Get Real

Real-Life Data in Drug Development

Bridging efficacy to effectiveness: The IMI GetReal project

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Co-leads WP4 (Evidence synthesis and predicting effectiveness)

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no [115303], resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.

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Disclaimer (Chrissie Fletcher)

- The views expressed herein represent those of the presenter and do not necessarily represent the views or practices of Amgen or the views of the general Pharmaceutical Industry.

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Innovative Medicines Initiative: *Joining Forces in the Healthcare Sector*

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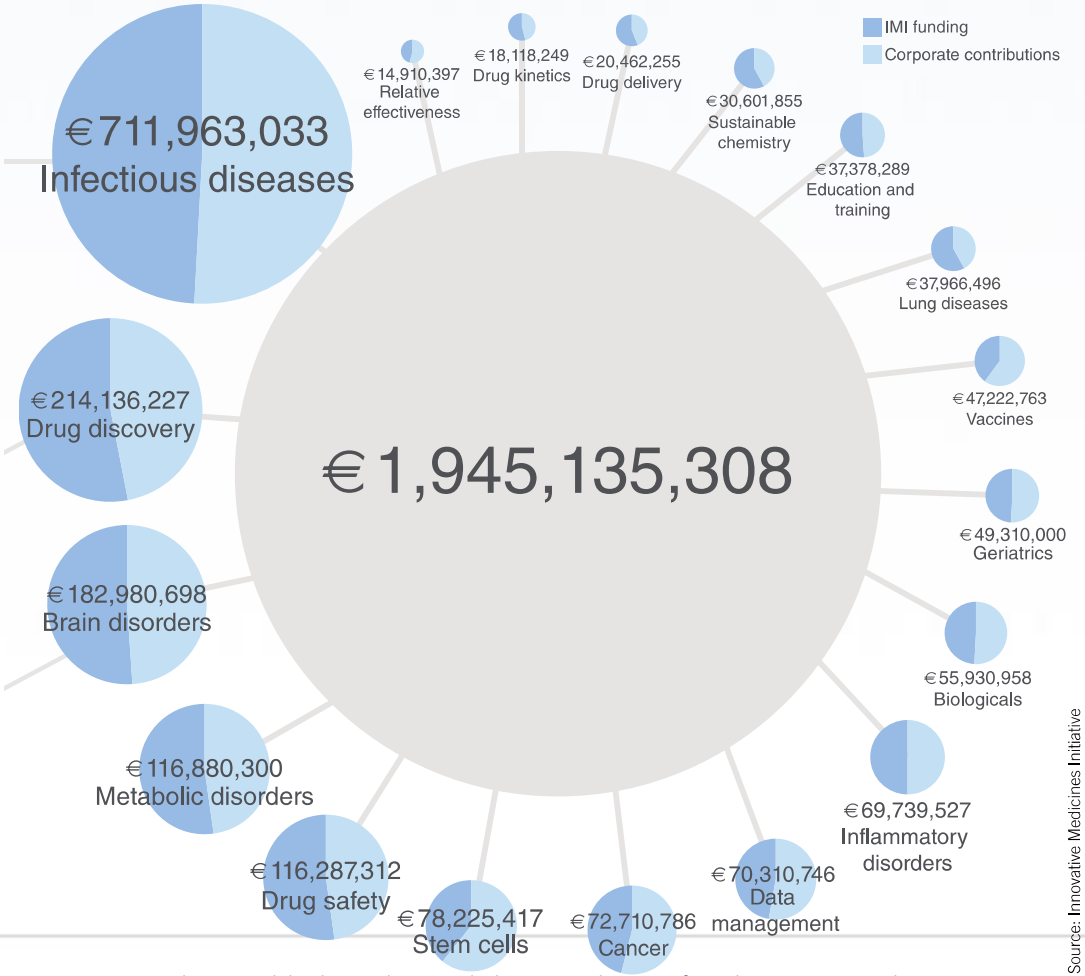
Areas of funding



Nat Med 2014;20:5.

