GetReal - Project No. 115546

WP1: Deliverable D1.6

Case Study on Metastatic Melanoma

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1. Executive Summary

The overall objective of GetReal Work Package 1 (WP1) is to develop a framework for incorporating real world evidence (RWE) in decision-making. The work package conducted several case studies which serve as implemented examples of how RWE could be used to provide better evidence of relative effectiveness of new drugs in different disease areas (e.g. multiple sclerosis, rheumatoid arthritis, and non-small cell lung cancer).

The case study on metastatic melanoma was one of the planned case studies. The overall objective of the case study on metastatic melanoma was to understand better how decision-making in pharmaceutical research and development, regulatory approval and health technology assessment (HTA) recommendations could be improved by an expansion in the nature of the evidence available to decision makers. More specifically, the case study on metastatic melanoma had the following aims:

1. Explore options for the combination of real world data (RWD) and randomized controlled trial (RCT) data to improve estimates of effectiveness for metastatic melanoma treatments at time of decision making.
2. Explore the potential for data on metastatic melanoma patients collected from social media sources to be included as part of evidence base for relative effectiveness research.

In order to address these aims the case study work group organized two workshops and conducted primary research. The first workshop was held on June 10th 2015 and the second on May 19th 2016.

During the first workshop delegates identified several challenges related to demonstration of effectiveness of melanoma treatments at the time of decision-making by payers or health technology assessors (HTAs). These included: inappropriate comparator selection, issues concerning the sequencing of medications, inadequate and incomplete quality of life (QoL) measurements, and the importance of identifying patient sub-populations.

Additionally, the results from the primary research aimed at answering the two aims mentioned above were presented and discussed at the second workshop.

The learnings and conclusions from the workshop include:

Accessing RWD in the form of individual patient-level data (IPD) from patient registries proved to be highly difficult due to several reasons, despite the team’s varied attempts to do so. Based on stakeholder input during the workshops, it appears that this remains a common issue faced by many within their different fields of work. This impedes research that makes use of RWD.

Despite the scarcity of RWD eventually available to the case study team and its aggregate nature, it was shown that supplementing RCT data with (sub-optimal) RWD available reduced uncertainties in the extrapolation of overall survival estimates. Unfortunately, lack of access to IPD from registries did not provide the team with the opportunity to explore the added benefit of using IPD for the same purposes, whereby information on covariates is more abundant.

Social media may present an efficient tool for the collection of patient-reported outcomes such as QoL, adverse events and treatment switching. Stakeholders expressed that while some issues may remain with regards to validation of results based on social media, as well as their generalisability, this data source may complement more traditional research methods currently used. However, opinions remain divided as to whether this new source of data can be used in practice within the near future.
Finally, both the case study team and external stakeholders voiced the need for additional examples on the use of RWD in effectiveness research, whether for drug development, regulatory or HTA purposes in the future. Stronger collaboration amongst stakeholders is needed to achieve this, more specifically to overcome issues of data accessibility, address methodological considerations and develop consensus around the appraisal of RWD.

2. Workshop 1

2.1 Workshop 1: Objectives
The first workshop on metastatic melanoma, held on Wednesday the 10th of June 2015, had several objectives:

1. Identify (missing) effectiveness challenges and prioritize which challenges are most likely to have the largest impact on drug development.
2. Identify which variables relating to patient populations and health outcomes are required to address effectiveness challenges.
3. Assess the issues for combining and analysing synthesised data on such variables from different registries, observational studies and RCTs.
4. Explore the expectations, limitations, and acceptability of using health data obtained from social media to be included as part of the evidence base for relative effectiveness research.
5. Discuss findings from focus group on patient perspectives on trial designs.

The workshop was attended by 28 delegates representing 15 different institutions from various stakeholder groups, namely: pharmaceutical industry, HTA organisations, regulatory agencies, patient organisations and clinicians.

2.2 Workshop 1: Description of Sessions
To address the five objectives of the first workshop, the day was divided into five main sessions (see Appendix A for the workshop agenda). The first break-out session discussed effectiveness challenges relating to metastatic melanoma treatments, as well as the relevance of RWD to address them. The second break-out session focused on data quality, comparability and transferability between patient registries in Europe, as well as the methodological issues faced in combining such data with RCT data and the analysis of pooled data. Thirdly, a brainstorming session focused on the use of RWD collected via social media in effectiveness research. Fourthly, findings from previous research on patient perspectives on clinical trials were presented. Finally, a selected panel representing all available stakeholder groups provided reflections on the day’s discussions.

2.3 Workshop 1: Findings
As described above, a total of five sessions were held at the workshop that each had a different focus. Below the discussions, findings and conclusions of the different sessions from the first workshop are outlined.

2.3.1 Break-Out Session 1: Effectiveness Challenges & RWE Relevance

Summary of Pre-Identified Effectiveness Challenges
It was mentioned by delegates that several effectiveness challenges are regularly encountered by HTA agencies in the field of oncology. The main examples thereof include: the choice of inappropriate comparators in phase III pivotal trials, extrapolation of long-term outcomes (e.g. on overall survival) from short-term RCT data and limited information on the management of reported adverse events in clinical practice. Therefore, although these were the pre-identified effectiveness
challenges in the case of ipilimumab, which served as the initial example for targeted metastatic melanoma therapies for this case study these were generalisable to other treatments in oncology.

Several delegates raised the point that similar experiences on the choice of inappropriate comparator have occurred recently. For example, nivolumab was recently compared to dacarbazine (DTIC) in phase III pivotal studies, despite ipilimumab being the best treatment alternative. The same goes for phase III studies comparing pembrolizumab with DTIC.

As to the extrapolation of long-term outcomes based on short-term RCT data, delegates alluded to the example of hazard-ratios for progression-free survival (PFS) of patients using vemurafenib. Although patients demonstrate a significant improvement in PFS, this response is short-lived, diminishing after an average of 6 months. Therefore, there is a need to assess long-term outcomes beyond the duration of RCT’s.

On the other hand, an effectiveness challenge unique to ipilimumab relates to the absence of RCT data in 1st line treatment using the approved dosage of 3mg/kg. Instead, the evidence presented for HTA submission demonstrated efficacy of the 10mg/kg dosage.

Additional Effectiveness Challenges
In light of the rapidly-changing treatment landscape in metastatic melanoma, as well as the various options available for first- and second-line therapy, the sequencing of treatments has become an important factor in relative effectiveness assessment. Therefore, delegates were of the opinion that treatment sequencing in metastatic melanoma patients of all stages should be an important aspect of real-world data collection and effectiveness research.

Delegates emphasized that gaps in information on Quality of Life (QoL) collected during clinical studies was commonplace. Although oncology-specific instruments used to measure QoL have been developed and validated, delegates indicated that these instruments are either too generic (i.e. not tailored to metastatic melanoma) or do not reflect what patients prioritise for QoL. For example, QoL questionnaires do not capture the psychological impact of PFS versus survival with disease progression.

Finally, discussions among groups emphasized the difficulties in identifying patient sub-populations based on covariates such as mutation status on key genes (e.g. B-RAF), presence of brain metastasis or presence of disease-specific biomarkers. Collection of data on such covariates is often fragmented, affecting the generalisability of conclusions made based on RCT cohort data.

Table 1: Pre-identified and additional effectiveness challenges

<table>
<thead>
<tr>
<th>Pre-identified effectiveness challenges</th>
<th>Effectiveness challenges identified in the workshop</th>
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<tbody>
<tr>
<td>Inappropriate comparator selection in pivotal studies</td>
<td>Sequencing in light of new innovative medications</td>
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<tr>
<td>Extrapolation of overall survival data from short-term RCTs</td>
<td>Gaps in Quality of Life measurements</td>
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<tr>
<td>Absence of understanding of how reported adverse events are managed in practice</td>
<td>Inability to identify patient sub-populations</td>
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<td>Absence of RCT data for first-line treatment at approved dosage</td>
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Relevance of RWE to address these challenges

Please see report “D1.5 Report – Metastatic Melanoma” for further information related to the choice for ipilimumab as the initial example and treatment landscape at the time of report publication at https://www.imi-getreal.eu/LinkClick.aspx?fileticket=82nQvF_78xk%3d&portalid=1
This section summarizes delegates’ comments on how RWE can help address pre-identified effectiveness challenges as well as missing effectiveness challenges mentioned above.

Inappropriate comparators choice in phase III clinical trials was cited multiple times by different delegates in the case of several treatments within the field of oncology. In some cases, the comparator was a non-registered treatment while in others, it did not reflect current standard of care (SOC). In order to retrospectively address such shortcomings in trial design, delegates referred to the possible use of RWE to predictively model effectiveness of alternative comparators to construct new arms in studies. In a field where innovative treatments are rapidly emerging causing a changing landscape of care pathways, real-world studies (RWS) which accommodate aspects such as treatment cross-over and sequencing, can be of great value.

Through discussions, it was apparent that health outcomes for treatments varied on a long-term basis as compared to those seen in the short durations of trials. Longitudinal data on patient outcomes available through patient registries, phase IV studies, pragmatic clinical trials (PCTs), and so forth, offer researchers better data on general long-term safety and outcomes of treatments. This in turn allows for the long-term follow-up of trial subjects beyond the trial’s allocated duration. Eventually, this also implies that extrapolations of long-term outcomes based on RWE would better reflect the clinical effectiveness of treatments.

Specific to the case of ipilimumab, the evidence available for 1st line treatment was based on a non-approved dosage (e.g. 10mg/kg instead of 3mg/kg). In the absence of RCT data comparing both dosages head-to-head, delegates indicated that using RWE in the form of individual patient data (IPD) from phase IV studies could help fill in evidence gaps within network meta-analyses (NMA). Eventually, this will allow for the construction of comparative cohorts at the approved dosage.

Delivery of healthcare and treatment pathways differ on a regional, national and international basis. As a result, treatment sequencing becomes an important factor to take into consideration during trial design. Among others, this relates to the choice of comparators in different contexts. RWE from various sources can be valuable in mapping out treatment pathways and drug utilization in the various contexts. Implications of this could guide researchers to thus select appropriate treatments, and especially treatment sequences, while designing clinical trials (both RCTs and RWS).

In general, patient populations in RCTs are selected based on strict inclusion and exclusion criteria. Although this is an important aspect in trial design for the establishment of causality and drug efficacy, results from RCTs are therefore not always generalisable to the broader patient population. RWD can provide information on a broader population that better reflects the clinical population. RWE can be used to simulate results in patients excluded from RCTs (e.g. elderly) and also to adjust for variability in outcomes between populations with different baseline characteristics. In addition to this, the use of RWD which comprehensively captures important patient characteristics (e.g. mutation status, presence of brain metastasis) may be useful in identification of patient subpopulations whose outcomes vary due to specific covariates. This identification of subpopulations could be used to inform research and set up studies targeted at specific subpopulations.

