Data Quality and Methodological Transparency in Pharmacovigilance

Ruwen Böhm, Christian Eggeling, Tsvetelin Polomski,
Daniela Heidebrecht, Leocadie von Hehn,
Thomas Herdegen, Hans-Joachim Klein

ruwen.boehm@pharmakologie.uni-kiel.de

Institut für Experimentelle und
Klinische Pharmakologie
UKSH, Campus Kiel

Wissen schafft Gesundheit

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Outline

- Why Pharmacovigilance?
- Cave-ats
- Conclusions

Pharmacovigilance to answer questions from clinics

drug

- Can orlistat cause flue???

adverse event

➔ Böhm R., Herdegen Th. [Risk of infection and liver damage by orlistat. Dtsch Apoth Ztg 2009, 149(32), S. 3623]

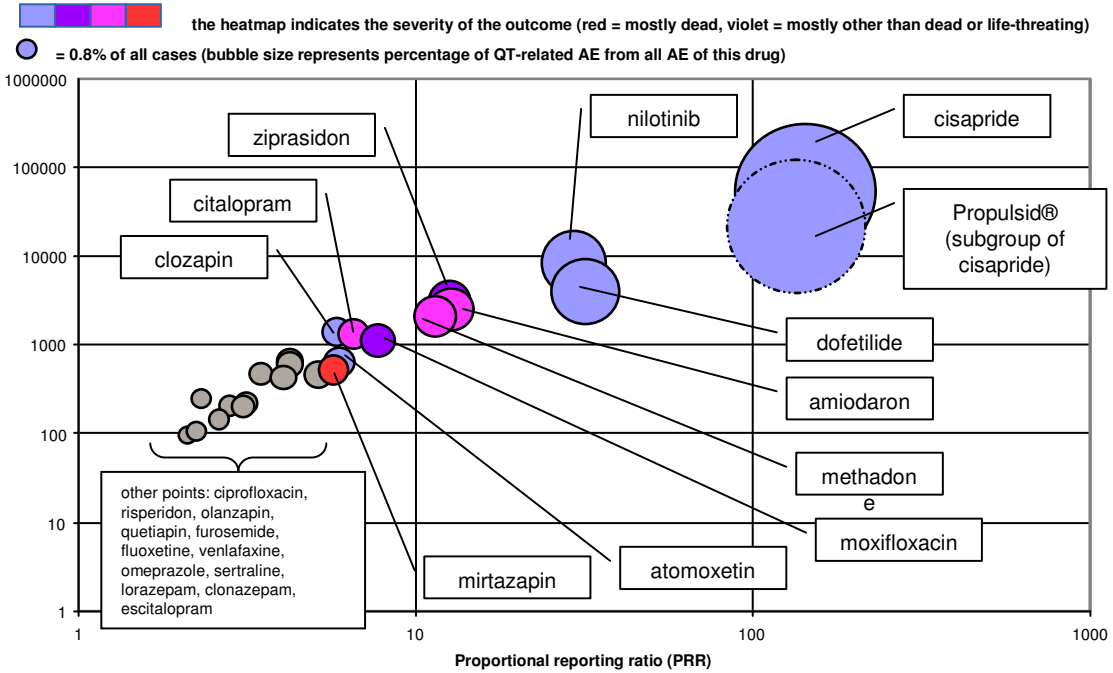
- Is there a particular risk for hypoglycemia for certain sulfunylurea or glinide drugs?

- ➔ Böhm R, Cascorbi I, Herdegen T: [Hypoglycemic risk of insulinotropic drugs]. Med Monatsschr Pharm 2009, 32(12):453-458.

- Is there a particular risk for Torsade de pointes after i.v. application of haloperidol?

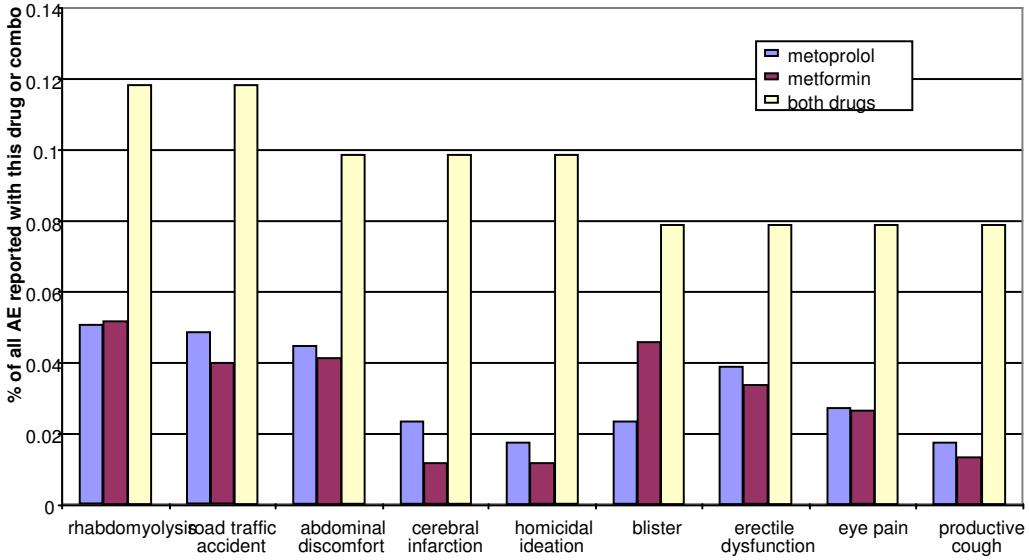
- ➔ Poster #129 “Cardiotoxicity of intravenous haloperidol – an update”

