Advancing Evidence Generation for New Drugs
IMI GetReal's Recommendations on Real-World Evidence

Launched in October 2013, IMI GetReal was a three year public-private partner consortium comprising 28 organisations. It included small and medium enterprises, pharmaceutical companies, patient organisations, academia, HTA agencies and drug regulators.

The aims of GetReal were to explore how robust new methods of real-world evidence (RWE) collection and synthesis could be adopted earlier in pharmaceutical R&D and the healthcare decision making process.

The project published various outputs on the use of RWE which are available at www.imi-getreal.eu and rwe-navigator.eu.

The unique nature of the project – bringing together experts from diverse backgrounds and organisations – helped generate important learnings on the use of RWE in effectiveness research. It also enabled the synthesis of recommendations that the consortium considers important to further advance evidence generation for innovative new drugs in Europe.

The GetReal Policy Expert Group[1] identified seven key themes that require attention and actions by stakeholders and policy makers regarding the use of **real-world data** (RWD) and **real-world evidence** (RWE) in effectiveness research for new drugs:

1) Integrity, quality, access and privacy protection of RWD sources

    a. **All stakeholders, including European HTAs, payers, regulators, researchers and the pharmaceutical industry should collaborate to develop and publish minimum requirements for the integrity and quality of RWD sources used to generate real world evidence submitted for decision making.**

> This work should take into account global regulatory activity in this area, including guidance to be developed by the US Food and Drugs Administration, and ongoing European initiatives such as the EMA's initiative for patient registries and EUnetHTA's standards for registers in HTA.

    b. **Regulators, HTAs, payers, researchers and the pharmaceutical industry should collaborate to characterise RWD sources and understand their strengths and weaknesses.**

> Real world data sources such as clinical audit, disease registry, survey and claims data show potential for increased utilisation amongst different stakeholders organisations. Closer communication between industry, regulators, HTA organisations, payers and collectors and depositors of these data to explore the utility of these types of data would help identify barriers that explain current underutilisation, and develop solutions to help overcome such barriers. This includes considerations relating to privacy protection of RWD sources. Funding should be made available to enable these activities.

---

[1] The following were members of the GetReal Policy Expert Group: Bart Barefoot (GSK), Francesca Cerreta (EMA), Sarah Garner (NICE), Wim Goettsch (ZIN), Alicia Granados (Genzyme), Michael Happich (Eli Lilly), Amr Makady (ZIN), Pall Jonsson (NICE), and Rob Thwaites (Takeda).

    c. Characterise barriers to access of RWD.

> All stakeholders – including patients, HTAs, payers, regulators, health care providers, data custodians, and the pharmaceutical industry should work collaboratively to understand the barriers – practical, cultural, and otherwise – to accessing data repositories, including registry data, and to implement solutions to enable effectiveness research to take place with these data. Surveys followed by stakeholder workshops are an effective means to achieving this.

    d. Identify and promote efforts to catalogue RWD sources. The Innovative Medicines Initiative and The European Medicines Agency are doing work in this area and this is an important building block in the agency's RWE strategy.

> Some commercial organisations have also catalogued RWE sources. This work should ideally be consolidated with a smaller set of stakeholders to ensure sustainability.

2) Guidance on RWE study design, evidence synthesis and interpretation in decision making

    a. Industry, HTAs, payers and regulators should collaborate to develop and publish pan-European guidance on RWE study design, evidence synthesis, and interpretation with respect to evidence submitted for decision making.

> The guidance should include case studies to distil learnings on acceptability and usefulness of RWE designs and methods in decision making. This work should take into account global regulatory activity in this area, including guidance to be developed by the FDA and ongoing European initiatives such as the EMA's initiative for patient registries and EUnetHTA's standards for registers in HTA. Priority areas for consideration of guidance development include:
>
>   i. Guidance on the use of historical controls (e.g. from claims data, electronic health records or linked disease registries) to inform assessment of a new breakthrough medicine. For instance when there is no suitable comparator or equipoise to randomize to placebo. Attention should be paid to how early this design can be introduced in asset evidence planning;
>
>   ii. Guidance on using single-arm experimental studies in effectiveness research for exceptional cases when RCTs are not feasible or ethical. This should build on work already done by the European Medicines Agency;
>
>   iii. Guidance on certification of data sources per research standards and mandatory sharing of validated algorithms to define conditions and endpoints in certified RWD sources to increase transparency and quality of RWE;
>
>   iv. Guidance on methods to assess and manage heterogeneity of effects in large distributed studies (many studies will be distributed across data sources/populations to drive efficiency);
>
>   v. Guidance on how to minimise selection bias;
>
>   vi. Guidance on the use of RWD in network meta analyses.
>
>   vii. Assessment of the feasibility and decision makers' acceptability of using individual patient-level observational data in combination with RCT data.