2.3.2 Break-Out Session 2: Data & Methodology

Patient characteristics and outcomes of interest
The second break-out session began with discussions on patient characteristics and outcomes of interest important for effectiveness research on metastatic melanoma treatments.
Patient characteristics deemed important by delegates for accurate identification of sub-populations, or alternatively population stratification, included mutation status (e.g. on the BRAF gene) and the presence of brain metastasis. Another important covariate for which data should be collected is the treatment history, sequencing of different drugs, as well as the duration of treatment.

There was a general consensus on three important domains for which outcomes should be measured, namely: effectiveness, QoL and safety. However, specific endpoints to measure these domains remains debatable.

Mortality, overall survival (OS) and progression-free survival (PFS) were three endpoints that were repeatedly mentioned as relevant to effectiveness. Especially in the case of real world clinical setting, where treatment cross-over is likely to occur, PFS was noted to be an important surrogate endpoint for overall survival. PFS is also suitable as a surrogate endpoint for overall survival in the case of clinical trials with a short-term follow-up. Should data on PFS not be available, time to next treatment (e.g. time to current treatment failure) may offer a suitable alternative for estimating PFS.

Concern was raised on the low and poor quality of data on QoL within patient registries, phase IV studies and RCTs. Several reasons presented by the delegates to explain this phenomenon are the lengthy, difficult and non-disease specific questionnaires, as well as their inability to adequately capture patients’ needs. A possible solution presented was the creation of a simpler questionnaire tailored to the specific needs of metastatic melanoma patients. Notwithstanding the poor quality of data currently available on QoL, delegates agreed that QoL should feature prominently in effectiveness research.

Although there was an agreement on the importance of safety as a domain in effectiveness research, little was mentioned during discussions regarding specific endpoints or considerations for assessing safety.

Issues with data quality, comparability and transferability

Data quality issues featuring in discussions were mostly focused on data present in patient registries. In general, delegates remarked that data integrity (i.e. the accuracy and robustness of input data), comprehensiveness and completeness of documented patient variables and outcome variables was difficult to monitor. One prime example of domains where data quality is an issue is QoL which although important, is usually non-comprehensive and incomplete.

Provided that registries are established to serve different purposes (e.g. product-specific vs. disease-specific), data elements collected on covariates, effect modifiers, patient characteristics, concomitant therapies and diagnostics can vary between different registries. There is often little communication and harmonization of data collection between registries across Europe.

Consequently, several aspects of comparability and transferability of data become affected. For example, the definitions of variables, the time points and frequency of data measurement, and the tools used to measure different data variables vary between different registries. Furthermore, different standards of care in Europe may contribute to confounding of outcome measures such as OS and PFS.

Delegates suggested that a comprehensive list of covariates, effect modifiers, patient characteristics, concomitant therapies and diagnostics data should be constructed for metastatic melanoma to improve quality, comparability and transferability of data on a European level. Standardisation of
data collection tools is a subsequent important step towards allowing analysis of registry data across Europe.

Options for combining registry data, phase IV data and RCT data

Discussions also focused on the methodological considerations of combining registry data, phase IV data and RCT data, and analyzing the synthesized evidence.

There was general agreement on the necessity of having data at individual patient level. This would provide researchers with the flexibility to combine and compare data on patient characteristics and outcome values at the level of individual study subjects. This will allow for investigation of the population and study design aspects used in RWE compared to RCTs (e.g. inclusion/exclusion criteria used in RCTs, different definitions and tools of endpoint measurements).

During discussions delegates indicated that an important point to keep in mind regarding data pooling from different sources is the need to do so in a non-naïve manner. Again, IPD data allows for adequate adjustment and stratification of covariates, highlighting the need for it.

One recommendation proposed to use a common plan to extract data from registries and phase IV studies and subsequently analyze these. The Observational Medical Outcomes Partnership guideline was mentioned in this context for the standardization of the format and content of observational data (http://omop.org)

On a different note, delegates emphasized that inclusion and exclusion criteria designed for clinical studies should reflect the clinical population of metastatic melanoma patients, e.g. the exclusion of elderly patients from phase III trials with stage III/IV melanoma, while a considerable portion of patients with metastatic melanoma are elderly.

Methodological possibilities for data analysis

Assuming data from different European registries were of good quality, comparable and transferable, and provided that non-naïve pooling thereof is possible, delegates were strongly of the opinion that such IPD data could contribute to developing disease models to describe the different stages of disease, namely stages III & IV. The available data may also allow for stratified analysis of different patient subpopulations, e.g. investigation of the treatment effect on patients in different stages of the disease. In addition to this, the new models would be able to assess the effects of treatment sequencing on health outcomes such as OS. This implies that analysis of relative effectiveness would be possible on different sequencing of treatments, rather than be limited to the comparison of two treatments.

Returning to the issue of inappropriate comparator selection in clinical studies, some delegates referred to the possibility of using pooled data from historical control arms in trials (phase III or IV alike) to predictively model missing active-control arms. Such modelling, previously performed by Bristol-Myers Squibb to simulate effects of DTIC using the Korn method,(1) could be improved as more data on DTIC becomes available via registries and phase IV studies. Delegates furthermore indicated that clinical trial simulations could be used to compare different simulation methods and evaluate their performance, which would be preferred to applying multiple methods to the data. However, regardless of the modeling methods eventually used, it remains important to check all model assumptions to verify its use to answer the research question at hand.

Ultimately, the synthesis of RWE with RCT data and subsequent analysis thereof (e.g. to develop disease models, simulate comparators, or model outcomes) renders synthesized evidence
appropriate for filling gaps in NMA networks. The specific use of registry data in network meta-analysis was recommended by delegates.

2.3.3 Break-Out Session 3: Brainstorming Session on Social Media

Limitations of social media

One of the main limitations mentioned during the brainstorming session were language challenges across Europe. For example, French patients may have difficulty understanding information on their disease, treatment and health posted in English.

Despite the fundamental concept of social media allowing sharing of information with multiple users, it is often the case that such information is not accessible by all users. More specifically, this means that users can determine who in the network can view the information they have posted. In practical terms, this often means that researchers do not have access to important, privately-shared information shared via social media. Therefore, many important insights might be missing from results based on analysis of social media data.

Another limitation mentioned by delegates was the possibility of duplicated posts, where the same post is reposted within the same topic or network. Such duplicate posts can directly lead to information bias, by skewing the distribution of measures of particular items of information collected. Therefore, duplicated posts have to be manually checked which increases the burden on researchers.

Furthermore, the sharing of multiple posts (i.e. repeatedly sharing similar posts on the same issue by a single user) also contributes to information bias, since a single user may have more influence on the frequency of recurrence of a specific item of information collected.

Finally, selection bias was another important limitation mentioned during discussions. To elaborate further on this, the population of patients who make use of social media do not represent the total clinical patient population. Often, patients who are younger, who are female, who are more experienced in the use of internet, or who are more keen on sharing their experiences are the ones more likely to share health-related data on social media.

Benefits of social media

During the brainstorming session on the use of social media to collect health data for effectiveness research, delegates informed the audience on the existence and nature of closed patient forums, whereby patients use closed social networking platforms to discuss aspects regarding their disease, treatment and health. Within closed patient forums, administrators screen content regularly to ensure that information shared by users is credible. This ensures that the quality of data collected via closed patient forums might be usable for research. Additionally, since content is screened users’ reputation is affected by the credibility of their posts.

According to delegates, patients are willing to complete surveys conducted via social media, as long as the aims and translatable benefits for the patients are clearly demonstrated to them. In fact, patients also find completion of surveys via social media more convenient than at clinical research centers.

Although it has previously been noted that selection bias and information bias are prominent in data collected from social media (e.g. multiple posts by more active members, duplicate posts, missing data), delegates have argued that the sheer volume of data available via social media can allow for
sufficient statistical power to minimize the impact of such biases on results. The use of forums or websites where posts of patients are curated can also adjust for over-posting.

**Possibilities for using social media in effectiveness research**

Prior to the brainstorming session, several examples of using social media in research were presented. The majority of examples focused on identification of adverse events posted on several social networking and blogging sites. As a result, some delegates affirmed that this can also be implemented in effectiveness research, provided that adverse events constitute one of the domains of effectiveness.

In general, delegates found adherence, QoL and adverse events good candidates for collection of health data via social media. Delegates were also of the opinion that due to the ability to monitor changes in QoL and identification of adverse events via social media, an opportunity for identifying patient subpopulations may exist. Furthermore, since follow-up of patients for clinical trials can prove difficult, delegates proposed that social media offers a more convenient manner by which researchers could monitor and follow-up patients during clinical studies.

### 2.3.4 Break-Out Session 4: Patient Perspectives on Clinical Trial Design

At the workshop the results from a patient survey, focus group and expert panel discussion on patients’ needs from trial design and the potential impact of different study designs for decision-makers were presented. No further discussions commenced at the workshop, and no further research will be conducted on this part by the case study on metastatic melanoma.

### 2.3.5 Break-Out Session 5: Panel Session

A recap of the day’s discussions was given by selected delegates who represented each of the attending stakeholder groups, namely: pharmaceutical R&D, HTA and regulatory agencies, patient organisations and registry owners. What follows is a summary of the main points raised during the panel discussion.

Firstly, one panelist emphasized the short-comings of RCTs conducted in metastatic melanoma patient populations. The main objection toward RCTs focused on the ethical implications of choosing an ineffective SOC as monotherapy arm, which might be due to the slow uptake of innovative treatments by regulatory agencies in a field with a rapid pace of innovations. Adaptive trial designs were suggested as a solution in such situations, because these designs are able to better incorporate rapid changes in SOC as well as patient needs. However, all panelists agreed that RCTs are a good tool in themselves when it comes to measuring causal effects.

Panelists agreed that, in addition to data from RCTs, RWE is important as supportive data. Furthermore, there seemed to be a general appetite among all stakeholders to use RWD. This implies there is a need to test different methods and assess how to incorporate and use RWD. The importance of finding a way to use RWE in determining which innovative therapies are most effective was also mentioned, which is especially important to HTA agencies who are challenged by the increasing number of oncology treatments.

Two missing effectiveness challenges were identified throughout the day, namely that on quality of life measurement and identification of patient sub-populations. Assessing quality of life was deemed important, however obtaining this determinant in a real-world setting proves to be difficult. One panelist suggested that the use social media could help solve this problem. Another problem in the assessment of quality of life are the difficult and extensive questionnaires, which do not reflect patient needs. The development of easier and more intuitive questionnaires to measure quality of

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life in metastatic melanoma patients was raised as an important item. Since RWD allows for a more extensive collection of patient characteristics the identification of sub-populations and capturing patients of interest may be possible.

