Bridging efficacy to effectiveness: The IMI GetReal project

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Innovative Medicines Initiative: Joining Forces in the Healthcare Sector

What is IMI?
Areas of funding

€ 1,945,135,308

- € 711,963,033 Infectious diseases
- € 214,136,227 Drug discovery
- € 182,980,698 Brain disorders
- € 116,880,300 Metabolic disorders
- € 116,287,312 Drug safety
- € 78,225,417 Stem cells
- € 72,710,786 Cancer
- € 70,310,746 Data management
- € 37,966,496 Lung diseases
- € 37,378,289 Education and training
- € 37,601,855 Sustainable chemistry
- € 47,222,783 Vaccines
- € 49,310,000 Geriatrics
- € 55,930,958 Biologics
- € 69,739,527 Inflammatory disorders

Nat Med 2014;20:5.

Source: Innovative Medicines Initiative
CRITICAL QUESTIONS REQUIRING JOINT APPROACH

- 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?

- 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?
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.
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.
Architecture of GetReal

Developing a framework for the assessment of development strategies addressing relative effectiveness objectives

Value of Registration RCTs & IIIb study designs informing RE at launch

Operational aspects of conducting RE research pre-launch

Evidence synthesis and modelling

Project management, Governance, Dissemination
Integration between work packages

WP1
Frameworks, processes and Policies
- Regulatory & HTA experts
- Links to networks
- External links
- Drug Development
- Regulatory
- Health Economists
- Case studies of drug development & review processes

WP2
Development Options
- Trial simulation
  - Use of EHR
  - Trial design
- Use of EHR
  - Trial design
- Patient-level trial data (pre and post authorisation) and observational data;

WP3
Operational Feasibility
- Clinical Operations
  - Statisticians & Epi
  - Patient groups
  - Medical ethics
- Epidemiology
- Case studies of Study design and delivery

WP4 Evidence
Synthesis and predictive modelling
- Analysts
  - Programmers
  - Developers
- Health Economists
- Patient–level trial data (pre and post authorisation) and observational data

WP5
Project Management and co-ordination

External expertise
Industry expertise
Background
WP1: Case study approach
Development strategy redesign workshops

Summary:
- **Information Sources**
  - Publicly available documents (reg, HTA)
  - Stakeholder interviews
  - Company commentaries & presentations
  - Original company source documents

- **Workshop 1 Outputs**
  - Discussion summary / minutes
  - Key scientific questions (sources of bias and uncertainty in REff)
  - Alternative development design options

- **Workshop 2 Outputs**
  - Discussion summary / minutes
  - Stakeholder insight & reactions to potential options
  - Scenario Summary
  - Contribute to decision framework
  - Publications

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

Clinical trials (efficacy)

Real world (effectiveness)
WP3: overcoming practical barriers in undertaking pre-launch RE research.

“In an increasingly complex world, sometimes old questions require new answers.”
WP4: Promote best practice in evidence synthesis and predictive modelling
Developing a predictive model for relative effectiveness

Flow of work

Internal validity
- RCTs (phase II)
- RCTs (phase III)
- Pragmatic RCTs
- Cohort studies
- Clinical databases

Assessment of studies and re-analysis where applicable

Network meta-analysis and meta-regression analysis

Incidence and prevalence data

Mathematical simulation model

Guidance and recommendations

External validity

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
**Key deliverables for GetReal**

