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Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

Introduction to PROTECT WP3 research & recommendations for statistical signal detection

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PROTECT Goal

To strengthen the monitoring of benefit-risk of medicines in Europe by developing innovative methods

to enhance early detection and assessment of adverse drug reactions from different data sources (clinical trials, spontaneous reporting and observational studies)

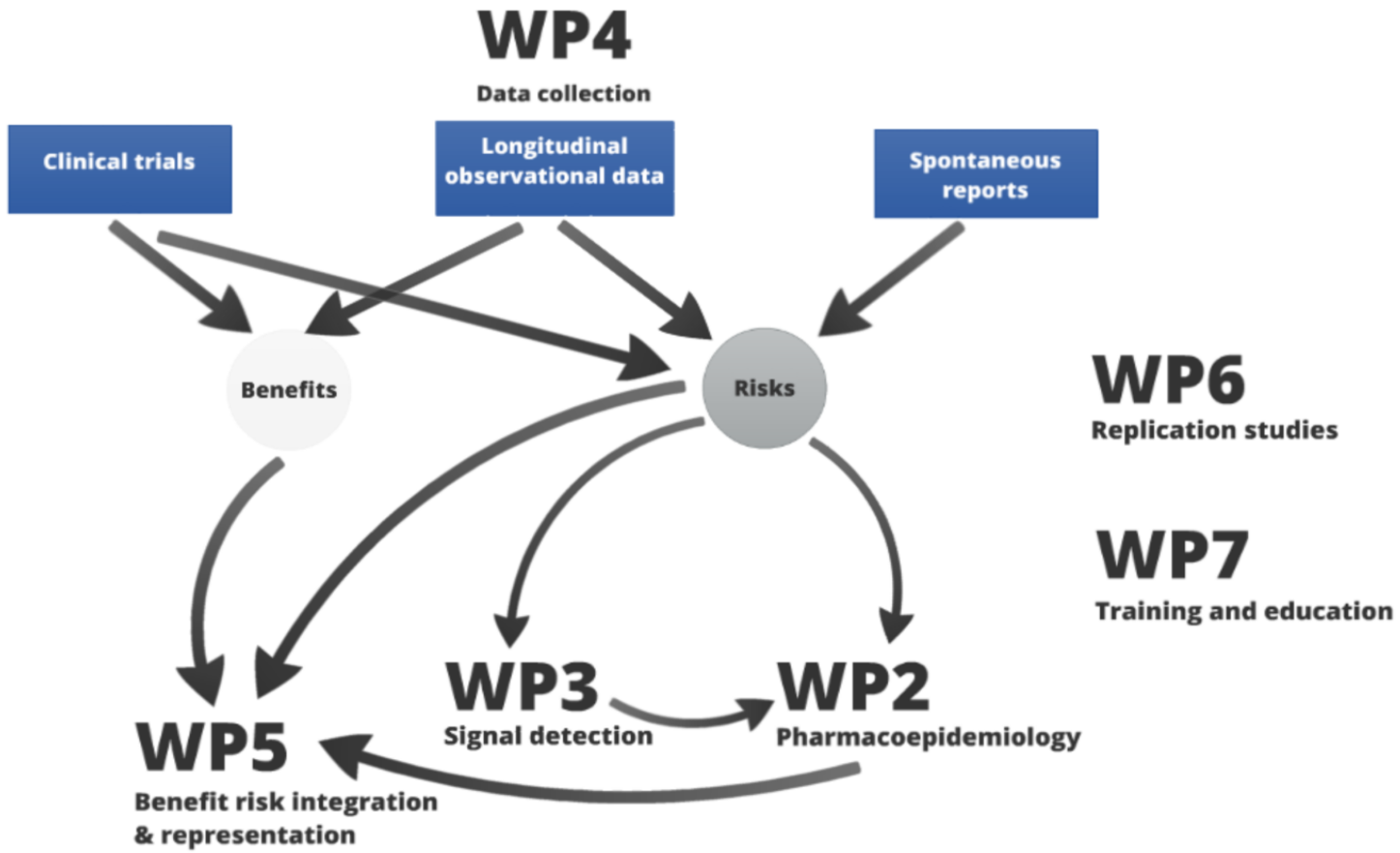
to enable the integration and presentation of data on benefits and risks

These methods will be tested in real-life situations.