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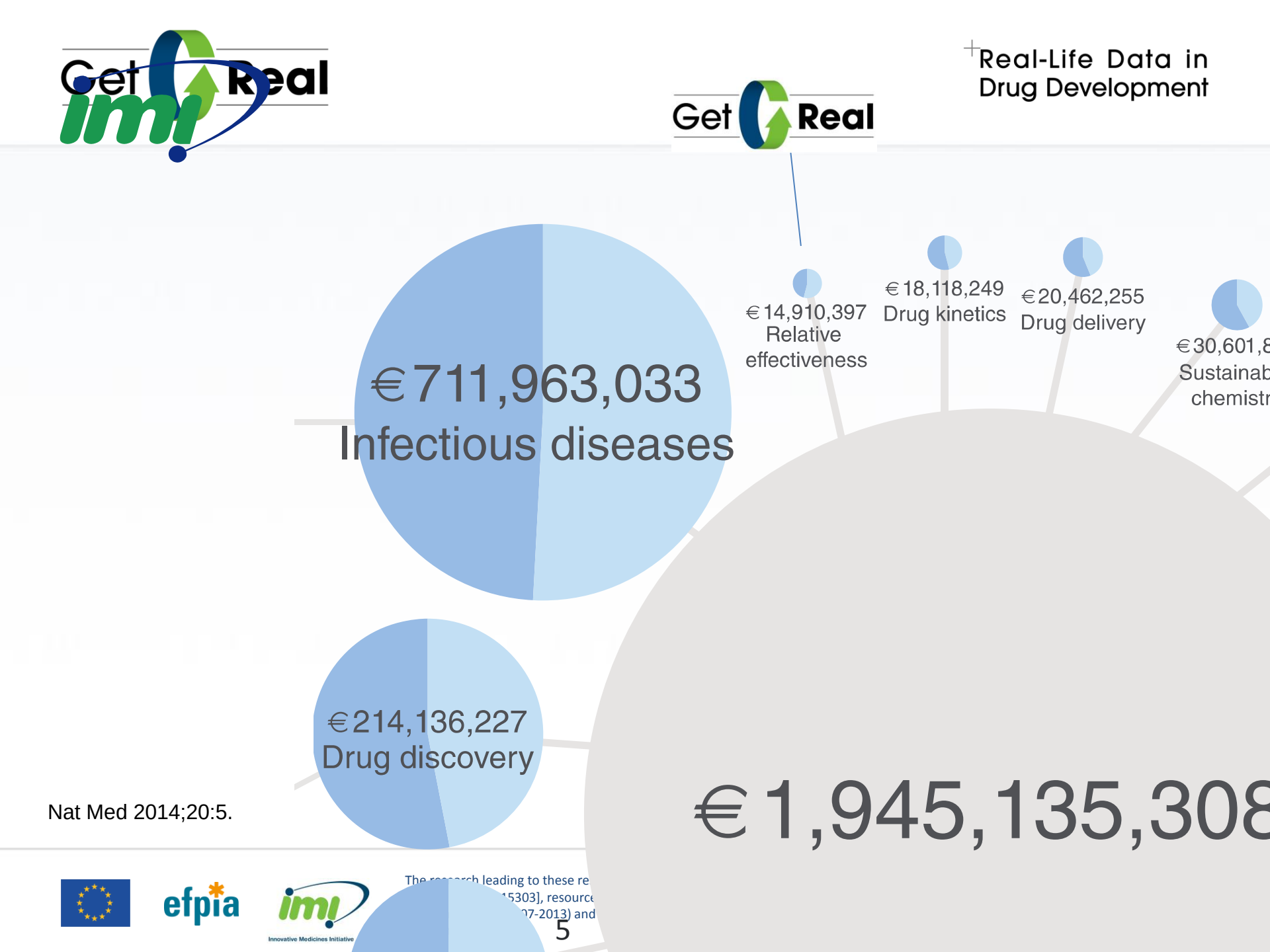

Nat Med 2014;20:5.

The research leading to these re
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07-2013) and

Background: GetReal

CRITICAL QUESTIONS REQUIRING JOINT APPROACH

Phase 3a	Phase 3b	Conditional Licensing	Conditional Access	Phase IV
"optimise"	"supplement"	?	?	"commit"

R & D decision

- What combination of possible studies will provide the most valuable information to customers controlling access - in order to maximise the probability of positive access outcomes ?
- What is the cost and feasibility of the study options pre-launch and what would be required as commitments post launch?
- How do options reconcile with the regulatory process?

HTA decision

- With all the available data, would we predict an improvement in patient outcome or care pathway efficiency over and above current practice in my healthcare system - with a reasonable level of certainty?
- Would we accept the uncertainty for a period of time while waiting for studies to complete or for new studies to be run?

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Background: GetReal

CRITICAL QUESTIONS REQUIRING JOINT APPROACH

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"optimise"	"supplement"	?	?	"commit"

In recent years there has been considerable attention paid to the post-authorisation evaluation of treatments in real world clinical practice in areas such as study design and data-analytical methodology for assessing relative effectiveness and use of registries and electronic healthcare records data.

It may be possible to improve the relevance and value (in terms of predicting effectiveness) of evidence available at initial market authorisation by incorporating these techniques into pre-authorisation drug development.

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GetReal: Project Vision

For pharmaceutical R&D and healthcare decision makers to better understand how real-world data and analytical techniques can be used to improve the relevance of knowledge generated during development, e.g., through innovation in clinical trial design. This can contribute to the knowledge base, particularly to inform clinical decision making and improve the efficiency of the R&D process.

Lasting impact of the project

To provide a methodological and analytical framework that informs policy and process evolution beyond the life of the project and at an international level; and to provide tools, techniques and training that ensure that the potential of real world data can be exploited in drug development.