As expected, limitations are also present in the use of RWD. During the workshop the focus of RWD was on the use of registry data. The workshop benefitted from attendance of representatives from a Dutch and an Italian registries who presented their view on the use of registry data. Both registries have a nation-wide coverage and collect comprehensive data on treatment and patient characteristics. One major difference between the registries is that the Dutch registry focuses on metastatic melanoma Phase III and IV patients, while the Italian registry includes melanoma patients from all stages. Comparability between registries is thus impacted by the purpose of the registry, since this determines the type of registry and the data elements collected therein. A recurrent issue during the day concerned the varying quality of registries, which begs the question on how to ensure that quality of registry data is equal across Europe.

Thus far, little collaboration exists between European registries and, delegates indicated that increasing such collaboration is important to allow for harmonisation and standardisation of data collection tools and patient characteristics and outcome variables. In doing so, it would become possible to combine registry data from different European registries to provide additional information on existing and novel treatments.

Regarding outcome measures for metastatic melanoma patients, panelists agreed that OS is the most important end point to determine. However, PFS was deemed the most important end point in the case of treatment cross-over. The importance of insights into treatment sequencing was also mentioned. The use of RWD from registries was seen as crucial to provide these insights on treatment sequencing.

2.3.6 Conclusions from Workshop 1
To conclude on workshop 1, the main findings and discussion points summarized above are related back to the five workshop objectives listed in the introduction.

First, prior to the workshop the case study team identified important effectiveness challenges in RCTs, namely: inappropriate comparator selection, difficulties in extrapolating overall survival data based on short-term RCTs, absence of understanding management of adverse events in practice, and absence of RCT data at approved dosage for first line treatments. During the workshop the importance of these pre-identified effectiveness challenges was confirmed by delegates. Additional effectiveness challenges encountered by delegates concerned the sequencing of medications, inadequate and incomplete QoL measurements, and the importance to identify patient sub-populations.

Second, to assess effectiveness using RWD, delegates indicated that mortality and OS are the primary endpoints of interest. PFS was mentioned as an important secondary endpoint, especially in the case of treatment cross-over. Other variables that delegates deemed important in the analyses of RWD were good measures of QoL, information on adverse events, treatment history, treatment sequencing, duration of treatment, and patient characteristics (e.g. mutation status or presence of brain metastasis).

Third, the most important aspect needed to combine data from registries, observational studies and RCTs and to subsequently analyse these are IPD. However, pooling of such data must be done while keeping in mind that data quality, comparability and transferability differs significantly across European registries, phase IV studies and RCT studies. Delegates indicated that RWD will make it
possible to perform stratified analyses, compare multiple treatments to one another as well as comparing different treatment sequences, model and simulate control arms in the case of inappropriate comparators, and to fill in gaps in NMA networks.

Fourth, some delegates were positive about the use of health data generated from social media to contribute in the assessment of relative effectiveness. The main potential for social media lies in collecting information on adherence, adverse events and QoL. Limitations concerned with social media are the access to content on closed sources of social media such as patient forums, selection and information bias, and language challenges. Benefits of social media include the verification of users' credibility or content within closed forums by content screeners, the convenience for patients to fill in surveys at home instead of by visiting clinical research centers, and the volume of data that allows for sufficient power to minimize the impact of information bias.

Fifth, although discussions did not focus on findings from the focus group on patient perspectives on trial design, talks held throughout the day delegates have highlighted the need for QoL measures to better reflect patient needs, as well as possible options for trial design that may reflect patient interests (e.g. PCT's).

Finally, it is important to mention that stakeholders should continue to openly discuss which study designs are needed to answer varying questions at different phases of the product lifecycle as well as the required types of evidence, whether from RCTs or RWD, to provide the relevant answers.

3. Research Methods and Results
The GetReal WP1 case study on metastatic melanoma endeavoured to explore options for the use of RWD to improve estimates on the effectiveness of treatments in clinical practice. Based on discussions and findings from the first workshop, the case study team attempted to address two distinct objectives: 1) exploring the use of RWD (e.g. registries, phase IV studies) in combination with RCT data to improve estimates of overall survival, and 2) the use of social media to gather patient perspectives on quality of life (QoL).

3.1 Use of RWD to improve estimates of overall survival
In order to explore the options of using RWD in combination with RCT data to improve extrapolation of overall survival, the metastatic melanoma case study initially aimed to collect IPD from three European registries. These registries originated from the Netherlands, France and Italy.

The Dutch registry included data on all patients in the Netherlands that have been diagnosed with metastatic melanoma. Both the French and Italian registries included a subsample (regional) of metastatic melanoma patients in the respective countries. Data available in all three registries included outcome measures (e.g. survival), side effects and QoL.

To apply for data access the case study team had to comply with the general procedure of each registry, which included filling out an application form and submitting a research proposal. These documents were subsequently reviewed by the scientific advice committee, general advisory committee, or both. Afterwards a final decision was made.

Although such a process seems straightforward, some tweaking was necessary in practice. For example, the applicants were sometimes encouraged by registry advisors to involve academic
groups which conventionally perform all statistical analyses for their registries as a means of increasing the chance of access approval. In some cases, this meant that internal clearance was required (as well as funding) for collaboration. The French registry and the Italian registry had similar issues to the Dutch registry. In the case of France, it was more difficult to submit a case for access to the data to the steering committee and due to this inability to engage with the registry steering committee, timelines for access to the data were unrealistic for the purposes of this case study. Representatives of the Italian registry were very willing to engage with the project team; however, a combination of the need to clean data before it could be made available and the expected timelines for approval by the steering committee made the timelines once again unrealistic.

Although the case study team had good hopes in getting access to the registry data by complying to such recommendations from registry holders, eventually all three registries approached declined the requests for data access or were unable to provide data in time for inclusion within this case study. Given the importance of access to RWD to inform regulatory, HTA and development decisions, this difficulty in ensuring access to different registry data is a key finding in itself.

Despite unavailability of registry data from the Dutch, French and Italian registries, the case study team decided to keep its research focus on improving the extrapolation of overall survival data from RCTs by incorporating overall survival data from alternative RWD sources.

3.1.1 Alternative RWD sources
The following RWD sources were available to the case study team:

1. Publications of melanoma patient registries: several scientific publications of European patient registries were identified that reported aggregate data as well as Kaplan-Meier (survival) curves.
2. SEER-Medicare database: the data originate from the Surveillance, Epidemiology and End Results (SEER) program of cancer registries that collect clinical, demographic and cause of death information for persons with cancer, and the Medicare claims database that registers covered health care services from the time of a person’s Medicare eligibility until death.

The team also had access to IPD from two phase III RCT trials conducted by BMS:

- Study 1 was a randomised double blind clinical trial in patients with previously untreated metastatic melanoma. (2) Patients received standard or experimental treatment. A total of 502 patients were randomised. The trial follow-up was 48 months.

- Study 2 was a randomised double blind clinical trial in patients with previously treated metastatic melanoma. (3) 923 Patients received one of 3 treatments. Patients were followed-up for 46-54 months.

3.1.2 Methods
One of the most common ways in which to extrapolate the results of RCTs is to fit one or more parametric survival models to the RCT data available, and use the parametric survival models to extrapolate beyond the follow-up time of the RCT. Examples of parametric survival models
conventionally used are: exponential, Weibull, Gompertz, log-logistic and log-Normal.(4) These were used in this case study.

Additionally, a non-parametric model based on local linear regression was employed. A nonparametric model is flexible in that it does not assume a shape of the response curve a priori.(5)

Non-informative extrapolation (Base case)
In the absence of data on long-term follow-up, non-informative extrapolations are conventionally carried out. The parametric statistical models described above and the non-parametric model were fit to available IPD from RCT by regression analyses. The follow-up time was extended from 48 months (the length of follow-up in the RCT) to 80 months. This was done by evaluating the estimated survival curves assuming no data were available from 48 months to 80 months. To establish the best-fitting model, the log-likelihood obtained from each individual parametric model was compared. A lower value indicates a better fit. The non-parametric model fit was compared to parametric model fit through visual inspection.

Simulating IPD from published real world studies and long-term follow-up
A literature search was performed to identify relevant studies that had reported Kaplan-Meier (KM) curves. Subsequently, an additional search was performed to identify a subgroup of studies that included patients with MM and which were similar to those included in the RCTs made available. Two such studies were identified.

- Joosse et al published long term estimates of survival of patients from the Munich cancer registry.(6) A total of 11,774 patients were selected from this registry. Total follow-up was 120 months. From this study survival probabilities at a median follow-up time of 80 months and for patients comparable to those in the available RCTs were available.

The published long-term survival estimates from Joosse et al (6) were used to assess the plausibility of the extrapolation strategies described in the following sections and are presented in the figures throughout for reference purposes only.

- Altomonte et al published KM curves of a 48 month study of patients receiving 10mg/kg Ipilimumab in Italian centres as part of a European expanded access programme.(7) The KM-curves were used to generate Individual Patient Data (IPD) using the approach proposed by Guyot et al.(8) Thus, this IPD could be combined with IPD data from RCTs to extrapolate long term survival.

Extrapolation using registry data
Data from the SEER-Medicare registry were used in combination with RCT data for extrapolation using the parametric and non-parametric survival models described above. IPD was generated from the life-table estimates obtained from the registry using a modification of the approach proposed by Guyot et al.(8) As a result of the uncertainty at the end of the follow-up time of the RCTs, due to censoring, the last 10%, 20% or 30% of the RCT data at the end of the follow-up period was removed and the IPD generated from the SEER-Medicare registry was blended with the RCT data to obtain estimates of survival up to 96 months. Note that for illustrative purposes, and due to the availability of data at the time of the workshop, the approach using RWD is demonstrated with one arm of the
RCT only. However, the methodological principles apply to any treatment arm in an RCT, subject to the comparability of patients in both the RCT and RWD.

To provide an estimate of long term overall survival the area under the curve restricted to 72 months of follow-up was estimated, i.e. AUC(72), together with its standard error. A restricted AUC measure is often used in Health Technology Assessment (HTA) agencies to establish the long term survival associated with a treatment.(9)

**Extrapolation using combined sources of evidence**

The IPD generated from the SEER-Medicare registry and the IPD from RCT were blended as described above (see Section ‘Extrapolation using registry data’). Additionally, the summary data from published results (e.g. Joosse et al (6)) was used to assess plausibility of the extrapolation using both the RCT and RWD sources.

Only the best fit parametric models, i.e. log-logistic and lognormal models and the non-parametric model are presented to illustrate the various approaches.

### 3.1.3 Results

**Results of Non-informative extrapolation (Base case)**

Both the log-logistic model and the log-Normal models fit the RCT data well as can be seen from Figure 1. The black curve is the estimated KM estimate from the RCT and the red and blue curves are the model fit. Both the log logistic and log-Normal model fit the data really well up to approximately 30 months. Due to uncertainty in the tail of the RCT follow-up (with approximately 20% of patients censored) the KM curve is no longer declining monotonically, which is resulting in a poor fit at the end of the RCT follow-up. The point estimate and 95% confidence interval (CI) obtained from Joosse et al (6) is also presented. In the absence of RWD the extrapolated survival curves do not approximate the effects observed in the real world. The results of the inclusion of RWD is described in subsequent sections.

