PROTECT’s Impact on Pharmacovigilance Practice:
An Industry Perspective

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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

Rapid Queries
Estimate expected risks in indicated populations

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

EMRs
Claims
Registries

Approval
Primary Sources for “Real World,” Post-Approval Signal Detection

Spontaneous Reports

- Electronic Health Records studies
  - Cohort / CC / Registry primary data studies

Medicine Approval

- Signal Detection
  - Any Medical Event
  - Designated Medical Events
  - Quantitative Algorithms

Signal Refinement

Signal Evaluation

Rapid
Detect the unexpected
Less persuasive

Time Consuming
Test the anticipated
Convincing
# Work Package 2
**Pharmacoepidemiology (co-leads: O Klungel, R Reynolds)**

<table>
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<th>Work Package</th>
<th>WG1 Databases</th>
<th>WG2 Confounding</th>
<th>WG3 Drug Utilization</th>
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<td><strong>WG coordinators</strong></td>
<td>Raymond Schlienger¹ (Novartis) Mark de Groot² (UU)</td>
<td>Nicolle Gatto (Pfizer) Rolf Groenwold (UU)</td>
<td>Joan Fortuny³,⁵ (Novartis) Luisa Ibanez (FIFC)</td>
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<td><strong>WP2 co-leaders</strong></td>
<td>Olaf Klungel (UU) - Robert Reynolds (Pfizer)</td>
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<td><strong>WP2 project manager</strong></td>
<td>Ines Teixidor (UU)</td>
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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 little 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)

# Work package 3

**Signal Detection (co-leads: N Noren, M Kayser)**

## WP3 Participants

### 74 persons from 19 partner organisations

<table>
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<tr>
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<th>First name</th>
<th>Affiliation Short Name</th>
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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

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.

Are we fine-tuning an outdated model?
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)
**Signal Detection in Pharmacovigilance**

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

**Preliminary results**

820 → 509 → 382 → 91

311 Not relevant terms

127 Already known

291 Dismissed

Merit further evaluation

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Slide from Niklas Noren (UMC)

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

http://PROTECTBenefitRisk.eu/
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

See also [www.imi-protect.eu](http://www.imi-protect.eu) for discussion of patient preference & B-R visualization
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

Approaches to Benefit-Risk Analysis of Medicines
Personal Observations
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