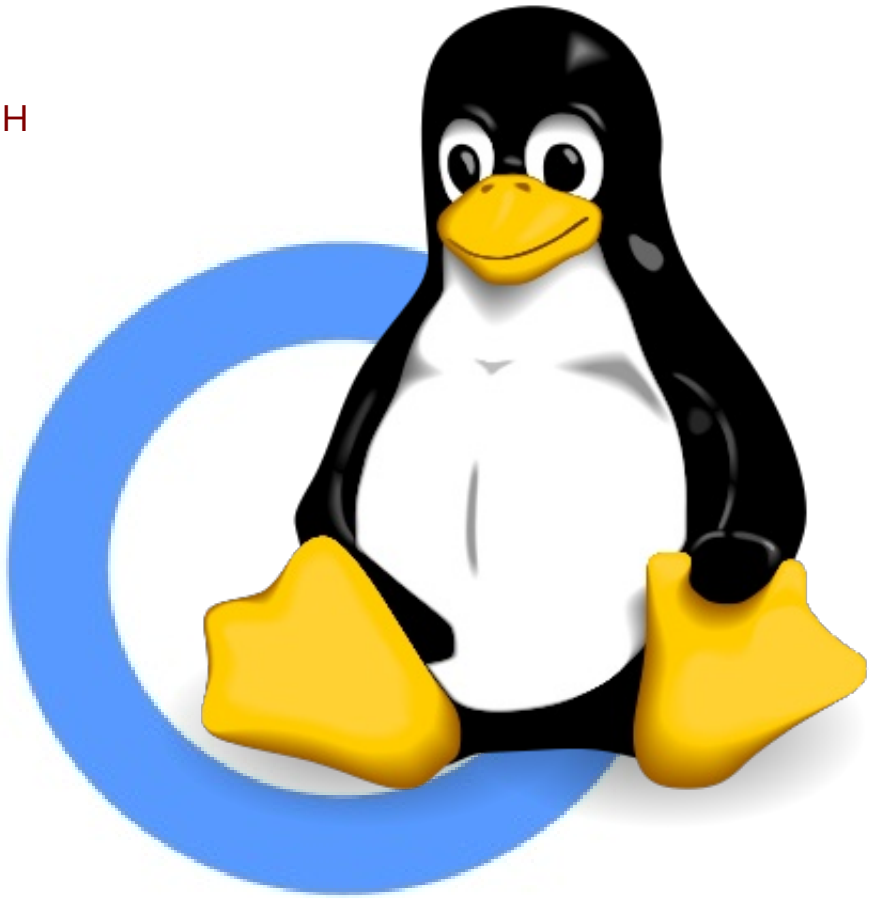
Open source tools for clinical research in a diabetes clinic

Iztok Štotl

University Medical Centre Ljubljana

Peter Beck

JOANNEUM RESEARCH Forschungsgesellschaft mbH

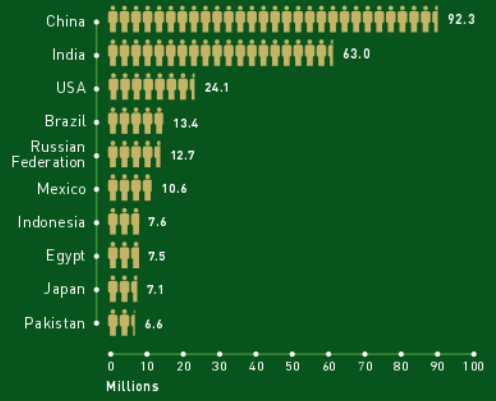


LINUX TAG

Berlin 2013

More than **371 million** people have diabetes.

TOP 10 COUNTRIES/TERRITORIES FOR PEOPLE WITH DIABETES (20-79 YEARS)



The number of people with diabetes is **increasing** in every country.

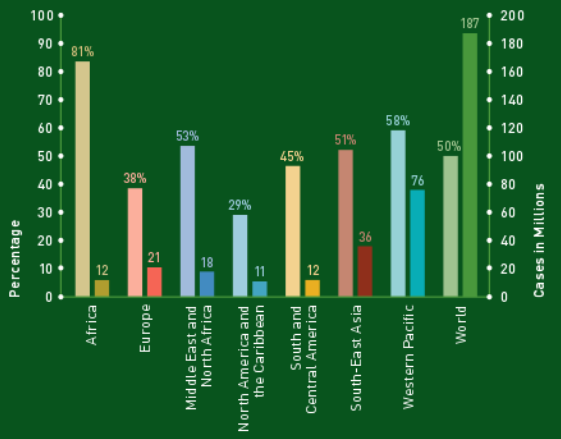
TOP 10 COUNTRIES/TERRITORIES FOR PREVALENCE* (%) OF DIABETES (20-79 YEARS)

	COUNTRY /TERRITORY	PREVALENCE (%)
1	Federated States of Micronesia	37.2
2	Nauru	30.1
3	Marshall Islands	27.1
4	Kiribati	25.5
5	Tuvalu	24.8
6	Kuwait	23.9
7	Saudi Arabia	23.4
8	Qatar	23.3
9	Bahrain	22.4
10	Vanuatu	22.0

*comparative prevalence

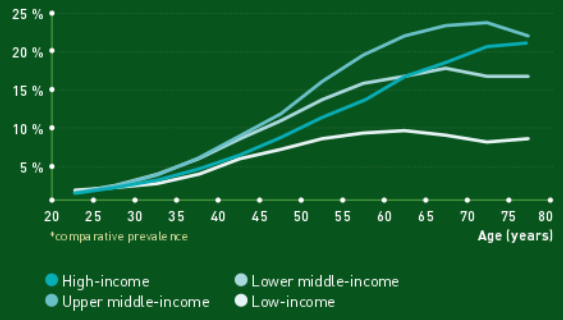
Half of people with diabetes **don't know** they have it.

UNDIAGNOSED PERCENTAGE AND UNDIAGNOSED CASES OF DIABETES (20-79 YEARS) BY REGION



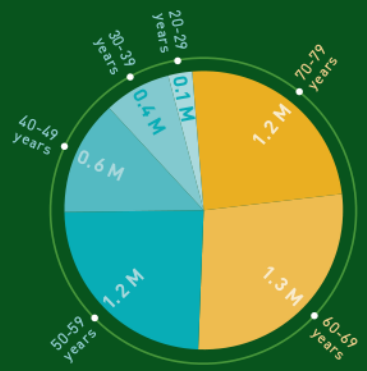
4 out of 5 people with diabetes live in **low- and middle-income** countries.

PREVALENCE* (%) ESTIMATES OF DIABETES (20-79 YEARS) BY INCOME GROUP AND AGE



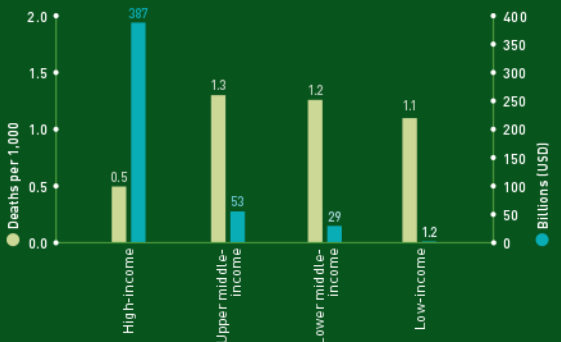
Half of people who die from diabetes are **under the age of 60.**

DEATHS ATTRIBUTABLE TO DIABETES BY AGE (20-79 YEARS)



4.8 million people **died** and **471 billion USD** were **spent** due to diabetes in 2012.