WP3 Overall Aim

To improve early and proactive signal detection from spontaneous reports, electronic health records, and clinical trials.

Relationship between PROTECT Work Packages



NOTE: Work Package 1 (project management and admin) is omitted from Figure 1 for the sake of clarity

WP3 Participants

74 persons from 19 partner organisations

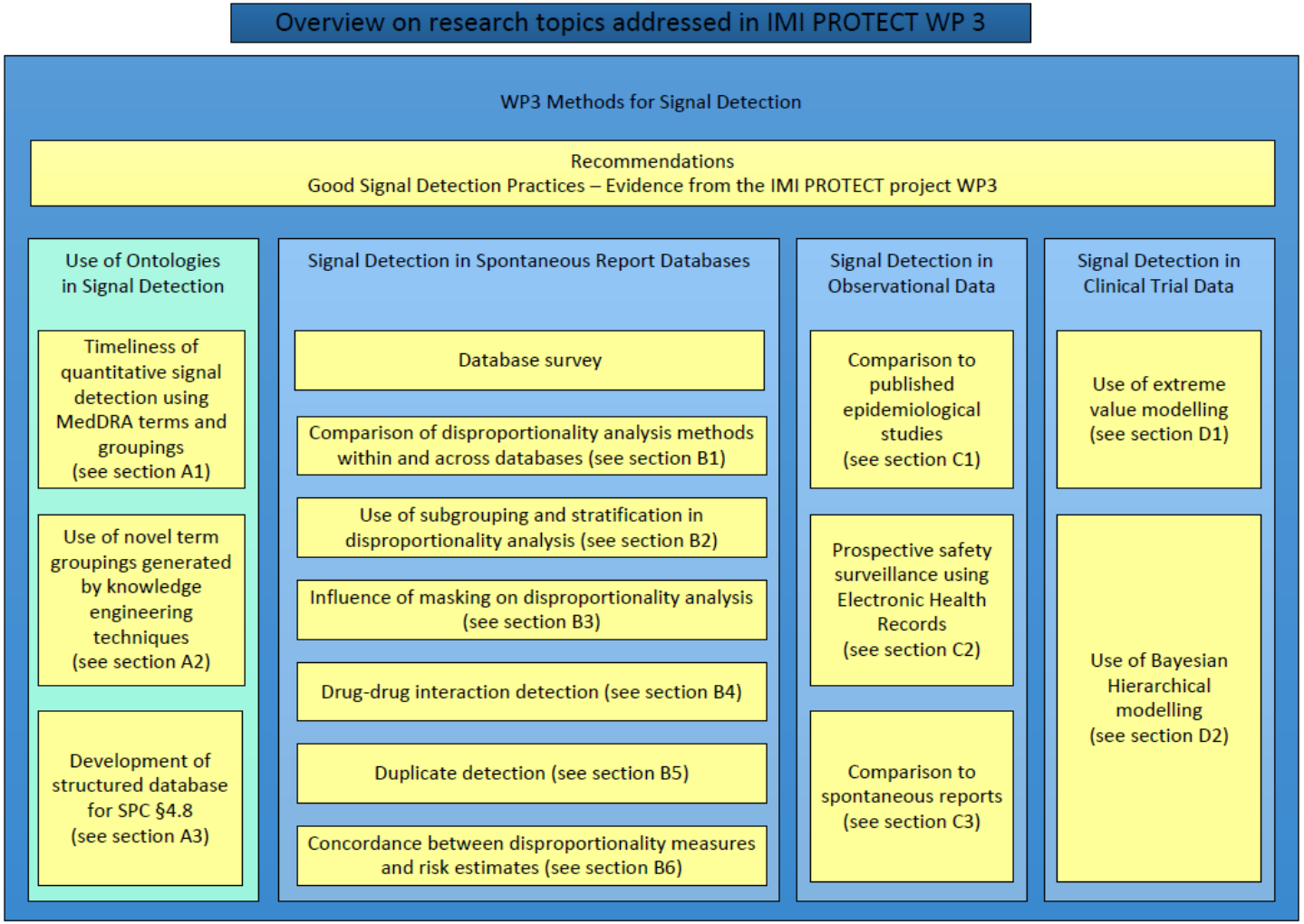
Surname	*First name*	*Affiliation Short Name*	*Role(s) Sub-package participation*
Ahlers	Christiane	Bayer	3.9
Ansell	David	Cegedim (Epic)	3.10
Arani	Ramin	AZ	3.1 / 3.8
Asiimwe	Alex	Lilly (formerly of AZ)	3.10
Bate	Andrew	Pfizer	3.4 / 3.10
Bech Fink	Dorthe	DHMA	3.3 / 3.11 / 3.12
Bergvall	Tomas	UMC	3.3 / 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

