GetReal - Project No. 115546

WP1: Deliverable D1.6 (Multiple Sclerosis Case Study)

Lead Organisations: NICE, Novartis, University of Leicester

The work leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement n° [115546], 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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Executive Summary

Work package 1 of IMI GetReal is facilitating stakeholder dialogue on the role of real-world evidence (RWE) through case studies which focus on relative effectiveness issues in several disease areas. In a series of pilot workshops, stakeholders considered challenges in establishing the relative effectiveness of multiple sclerosis (MS) medicines. Alternative solutions were proposed for using RWE to mitigate these challenges: participants provided views on the usefulness and acceptability of solutions and the potential impact on regulatory and reimbursement decision making.

Three approaches were proposed:

1) supplementing trial results with RWE in network meta-analysis (NMA) to generate relative effectiveness estimates;
2) incorporating RWE in NMA to support simulations informing trial designs;
3) using risk equations derived from RWE to inform risk stratified trial designs.

In the workshops, stakeholders welcomed the proposals as additional options for reducing decision-making uncertainty. However, concerns were raised around potential biases that could be introduced by including RWE in these ways. The inclusion of RWE would most likely be considered as supportive of or adding context to regulatory submissions, but could be more central in HTA decision making and early medicine development if appropriate quality control measures are put in place to mitigate biases commonly associated with non-interventional data.

For the use of RWE to become more acceptable by decision makers, standard methods for data synthesis should be developed, as well as guidelines to ensure transparency in selection of data sources and data synthesis.
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1. Introduction

1.1. GetReal Project and Work Package 1 (WP1) case studies

The overall aim of the GetReal programme is to show how robust new methods of real-world evidence (RWE) collection and synthesis may be adopted earlier in pharmaceutical R&D and the healthcare decision making process. This depends on a shared understanding of relative effectiveness and the ‘early’ use of real world data in the evidence generation process. The objective is for healthcare decision makers be able to assess the added value (in particular the relative effectiveness) of new medicines using the most appropriate evidence base, and for pharmaceutical R&D to develop studies and evidence generation plans that are robust and meet the needs of external decision makers.

Real-world data (RWD): an umbrella term for data regarding the effects of health interventions (e.g. benefit, risk, resource use, etc.) that are not collected in the context of conventional randomised controlled trials. Instead, RWD is collected both prospectively and retrospectively from observations of routine clinical practice. RWD can be obtained from many sources including patient registries, electronic medical records, and observational studies.

The aim of GetReal Work Package 1 (WP1) is to develop a common understanding amongst healthcare decision makers and pharmaceutical R&D of the acceptability and usefulness of innovative development programmes which use real-world data to estimate the effectiveness of new medicines. The use of such data is likely to be most valuable where it is anticipated that relative effectiveness estimates based on conventional (trial-centred) approaches may be challenged by regulatory or reimbursement agencies.

The centrepiece of GetReal WP1 is a series of disease area case studies, consisting of one or two workshops, supporting preparatory work and analyses/simulations, in which:

- ‘Effectiveness challenges’ experienced by previous medicines seeking authorisation and reimbursement are identified and understood (first workshop)
- Potential uses of RWE to address such challenges are considered (first workshop)
- Illustrative analyses/simulations are undertaken to demonstrate these particular uses of RWE
- Results are presented, and the value and acceptability of these analyses is assessed by different decision-makers: pharma R&D, regulators, reimbursement/HTA agencies, including the perspectives of patients and clinicians (second workshop)
• Learnings from the case study are reported separately; they are also used to inform guidance on the use of RWE in medicine development and approval, to be organised within a decision framework being developed by GetReal WP1.
2. Multiple sclerosis case study

This GetReal case study considered disease-modifying therapies (DMTs) for multiple sclerosis (MS) that have recently received marketing authorisation and subsequently gone through health technology assessment (HTA) in Europe. The disease area is complex and the medicines have experienced challenges in demonstrating effectiveness in both the regulatory and HTA processes. The overall aim of the case study was to identify development options that might reduce stakeholder decision-making uncertainty by including RWE earlier (before marketing authorisation) in the clinical development of MS therapies. Ultimately it is envisaged that the output from this case study, presented in this report, combined with that from other GetReal work packages, will contribute to practical guidance in the form of toolsets and a framework that outlines available options for reducing decision-making uncertainty.

2.1. Case study structure

Three workshops were held as part of the case study in May and November of 2014 and in April of 2015 (Figure 1). In the first workshop, participants identified the key challenges of establishing the relative effectiveness of MS therapies and proposed approaches that incorporated RWE to address these issues (an overview of the issues identified and approaches proposed is provided in Table A1 in Appendix A). The most highly ranked issues and solutions, as prioritised by workshop participants (Table A2), were then tested in analytical simulations undertaken by the University of Leicester using publically available clinical data. The preliminary results of these analyses were presented in the second workshop and participant feedback was sought with respect to the usefulness and acceptability of the preliminary results. Based on participant feedback, these analytical approaches were further developed using trial data made available by Novartis and presented in the third workshop before an audience that included stakeholders external to GetReal. While the first two workshops helped shape the analytical approaches ultimately developed in this case study, they were also used to pilot the methods for obtaining stakeholder feedback with GetReal members.

Prior to each workshop briefing documents were prepared and distributed to participants in advance to provide a detailed overview of workshop discussion content and activities. These documents also provided an overview of the disease background and therapeutic landscape and described the methodology and results of the analytical simulations undertaken; they can be found in full in Appendix B.
2.2. Case study focus

In this case study, three analytical approaches that use RWE were proposed as a response to challenges related to the demonstration of relative effectiveness of MS treatments. The effectiveness challenges and the corresponding RWE solutions are briefly summarised below:

Challenge i. There are many available MS treatments but not all available data is used to derive relative effectiveness estimates

Proposed solution: Supplementation of relative effectiveness estimates with RWE in Network Meta-Analysis (NMA)

Network meta-analysis (NMA): An extension of meta-analysis, allowing for the comparison of the relative effects of multiple treatments, both with or without the presence of a common comparator against which all interventions are studied. NMA methods include mixed treatment comparison, indirect treatment comparison, and pairwise meta-analysis.

- This analytical approach uses NMA to support estimates of treatment effectiveness by synthesising available sources of information including RWE. Analytical weighting techniques are applied to the RWE in the network to examine the impact this may have on power and uncertainty.
The approach may be of value to regulatory and HTA agencies by enabling indirect comparisons of relative effectiveness to be made between therapies when the clinical trial network is incomplete (i.e. RWD are used to broaden the evidence base).

Simulations showed that assigning increasing weight to available RWE in a NMA had relatively little impact on point estimates of effectiveness of medicines, but increased corresponding levels of uncertainty. Although the inclusion of RWE in NMA might generally be expected to reduce the uncertainty of treatment effect estimates, it can however also increase uncertainty, as was shown.

