Making evidence at launch more ‘real world’: pragmatic trials, current developments and operational challenges

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IMI GetReal
Workshop overview

- Introduction into topic – 15 min
- Workshop introduction – 5 min
- Case study work (4 questions) – 40 min
- Plenary discussion of questions & group work – 30 min
Innovative Medicines Initiative: Joining Forces in the Healthcare Sector
The IMI Portfolio

€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

€118,249
Drug kinetics

€20,662,256
Drug delivery

€37,378,289
Education and training

€37,966,496
Lung diseases

€47,222,783
Vaccines

€49,310,000
Geriatrics

€55,930,958
Biologics

€69,739,527
Inflammatory disorders

€70,310,746
Data management

€30,601,855
Sustainable chemistry

€37,378,289
Education and training

Source: Innovative Medicines Initiative

Nat Med 2014;20:5.
Overall aim of IMI GetReal

GetReal aims to show how robust new methods of RWE collection and synthesis could be developed and considered for adoption earlier in pharmaceutical R&D and the healthcare decision making process. This will require companies, healthcare decision makers and other stakeholders to work together to generate a consensus on best practice in the use of RWE in regulatory and reimbursement decision-making.

Alternative evidence generating strategies will deliver more focused research in pharmaceutical R&D, and allow healthcare decision makers to be more certain when providing patients with access to new treatments.
# Public/SME partners

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EFPIA partners

GlaxoSmithKline
Amgen
AstraZeneca
Bayer Pharma
Boehringer Ingelheim
Bristol Myers Squibb
Eli Lilly
F. Hoffmann-La Roche
Janssen Pharmaceutica
Merck KGaA
Merck Sharp & Dohme Corp.
Novartis Pharma AG
Novo Nordisk
Sanofi-Aventis
Takeda Development Centre
Activities of IMI GetReal

1. Collaborating with key stakeholders in medicine development to assess: the acceptability and usefulness of Real World Evidence (RWE), and approaches to the analyses of RWE.

2. Studying the scientific validity of RWE study designs and analytical approaches.

3. Identifying the operational challenges of performing RWE studies early in the medicine development process and developing practical solutions to address these.

4. Identifying and sharing best practice in evidence synthesis and predictive modelling of different types of data to estimate effectiveness of medicines.
Architecture of IMI GetReal

WP2
- Value of Registration RCTs & IIIb study designs informing RE at launch

WP3
- Operational aspects of conducting RE research pre-launch

WP4
- Evidence synthesis and modelling

WP1
- Developing a framework for the assessment of development strategies addressing relative effectiveness objectives

WP5
- Project management, Governance, Dissemination
Results and outputs of GetReal

Results of GetReal
- Better understanding of translating efficacy in effectiveness and knowledge gaps;
- More efficient methods for data synthesis;
- Better understanding of the acceptability of information from real-world evidence approaches;
- Understanding potential barriers and providing potential solutions for successful execution of pragmatic trials;
- Clarity on drivers for decision-making on business cases in companies;
- Raising understanding of decision making processes from different perspectives.

Outputs (examples, not exhaustive)

Tools
- Software to support evidence synthesis (WP4)
- Tools for trial design (WP3)

Frameworks
- Framework for decision making (w links to tools) (WP1)

Networks
- Platform for discussing RWE (research) issues with relevant (policy)stakeholders (all WPs)

Knowledge/insights
- Education and training materials (all WPs).
- Reports & publications (all WPs)
Visit the GetReal website:
imi-getreal.eu
Introducing GetReal work package 3

The context:

The early (possible pre-launch) implementation of research to investigate the effectiveness of medicines in the real world, such as pragmatic trials, can raise many operational challenges.

“We definitely experienced that the willingness to participate decreased the more complex the trial got.” – pharmaceutical industry investigator

Obtaining real-world evidence: the Salford Lung Study

Once you start to implement [a pragmatic study, people start to try and apply the normal rules to a new setting, so: the way we’ve always done it is how we are going to do this now, in this study. And that has created barriers. It is not one specific thing, but the impact on all areas from recruitment to monitoring, to ECRS, all sorts of things and the big challenge is getting people to think outside the box and to let go of the old processes as far as possible, whilst still ensuring obviously patients’ safety and the robustness of the study.” – pharmaceutical industry investigator
Pragmatic Trials (PT)

- **First mentioned** in Schwartz and Lellouch (1967): ‘explanatory’ vs ‘pragmatic’

- **Typical features:**

**Explanatory Trial:**

*Can intervention work under ideal circumstances?*

- High internal validity
- Selective inclusion criteria
- Controlled environment
- Mostly phase II-III
- Focus on treatment per se
- Randomized!

**Pragmatic Trial:**

*Does intervention work in real life?*

- Internal validity + generalizability
- Broad inclusion criteria
- Real world setting
- Mostly phase IV (currently!)
- Focus on tx strategy
- Randomized!
Designing trials that are fit for purpose

Focus on trial design choices which determine the applicability of a trial (not internal validity)

To be used by multidisciplinary team designing trial, makes judgements explicit

Ref: BMJ 2015; 350: h2147 | doi: 10.1136/bmj.h2147
WP3: From the drawing board to the real world

- Design choices strongly influence the operational feasibility and scientific quality of a trial.

- For example:
  - Cost
  - Duration
  - Monitoring requirement
  - Legal/ethical aspects
  - Generalisability
  - Precision
  - Validity
  - Etc.
Where do we face operational challenges in a pragmatic trial design?

Source: GetReal & www.spirit-statement.org
Workshop – learning objectives

- To recognize different design options for pre-launch pragmatic relative effectiveness (RE) trials that aim to better meet HTA needs.

- To identify operational challenges in setting-up and conducting pragmatic RE trials.

- To assess the impact of these design options & their operational challenges on study validity, precision and generalizability and to identify areas of further research needs.
Workshop - setup

- 1 case example
- 4 questions
- 40 min of preparatory work
- 30 min plenary discussion
Workshop – case example

- New oral anti-inflammatory asthma medicine;
- Compare real-world effectiveness to usual care (first line asthma controller) in a pre-launch trial;
- Primary outcome: asthma-control (measured by Asthma Control Questionnaire [ACQ]);
- Include representative population.
Question 1

Study setting:
- Which settings can you choose to conduct this trial?
- Impact on generalizability?
- Impact on (operational) feasibility? (e.g. recruit the sites, get the sites trial-ready etc.)
Study population:
- What are the operational/methodological challenges of incorporating a study population that represents real-world?
**Question 3**

**Intervention & comparator:**
- How can usual care be incorporated as a comparator? (e.g. What is usual care? And how do you handle diversity of treatment?)
- What are the consequences of design choices for generalizability, validity & feasibility?
- How would you supply the drug? What are the options with their advantages and disadvantages?
Question 4

Monitoring/safety:
– Given your answers to the previous questions, what are consequences for monitoring/safety in your pragmatic trial?
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Thank You

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Workpackage 3 of the IMI GetReal project

www.imi-getreal.eu

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