PROTECT

imi efpia

Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

The PROTECT project

An Innovative Public-Private Partnership for New Methodologies in Pharmacovigilance and Pharmacoepidemiology

ISoP 10th Annual Meeting, 3-6 November 2010, Accra, Ghana

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

PROTECT is receiving funding from the European Community's Seventh Framework Programme (FP7/2007-2013) for the Innovative Medicine Initiative (www.imi.europa.eu).

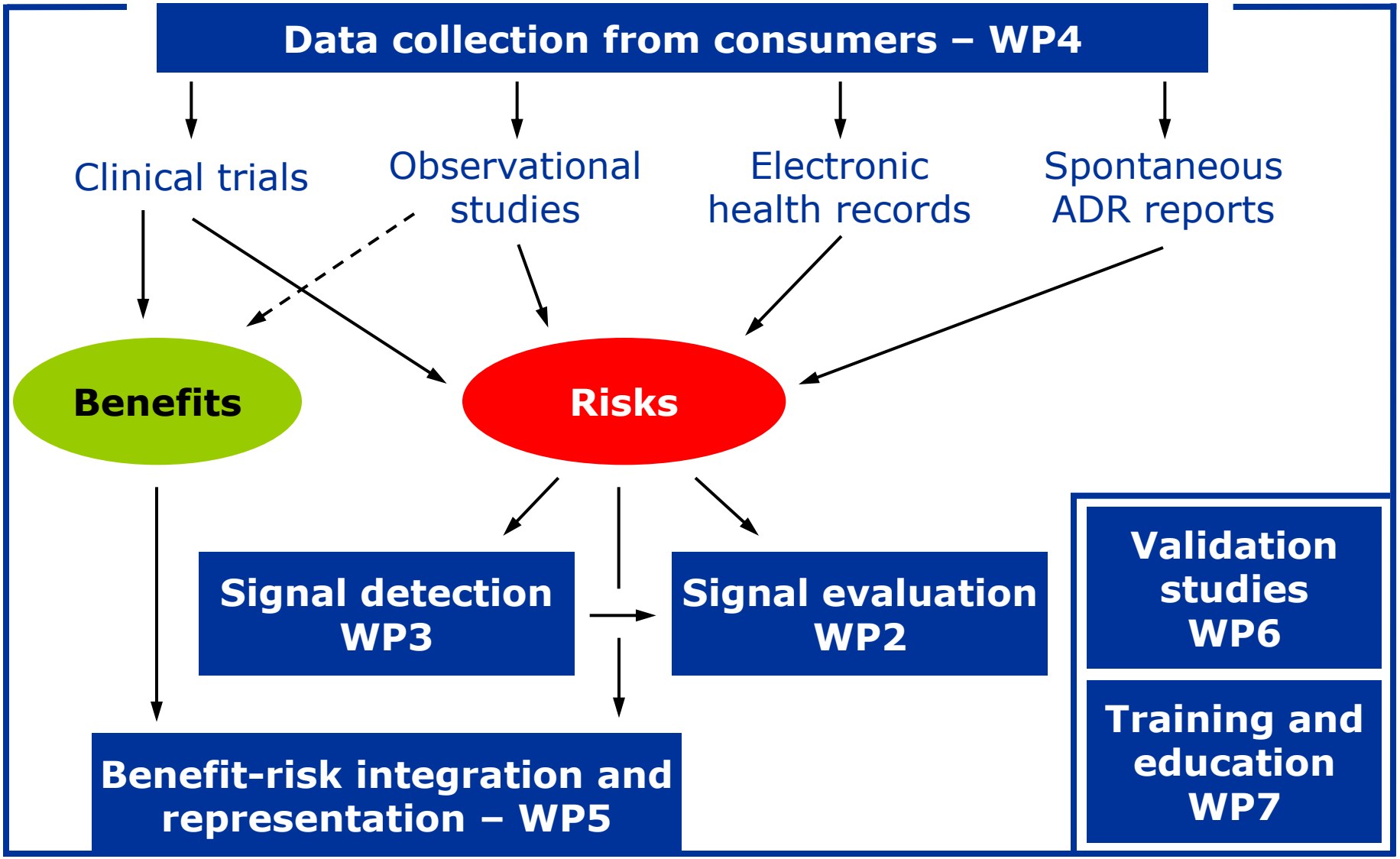
PROTECT Goal

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.


