IMI1 Final Project Report Public Summary

Project Acronym: GETREAL

Project Title: Incorporating real-life clinical data into drug development

Grant Agreement: 115546
Project Duration: 10/2013 - 03/2017

1. Executive summary

1.1. Project rationale and overall objectives of the project

The objective of GetReal is 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 and secondly, to identify and develop best practice methods that can be used to translate the randomised clinical trial (RCT) data that are generated by pharmaceutical companies for marketing authorisation, in combination with other study data (observational, safety, 'real world' therapy), into reliable and precise estimates of relative treatment effect.

GetReal achieved this goal through:

- the use of case studies to identify where uncertainty in the effectiveness of new medicines was a particular issue for decision makers, by examining data gaps that triggered delays, restrictions or requirements for post-authorisation studies.
- a systematic approach to understanding this "efficacy/effectiveness" gap to identify study design attributes that could alternatively have been incorporated in the pre-authorisation studies.
- addressing operational aspects of conducting pragmatic and adaptive clinical trial designs pre-authorisation, by developing a better understanding of how current methodology and study designs developed and used mainly for post launch trials can be applied successfully to investigational (pre-authorisation) medicines, identifying potential operational solutions to key issues.

1.2. Overall deliverables 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. Specific deliverables include:

- The creation of a shared framework to guide discussions on the inclusion of alternative study designs in medicine development strategies. The objective is to be able to identify options that meet the needs of all relevant parties as a medicine transitions through development stages to appropriate use in the clinical setting, while also increasing the efficiency and/or reducing the cost of the research and development process. This should be achieved without compromising the robustness of the data for decision-making both from a regulatory and HTA perspective.

- Insights and methods to understand how different clinical study designs can inform the assessment of effectiveness and improve the relevance of pre-authorisation drug development studies for real world application.

- A feasibility assessment of alternative study designs with templates, recommendations and guidelines for operationalising pragmatic trials pre-launch. These will be made available for use by R&D organisations to use in clinical operations and to regulatory and HTA bodies to use in scientific advice discussion.

- Best practice methods and guidance for data analysis. Tools for evidence synthesis and predictive modelling of effectiveness in user-friendly software that enables decision makers to apply such analyses in a transparent and reproducible manner. It is envisaged that the methods guidance and tools developed by GetReal will subsequently be used by EFPIA partners, for instance in their submission files for the RE pilots of EUnetHTA, as well as by HTA agencies in their assessment of these submission files.

- Education and training materials on a remote e-learning platform intended to increase knowledge and skills about topics that are at the core of the GetReal project, with a particular emphasis on the connection between methodology development and its practical applications within companies, regulatory agencies and HTA bodies.

1.3. Summary of progress versus plan since last period

WP1 - Developing a framework for the assessment of development strategies that provide evidence of relative effectiveness.

All case study workshop reports have been completed and are now available through the RWE Navigator. The 'RWE Navigator' (https://rwe-navigator.eu) was successfully launched late last year. The RWE Navigator provides publically available guidance on the generation and use of RWE in early drug development and subsequent clinical effectiveness assessments. It also serves as a portal to the deliverables of GetReal. In collaboration with the Massachusetts Institute of Technology (MIT), WP1 also successfully the developed a bespoke simulation software which enables users to simulate the impact of implementing alternative evidence generation strategies. The tool is available from the GetReal website (www.imi-getreal.eu). Work package 1 members have engaged extensively with stakeholders outside the project through a variety of dissemination activities in the form of publications, conference presentations and webinars with the aim of driving external engagement and adoption of the RWE Navigator. The learnings obtained from the work and engagement with stakeholders by WP1 has culminated in the development of RWE Policy recommendations which are available from the GetReal website(www.imi-getreal.eu).