**Challenge ii. Real-world data is not routinely implemented in clinical trial design strategies**

**Proposed solution: Trial design informed by NMA and RWE available at various stages of development**

- This analytical approach relies on trial-based modelling techniques informed by effectiveness estimates generated from NMAs that include RCT data and RWE. Analyses at key stages of the clinical development programme of a medicine are done to identify the most efficient designs possible given the available body of evidence.

- The approach is of most interest to Pharma R&D groups who wish to design clinical trials, by understanding the power of alternative designs (with potentially different costs and durations) required to detect effect differences. It may also be useful for regulatory and HTA bodies when faced with the question of whether the observed effects from a Phase III trial reflect treatment benefits in a real world setting (outside clinical trials).

- Simulations showed that inclusion of RWE with a NMA in planning a clinical development strategy could result in a more efficient development programme (e.g. smaller Phase III studies).

**Challenge iii. Uncertainty of treatment effects in subgroups based on pivotal trial populations**

**Proposed solution: Risk stratified trial design using risk equations informed by RWE**

- This analytical approach uses RWE to inform the design of a risk-equation (risk score) that is used to stratify MS patients based on their risk of relapse in simulated trials. The power and uncertainty of the simulated trials can then be used to inform future study design.

- Such a prospective approach could be of value to patients and Pharma R&D by tailoring study design to disease severity and thereby reducing patient recruitment times and study costs. Moreover, patient populations showing particularly robust treatment effects in risk-stratified trials, could be eligible for expedited access to medicines.
Simulations showed that when low, medium and high risk patients from the TRANSFORMS pivotal trial for fingolimod were analysed separately (rather than as a single cohort) the power of the trial was highest in higher risk patients. This could have significant implications for a drug development programme where a high risk population would require a smaller/quicker trial that doesn’t sacrifice uncertainty, while lower risk population could be studied subsequently or in parallel.

A more detailed overview of the methodology and results for each approach can be found Appendix B.

2.3. Case study workshop activities

Case study workshops combined short presentations, breakout sessions and general discussions to assess the impact on stakeholder decision making of incorporating RWE in clinical development. While each of the three workshops evaluated content at different stages of completion, their principal aim was to understand stakeholder views regarding the usefulness and acceptability of the analytical methods demonstrated, and their impact on decision making in medicine development, authorisation, assessment and use. An additional aim of the case study was to pilot the GetReal case study methodology and seek feedback regarding its suitability for engaging with stakeholders and eliciting their feedback. Group discussions focussed on the implications of adopting the analytical approaches in decision-making and groups were tasked with providing insight from their stakeholder perspective on various pre-defined questions relating to the topics at hand. Individual feedback was collected in various ways including flip charts and on ‘Post-It’ notes before being fed back to the general workshop audience in plenary discussions. It was envisaged that by having all group members voice and discuss their opinions, points of consensus could be identified as well as divergent views, which could be fed back to all workshop participants by the group facilitator. Facilitators were assigned and tasked with engaging participants and initiating discussion as well as feeding back output to the rest of the workshop audience. The Chatham House Rule was applied in all workshops, and output collected is not attributed to any one person or institution in the final workshop documents.

2.4. Decision-making perspectives

In order to identify development options that could help to reduce stakeholder decision-making uncertainty, it was important to understand stakeholder views regarding the usefulness and acceptability of the analytical methods and their potential impact on decision making in medicine development, authorisation, assessment and use. To this end, up to three decision-making perspectives were considered for the three proposed approaches, namely:
| Pharma R&D, who make decisions on medicine development including design and funding of evidence generation programmes and constituent studies. | Regulatory organisations at country and above country-level, who provide marketing authorisation based on evidence of product quality, safety and efficacy. | HTA organisations who advise, and in some cases make decisions on reimbursement of new medicines, based on evidence of safety, efficacy and in particular the (relative) effectiveness of new medicines for their populations. |

Regulatory and HTA organisations are working increasingly closely on providing scientific advice to pharmaceutical companies on proposed studies and evidence development programmes, as well as assessment of relative efficacy and effectiveness at the time of submission. Their decisions are also informed by the perspectives of clinicians and patients, whose views are also sought in GetReal case studies.
3. Results

The perspective of each stakeholder group was assessed by evaluating responses to the following questions relating to the use of each approach in the development of MS therapies:

- Could you envisage using this approach in your decision-making process? (Usefulness)
- Are there situations where this approach is particularly useful (or not at all useful)? (Situations)
- What issues might stand in the way of adopting the approach? (Issues)
- How can the implications of this approach best be communicated to engage a broad range of stakeholders? (Communication)

Participant responses to each question are provided below for each of the analytical approaches assessed. NB: not all approaches were examined from the perspective of all the stakeholder groups attending the workshop.

**Approach 1: Supplementation of trial results with real world evidence in NMA to generate estimates of relative efficacy/effectiveness**

In disease areas where numerous treatments are available for a single indication, decision makers must rely on numerous sources of information when undertaking approval/appraisal decisions. In this regard robust synthesis of available data sources is important. This approach explored the role for RWE synthesised in NMA to reduce the uncertainty of efficacy/effectiveness estimates and thereby facilitate decision making by regulators and HTA bodies. NMA is used to support estimates of treatment effectiveness by synthesising available sources of information including RWE.

**Table 1: Summary of stakeholder responses regarding supplementation of trial results with RWE in Network Meta-Analysis (NMA) to generate relative effectiveness estimates**

<table>
<thead>
<tr>
<th></th>
<th>Regulators</th>
<th>HTA bodies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Useful in decision making?</strong></td>
<td>Unlikely</td>
<td>Yes, as long as the addition of RWE into the NMA does not increase decision uncertainty; robustness of the methodology is established; and sensitivity analyses are conducted. NMA is especially useful for multiple comparators in the absence of head-to-head evidence (latter is preferred). Acceptability of this approach varies across individual agencies.</td>
</tr>
<tr>
<td><strong>Situations</strong></td>
<td>Support background on disease area and provide context in regulatory submissions; provide confirmatory analyses of pivotal trials; to support PAES; to generalise pivotal trial findings</td>
<td>Specific scenarios where it is difficult to recruit subjects for RCTs: orphan drugs; breakthrough innovations in areas of unmet need where there is limited prospect of RCT data; demonstrating relative effectiveness, rather than relative efficacy.</td>
</tr>
</tbody>
</table>
Issues / limitations

- Dependence on unverifiable assumptions; bias associated with RWE

Methodology: the approach is relatively untested and needs further validation

Data: quality of RWE remains concern and the introduction of bias could be an issue; transparency is needed both in selection of studies/data and the application of the analytical methods

Practical: some HTA bodies need additional technical knowledge in order to appraise these types of data.