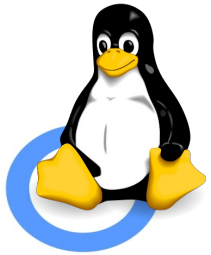
HEALTHCARE EXPENDITURES AND DEATHS PER 1,000 DUE TO DIABETES BY INCOME GROUP



Source od data: IDF Diabetes World Atlas; http://www.idf.org/

Different IT problems in clinical diabetology

- Standardisation of Electronic Medical Record (still a lot of work to do)
- Hospital and ambulatory information systems (mostly proprietary and closed source)
- Telemedicine, PHR and different medical gadgets (insulin pumps, sensors ...)
- **Data management in Clinical research**
- **Computerised diabetes registries**

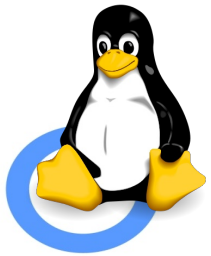


University medical centre Ljubljana, Department of Endocrinology, Diabetes and Metabolic Diseases

Small department with inpatient and outpatient diabetes clinic

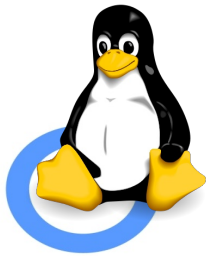
Own servers:

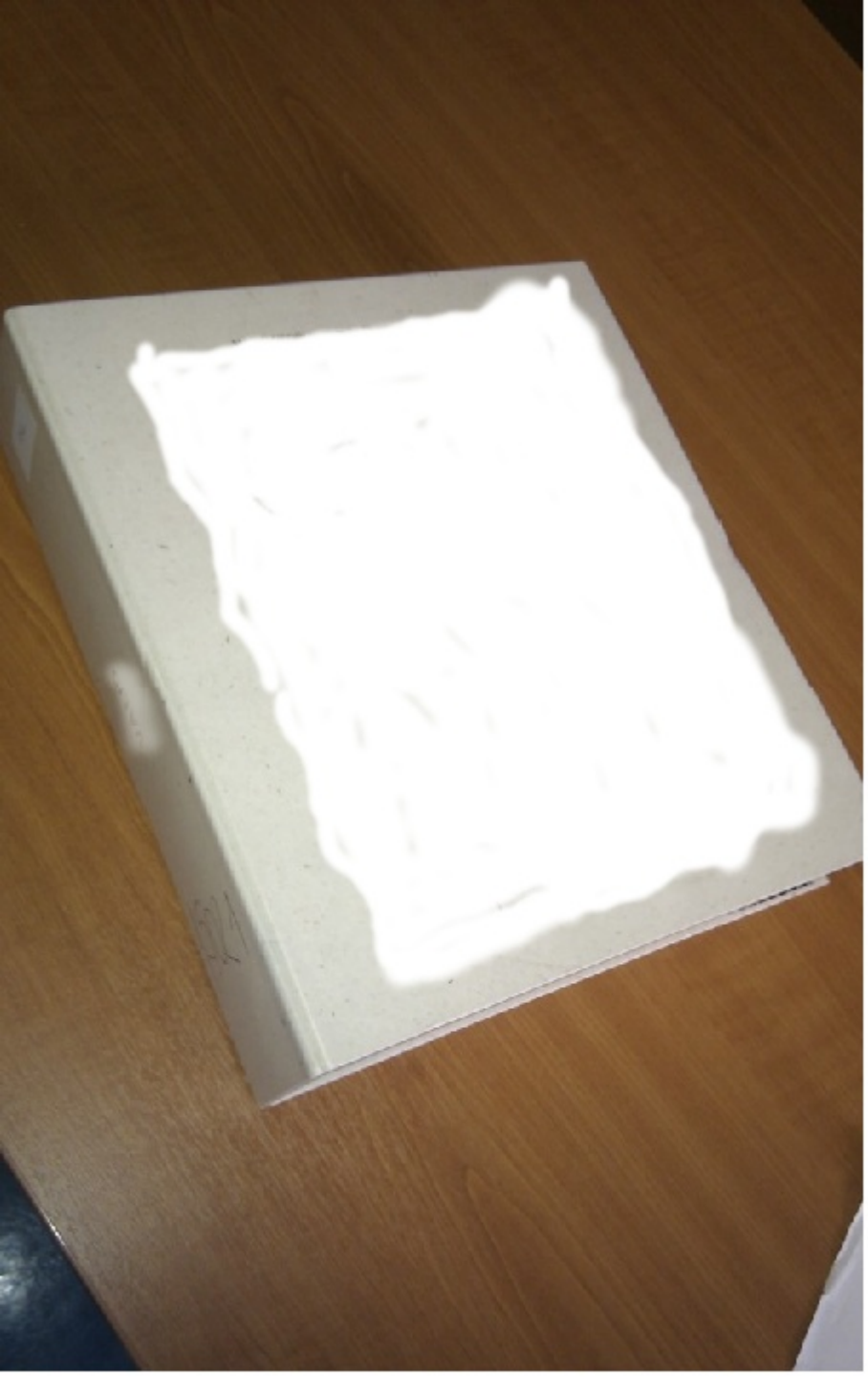
- Centos
- KVM virtualisation
- Apache/Tomcat in different VM's



Clinical data for research

- Different data sources
    - laboratories
    - bedside data
    - different departments
    - multicentric/international research
- Strict regulations
- Complex research protocols
- Monitoring of research progress
- Long term archiving of data



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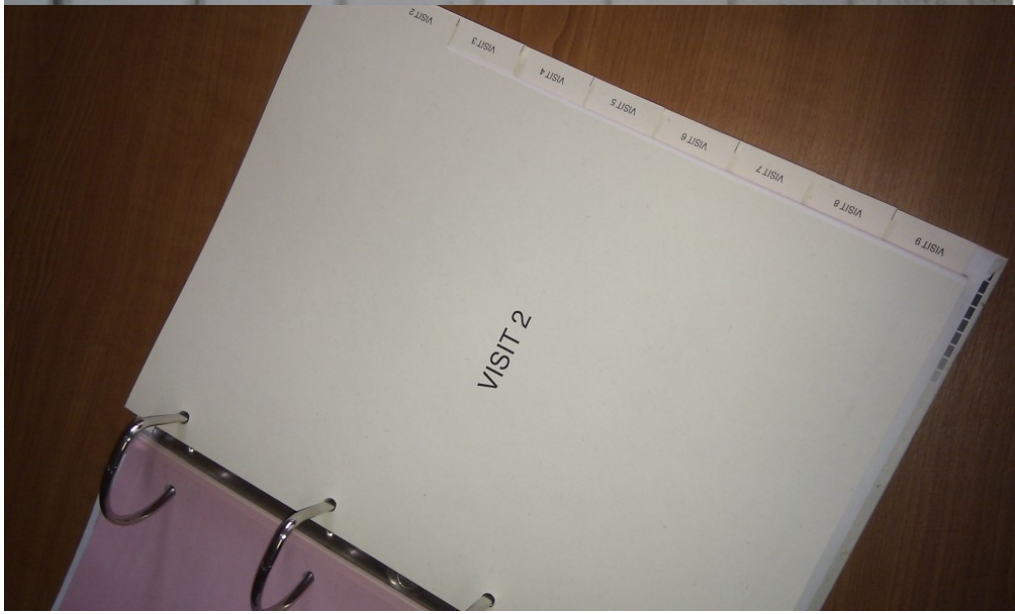
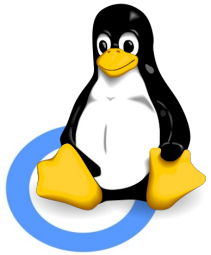

VISIT 2
VISIT 3
VISIT 4
VISIT 5
VISIT 6
VISIT 7
VISIT 8
VISIT 9

Simple electronic forms (.xls, .mdb, ..)

+ easy to develop
+ low price

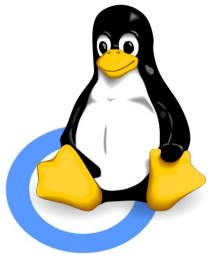
- not practical for complex protocols
- bad for big research teams, multicentric studies
- without tracking changes, not compliant with regulations
- not flexibile enough, lack of support for different data formats
- archiving not complete (signatures, modifications tracking)



„Tailored“ - custom made applications

+ web/desktop applications
+ everything can be customised

- time consuming
- $$$ - price to high for small research teams
- bad reusability
- public clouds not an option (privacy, regulations)
- propriatary solutions (expensive, lock-in ...)



OPEN ACCESS Freely available online

PLoS MEDICINE

Essay

Could an Open-Source Clinical Trial Data-Management System Be What We Have All Been Looking For?