WP2 - Understanding how different pre-authorization clinical studies could inform the assessment of Relative Effectiveness

To better understand the discrepancy in evidence provided by pre-registration studies and data required by HTA bodies, a qualitative review of all pre- and post-registration studies submitted to and assessed by the HAS between 2011 and 2014 has been conducted and the report can be accessed via the GetReal website (www.imi-getreal.eu) or RWE Navigator (https://rwe-navigator.eu). In summary the lack of evidence on effectiveness was found to raise specific concerns, when the uncertainty rested on 1) compliance with the "terms of use" and prescription requirements (e.g., identification and description of the population and prescribers, duration and dosage of treatment,

adherence) and 2) the impact on "morbidity/mortality". Eight case examples, where post-registration studies did not confirm the expected effectiveness of the drug, were selected for further investigation and the key drivers for the efficacy-effectiveness gap described (report accessible via GetReal website (www.imi-getreal.eu) or RWE Navigator (https://rwe-navigator.eu). In summary our recommendations were to 1) utilise epidemiological data (e.g., disease registries) to better define the target population (e.g., with unmet medical needs), and the current medical practice (e.g., "standard of care", treatment patterns) earlier in development, and 2) make pre-authorization RCTs more pragmatic by: recruiting treating physicians (e.g., to involve General Practitioners); including a broader patient population, investigating long-term outcome, by continuing the trial in an open label design.

A comprehensive review of the literature has been conducted to describe the design parameters and analytical tools routinely used to estimate effectiveness before launch. This review describes the PRECIS design dimensions that were the most frequently relaxed in an attempt to make trials more pragmatic and those that were rarely changed (manuscript in submission).

Methods to identify the likely drivers of the efficacy-effectiveness gap ahead of market authorization were developed, including: the use of structured literature review, experts' interviews, and/or data analyses. Those were tested in four case studies (schizophrenia REF, Hodgkin's Lymphoma (manuscript in submission) and diabetes (Ankarfeldt M, et al., Clin Epidemiol. 2017 Jan 23; 9:41-51). The statistical issues raised by (1) the conduct of randomized Pragmatic Trials were assessed (Candish J, et al., BMC Medical Research Methodology, 2017 Jan 31;17(1):17) and solutions suggested, through various simulation studies (dealing with differential refusal rates in cohort multiple RCTs (Pate A, et.al. BMC Med Res Methodol. 2016 Aug 26;16(1):109) and managing heterogeneity in "standard of care" (article in preparation); and (2) the conduct of observational studies just after launch were assessed (i.e., exploring and managing potential channelling (confounding) bias (Ankarfeldt M, et al., Clin Epidemiol. 2017 Jan 18; 9:19-30). Through this work GetReal investigators have also proposed a new "enriched RCT method" which, through the use of predictive modelling, enables the inclusion of a sub-sample of patients otherwise excluded from traditional RCTs to enable RCTs to better estimate effectiveness.

WP3 - Addressing operational aspects of conducting pragmatic / adaptive clinical trial designs earlier in the drug development process, possibly pre-launch

We have completed a comprehensive review of the impact that choices made during the design of a pragmatic trial make with respect to practical implementation, generalizability, validity and precision, as well as ethical & stakeholder acceptability. The outcome of this work has been accepted for publication in the Journal of Clinical Epidemiology as a series of 8 manuscripts describing challenges faced and can be accessed via the GetReal website (www.imi-getreal.eu).

In addition, several manuscripts describing ethical aspects of Pragmatic Trial implementation have been published and can be accessed via the GetReal website (www.imi-getreal.eu). A manuscript describing the perspective on the utility of Pragmatic trials from pharmaceutical companies is currently in preparation.

A software tool Pragmagic (www.pragmagic.eu) has been developed to formally visualize the complex interplay between design choices of pragmatic trials and their operational challenges and impact which is currently undergoing testing by study-teams currently planning pragmatic trials. This will help to further refine the tool and increase its fitness for purpose for the intended users.

WP4 - Promoting best practice in evidence synthesis and predictive modelling of relative effectiveness

The last case study was completed and a report completed which discussed the advantages and limitations of the proposed statistical/mathematical approaches, and give guidance for application of the methods used in this case study.