b. **Best practice guidelines on the use of pragmatic clinical trial designs will help to allay uncertainties in the design of future pragmatic clinical trials that include randomisation of patients.**

> Collaborative efforts such as case studies and evidence synthesis from disparate sources will also provide insight in this respect.

c. **The use of social media as a potential source of RWE should continue to be explored.**

> Pharmaceutical companies, regulators, HTA agencies and online resources (such as PatientsLikeMe) are already analysing social media for pharmacovigilance, and in some instances, effectiveness insights. As an example, a study by GetReal indicated that patient-powered research networks could have a role in effectiveness research. We recommend building on these existing efforts by adding in elements of clinical understanding and patient behaviour/preference elements.

3) Standards for decision makers' use of RWE in decision making

a. **Public decision makers, including regulators, HTA bodies and payers should develop and publish policies on their use of RWE.**

> Greater transparency and clarity in how these decision makers ultimately use RWE has the potential to spur and influence data infrastructure investments, the collection and utilisation of high quality RWD, data sharing, and the translation of RWD into relevant and actionable RWE that can improve decision making and patient outcomes.

b. **Acceptability by all stakeholders of RWE could be improved by the development of specific guidelines based on templates set out by existing collaborations such as EUnetHTA, GRADE and the Cochrane Collaboration and would facilitate transparency and broader adoption.**

c. **Learnings from conditional reimbursement schemes in Europe to date should be used to highlight opportunities for using RWE as part of future conditional reimbursement schemes.**

d. **Routine use of large national RWD sources should be considered by all stakeholders including the pharmaceutical industry, regulators, HTAs, payers, clinicians and patients, taking into account requirements for data standards, integrity and quality.**

4) RWE training and education

a. **Specialised skills are necessary to generate high quality RWE and to properly interpret and apply RWE. Regulators, HTA bodies, payers, and the pharmaceutical industry should consider the training and development needs of their staffs and how they will acquire and maintain these skills.**

> The GetReal consortium has developed training programmes which are aimed at addressing various applications of RWD.

5) Broader involvement of stakeholders, especially patients and healthcare professionals, in RWE generation and use of RWD

a. **The role of patients in scientific advice and subsequent decision making should be defined.**

> There is an opportunity for coordination and support actions to facilitate this. True and effective patient involvement in the decision-making process can only be achieved by enforcing strong and well-functioning mechanisms of accountability between patients and decision makers. For these mechanisms to become reality, decision makers should ensure that:
>
>   i. Patients and healthcare professionals are involved at all stages of decision-making processes;
>
>   ii. Patients are regarded as proper research partners rather than mere data sources;
>
>   iii. Appropriate information is provided before, throughout, and following the conclusion of the research process so that patients can be made aware of the outcomes.

b. **Ensure appropriate communication is provided to patients regarding real-world studies.**

> High-quality information builds on clear, easily understandable language. Researchers should clearly explain how RWE studies differ from other, more traditional research strategies, the rationale behind why the research is undertaken, and the nature of the benefits and risks of participation so that patients can make fully informed decisions regarding their participation.

6) Emphasis on a joint (regulatory/HTA/payer) scientific advice process

a. **Assessments likely to rely substantially on non-randomised data should be identified at the earliest possible stage of scientific advice. The relevant agencies should, as part of this process, give an early signal regarding the acceptability of such RWE.**

> The joint scientific advice process is an opportunity to establish in a timely manner that there is an expectation for access to patient level data to be sought.

b. **Joint scientific advice process is an opportunity to incorporate the perspectives of a wider group of stakeholders, especially patients and healthcare professionals, who will be impacted by decisions made at this stage.**

7) Construction of a standing forum and linking with ongoing initiatives

a. **A pan-stakeholder forum should be established to facilitate further discussions on the acceptability of novel RWE study designs and analytical methods.**

> The GetReal consortium has built a strong foundation for stakeholder engagement and dialogue. Continued discussions are essential to further develop understanding of uncertainties associated with effectiveness of new drugs, and to explore how these uncertainties can be resolved. Further funding by IMI would ensure this dialogue continues beyond the duration of the GetReal project.

b. Programs that support the development of policies and methods for using RWD must be sustainable.

Sustainability could be strengthened by including European and non-European agencies and stakeholders in these programs.