PROTECT

imi efpia

Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

The future of benefit/risk assessment in Europe: The PROTECT programme

Symposium "Relativity in the Evaluation of Medicines"

What evidence is needed?

Xavier Kurz, European Medicines Agency

Wallace Collection, London, November 15th 2010

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

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

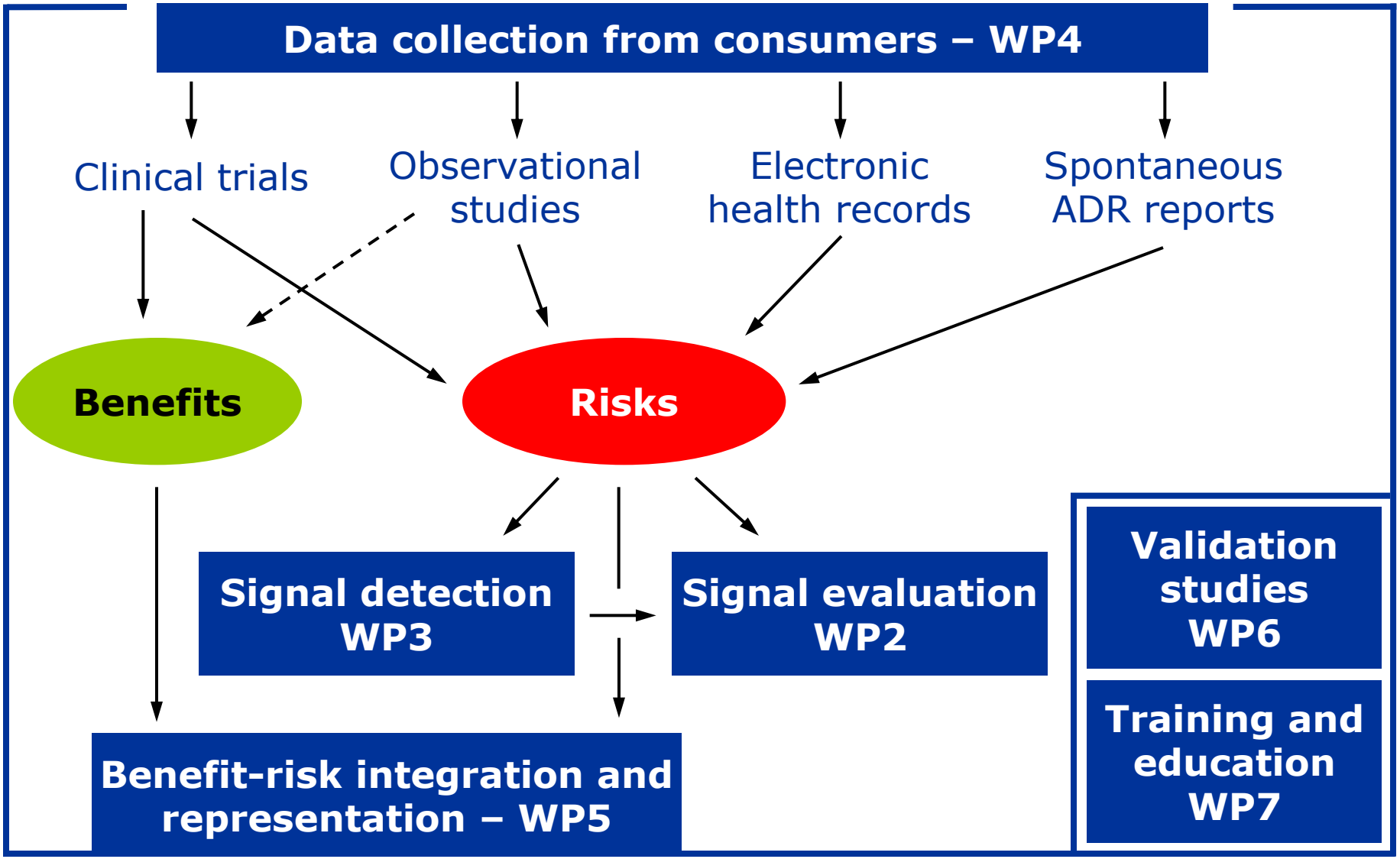
PROTECT Goal

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

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

Work Package 2 – WG1 Databases

- 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

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

Work Package 2 – WG2 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

Work Package 2- WG3 Drug Utilisation

- 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 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

WP 4 will address limitations of data capture through conventional methods such as health care professionals and electronic health records.