Data collection from consumers – WP4
Clinical trials
Observational studies
Electronic health records
Spontaneous ADR reports
Benefits
Risks
Signal detection WP3
Signal evaluation WP2
Validation studies WP6
Training and education WP7
Benefit-risk integration and representation – WP5

Partners

Public

Regulators:
EMA (Co-ordinator)
DKMA (DK)
AEMPS (ES)
MHRA (UK)

Academic Institutions:
University of Munich
FICF (Barcelona)
INSERM (Paris)
Mario Negri Institute (Milan)
University of Groningen
University of Utrecht
Imperial College London
University of Newcastle Upon Tyne

Others:
WHO UMC
GPRD
IAPO
CEIFE

SMEs:
Outcome Europe
PGRx

Private

GSK (Deputy Co-ordinator)
Sanofi- Aventis
Roche
Novartis
Pfizer
Amgen
Genzyme
Merck Serono
Bayer Schering
Astra Zeneca
Lundbeck
NovoNordisk

WP 2: Framework for pharmacoepidemiological studies

Objectives:

To:

- develop
- test
- disseminate

methodological standards for the:

- design
- conduct
- analysis

of pharmacoepidemiological studies applicable to:

- different safety issues
- using different data sources

Art is made to disturb. Science reassures.

Georges Braque

Is it always true ?

Two studies on the use of statins and the risk of fracture done in GPRD around the same period by two different groups.

	Meier et al., 2000		Van Staa et al., 2001	
Statins only	*Current use*	0.55 (0.44-0.69)	*Current use*	1.01 (0.88-1.16)
	N prescriptions		Time since use	
	- 1-4	0.51 (0.33-0.81)	- 0-3 months	0.71 (0.50-1.01)
	- 5-19	0.62 (0.45-0.85)	- 3-6 months	1.31 (0.87-1.95)
	- 20	0.52 (0.36-0.76)	- 6-12 months	1.14 (0.82-1.58)
			- > 12 months	1.17 (0.99-1.40)
	Recent use	0.67 (0.50-0.92)		
	Past use	0.87 (0.65-1.18)	*Past use*	1.01 (0.78-1.32)
Statins (current) and type of fractures	Femur	0.12 (0.04-0.41)	Hip	0.59 (0.31-1.13)
	Hand, wrist or arm	0.71 (0.52-0.96)	Radius/ulna	1.01 (0.80-1.27)
	Vertebral	0.14 (0.02-0.88)	Vertebral	1.15 (0.62-2.14)
	Other	0.43 (0.23-0.80)		

Why such a difference ?

		Meier et al., 2000		Van Staa et al., 2001
Source population		370 GPRD practices		683 GPRD practices
Study period		through Sept 1998		through July 1999
Design		Selected case control (3 cohorts)		Conventional case-control
N Cases		3,940		81,880
N Controls		23,379		81,880
Age	*50-69*	52.2%	*50-69*	47.9%
	70-79	28.9%	*70-84*	38.9%
	80-89	18.9%	*≥85*	13.2%
Sex	*Female*	75.0%	*Female*	75.6%
BMI	*≥25*	57.3%	*≥25*	52.3%

- Different patients (source population, study period, exclusion criteria)
- Study design (e.g. matching criteria for age)
- Definition of current statin use (last 6 months vs. last 30 days)
- Possibly different outcomes (mapping)
- Possibly uncontrolled/residual confounding

Work Package 2

Work plan

- Three Working Groups (WG1-WG3)
  - Databases
  - Confounding
  - Drug Utilisation

Work Package 2 - Databases

WG 1 – Databases: Work Plan

- Conduct of 5 adverse event - drug pair studies in different EU databases
  - Selection of 5 key adverse event - drug pairs
  - Development of study protocols for all 5 pairs
  - Compare results of studies
  - Identify sources of discrepancies

Work Package 2 - Databases

WG 1 – Databases: Progress status

Selection of 5 key adverse events and drugs

- Selection criteria:
  - Adverse events that caused regulatory decisions
  - Public health impact (seriousness of the event, prevalence of drug exposure, etiologic fraction)
  - Feasibility
  - Range of relevant methodological issues

Work Package 2 - Databases

WG 1 – Databases: Progress status

Selection of 5 key adverse events and drugs

- Initial list of 55 events and >55 drugs
- Finalisation based on literature review and consensus meeting
- Protocol under development