More clinical applications: Poster #229



which drug causes an adverse event?

detection of drug-drug-interactions



Mining a new „big data“ source

(primarily U.S. FDA AERS pharmacovigilance data 1997-2015)

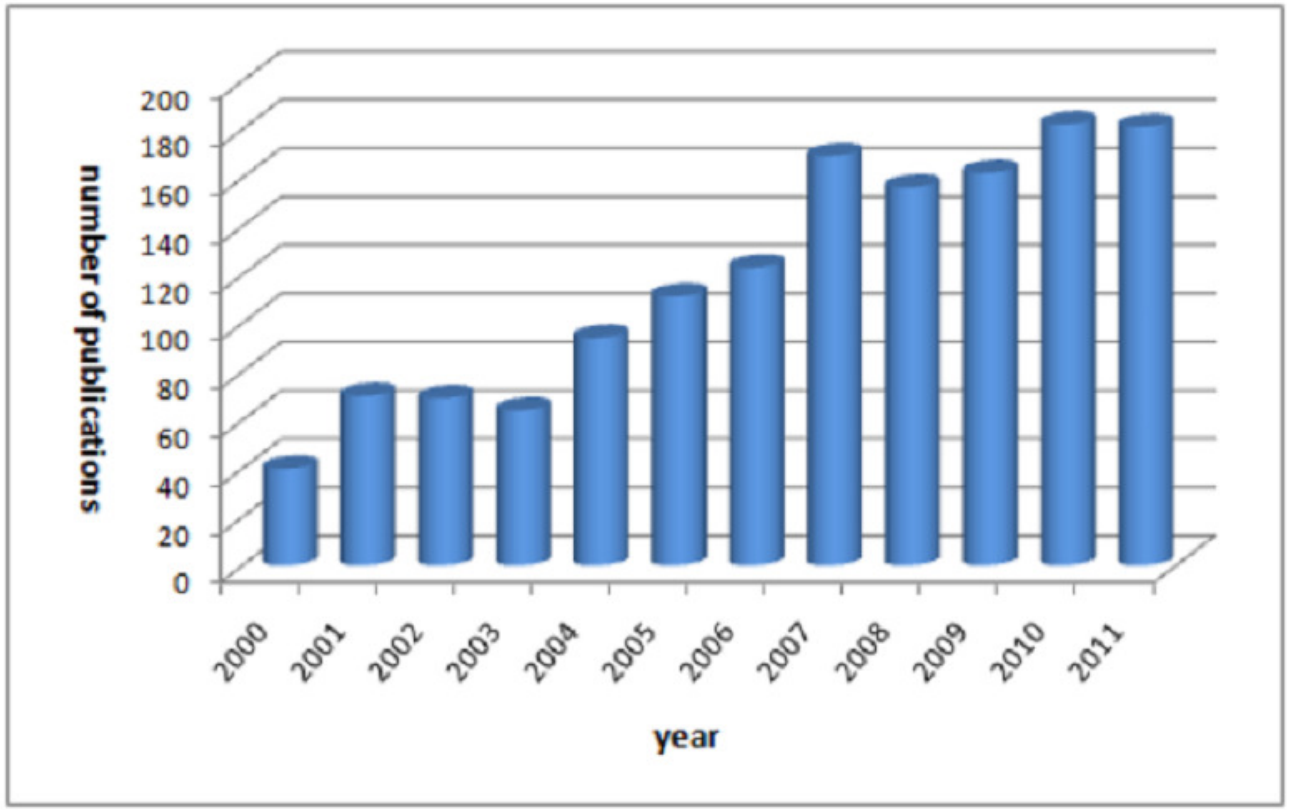


Figure 1.
PhV DMA research evolution described by volume of publications per year indexed in PubMed. 2011 volume is effectively larger due to delayed indexing.