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 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

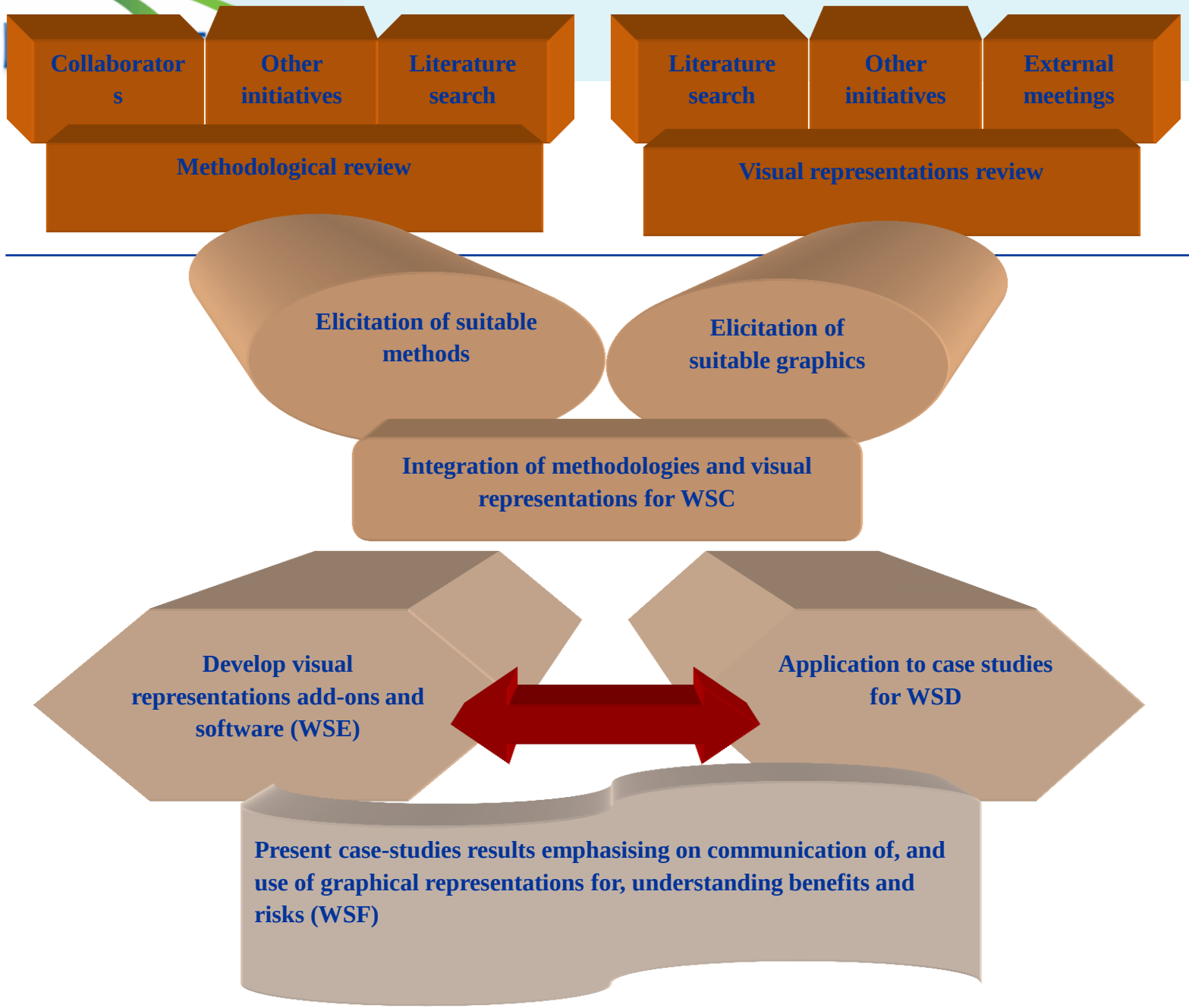
Considerations given to:

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

➔ From pre-approval to post-approval B-R assessment

➔ Individual and population-based decision-making

➔ Possible interdependencies with other PROTECT WPs and projects


Collaborators
Other initiatives
Literature search
Methodological review
Literature search
Other initiatives
External meetings
Visual representations review
Elicitation of suitable methods
Elicitation of suitable graphics
Integration of methodologies and visual representations for WSC
Develop visual representations add-ons and software (WSE)
Application to case studies for WSD
Present case-studies results emphasising on communication of, and use of graphical representations for, understanding benefits and risks (WSF)

Work Package 5: 1. Review of methodologies

- To identify, review and appraise existing reviews on benefit-risk assessment methodologies
- To perform systematic review and appraisal of visual methods of benefit-risk representation.
- To recommend candidate methodologies and visualisation techniques to be taken forward to case-studies.

  This task will be achieved by establishing criteria that will include ability to address decision-making for medicines for different stakeholders.

Work Package 5: 1. Review of methodologies

- Identify reviews related to benefit-risk assessment (e.g. EMA B-R assessment project) and other relevant fields (HTA)
- Appraisal of quality of reviews
- Appraisal strategy of B-R assessment methods based on statistical and other criteria, e.g.

  - Logically sound
  - Transparency
  - Interpretable
  - Reproducible results
  - Exploration of uncertainty
  - Acceptability of results
  - Practicality
  - Generality

Work Package 5: 2. Choice of cases studies

Wave 1

- Tysabri (natalizumab)
- Acomplia, Zimulti (rimonabant)
- Raptiva (efalizumab)
- Ketek (telithromycin)

Possibly for Wave 2

- Vioxx (rofecoxib)
- Herceptin (trastuzumab
- Thalidomide

Rezulin (troglitazone)

Atypical antipsychotics, sertindole

Xigris (drotrecogin alpha)

Work Package 5: 3. Data for cases studies

- To identify the data needed to model the four drugs of Wave 1 incl. from clinical trials and post-approval reports
- Purpose is to document favourable effects, unfavourable effects and uncertainties
- Same data may be used in various models
- Data supplemented by value judgments and assessment of uncertainty.

Publicly available data or data provided by Companies/agencies.

Work Package 5:

4. Identification/development of software for B/R.
5. Application of methodology, recommendations, finalisation of tools, protocols for validation studies.

PROTECT

PROTECT is not the EMA Benefit-Risk Assessment Project

Development and testing of tools and processes for balancing multiple benefits and risks as an aid to informed regulatory decisions about medicinal products.

Collaboration

EMA
CHMP
London School of Economics
University of Groningen

PROTECT is not the EMA Benefit-Risk Assessment Project

Objectives

- to adapt or develop tools and processes that could be used to conceptualise and make explicit benefit-risk trade-offs
- to provide an aid to regulatory decision-making
- to provide an aid for training of assessors
- to provide an aid for communicating benefit-risk decisions to stakeholders.

EMA Benefit-Risk Assessment Project

Work plan

Five Work Packages (1/2009 – 12/2011)

1. Description of current practice
2. Applicability of current tools and methods
3. Field tests of tools and methods
4. Development of tools and methods for B/R
5. Training module for assessors

EMA Benefit-Risk Assessment Project

Expected impact

- Improve the quality of benefit risk assessments
- Improve transparency and consistency of benefit risk assessment
- More auditable and robust benefit risk assessment
- Harmonise benefit risk assessment across the European network

EMA Benefit-Risk Assessment Project

WP1. Description of current practice

- 5 Participating Agencies (ES, FR, NL, SE, UK)

  42 people interviewed

- Main findings
  - **Multiple Benefits and Risks definitions**
  - B/R are balanced intuitively, no systematic approach
  - Different importance given to effects and uncertainties
  - Agreement that assessment of B/R balance is difficult

EMA Benefit-Risk Assessment Project

WP2. Applicability of current tools and processes for regulatory benefit risk assessment

Review of approaches for balancing benefits and risks in decision-making about medicinal products, with illustration with a case study.

Each review completed by evaluation of usefulness to regulators for decisions at both pre-and post approval stages.