GetReal has published a number of best practice and recommendations in the field of evidence synthesis and prediction modelling:

- Three publications in Research Synthesis Methods reviewing and summarizing state-of-the art methods for network meta-analysis (NMA), individual participant-level data (IPD) meta-analysis and mathematical modelling to predict effectiveness from efficacy
- Three publications (in Statistical Methods in Medical Research, Statistics in Medicine and Value in Health) applying and comparing methods in NMA including non-randomized evidence, NMA including IPD and predicting drug effectiveness prior to launch, including recommendations on the use of these methods

These recommendations and methodological advances were discussed during a workshop with academia, industry, HTA and regulatory agencies to seek feedback on the new methods explored.

All publications and white papers can be accessed via the GetReal website (www.imi-getreal.eu).

An updated version of the ADDIS software tool (a data management and analytical tool for evidence based decision making in health care), is now publically available (addis.drugis.org).

WP5 - Project Management & Integration

In the final year of GetReal we have spent a significant amount of time on stakeholder engagement and project dissemination activities. Through a series of well attended webinars and stakeholder events, the deliverables of GetReal have been socialised with key stakeholder groups where there have been high levels of engagement both with respect to providing insight to shape the outputs of GetReal as well as driving uptake of the tools and methods generate in GetReal.

Education and Training

Education and training outputs from GetReal have been focused on the course: *Real World Evidence in Medicine Development*. The overall aim of the course is to introduce participants to the topics covered by the GetReal project: the rationale for considering use of RWE in drug development, bridging the gap between efficacy and effectiveness, specific developments in study design and analytical techniques, and how to incorporate these into evidence development programs for new drugs. There is a particular emphasis on establishing a common understanding of the concepts and methods, and connecting these to their practical applications within companies, regulatory agencies

and HTA bodies. Course participants are drawn from a variety of disciplines and organisations, initially prioritising GetReal member organisations.

This is an interactive, online, remote learning course hosted on the Elevate education platform at UMCU Utrecht. Course participants are taken through five course modules (Learning Units) consisting of a blend of various educational activities: web lectures (from leading members of GetReal Work Packages), background reading, individual and group discussion assignments, tests and voting activities or peer feedback assignments and a concluding group Webinar. Course participants are encouraged to use the platform to give feedback, share insights/experience and build on the contributions of fellow students.

Course modules have been pilot tested using participants from GetReal partner organisations, and the full course is now 'ready to go' later in 2017 depending on continuing funding to support course marketing and administration. For the first two years' participation in the course will be restricted to GetReal participant organisations

1.4. Significant achievements since last report

In December, the team successfully launched the 'RWE Navigator' (https://rwe-navigator.eu) a publicly available real-world evidence resource. The RWE Navigator aims provide guidance on the use of real-world data, real world study designs and synthesis of real-world data to a broad range of stakeholders including health outcomes scientists, regulators, payers, physicians and patients.

The RWE Navigator (in addition to the GetReal website www.imi-getreal.eu) has also been designed to signpost stakeholders to outputs and deliverables from the GetReal project, including:

- "TOOLBOX: Methodological Tools and Key Outputs from GetReal WP2" which summarises the methods and tools developed in GetReal for better estimating the effectiveness of drugs ahead of market authorization including the "enriched RCT method" which, through the use of predictive modelling, enables the inclusion of a sub-sample of patients otherwise excluded from RCTs. This approach which has been tested through a simulation study, enhances the ability of RCTs to better estimate effectiveness of drugs (Karcher H, et al. "Optimal design of pre-authorization trials for effectiveness evaluation in schizophrenia", ISPOR 2017).
- PRAGMAGIC (www.pragmagic.eu), a decision support tool that has been developed to formally visualize the complex interplay between design choices of pragmatic trials and their operational challenges; guidance and recommendations on evidence synthesis and modelling to predict real-world effectiveness accumulated through methods reviews, case studies and stakeholder feedback.
- Open-source ADDIS software platform, addis.drugis.org, for evidence synthesis and benefit-risk analysis: Users can import study data sets, e.g. from clinicaltrials.gov, run (network) meta-analyses, meta-regressions (and benefit-risk analyses). The statistical package created in R for the analyses (GeMTC) was also released separately.