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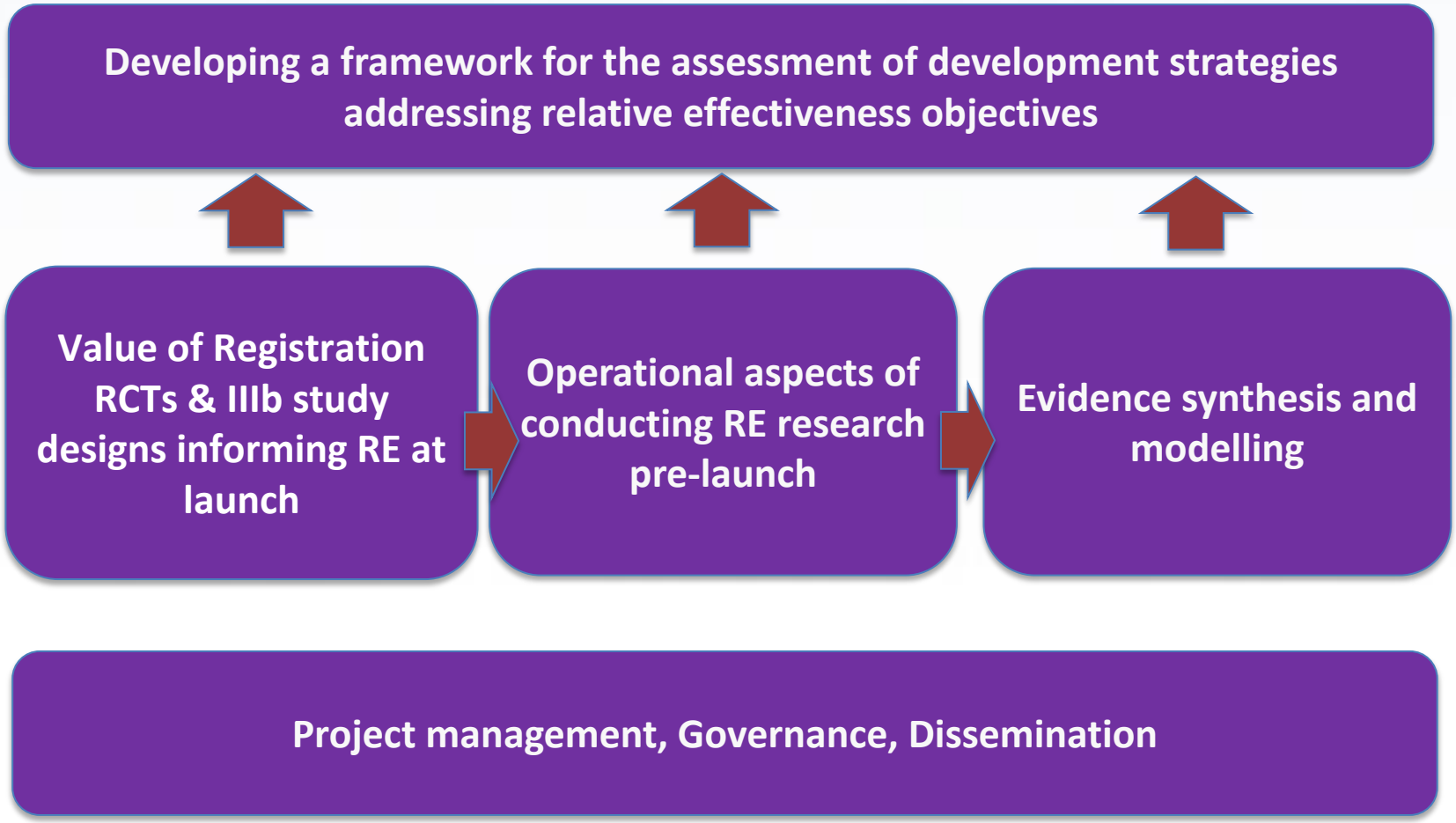
Architecture of GetReal