Protocol and reports for WP1 and WP2 published on:

EMA website → Special Topics → Benefit-Risk Methodology

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

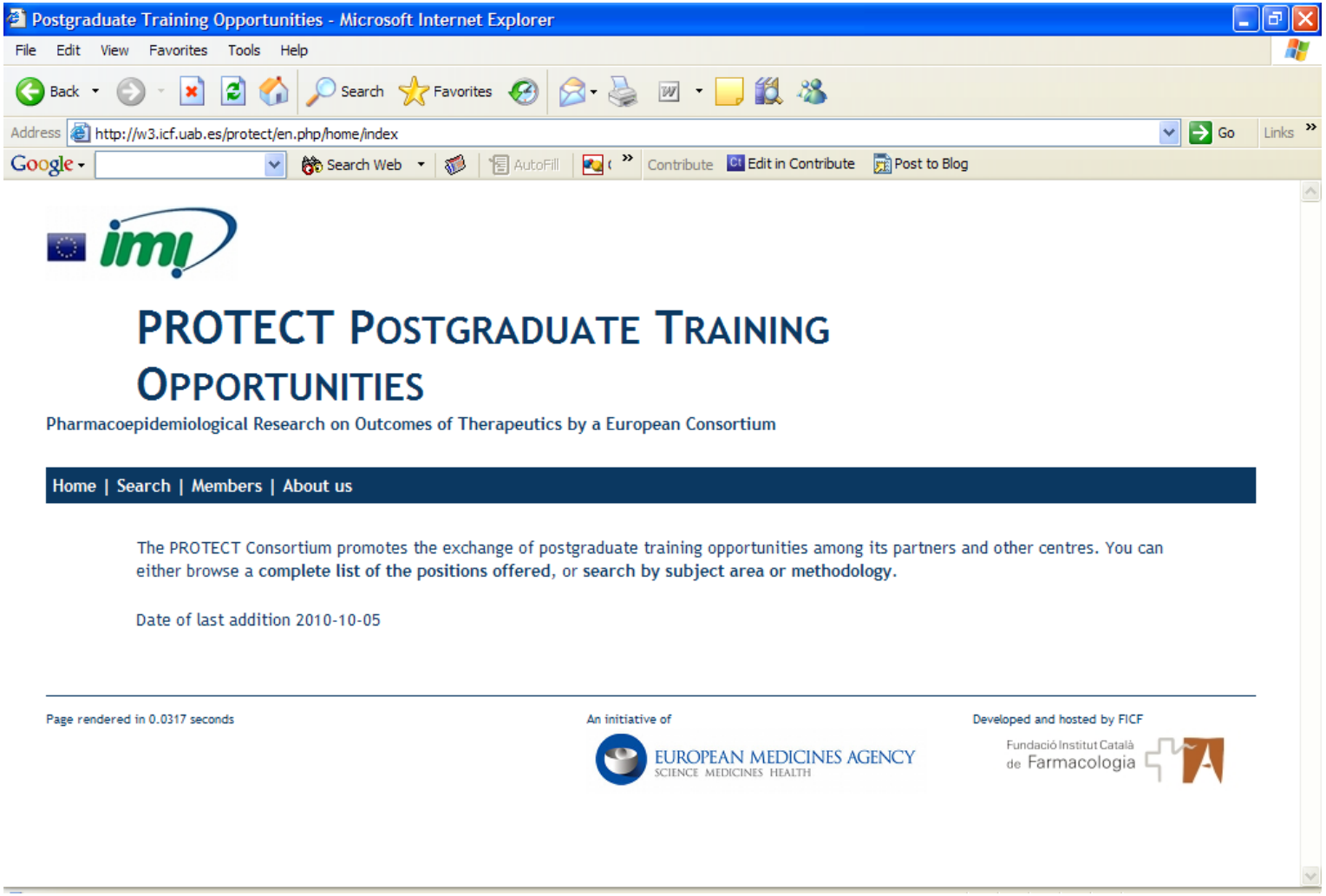
- Creating a comprehensive list of data sources
  - Review of European databases (EHC, cohorts, registries)
  - ENCePP
  - EFPIA
- Outcomes will be evaluated in light of the inventory of data sources (e.g. type of data, covariate information, mode of collection, type of prescription data, etc)