- A review and summary of state-of-the art methods for network meta-analysis (NMA), individual participant-level data (IPD) meta-analysis and mathematical modelling to predict effectiveness from efficacy (access via www.imi-getreal.eu)
- A review, applying and comparing methods in NMA including non-randomized evidence, NMA including IPD and predicting drug effectiveness prior to launch, including recommendations on the use of these methods (access via www.imi-getreal.eu)
- Education and training materials on a remote e-learning platform intended to increase knowledge and skills about topics that are at the core of the GetReal project, with a particular emphasis on the connection between methodology development and its practical applications within companies, regulatory agencies and HTA bodies (access via www.imi-getreal.eu)
- SureReal, a bespoke simulation software which enables users to simulate the impact of implementing alternative evidence generation strategies (access via www.imi-getreal.eu)

Throughout the year GetReal hosted a series of 5 webinars to support the dissemination of outputs from each of the work packages the details of each of which can be accessed via the GetReal Website as well as two major stakeholder events attracting participants from academia, industry, regulatory bodies and HTAs from across Europe.

As a consortium GetReal presented 32 abstracts at conferences, have 20 manuscripts in preparation, submission or in press in high impact journals such as Journal of Clinical Epidemiology, Value in Health and Drug Discovery Today.

1.5. Potential impact and main dissemination activities and exploitation of results

As healthcare budgets continue to come under strain across Europe, it is essential that decision makers and healthcare providers are in the position to make informed decisions about the value of any new medicine to the healthcare ecosystem. However, traditionally evidence of real world relative effectiveness is not gathered until many years after market authorisation when there is sufficient observational data available surrounding the use and economic benefit of the medicine. GetReal has provided the methodological approaches and tools as well as the educational support required 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 much earlier during medicines development. This enables pharmaceutical companies to change their approach to drug development and provide the data required for decision makers to better understand the likely real world effectiveness as part of marketing authorisation application.

However, it is recognised that the approach to health technology evaluation varies across Europe. To this end, GetReal has created a map of the organisations involved generally and specifically in activities and projects related to real-world data (RWD) and real-world evidence (RWE) or whose remit included the evaluation of RWD/RWE data. This has been coupled with a review of European stakeholders' policies and perspectives on using RWD for early drug development and clinical effectiveness assessment. This piece of work also incorporated insights from several decision makers on the

advantages, disadvantages, and obstacles encountered when collecting and using RWD. Together this work has enabled the synthesis of policy recommendations that the consortium considers important to further advance evidence generation for innovative new drugs in Europe. Alongside organisations such as EUNetHTA, the outputs from GetReal will play a critical role in this harmonisation process through providing the much needed methodologies, tools and educational support required.

Of particular note GetReal has delivered:

- Evidence synthesis methods including real-world data, both on aggregate and individual participant level, help to get better estimates of relative effectiveness of treatments. This enables policy makers in the health sector, clinicians and individuals to make well-informed decisions regarding treatment prescription and reimbursement. We provide recommendations on the use of these methods that were developed and explored in a series of case studies.
- Methods to predict treatment effectiveness prior-to-launch provide insights on how randomized controlled trial results can be generalized to the real world. This is of interest to drug developers as well as regulatory and HTA agencies to be able to define the target population for the treatment. We explored such prediction methods in a case study on rheumatoid arthritis and give recommendations on their implementation.
- Tools for better estimating the effectiveness of drugs ahead of market authorization including the "enriched RCT method" which, through the use of predictive modelling, enables the inclusion of a sub-sample of patients otherwise excluded from RCTs. This approach which has been tested through a simulation study, enhances the ability of RCTs to better estimate effectiveness of drugs
- PRAGMAGIC. It has been recognized that pragmatic trials can help providing answers in this context however complexities in overcoming the operational challenges have often hampered these efforts. Both WP3's publications as well as the decision tool PRAGMAGIC can help study teams to make well-informed decisions when planning pragmatic trials.
- Brought together within the framework of the RWE Navigator (https://rwe-navigator.eu), the outputs of GetReal are accessible and informative to patients making decisions about their treatment choices, to physicians understanding the relative effectiveness of different treatment options in different patient populations, to regulators and HTAs understanding the effectiveness risk benefit of new medicines and drug developers investing in those medicines with the highest probability of success.