Antidepressants (incl. Benzodiazepines) **- Hip Fracture**
Antibiotics - **Acute liver injury**
Beta2 Agonists **- Myocardial infarction**
Antiepileptics - **Suicide**
Calcium Channel Blockers - **Cancer**

Work Package 2 – Confounding

WG 2 – Confounding: Work Plan

- Objective
  - To evaluate and improve innovative methods to control confounding
- Method
  - Creation of simulated cohorts
  - Use of methods to adjust for observed and unobserved confounding

    e.g. time-dependent exposure, propensity scores, instrumental variables, prior event rate ratio (PERR) adjustment, evaluation of measures of balance in real-life study

Work Package 2- Drug Utilisation

WG 3 - Drug Utilisation: Work Plan

- Use of national drug utilisation data (incl IMS)
- Inventory of data sources on drug utilisation data for several European countries
- Evaluation and dissemination of methodologies for drug utilisation studies in order to estimate the potential public health impact of adverse drug reactions
- Collaboration with EuroDURG agreed

Work Package 3: Signal Detection

Objective:

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

Work Package 3: Signal Detection

Scope

- Develop new methods for signal detection in Individual Case Safety Reports.
- Develop Guidelines for signal detection and strengthening in Electronic Health Records.
- Implement and evaluate concept-based Adverse Drug Reaction terminologies as a tool for improved signal detection and strengthening.
- Evaluate signal detection based on Suspected Unexpected Serious Adverse Reactions from clinical trials.
- Recommendations for good signal detection practices.

Work Package 3: Sub-projects

1. Merits of disproportionality analysis
2. Structured database of known ADRs
3. Risk estimates from trials
4. Signal detection recommendations
5. Better use of existing ADR terminologies
6. Novel tools for grouping ADRs
7. Other information to enhance signal detection
8. Signal detection based on SUSARs
9. Subgroups and risk factors
10. Signal detection in Electronic Health Records
11. Drug-drug interaction detection
12. Duplicate detection

Work Package 3 - Structured database of SPC 4.8

Sub-project 2: Wok Plan and progress

- The availability, in **structured**, format of already known ADRs would allow for
  - Triaging out known ADRs
  - Automatic reduction of masking effects
- Approach:
  - Manual identification
  - Pooling of existing structured information (?)
  - Free text extraction!
- Progress to date:
  - **348**/375 SPCs (substances) in pilot data set completed.

Work Package 3 - Structured database of SPC 4.8

- Proof-of-concept analysis of free text extraction algorithm
  - Initial match rate increased from 72% to 93%

Drug	SPC Term	Verbatim match	Fuzzy matching algorithm
Aclasta	FLU-LIKE SYMPTOMS		***Flu symptoms***
Advagraf	OTHER ELECTROLYTE ABNORMALITIES	-	Electrolyte abnormality
Advagraf	PAIN AND DISCOMFORT	-	Pain and discomfort NEC
Advagraf	PRIMARY GRAFT DYSFUNCTION	-	Primary graft dysfunction*
Advagraf	PRURITUS	PRURITUS	Pruritus*
Advagraf	PSYCHOTIC DISORDER	PSYCHOTIC DISORDER	Psychotic disorder*
Advagraf	PULSE INVESTIGATIONS ABNORMAL	-	***Investigation abnormal***
Advagraf	RASH	RASH	Rash*
Advagraf	RED BLOOD CELL ANALYSES ABNORMAL	-	***Red blood cell analyses****
Advagraf	RENAL FAILURE	RENAL FAILURE	Renal failure*
Advagraf	RENAL FAILURE ACUTE	RENAL FAILURE ACUTE	Acute renal failure, Renal failure acute*
Advagraf	RENAL IMPAIRMENT	RENAL IMPAIRMENT	Renal impairment*
Advagraf	RENAL TUBULAR NECROSIS	RENAL TUBULAR NECROSIS	Renal tubular necrosis*
Advagraf	RESPIRATORY FAILURES	-	Respiratory failure, Failure respiratory
Advagraf	RESPIRATORY TRACT DISORDERS	-	Respiratory tract disorders NEC
Advagraf	SEIZURES	-	Seizure, Seizures*
Advagraf	SHOCK	SHOCK	Shock*

