PROTECT's Impact on Pharmacovigilance Practice: An Industry Perspective

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Pfizer
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Disclosures

- I am an employee and shareholder of Pfizer, Inc.
- I am an Adjunct Associate Professor of Epidemiology at the Tulane School of Public Health and Tropical Medicine
- I was co-chair of PROTECT Work Package 2 and a member of the PROTECT Scientific Steering Committee
- This presentation reflects my views and not necessarily those of my employer or those of other PROTECT participants

With Thanks To

- Olaf Klungel, Utrecht U
- Mark de Groot, Utrecht U
- Raymond Schlienger, Novartis
- Andrew Bate, Pfizer
- Rolf Groenwold, Utrecht U
- Nicolle Gatto, Pfizer
- Niklas Noren, UMC

Outline

- Briefly, how epidemiology is applied for drug development and pharmacovigilance

- The potential impact on industry practice of PROTECT outputs from Work Packages 2, 3 & 5
  - Pharmacoepidemiology research networks
  - Methods for the control of confounding
  - Signal detection of Spontaneous Reports databases
  - Use of EHRs for hypothesis-free signal detection
  - Benefit-risk assessment, in particular quantitative approaches

- Conclusions

How Epidemiologists Contribute to Drug Development and Safety Assessment

Characterize Patient Risk Profile

Evaluate Medication Risk

Standing Cohorts

- EMRs
- Claims
- Registries

Rapid Queries
Estimate expected risks in indicated populations

Approval

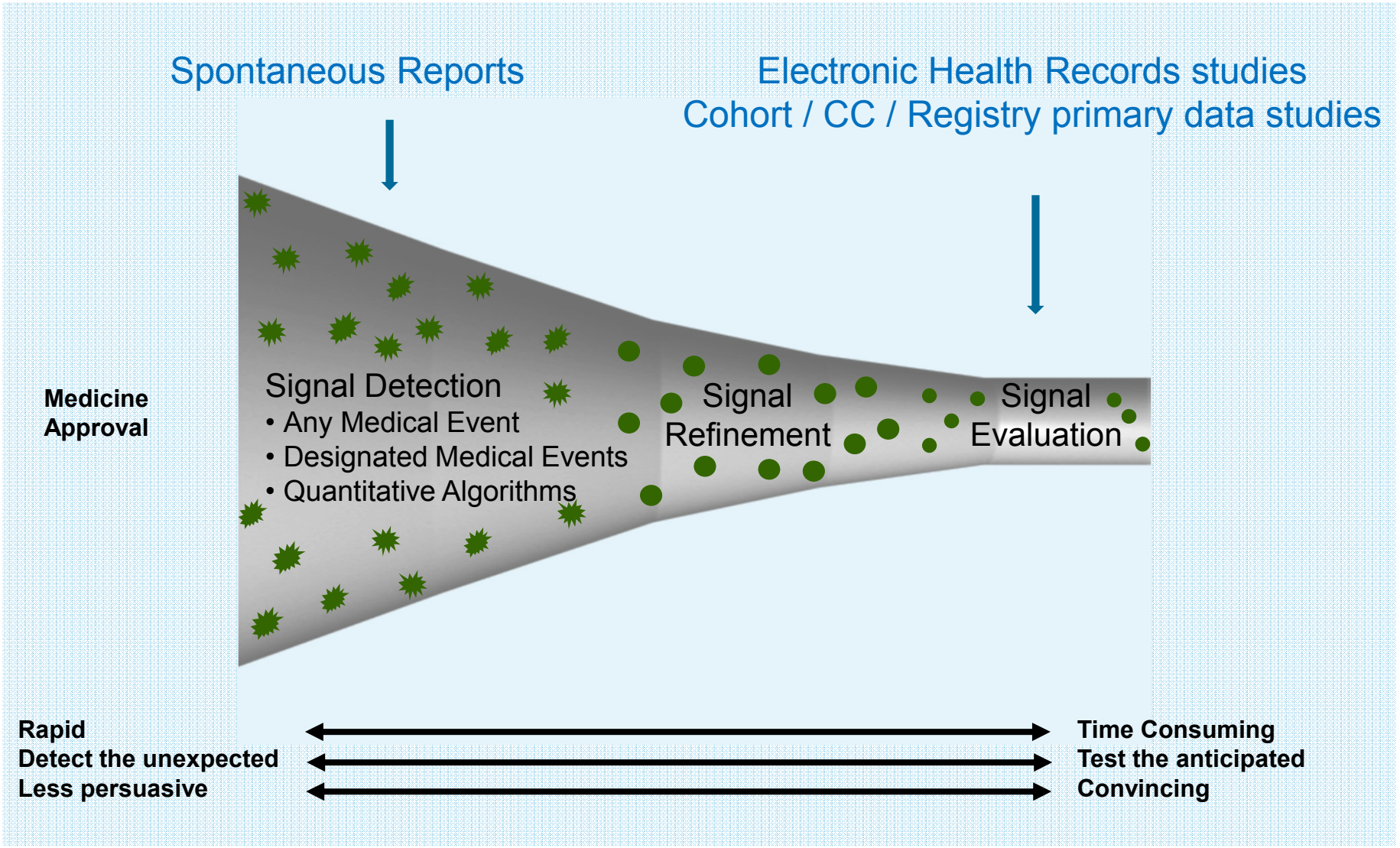
Active Surveillance
Monitor and detect signals in defined patient cohorts using novel analytic tools