Through a well-structured stakeholder outreach strategy GetReal has engaged with a broad range of stakeholders ranging from patients and clinicians to pharmaceutical employees and public sector employees involved in the assessment of new drugs to ensure that the tools created within GetReal meet the needs of all key stakeholder groups. GetReal members have also conducted a number of dissemination events to raise awareness of the tools encouraging uptake and use. Uptake is critical to the overall ambition of GetReal and long term impact.

Each work package hosted workshops around specific scientific questions bringing together representatives from pharmaceutical companies, academia, patient organisations and representation from HTAs and regulatory bodies from across Europe and the US to share perspectives and contribute the proposed solutions. These stakeholder workshops provided a platform to present our work to a

broad scientific and non-scientific audience, and to tailor the results to the specific needs of the stakeholders.

In its final year GetReal hosted two major public stakeholder events. The GetReal Stakeholder Conference 'Putting Real World Healthcare Data to Work' held on June 17th 2016 in London attracted the participation of approximately 100 individuals including key representatives from EMA, MHRA, HTA (AIFA, ZIN, EUnetHTA), industry, academia and patient organisations (Melanoma Patient Network Europe, Melanome France, WFIP). The purpose being to consult on the utility of the tools being generated and seek input for refinement. The GetReal closing meeting 'Delivering tools for real-world evidence development' held on November 24th 2016 in Brussels, attracted participation from approximately 150 individuals, including participants from the consortium as well as a wide range of external stakeholders, who were able to gain hands on experience with all the GetReal tools as prototypes of all the tools were made available for demonstration purposes.

A series of well-structured webinars were held to introduce the major deliverables of GetReal: An introduction to effectiveness research and navigating real world solutions; the evaluation of operational challenges in Pragmatic Trials; new analytical methodologies & supporting software and white papers; and the education and training courses. The webinars and the Navigator have attracted a high level of interest which is being measured and tracked by the consortium.

In December, the team successfully launched the 'RWE Navigator' (https://rwe-navigator.eu), a publicly available real-world evidence resource. The RWE Navigator aims provide guidance on the use of real-world data, real world study designs and synthesis of real-world data to a broad range of stakeholders including health outcomes scientists, regulators, payers, physicians and patients.

The RWE Navigator has also been designed to signpost stakeholders to outputs and deliverables from the GetReal project.

As a consortium GetReal have presented 32 abstracts, and have 20 manuscripts in preparation, submission or in press in high impact journals such as Journal of Clinical Epidemiology, Value in Health and Drug Discovery Today.

1.6. Lessons learned and further opportunities for research

GetReal had the ambitious objective to embed the use of real-world data and analytical techniques into the heart of research and development and healthcare decision making. It is in the interest of all key stakeholders to better understand how RWE can inform medicine development and utilisation; however, there are few forums available to enable scientific debate and discussion between these groups (industry, academia, regulators, payers, physicians and patients). The GetReal public-private partnership has provided this unique opportunity. Building trust between diverse stakeholders has required considerable time and effort and our success really does reflect the willingness of all individuals on the team to take time to listen and appreciate each other's perspectives.

The following could not have been possible without the PPP platform:

Learning from different perspectives: Getting immediate input from participating stakeholders enabled us to make the topic, content and project results useful for all parties in addition to get a much deeper understanding about each other's views and needs. This helped us to identify long perceived misperceptions and create much needed trust.

Data Sharing: The case studies conducted have required collaboration between industry and academia with an unprecedented level of sharing of both data and insight amongst partners.

Creating mutually beneficial solutions: For example, methods developed within academia were shared with industry and HTA members, and the methods were adapted in a collaborative effort to satisfy the needs and conditions of an industry/HTA environment.

Learnings for future PPPs

An after action review was conducted among members of the consortium.