Communication / adoption

- Develop standards; improve transparency of methodology; ensure assumptions are explicit

- Improve transparency of methodology and ‘user-friendliness’; develop pan-European guidelines and disease specific models

PAES = post authorisation efficacy studies. NB: Representatives of pharma R&D were asked to focus on approach 2.

Perspective of regulators

Usefulness

Participants noted that the decision making process of regulators is different from that of Pharma R&D developers and HTA agencies. For this reason there were some reservations about how useful this approach would be in a regulatory setting, in which the focus is on efficacy rather than effectiveness. It was mentioned that while the approach may have some intrinsic utility for pharma R&D, for example when deciding whether their trial designs are sufficiently powered, this is beyond the scope of the decision making that regulators would undertake during the review of a regulatory submission. It was also felt that more discussion about the specific type of RWE used in this approach would be required.

Situations

Arguments were put forward for opportunities where this approach could potentially add value to decision-making by supporting and providing context to a regulatory submission:

- Support data on the epidemiology and background of the disease
- Strengthen effect estimates in rare diseases
- Improve effect estimates in disease subgroups
- Confirmatory analyses of pivotal trials
- Support extrapolation of effects observed in pivotal trials
- To support Post-Authorisation Efficacy Studies (PAES)
- Generalise findings from pivotal trials

Issues

There was concern that in general the approach relied on assumptions that were unverifiable and additionally would be subject to the same biases generally associated with RWE studies.
This in turn would increase uncertainty rather than reduce it. It was felt that standards would have to be set in place before the method would be seen as an acceptable aid in stakeholder decision-making.

Communication

It was felt that more work would be required before the results of this type of approach could be beneficial in a regulatory decision-making context, and importantly the process would have to be transparent with all the assumptions stated clearly. The use of a framework similar to the CONSORT Statement could help to improve transparency and deliver required information on the quality of the studies synthesised in the network.

Perspective of HTA bodies
Usefulness

A range of views, from sceptical to favourable, were expressed by the participants regarding the acceptability of incorporating RWE in NMAs. The main reservation concerning this approach related to the fact that there is no accepted methodology yet for incorporating RWE in this way. It was felt that NMAs have inherent problems and uncertainties, and that incorporation of RWE, with potential biases, compounded the issues and reduced confidence in the results. Participants expressed the view that NMAs have a role in disease areas with multiple comparators where head-to-head comparisons are not available. The approach of incorporating RWE in the data synthesis was supported by some participants in situations where limited RCT data are available, such as in orphan disease areas, and others indicated that there could be advantages of including RWE in this way as the results could better reflect real-live relative effectiveness, rather than relative efficacy. It could also be useful for ranking of treatments based on absolute effect estimates. In any case, the impact of introducing RWE in this way should be assessed by means of sensitivity analyses, which should be pre-specified and hot post-hoc. Participants were in agreement that transparency around methodology and selection of source data/studies is needed, and further demonstration of the robustness of the approach is required.

Situations

The approach could be useful in situations where there are no RCT data available or where there are multiple comparators or differences in best standard of care across jurisdictions. Specific scenarios could be situations where it is difficult to recruit participants in RCTs; for orphan drugs; and for breakthrough innovations in areas of unmet need where there is limited prospect of RCT data. This approach could also potentially reduce decision-making uncertainty when pivotal RCTs are not generalisable to the populations of interest. The approach may also
be useful for treatment ranking, rather than demonstrating relative efficacy. Guidance is needed when NMA is applicable. Some participants expressed preference for incorporating RWE in NMAs only when no RCT data are available, rather than as an add-on where RCT data are readily available.

Issues

Issues raised by participants concerned data quality, methodology and practical issues. On data quality, the use of observational data could introduce bias, for instance selection bias and/or publication bias. Increased heterogeneity of studies may also widen the confidence intervals for RE estimates, leading to a limited value for decision making or rendering the approach unusable. Participants stated that an understanding of the quality of the source evidence to be included in the NMA is required, and in particular quality checks of the observational data ultimately used would be necessary. Appropriate endpoints in the real-world studies also need to be available in order for this option to be viable. On the issue of methodology, participants felt that transparency was needed regarding the methodology and the assessment of its appropriateness for use in a particular situation. The development of an agreed standard method is required. The approach may also be limited by practical issues, such as the additional time required to conduct the data synthesis and for HTA bodies to scrutinise the application of the method and the results. Participants also expressed a view that the required experience and skills to apply/assess this approach may be lacking in some HTA agencies.

Communication

It was felt that the approach has to be made more ‘user-friendly’ as it is too technical and not sufficiently transparent. There is however an appetite for development of disease-specific analytical platforms (for NMA) that could be used across jurisdictions. The development of specific guidelines based on templates set out by existing collaborations such as EUnetHTA, GRADE and the Cochrane Collaboration could facilitate transparency and broader adoption. More emphasis should also be placed on explicitly indicating how RWE contributes to the effectiveness estimate as part of the expanded NMA. In terms of impact on the wider set of stakeholders, it was felt that the approach has some potential to provide patients and clinicians with additional information on effectiveness when used for ranking treatments based on absolute treatment effects.
Approach 2: Use of NMA including real-world evidence to support trial design at different stages of development

Traditionally pharma R&D has focused on designing pivotal trials to meet the criteria necessary to gain regulatory approval. This has generally meant the exclusion of real-world data during early development planning in favour of using more controlled sources of information acquired through interventional programme designs. However, with the growing need to demonstrate clinical effectiveness on the road to reimbursement, pharma R&D has had to reconsider the approach it takes in the early stages of programme development. This approach attempted to facilitate early development programme planning and improve trial efficiency by tapping into the existing body of RWE available prior to the design of a pivotal trial.

Table 2: Summary of stakeholder responses regarding use of NMA including real world evidence to support trial design at different stages of development

| Pharma R&D |
|-----------------|--------------------------|
| **Useful in decision making?** | Yes – programme planning; ‘sanity check’ on traditional approaches |
| **Situations** | Limited evidence base or no head-to-head RCT data available; when differences in effects reported by RCTs and RWE is known or suspected |
| **Issues / limitations** | Availability of RWE at design stage; in MS differences in endpoint definition and measurement of relapse over time and between RCTs/RWE studies; demonstration of efficacy and safety in regulatory submission is still the leading driver of trial design |
| **Communication / adoption** | Gradual buy-in by pharma R&D (NMA alone, NMA with RWE, then use in trial simulation) required; pitch as a decision support tool for pharma R&D groups; case studies: proof of principle and discussion of context (e.g. disease area issues); address early, possibly in Scientific Advice but as part of a clear overall evidence generation strategy; potential of approach to address issues in trial design other than those related to relative effectiveness |

Perspective of pharma R&D

Usefulness

From a development programme planning perspective, this approach was considered useful as a “sanity check” for traditional analyses, which could add value by increasing the efficiency of a development programme. Similar trial modelling approaches are already implemented on a smaller scale by pharma R&D, and the approach demonstrated just expands upon those strategies. Some concern was expressed about the credibility of what is currently done – i.e. the potential for more rigour to be used in trial planning (especially for big investment...
decisions). Nonetheless, expanded implementation of the approach was considered as both needed and feasible in the current pharma R&D landscape.