Post Approval Safety Studies
Compare medication risks in the real world, as prescribed and taken during routine clinical practice

Risk Minimization
Evaluate the effectiveness of risk minimization measures (e.g., label/education)

Benefit Risk Assessment
Develop frameworks for integrating B-R data and assessing patient preference

Primary Sources for "Real World," Post-Approval Signal Detection



Work Package 2
Pharmacoepidemiology (co-leads: O Klungel, R Reynolds)

	WG1 Databases	WG2 Confounding	WG3 Drug Utilization
Number of participants	n=51 37 public, 14 private	n=10 8 public, 2 private	n=10 7 public, 3 private
Public partners	EMA, LMU-Muenchen, Witten University[4], AEMPS, CEIFE, CPRD, DKMA and UU	UU	FIFC, LMU and Witten University[4]
Private partners	Amgen, AZ, Genzyme, GSK, La-Ser, Merck, Novartis, Roche and Pfizer	Amgen, Novartis and Pfizer	Amgen, Novartis and Roche
WG coordinators	Raymond Schlienger [1] (Novartis) Mark de Groot[2] (UU)	Nicolle Gatto (Pfizer) Rolf Groenwold (UU)	Joan Fortuny [3,5] (Novartis) Luisa Ibanez (FIFC)
WP2 co-leaders	Olaf Klungel (UU) - Robert Reynolds (Pfizer)		
WP2 co-leaders alternates	Tjeerd van Staa (LSHTM) - Jamie Robinson (Roche)		
WP2 project manager	Ines Teixidor (UU)		

[1] from October 2010 replacing John Weil (GSK), [2] from 1 February 2011 replacing Frank de Vries (UU), [3] from 15 March 2012 replacing Hans Petri (Roche),
[4] New partner, accession approved by SC in January 2013 [5] Departed Novartis in 2014

Consistency in Results Across EHR Databases
Methodological Determinants of Drug-AE Associations

- **Study design**
  - Case-only estimates > Cohort/NCC/CC estimates
- **Databases**
  - Some variation in size of estimate, direction consistent for AB/ALI, AD-BZD/HIP, LABA/AMI
  - Large variation in size & direction of estimate for databases (AED/SUI)
- **Study population**
  - Impact of AED users versus epilepsy, population based versus nested (AB, CCB)
  - No impact of indication (asthma, copd)
- **Outcome definition**
  - Small impact on AB/ALI associations
  - Large impact on AED/SUI associations

See forthcoming *PDS* Supplement
www.imi-protect.eu

Consistency in Results Across EHR Databases
Enabling EHR Database Networks: Lessons Learned

- Establish and test governance for communication and collaboration
- Develop a common protocol with great detail to reduce methodological differences and “interpretation” by researchers
- Conduct analysis in parallel in multiple DBs versus “a priori” pooling of DBs
  - Cherish heterogeneity and explore its sources
- To test robustness of findings conduct multiple sensitivity analyses:
  - Multiple designs ?
  - Exposure (e.g., Individual AEDs), outcome (e.g., SUI), confounding adjustment
- Is replication needed if parallel analysis is consistent?