<table>
<thead>
<tr>
<th>Deliverable</th>
<th>Details</th>
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<tbody>
<tr>
<td>A decision-making framework to aid the design of drug development strategies.</td>
<td>This will lay out the different study design options and associated pros and cons from key stakeholder perspectives including acceptability in evidence review processes.</td>
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<tr>
<td>Recommendations will be made for regulatory and HTA policy development.</td>
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<tr>
<td>Guidance and publications on methodologies for conducting and analysing relative effectiveness research pre-authorisation</td>
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<tr>
<td>Guidance and publications on methodologies for using EHR in conducting studies pre-authorisation</td>
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<tr>
<td>Guidance, publications and practical tools and templates to address operational, statistical and ethical issues in conducting pragmatic/adaptive designs pre-authorisation</td>
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<tr>
<td>Guidance and publications on methodologies for conducting data synthesis integrating a wide range of source studies of different types</td>
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<tr>
<td>Software for conducting data synthesis integrating a wide range of source studies of different types</td>
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<td>Training and education resources</td>
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The GetReal objectives concern predicting relative effectiveness, but the WP programme will have to define with the EFPIA companies research protocols that remain pre-competitive and it is not intended that GetReal publishes on relative effectiveness of specific drugs of EFPIA companies.

Reviews of past decisions on drug development and study design and drug assessment are to gain insight to advise future drug development; not to criticise past decisions, revise assessments, or make recommendations on launched drugs.
The need for Pharma input

- Participation in workshops and discussion in more detail
- Use a real example as basis for what if scenarios
- Collaborate with reanalysis, novel designs, simulations building from real example
- Share patient-level data for evidence synthesis and modelling
- Response to questions and surveys
• Strong interest in conducting pragmatic trials in IIIb/IV
• Incorporate learning into R&D policy and procedures
• Apply analytical and modelling solutions to studies starting now, reporting in next 1-3 years
• Build strong relationships with GetReal partners in HTA, academia, EMA, EFPIA
• Deliver credible, relevant evidence to inform decision making at time of market authorisation
Current Status – progress after first year

- Conference presence in 2014
  - 25-27 March – EuroMeeting of the DIA in Vienna
  - 18 June – HTAi annual meeting in Washington
  - 19 June – DIA main meeting in San Diego
  - 8-12 November - ISPOR 17th Annual European Congress, Amsterdam

- Draft publications
  - 6 research papers under review
  - 4 abstracts approved

- Case study topics
  - WP1: MS, Met Melanoma, NSCLC, RA (+1 other)
  - WP2: Schizophrenia, MI, AF, Hodgkin’s Lymphoma, Diabetes
  - WP3: Depression
  - WP4: Schizophrenia, Depression, RA, Hodgkin’s Lymphoma

- WP1 pilot workshops in MS
- Health Check carried out, recommendations made to GetReal
Learnings after first year

- It takes time to build relationships and select appropriate case studies.
- Case study selection: be specific on diseases or drug class before consortium starts.
- EFPIA group engagement:
  - ensure senior representatives that can make things happen in their own organisation
  - ensure proactive approach to tasks: sometimes too passive
  - clarity of roles of EFPIA vs academic at the start
- Start External Communications at very start of project
- Make better use of governance structure
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.
Welcome to the GetReal Website!

Launched in October 2013, GetReal is a three-year project of the Innovative Medicines Initiative (IMI), a EU public-private consortium consisting of pharmaceutical companies, academia, HTA agencies and regulators (e.g., NICE, HAS, EMA and ZIN), patient organisations and SMEs.

GetReal aims to show how robust new methods of RWE collection and synthesis could be adopted earlier in pharmaceutical R&D and the healthcare decision making process. The consortium is doing this by:

- Bringing together healthcare decision makers, academics, pharmaceutical companies, clinicians, and other societal stakeholders;
- Assessing existing processes, methodologies, and key research issues;
- Proposing innovative trial designs and assessing the value of information;
- Proposing and testing Innovative analytical and predictive modelling approaches;
- Assessing operational challenges and proposing and testing the impact of solutions;
- Creating new decision making support, and building tools to allow for the evaluation of development programmes and use in the assessment of the value of introducing new treatments;
- Sharing and discussing deliverables with healthcare decision makers, academics, pharmaceutical companies, clinicians, and other societal stakeholders;

For more information:
Visit the GetReal website: imi-getreal.eu
Ask