GetReal: Clinical effectiveness in drug development

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WP4 Leaders

Relative Effectiveness (RE)

- *"the extent to which an intervention does more good than harm compared to one or more alternative intervention for achieving the desired results when provided under the usual circumstances of health care practice"*

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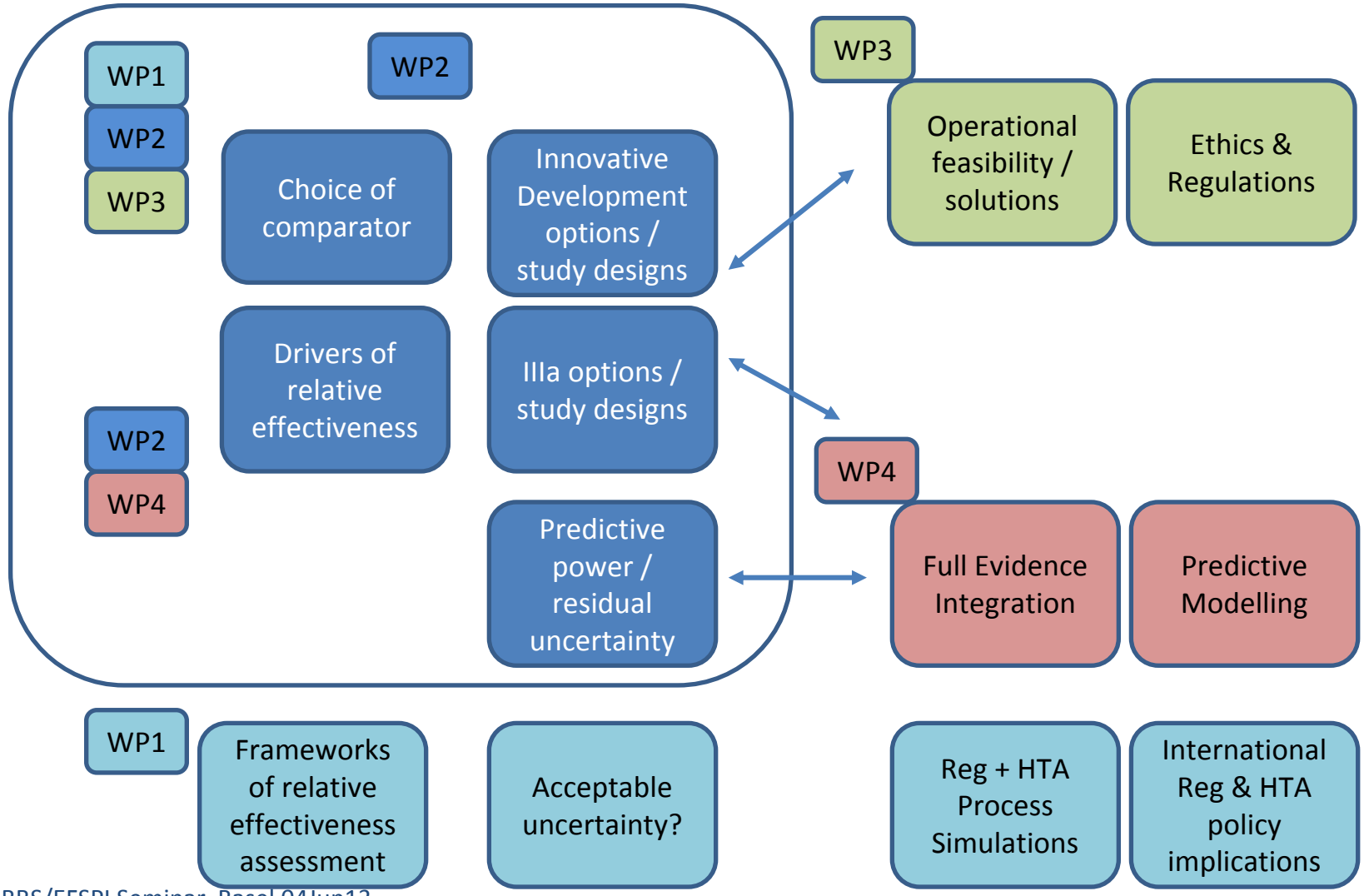
IMI GetReal: Work Package Themes



GetReal WP Leaders

- Sarah Garner, NICE and University of Oxford (WP1)
  - *GSK*
- Lucien Abenhaim, LA-SER, Paris (WP2)
  - *Sanofi*
- Diederick Grobbee, University Medical Center Utrecht (WP 3,5)
  - *Lilly*
- Matthias Egger, University of Bern (WP4)
  - *GSK*