Greg W. Fegan, Trudie A. Lang*

Difficulties in Meeting the Demands of Regulators and Guidelines

In Europe, it is a legal requirement to conduct clinical trials in accordance with the International Conference on Harmonisation's guidelines on good clinical practice (see http://www.ich.org/). A recent editorial reported that this directive has led to a decline in the number of trials being conducted by independent academic groups [1]. One

Box 1. An Introduction to Open-Source Software: Definitions and Required Reading

1. Ten Things You Didn't Know about Open Source (http://www.tectonic.co.za/view.php?id=1465)
2. Definition of Open-Source Software
   a. Free redistribution
   b. Source code
   c. Derived works

absence of guidance from regulatory agencies such as the European Medicines Agency and United States Food and Drug Administration about how to evaluate the many competing systems available, and indeed what the actual requirements are for trials where the data will be needed for a regulatory submission. This is particularly important with respect to trials evaluating products for neglected diseases, which are often carried out

REDCap™ Research Electronic Data Capture	OpenClinica Open Source for Clinical Research
Vanderbilt University	OpenClinica, LLC
Standard/LTS	Community/Enterprise
Available only for non-commercial research purposes	Lesser General Public License
Apache/PHP/MySql	Tomcat/J2EE/Postgres or Oracle
	Certifikate FDA 21 part 11

Trends


Map of REDCap Consortium Partners
View fullscreen map
Map
Satellite
Hybrid
North Sea
United Kingdom
Denmark
Lithuania
Vilnius
Minsk
Belarus
Hamburg
Netherlands
Poland
Belgium
Germany
Prague
Czech Rep
Krakow
Lviv
Kyiv
Ukraine
Celtic Sea
Vienna
Slovakia
Austria
Hungary
Moldova
Kryvyi Rih
Zagreb
Odessa
Romania
Bay of Biscay
France
Croatia
Torino
Marseille
Serbia
Bucharest
Italy
Rome
Bulgaria
Barcelona
Madrid
Portugal
Istanbul
Ankara
Map data ©2012 Google, Tele Atlas - Terms of Use
60,000
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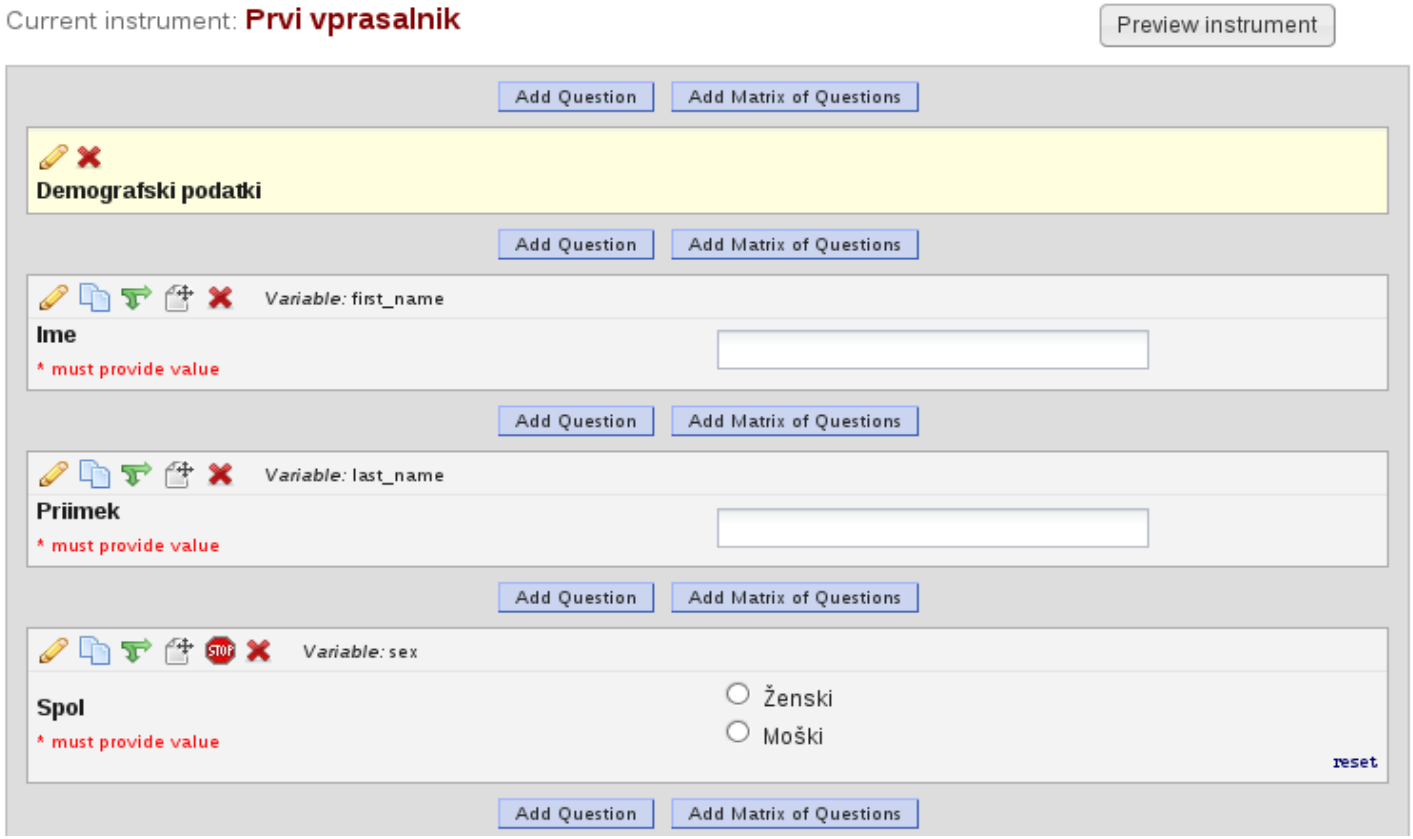
2010-02
2010-09
2011-04
2011-11
2012-06

CRF (clinical research form) editor



Univerzitetni klinični center Ljubljana

Klinični oddelek za endokrinologijo, diabetes in bolezni presnove

Angiografije diabetes 2012/1

Demographics

Share this instrument

VIDEO: Basic data entry (16 min)

Download PDF of - select PDF download option -

Editing existing Identifikacijska številka 1 [redacted])

Identifikacijska številka	1 (To rename this record, modify the value immediately below.)
Identifikacijska številka	1
Splošni podatki	
Ime	[redacted]
Priimek	[redacted]
Datum rojstva	1943-03-19 Today Y-M-D
Spol	Moški
Form Status	
Complete?	Complete
Lock this record for this form? If locked, no user will be able to edit this record on this form until someone with Lock/Unlock privileges unlocks it.	Lock

Save Record
Save and Continue
Save and go to Next Form

-- Cancel --

Delete Record

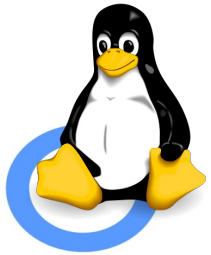
Additional features

Redcap:

- Tablet computers
- Data Transfer Service (DTS) – push or pull data
- Randomisation module
- Very friendly user interface
- Surveys

Openclinica:

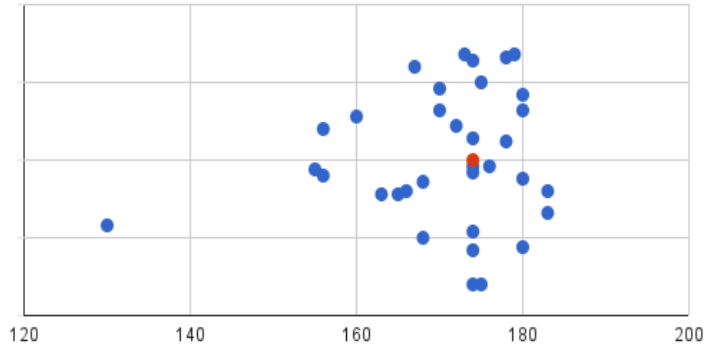
- Very good REST/SOAP infrastructure / easy customisation
- Discrepancy management (GUI entry and WS)
- CDISC ODM



Trenutna telesna višina v cm : Refresh Plot

Total (N)	Missing	Unique	Min	Max	Mean	StDev	Percentile					
							.05	.10	.25	.50 Median	.75	.90
34	1 (2.9%)	19	130.00	183.00	170.71	10.39	142.50	156.00	166.50	174.00	178.00	180.00

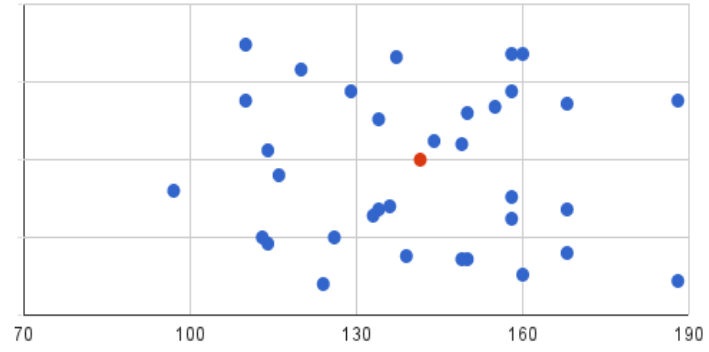
Lowest values: 130, 155, 156, 156, 160
Highest values: 180, 180, 180, 183, 183