Figure 1 shows a graphical illustration of the results of the model fit of the log logistic and log-Normal model (right panel) for Study 1.

**Figure 1 Left panel: Non-informative log-logistic extrapolation of RCT data. Right panel: Non-informative lognormal extrapolation of RCT data.**
Similar results were observed for Study B. Table 2 provides a summary of the results of the fit for Study B. A smaller value indicates a better statistical fit.

**Table 2 Model fit results for Study B**

<table>
<thead>
<tr>
<th>Model</th>
<th>-2xloglikelihood (-2LL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exponential</td>
<td>3835.5</td>
</tr>
<tr>
<td>Weibull</td>
<td>3835.5</td>
</tr>
<tr>
<td>Log-normal</td>
<td>3759.5</td>
</tr>
<tr>
<td>Log-logistic</td>
<td>3757.7</td>
</tr>
</tbody>
</table>

Results of simulation of IPD from published real world studies and use of long term follow-up
The published KM curves were digitized and the KM curves were regenerated. The regenerated curves were then plotted against the RCT data to see whether extrapolation was feasible. Figure 2 presents the digitised curve and the KM estimates from Study 1. Note that the KM curve from Altomonte et al (48 month follow-up) was extended to 120 months in order to be able to benchmark the estimates observed from the Joosse et al RWD study.(6,7)

**Figure 2 Overall survival of published RWD and Study 1**
Due to the number of censored individuals, there is uncertainty in the tail of the follow-up at 48 months, making it difficult to extrapolate the results of the RCT data. This highlights the need for data and models that can accurately estimate the measured RCT data and predict the long term follow-up.

One approach that can be applied to predict long term survival from RCT and long term summary data is to use a non-parametric model. Figure 3 illustrates the result of the non-parametric regression model. Due to its flexibility, this model is able to accurately assess the RCT data and extend the survival model to the OS value observed in published summary RWD from Joosse et al.(6)

**Figure 3 Extrapolation of RCT study results from published RWD (Joosse et al.)**

As can be seen from Figures 1, 2 and 3, long-term summary data can be very useful for assessing the adequacy of the fit. The non-parametric model allows for linear regression to match the long-term
data available from Joosse et al. (6) This model becomes very interesting in the case when there are estimates of OS at multiple time points obtained from long-term RWD. This increases the accuracy of the extrapolation as the amount of summary RWD increases. However, the nonparametric extrapolations rely on the researchers’ acceptability of the face value of the summary RWD.

Results of extrapolation using registry data
The SEER-Medicare data was used to extrapolate the short-term survival data in an attempt to reduce the uncertainty of the extrapolation, i.e. by increasing the numbers of patients with follow-up beyond 48 months. As described above, there is uncertainty in the tail of the follow-up from RCT due to the number of censored individuals. For the purposes of this analysis 10% of the data from RCT were excluded to remove some uncertainty in the follow-up phase. The data was then augmented with the IPD data obtained from SEER-Medicare. The results of the extrapolation using the RCT data of Study one with the SEER-Medicare IPD are presented in Figure 4.

Figure 4 Extrapolation of RCT data using SEER-Medicare data.

The SEER-Medicare estimates of survival up to approximately 48 months would seem to differ from the survival estimates of the RCT. However, the extrapolation of the RCT data follow the same pattern as the long term survival results from the SEER-Medicare registry.

Blending of SEER-Medicare and RCT data resulted in a reduction in the uncertainty of long-term estimates of OS, compared to the non-informed extrapolation (base case). The point estimate (standard error (SE)) for AUC(72) for the uninformed extrapolation was 15.7 (1.2) months. The point estimate (SE) for the extrapolation using RWD was 14.8 (1.1) months.

3.1.4 Conclusion
Various models were used to extrapolate OS based on RCT and RWD. The log-logistic and log-Normal models performed the best among the parametric models. The non-parametric model is flexible, estimated the RCT data extremely well, and is able to extrapolate to long-term estimates from summary RWD (Joosse et al (6)) by linear regression. The uncertainty in the extrapolation will decrease when more long-term data becomes available.
The use of simulated IPD from published KM curves from registry studies and SEER-Medicare data decreased the uncertainty of extrapolated OS survival estimates compared to the non-informative extrapolation. Although the extrapolation using published KM curves may be useful, the added value is limited in cases when the follow-up of RWD is similar to that in the RCT(s).

Summary RWD (Joosse et al. (6)) was used throughout to assess the plausibility of the extrapolations. However, more research is needed to incorporate the use of long-term summary RWD with IPD from both registries and RCTs.

3.1.5 Discussion
The use of the SEER-Medicare registry allowed for extrapolation of RCT data to establish long term survival with reduced uncertainty. IPD from published KM curves from registry publications was consistent with findings from the RCT. However, the follow-up of patients in this data source was similar to those in the RCT so did not allow for long term extrapolation. Combination of both sources of data, RCT and RWD (summary and IPD) can be useful tool for extrapolating long term survival. The uncertainty of the long term extrapolation can be reduced, while also assessing the plausibility of the extrapolation.

However, the current landscape regarding the use of registry data is difficult to manoeuvre. It can be difficult to obtain IPD from registries. Even when registry data are available only summary statistics are sometimes provided. Although summary statistics are useful, this can limit the analyses that can be performed using RWD, i.e. such as the adjustments for patient characteristics that have an impact on their long term survival, e.g. the Eastern Cooperative Oncology Group (ECOG) status at baseline.

The analyses presented here excluded 10% of the RCT data at the end of the follow-up period to remove some of the uncertainty in the tail of the survival distribution due to patients being censored. Removal of more data (e.g. 20% or 30%) was explored but this can impact the ability of statistical models to fit the RCT data. Therefore, this was not recommended in this case study, also in accordance with general recommendations.(10)

The use of IPD and summary data was useful for extrapolation of OS and to assess the plausibility of the extrapolation. However, further research is needed to evaluate different approaches and assess the impact of using summary data. This research could include Bayesian model averaging techniques (11) or constrained regression models (12).

3.2 Use of social media to collect patient perspectives on QoL
The second objective of the metastatic melanoma case study is to explore the potential of social media to collect melanoma patient perspectives on QoL. For the purpose of this document we have defined social media as ‘a group of Internet-based applications that allow the creation and exchange of user generated content’. (13)

Initially, the case study team performed an explorative literature review on the potential of social media to collect health data for cancer(presented at the first workshop). This review demonstrated that in oncology, social media is mainly used for assessing adverse events by collecting health data from forums. Social media was also shown to be effective in extracting information on treatment
switching and adherence behaviour, as well as collecting patient perspectives on QoL. These three aspects are also important in relative effectiveness, showing that social media could inform REA. However, it should be kept in mind that this type of data should be regarded as complementary to traditional forms of research.

One difficulty in assessing relative effectiveness in metastatic melanoma relates to the short follow-up time of most RCTs. Therefore, information on overall survival may not be accurate. Additionally, as overall survival trends increase with the introduction of new therapies, the QoL associated with such survival prolongation becomes increasingly important to decision-makers. In such cases QoL may provide relevant information for the relative effectiveness of treatments. However, in both RCTs and registries, it is often difficult to capture QoL data due to various logistical reasons; such as the short follow-up period incorporated in trials and motivating patients to fill out QoL questionnaires. Additionally, patient advocates indicated at the first metastatic melanoma workshop that current questionnaires may insufficiently reflect their needs, decreasing their readiness to complete them. Social media could be an accessible and cost-efficient solution to collecting patient QoL data and exploring their perspectives on QoL. Therefore, the case study team evaluated to what extent patient perspectives on QoL could be assessed via social media. The following research questions were considered:

1. What do patients find important regarding QoL?
2. How do these aspects relate to current melanoma-specific questionnaires on QoL?
3. Is there a difference in patient perspectives on public and closed social media channels? (e.g. public forum vs. closed Facebook group)
4. How do patients on social media compare to the general melanoma patient population?

To answer these research questions the case study team collaborated with Melanoma Patient Network Europe (MPNE). This European patient organisation provides a platform for national patient networks that provide access to accurate information in the patients’ own language and support that is appropriate to their cultural context. The national networks from Denmark, France, Germany, Italy, Macedonia, Romania, the Netherlands, Norway, Scotland, Spain, Switzerland and the United Kingdom are members of MPNE.

3.2.1 Methods
Melanoma patient perspectives regarding QoL were collected in two ways:

1. Survey on patient perspectives regarding QoL:
   a. In collaboration with MPNE, the case study team developed a survey that consisted of both open and closed questions regarding patient perspectives to QoL, and patient & disease characteristics.
   b. MPNE provided a link to the survey on their website
   c. MPNE advertised the survey on several social media channels:
      1. MPNE closed Facebook Group
      2. MPNE closed LinkedIn Group
      3. Other Facebook groups
      4. Twitter
   d. The survey was actively advertised for four weeks on aforementioned social
media channels. In addition, MPNE also advertised the survey via their mailing list in the last two weeks.

2 Use of forum posts to identify patient perspectives regarding QoL:
   a Forum posts were collected from the publicly accessible forum of the Melanoma International Foundation (MIF) (15)
   b Selection of this forum was based on the following criteria: 1) the site had been active for >5 years, 2) at least 100 posts were identified using the search terms ‘stage, melanoma and/or skin cancer’, and 3) >10 new posts per week.
   c 81 search terms were used to identify posts that discussed QoL
   d Identified posts were then extracted from the forum (without login into the forum)

Survey responses and forum posts mainly constituted of free text, therefore, content analysis was performed to identify key themes. Two researchers independently assessed completed surveys and included forum posts. Themes identified were compared to questions used in three current QoL questionnaires (EORTC QLQ-C30, EORTC QLQ-MEL38, FACT-M).

Results are stratified by patient and carer status, patients are additionally stratified according to melanoma stage. The quantitative composition of patients present in the survey and forum will be compared to each other, and to figures from literature on the overall melanoma population.

At the time of the second workshop, the case study team had not yet performed the analyses of the forum posts. Therefore, the results section will only focus on the results obtained from the survey, and compare these with questions posed in current QoL questionnaires.

3.2.2 Results
In total, 72 patients with stage I to IV melanoma, and 19 carers completed the survey (Figure 5). For patients the subsequent analysis have been stratified by stage, due to the low number of respondents the analysis for carers have not been stratified by stage.