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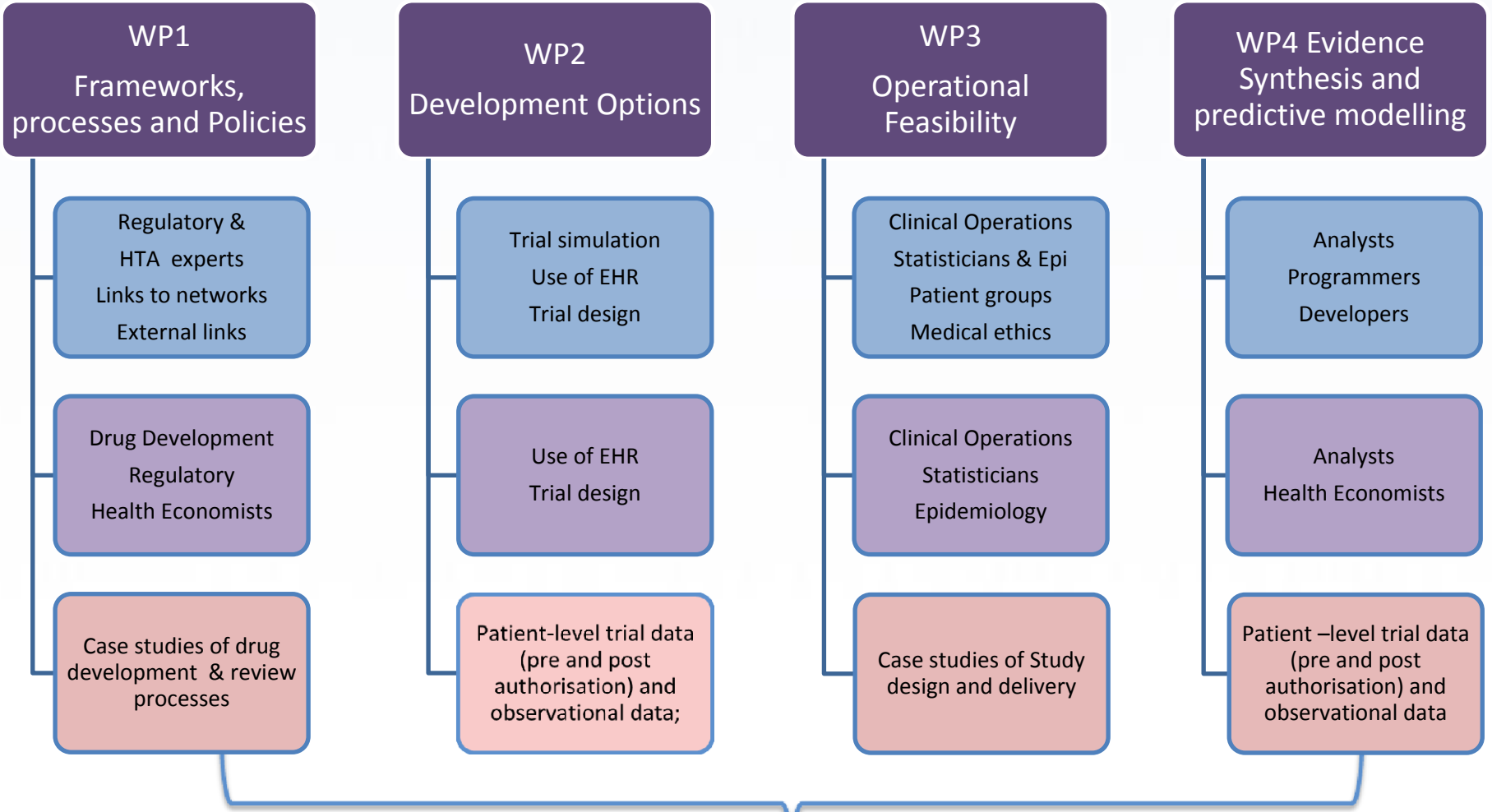
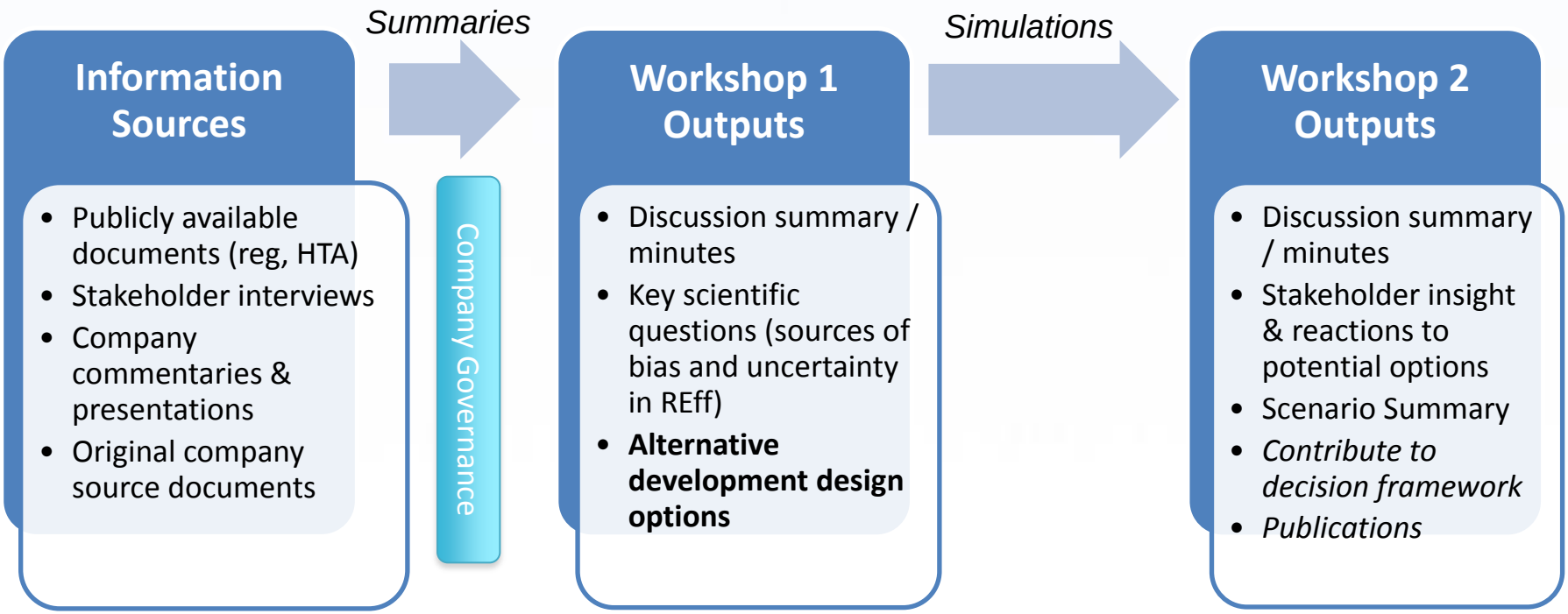
Integration between work packages



Initiative Joint Undertaking under grant
the European Union's Seventh Framework

WP1: Case study approach
Development strategy redesign workshops



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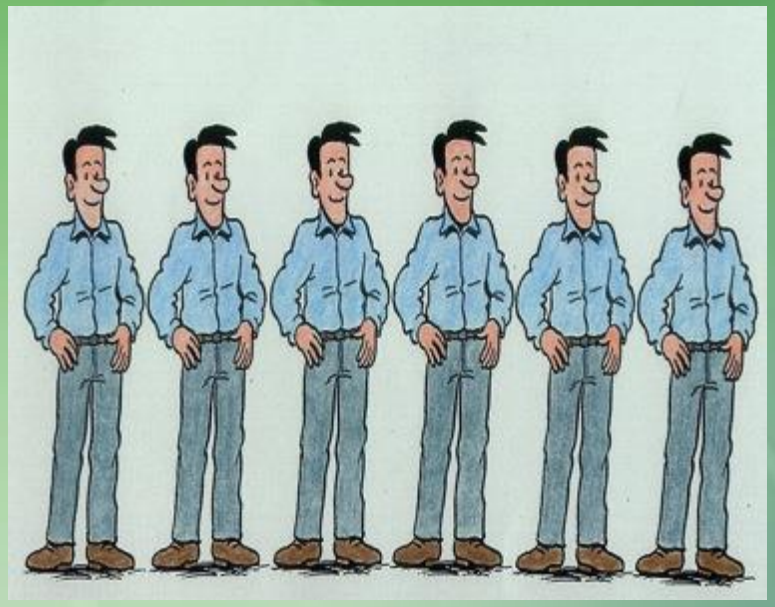
WP 2: better understand the gap (drivers) between efficacy & effectiveness