Work Package 7: Training & communication

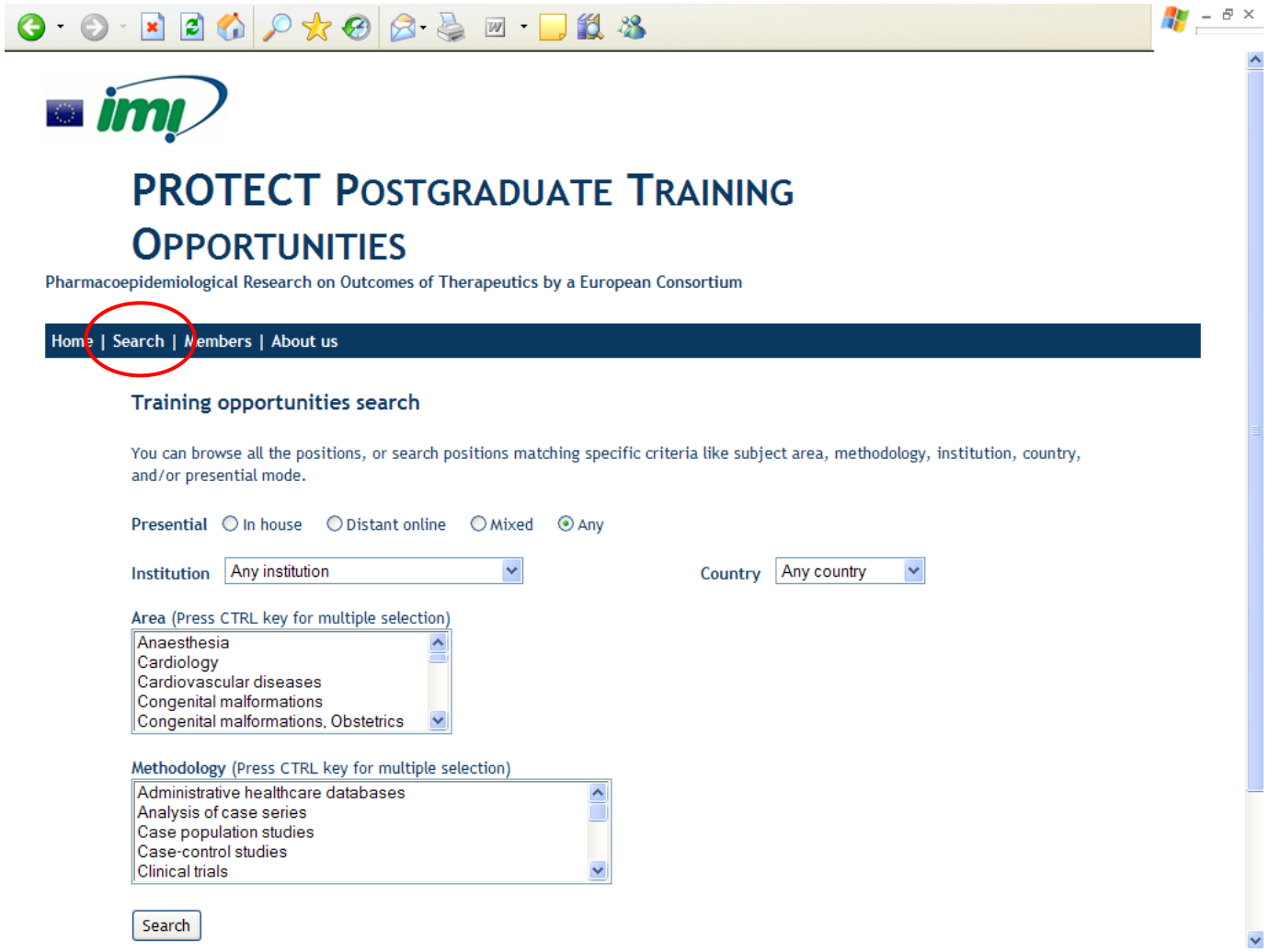
Objective:

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

Work Package 7: Mock Up Training Platform



Work Package 7: Mock Up Training Platform



More information on PROTECT?

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