Figure 5 Distribution of respondents according to patient or carer status, and disease stage.
<table>
<thead>
<tr>
<th>Gender</th>
<th>Survey Sample</th>
<th>Reference Population</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stage I</td>
<td>Stage II</td>
<td>Stage III</td>
</tr>
<tr>
<td>Female</td>
<td>83%</td>
<td>70%</td>
<td>75%</td>
</tr>
<tr>
<td>Age &lt; 50</td>
<td>40%</td>
<td>43%</td>
<td>46%</td>
</tr>
<tr>
<td>Age &gt; 50</td>
<td>60%</td>
<td>57%</td>
<td>54%</td>
</tr>
</tbody>
</table>

<table>
<thead>
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<th>Highest educational level</th>
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<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stage I</td>
<td>Stage II</td>
<td>Stage III</td>
</tr>
<tr>
<td>No school</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Primary school</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Secondary school</td>
<td>11%</td>
<td>20%</td>
<td>25%</td>
</tr>
<tr>
<td>College</td>
<td>22%</td>
<td>10%</td>
<td>31%</td>
</tr>
<tr>
<td>University</td>
<td>50%</td>
<td>60%</td>
<td>38%</td>
</tr>
<tr>
<td>Higher degree</td>
<td>17%</td>
<td>10%</td>
<td>6%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Melanoma diagnosis</th>
<th>Survey Sample</th>
<th>Reference Population</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stage I</td>
<td>Stage II</td>
<td>Stage III</td>
</tr>
<tr>
<td>&lt; 1 month ago</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1 – 3 months ago</td>
<td>6%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3 – 6 months ago</td>
<td>17%</td>
<td>-</td>
<td>7%</td>
</tr>
<tr>
<td>6 – 12 months ago</td>
<td>28%</td>
<td>10%</td>
<td>13%</td>
</tr>
<tr>
<td>1 – 2 years ago</td>
<td>6%</td>
<td>20%</td>
<td>7%</td>
</tr>
<tr>
<td>2 – 5 years ago</td>
<td>22%</td>
<td>50%</td>
<td>40%</td>
</tr>
<tr>
<td>&gt; 5 years ago</td>
<td>22%</td>
<td>20%</td>
<td>33%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of Melanoma</th>
<th>Survey Sample</th>
<th>Reference Population</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stage I</td>
<td>Stage II</td>
<td>Stage III</td>
</tr>
<tr>
<td>Cutaneous melanoma</td>
<td>44%</td>
<td>70%</td>
<td>57%</td>
</tr>
<tr>
<td>Ocular/ Uveal/ Choroidal</td>
<td>50%</td>
<td>10%</td>
<td>7%</td>
</tr>
<tr>
<td>Mucosal melanoma</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>I don’t know</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>6%</td>
<td>20%</td>
<td>36%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Country of residence</th>
<th>Survey Sample</th>
<th>Reference Population</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stage I</td>
<td>Stage II</td>
<td>Stage III</td>
</tr>
<tr>
<td>Belgium</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>France</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Germany</td>
<td>17%</td>
<td>10%</td>
<td>13%</td>
</tr>
<tr>
<td>Country</td>
<td>UK</td>
<td>Other*</td>
<td></td>
</tr>
<tr>
<td>-------------</td>
<td>----</td>
<td>--------</td>
<td></td>
</tr>
<tr>
<td>Ireland</td>
<td>6%</td>
<td>11%</td>
<td></td>
</tr>
<tr>
<td>Italy</td>
<td>6%</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Netherlands</td>
<td>6%</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>Norway</td>
<td>6%</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>Romania</td>
<td>11%</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>UK</td>
<td>50%</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>Other*</td>
<td>17%</td>
<td>5%</td>
<td></td>
</tr>
</tbody>
</table>

*5 respondents originated from the USA and 1 respondent from Serbia; (18) Bay et al. 2015; (19) Eriksson et al. 2014;
Respondents’ demographics differed from the general melanoma patient population regarding gender and educational level (Table 3). However, educational level corresponded to the general social media population, where individuals with lower levels of education are less likely to use social media. (16) Most respondents had been diagnosed with melanoma 2 or more years ago, and were diagnosed with cutaneous melanoma. Although the design of this study focused on an European overview of melanoma patient perspectives to QoL most respondents originated from the United Kingdom (~50%), which may be due to the survey only being available in English. However, melanoma patients from other European countries were also represented in our study sample.

Most respondents accessed the survey via Facebook (Table 4), which was expected since it has been shown that in 2015 72% of individuals who use the internet make use of Facebook. (17) Individuals who use the internet make use of LinkedIn (25% in 2015) and Twitter (23% in 2015) to a lesser extent, as is confirmed by our findings.

Table 4 Social media channels where respondents retrieved the survey

<table>
<thead>
<tr>
<th>Social media:</th>
<th>Patients (n=72)</th>
<th>Carers (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stage I (n=18)</td>
<td>Stage II (n=10)</td>
</tr>
<tr>
<td>MPNE closed Facebook page</td>
<td>22%</td>
<td>30%</td>
</tr>
<tr>
<td>Other Facebook page</td>
<td>50%</td>
<td>40%</td>
</tr>
<tr>
<td>MPNE website</td>
<td>11%</td>
<td>20%</td>
</tr>
<tr>
<td>MPNE LinkedIn group</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MPNE mailing list</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Twitter</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Other*</td>
<td>17% (n=3)</td>
<td>10% (n=1)</td>
</tr>
</tbody>
</table>

*Respondents reported the following channels as other: Berlin Support Group (n=2), Melanoma Romania Association (n=1), Ocumel UK (n=2), Melanoma Mates UK (n=2), Dutch Melanoma Association Forum (n=2), Norwegian Melanoma Association (n=1)

The overall QoL rating of respondents in our sample has a similar distribution as is presented by the EORTC as their reference value.(20) This indicates that our survey sample is representative of melanoma patients regarding QoL, both overall and stratified by stage (data not shown).

Table 5 Overall Quality of Life

<table>
<thead>
<tr>
<th></th>
<th>1 (very poor)</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7 (excellent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survey Sample</td>
<td>2%</td>
<td>2%</td>
<td>10%</td>
<td>11%</td>
<td>27%</td>
<td>28%</td>
<td>19%</td>
</tr>
<tr>
<td>(All Respondents)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

|                   | 2%            | 2%      | 8%      | 17%     | 28%     | 27%     | 16%           |
| EORTC Reference Value (20) |            |         |         |         |         |         |               |

(20) Scott et al. 2008
Figure 6 shows which themes in QoL are most important to our study sample, namely family, having a normal life, being able to enjoy life, having good care, being capable, and having support. Although family is mentioned as most important theme in QoL by all patients, when stratifying patients by stage there seems to be a difference in the themes that are important to their QoL (Table 6). However, this difference may be due to the small number of respondents in each stratum. Carers are shown to mention different themes that are important in QoL of patients than patients themselves.

Figure 6. Which aspects are most important to melanoma patients regarding their QoL

| Table 6 Top 10* key themes that are most important in QoL of melanoma patients |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                | All Respondents | Patients        | Carer           |
|                                | Stage I         | Stage II        | Stage III       | Stage IV        |
| Family                         | Family          | Family          | Family          | Family          | Capability      |
| Normal Life                    | Good Care       | Fear            | Worry           | Good Medicine   | No Adverse      |
| Enjoy Life                     | Enjoy Life      | Normal Life     | Therapy Burden  | Normal Life     | Events          |
| Capability                     | Finances        | Capability      | Counselling     | Capability      | PainFree        |
| Good Care                      | Normal Life     | Good Doctors    | Enjoy Life      | Enjoy Life      | Drug            |
| Support                        | Support         | Good Health     | Support         | Good Care       | Effectiveness   |
| PainFree                       | Access Medicine | Normal Life     | Good Care       | Good Care       | Family          |
| Fear                           | Fear            | PainFree        | Good Doctors    | Good Health     | Normal Life     |
| Good Doctors                   | Good Doctors    | Relapse         | Not to Worry    | Good            | Access Medicine |
| Good Health                    | Capability      | Worry           | PainFree        | Information     | Cure            |
| Good Meds                      | Friends         | Good Health     | Access Medicine | Finances        | Good Care       |
|                                | Good Health     | Worry           | Friends         | Good Health     | Good Health     |
|                                | No Anxiety      | PainFree        | PainFree        |                      | Uncertainty     |
|                                | Patient Network |                 |                 |                      |                 |
As part of this study, we have compared the themes identified with the survey to the questions used in three current QoL questionnaires (EORTC QLQ-C30, EORTC QLQ-MEL38, and FACT-M).

In the survey closed questions were posed where patients and carers could rate the relevance of the questions used in the generic cancer QoL questionnaire of the EORTC (QLQ-C30). We showed that patients with different disease stages rate the relevance of questions differently, for example ‘Trouble doing strenuous activities’ was rated at no relevant (at all) by the majority of stage I and II patients, while ~50% of stage III and IV patients found this a relevant question. Although differences are seen in how patient with different disease stages rate questions from the QLQ-C30, it proved to be difficult to relate what respondents mention in the open ended question of the survey to how respondents rate these closed question on QLQ-C30.

Regarding both the EORTC QLQ-Mel38 and the FACT-M questionnaires, which are melanoma specific QoL questionnaires, our survey showed that some questions seem relevant to our study sample while others seem less relevant (Table 7). In addition, wording may differ between patients and the questions in these two questionnaires. For example, the EORTC QLQ-MEL38 asks ‘Have you had problems with pain at or near your melanoma site?’ while patients focus more on being painfree in the open-ended questions of the survey. The FACT-M, for example, states ‘I have a lack of energy’ while patients focus more on having enough energy. Patients seem to have a more positive tone in general compared to the questions in the melanoma specific QoL questionnaires. This raises the questions how such a difference in tone may affect patients’ responses or their willingness to fill in QoL questionnaires.

Table 7 Examples of questions in two melanoma specific QoL questionnaires that seem relevant and less relevant to respondents of the survey

<table>
<thead>
<tr>
<th>EORTC QLQ-MEL38</th>
<th>FACT-M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Questions that seem <strong>relevant</strong> in our study sample</td>
<td>Questions that seem <strong>relevant</strong> in our study sample</td>
</tr>
<tr>
<td>Have you felt able to carry on with things as normal?</td>
<td>I get emotional support from my family.</td>
</tr>
<tr>
<td>Have you felt confident that a psychological support service would be available if you needed it?</td>
<td>I worry that my condition will get worse.</td>
</tr>
<tr>
<td>Have you received realistic and reliable information about the extent (spread) of your disease?</td>
<td>I am able to enjoy life.</td>
</tr>
<tr>
<td>Have you been given enough time to think about the treatment options available to you?</td>
<td>I get headaches.</td>
</tr>
<tr>
<td>Have you had swelling near your melanoma site?</td>
<td>I have pain at my melanoma site or surgical site.</td>
</tr>
<tr>
<td>Have you felt able to accept that melanoma is a serious condition?</td>
<td>I have good range of movement in my arm or leg.</td>
</tr>
</tbody>
</table>
3.2.3 Conclusion
In conclusion, social media provides a valuable tool in assessing patient perspectives regarding QoL, however results are difficult to generalize to the broader melanoma patient population. Differences emerge between what patients and carers consider important for QoL. Melanoma-specific QoL questionnaires that are currently available do not seem to correlate fully with what patients view as important in QoL, particularly wording differs.