Trenutna telesna teža v kg: Refresh Plot

Total (N)	Missing	Unique	Min	Max	Mean	StDev	Percentile					
							.05	.10	.25	.50 Median	.75	.90
34	1 (2.9%)	22	97.00	188.00	141.62	22.69	103.50	111.50	122.00	141.50	158.00	168.00

Lowest values: 97, 110, 110, 113, 114
Highest values: 168, 168, 168, 188, 188

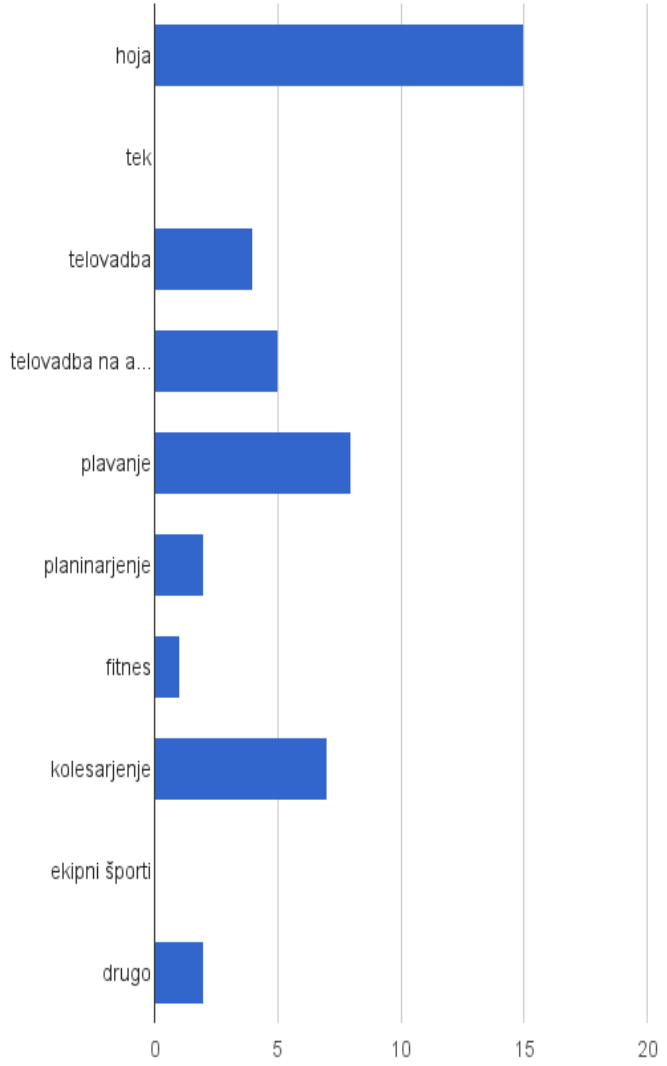


Katere vrste športa ali rekreacije se navadno udeležujete ?: Refresh Plot |

View as Bar Chart ▼

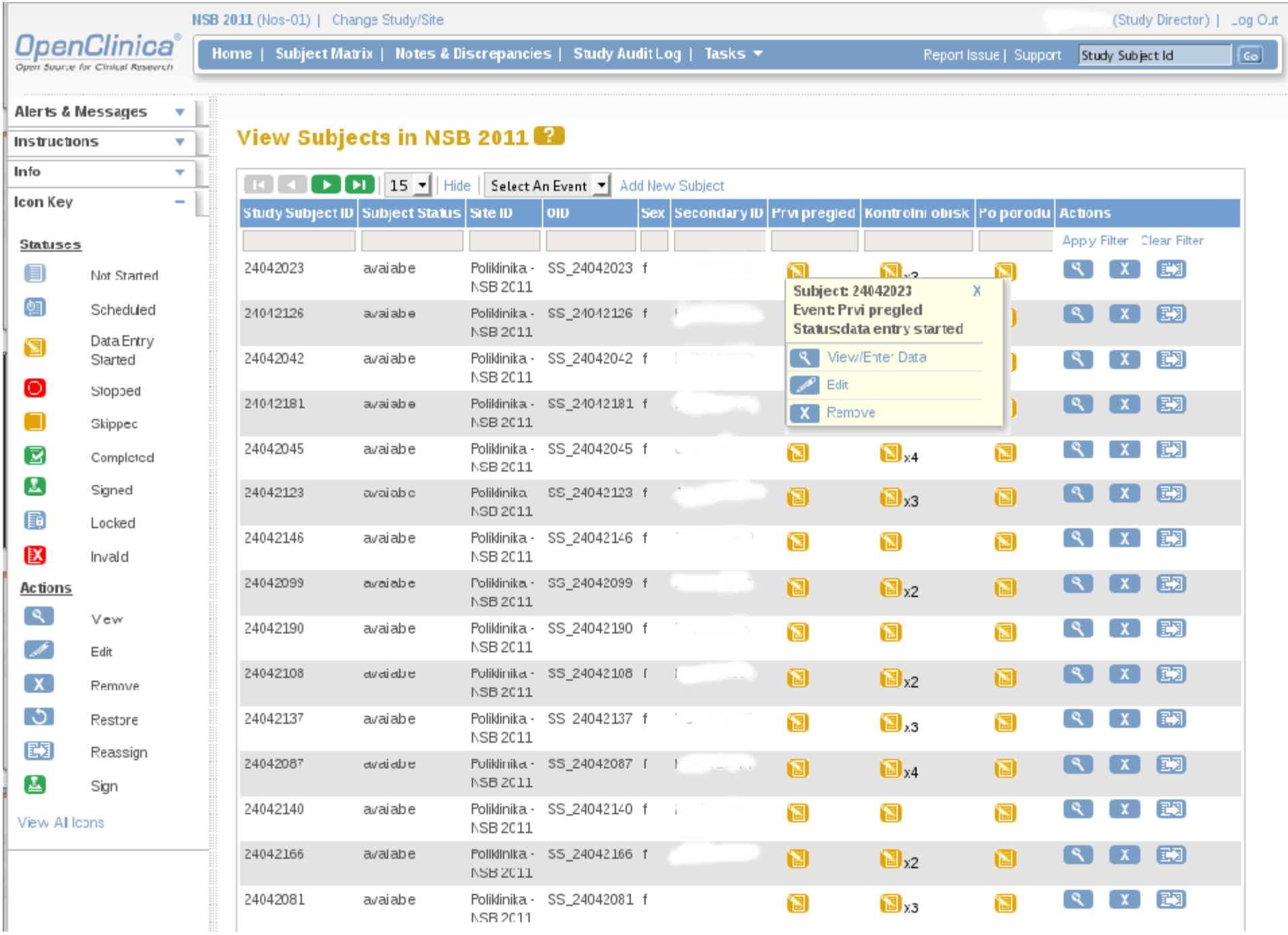
Total (N)	Missing	Unique
20	15 (42.9%)	1

Counts/frequency: hoja (15, 75%), tek (0, 0%), telovadba (4, 20%), telovadba na aparatih doma (Orbitrek, sobno kolo) (5, 25%), plavanje (8, 40%), planinarjenje (2, 10%), fitnes (1, 5%), kolesarjenje (7, 35%), ekipni športi (0, 0%), drugo (2, 10%)



Data export

	Download Syntax & Data
Microsoft Excel You may download the survey results in CSV (comma-separated) format, which can be opened in Excel. You have the choice of downloading the data either with the full headers and answer labels or just with the answer codes (i.e. raw data). *NOTE: If you are using a version of Microsoft Excel prior to Excel 2007, due to limitations the data will only be read to 255 columns when opened.*	EXCEL CSV Labels · EXCEL CSV Raw Send file?
SPSS Statistical Analysis Software Instructions: Download and save all 3 files on the right to a common location. First, double-click on the Pathway Mapper (.bat) file, which will run quickly and invisibly. (If you are not using a Windows operating system, such as Mac or Linux, please see the *Additional Instructions*.) Now double-click on the *.sps file, which will open SPSS. When the file is loaded and displayed, choose Run-->All from the top menu options. This action will launch the script that will automatically read in all data and manipulate data fields with labels, option values, etc. Additional instructions	SPSS · DATA CSV Pathway Mapper Send file?
SAS Statistical Software Instructions: Download and save all 3 files on the right to a common location. First, double-click on the Pathway Mapper (.bat) file, which will run quickly and invisibly. (If you are not using a Windows operating system, such as Mac or Linux, please see the *Additional Instructions*.) Now double-click on the *.sas file, which will open SAS. When the file is loaded and displayed, choose Run (or Run-->Submit) from the top menu options. This action will launch the script that will automatically read in all data and manipulate data fields with labels, option values, etc. Additional instructions	SAS · DATA CSV Pathway Mapper Send file?
R Statistical Software Instructions: Use command read.csv('filename') to read in data file.	R · DATA CSV Send file?
STATA Analysis and Statistical Software Instructions: Download both files to common location and double-click on *.do file. This action will launch the script that will automatically read in all data and manipulate data fields with labels, option values, etc.	STATA · DATA CSV Send file?