Better option:
Flu like symptoms

Better option:
Red blood cell abnormal

Work Package 3 – Database survey

- Scope:
  - EudraVigilance, VigiBase
  - National data sets: AEMPS, BFARM, DKMA, MHRA
  - Company data sets: AZ, Bayer, Genzyme, GSK
- Focus:
  - # reports, # drugs and # ADR terms
  - Types of reports (AEs or ADRs, Vaccines, Seriousness, ...)
  - Additional information (presence of data elements available for stratification and sub-setting, e.g. demographics)
  - Supporting systems (analytical methods, medical triages)

Work Package 3 - Better use of existing terminologies

- Proof of concept
  - Temozolomide
  - Not illustrating timeliness – VigiBase as of Feb 2009

Term	Level of terminology	# Reports	IC
Erythema Multiforme	PT	13	**+0.30**
Stevens-Johnson Syndrome	PT	19	**+0.68**
Toxic Epidermal Necrolysis	PT	6	**+0.51**
Bullous Conditions	HLT	42	**-0.01**
Severe Cutaneous Adverse Reactions	SMQ	47	**-0.04**
Erythema Multiforme	WHO-ART HLT	35	**+0.46**

Work Package 3 - Signal detection from clinical trials

- Proof of concept example:
  - Two 96 week parallel group studies in HIV population
  - Terminated early at week 32 because of an unexpected safety issue (severe liver toxicity)
  - Identified on receipt of a Serious Adverse Event index case
- Analysis:
  - Retrospective data analysis and safety review
  - Laboratory data analysis at a population level
  - Other novel methods

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Work Package 3 - Signal detection in EHRs

- Overall scope:
  - EHRs versus ICSRs for early signal detection
  - Confirmatory vs exploratory data analysis
- Focus so far has been on the adaptation of an existing analytical platform to THIN
- Next steps:
  - Detailed study protocol
  - Ethics approval

Work Package 4: Data collection from consumers

Objectives:

To assess the feasibility, efficiency and usefulness of modern methods of data collection including using web-based data collection and computerised, interactive voice responsive systems (IVRS) by telephone

Work Package 4 - Project Definition

- Prospective, non interventional study which recruits pregnant women directly without intervention of health care professional
- Collect data from them throughout pregnancy using either web based or interactive voice response systems (IVRS):
  - medication usage, lifestyle and risk factors for congenital malformation
- Compare data with that from other sources and explore differences
- Assess strengths and weaknesses of data collection and transferability to other populations

Work Package 4 - Issues with current methods

Using health care professionals to capture data

- Expensive and data capture relatively infrequent
- Will miss drug exposure before comes to attention of HCP
- Patients may not tell truth about “sensitive” issues

Work Package 4 - Issues with current methods

Using EHR records

- non prescription medicines, homeopathic and herbal medicines not captured
  - ? Women switch to "perceived safer" medicines
- Medicines prescribed/dispensed may not be medicines consumed – problem with p.r.n. medicine
- EHR may miss lifestyle and "sensitive" information

Work package 4 - Study population

- 4 countries:

  Denmark 

  United-Kingdom 

  The Netherlands 

  Poland (tbc) 

- 1400 pregnant women per country
  - Self identified as pregnant
  - Volunteers may not be "typical" of pregnant population – can characterise

Work Package 4: Patient workflow overview

Study subject picks up a leaflet in a pharmacy or browses specific web sites to find out about the study in one of 4 countries.

Study subject enrolls for the web or phone (IVRS) method of data collection.

Web

n = 1200 per country

Study subject completes the surveys online.

IVRS

n = 200 per country

Study subject completes the surveys via an outbound reminder or by inbound call she initiates.

Final outcome survey is completed at the end of pregnancy.

Work Package 5: Benefit-risk Integration and Representation

Objectives:

- To assess and test methodologies for the benefit-risk assessment of medicines
- To develop tools for the visualisation of benefits and risks of medicinal products

➔ Perspectives of patients, healthcare prescribers, regulatory agencies and drug manufacturers

➔ From pre-approval through lifecycle of products

Work Package 5: Work Plan

1. Review of methodologies used to model effects of medicines, elucidation of patients' preferences and integrating effects and preferences.

   Review of methodologies for graphical representation and visualisation techniques.

2. Selection of case studies (waves 1 and 2)
3. Data selection/requirements for case studies
   - Wave 1: Raptiva, Tysabri, Acomplia, Xigris, Ketek
4. Identification/development of software for B/R.
5. Application of methodology, recommendations, finalisation of tools, protocols for validation studies.