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GetReal Partners

Academic	EFPIA	Regulatory, HTA, Other
The London School of Hygiene and Tropical Medicine	AstraZeneca	College voor Zorgverzekeringen
University of Ioannina	Bristol Myers Squibb	European Medicines Agency
University College London	Boehringer Ingeiheim	European Organisation for Research and treatment of Cancer
University of Leicester	GlaxoSmithKline	European Network for Health Technology Assessment
University Medical Center Utrecht	Janssen Pharmaceutica NV	General Pharmaceutical Council
University Medical Center Groningen	Merck Sharp & Dohme Corp	Haute Autorité de Santé
Universitaet Bern	NOVO NORDISK A/S	International Alliance of Patients' Organizations
	Sanofi-Aventis Research and Development	National Institute for Health and Clinical Excellence

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Aims: WP2

- Examine clinically meaningful patient subgroups based on actual care pathways.
- Use of drugs within defined treatment strategies.
- Most relevant outcome measures /endpoints.
- Patient and healthcare organisation factors that may drive variability of patient outcome in actual clinical practice for any given treatment strategy.
- Most appropriate comparator/s (drug and non-drug treatment strategies) for key subgroups.

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Aims WP3

- Develop a better understanding of how study designs used mainly for post launch RE can be applied successfully to investigational (unlicensed) medicines.
- Assess designs against current regulatory guidance/opinion and operational challenges:
  - Degree to which design meets HTA agencies' technical guidance
  - Any conflict with regulatory guidance
  - Ethical/legal issues concerning study of investigational medicines
  - Operational impacts of different designs

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Aims WP4

- Examine how RE be estimated from phase II and III RCT efficacy studies alone
- How should RCTs, additional relative effectiveness studies and observational data best be integrated to address specific decision making needs of regulatory and HTA bodies at launch?
- How can relative effectiveness in one country be modeled from raw data on relative effectiveness in another?

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Aims WP1

- Create the decision-making framework for Pharma R&D for the systematic identification and assessment of different development strategies, considering:
  - the incremental value of information from the study programme in the estimation of relative effectiveness at launch and after launch
  - the technical and practical challenges of different designs
  - the interaction with regulatory, HTA and other review processes.

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ORIGINAL CONTRIBUTION

Risk of cardiovascular events and rofecoxib: cumulative meta-analysis

Peter Jüni, Linda Nartey, Stephan Reichenbach, Rebekka Sterchi, Paul A Dieppe, Matthias Egger

The Hazards of Scoring the Quality of Clinical Trials for Meta-analysis

Peter Jüni, MD
Anne Witschi, MD
Ralph Bloch, MD, PhD
Matthias Egger, MD, MSc

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RESEARCH

Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis

mes associated with drug-eluting and bare-metal
: a collaborative network meta-analysis

er,* Simon Wandel,* Sabin Allemann, Adnan Kastrati, Marie Claude Morice, Albert Schömig, Matthias E Pfisterer, Gregg W Stone,
osé Suarez de Lezo, Jean-Jacques Goy, Seung-Jung Park, Manel Sabaté, Maarten J Suttorp, Henning Kelbaek, Christian Spaulding,
nelli, Paul Vermeersch, Maurits T Dirksen, Pavel Cervinka, Anna Sonia Petronio, Alain J Nordmann, Peter Diem, Bernhard Meier,
Stephan Reichenbach, Sven Trelle, Stephan Windecker, Peter Jüni

Whether the two drug-eluting stents approved by the US Food and Drug Administration—a
ing stent and a paclitaxel-eluting stent—are associated with increased risks of death, myocardial
stent thrombosis compared with bare-metal stents is uncertain. Our aim was to compare the safety and
f these stents.

Lancet 2007; 370: 937–48
See Comment page 914
*Contributed equally to this report

ıbach, senior research fellow,[1,4] Simon Wandel,
eatrice Tschannen, research fellow,[1] Peter M Villiger,
Matthias Egger, head of department and professor of
ivision and professor of clinical epidemiology[1,2]