Regarding social media, research is still ongoing to assess the differences and/or similarities between public social media (forum posts) and closed social media (the survey).

4. Workshop 2

4.1 Workshop 2: Objectives
The aim of the second workshop was to understand stakeholder views regarding the usefulness, and acceptability of the approaches demonstrated for using real-world data (RWD), and their potential impact on decision-making in pharmaceutical development, assessment, applicability, and authorization.

The workshop was attended by 37 delegates representing 20 different institutions from 6 stakeholder groups, namely: pharmaceutical industry, HTA organisations, regulatory agencies, patient organisations, academia and clinicians.

4.2 Workshop 2: Description of Sessions
The day focused on three main topics (see Appendix B for the workshop agenda). The first topic involved experiences with availability and accessibility of RWD from patient registries. The second topic discussed the added value and potential of using RWD to extrapolate overall survival. The third topic focused on the potential use of social media to collect patient perspectives on quality of life (QoL).

Workshop participants were divided into four mixed groups during a break-out session whereby delegates discussed the first two topics cited above. The third topic was discussed in a plenary format.

4.3 Workshop 2: Findings

4.3.1 Experiences with availability and accessibility of RWD from patient registries
The metastatic melanoma case study team initially aimed to gain access to IPD from three European patient registries. These registries originated from France, Italy and the Netherlands. Depending on the quality and comparability of these registries, the team intended to combine IPD from these registries and subsequently examine long-term outcomes (overall survival in particular) for several melanoma treatments. Unfortunately, all three registries approached declined the requests for data access or were unable to provide data in time for inclusion within this case study. The main reasons for declining access were potential privacy concerns, reluctance to lose control over their data or ownership of findings based on their data, and the timelines for access to data were restrictive.
During the first break-out session, workshop participants provided feedback and insight on the following discussion points:

1. Experiences in accessing RWD from registries (e.g. difficulties in negotiating access to data, delivery of aggregate data (AD) rather than IPD).
2. Alternative registry governance mechanisms that ensure access to data (e.g. prioritizing patient benefit above organizational goals).

**Stakeholders experiences in accessing RWD from registries**

Delegates indicated that gaining access to registry data is a recurring issue, with few exceptions. Accessibility to disease specific registries is particularly difficult, as opposed to product registries. An example was provided whereby access to data from a particular registry was denied without the provision of justifications. In another couple of examples, access to data was denied on behalf of ongoing PhD theses and academic research. Contrastingly, two delegates stated that access to data was granted under the provision that conducted analysis would not interfere with work being done by the PhD students simultaneously working on the registry data.

Surprisingly, delegates noted that accessibility of registry data may depend on the disease area in question (e.g. access to registry data on chronic diseases may be easier than for oncologic indications). For example, delegates indicated that researchers of the GetReal rheumatoid arthritis case study were actively approached by the registry to inform them of the availability of a new update of the data.

Some delegates expressed their concerns about the inaccessibility of registry data at the workshop. It was indicated that patients are usually willing to share their data for research, which implies that patient consent conventionally should not constitute an obstacle for RWD use in research by groups not directly associated with the registries concerned. Hence it was deemed unacceptable that researchers, other than those involved with the concerned registry, face such difficulty in accessing the needed RWD.

In the few cases where access to data was granted, usually summary or aggregate data (AD) was provided, rather than IPD. This could present several obstacles, depending on planned analyses, since AD does not conventionally include detailed information on covariates. As a result, it becomes difficult for research teams to examine the effects of covariates on observed outcomes. This is a strong limitation in the field of metastatic melanoma, where patient characteristics, as well as treatment patterns may have a considerable effect on overall survival. Consequently, many delegates shared the opinion that IPD from registries should be considered the gold standard for using RWD in long-term extrapolations.

Even when IPD is granted to external research teams, the length of time needed to clean such data presents another obstacle for its use for analysis. An example was cited for research conducted in the field of rheumatoid arthritis whereby the project team needed 3 months to prepare the data for subsequent analysis.

One important point discussed by delegates regarding the collection of RWD (e.g. within registries) is the lack of incentive for long-term follow-up. Delegates indicated that it is important to develop incentives in place for the collection of RWD beyond HTA approval, in order to ensure that
stakeholders such as pharmaceutical industry, clinicians and others continue to record RWD of robust quality. Disincentive measures (e.g. price renegotiations) could be considered in cases of product-registries, yet may not apply to disease registries. Another important limitation delegates noted was the difference in the quality of registries incorporating routinely collected data versus disease registries; the latter being generally considered to be of higher quality.

Several critical aspects were mentioned by workshop delegates for stakeholders attempting to access data from registries, namely:

- **Time**: research teams often underestimate the time required for their requests to undergo the full application procedures adopted by registries.
- **Legal aspects**: guaranteeing patient consent may be cumbersome and current European legislation on privacy of health data are also highly restrictive.
- **Connection/network**: delegates indicated that it is crucial to have internal connections with the registry (with the owners or the researchers involved in the analysis) to help initiate dialogue on applications for data access.
- **Collaboration with registry holders or researchers involved in the data analysis of the registry**: working together with the PhD students and researchers directly involved with approached registries can be quite constructive.
- **Experience of researchers on project team**: external researchers may be too inexperienced or unfamiliar with the type of data available from approached registries.
- **Practicalities in data handling**: on-site access to data may be a viable option, should data exportation be prohibited.
- **Outsource the analysis to the registry**: a project team can outsource the analysis to the research team directly associated with the registry. In this construction, the project team receives the summary of results needed to proceed with their interpretation of findings.
- **Purchasing registry data**: registries in the US and also some European countries provide the possibility to purchase their data. Although this may be an option, it can be very costly thus require substantial funding.

**Alternative registry governance mechanisms**

Delegates indicated that one of the most important aspects regarding setting up a registry and governing it, is the need of general understanding within society of the purpose of the data collection. It is believed that by emphasizing the patient-centered goals behind collecting and analyzing RWD, multiple stakeholders should be able to devise relevant governance mechanisms for setting up, funding and arranging data access for registries. This entails that all stakeholders deemed relevant should participate in steering committees of these initiatives, whereby a spirit of joint action is crucial for success.

At the moment, registries are set up based on undisclosed contracts, leading to situations where it is difficult to deduce why accessibility is difficult and which stakeholders are most involved in deciding on accessibility. Therefore, making such contracts transparent is another critical step for moving forwards.

Furthermore, there should be agreement on the type of data (e.g. PFS and/or OS, time of follow-up, biomarkers) to be collected, who collects the data, as well as a standardized procedure for the data collection. Delegates indicated that this has been an issue in some instances where the right level of
data was unavailable. Delegates indicated that promoting minimum datasets would be ideal. The European PARENT project could provide insights into these aspects, because they are drafting a guideline for the start-up of registries. This guideline would provide information on, for example the minimum dataset required as well as tools for standardized data collection.

In addition to these main points, delegates mentioned other important aspects relating to alternative governance mechanisms, namely:

- A SENTINEL-type approach: this is a database run and maintained by the Food & Drug Administration (FDA) in the U.S. In this structure, search queries can be sent by external researchers to participating databases, returning data on the requested information.
- Access to claims databases is conventionally easier than that of disease registries. However, their use is only relevant for effectiveness research through coupling to other databases such as mortality databases.

Other important points mentioned
In addition to the points listed above regarding the specific points discussed during break-out sessions, the following topics were mentioned which, though not corresponding to the topics of break-out sessions, are important for the general discussion on RWD.

Delegates indicated that RWD was particularly useful in the following instances: assessing rare diseases, mapping the natural history of disease, extrapolation of outcomes when specific patients are excluded from trials (e.g. in metastatic melanoma this includes patients with brain metastasis or elevated LDH levels), sub-group analyses related to biomarkers, genetics profiles, etc.

Delegates noted that the current landscape of registries is unsustainable; at the moment, there are large numbers of registries across Europe leading to a high registry burden. Consequently, it is becoming increasingly difficult to ensure and maintain the quality of all registries available. To limit the number of registries and the burden this poses to patients and doctors alike, it was noted that use should be made of existing data sources (e.g. linking existing databases or making use of electronic health records). Using such an approach may be possible, but depends on the disease and the covariates needed. However, not all delegates were fond of this approach, especially due to varying qualities and data structures between different RWD sources.

Finally, some delegates wondered whether access to IPD from registries is necessary or if AD would be sufficient to perform analysis. Other delegates indicated that the necessity of IPD depends on the research aim and analysis, for example IPD is particularly important when trying to combine data (e.g. from different registries or to RCT data).

4.3.2 Added value of RWD for extrapolation of overall survival
In light of not gaining access to RWD from registries, the case study team was able to identify RWD from two alternative sources: scientific publications of registries, and summary data from (lifetables) the SEER-Medicare database (a U.S. based registry). These data sources were used to augment the available RCT data to improve the extrapolation of long-term overall survival. The following approaches were considered:
Base Case: Non-informative extrapolation of the RCT

Approach 1: Extrapolate the RCT using scientific publications, by recreating IPD from published Kaplan Meier curves and use a long-term follow up study as a reference

Approach 2: Extrapolate the RCT using the SEER-Medicare database, by recreating IPD from the summary data available from the SEER-Medicare database

Approach 3: Extrapolation of the RCT using the combined sources of RWD

During the break-out session, workshop participants discussed the added value of RWD for extrapolation of overall survival by addressing the following points:

1. Stakeholders’ acceptability of alternative approaches conducted by the case study team (e.g. Is this approach intuitive and acceptable? What would stakeholders have done otherwise?)
2. The added value of how RWD was used in this example and the impact these results would have had on decision-making within stakeholder organizations.

**Stakeholders acceptability of presented approaches**

Several delegates indicated that from a decision-making perspective, the use of RWD and the approaches used in this case study may be acceptable, because making assumptions is part of data analysis. However, it is important that regulatory and HTA authorities and pharmaceutical industry discuss which assumptions are acceptable in particular contexts. In this case, a lot of detail is necessary for discussion and there is a need to know up front what will and should be done regarding collection and analysis of RWD, which proves to be difficult.

On the other hand, some delegates indicated that the RWD and approaches used in this case study are inappropriate and unacceptable for HTA decision-making purposes, due to the low quality of available registry data. Such RWD may only be acceptable if substantial differences would be observed between treatment alternatives, and then only as complementary to RCT data.