NSB 2011 (Nos-01) | Change Study/Site
(Study Director) | Log Out
OpenClinica
Open Source for Clinical Research
Home | Subject Matrix | Notes & Discrepancies | Study Audit Log | Tasks
Report Issue | Support
Study Subject Id
Go
Alerts & Messages
Instructions
Info
Icon Key
Statuses
Not Started
Scheduled
Data Entry Started
Stopped
Skipped
Completed
Signed
Locked
Invalid
Actions
View
Edit
Remove
Restore
Reassign
Sign
View All Icons
View Subjects in NSB 2011
15
Hide
Select An Event
Add New Subject
Study Subject ID
Subject Status
Site ID
OID
Sex
Secondary ID
Prvi pregled
Kontrolni obisk
Po porodu
Actions
Apply Filter
Clear Filter
24042023 avaiabe Poliklinika - NSB 2011 SS_24042023 f
Subject: 24042023
Event: Prvi pregled
Status:data entry started
View/Enter Data
Edit
Remove
24042126 avaiabe Poliklinika - NSB 2011 SS_24042126 f
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24042181 avaiabe Poliklinika - NSB 2011 SS_24042181 f
24042045 avaiabe Poliklinika - NSB 2011 SS_24042045 f x4
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24042146 avaiabe Poliklinika - NSB 2011 SS_24042146 f
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24042166 avaiabe Poliklinika - NSB 2011 SS_24042166 f x2
24042081 avaiabe Poliklinika - NSB 2011 SS_24042081 f x3

Conclusions

+

- Excelent stabillity
- Very good support/very active community
- Low cost of ownership

-

- ?

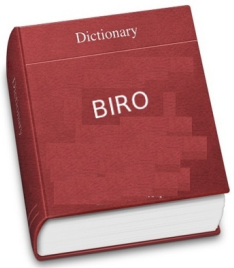
"EUropean Best Information through Regional Outcomes in Diabetes" (EUBIROD)

Public health project in the field of diabetes sponsored by the European Union

Goal: to create extensive report on several regions in Europe in diabetes care

EUBIROD

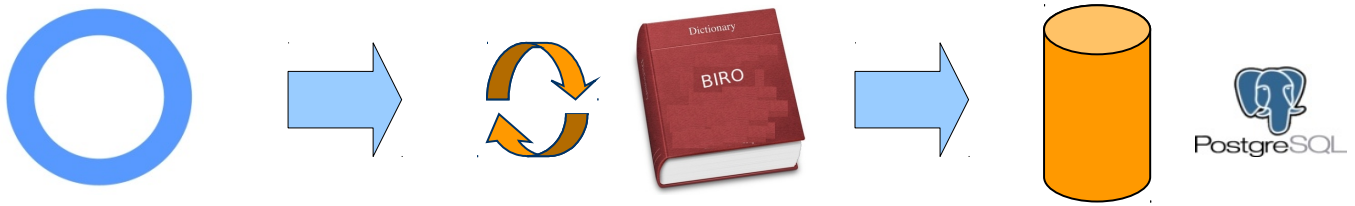
BIRO Core EU Dataset



N=48

1. ID Patient
2. ID Centre
3. Type of Diabetes
4. Sex
5. Date of Birth
6. Date of Diagnosis
7. Episode Date
8. Smoking Status
9. N.Cigarettes (x day)
10. Alcohol Intake (g/x day)
11. Weight
12. Height
13. BMI
14. Systolic Blood Pressure
15. Dyastolic Blood Pressure
16. HbA1c
17. Creatinine
18. Microalbumin
19. Total Cholesterol
20. HDL
21. Tryglicerides
22. Eye Examination
23. Retinopathy Status
24. Maculopathy Status
25. Foot Examination
26. Foot Pulses
27. Foot vibration
28. End Stage Renal Failure
29. Renal Dyalisis
30. Renal Transplant
31. Stroke
32. Foot Ulceration
33. Acute Myocardial Infarction
34. Laser
35. Hypertension
36. Blindness
37. Amputation
38. Antihypertensive Medication
39. Hypoglicemic Drug Therapy
40. Oral Drug Therapy
41. Pump Therapy
42. Nasal Therapy
43. Average Injections (x day)
44. Self monitoring
45. Diabetes Specific Education
46. Lipid Lowering Therapy
47. Anti-platelet Therapy
48. Patient enrollment in DMP for diabetes

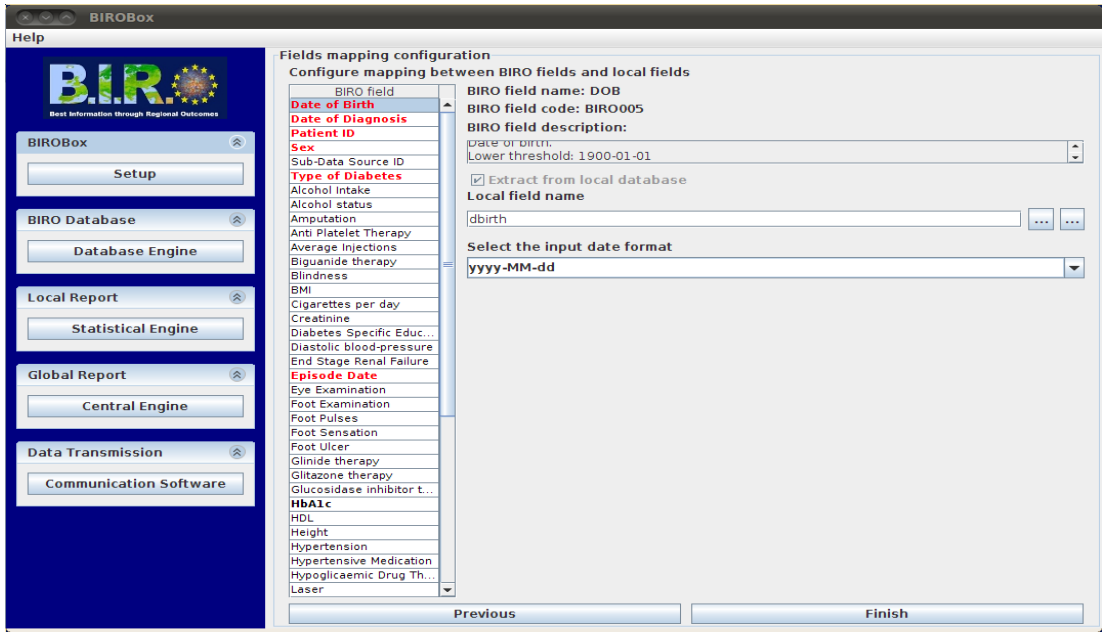
1. step: Discard Heterogenity from primary sources