Clinical trials (efficacy)

Real world (effectiveness)

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Examples of WP2 activities

Identification of Drivers of Effectiveness	Assessment of design parameters and analytical tools to better anticipate effectiveness
Efficacy to Effectiveness gaps (Literature review → Publication)	Phase 2/3 trials that tried to address effectiveness (Literature review)
Exploring case studies in Schizophrenia, Anti-hypertensives, Hogkins Lymphoma,	Use of simulation studies to assess analytical tools used in different types of trials (e.g. pre and post launch clinical trials, observational studies, pragmatics trials)

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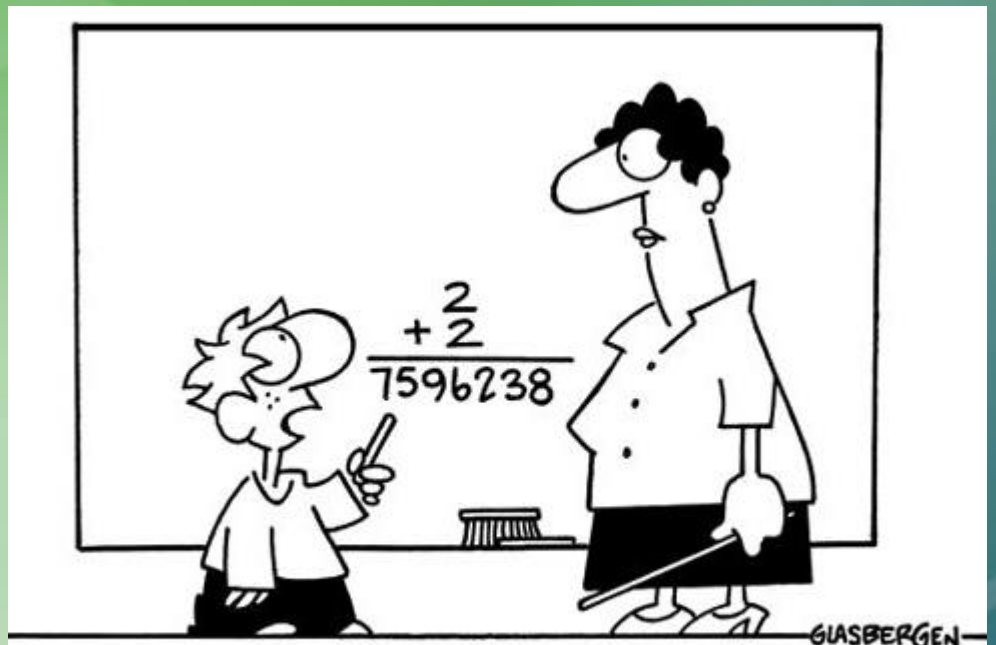
WP3: overcoming practical barriers in undertaking pre-launch RE research.



"In an increasingly complex world, sometimes old questions require new answers."

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WP3 focus on peri-launch relative effectiveness studies and pragmatic trial designs

Aim:

- Identify operational challenges (per design feature)
- Analyse impact on practical feasibility of PT, acceptability, generalizability and bias
- Offer solutions for operational challenges (where possible)

→ Help PT designers to be aware of consequences of their choices & maximize the pragmatic nature of the study design while ensuring operational feasibility

Key activities:

- Literature reviews & stakeholder interviews to identify operational challenges
- Create a structure which describes & links design features – operational challenges – implications & interrelationships in a usable way
- Develop practical solutions to specific operational challenges
- Create a toolbox which brings all knowledge together