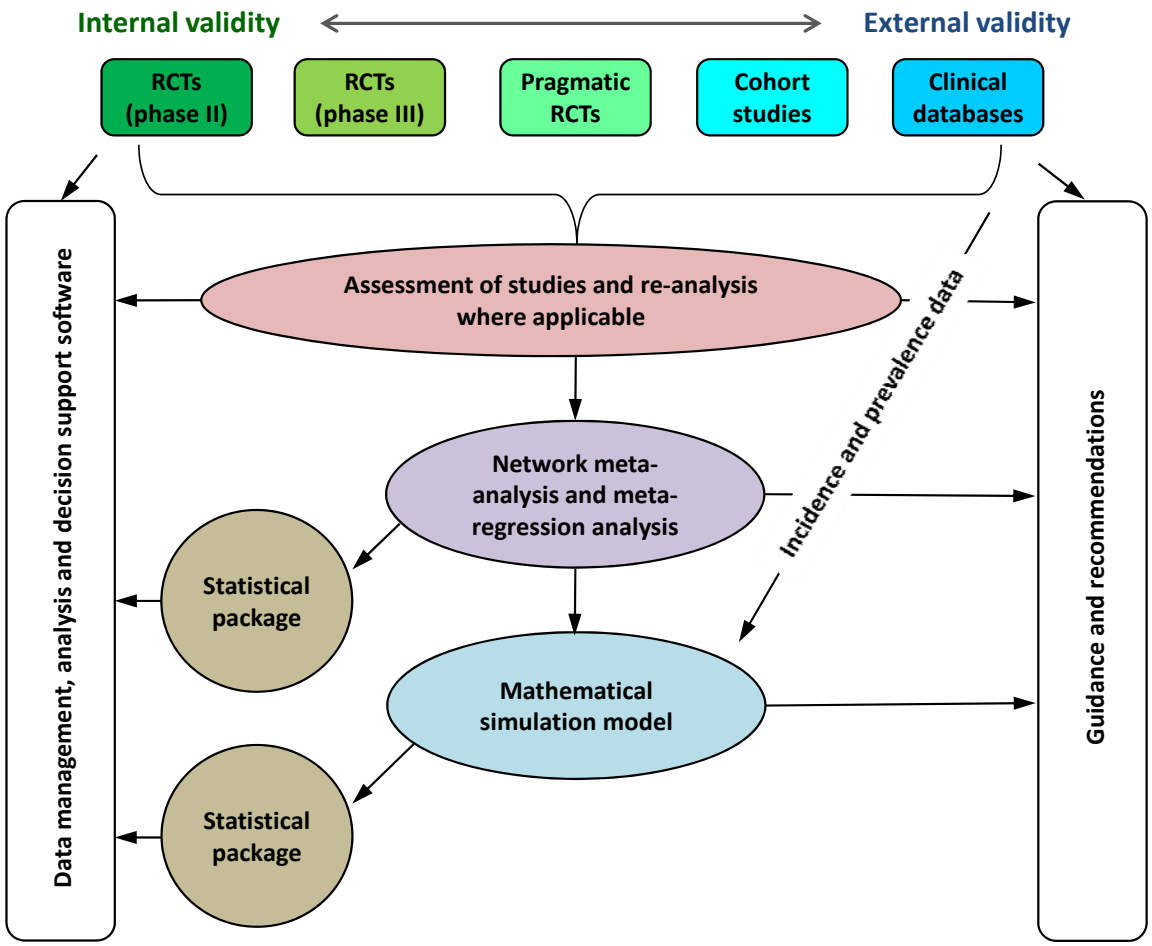
al ther
HIV transmission in South
hematical modelling analy

dy Aubrière[a], Matthias Egger[a], Leig
ela Garone[d], Thomas Gsponer[a], Gil
le[b], Mary-Ann Davies[b], Timothy B.
a Keiser[a], for IeDEA Southern Afric

Objectives: In low-income settings, treatment failure is often identified using
count monitoring. Consequently, patients remain on a failing regimen, resu

IMI GetReal WP4 Overview

Flow of work



Tasks

1) Identify suitable case-studies

2) Assess patient characteristics and risk of bias

3) Re-analyze individual patient data if available

4) Obtain best estimates of RE for different patient groups

5) Predict RE and absolute benefits and harms in different patient groups

6) Develop user-friendly software

7) Develop guidance and recommendations

Issues to be addressed in case studies

Issue
Surrogate to patient- relevant endpoint
Adherence in trial versus real world
Lack of direct comparison
Long term vs short term outcomes
Impact of different patient characteristics / background therapy and comorbidity
Aggregate versus IPD data, publication bias
Impact of study design / risk of bias
Extrapolating from one setting to another
Switching of drugs in trials
Progression free survival versus overall survival