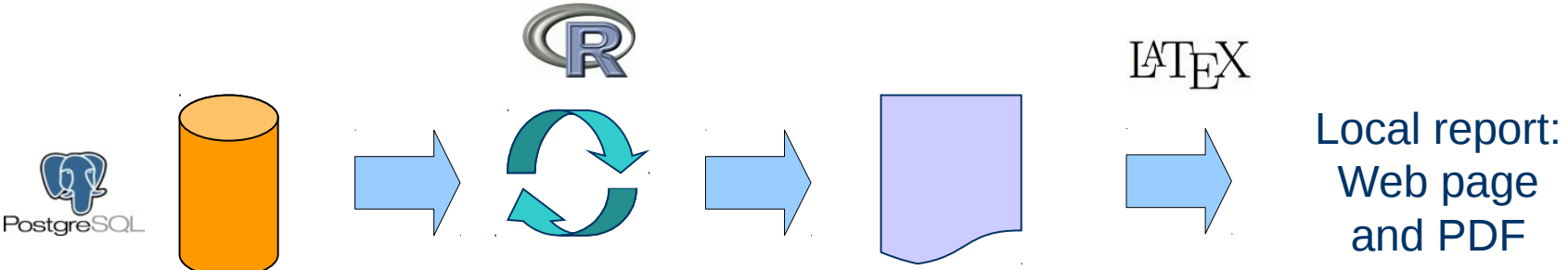
Diabetes clinic/region/country

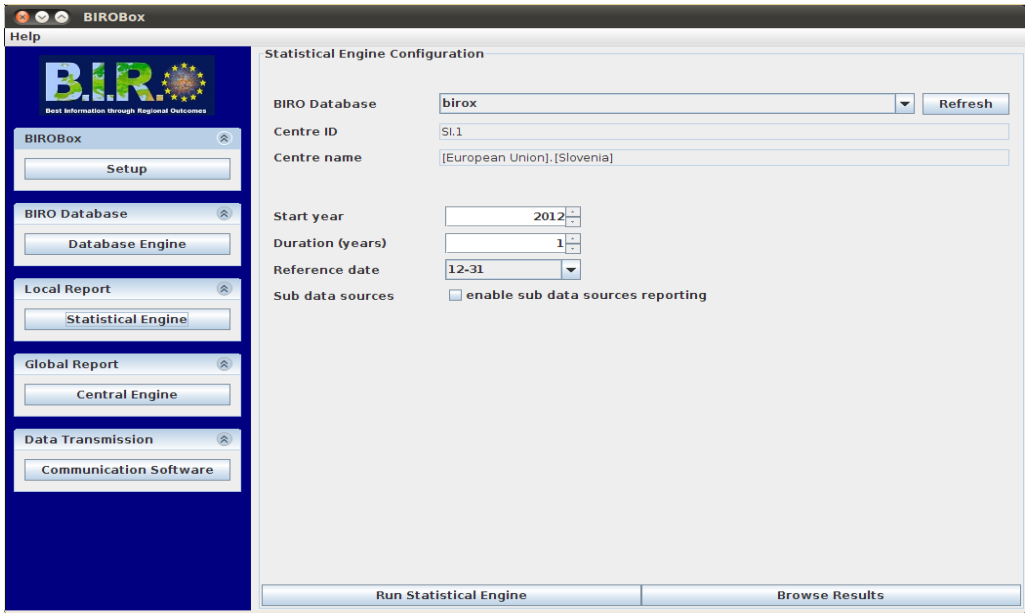
Mapping to standard

Standardized database



2. step: Local statistical analysis



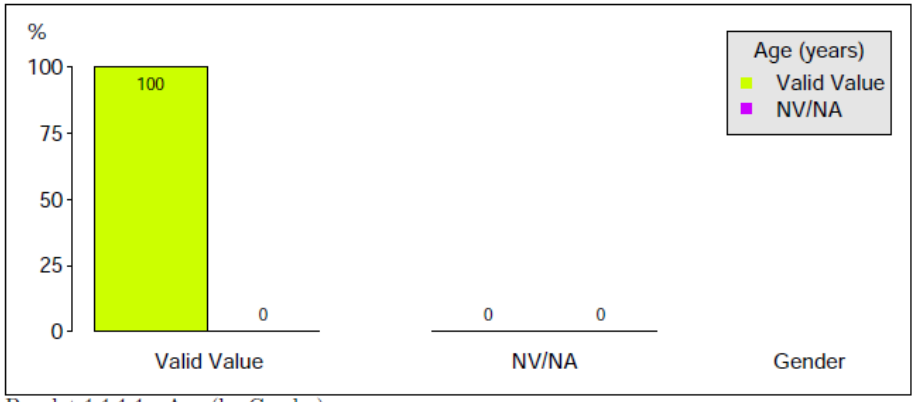


Contents

Age	Valid Value (%)	NV/NA (%)		N (%)
Valid Value	118156 (100.0)	0(0.0)		118156 (100.0)
NV/NA	0 (0.0)	0(0.0)		0 (0.0)
TOTAL	118156(100.0)	0(0.0)		118156 (100.0)

Table 1.1.1.1 : Age (by Gender)

	CMH Chi-Square
Value	Too many cells have 0 obs

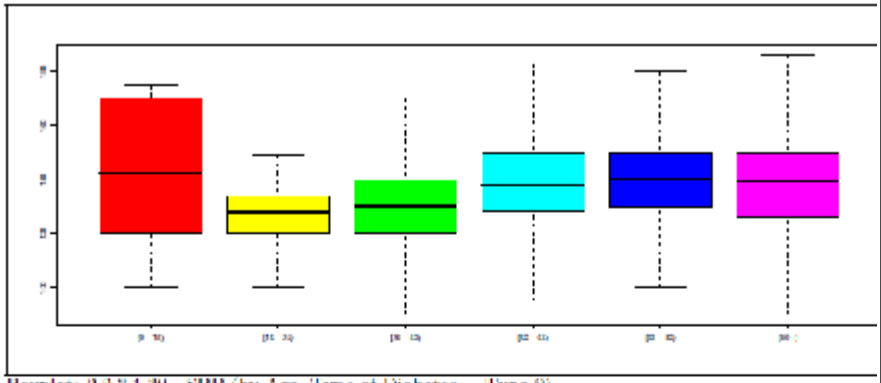


Barplot 1.1.1.1 - Age (by Gender)

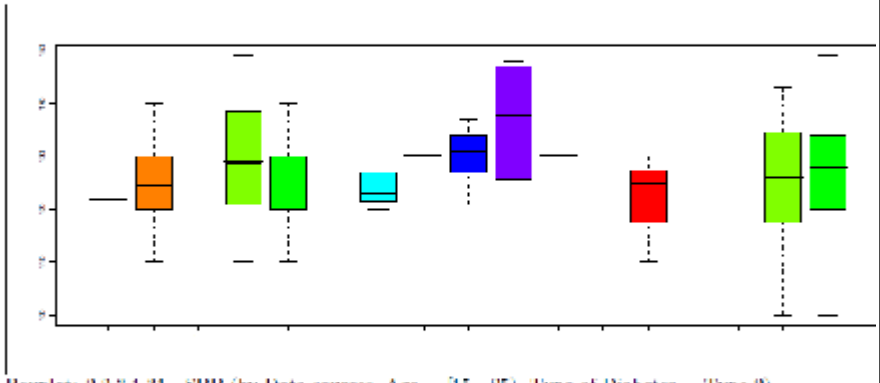
Age	Male (%)	Female (%)		N (%)
[0 - 15)	482 (0.8)	490(0.9)		972 (0.8)
[15 - 25)	1104 (1.8)	1009(1.8)		2113 (1.8)
[25 - 50)	8867 (14.3)	6613(11.8)		15480 (13.1)
[50 - 65)	22623 (36.5)	16056(28.6)		38679 (32.7)
[65 - 80)	23731 (38.2)	23834(42.5)		47565 (40.3)
[80 +)	5249 (8.5)	8097(14.4)		13346 (11.3)
TOTAL	62056(52.5)	56099(47.5)		118155 (100.0)

Table 1.1.1.2 : Age (by Gender)

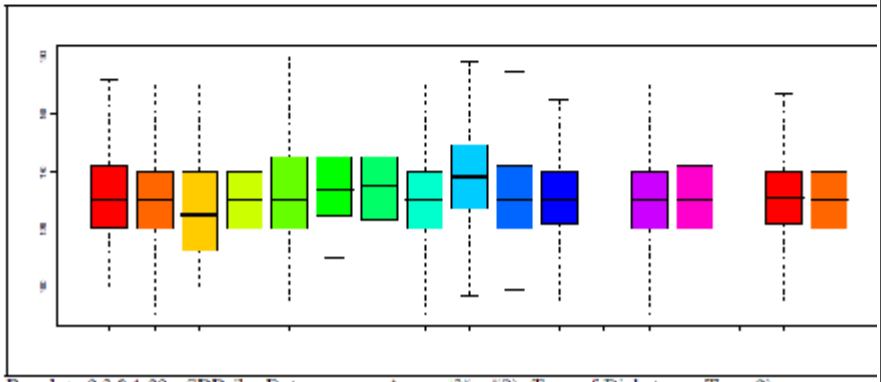
	CMH Chi-Square	p.value	df
Value	1759.6126	0	5