Work Package 6: Validation

Objective:

To validate and test the transferability and feasibility of methods developed in PROTECT to other data sources and population groups.

Start in September 2010

Work Package 6 - Inventory of data sources

- Creating a comprehensive list of data sources
  - Review of European databases (EHC, cohorts, registries)
  - ENCePP
  - EFPIA
- Outcomes will be evaluated in light of the inventory of data sources (e.g. type of data, covariate information, mode of collection, type of prescription data, etc)

Work Package 7: Training & communication

Objective:

To identify training opportunities and support training programmes to disseminate the results achieved in PROTECT.

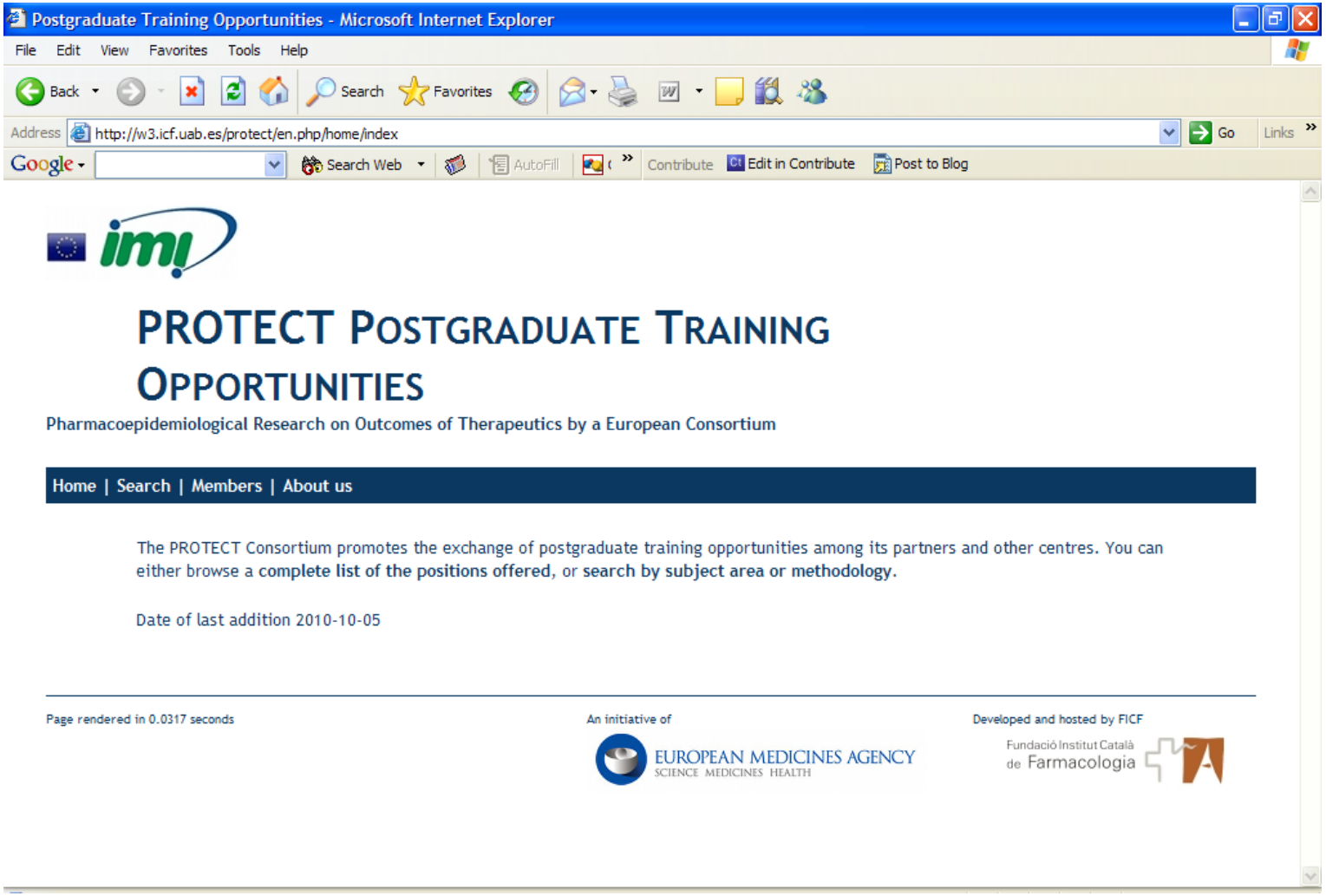
Work Package 7: Scope

- Development of a platform of training opportunities.
- Regular interaction with EU2P Consortium.
- Communication Plan: draft list of conferences and other international forums suitable for the presentation of the results of PROTECT.