Situations

Several situations were cited during group discussion in which this approach could add value to development planning:

- When little or no head-to-head RCT data are available for the medicine of interest, but data (RCT and/or RWE) are available for appropriate comparators
- In crowded markets with many available choices of medication allowing for a large network to be developed
- When there is a known/suspected difference in reported effects between the available RWE and RCT data

Issues

As this approach inherently relies on RWE to inform trial design, the availability of RWE studies at the design stage is a key limiting factor for its implementation - especially for first in class medications for which appropriate comparators may not exist. In MS there are differences in the definition of endpoints and the reporting of relapses between RWE and RCT studies. It is known that reported frequency of relapse has reduced over time in clinical studies (for instance when looking at placebo arms over time), leading to difficulty in comparing older trials (subjects receiving interferons and glatiramer acetate) and newer ones (subjects receiving fingolimod, for example). This is mainly due to changes in diagnostic criteria, evolution in the stringency of relapse definition, and overall awareness of MS leading to earlier diagnosis. These issues challenge the usefulness of RWE in this context. Lastly, it was acknowledged that while this approach may improve trial efficiency (to deliver RE estimates), this may not be a compelling argument for use of the approach in Pharma R&D, which is still very much driven by meeting the efficacy and safety criteria of regulators.

Communication

While it was acknowledged that such an approach could add value to early development planning, it was generally felt that in order for adoption to take place, buy-in from external stakeholders aware of the benefits and risks of the approach would be crucial. Achieving buy-in should be phased to focus first on the acceptance of NMA methodology itself to support decision making, then on the use of RWE in NMA, before (ultimately) the trial simulation approach could be implemented more routinely in Pharma R&D decision making. Within Pharma R&D, internal demonstrations of the approach would be necessary, the focus being on its use as a decision support tool for use during development planning stages. Information regarding the approach could be disseminated through case studies, allowing for proof of principle and context-specific issues. If used to define trials there may be some value in
addressing this early with external decision makers (for instance in scientific advice), but as part of a clear strategy of evidence development (including how to ‘bridge’ trial results to specific HTA populations). The approach has potential to address issues in trial design other than relative effectiveness.
**Approach 3: Risk-stratified trial design informed by risk equations using real-world evidence**

A commonly cited effectiveness challenge for several recently appraised MS therapies is the uncertainty of treatment effects in subgroups derived from pivotal trial populations. These subgroup analyses are intended to position therapies for more aggressive forms of the disease but as a result of their small size and post hoc nature are often criticised by regulators and HTA bodies alike. This approach attempted to use RWE to design a risk equation that would inform risk-stratified trials *a priori* using observational data, thereby mitigating some of the uncertainty associated with *a posteriori* subgroup analysis.

**Table 3:** Summary of stakeholder responses regarding risk stratified trial design using risk equations informed by RWE

<table>
<thead>
<tr>
<th></th>
<th>Pharma R&amp;D</th>
<th>Regulators</th>
<th>HTA bodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Useful in decision making?</td>
<td>Yes - early development planning; reducing trial burden</td>
<td>In certain situations – but more information required</td>
<td>Yes, especially where RWE allows incorporation of clinically important endpoints</td>
</tr>
<tr>
<td>Situations</td>
<td>Where targeting of novel therapies is accepted as essential; natural history well understood; 2nd line treatment development planning</td>
<td>Phase II study design; differential treatment effects</td>
<td>Design of adaptive pathways; trial design for orphan diseases with high heterogeneity</td>
</tr>
<tr>
<td>Issues / limitations</td>
<td>No clinical consensus on meaning of ‘high-risk’; risk of leaner dataset for regulatory submission; commercial threat</td>
<td>Dependent on IPD; validation of risk profiles; implications of assumptions used</td>
<td>Clinical buy-in for risk factor selection; generalisability; relevance of RWE (based on older medicines) to newer medicines may be limited</td>
</tr>
<tr>
<td>Communication / adoption</td>
<td>General lack of awareness; case studies evaluating stakeholder impact</td>
<td>Improved transparency; reduced methodological complexity; increase awareness</td>
<td>Predefined protocol; transparency</td>
</tr>
</tbody>
</table>

*IPD = independent patient data*
Perspective of pharma R&D

Usefulness

The risk-stratified approach was regarded as an attractive and useful strategy for early development planning and for reducing trial burden, as well as a means of identifying added value in the current healthcare system. The approach could provide pharma R&D with an evidence-based decision-making tool to inform the planning of a potential development programme. This could entail scenario analysis in which different risk factors and outcomes would be simulated prior to executing an actual development programme thereby contributing to more efficient trial designs with reduced recruitment times and trial sizes. It was generally felt that such decision-making strategies are currently underutilised in pharma R&D development planning and should be encouraged.

Situations

Acknowledging the large number of available disease-modifying therapies available in MS and a high level of understanding available about risk factors and natural history of the disease, some participants indicated that risk-stratified trial design is likely to be useful in targeting new therapies, especially for aggressive forms of MS. Ideally, the approach should be implemented in all pharma development programmes (maybe even as a first priority in programmes that involve large investments). It was mentioned that the approach could add value to development planning where a new medicine is not suitable for first-line treatment but could be targeted to patients with more aggressive disease as a second-line therapy.

Issues

In the simulations demonstrated at the workshop a subgroup of patients were identified as having a ‘higher risk’ of relapse. Group discussion suggested that there is currently no clear consensus on what a ‘high risk’ group means in MS. It was also felt that trials relying on a reduced population of risk-stratified patients might deliver a ‘leaner’ dataset for regulatory submission, which has the risk of not providing sufficient safety data for regulators on which to base their decisions regarding marketing authorisation. Relying on smaller patient groups for regulatory submissions with a more narrowly defined indication was also flagged as a potential commercial threat to Pharma, where broader patient populations would be ruled out, however this threat could be mitigated in iterative licence approach, such as in adaptive pathways.

Communication

It was felt that there is a general lack of awareness within pharma R&D of using this approach in development planning, and sufficient time and resources would have to be invested before it could be implemented routinely. Communicating the value of this approach to stakeholders would is likely to be best achieved through case studies evaluating
the method and testing the impact of the outputs on stakeholders. Patients and their treating clinicians may also benefit from *a priori* risk-quantification offered by this approach offers, compared to *post-hoc* subgroup analyses frequently undertaken to position MS treatments for more aggressive disease indications at regulatory approval. Before adoption of the approach in routine Pharma R&D development planning, the implications from a commercial perspective would also have to be considered.