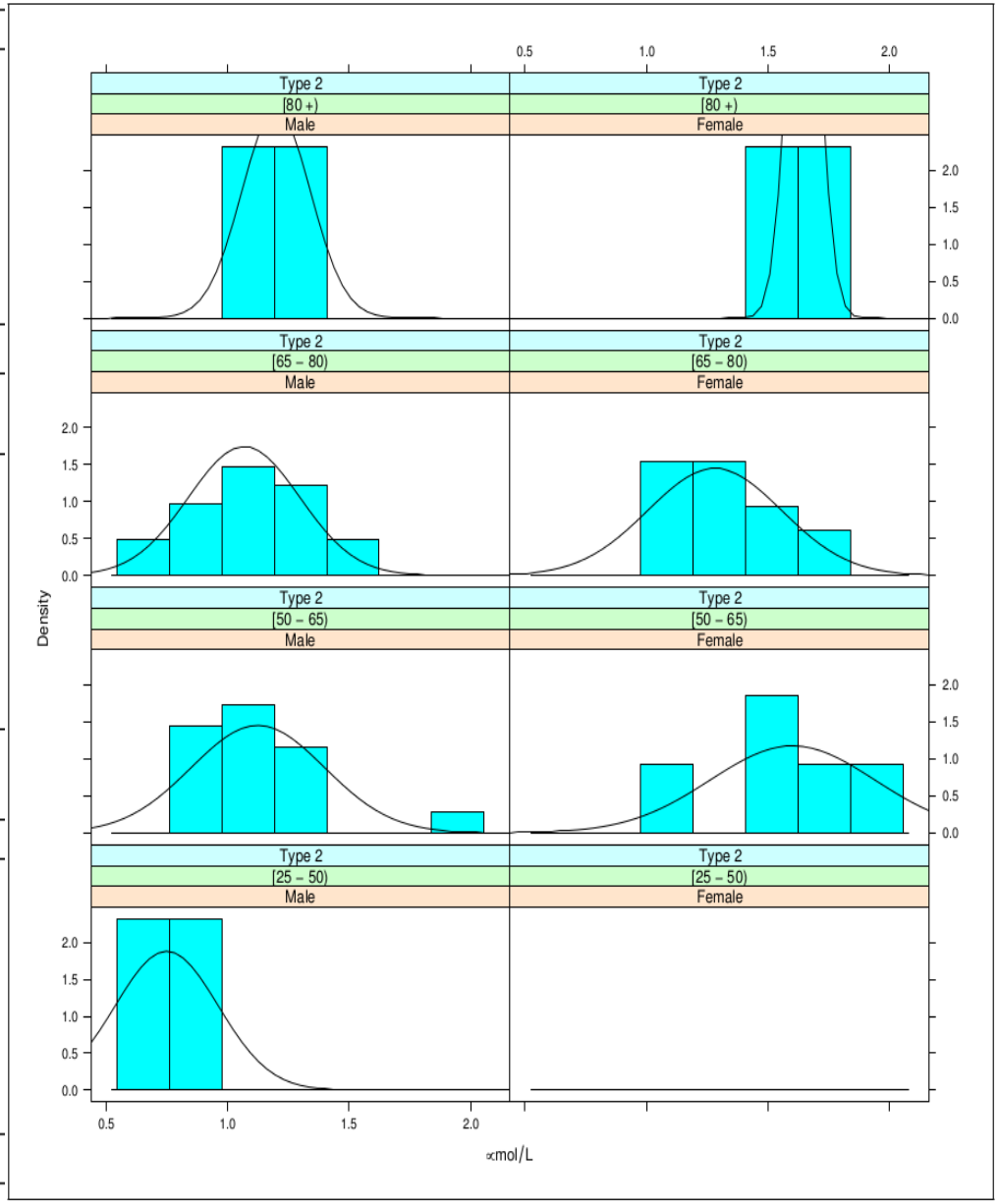
Boxplot: 2.2.3.1.30 - SBP (by Age, Type of Diabetes = Type 2)



Boxplot: 2.2.3.1.31 - SBP (by Data sources, Age = [17 - 25], Type of Diabetes = Type 2)

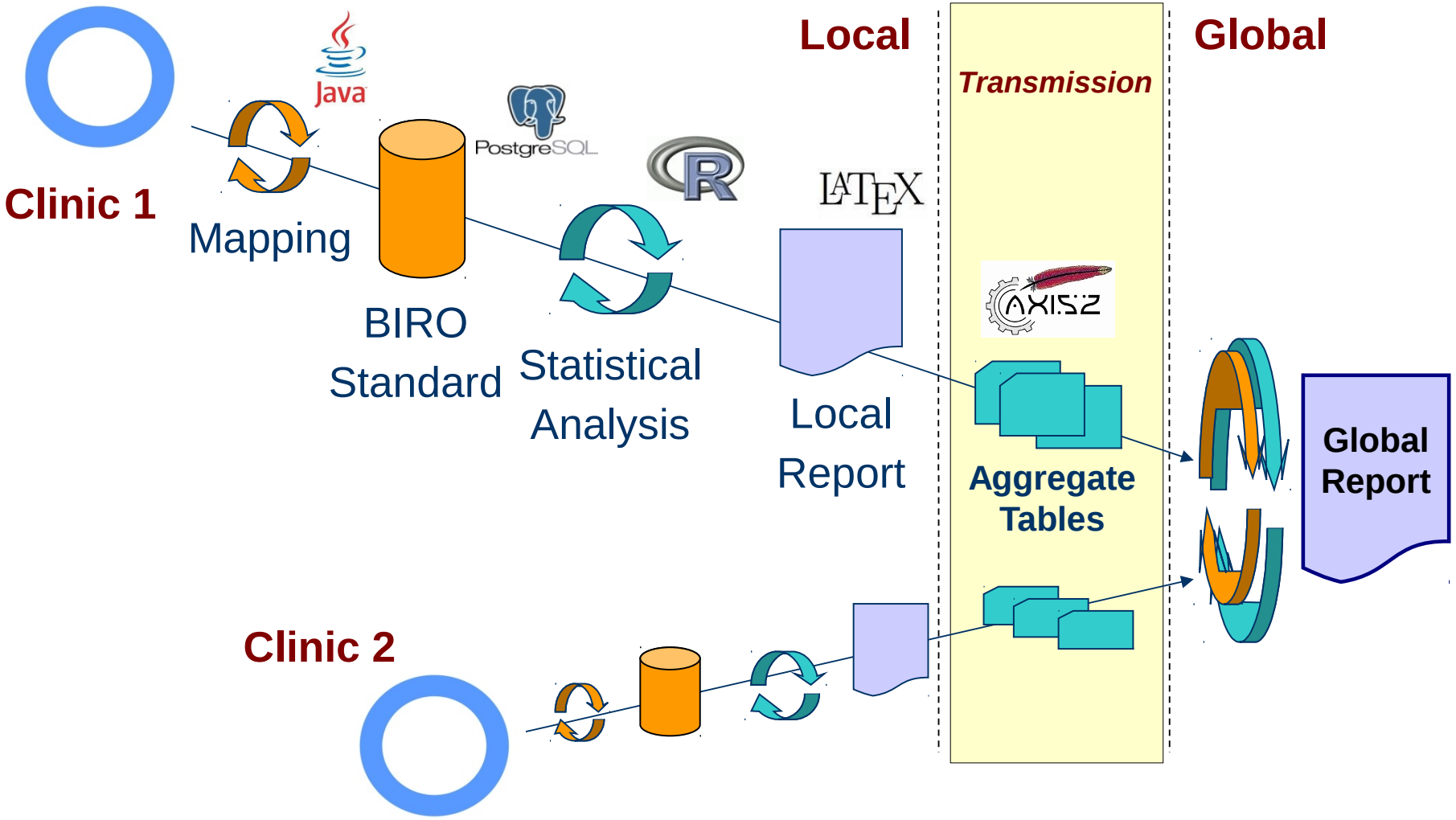


Boxplot: 2.2.3.1.32 - SBP (by Data sources, Age = [25 - 50], Type of Diabetes = Type 2)



Trellis density plot: 2.2.3.4.2 - HDL * Gender * Age (Type of Diabetes = Type 2)