Methods for Control of Confounding
Research Questions and Conclusions

Multiple Potential Confounders	Study of adverse event with multiple potential confounders	• Selection of confounding variables should not be based on observed associations with exposure, but rather be pre-specified
Rare Outcome, Many Confounders	Study of a relatively rare adverse event with a large battery of unmeasured potential confounders	• Use propensity scores • Use balance measure to assess quality of PS model
Time Dependent Confounding	Study of time-varying treatment with a time-dependent confounder meeting criteria for an intermediate variable	• Compare MSMs to PS • MSMs perform better than typical PS adjustment
Unmeasured Confounding	Study with a strong possibility of unmeasured confounding	• Test IV analysis, SCCS • Sensitive to violation of assumptions

Methods for Control of Confounding
Lessons Learned

- Impact of adjustment differed across databases
  - Most covariates, including lifestyle factors, had litte impact after adjusting for age and sex
- Different methods for observed confounding (PS, conventional regression adjustment) yield similar effect estimates in empirical studies
- MSMs confirmed to be best practice for time-varying confounding
- Methods for unmeasured confounding are very sensitive to violations of assumptions and not yet ready for broad implementation
- Importance of sensitivity analyses (quantitative assessment)

Groenwold et al. *Eur J Epidemiol* 2011; Belitser et al. *PDS* 2011; Ali et al. *JCE* 2015; Ali et al. *PDS* 2014; Groenwold et al. *PDS* 2011; Ali et al. *Eur J Epidemiol* 2013; Ali et al. *Epidemiology* 2014; Uddin et al. *PDS* 2014; www.imi-protect.eu

Work package 3
Signal Detection (co-leads: N Noren, M Kayser)

WP3 Participants

74 persons from 19 partner organisations

Surname	*First name*	*Affiliation Short Name*	*Role(s) Sub-package participation*
Ahlers	Christiane	Bayer	3.9
Ansell	David	Cegedim (Epic)	3.10
Arani	Ramin	AZ	3.1 / 3.8
Asiimwe	Alex	Lilly (formerly of AZ)	3.10
Bate	Andrew	Pfizer	3.4 / 3.10
Bech Fink	Dorthe	DHMA	3.3 / 3.11 / 3.12
Bergvall	Tomas	UMC	3.3 / 3.4 / 3.10 / 3.11
Bhayat	Fatima	Takeda (formerly of AZ)	3.10
Bousquet	Cedric	INSERM	3.6 leader; 3.1 / 3.3 / 3.4
Brobert	Gunnar	Bayer	3.10
Brueckner	Andreas	Novartis (formerly of Bayer)	3.9 leader; 3.4
Candore	Gianmario	EMA	3.1 / 3.4 / 3.8
Cappelli	Benedicte	EMA	3.3
Caster	Ola	UMC	3.6/ 3.10
Cederholm	Susanna	UMC	3.10
Declerck	Gunnar	INSERM	3.6
Duke	Susan	GSK	3.9
Dupuch	Marie	INSERM	3.6
Edwards	Ralph	UMC	3.10
Ellenius	Johan	UMC	3.06
Grabar	Natalia	INSERM	3.6
Guy Bauchau	Vincent	GSK	3.7 / 3.8
Hauben	Manfred	Pfizer	3.7
Heer-Klopottek	Elke	Bayer	Administrative coordinator
Hill	Richard	UMC	3.5 leader
Hopstadius	Johan	UMC	3.1 / 3.5
Jaulent	Marie-Christine	INSERM	3.5 / 3.6
Juhlin	Kristina	UMC	3.1 / 3.4 / 3.8 / 3.10 / 3.11
Karimi	Ghazaleh	UMC	Support / coordination; 3.10
Kayser	Michael	Bayer	WP3 co-leader; 3.4 / 3.9
Laursen	Mona Vestergaard	DHMA	3.4
Lazaro	Edurne	AEMPS	3.4 / 3.5 / 3.12
Lerch	Magnus	Bayer	3.1 / 3.5 / 3.6
Lindroos	Hanna	UMC	3.12
Macia	Miguel	AEMPS	3.2 leader; 3.4 / 3.5 / 3.12
Maignen	Francois	EMA	3.7 leader; 3.4
Mallick	Anngret	Bayer	3.2 / 3.9
Manlik	Katrin	Bayer	3.1 / 3.4
Montero	Dolores	AEMPS	3.4