**Perspective of regulators**

**Usefulness**

It was acknowledged that this is a useful approach in certain circumstances. As far as subgroup analysis is concerned, it was felt that the specific method used to derive patient subgroups is less important than the clinical validity and clinical relevance of the subgroup itself. Ultimately, the key to deciding whether an approach is useful to regulators and developers should be driven by whether it helps to provide sufficient safety information on which to base marketing authorisation.

**Situations**

The approach was suggested as being potentially useful in contributing to Phase II study design when a published risk equation is already available. It was suggested that risk stratification based on observational data could provide further evidence of effect modifiers. Furthermore, given the large number of medicines available for similar MS indications, class effects exist and stratifying populations based on disease risk/severity could provide decision makers with more certainty as to differential treatment approaches that could be considered in discrete subpopulations of patients.

**Issues**

In order to derive the risk equation used to stratify patients, the approach as demonstrated at the workshop depended on the availability of individual patient data (IPD). It was felt that some clinical validation of the derived risk profiles would be required as they might differ from established profiles already identified for existing medicines as outlined in regulatory documents (for instance in the EPARs). Because MS is a very heterogeneous disease, more information would have to be specified in regulatory submissions regarding the factors that might drive the clinical effects defining each risk stratum should the approach be adopted. In the example used in the workshop, results were based on the assumption that each defined risk stratum maintained a constant treatment effect: more testing would be required to determine the implications of this assumption on estimates of efficacy.

**Communication**
It was felt that the approach could be communicated to stakeholders on the basis that by focussing on a risk-stratified population the benefit-risk balance of a medicine with potentially severe side-effects would be more favourable in high-risk patients with severe forms of the disease. Before such an approach could become mainstream it would have to be made more familiar to stakeholders by improving the transparency and reducing its inherent complexity. It was suggested that building awareness of how and why the method was developed could help build stakeholder understanding.

**Perspective of HTA bodies**

**Usefulness**

Comments made by participants related to the general use of risk stratification, rather than using RWE to inform risk equations. It was mentioned that the concept of using risk-defined subgroups is not something new and is employed already in HTA and by Pharma where trials enrolling high-risk patients are developed. However, using RWE could be a useful starting point for piloting adaptive pathways in which the determination of risk would not be constrained by the exclusion criteria of RCTs. In the context of an adaptive pathway, high-risk patients could be recruited first and lower risk patients focussed on in subsequent or parallel studies. It was also suggested that the approach could be beneficial as a tool used to support early Scientific Advice discussions during early medicine development.

**Situations**

It was suggested that such an approach could add value to designing adaptive pathways particularly for populations with diseases for which there is currently a high unmet therapeutic need. Individuals most likely to benefit from the treatment could be exposed first, and any potential benefits could be passed on to lower-risk patients in subsequent studies. Such an approach would also be useful for making reimbursement decisions based on risk-sharing schemes, including coverage with evidence development. It was felt that the approach would be particularly suitable for designing trials in rare diseases with high heterogeneity.

**Issues**

The main limitation raised for this approach related to selection of the endpoints used ultimately to derive the risk equation. Participants enquired to what extent buy-in from the clinical community had been achieved regarding the selection of endpoints (in the MS example presented), and whether consensus could be achieved in this respect. Selected endpoints need to be of clinical relevance to be useful in risk stratification; some participants proposed that endpoints from observational studies could be useful in this regard. It was felt that in general effectiveness estimates relating to one risk group cannot
be extrapolated to other risk groups. The quality and relevance of RWE (based on older treatments) for applicability to studies of newer medicines may also be limited.

Communication

In order to facilitate the implementation of this approach in routine decision making, it was stated that a pre-defined protocol would have to be established, with input and acceptance by both regulatory and HTA bodies. Having achieved this, early dialogue among stakeholders on how the approach could best be implemented in study planning and design would be essential in order for value to be added further downstream in the development programme i.e. in regulatory and HTA submissions.
4. Conclusions

This case study provided a platform on which stakeholder perspectives regarding the use of RWE to reduce decision making uncertainty in the development and assessment of MS therapies could be evaluated. Being the first case study undertaken by Work Package 1, it also provided a means of testing workshop methodology and identifying the challenges of bringing together often disparate stakeholder groups which could be applied to subsequent case studies in this series. This section summarises the key conclusions identified regarding the use of RWE in an MS-decision making context followed by some general learnings related to undertaking a collaborative project of this nature.

4.1. Learnings regarding the analytical approaches evaluated

1. Multiple sclerosis specific observations on the use of RWE:

MS is a disease area that lends itself to the use of methodologies that can make use of the existing body of MS evidence to inform trial design and improve estimates of relative effectiveness. Numerous treatments are currently available for MS and the synthesis of existing real-world data in network meta-analysis could benefit relative effectiveness estimation in HTA submissions. Synthesis of effect measures for existing treatments can also aid pharma R&D in preliminary trial modelling and design.

Acknowledging the available knowledge about risk factors and the natural history of MS, risk-stratified trial designs informed by risk-equations derived from RWE parameters could be useful when targeting new MS therapies, especially for aggressive forms of MS. These prospective, risk-stratified approaches could also reduce the uncertainty often encountered during HTA assessment of MS therapies by replacing post hoc subgroup analyses.

These analyses use RWE already available in the form of extensive patient registries in many countries where MS prevalence is high. However, for these approaches to be feasible, the differences in endpoint definition and the measurement of MS relapses over time, as observed between RCTs and RWE studies, would have to be resolved.

2. General recommendations regarding use of RWE:

While the workshop’s key focus was on evidence synthesis in MS, more general conclusions on the use of RWE were also identified. RWE could be useful in specific scenarios where it is difficult to recruit subjects for RCTs; for breakthrough innovations in areas of unmet need where there is limited prospect of RCT data; for demonstrating relative effectiveness, rather than relative efficacy, and; in situations where RWE allows for the incorporation of clinically important endpoints. Of importance, it was demonstrated that the targeted use of RWE by pharma R&D could improve early development planning and reduce trial burden.
Importantly, RWE would only facilitate stakeholder decision-making and reduce uncertainty if the robustness of the methodology used was established and sensitivity analyses were conducted. All stakeholders indicated that the quality of the RWE ultimately used in analysis remains a concern and the introduction of biases could be an issue; therefore, transparency is needed both in selection of studies/data and the application of any analytical methods. Moreover, while novel development strategies that could mitigate common relative effectiveness issues were the focus of this workshop, participants echoed the fact that demonstration of efficacy and safety in regulatory submission is still the leading driver of trial design.

3. Recommendations related to methodology (network meta-analysis):  

It is conceivable that these RWE-incorporating strategies could be adopted for technologies in different disease areas. RWE in NMA would be useful when done early in development to provide extra information on effectiveness differences when planning new trials; and when considering stratification by risk or other factors. Moreover, synthesis of RWE in this manner could provide extra information on relative effectiveness at launch when there may be insufficient evidence on specific outcomes because RCTs have not included them or it is not feasible to undertake them using an interventional approach. NMA would be especially useful for deriving effectiveness estimates in other disease areas in which multiple comparators are available but head-to-head evidence is lacking. The acceptability of such methodology would depend on whether issues with NMA in general (study selection, heterogeneity etc.) would be compounded by including RWE.