WP3 Sub-packages

Sub-packages	Leader
3.01 Merits of disproportionality analysis	EMA
3.02 Concordance with risk estimates	AEMPS
3.03 Structured database of SPC 4.8	EMA
3.04 Signal detection recommendations	AZ
3.05 Better use of existing ADR terminologies	UMC
3.06 Novel tools for grouping ADRs	INSERM
3.07 Other information to enhance signal detection	EMA
3.08 Subgroups and stratification	MHRA & EMA
3.09 Signal detection from clinical trials	Bayer/Novartis
3.10 Signal detection in EHRs	UMC
3.11 Drug-drug interaction detection	Roche
3.12 Duplicate detection	MHRA

Categorisation of WP3 sub-packages



(References in brackets are to relevant sections of the WP3 Recommendations Report)

WP3 backgrounds & goals

- Quantitative approaches well established in signal management systems nowadays
- Ongoing attempts to improve good signal detection practices but a number of research questions remain
- Overall goal of WP3 is to increase efficiency of signal detection practices
  - Focus of WP3 was primarily on quantitative signal detection methods
    - In practice signal detection relies on quantitative and qualitative methods
- Most comprehensive research programme so far on different SD methods across a broad range of organisations and databases?

Use of Ontologies in Signal Detection

- Three Sub-packages:
  - How to best use hierarchical terminologies to perform quantitative signal detection and the appropriate level of granularity
  - How more advanced medical informatics approaches can contribute to signal detection
  - Existence of systematically recorded and stored repositories of known ADRs, to facilitate focus of tools on the unknown
- Groups of PTs used in clinical trials data also looked at as apart of WP3.9

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Signal Detection in Spontaneous data

- Six Sub-packages:
  - Performance characteristics of quantitative signal detection approaches and variation across datasets of AE reports
  - the value of sub-grouping and stratification
  - Performance and value of algorithms for duplicate detection
  - Detection of drug-drug interactions
  - The impact of masking on quantitative signal detection
  - Whether concordance exists between the Proportional Reporting Ratio (PRR) and estimates of risk from studies

Signal Detection in Observational & Clinical Trials data

- Observational data:
  - Comparison to published epidemiological studies
  - Prospective safety surveillance using EHRs
  - Comparison to spontaneous reports

- Clinical Trials data:
  - Use of extreme value modelling
  - Use of Bayesian Hierarchical modelling

How the work was delivered

- Ambitious programme of work!
- Research undertaken between September 2009 and February 2015
- 12 sub-packages (s-p) managed autonomously (mostly) but good overlap in personnel and regular meetings of s-p leads ensured dissemination of progress and emerging results
- A number of s-ps fed into or exploited outputs from earlier ones:
  - S-p #4 database survey across partners provided background info
  - S-p #5 (existing groupings) informed s-p #6 (novel groupings)
  - Macros and methodology used in s-p 3.1 (SD performance) were adapted by s-p 3.8 (sub-groups)