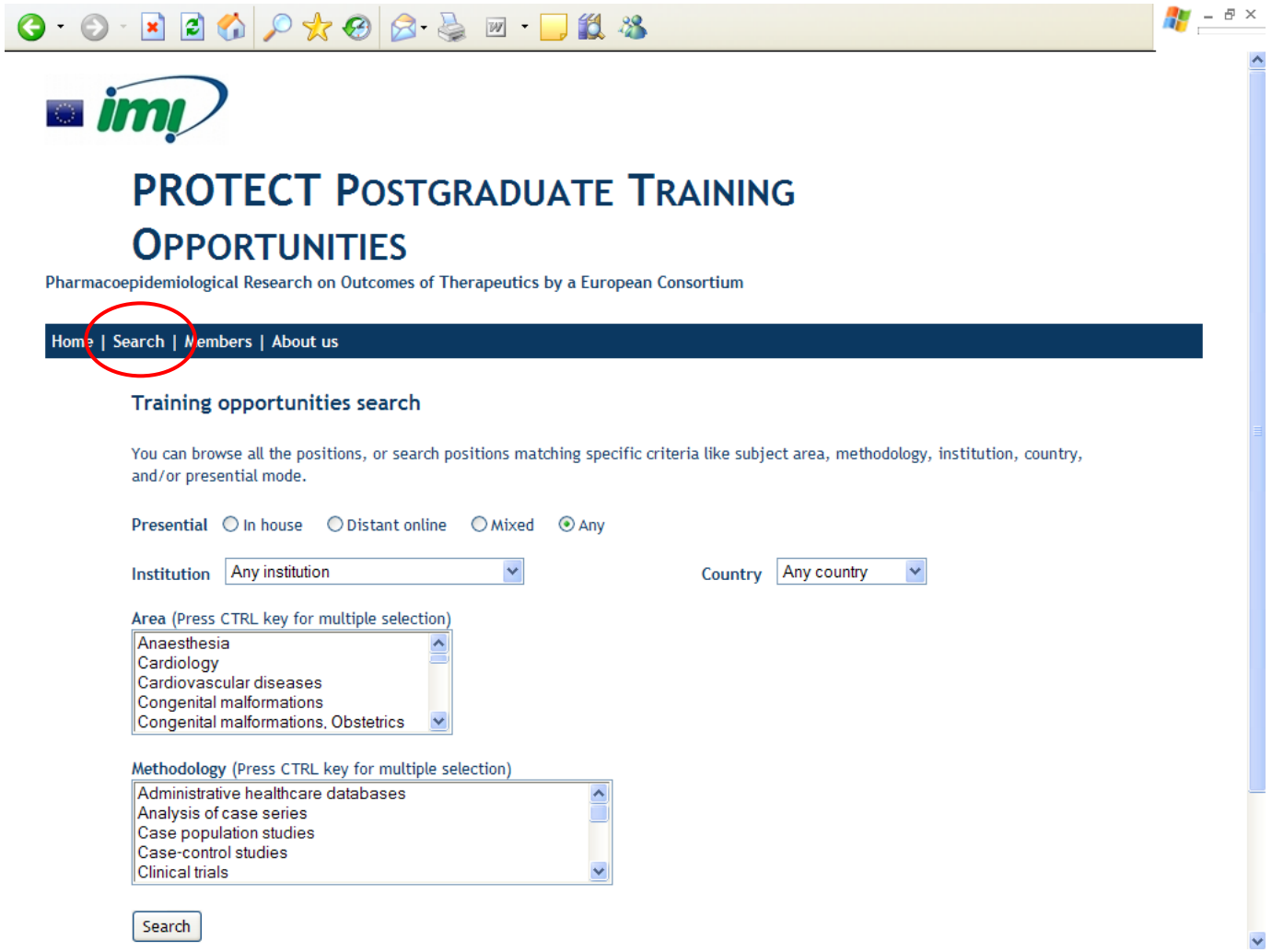
Work Package 7: Mock Up Training Platform

Postgraduate Training Opportunities - Link

Work Package 7: Mock Up Training Platform



Work Package 7: Mock Up Training Platform



More information?

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