In this workshop pharma R&D and HTA bodies were most optimistic regarding the potential incorporation of the methodology in their decision making processes depending on the disease area or issues being raised. However, from a regulatory perspective the methodology would likely contribute to supporting RCT data or adding context to regulatory submissions.

The workshop suggested a phased approach could be implemented to achieve greater acceptance of the methodologies evaluated here. Focus should initially be on the acceptance of NMA methodology itself to support decision making, then on the use of RWE in NMA, before (ultimately) the trial simulation approach could be implemented more routinely. Acceptability by all stakeholders 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. More emphasis should also be placed on explicitly indicating how RWE contributes to the effectiveness estimate as part of the expanded NMA.
4.2. Learnings regarding workshop logistics and cross-collaboration

The following points were collected during the course of the case study and may be of benefit in the organisation of other cross-collaborative projects in which diverse stakeholder groups are brought together.

**Incorporation of stakeholder perspectives:** Overall the workshops were well received by participants having a good balance of short presentations and group and plenary discussions that engaged the audience well and led to valuable feedback. In the earlier workshops, however, many participants were of the opinion that the missing perspective was that of the clinician. It was understood that in these early workshops invitations were limited for logistic reasons, but that in the ultimate workshop study clinicians would be present to offer their insight.

**Workshop briefing materials:** Briefing packets were prepared and circulated to workshop participants prior to each workshop to provide background on the technical details of discussion and the order of events on the day. Early versions of the briefing document, although concise and well structured, were considered too technical by some participants and an attempt was made to structure subsequent versions in a manner that would be generalizable to a broader stakeholder audience. Moreover, to provide a better balance between the technical and programme aspects of the case-study, it was suggested that a technical forum or a webinar could be held prior to the final workshop. The forum/webinar would focus on the technical issues related to the simulations and would be open to anyone interested. The University of Leicester group hosted such a technical forum a few days prior to the final case study workshop and received positive feedback from attendees. Similarly, an introductory teleconference was organised following the technical webinar to bring external workshop invitees who may not have been familiar with the GetReal project up to speed prior to the workshop.

**Workshop logistics:** Overall, participants agreed that the workshop venues were suitable and the meeting was logistically sound. Experimentation with different discussion formats in breakout sessions such as the ‘World Café’ approach worked well but it was mentioned that discussions were more general than the questions that were actually posed during the breakout sessions. Due to administrative aspects of workshop organisation such as the procurement of confidentiality agreements from external invitees, it is suggested that at least two months prior notice is given to external invitees before the date of the workshop.
### APPENDIX A

**Table A1:** Challenges contributing to uncertainty of relative effectiveness estimates for MS therapies and solutions as proposed by workshop participants, May 15, 2014.

<table>
<thead>
<tr>
<th>Challenges and proposed solutions for MS treatment development</th>
<th>Considerations for each challenge/solution</th>
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</table>
| **1. Changes in standard of care over time** (PROPOSED SOLUTION: Development of cross-collaborative patient registries) | - issues with historical data: bias, discontinuation, unknown switching patterns, differences between regions  
- cohort studies vs. registries: registries are much cheaper  
- solutions: large registries, sharing of data, routinely collected data, need to link national registries  
- acceptability high (and need is high), but there is a need to scope the feasibility |
| **2. Incorporating patient perspective** (PROPOSED SOLUTION: MCDA; Electronic patient reported outcomes) | - currently little data on patient outcomes  
- MCDA too complicated, not worth the time and effort, acceptability low  
- patient’s involvement important but not MCDA - need for collecting data on patient relevant outcomes: symptoms (fatigue, HRQoL)  
- interest in 3 groups of outcomes: mortality, morbidity and quality of life |
| **3. Big investment in the time/cost of development.** (PROPOSED SOLUTION: Supplement RCTs with RWE) | - design trials with severe patient population followed by enlarged population  
- sharing comparator arms  
- supplement phase 3 trials with RWE  
- data on safety |
| **4. Understanding of benefit/risk balance of treatments.** (PROPOSED SOLUTION: Supplementary information to reduce uncertainty in decision-making) | - need for better understanding of trade-offs  
- design scales that measure benefits (PROs) – needs to be done in collaboration between stakeholders |
| 5. Appropriate design of RCTs – including comparator and sample size (PROPOSED SOLUTION: Look at gaps in NMA. Use RWE to design and power supplementary studies.) | • Undertake NMA before executing trial to identify issues relating to effect estimates. Fill in gaps using real-world data.  
• Develop new ways to look at historical data (relates to WP4) |
|---|---|
| 6. Uncertainty of indirect analyses including comparators and placebo arms (PROPOSED SOLUTION: Replace “old” trials with relevant RWE based studies) | • acceptability: try different scenarios of incorporating RWE - try not to prejudge attitudes, see what RWE does, present to stakeholders and observe reaction  
• idea: used pre phase III trial RWE to inform the trial design, incorporate RWE collected during and post-trial |
| 7. Multiple and/or changing comparators (PROPOSED SOLUTION: Adaptive trial design, stepped-wedge designs, cluster RCTs, NMA, cohort) | • Run adaptive design in phase 2 to focus phase 3 trials. Some industry partners are keen to do this. |
| 8. Better understanding of outcome measures (PROPOSED SOLUTION: Collect outcome measures in RWE and do regression analysis. Validate the correlation.) | • Feasible  
• Should be scoped out before taken further, i.e. how much work (if any) has been done on this. Are there acceptable methodologies? |
| 9. Natural history data | • Two scenarios: untreated and standard of care on treatment  
• Can use placebo arms of RCTs for untreated patients, however ethical aspects of placebo arms may be becoming questionable given availability and efficacy of other treatments |
| 10. Need for more efficient RCT design to enable subgroup analyses | • baseline risk/severity difficult to assess as criteria vary across countries (e.g. 1 relapse in previous year as indicator of severity in one country, two relapses in other) - severity well defined for CVD but not MS  
• adaptive analysis plan where all relevant factors collected; pre-planned analysis on risk factors |
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<th>where definition of risk factors can change</th>
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<table>
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<tr>
<th>Challenge</th>
<th>Details regarding methodology of mitigating approach</th>
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<tbody>
<tr>
<td><strong>1. Big investment in the time/cost of trial development</strong></td>
<td>Network-meta analysis (NMA) (with and without the appropriate use of pre-phase III data and RWE) prior to the launch of fingolimod will be undertaken in order to (a) inform appropriate choice of comparator, and (b) to also identify gaps in evidence network which could be filled with RWE and consequently predict the effects in these future studies.</td>
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<tr>
<td><strong>2. Appropriate design of RCTs – including appropriate comparator and sample size</strong></td>
<td>Simulation of a cohort to construct an RCT (over a long-term time horizon; in a real world setting). This would potentially use the control arms of previously conducted RCTs to derive a risk equation, which could, for example, stratify patients into severe, moderate, and mild groups. The risk equation, combined with RCT effect estimates, could then be used to simulate alternative RCTs. More specifically these could be stratified by risk, and possibly simulated with and without an adaptive monitoring/analysis strategy together with and without RWE used in analysis in order to estimate the potential impact of different design/analysis strategies.</td>
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<td><strong>3. Incorporating patient perspective</strong></td>
<td>Identification/estimation of patient preferred outcomes (PPO). PPOs may be more often collected in RWE studies. Consequently the potential use of RWE to predict what the effect estimates would be in RCTs if PPOs had been collected will be explored.</td>
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APPENDIX B