Surname	*First name*	*Affiliation Short Name*	*Role(s) Sub-package participation*
Norén	Niklas	UMC	WP3 co-leader; 3.5 / 3.10 leader 3.1 / 3.3 / 3.4 / 3.6 / 3.8 / 3.11 / 3.12
Opitz	Nils	Bayer	3.3 /3.6 /3.9
Östlund	Klas	UMC	3.12
Painter	Jeffrey	GSK	3.1 / 3.8
Pariente	Antoine	INSERM	3.7
Pinkston	Vlasta	GSK	3.1 / 3.4
Pospisil	Jutta	Bayer	3.2
Prelle	Annette	Bayer	Support / coordination
Quarcoo	Naashika	GSK	3.1 / 3.4 / 3.8
Roberts	Gilly	GSK	3.2
Rottenkolber	Marietta	LMU-Muenchen	3.1 / 3.4 / 3.7
Sahlin	Anette	UMC	Support / coordination
Sandberg	Lovisa	UMC	3.10
Savage	Ruth	UMC	3.10
Seabroke	Suzie	MHRA	3.8 leader; 3.1, 3.4
Slattery	Jim	EMA	WP3 alternate co-leader; 3.1 / 3.3 leader 3.2 / 3.4 / 3.8 / 3.9
Soeria-Atmadja	Daniel	UMC	3.8 / 3.11
Soriano Gabarro	Maria Montserrat	Bayer	3.10
Southworth	Harry	AZ	3.4 / 3.9
Souvignet	Julien	INSERM	3.6
Star	Kristina	UMC	3.10
Strandell	Johanna	UMC	3.3 / 3.11
Sund	Torbjörn	UMC	3.12
Thakrar	Bharat	Roche	WP3 alternate co-leader ; 3.11 leader 3.4 / 3.2
Thompson	Mary	Cegedim	3.10
Tran	Bruno	TGRD /Europe	3.9
Tregunno	Phil	MHRA	3.12 leader; 3.4 / 3.5
Trombert	Béatrice	INSERM	3.06
van Holle	Lionel	GSK	3.4 / 3.7 / 3.8
Vangerow	Harald	Lilly	3.10
Vardar	Taner	ME	3.3 / 3.6 / 3.7 / 3.9
Watson	Sarah	UMC	3.10
Willemsen	Arnold	Genzyme	
Wisniewski	Antoni	AZ	3.4 leader; 3.1 / 3.2 / 3.8
Wong	Jenny	MHRA	3.1

Signal Detection in Pharmacovigilance
SRS Data Mining

- Candore *et al*. compared the performance of a number of commonly used data mining algorithms
- Spontaneous report databases from national and international pharmacovigilance organisations and pharmaceutical companies
- (One of the) Results
  - Over the life-time of a product there is a reduction in precision of any quantitative signal detection algorithm
- Potential Impact
  - Commonly similar thresholds/cut offs are used to trigger clinical review
  - For companies with large portfolios this may lead to change in data mining practice for the parts of product portfolio which have been marketed for many years, e.g. generic portfolios

Candore, G., Juhlin, K., Manlik, K., Thakrar, B., Quarcoo, N., Seabroke, S., ... & Slattery, J. Comparison of statistical signal detection methods within and across spontaneous reporting databases. *Drug Safety*, 1-11, 2015.

Signal Detection in Pharmacovigilance
Duplicate Detection

- Effective analysis of SRS requires reliable data and one challenge is report duplication
- Report duplication is known to occur for a diverse range of reasons
- Many organizations rely on rule-based detection but probabilistic record matching (PRM) is an alternative
- PRM demonstrated a high PPV when compared to rule based
- Potential Impact
  - Might enhance ability to accurately and quickly identify likely duplications, and in doing so improve signal detection procedures

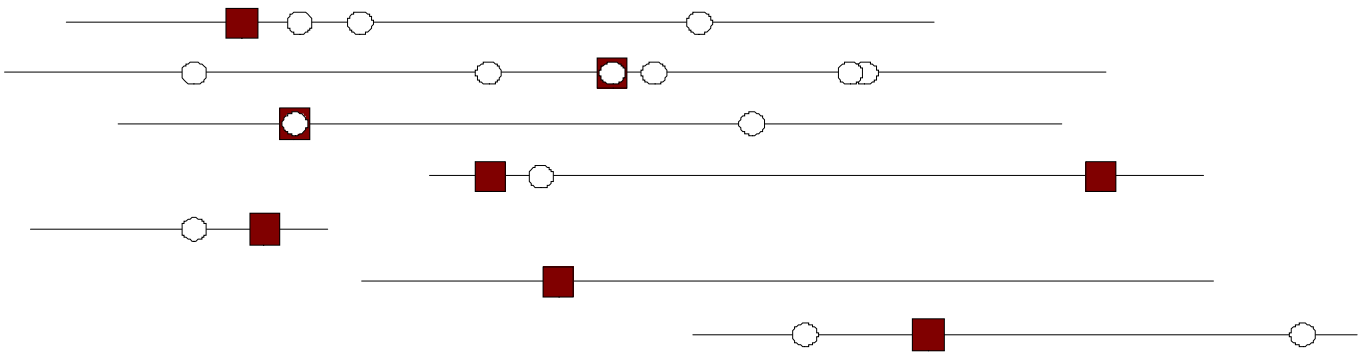
Tregunno PM, Fink DB, Fernandez-Fernandez C, Lazaro-Bengoa E, Noren GN. Performance of probabilistic method to detect duplicate individual case safety reports. Drug Safety 2014/;37(4):249-58.