An important point to keep in mind, is that the approaches applied are inferior to using IPD from registries to demonstrate the value of RWD in long-term extrapolations of overall survival. However, should the case study team have had access to IPD, the following issues would still pertain to delegates’ acceptability of RWD use in this context:

- Representativeness of the data (generalisability).
- Duration of extrapolation in relation to the study period of RCTs.
- The goodness-of-fit of the analysis performed (e.g. how well do the curves fit to the synthesized data).
- Potential to assess sub-groups excluded from RCTs.
- Early access to patients coupled with systematic collection of data to learn the benefit and risks involved (MAPPs and conditional reimbursement as enablers).
- Clearly defining the data-model and data architecture before collection commences to ensure that the quality of RWD is as optimal as possible.

**Added value of RWD on extrapolation of overall survival**

Regarding this specific case study, delegates expressed strong concerns on extrapolation of overall survival based on aggregate registry data. However, delegates also indicated that extrapolation beyond the RCT timeline is an issue where RWD could provide a solution as long as a step-wise approach is used (e.g. where different scenarios are presented). The use of RWD may provide...
additional confirmation on the external validity of treatment alternatives. However, delegates voiced their concern regarding the generalisability of results based on only a selection of registries & publications to other available studies. Despite this, the discussed methods were deemed potentially helpful for other trials where there are few events.

Moreover, delegates indicated that such analysis present a starting point and further research would be needed to confirm findings. Delegates indicated that more case studies, and thus more experience with RWD, is important. It would also be beneficial to assess the extent to which actual IPD would improve the analysis and results done thus far.

RWD may be of added value regarding conditional reimbursement, whereby RWD could provide a reality check regarding real-world outcomes on overall survival after a pre-specified period of time. However, delegates indicated that agreement among involved stakeholders on a minimum dataset of covariates & outcome measures (e.g. treatment patterns, overall survival, response to treatment) is critical. Delegates also indicated that consensus on outcome measures is important as well as appropriate surrogate measures (e.g. standardized progression free survival for analysis on short-term basis and overall survival after a longer follow-up period for later analysis).

Delegates indicated that one of the major challenges with use of RWD in decision-making is the interpretation of results based on its analysis. To facilitate this, delegates mentioned the importance of transparency regarding biases and limitations associated with the data and analyses performed. On a different note, delegates wondered whether as statistical analysis became more complex that uncertainty regarding the interpretability and value of results would increase.

One issue that should be kept in mind is that not all HTA agencies would accept the use of RWD in this context. This raises the question: how could HTA agencies adapt their strategies in light of new oncologic therapies gaining marketing authorization on the basis of phase II studies, and sparse to no phase III study data?

**Other important points mentioned**

Delegates touched upon several aspects of RWD use in conditional reimbursement or MAPPs contexts. To begin with, RWD may be particularly useful for extrapolations on outcomes of first-in-class medications. Secondly, delegates indicated that the quality of data provided within conditional reimbursement framework is often of poor quality. According to some, this may be due to the limited time frame available to collect the required RWD. For example, NICE provides up to 2 years for additional data collection within the Cancer Drugs Fund and ZIN a maximum of 4 years. Delegates debated whether such time periods are sufficient for the collection of adequate RWD for decision-making.

Another point noted the difference between exhaustive registries versus tailored registries. On the one hand, exhaustive registries are thought to be operationally difficult (e.g. patient loss, motivation to maintain registries), on the other hand within tailored registries the definitions of outcomes and covariates is highly important (e.g. PFS, treatment patterns).

Delegates indicated that RWD has further potential within the following contexts:

- If RWD could lead to a reduction of the (decision) uncertainty (especially beneficial for HTAs).
• Assessing long-term side effects in earlier stages of research (e.g. pharmacovigilance).
• Inform research regarding alternative trial designs.
• Collect more relevant parameters (e.g. QoL).
• Use RWD for comparator arms of RCTs.

Delegates suggested that RWD may provide a starting point for future analysis. In addition, some delegates indicated that RWD has the potential to possibly act as a basis for the validation of RCT results, while other delegates indicated that RWD based on low quality sources should never be used to validate RCT results (the opposite would be possible though). Therefore, assessing the quality of RWD and reliability of results is important in this situation. To do so, a toolkit would be necessary to assess the quality of RWD available and provide guidance on best practices on methodology for analyzing and interpreting RWD.

4.3.3 Potential of social media to collect patient perspectives on QoL
The metastatic melanoma case study team used social media to assess patient perspectives regarding QoL, by distributing an online survey via the social media channels of Melanoma Patient Network Europe (MPNE). These results showed that patients rank family, having a normal life and actually being able to enjoy life as most important regarding their QoL. However, it was also shown that this differs between patients with different disease stages. Furthermore, when comparing patient preferences to existing QoL questionnaires, it can be argued that some questions featuring in QoL questionnaires, whether generic, cancer-specific or melanoma-specific, do not seem relevant to the patient population who filled in the online survey.

During the plenary session, workshop participants focused on the potential of social media to collect patient perspectives on QoL by discussing the following points:

1. Delegates’ own experiences in using social media for relative effectiveness research (e.g. adverse events, adherence, QoL).
2. Acceptability regarding the presented results generated by use of social media in light of strengths and limitations (e.g. cost-effectiveness vs. generalisability).

Stakeholders’ experiences in using social media for effectiveness assessment
Delegates mentioned the use of patient powered networks (PCORI) in the US to collect patient views and perspectives. Furthermore, regulatory agencies are becoming increasingly interested in patient engagement in decision-making. Although social media may provide a potential tool to better incorporate patient perspectives into decision-making, regulators are not sure if it is the best tool to do so.

Several pharmaceutical companies have experience with the use of social media, for example in assessing patient perspectives on treatment preferences, switching behaviour, and identifying adverse events. Another example given related to their collaboration with patientslikeme (www.patientslikeme.com), an online patient network where patients can discuss their disease, treatment, etc. It is envisaged to develop a disease specific patient reported outcome measure (PROM) based on patient perspectives gained via patientslikeme. In this specific case the smartphone would be used to interact with patients, as well as buying data from patientslikeme, and holding focus groups.
Both pharmaceutical companies and HTA agencies indicated the importance of social listening via social media.

In general, however, it was notable that experience in using social media specifically for REA by different stakeholders remains limited.

**Stakeholder acceptability regarding the conducted research on the use of social media**

Several issues were mentioned by delegates regarding the use of social media in this case study. Firstly, with such small numbers it would be wise to be careful when assuming differences between stages. Secondly, there is a difference between QoL and HRQoL, which may explain why it is difficult to relate the coding of the survey to the QLQ-C30 questions. Furthermore, such a difference in definition may make inferences inappropriate.

HTA agencies indicated that it is difficult and challenging to use social media data in assessments. Some delegates indicated that social media is not useful for regulatory or HTA decision-making at all. One of the major drawbacks is validating authenticity of study subjects, which has negative implications on the extent one can trust this source. In general, HTA agencies seem to find this source untrustworthy and therefore should not be used in regulatory or HTA decision-making. Delegates indicated that it is still too early for using such data, it may be more acceptable in ten years’ time. Furthermore, delegates suggested that RWD from more conventional RWD sources (e.g. registries) should be accepted by all stakeholders before data from social media would become acceptable. Therefore, we are still far away from actually implementing this data source. However, a pilot study with a chronic disease would be useful to assess the potential of social media further.

Delegates indicated that validated QoL questionnaires remain important for decision-making, and that social media could provide an opportunity to gain patient perspectives regarding such questionnaires. However, delegates do not see social media as the medium to gather actual QoL data. Delegates from HTA agencies indicated that social media could supplement traditional forms of research, as well as show differences between countries. Patient advocates indicated that social media is a great tool for sharing experiences, by the generation of valuable qualitative data.

Delegates indicated that it may be useful to consider commercial tools for data-mining social media (these tools are already used in big data). However, delegates wondered whether such approaches actually answer clinically relevant questions, since the approaches are often designed to identify correlations within the dataset before a strict research question is defined (i.e. hypothesis-generating analysis). This contradicts the traditional evidence-based research approaches.

**5. Conclusions**

Accessing RWD in the form of IPD from patient registries proved to be highly difficult due to several reasons, despite the team’s varied attempts to do so. Based upon stakeholder input during workshops, it appears that access to RWD in the form of IPD from registries remains an endemic issue faced by many stakeholders within their different fields of work. This impedes research into the use of RWD for extrapolation of long-term outcomes in practice.
Despite the scarcity of RWD eventually available to the case study team and its aggregate nature, it was shown that supplementing RCT data with (sub-optimal) RWD available reduced uncertainties in the extrapolation of overall survival estimates. Unfortunately, lack of access to IPD from registries did not provide the team with the opportunity to explore the added benefit of using IPD for the same purposes, whereby information on covariates is more abundant.

Social media may present an efficient tool for the collection of patient-reported outcomes such as QoL, adverse events and treatment switching. Stakeholders expressed that while some issues may remain with regards to validation of results based on social media, as well as their generalisability, this data source may complement more traditional research methods currently used. However, opinions remain divided as to whether this new source of data can be used in practice within the near future.

Finally, both the case study team and external stakeholders voiced the need for additional examples for the use of RWD for effectiveness research, whether for drug development, regulatory or HTA purposes in the future. Stronger collaboration amongst stakeholders is needed to achieve this, more specifically to overcome issues of data accessibility, address methodological considerations and develop consensus around the appraisal of RWD.

6. Deviations from Description of Work
There are no deviations from the description of work.
Appendix A: Workshop 1 Agenda

Final Agenda
GetReal WP1 First Workshop on Metastatic Melanoma
June 10th 2015 10:00 – 17:00
Thistle Holborn Hotel, The Kingsley
Bloomsbury Way, London, WC1A 2SD

Workshop overview: This workshop combines group break-out sessions and plenary discussions in order to understand how Real World Data (RWD) can be integrated into early drug development and relative effectiveness assessment of new treatments at the time of initial regulatory and Health Technology Assessment (HTA) decision making.

Workshop objectives: Several objectives can be identified for the first metastatic melanoma case study workshop:
1. Identify (missing) effectiveness challenges and prioritize which challenges are most likely to have the largest impact on drug development.
2. Identify which variables relating to patient populations and health outcomes are required to address effectiveness challenges.
3. Assess the issues for combining and analysing synthesised data on such variables from different registries, observational studies and Randomized Controlled Trials (RCTs).
4. Explore the expectations, limitations, and acceptability of using health data obtained from social media to be included as part of the evidence base for relative effectiveness research.
5. Discuss findings from focus group on patient perspectives on trial designs.

Workshop output: As a result of the discussions held at the workshop the case study work group will refine and complete the plan on RWD collection and data analysis. Moreover, discussions will inform the work group on how to proceed with research on the value of social media in relative effectiveness research. The finalised research plans will be shared with workshop delegates by August 2015 for their feedback.

The Chatham House Rule applies to this meeting:
When a meeting, or part thereof, is held under the Chatham House Rule, participants are free to use the information received, but neither the identity nor the affiliation of the speaker(s), nor that of any other participant, may be revealed.