Approaches for incorporating RWE

The simulated development scenarios used here to illustrate each approach rely on clinical information from the fingolimod development programme. It should be noted that fingolimod 1.25mg is not the label dose (0.5mg) for this medicine and is used in examples herein only for illustrative purposes.

B.1. Use of NMAs and RWE to improve measures of relative effectiveness

B.1.1. Rationale
Regulators and HTA bodies often rely on limited data on which to base their decisions regarding the relative efficacy/effectiveness of new medicines. Approaches that could improve the robustness of treatment estimates, could ultimately reduce uncertainty in decision making for these stakeholders and thereby expedite access to medicines for MS patients. While increasing trial sample size may improve the robustness of treatment effect estimates it is also a more costly option for developers. This simulation considers the synthesis of treatment effects in a network-meta analysis (NMA) to investigate the impact that this would have on uncertainty of the annualised relapse rate (ARR) estimate. The premise behind this approach is that effects collected from other existing real-world studies synthesised in a NMA could be used to strengthen ambiguous effect estimates by reducing the underlying degree of uncertainty. Changes in the level of uncertainty of the effect estimate depending on how much weight is given to the RWE in the NMA is also considered.

B.1.2. Methods
Data on the annualised relapse rate of DMTs from studies published up to the time of the fingolimod HTA submissions was collected through a literature review. To obtain estimates of relative effectiveness (e.g. ARR ratio) for fingolimod and other comparators, a NMA combining both available RCT and RWE was undertaken using the RWE at ‘face-value’, i.e. as if it were treated equally with the RCT evidence. Further analyses (e.g. hierarchical or power transform prior weighting analyses) down-weighted the RWE in the network to evaluate the impact on the treatment effect estimates, and in particular the level of uncertainty surrounding them.

B.1.3. Results
Figure B1 shows a network diagram including both RCT and RWE available for various DMTs up to the time of the HTA submissions for fingolimod.
When the NMA estimated treatment effects included both RCT and RWE studies, levels of uncertainty (as determined by standard errors) were generally smaller than those when only one source of evidence was used in the NMA.

Regardless of the weighting analysis used (e.g. hierarchical or power transform prior analysis), there was relatively little impact (at least in terms of the point estimates for the annualised relapse rate ratios) of assigning increasing weight to the RWE (up to including it at ‘face-value’) in the NMA.

As the value of the annualised relapse rate ratio for fingolimod 1.25 mg vs. placebo was down-weighted for RWE in the NMA, the point estimates remained fairly stable but the 95% credible interval limits actually widened as more weight was given to the RWE i.e. the level of uncertainty increased.

### B.1.4. Conclusions

Summary:
It was shown how RWE can be included in a NMA using weighting methods for the adjustment of RWE to account for potential biases. However, sensitivity analyses are required in any practical application to assess how results may differ in practice.

Whilst the inclusion of RWE in NMA would generally be expected to reduce uncertainty of treatment effect estimates, it can however also increase it, as has been shown in this case study. Inclusion of
RWE, as shown here, may increase the overall level of heterogeneity and thereby increase the uncertainty of the estimated treatment effects. This is due to variability in endpoint definition and measurement between real-world clinical practice and RCTs.

This approach would provide decision makers with treatment estimates based on a larger body of evidence that includes a broader range of patient demographics and clinical characteristics than traditionally considered in RCTs alone. The implication of adopting this approach for pharma R&D groups is that they would have a larger (and possibly more representative) evidence/value dossier to submit to regulatory/assessment agencies. Regulators and HTA bodies would have to consider whether or not the RWE used is sufficiently credible, whether the analyses are acceptable, and how to interpret and ultimately use the results. As this approach impacts the uncertainty levels of all treatments included in the NMA similarly, it could be useful for ranking available therapies based on their derived treatment effect estimates.

**B.2. Trial design informed by NMA and RWE at various stages of development**

**B.2.1. Rationale**

Identifying methods that optimise clinical trial design and improve the robustness of treatment estimates has important implications for patients and medicine developers alike. In this section, the use of NMA to synthesise sources of RWE available prior to the design of pivotal studies for fingolimod is explored with the aim of determining whether the early and strategic use of this information can alter decision making during trial development and inform the design of more efficient clinical trials. The approach is based on the premise that empirically derived estimates of relative effectiveness synthesised from an existing body of available evidence could more precisely inform key parameters of future study design (e.g. size) and thereby reduce decision making uncertainty for Pharma R&D. Such an empirical approach to decision making may also provide more transparency at the regulatory or HTA assessment stages e.g. with respect to the relevance of observed effectiveness estimates. In an actual development scenario, trial developers could use this prospective simulation approach to define the parameters (e.g. relative effectiveness estimates and size) and model a future trial informed by the available body of RWE and RCTs.

**B.2.2. Methods**

Predictive simulations are undertaken to define the trial parameters (e.g. relative effectiveness estimates and size) which are then used to model a future trial using trial-based modelling techniques (9). In this workshop the clinical development program for fingolimod was used to test the approach and reference is made to this medicine in the more detailed description below.

**Predictive simulations:**

1.) NMAs are first constructed to obtain treatment effect estimates (i.e. annualised relapse rate, ARR, and standard error) for all known comparators using RCT and RWE sources available following Phase II and prior to each Phase III pivotal trial of fingolimod

2.) These treatment effects are then used to predict the relative effectiveness estimates (i.e. ARR ratio between treatments with confidence intervals) of simulated trials for fingolimod and to inform optimal trial size (depending on desired sensitivity and specificity levels).

**Trial-based modelling:**

3.) Trial-based modelling techniques (9) informed by the results of the predictive simulations and the estimates from the observed trials, are then used to simulate hypothetical future trials of varying samples sizes. Based on the desired power and specificity of the simulated trials, the optimal sample size of a future study can be estimated.
B.2.3. Results

In order to test this approach and determine whether it could add value/efficiency to trial design, aspects of the original fingolimod development programme were used so that simulated trial parameters could be compared to those from the actual studies.