The majority of feedback was received on aspects of collaboration; team dynamics/ways of working; communication and project management

- The project has provided a generally positive experience in terms of collaboration between the public and private partners, with many opportunities to share knowledge and expertise – it was noted that there are not many platforms of this type, so this was a unique opportunity.
- Communication generally improved during the lifespan of the project but we note that clear goals and deliverables at the start of the project with defined cross-WP interactions will avoid both silo behaviour and duplication of effort.
- A mixed response was received on the project management with different opinions on the same subject e.g. the definition of deliverables. Some felt that deliverables were too loosely defined while others felt too restricted by the description of work. Most agreed that the project was either too ambitious or too short, but in general had too many planned deliverables. The added value of a project management function within each work package, as well as at overall project (EPMT) level, was recognised by the consortium.
- Some partners, both from the industry and public side, had only signed up with a minimum FTE or only had limited expertise in the subject and were therefore not able to contribute to the work package in a meaningful way. Further, especially on the private side, frequent changes in people assigned to the project work were felt as disruptive. We therefore recommend to assess prior to commencement which expertise has to be provided by partners and what FTE is minimum to deliver. A minimum level of FTE requirement should be established for partners.
- While the contact with some private institutions was very intense, some project partners showed little interest in the project work. We recommend that private institutions are encouraged to participate actively in the project meetings and contribute to the project deliverables. In this way, it can be ensured that insights gained and methods developed within the project reach a broad audience.
- Work Package Leaders play an essential role in the success of IMI projects. In addition to their scientific expertise it is important to ensure that these individuals have the expertise, leadership

skills and time required to lead a diverse group to align deliver around a single goal. A role description may be useful for future team to ensure clarity around roles and responsibilities.

- Raise and maintain expectations of project partners through energetic, clear and positive communication, consultation and feedback. Fostering a climate of trust amongst all members is critical to success: good governance, transparency on task division, maintaining dialogue and consensus on project aims are all critical factors.

Further research is recommended in the following areas:

- As an output of GetReal we have developed recommendations for future research and policy options – please see D1.10 – Recommendations for future research and policy options

    Addtional aspects include
    - understanding how well RWE is discussed at early scientific advice e.g. Work with EMA and EUNetHTA to monitor and report from recent and future advice sessions

    - Comparator in pragmatic trials: Development of a decision tree to help pragmatic trial designers define an appropriate comparator (with high generalizability to daily practice) for more pragmatic trials, based on existing guidelines on choice of comparator treatments (EUnetHTA) & systematic review and analysis of studies where a usual care arm has been incorporated to define possible approaches, including pro's and con's

    - Review of currently used strategies to improve recruitment and their effects on the population included in the study and therefore on generalizability of trial results, leading to recommendations on suitable strategies for improving recruitment in pragmatic trials.

    - Further validation and evaluation of the added value of the decision support tool, PragMagic, for designing pragmatic trials. By comparing baseline ideas regarding trial design (i.e. without use of the tool) and awareness of possible operational challenges with trial design and awareness of possible operational challenges after using the tool with multiple study teams, as well as more qualitative assessments of usefulness and additional needs for the study team.

    - Building guidelines involving international experts, on the statistical methods and tools to be used in pragmatic trials, to overcome the following issues, including – but not restricted to – selection bias due to differential refusal rates in cohort multiple RCTs, or outcome measure in heterogeneous "standard of care" arm.

    - Ethical/Legal/Regulatory Expert review to establish conditions for the provision and/or payment of study medication in industry sponsored pragmatic trials. Outcome should be a guideline/Decision Tree for determining who provides study medication, who pays for this and other criteria (including training of personnel).

    - Network meta-analysis (NMA):

        - Research on the properties of methods to obtain a treatment hierarchy (ranking) in NMA.
        - Research on the inclusion of single arms in NMA, in particular, when this is appropriate and how this should be done.

    - Individual participant-level data (IPD) in evidence synthesis
        - Further methodological research on the advantages of IPD in evidence synthesis, and under what circumstances IPD retrieval is likely to be advantageous.

- Evaluation of existing data sharing possibilities for IPD from randomized and non-randomized studies and research on ways how to overcome operational hurdles in the data sharing process.
- Research on how to statistically analyse and include pragmatic trials in (N)MA.
- Further case study work and simulation studies to establish definitive recommendations on how the inclusion of NRS and/or IPD into NMAs and modelling to predict effectiveness can support health-care decision making.