Signal detection in Pharmacovigilance

Slide from Niklas Noren (UMC)

Signal Detection in Pharmacovigilance
EHR Data for Hypothesis-free Signal Detection

Can longitudinal observational data offer an alternative?



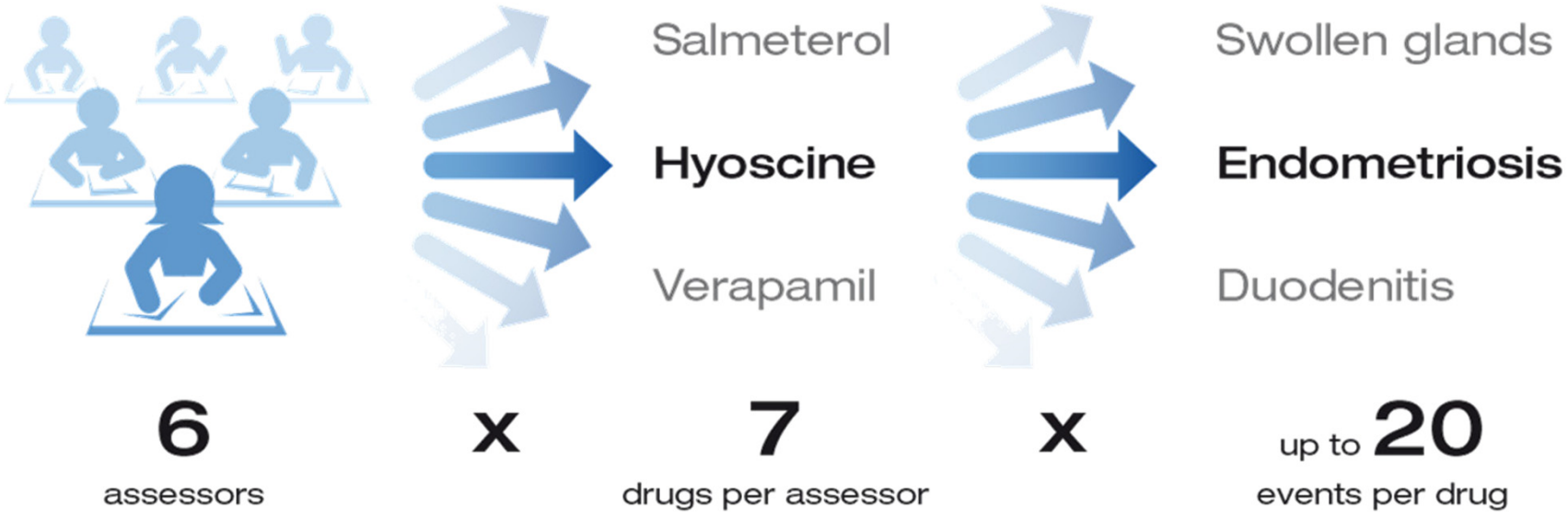
What would real-world signal detection in electronic medical records look like and what value can it bring?

Slide from Niklas Noren (UMC)

EMRs and Insurance Claims Data as Compared to Spontaneous Reports for Surveillance

- Rich longitudinal data
  - Time stamped diagnoses (without any requirement of clinical suspicion)
  - Recorded exposure; and reliable non-exposure
  - Detailed information on disease history prior to drug exposure
  - Other data: test results, hospital referrals and admissions, surgical procedures, notes, symptoms, signs and administrative data
  - Much data in structured fields but different databases may use different terminologies
  - Often linked/can be linked to other healthcare data
  - But challenging for screening that no clinical suspicion link between prescription and outcome

Signal Detection in Pharmacovigilance
Hypothesis-free Signal Detection Pilot in UK THIN (1)