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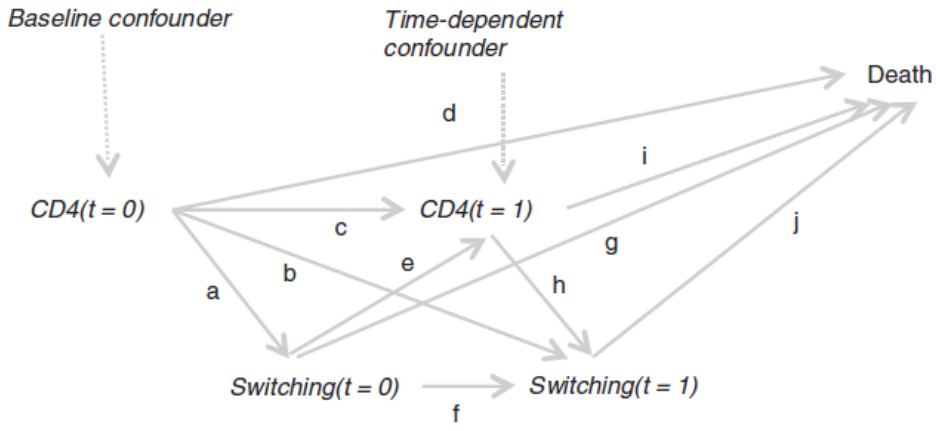
Possible case studies

Disease area	Interventions	Indication
Diabetic medicine	Pioglitazone, Rosiglitazone, Troglitazone	Glycemic control
Cardiovascular	Clopidogrel, Prasugrel, Ticagrelor	Platelet inhibition
	Drug eluting stents: PROMUX/TAXUS, CYPHER, XIENCE Xpedition	Coronary artery patency
Oncology	ESAs	Anaemia
	Rituximab	Low grade non-Hodgkin lymphoma (first-line)
	Aromatase inhibitors	Breast cancer
Respiratory	Bronchodilators	Asthma
Neurology	Bromocriptine, Cabergoline, Pramipexole, Ropinirole	Parkinson disease
	Fingolimod, Glatiramer, Interferon beta (1a/1b), Natalizumab, Teriflunomide	Relapsing-remitting multiple sclerosis

Estimate RE from observational studies

- Use DAGs to understand role of different variables as potential (time-dependent confounders).
- Use statistical methods that minimize bias (for example marginal structural models) in estimates of RE.



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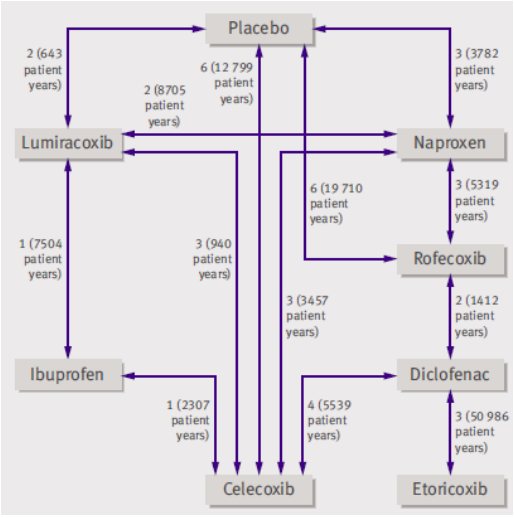
Do (network) meta-analyses of RCTs and subgroups from RCTs

- Bayesian hierarchical random effects models for mixed multiple treatment comparisons.
- Use standard random-effects meta-regression and Baysian models to identify determinants of RE.
- Refine ADDIS software package.



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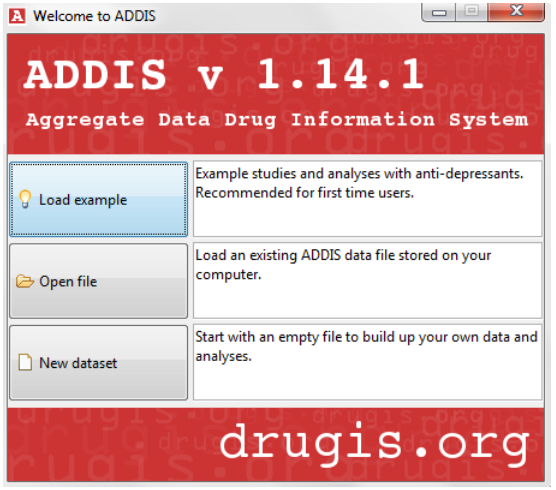

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Model RE under different scenarios

- Use mathematical (multi-state) simulation models to predict RE under different scenarios, in different populations.

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WHAT'S A STANDARD ERROR?
EXPECTING AN EASY ANSWER