Harpaz 2012

Non-clinical applications of pharmacovigilance

- Hospital administration:
  Purchase decisions for the pharmacy dept.
- Lawyers:
  Arguments for legal proceedings
- Investors, e.g., stock market:
  Bullish Vs. Bearish
- Webmasters:
  Traffic and thus ad revenue generation

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Mistakes in Pharmacovigilance

OpenVigil Cave-at document

Version 2.0.2 (2014-09-15, ruwen.boehm@pharmakologie.uni-kiel.de)

The practical usage of pharmacovigilance data like the FDA FOI AERS data (LAERS, FAERS) is limited by the following methodical problems and shortcomings of the spontaneous reporting system:

shortcoming	explanation	consequences for data analyses	examples
under-reporting	In several jurisdictions health care professionals are not legally bound to file adverse events. Overlooking adverse events or non-reporting because of heavy workload often lead to under-reporting which is estimated to range between 1:10 to 1:100.	Absolute numbers of cases might range 10-100 times higher. Cases for rarely used drugs might be missing.	Phenprocoumon is commonly used in Germany but not in the US. There are some records for this drug in the US FDA data but they probably do not allow any further analysis.
over-reporting	The act of reporting and the choice of a primary and secondary suspected drug causing an event is dependent how important and plausible this issue appears to a physicians or patient. Different overview of literature could skew the number of reports per drug or per adverse event. More extensively used drugs have higher total numbers of records.	Queries should not always rely on the item that specifies which drugs are suspected to cause the reaction (DRUG.ROLE_COD in the AERS database). This is particulary important for signal detection which aims to discover relations hereto unknown.	If a certain problematic adverse reaction is finally reported in the media, spontaneous reporting peaks. E.g., once the propofol infusion syndrome was reported, it was seen everywhere.
drug usages vs reports vs cases	As of today, counting is usually done on individual safety reports. However, several drug usages make up one report. Several reports belong to one patient.	Most researchers are probably interested in counting affected patients. However, as of today, OpenVigil and others perform counting on single reports. If you focus on dosage-dependent adverse reactions, looking on drug usages might be the best option. If you focus on allergic reactions, numbers of patients might be most appropriate.	see the varenicline/darvocet-example below at "multiplicate reports": 13 reports originate from only 3 patients.
missing denominator	The total amount of use for a drug (e.g., defined daily dose (DDD) or total number of applications) is not gathered in traditional pharmacovigilance data. Therefore, any normalizations or relations to the real world (e.g., odds ratio, risks) are difficult.	A rough estimate of drug usage and therefore substitute of DDD might be the total number of reports which include this drug.	The German arznei-telegramm 2001(42):47 shows prescription data of metamizol (USAN dipyrone) and reported agranulocytosis. Keller 2006 tries to estimate the incidence of adverse reactions using drug dispension data from pharmacies.
wrong data	Reporters might accidentally use wrong form fields for items or mix up cases.	Cleaning the data might catch some of these cases.	The antidepressant paroxetine flags a signal for the adverse event depression, i.e., has statistically to be considered to have depression as adverse reaction. However, depression might have been coded as adverse event together with "drug failure" or something similar. Additionally, in some reports, indication and reaction might have been mixed up. Finally, clinical trials show that there might be a subgroup that does not benefit from paroxetine but instead develops further psychiatric symptoms. Since at least these 3 groups are mixed together in the data, no further anaylsis can be done.
missing data	Reporters might not have all necessary data available or they cannot afford the time of entering all available data due to their workload. Some important data (e.g., magnesium level on Torsades de pointes onset) are not gathered in traditional pharmacovigilance data.	These records with missing data can be filtered out or some kind of extrapolation might be applied.	The WHO ranks report according to their quality.
duplicate or multiplicate records	A report might be reported by the sponsor of a trial, the affected participant and his general practitioner. Reports might be sent to a domestic and a foreign database and consequently be reported in duplicate to larger multi-national databases (e.g., VigiBase).	Checks for records with different case numbers but the same age, sex, date of onset of adverse event and other database items can catch these kind of multiplicates.	Harpaz et al. (2010) detected that in the 2008 data, searching for the combination of drug "varenicline", pharmaproduct "davocet" and adverse event "abnormal dreams" show a strong signal. OpenVigil 2.0 finds 13 reports. However, looking at the demographic data and the CASE_ID field, these 13 reports originate from only 3 patients.
no use of dictionaries or strict formatting	Data from some pharmacovigilance databases like FAERS is not completely sanitized and does not follow a single naming scheme for drugs (like WHO-DD or XEVMPD) or a single format for dosages. It does, however, use MedDRA to code the adverse event.	Sanitize your data by using external data sources like drugname databases. This is done automatically in OpenVigil 2; however, approx. 30% of the raw FAERS data is discarded because no drugname could be recognized. Be sure to manually sanitize certain data items if you rely on them for an anlysis!	As of 2014-08-22, OpenVigil 2.0 can not recognize the putative brandname "sudafed 12 hour", thus missing approx. 1766 individual safety records. Our primary drugname-mapping source, the DrugBank, cannot precisely map this to one drugname. As of 2014-08-22, OpenVigil 2.0 can not parse the dosage "75 MG EACH MORNING, 150 MG EACH EVENING", although such a notation is well understandable for human users.
plausibility	Besides formal inconsistency (e.g., the gas xenon cannot be applied by intravenous route), the mechanism needs to be explained (e.g., some licensed lipid lowering drugs (e.g., orlistat) are connected to pharmacologically unexplainable adverse reactions (e.g., influenza).	Health care professionals should browse the list of case reports and manually correct inplausibilities and inconsistencies. This implies that any statistical findings cannot be used in legal proceedings.	A lawyer sought to attest that patients with lack of an enzyme who are on low dosages of a drug containing this enzyme as supplement are experiencing more adverse reactions than those who get the higher dosage. This approach has several errors: no biological plausibility, hypothesis testing instead of generation, reliance solely on statistics to find true adverse reactions.
hypthesis generation only	Pharmacovigilance allows mostly just hypothesis generation but not testing due to the above mentioned shortcomings.	Hypothesis generation is fine; if you aim to test a hypothesis you have to be very careful whether this is possible or whether the available pharmacovigilance data might be misleading (e.g., over-reporting, comparing results to a different population)	
confounders	Pharmaproducts can contain several drugs. Unrelated drugs might pop up as signal because they are always in combination with the drug causing the reaction. The same applies for two separate drugs/ pharmaproducts that are often used for the same indication.	When a case series is identified, a closer look should be cast on the medication lists.	Hydrochlorothiazide is routinely added to various other (potassium-sparing) diuretics and antihypertensives. Thus, hydrochlorothiazide might get associated with adverse reactions to antihypertensives.
human errors	Both human errors during software development as well as during software usage can result in distortion of data.	Your method section must list the exact access date of data sources and the exact version number of any software used to analyse the data. Any scripts used to manipulate or analyse the dataset must be published.	An error in OpenVigil prior to version 1.2.6 led to 145 reports in an analysis of warfarin and haematemesis to be not considered (see tutorial to learn more about the consequences).
counting issues	Pharmacovigilance data sources like AERS consist of reports, linked to an ISR, linked to an CASENO. One case can consist of several ISR submitted at several stages.	Most types of queries should use unique cases (in SQL term: DISTINCT DEMO.CASENO). Additional checking for multiplicates is advised (see above).	DEMO contains 5,337,037 reports, 5,332,211 of which are unique, referring to 4,139,662 individuals. (Without checking for multiplicates.)