- An alternative TRANSFORMS trial was modelled using the treatment effects obtained from a NMA that included RCT and RWE available before Phase III of the fingolimod development programme. The simulated trial exceeded 90% power when using 284 patients per arm.

- A comparative analysis of the effectiveness parameters reported in the original TRANSFORMS trial indicated that at 284 patients per arm the same treatment effects would have been achieved at 85% power. In other words, given that the original TRANSFORMS study was powered to 90% using 420 patients per arm, very similar treatment effects were obtained with a 30% reduction in patient numbers and a marginal drop of 5% in power using the RWE informed study design.

- Similar evaluations were performed for the other two pivotal studies of the fingolimod Phase III development programme; FREEDOMS and FREEDOMS II. It was demonstrated that had available RWE and RCT data been used to inform the design of these studies, 90% power could have been attained by recruiting fewer patients per arm compared with the original trials.

- Using the simulated studies for fingolimod together with published estimates of patient recruitment rates from the original studies, alternative clinical development strategies for fingolimod were compared and contrasted with the original Phase III programme (Figure B2):

![Figure B2](image-url)

**Figure B2:** Overview of recruitment times of the original fingolimod Phase III program trials (Original), and projected recruitment scenarios for a hypothetical Phase III programme that used RWE to inform study design.

- Alternative I: Had RWE been used to inform the size of the TRANSFORMS study, and the same patient sizes were also used in the FREEDOMS and FREEDOMS II studies, the alternative development programme would result in a saving of 6 or 7 months per study.

- Alternative II: Clinical trial simulations of the FREEDOMS trials, showed that the FREEDOMS II trial required a similar number of patients as the FREEDOMS trial (567 in total). In this option, the estimated reduction in recruitment times would be 6 months for TRANSFORMS, 11 months for FREEDOM and 16 months for FREEDOMS II.
• A comparison of the relative effectiveness estimates (e.g. annualised relapse rate ratios) between MS therapies in a NMA that included the simulated phase III trials for fingolimod, and a NMA that used the original trials, was also done. The annualised relapse rate ratios and standard error estimates were very similar in both NMAs, with only a marginal increase in uncertainty despite the comparatively larger reduction in sample size in the NMA that included the simulated trials. Moreover, the NMA based on the simulated trials did not alter the ranking order of the absolute treatment effects of the medicines included in the NMAs (see Figure B1 for other medicines included), indicating that the (simulated) smaller studies did not alter the overall evidence of effect.

**B.2.3. Conclusions**

**Summary:**

• It was shown that inclusion of RWE when planning a clinical development strategy could result in a more efficient development programme compared to when it is based on RCT data alone. This could lead to substantial savings in recruitment time and subsequently reduce the cost of drug development ultimately leading to favourable pricing for patients.

• RWE can provide evidence of effectiveness in real world patients not measured in a RCT. While a benefit (i.e. smaller Phase III studies) of including RWE in the development strategy was shown, it should be noted that there may be instances when the inclusion of RWE may result in requiring a larger study/development programme.

Based on the presented results, the use of RWE at key stages of a development programme could result in smaller clinical trials, limiting the exposure of patients to experimental treatment without loss of evidence of effectiveness. This strategy may result in earlier regulatory and HTA approval and can contribute to addressing the medical need of patients and patient groups. Using this approach to inform clinical trial development planning could be beneficial to regulatory and HTA bodies when assessing the effectiveness of a drug because the underlying effect estimates may be more representative of the patient population(s) likely to use the medicine in a real world clinical setting.

**B.3. Alternative risk stratified trial design informed by RWE**

**B.3.1. Rationale**

A risk equation in the current context can be used to determine what characteristics may impact on a patient’s probability (risk) of having a relapse. Whilst there have been numerous risk equations published for patients with MS, the majority rely on disability status as the main measure of disease. Although disability is an important long term outcome for patients, many recent RCTs in the field have used annualised relapse rate as the main endpoint of interest. *A de novo* risk equation was developed in this section using the PEARL RWE study that focused on the use of pharmaceuticals other than fingolimod/Gilenya (10). PEARL is an example of a RWE study which might reasonably be expected to be available prior to designing a Phase III programme. The impact, in terms of patient numbers and uncertainty/power, of this risk-stratified approach utilizing RWE to potentially re-design the TRANSFORMS RCT of fingolimod is evaluated. It is hoped that such a prospective approach can be of value to Pharma R&D during study planning and be used to optimise patient recruitment times, thereby reducing both study costs and patient burden.
B.3.2. Methods

- **Derivation of the risk equation:** Using the baseline characteristics of the TRANSFORMS RCT, and the conditional distributions of years from diagnosis and relapses in the previous 12 months from the PEARL study, individual patient data was simulated and a risk score for each patient was calculated.

- **Trial simulation:** Patients were stratified into tertiles of risk of relapse (low, medium and high). The number of relapses for each patient was determined and trial-based modelling techniques (9) were used to simulate hypothetical trials.

- A series of analyses were then undertaken on the simulated RCTs to gauge the impact of risk-stratified trial design on sample size and power:
  - Analysis without risk-stratification (control)
  - Adjustment by risk strata
  - Stratification of patient population based on risk of relapse

B.3.3. Results

To determine whether adjustment for the stratification variable could lead to an increase in statistical power, a comparison of the simulated TRANSFORMS trial was done both adjusted and unadjusted for the underlying risk of relapse. There was no difference in the statistical power obtained in the adjusted and unadjusted estimates of relapse.

In analyses done for each of the risk strata separately, the level of power for the high risk simulated population was increased at all the simulated sample sizes when compared to the medium and low risk populations. For example, the simulated TRANSFORMS trial using the high risk population would require 325 patients per arm to achieve 90% power as compared with to the unstratified original study which required 420 patients to achieve the same power (Figure B3).

![Figure B3: Power curves for varying sample sizes of a risk-stratified TRANSFORMS RCT for each of the risk strata separately.](image)
B.3.4. Conclusions

Summary:

- A RWE study was used to develop a risk equation to determine the patient characteristics that could impact on response to therapy. Clinical trial simulations showed that when including low medium and high risk patients in the model and adjusting for the stratification variable, the power of the study was not affected.
- When low, medium and high risk patients were analysed separately it was shown that power was higher in the higher risk populations.

These findings could have implications for drug development planning. By stratifying patients on their likelihood to reach a defined endpoint (e.g. relapse), it may be possible to design trials using fewer patients. For example, a separate smaller trial may be developed to investigate treatment effects in patients with higher risk of relapse; patients with lower risk could then be studied subsequently or in parallel, depending on the context and chosen strategy.
Deviations from Description of Work

None

Ethics:

Do you consider the deliverable is in compliance with the GetReal Ethics section in DoW?

☐ Yes

☐ No (if not please add comments):

☐ Not applicable

☐ No: major changes needed, please comment (re-review required)