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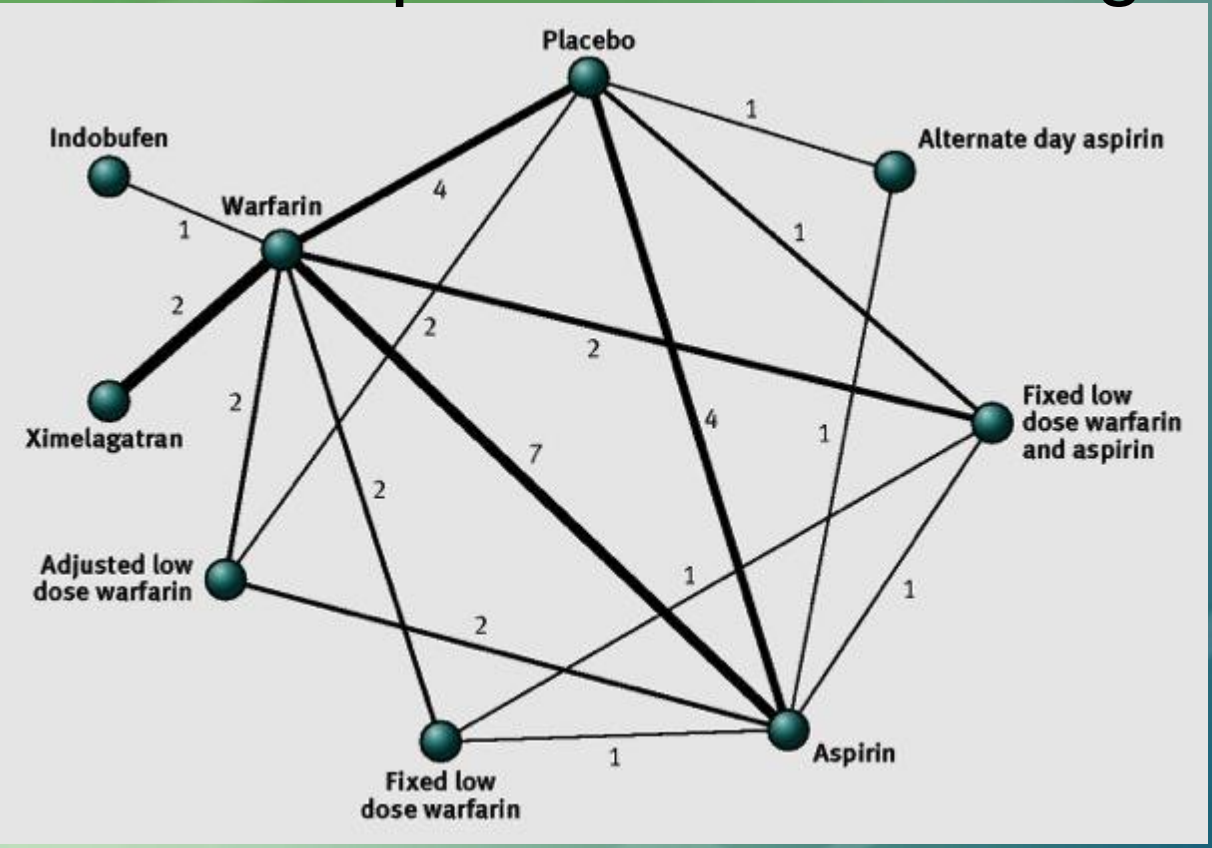
WP4: Promote best practice in evidence synthesis and predictive modelling



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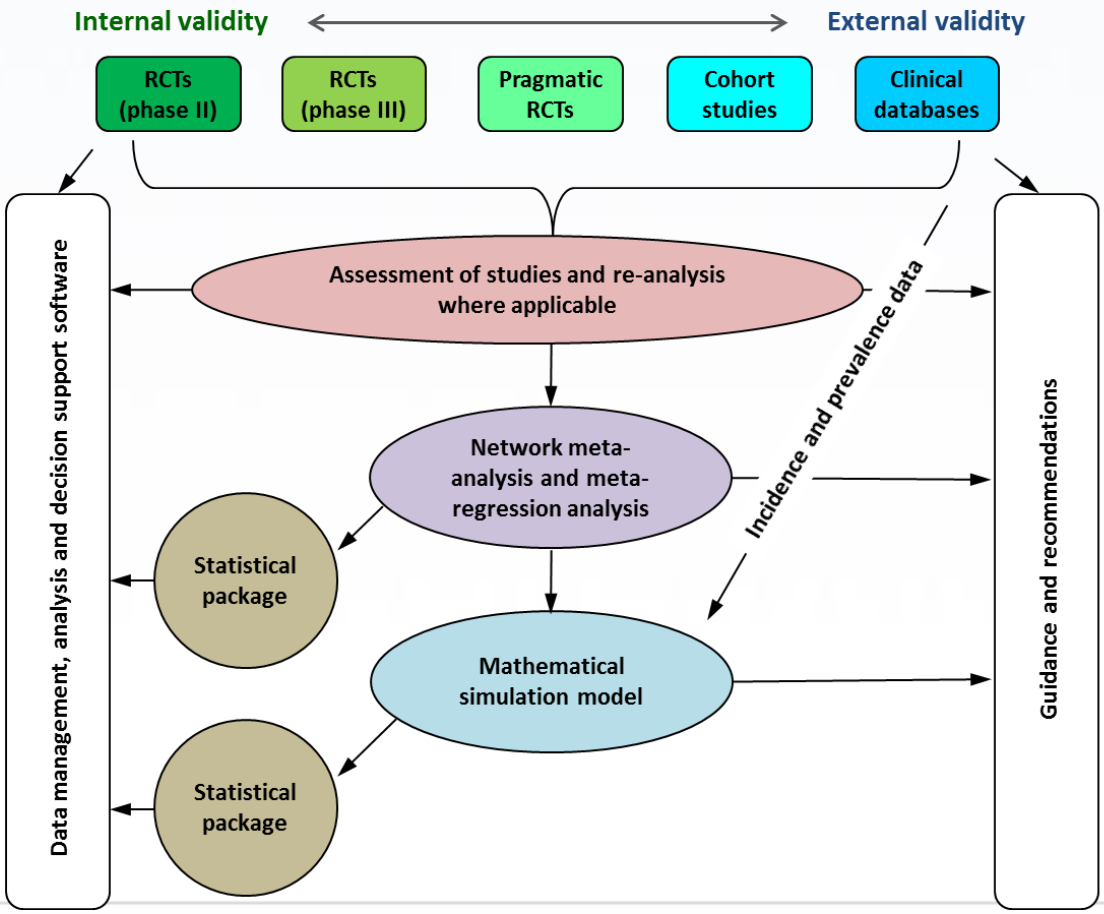
WP4 Developing a predictive model for relative effectiveness