All examples are based on FDA LAERS and FAERS from 2003-10-6 to 2013-12-31 (OpenVigil 1) or FDA LAERS data from 2003-10-6 to 2012-06-30 (OpenVigil 2), extracted prior to 2014-09-15. Figures may change during further development of software and data import filter.

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  - Human and software errors
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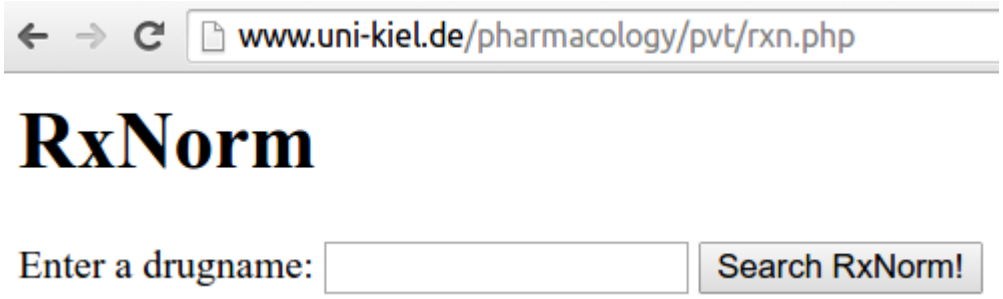
“Drugnames”

COUMADIN (WARFARIN SODIUM)
COUMADIN (WAFRARIN SODIUM)
WARFARIN
WARFARIN POTASSIUM
COUMADIN (WARFARIN SODIUM) (5 MILLIGRAM) (WARFARIN SODIUM)
WARFARIN (WARFARIN /00014801/)

WARFARIN UNKNOWN
BRODIFACOUM (SUPERWARFARIN)
UNSPECIFIED BLOOD THINNING TABLETS
ANTIVITAMIN K ANTICOAGULANT
BLINDED: WARFARIN SODIUM
RIVAROXABAN 20MG OD OR WARFARIN OD (1, 2.5 OR 5MG)

Public drugname mappers

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RIVAROXABAN 20MG OD OR WARFARIN OD (1, 2.5 OR 5MG)
→ rivaroxaban (100% score)

WARFARIN (BLINDED)
→ warfarin (100% score)

COUMADIN (WARFARIN SODIUM)
→ coumadin (100% score)
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Spelling corrections

- Flomax® (tamsulosin) vs
  Volmax® (salbutamol)
- iodine vs
  Lodine® (etodolac)
- amrinone (USAN **in**amrinone) vs
  amiodarone

How does OpenVigil 2 handle drugnames?