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>09:30</td>
<td>Registration &amp; Coffee</td>
<td>N/A</td>
</tr>
</tbody>
</table>
| 10:00 (5 min) | Opening remarks:  
- Administration (Health & Safety, Facilities, etc)  
- Introductions | Rachel Kalf            |
| 10:05 (15 min) | Workshop start:  
- The GetReal project  
- Focus for the day (outputs & objectives) | Chair (Wim Goettsch) |
<p>| 10:20      | Presentation on the effectiveness challenges in decision-  | Amr Makady             |</p>
<table>
<thead>
<tr>
<th>Time</th>
<th>Event Description</th>
<th>Facilitators</th>
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<tbody>
<tr>
<td>10:50</td>
<td>Break-out session 1</td>
<td>Group facilitators: Amr Makady, Michael Lees, Mike Chambers, Reynaldo Martina</td>
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<tr>
<td></td>
<td>Tea/Coffee available on the way to breakout rooms</td>
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<tr>
<td></td>
<td>Identify and prioritize missing effectiveness challenges for decision-making and discuss how RWD may contribute to addressing such effectiveness challenges.</td>
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<tr>
<td>11:35</td>
<td>Plenary: Facilitators feedback from each break-out group (5 minutes each)</td>
<td>Chair</td>
</tr>
<tr>
<td>11:55</td>
<td>Presentation outlining the data sources available, analyses performed for cross evidence synthesis, and analysis plans for cross evidence synthesis and predictive modelling.</td>
<td>Michael Lees</td>
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<tr>
<td>12:40</td>
<td>Lunch break</td>
<td>N/A</td>
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<tr>
<td>13:40</td>
<td>Break-out session 2</td>
<td>Group facilitators: Amr Makady, Michael Lees, Mike Chambers, Reynaldo Martina</td>
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<td></td>
<td>Identify and prioritize issues related to data quality and definition of outcome variables as well as statistical methodologies available to perform data synthesis.</td>
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<tr>
<td>14:25</td>
<td>Plenary: Facilitators feedback from each break-out group</td>
<td>Chair</td>
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<td></td>
<td>Tea/Coffee available on the way to plenary room</td>
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<tr>
<td>14:50</td>
<td>Social Media:</td>
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<tr>
<td></td>
<td>- Introduction to social media</td>
<td>Rachel Kalf</td>
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<td></td>
<td>- Presentation on the Novartis social media pilot</td>
<td>Valéry Risson</td>
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<td></td>
<td>- Case study research on social media</td>
<td>Rachel Kalf</td>
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<td></td>
<td>(20 min incl. 5 min Q&amp;A)</td>
<td>Facilitator: Chair</td>
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<td>(10 min)</td>
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<td>(15 min)</td>
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<td>15:40</td>
<td>Patient perspectives</td>
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<td></td>
<td>- Presentation on the findings from the focus group on patient perspectives on trial design conducted at the MPNE conference</td>
<td>Sarah Garner</td>
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<tr>
<td>16:00</td>
<td>Panel discussion</td>
<td>Panel: Bettina Ryll, Jorge Camarero, Sarah Garner, Paolo Ascierto, Michael Lees</td>
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<tr>
<td></td>
<td>- Each panellist provides individual feedback on the days impressions (5 min each)</td>
<td>Facilitator: Chair</td>
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<td></td>
<td>- Open floor discussion</td>
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<tr>
<td>16:40</td>
<td>Summary, main outcomes of the day and next steps</td>
<td>Chair</td>
</tr>
<tr>
<td>17:00</td>
<td>Workshop End</td>
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**Guidance and Tips for Today’s Discussions**
Break-out session 1

Objective: In the presentation, several key effectiveness challenges will be highlighted. The objectives of this break-out session are two-fold: to gain your insights on your thoughts on the listed challenges (e.g. are any missing? which have the largest impact on drug development?) and secondly to discuss whether RWD can be used to help address the challenges mentioned. Briefly summarised, these effectiveness challenges relate to the following:

1. Inappropriate comparator selection in gp100 in 2nd line pivotal studies
2. Extrapolation of overall survival (OS) data from short-term RCTs in 1st and 2nd line patient populations
3. Absence of understanding of how reported adverse events (AEs) are managed in practice
4. Absence of RCT data for first-line treatment at approved dosage (3mg/kg)

In order to stimulate your thoughts on whether RWD can be used to address such effectiveness challenges, please see the questions below:

1. Pharmaceutical R&D: What is the value of inclusion of RWD from patient registries earlier on during drug development to improve estimations of relative effectiveness? How acceptable is the use of RWD from such registries to estimate relative effectiveness for HTA/RA stakeholders? What is the usability of RWD derived from registries in different member states for the estimation of the effectiveness of drugs on an European level?
2. HTA Agencies: To what extent can RWD be used to validate and/or improve generalisability of relative effectiveness estimates submitted as part of HTA submissions? How acceptable is the use of RWD to do so? What is the usability of RWD derived from registries in different member states for the estimation of the effectiveness of drugs on an European level?
3. Regulatory Agencies: To what extent can RWD be used to validate and/or improve generalisability of relative effectiveness estimates submitted as part of marketing authorisation applications? How acceptable is the use of RWD to do so? What is the usability of RWD derived from registries in different member states for the estimation of the effectiveness of drugs on an European level?
4. Patient Organisations: How can RWD be used to accelerate access to innovative and effective medicines for patients?
5. Registry owners: How can the data generated through individual registries be used to more effectively assess the value of a new treatment at the time of initial marketing authorisation? How can these data be used alongside data from other registries or cohort studies in order to increase the impact?

Break-out session 2

Objective: To identify issues related to data quality, comparability and transferability between different RWD sources (i.e. registries & phase IV studies), discuss the selection and definitions of important outcome variables, as well as statistical methodologies available to perform analysis of synthesised RWD & RCT data to address effectiveness challenges.

To help stimulate your discussion, please refer to the following questions:

- What are the issues related to the data quality of data from registries (e.g. completeness, comprehensiveness, comparability and transferability)?
- Which variables from registries and RCTs are required to assess relative effectiveness?
- What are the issues related to differences in definition of variables between registries?
- What are the options for combining data from registries to data from RCTs?
- What are the options for analyzing data from registries and for the combined registry and RCT data? For example:
  - Evidence synthesis using individual patient data (IPD) from patient registries (including a data quality assessment)
  - Cross-design evidence synthesis using IPD data
- Cross-design evidence synthesis using phase III/IV study data and registry data
- Predictive modelling of relative effectiveness (via network meta-analysis, propensity scoring, or other method)

Social media
Objective: Explore the potential for data on metastatic melanoma patients collected from social media sources to be included as part of evidence base for relative effectiveness research.
Questions:
- Would the use of health data obtained from social media in effectiveness research be acceptable?
- How can social media be used in the assessment of effectiveness during early and/or late drug development process?
- What are the expected limitations of health data obtained from social media?

Patient perspectives
Objective: Explore the possibilities for developing novel real-world study designs during drug development that better incorporate patient preferences.
Questions:
- What are potential different approaches to designing novel real-world studies that accommodate patient preferences?
- How should we address and measure quality of life better through incorporation of patient perspectives?
Appendix B: Workshop 2 Agenda

Agenda for IMI GetReal WP1 Workshop:

Use of Real World Evidence to Inform Relative Effectiveness Estimates for Metastatic Melanoma

Thursday May 19th 2016
09:30 – 17:00

Venue:
National Healthcare Institute (ZIN)
Eekholt 4
1112 XH Diemen, the Netherlands

Workshop overview:
This workshop combines group break-out sessions and plenary discussions in order to explore whether real world data (RWD) can be used for relative effectiveness assessment (REA) within metastatic melanoma and if it provides an added value.

The workshop will focus on three aspects: 1) Our experiences with availability and accessibility of registry data, 2) the added value and potential of using real world data to extrapolate overall survival, and 3) the potential of social media to collect patient perspectives on quality of life (QoL).

Workshop objective:
To understand stakeholder views regarding the usefulness and acceptability of the approaches demonstrated, and their potential impact on decision making in medicine development, authorisation, assessment, and use.

The Chatham House Rule applies to this meeting:
When a meeting, or part thereof, is held under the Chatham House Rule, participants are free to use the information received, but neither the identity nor the affiliation of the speaker(s), nor that of any other participant, may be revealed.
<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
<th>Presenter</th>
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<tbody>
<tr>
<td>09:30 – 10:00</td>
<td>Registration &amp; Coffee</td>
<td>N/A</td>
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<tr>
<td>10:00 – 10:15</td>
<td>Opening remarks: introduction &amp; announcements</td>
<td>Diana Delnoij &amp; Chair</td>
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<tr>
<td>10:15 – 11:00</td>
<td>Presentation: Experiences with registries (incl. Q&amp;A)</td>
<td>Amr Makady &amp; Michael Lees</td>
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<td>11:00 – 12:15</td>
<td>Presentation: Results on using RWD to inform extrapolation of overall survival (incl. Q&amp;A)</td>
<td>Keith Abrams &amp; Reynaldo Martina</td>
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<td>12:15 – 13:00</td>
<td>Lunch</td>
<td>N/A</td>
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<tr>
<td>13:00 – 14:00</td>
<td>Break-out session 1</td>
<td>Group facilitators: Amr Makady, Rachel Kalf, Michael Lees, Jessica Davies</td>
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<td>Tea/Coffee available in the breakout rooms</td>
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<td>14:00 – 14:20</td>
<td>Plenary: Facilitators feedback from each break-out group</td>
<td>Chair</td>
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<tr>
<td>14:20 – 15:05</td>
<td>Presentation: Results on using social media to collect patient perspectives on QoL</td>
<td>Rachel Kalf</td>
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<td>15:05 – 15:25</td>
<td>Coffee Break</td>
<td>N/A</td>
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<tr>
<td>15:25 – 16:00</td>
<td>Break-out session 2</td>
<td>Group facilitators: Amr Makady, Rachel Kalf, Michael Lees, Jessica Davies</td>
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<td>Tea/Coffee available in the breakout rooms</td>
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<tr>
<td>16:00 – 16:20</td>
<td>Plenary: Facilitators feedback from each break-out group</td>
<td>Chair</td>
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<tr>
<td>16:20 – 17:00</td>
<td>Panel session &amp; Workshop closing remarks</td>
<td>Panel: 1 Regulatory 1 Pharma 1 Patient/Registry Facilitator: Chair</td>
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<td>- Each panellist provides individual feedback on the days impressions (5 min each)</td>
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<td>- Open flood discussion</td>
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<td>- Closing remarks by chair</td>
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<tr>
<td>17:00 – 18:00</td>
<td>Drinks</td>
<td>N/A</td>
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8. References


(3) Sanford M. Ipilimumab in previously treated patients with advanced melanoma. Biodrugs 2012; 26 (3): 185-193


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)