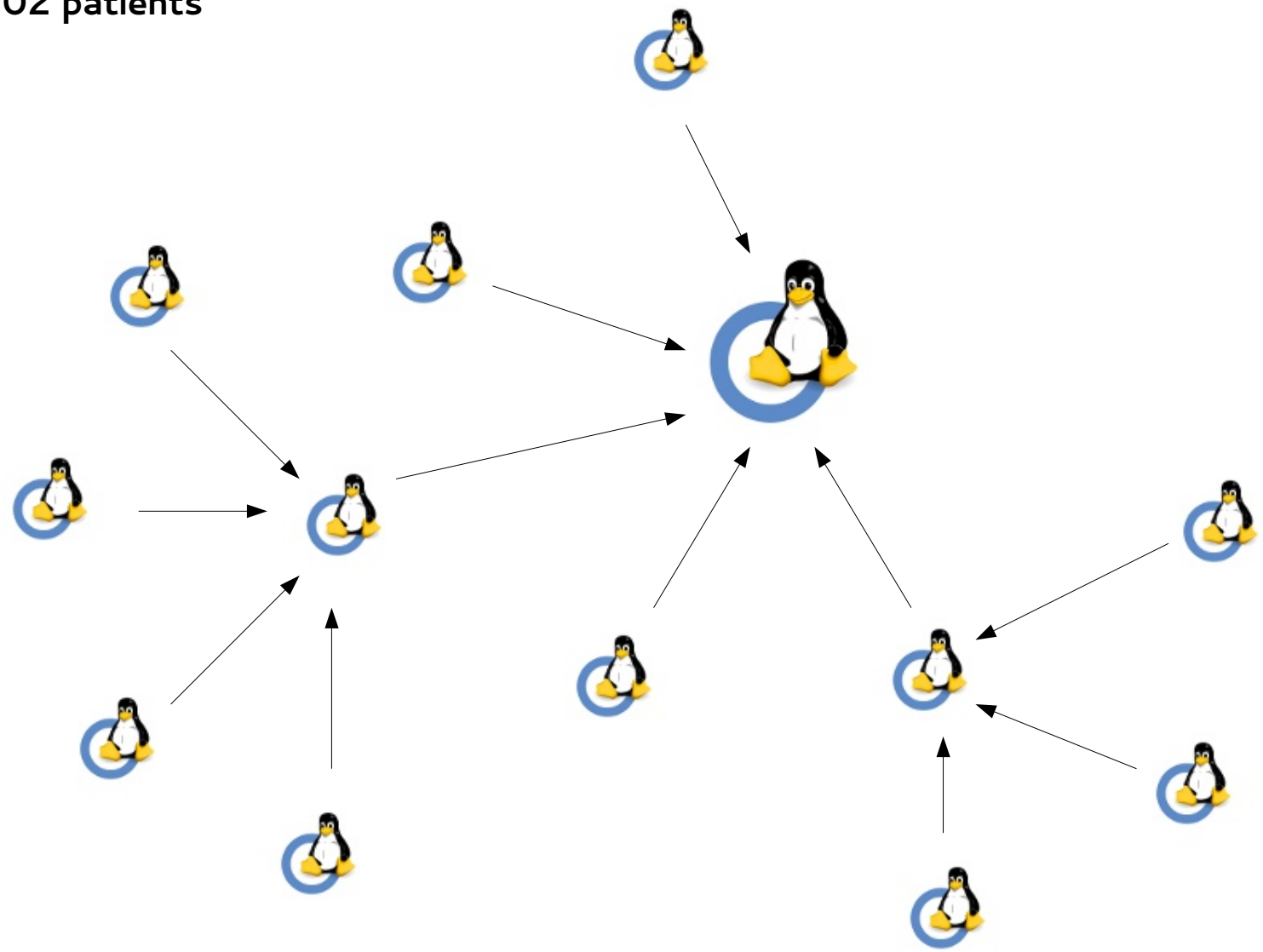
The complete BIRO model
www.biro-project.eu



Report 2010:

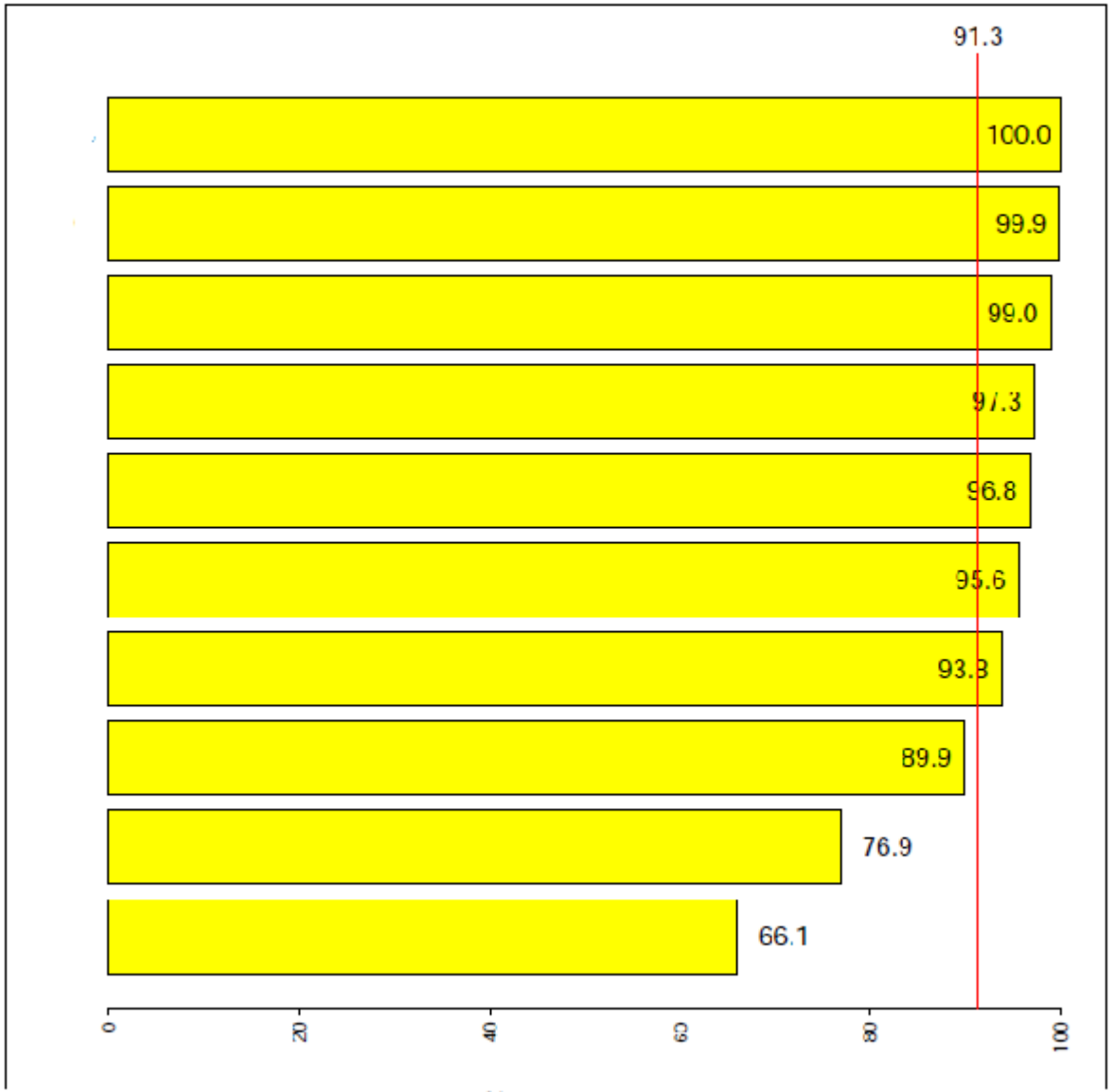
Centres from 19 european countries

N=199,902 patients



5.2.4 % of subjects receiving at least one foot examination within the last 12 months

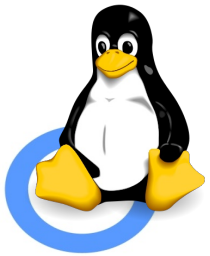
Type of Diabetes = Type 2



Barplots: 5.2.4.239 - Adjusted Rates 5.2.4 % of subjects receiving at least one foot examination within the last 12 months

BIROX Linux

- Solves problem of software distribution and upgrades
- VirtualBox Linux appliance – based on Ubuntu
- Upgrades of software through repository/system update
- Includes:
  - BIROBox – Java desktop Client
  - Preconfigured postgress database, R, LaTeX, Java
  - Documentation
  - Some additional tools



Collaboration

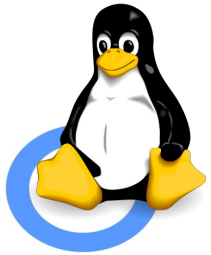
Mediawiki: distribution of EHR data model proposal

www.EndoDiab.si

dotCMS (opensource java CMS):
- distribution of clinical guideliness
- education materials
- events
- patient information site

Alfresco: paper forms repository

Moodle: education



Open source development model

- easier debugging
- feature additions and customization for special needs
- transparency of patient data manipulation
- free as in beer (othervise often very expensive and unaffordable to small departments)

Questions ...