- Only dosages and very few other (known) elements are discarded from the drugname
  → keywords like “blind” etc. are retained
- Only exact matches of the remaining elements; all matches must be non-contradictory
  → unknown elements let the mapping fail
- Restrictive spelling correction (validated internal list)

➔ loss of 28% of records of low data quality

- manual drug mapping interface in OpenVigil 2

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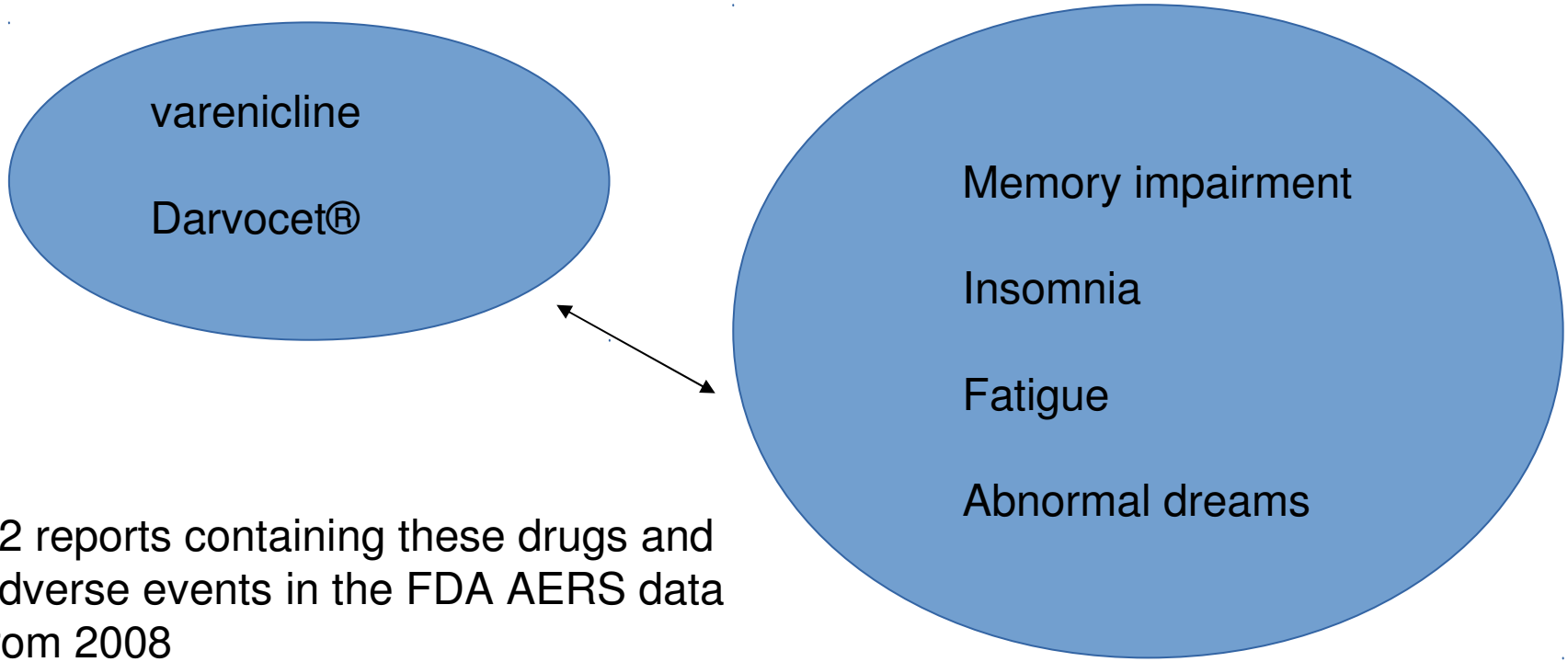
Signal distortion by multiplicates



52 reports containing these drugs and adverse events in the FDA AERS data from 2008
→ very strong signal for a putative ADR

Harpaz 2010, Harpaz 2012

52 Reports → 2 Cases

ISR	CASENO	AGE	GNDR_COD
5720314	6606588		F
5725407	6606588		F
5730698	6606588		F
5733756	6606588		F
5739400	6606588		F
5745564	6606588		F
5748300	6606588		F
5754359	6606588		F
5761683	6606588		F
5775505	6606588		F
5779565	6606588		F
5792486	6606588		F
5798936	6606588		F
5804940	6606588		F
5807898	6606588		F
5817165	6606588		F
5823641	6606588		F
5827849	6606588		F
5831253	6606588		F
5832879	6606588		F
5839127	6606588		F
5846900	6606588		F
5848843	6606588		F
5853362	6606588		F
5856680	6606588		F
5860082	6606588		F