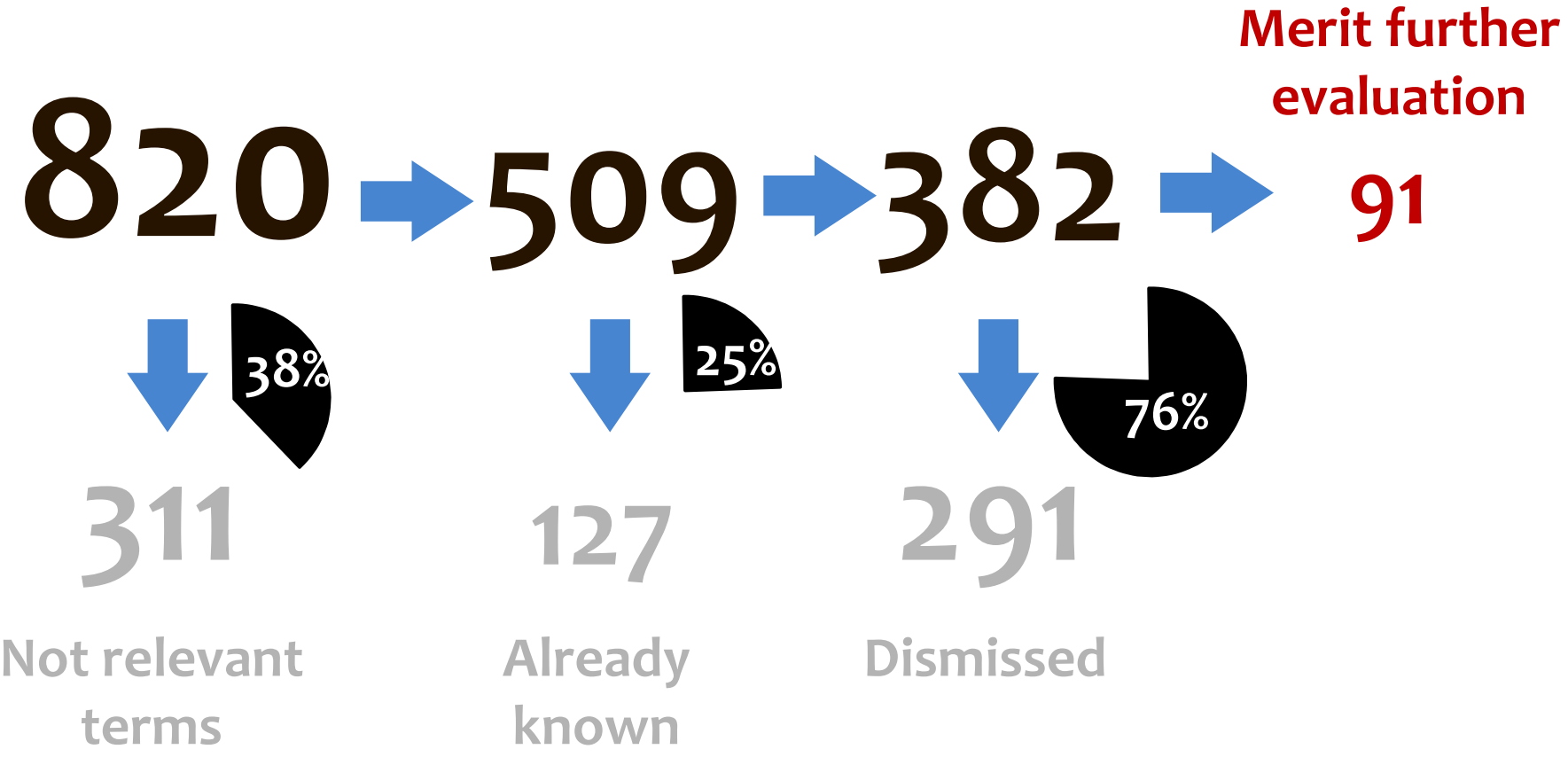


Slide from Niklas Noren (UMC)

Cederholm et al. Structured Assessment for Prospective Identification of Safety Signals in Electronic Medical Records. *Drug Safety* 2015 38:87-100

Signal Detection in Pharmacovigilance
Hypothesis-free Signal Detection Pilot in UK THIN (2)

Preliminary results



Slide from Niklas Noren (UMC)

Cederholm et al. Structured Assessment for Prospective Identification of Safety Signals in Electronic Medical Records. *Drug Safety* 2015 38:87-100

Signal Detection in Pharmacovigilance
Hypothesis-free signal detection pilot in UK THIN (3)

"Safety signal detection in longitudinal observational data should include **clinical, pharmacological, and epidemiological review** of identified temporal associations"

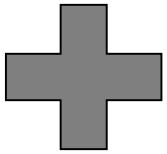
"Longitudinal observational data should be further explored as a **complement** to individual case reports for safety signal detection, but are **not in a position to replace** individual case reports for this purpose"

Slide from Niklas Noren (UMC)

Cederholm et al. Structured Assessment for Prospective Identification of Safety Signals in Electronic Medical Records. *Drug Safety* 2015 38:87-100

Signal Detection in Pharmacovigilance
Hypothesis-free Signal Detection Pilot in UK THIN (4)