Flow of work



Activities

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

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WP4 Best practices in evidence synthesis and predictive modelling

Evidence synthesis and mathematical modelling for assessing treatment effects across populations: current practice and recommendations

GetReal methods review group

Mark Belger[1], Silvie Bozzi[2], Maximo Carreras[3], Thomas Debray[4], Orestis Efthimiou[5], Matthias Egger[6]*, Christine Fletcher[7], Rolf H. H. Groenwold[4], Sandro Gsteiger[6], Noemi Hummel[6], Gablu Kilcher[6], Brice Kitio-Dschassi[2], Amr Makady[8], Brigitta Monz[9], Karel G.M. Moons[4], Klea Panayidou[6], Johannes B. Reitsma[4], Georgia Salanti[5], Aijing Shang[3], Sven Trelle[6], Gert van Valkenhoef[10]

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WP4 have generated 3 publications of best practices in evidence synthesis and predictive modelling

Methods for network meta-analysis: a systematic review

Orestis Efthimiou[1], Thomas P. A. Debray[2], Gert van Valkenhoef[3], Sven Trelle[4,5], Klea Panayidou[4], Karel G. M. Moons[2], Johannes B. Reitsma[2], Aijing Shang[6] and Georgia Salanti[1] on behalf of GetReal methods review group[1]

Methods for Individual Participant Data meta-analysis of relative treatment effects: a systematic review

Thomas P. A. Debray[1], Rolf H. H. Groenwold[1], Gert van Valkenhoef[2], Orestis Efthimiou[3], Noemi Hummel[4], Karel G. M. Moons[1], Johannes B. Reitsma[1] on behalf of GetReal methods review group[*]

1 accepted and 2 under review with *Research Synthesis Methods*

Mathematical modelling for predicting real world effectiveness from RCT efficacy data: a systematic review

Klea Panayidou[1], Sandro Gsteiger[1], Gablu Kilcher[1], Matthias Egger[1], Maximo Carreras[2], Orestis Efthimiou[3], Thomas Debray[4], Sven Trelle[5], Noemi Hummel[1] on behalf of the GetReal methods review group*

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Examples of methodology being explored in WP4 case studies – evidence synthesis

IPD network meta-analysis: one-stage or two-stage?

Thomas Debray, Ewoud Schuit, Orestis Efthimiou, Jeroen Jansen, John Ioannidis, Karel Moons on behalf of the IMI Getreal Consortium

Background: Individual participant data meta-analysis (IPD-MA) can be conducted to compare the relative efficacy of multiple treatments. It is currently unclear whether a so-called one-stage or two-stage approach is preferred, and which type of model should be implemented.

Methods: We describe and compare 3 approaches for IPD-MA of multiple treatments: a one-stage network meta-analysis (NMA) approach, a two-stage NMA approach using arm-level evidence and a two-stage NMA approach using trial-level evidence.

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Examples of methodology being explored in WP4 case studies – evidence synthesis (cont.)

- To **jointly synthesize** evidence on **relative treatment effects** coming from RCTs as well as observational studies.

- For this we will **assess existing methodology** and **develop new methods** for combining IPD and AD from randomized trials as well as IPD from observational studies in a network meta-analysis (NMA).

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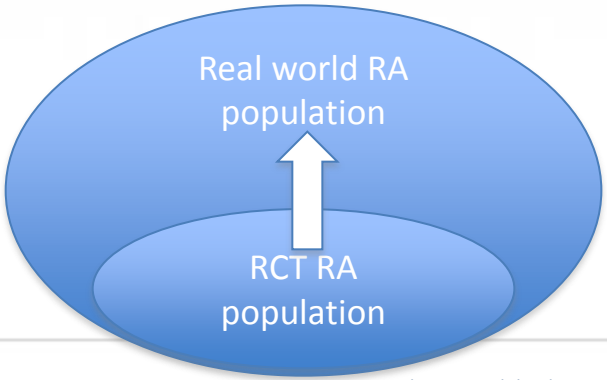
Examples of methodology being explored in WP4 case studies – predictive modelling

- Assessment and description of possible efficacy-effectiveness gaps, i.e. differences in the outcomes observed in clinical practice as compared to randomized controlled trials (RCTs)
- Combination of results from different study and data types, and use of mathematical modelling to predict real-world effectiveness
  - generalization of results from RCTs
  - description and prediction of treatment effects in particular subgroups of patients that may be non- or under-represented in RCTs



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Examples of methodology being explored in WP4 case studies – predictive modelling (cont.)

- Approaches identified in systematic review
  - Micro-simulation model
  - Discrete event simulation model
- «Simple» prediction models, using
  - covariate-by-treatment interactions from RCTs, and
  - differences in covariate distributions in RCTs vs. observational studies,

  to derive treatment effect estimates in real-world population
- Bayesian hierarchical meta-regression model
  - Combine all available evidence in one model: observational and RCT, AD and IPD

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WP4 review of evidence synthesis and predictive modelling software

Meta-analysis user interfaces:

1. ADDIS 1.x http://drugis.org/software/addis1/
2. RevMan http://tech.cochrane.org/Revman
3. Comprehensive meta-analysis http://www.meta-analysis.com/
4. OpenMetaAnalyst http://www.cebm.brown.edu/open_meta
5. MetaXL http://www.epigear.com/index_files/metaxl.html
6. MIX http://www.meta-analysis-made-easy.com/
7. MetaEasy http://www.jstatsoft.org/v30/i07
8. MetaWin http://www.metawinsoft.com/
9. RcmdrPlugin.MA http://cran.r-project.org/web/packages/RcmdrPlugin.MA/index.html
10. ProMeta http://www.internovi.com/prometa-meta-analysis-software/
11. ClinTools http://www.clintools.com/
12. MetaLight http://eppi.ioe.ac.uk/cms/Default.aspx?tabid=3086

Meta-analysis statistical packages:

1. GeMTC R package http://cran.r-project.org/web/packages/gemtc/index.html
2. pcnetmeta R package http://cran.r-project.org/web/packages/pcnetmeta/index.html
3. netmeta R package http://cran.r-project.org/web/packages/netmeta/index.html
4. copas R package http://cran.r-project.org/web/packages/copas/index.html
5. meta R package http://cran.r-project.org/web/packages/meta/index.html
6. metafor R package http://cran.r-project.org/web/packages /metafor/index.html
7. metaLik R package http://cran.r-project.org/web/packages/metaLik/index.html
8. rmeta R package http://cran.r-project.org/web/packages/rmeta/index.html
9. bspmma R package http://cran.r-project.org/web/packages/bspmma/index.html
10. metamisc R package http://cran.r-project.org/web/packages/metamisc/index.html
11. mmeta R package http://cran.r-project.org/web/packages/mmeta/index.html
12. metatest R package http://cran.r-project.org/web/packages/metatest/index.html
13. metagen R package http://cran.r-project.org/web/packages/metagen/index.html
14. PubBias R package http://cran.r-project.org/web/packages/PubBias/index.html
15. selectMeta R package http://cran.r-project.org/web/packages/selectMeta/index.html
16. SAMURAI R package http://cran.r-project.org/web/packages/SAMURAI/index.html
17. extfunnel R pac kage http://cran.r-project.org/web/packages/extfunnel/index.html
18. mvmeta R package http://cran.r-project.org/ web/packages/mvmeta/index.html
19. mvtmeta R package http://cran.r-project.org/web/packages/mvtmeta/index.html
20. metaSEM R package http://r-forge.r-project.org/projects/metasem/
21. dosresmeta R package http://cran.r-project.org/web/packages/dosresmeta/index.html
22. robumeta R package http://cran.r-project.org/web/packages/robumeta/index.html
23. Gmisc R package http://cran.r-project.org/web/packages/Gmisc/index.html
24. ipdmeta R package http://cran.r-project.org/web/packages/ipdmeta/index.html

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WP4 review of evidence synthesis and predictive modelling software

Predictive modeling user interfaces:

1. SIMUL8 http://www.simul8.com/
2. EMMA https://simtk.org/home/emma
3. TreeAge https://www.treeage.com/
4. Arena http://www.arenasimulation.com/
5. ItemSoft Markov Analysis software http://www.itemsoft.com/markov.html
6. Microsoft Excel

Predictive modeling statis tical packages:

1. genSurv R package http://cran.r-project.org/web/packages/genSurv/index.html
2. PermAlgo R package http://cran.r-project.org/web/packages/PermAlgo/index.html
3. complex.surv.data.sim R package http://cran.r-project.org/web/packages/complex.surv.dat.sim/index.html
4. prodlim R package http://cran.r-project.org/web/packages/prodlim/index.html
5. gems R package http://cran.r-project.org/web/packages/gems/index.html
6. simMSM R package http://cran.r-project.org/web/packages/simMSM/index.html
7. simPH R package http://cran.r-project.org/web/packages/simPH/index.html
8. survsim R package http://cran.r-project.org/web/packages/survsim/index.html
9. msm R package http://cran.r-project.org/web/packages/msm/index.html
10. etm R package http://www.jstatsoft.org/v38/i04
11. Epi R package http://www.jstatsoft.org/v38/i06
12. mstate R package http://www.jstatsoft.org/v38/i07
13. timereg R package http://www.jstatsoft.org/v38/i02
14. mhsmm R package http://www.jstatsoft.org/v39/i04
15. ggm R package http://www.jstatsoft.org/v15/i06

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Key deliverables for GetReal

Deliverable
A decision-making framework to aid the design of drug development strategies. This will lay out the different study design options and associated pros and cons from key stakeholder perspectives including acceptability in evidence review processes.
Recommendations will be made for regulatory and HTA policy development.
Guidance and publications on methodologies for conducting and analysing relative effectiveness research pre-authorisation
Guidance and publications on methodologies for using EHR in conducting studies pre-authorisation
Guidance, publications and practical tools and templates to address operational, statistical and ethical issues in conducting pragmatic/adaptive designs pre-authorisation
Guidance and publications on methodologies for conducting data synthesis integrating a wide range of source studies of different types
Software for conducting data synthesis integrating a wide range of source studies of different types
Training and education resources

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Lessons Learned

- It takes time to build relationships and select appropriate case studies
- Case study selection: be specific on diseases or drug class before consortium starts
- Be clear on roles and responsibilities
- Start External Communications at very start of project
- Make better use of governance structure

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Conclusions

- GetReal aims to deliver a framework for decision making developed jointly by Regulatory, HTA and Industry experts
- GetReal aims to provide practical solutions to enable implementation of studies with greater value of information for relative effectiveness assessment
- GetReal will utilise recent advances in methodology to reliably predict effectiveness from available data sources
- GetReal aims to align innovation in evidence generation with evolution of regulatory and HTA processes

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  imi-getreal.eu