ISR	CASENO	AGE	GNDR_COD
5870223	6606588		F
5872822	6606588		F
5875821	6606588		F
5878262	6606588		F
5887085	6606588		F
5895043	6606588		F
5907868	6606588	51	F
5908455	6779317	31	M
5913038	6779317	31	M
5915428	6779317	32	M
5915614	6606588	51	F
5922981	6606588	51	F
5923020	6779317	31	M
5924321	6606588	51	F
5929880	6606588	51	F
5929979	6779317	31	M
5939203	6606588	51	F
5945356	6606588	51	F
5950910	6779317	31	M
5952525	6606588	51	F
5955691	6606588	51	F
5967498	6606588	51	F
5969314	6606588	51	F
5969706	6779317	31	M
5971373	6779317	31	M
5974110	6606588	51	F

Harpaz 2010

How does OpenVigil 2 handle multiplicates

- Detection of multiplicates on report basis
- Output of FDA case_id for statistical analysis

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Signal distortion by human and software errors

Table 2. Signal scores for warfarin-, aspirin- and clopidogrel-associated haematemesis.

Statins	N	PRR (kai2)	ROR (95% two-sided CI)	IC (95% two-sided CI)
Warfarin	268	1.991 (131.982)	2.006 (1.778, 2.234) *	0.985 (0.811, 1.158) *
Aspirin	332	6.469 (1525.210) *	6.566 (5.889, 7.244) *	2.661 (2.504, 2.818) *
Clopidogrel	235	2.254 (163.238) *	2.270 (1.995, 2.544) *	1.160 (0.975, 1.346) *

N: the number of co-occurrences; PRR: the proportional reporting ratio; ROR: the reporting odds ratio; IC: the information comp

Sakaeda 2013

OpenVigil 2 can find 162 reports (out of 140 unique cases) and calculates – based on the counting of reports – a PRR of 3.109 and a ROR of 3.122.

Re-calculation of Sakaeda 2013 – data source

Data files and filtering	**all reports**
all files and 2003-12-31 >FDA_DT < 2010-01-01	2234986
all reports in these quaterly files	2234929
only these quaterly files and 2003-12-31 > date < 2010-01-01	
FDA_DT	2234923
EVENT_DT	1655915
MFR_DT	2180288
FDA_DT minus data files DEMO04Q1 till DEMO05Q2	1805798
Sakaeda 2013	2231029
raw line count (minus headers)	2234931

cf. OpenVigil tutorials

Re-calculation of Sakaeda 2013 – filtered reports

Source	n
OpenVigil 1 GUI without DEMO data prior to 2005Q3	268, maybe more
OpenVigil 1 SQL without DEMO data prior to 2005Q3	256 reports, maybe more or less (for 212 individuals)
OpenVigil 1 SQL (full LAERS data)	413 (for 316 individuals according to CASENO, some less because of multiplicates)
OpenVigil 2 GUI	162 (for 140 individuals according to CASE)
Sakaeda 2013	268

Regulatory bodies

The U.S. (FDA) and Germany (BfArM) use a commercial software package:

„.. Source code for gps/mgps has never been made available..”

“…Oracle is not aware of any other implementation of MGPS that has been verified by running the same database through the two different programs….”

(William DuMouchel, PhD. Chief Statistical Scientist, Oracle Health Sciences, pers. comm. 2014)

Good Clinical Practice...