Longitudinal observational data



Denominators

Longitudinal

'Objective'

No clinical suspicion

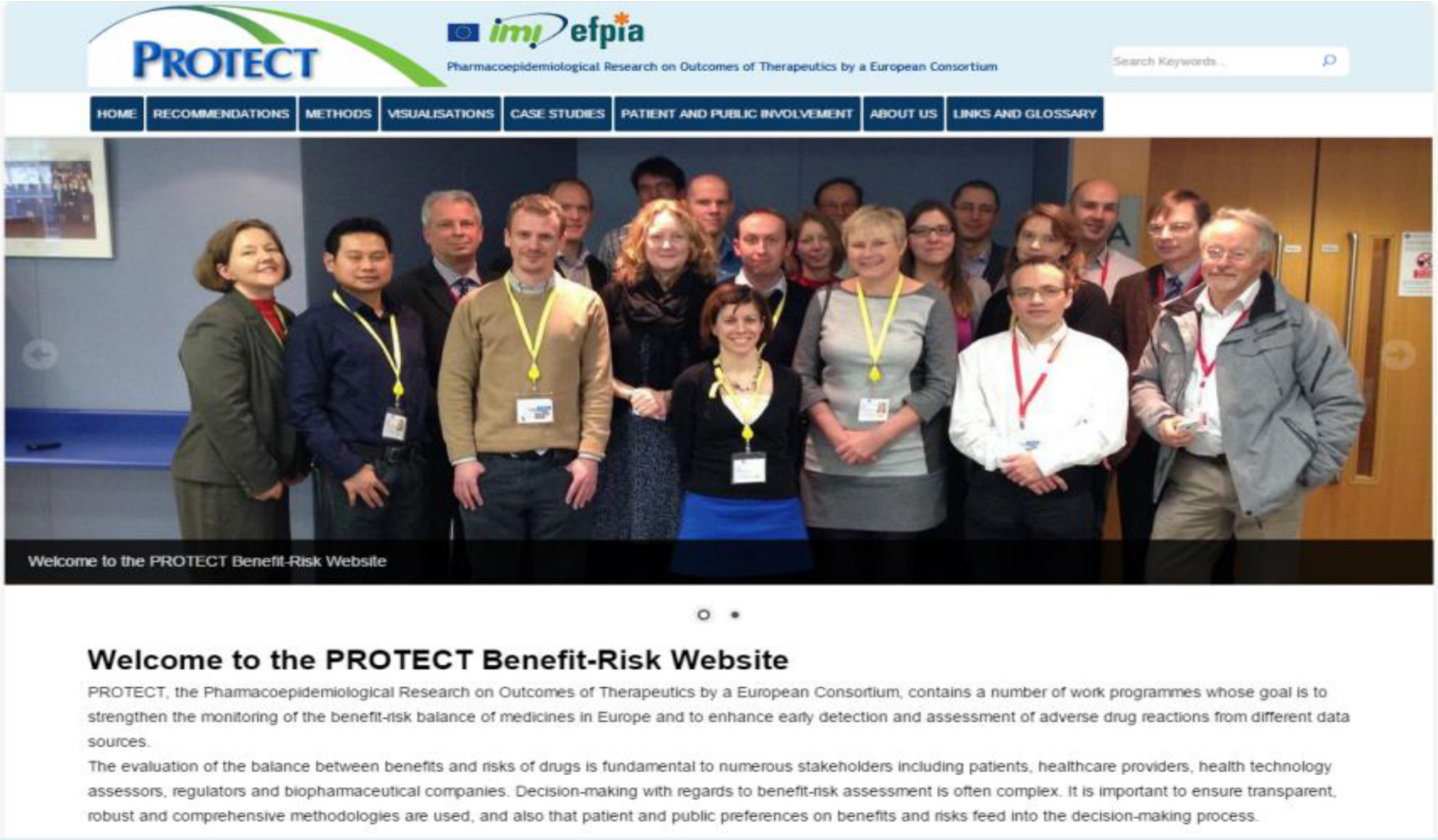
Data not collected for causality assessment

Restricted scope

Slide from Niklas Noren (UMC)

Cederholm et al. Structured Assessment for Prospective Identification of Safety Signals in Electronic Medical Records. *Drug Safety* 2015 38:87-100

Work Package 5
Benefit-Risk Analysis (co-leads: D Ashby, A Micaleff)

