comprised of DCS + ANDIS + GoDARTS (N=5723)



Take home messages

- Nous avons pu montrer que **l'analyse de multiples cohortes** cliniques est possible à travers un **système fédéré** et **l'harmonisation** des données en utilisant CDISC-SDTM
- Une partie des analyses peut être effectuée comme si les données avaient été “poolées” physiquement, sans toutefois **qu'aucune donnée individuelle de patient** ne quitte son environnement local
- L'analyse de donnée en système fédéré peut bénéficier d'une **puissance statistique augmentée** par l'analyse groupée de plusieurs cohortes, tout en respectant les contraintes **légalés et éthiques**.

RHAPSODY Core Federated DB Team @ Vital-IT, SIB

Federated Database



Dmitry Kuznetsov



Iulian Dragan

Cohort harmonization



Frédéric Burdet



Mark Ibberson –
Scientific Lead

Scientific Portal



Robin Liechti



Lou Götz



Fabio Lehman



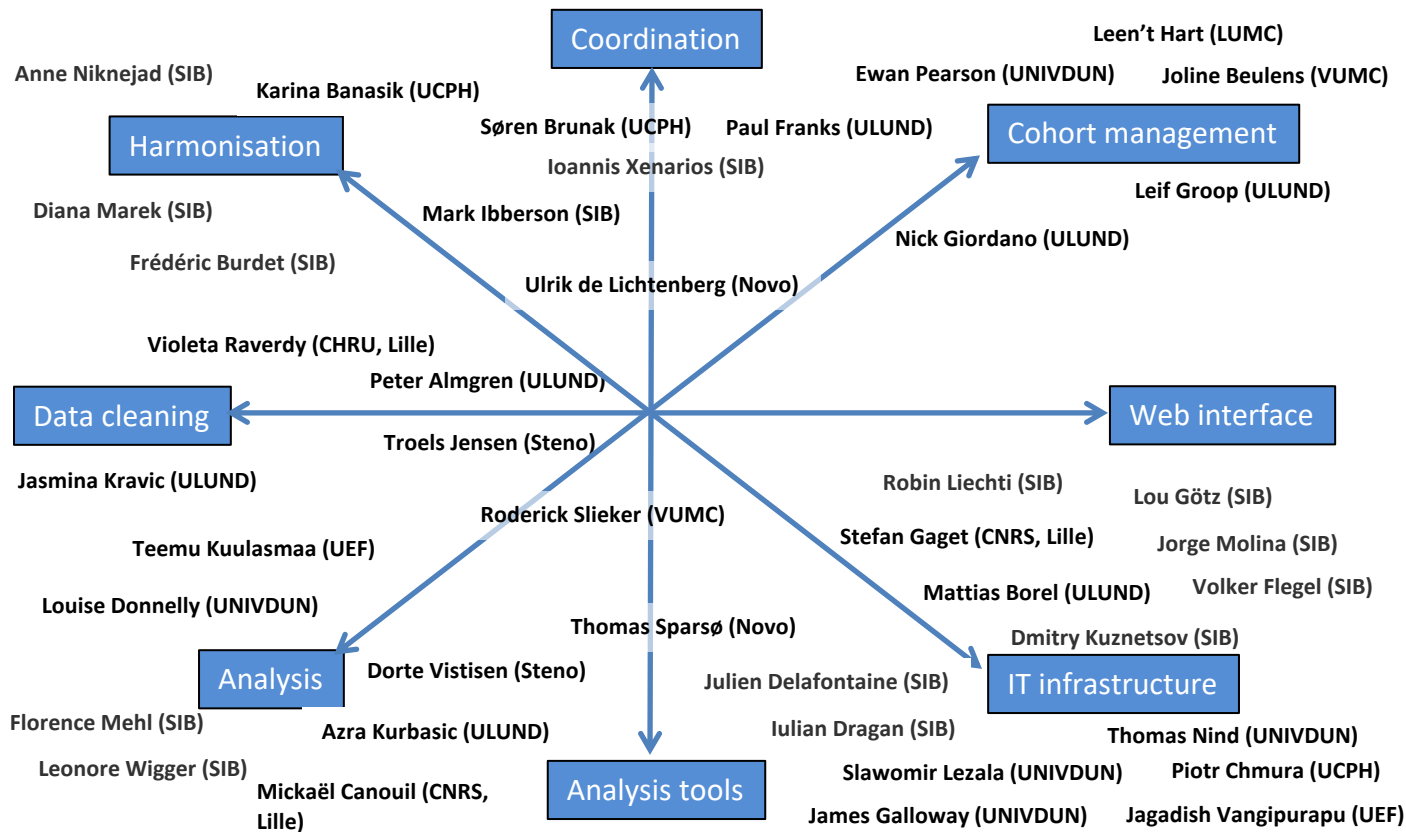
Diana Marek



Anne Niknejad



RHAPSODY Federated DB Team



Merci

Slides backup

20 institutional partners all over Switzerland

heig-vd
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DU CANTON DE VAUD
www.heig-vd.ch

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Friedrich Miescher Institute
for Biomedical Research

**University
of Basel**

Swiss TPH

ETH
Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich

**University of
Zurich**

Agroscope

Zürich University
of Applied Sciences

zhaw

SIAF

EPFL

Unil
UNIL | Université de Lausanne

**LUDWIG
CANCER
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**UNI
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UNIVERSITÉ DE Fribourg
UNIVERSITÄT Fribourg

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U^s
Università
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italiana

IOR
Institute of Oncology Research