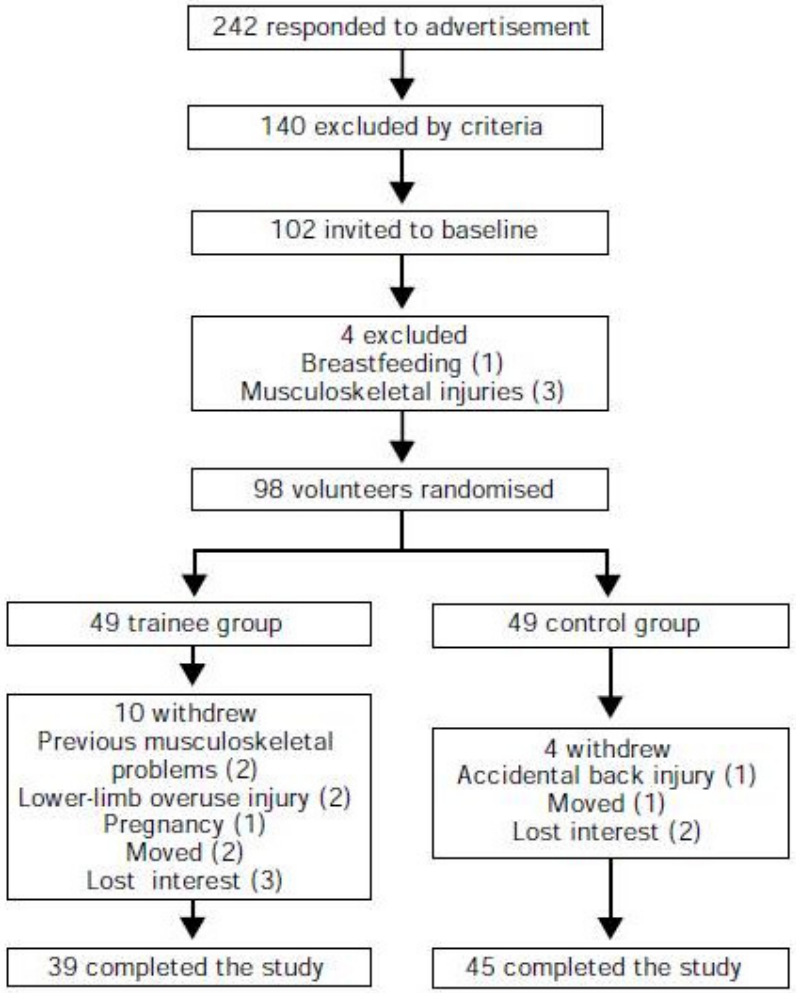

Figure 1: **Trial profile**

LaMorte 2015, Boston University School of Public Health

... good pharmacovigilance practice!

Overview of this OpenVigil installation

OpenVigil version: OpenVigil v1.2.7-nightly-20150206
PHP version: 5.2.17
PHP MySQL extension version: 1.0
MySQL version: 5.5.10-log

Installed data files:

DEMO04Q1 DEMO04Q2 DEMO04Q3 DEMO04Q4 DEMO05Q1 DEMO05Q2 DEMO05Q3 DEMO05Q4 DEMO06Q1 DEMO06Q2 DEMO06Q3 DEMO06Q4 DEMO07Q1 DEMO07Q2 DEMO07Q3 DEMO07Q4 DEMO08Q1 DEMO08Q2 DEMO08Q3 DEMO08Q4 DEMO09Q1 DEMO09Q2 DEMO09Q3 DEMO09Q4 DEMO10Q1 DEMO10Q2 DEMO10Q3 DEMO10Q4 DEMO11Q1 DEMO11Q2 DEMO11Q3 DEMO11Q4 DEMO12Q1 DEMO12Q2 DEMO12Q3 DEMO12Q4 DEMO13Q1 DEMO13Q2 DEMO13Q3 DEMO13Q4 DRUG04Q1 DRUG04Q2 DRUG04Q3 DRUG04Q4 DRUG05Q1 DRUG05Q2 DRUG05Q3 DRUG05Q4 DRUG06Q1 DRUG06Q2 DRUG06Q3 DRUG06Q4 DRUG07Q1 DRUG07Q2 DRUG07Q3 DRUG07Q4 DRUG08Q1 DRUG08Q2 DRUG08Q3 DRUG08Q4 DRUG09Q1 DRUG09Q2 DRUG09Q3 DRUG09Q4 DRUG10Q1 DRUG10Q2 DRUG10Q3 DRUG10Q4 DRUG11Q1 DRUG11Q2 DRUG11Q3 DRUG11Q4 DRUG12Q1 DRUG12Q2 DRUG12Q3 DRUG12Q4 DRUG13Q1 DRUG13Q2 DRUG13Q3 DRUG13Q4 INDI04Q1 INDI04Q2 INDI04Q3 INDI04Q4 INDI05Q1 INDI05Q2 INDI05Q3 INDI05Q4 INDI06Q1 INDI06Q2 INDI06Q3 INDI06Q4 INDI07Q1 INDI07Q2 INDI07Q3 INDI07Q4 INDI08Q1 INDI08Q2 INDI08Q3 INDI08Q4 INDI09Q1 INDI09Q2 INDI09Q3 INDI09Q4 INDI10Q1 INDI10Q2 INDI10Q3 INDI10Q4 INDI11Q1 INDI11Q2 INDI11Q3 INDI11Q4 INDI12Q1 INDI12Q2 INDI12Q3 INDI12Q4 INDI13Q1 INDI13Q2 INDI13Q3 INDI13Q4 OUTC04Q1 OUTC04Q2 OUTC04Q3 OUTC04Q4 OUTC05Q1 OUTC05Q2 OUTC05Q3 OUTC05Q4 OUTC06Q1 OUTC06Q2 OUTC06Q3 OUTC06Q4 OUTC07Q1 OUTC07Q2 OUTC07Q3 OUTC07Q4 OUTC08Q1 OUTC08Q2 OUTC08Q3 OUTC08Q4 OUTC09Q1 OUTC09Q2 OUTC09Q3 OUTC09Q4 OUTC10Q1 OUTC10Q2 OUTC10Q3 OUTC10Q4 OUTC11Q1 OUTC11Q2 OUTC11Q3 OUTC11Q4 OUTC12Q1 OUTC12Q2 OUTC12Q3 OUTC12Q4 OUTC13Q1 OUTC13Q2 OUTC13Q3 OUTC13Q4 REAC04Q1 REAC04Q2 REAC04Q3 REAC04Q4 REAC05Q1 REAC05Q2 REAC05Q3 REAC05Q4 REAC06Q1 REAC06Q2 REAC06Q3 REAC06Q4 REAC07Q1 REAC07Q2 REAC07Q3 REAC07Q4 REAC08Q1 REAC08Q2 REAC08Q3 REAC08Q4 REAC09Q1 REAC09Q2 REAC09Q3 REAC09Q4 REAC10Q1 REAC10Q2 REAC10Q3 REAC10Q4 REAC11Q1 REAC11Q2 REAC11Q3 REAC11Q4 REAC12Q1 REAC12Q2 REAC12Q3 REAC12Q4 REAC13Q1 REAC13Q2 REAC13Q3 REAC13Q4 RPSR04Q1 RPSR04Q2 RPSR04Q3 RPSR04Q4 RPSR05Q1 RPSR05Q2 RPSR05Q3 RPSR05Q4 RPSR06Q1 RPSR06Q2 RPSR06Q3 RPSR06Q4 RPSR07Q1 RPSR07Q2 RPSR07Q3 RPSR07Q4 RPSR08Q1 RPSR08Q2 RPSR08Q3 RPSR08Q4 RPSR09Q1 RPSR09Q2 RPSR09Q3 RPSR09Q4 RPSR10Q1 RPSR10Q2 RPSR10Q3 RPSR10Q4 RPSR11Q1 RPSR11Q2 RPSR11Q3 RPSR11Q4 RPSR11Q4 RPSR12Q1 RPSR12Q2 RPSR12Q3 RPSR12Q4 RPSR13Q1 RPSR13Q2 RPSR13Q3 RPSR13Q4 THER04Q1 THER04Q2 THER04Q3 THER04Q4 THER05Q1 THER05Q2 THER05Q3 THER05Q4 THER06Q1 THER06Q2 THER06Q3 THER06Q4 THER07Q1 THER07Q2 THER07Q3 THER07Q4 THER08Q1 THER08Q2 THER08Q3 THER08Q4 THER09Q1 THER09Q2 THER09Q3 THER09Q4 THER10Q1 THER10Q2 THER10Q3 THER10Q4 THER11Q1 THER11Q2 THER11Q3 THER11Q4 THER12Q1 THER12Q2 THER12Q3 THER12Q4 THER13Q1 THER13Q2 THER13Q3 THER13Q4