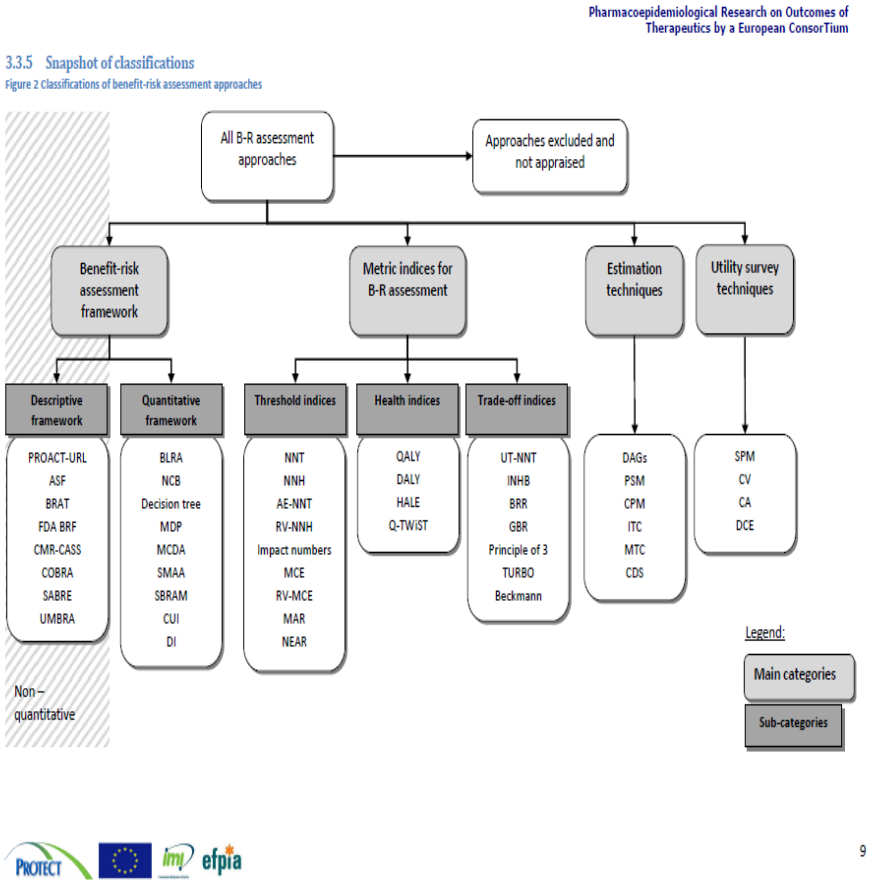


http://PROTECTBenefitRisk.eu/

Approaches to Benefit-Risk Analysis of Medicines

Qualitative versus Quantitative Methods

- Qualitative approaches are subjective and descriptive
- Quantitative frameworks synthesize multiple benefits and risks criteria into summary measures
- Allows evaluation of the same data from perspectives of different stakeholders
- Quantitative models/frameworks: BLRA, NCB, MDP, MCDA, SMAA, SBRAM, CUI, DI, Decision tree



PDS 2014; 23:667-678

See also www.imi-protect.eu for discussion of patient preference & B-R visualization

Approaches to Benefit-Risk Analysis of Medicines
Personal Observations

PhRMA BRAT (Semi-Quantitative)

- Not as user friendly as expected
- Subjective, not reliably reproducible
- Time consuming
- Highly resource intensive

MCDA (Quantitative)

- Methodological advantages over older quantitative methods
- Needs pre-specified “weights” by coordination with multiple experts
- Significant technical expertise and programming capability
- Resource intensive

A Newer Model with Key Advantages? Stochastic Multicriteria Acceptability Analysis (SMAA)

- **SMAA, a variant of MCDA, is a newer model with key advantages[1]**
  - Accounts for sampling variations in criteria measurements
  - Exact numerical weights not required
    - Less dependent on predefined “weighting” of criteria by decision makers
  - Open-source software available for analysis (JSMAA)
    - User friendly interface with graphical output

- **Tested by IMI PROTECT**
  - IMI PROTECT case studies: Rimonabant, Telithromycin and Warfarin
  - Useful to compare these case studies to recent publications where SMAA used to evaluate the benefit risk of anti-depressants & NSAIDs

[1] *Statist. Med. 2011, 30 1419-1428*

Conclusions

Reinforces

Pre-specify confounders, PS and balance measures, MSMs, skepticism about IV analysis, EHRs at this stage unable to capture some outcomes well

Emphasizes

- Research networks
- Transparency for reproducibility
- Evaluating difference: Sensitivity analyses
  - Designs, outcomes, potential bias, balance measures, etc.
- Replication
- New uses for structured & unstructured data
- Continued exploration of B/R tools for decision making