What was delivered 1/2

- See Key achievements of PROTECT @ http://www.imi-protect.eu/results.shtml
- Hill R, Hopstadius J, Lerch M, Norén GN. An attempt to expedite signal detection by grouping related adverse reaction terms. Drug Saf 2013; 35(12): 1194-5.
- Declerck G, Bousquet C, Jaulent MC. Automatic generation of MedDRA terms groupings using an ontology. Stud Health Technol Inform 2012; 180:73-7.
- Souvignet J, Declerck G, Trombert B, Rodrigues JM, Jaulent MC, Bousquet C. Evaluation of automated term groupings for detecting anaphylactic shock signals for drugs. AMIA Annu Symp Proc. 2012;2012:882-90.
- Slattery J.; Cappelli B.; Bergvall T.; Opitz N.; Kurz X. A structured database of adverse drug reaction based on information from the summary of product characteristics. Drug Saf 2013; 35(12): 1192-3
- Candore G, Juhlin K, Manlik K, Thakrar B, Quarcoo N, Seabroke S, Wisniewski A, Slattery J. Comparison of statistical signal detection methods within and across databases. *Submitted.*
- Seabroke S. et al. The use of stratification and subgroup analyses in statistical signal detection. *Article in preparation*
- Maignen F, Hauben M, Hung E, Van Holle L and Dogné JM. A conceptual approach to the masking effect of measures of disproportionality. Article first published online: 15 NOV 2013 | DOI: 10.1002/pds.3530.

What was delivered 2/2

- Maignen F, Hauben M, Hung E, Van Holle L and Dogné JM. Assessing the extent and impact of the masking effect of disproportionality analyses on two spontaneous reporting systems databases. Article first published online: 15 NOV 2013 | DOI: 10.1002/pds.3529.
- Soeria-Atmadja D, Juhlin K, Thakrar B, Norén GN. Evaluation of Statistical Measures for Adverse Drug Interaction Surveillance Pharmacoepidemiology and Drug Safety 2014; 23(S1):294-295
- Philip Michael Tregunno, Dorthe Bech Fink, Cristina Fernandez-Fernandez, Edurne Lázaro-Bengoa, G. Niklas Norén. Performance of Probabilistic Method to Detect Duplicate Individual Case Safety Reports. Drug Safety 2014; 37(4):249-258.
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- Harry Southworth. Predicting potential liver toxicity from phase 2 data: a case study with ximelagatran; Statistics in Medicine: Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/sim.6142; 12-Mar-2014.
- Andreas Brueckner, Christiane Ahlers, Nils Opitz, Anngret Mallick. Identification of Adverse Drug Reaction Candidates. *Article in preparation*

Recommendations report

- Attempt to distil key learning from WP3 into practical recommendations
- Intended to inform pharmacovigilance professionals, particularly those with an interest in research and methods development
- Not intended to be comprehensive treatise on quantitative signal detection!!

Recommendations report

- 39 separate recommendations
  - many based on comparative analyses across databases from different settings
  - in several data sources (spontaneous, clinical trials, EHRS)
- 26 recommendations for future research
- Principally based on the outcomes of the research conducted under the auspices of the WP
- A broad cross-section of databases and data source were employed in the work package
  - Generalisability to other databases and data sources to be considered
  - Especially in smaller databases of AE reports

WP3 - How was it achieved?

- Renowned expertise in safety signal detection research
- Good collaboration across partners
  - Face-to-face meetings twice a year
  - Good mix of skills to support the overall effort
  - Progressive accumulation of mutual trust
- Overall good retention of personnel over 5 years, especially amongst the WP and s-p leaders
- Adaptability of plans to ensure exploitation of opportunities and retain relevance
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Questions?