Number of raw lines that could not be parsed and records that could not be imported: unparsed lines: 283 / non-imported records: 0
Last import of data files was done on 2014-09-12 13:41:56
These files contain records for the period from 2003-10-06 to 2013-12-31 (according to DEMO.FDA_DT).

Summary of all registered tables (FDA data and additional calculated/contributed data) and number of records:

table	fields	#records	#unique records
DEMO	ISR CASENO I_F_COD FOLL_SEQ IMAGE EVENT_DT MFR_DT FDA_DT REPT_COD MFR_NUM MFR_SNDR AGE AGE_COD GNDR_COD E_SUB WT WT_COD REPT_DT OCCP_COD DEATH_DT TO_MFR CONFIG REPORTER_COUNTRY DSRC	5337037 CASEs: 5337037	5332211 unique CASEs: 4139662
DMAP	ISR DRUG BRAND EXTRA DOSE ROUTE	0	0
DRUG	ISR DRUG_SEQ ROLE_COD DRUGNAME VAL_VBM ROUTE DOSE_VBM DECHAL RECHAL LOT_NUM EXP_DT NDA_NUM DSRC	19388354	5332173
DSRC	FNAME DT NERR_PARSER NERR_SQL TERR_PARSER TERR_SQL		
INDI	ISR DRUG_SEQ INDI_PT DSRC	9441806	4368232
OUTC	ISR OUTC_CODE DSRC	4810836	3821421
REAC	ISR PT DSRC	19239224	5332151
RPSR	ISR RPSR_COD DSRC	1992810	1076669
THER	ISR DRUG_SEQ START_DT END_DT DUR DUR_COD DSRC	7835655	3550800

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Conclusions

- Publications should include comprehensive **material and methods** section which allows reproduction of the result section
- Where appropiate, datasets or algorithms should be included in the **supplementary material**
- This way, the scientific community can comment on the results (**no „black box“!**)
  and help to improve the analysis method