ELSEVIER

feature

Early Access to Medicines Scheme: real-world data collection

Hok Pang[1], Meng Wang[1], Christopher Kiff[1], Mira Soni[2], Dara Stein[2] and David Tyas[1],
David.Tyas@bms.com

Real-world data (RWD) generated during the pre-approval phase could be supplementary to primary clinical trial outcomes; however, as we discuss here, a data collection framework is needed to ensure the validity and applicability of these data.

Introduction

The Early Access to Medicines Scheme (EAMS) in the UK was established in 2014 [1]. EAMS provides access to highly innovative medicines that address a significant, unmet medical need and are likely to offer considerable benefit over existing treatment options [2], but do not yet have marketing authorization. The Medicines and Healthcare Products Regulatory Agency (MHRA) administers the two-step process for EAMS by first granting the Promising Innovative Medicine designation (PIM) and then by awarding the EAMS scientific opinion (SO) [1]. The SO is based on the benefit–risk balance of the medicine demonstrated in the clinical trial data available when the EAMS submission was made [1]. A positive SO is valid for 1 year and can be renewed. The MHRA opinion does not replace the normal licensing procedures, but medicines with a positive SO can be accessed by patients from 12–18 months ahead of marketing authorization [1]. The initial EAMS application is made by the pharmaceutical drug manufacturer, but during EAMS, the request for the medicine with a positive SO is led by physicians and occurs on an individual patient basis.

Although several early-access programs across Europe and the USA have collected RWD outcomes, only a few appear to have incorporated into their guidelines the possibility of systematic collection of RWD to provide knowledge of the value of a product outside of a clinical trial setting. These include the UK EAMS, France Authorization for Temporary Use (ATU), and Italian Compassionate Use Programs [3–5].

In the UK, Health Technology Assessment (HTA) bodies, such as the National Institute for Health and Care Excellence (NICE), issue reimbursement guidance at the time of marketing authorization. Thus, the evidence assessment needs to be conducted in parallel with the marketing authorization process. Randomized clinical trials aim to demonstrate clinical efficacy and safety within a controlled environment. However, patient populations in clinical trials might not be fully representative of a real-world world population (e.g., marketing authorization applications based on clinical trials conducted in Asia may need additional RWD to support the use of the medicine in a Western population). HTA bodies evaluate the clinical and cost effectiveness of new therapies within their healthcare system and, therefore, are concerned with using high-quality RWD to inform their decision making. Currently, RWD collection before market authorization is not common practice because the therapies are not yet clinically available and data collection occurs outside of the scope of the clinical trial regulations. However, given the increased interest in RWD, HTA regulators are working to evaluate methods to incorporate RWD for appraisals before marketing authorization [6].

The MHRA guidance permits data generated through EAMS to be used to support marketing authorization applications [3]. Additionally, these guidelines suggest that EAMS data collection must include, at a minimum, information on patient demographics, disease characteristics, dose and duration of treatment, comorbidities, concomitant medications, adverse events, and other factors known to affect efficacy or other outcomes of importance [3]. Incorporation of additional data collection in EAMS, including long-term outcomes and patient-reported outcomes, must be agreed upon by all parties, including the National Health Service (NHS), HTA bodies, clinicians, and

https://doi.org/10.1016/j.drudis.2019.06.009

patients, on a case-by-case basis [7]. Although RWD collection is encouraged in EAMS and is one of the aims of the program, there is currently no framework for how to collect and incorporate these data for HTA submissions. As the use of RWD to support reimbursement and healthcare decision-making continues to grow, additional guidance on the use of RWD in EAMS and robust systems to collect the data, are necessary to facilitate ethics submission, enable consistency in data collection, and improve acceptability of this research for HTA submissions.

Between April 2014 and March 2019, 33 EAMS applications were submitted [8]. The MHRA awarded 23 EAMS positive SOs [8] and, of these, six were received by Bristol-Myers Squibb. In the most recent of these EAMS programs, Bristol-Myers Squibb collaborated with Evidera, a business unit within Pharmaceutical Product Development, LLC, a global contract research organization, to successfully collect additional (nonroutine) RWD in an oncology EAMS. These data included disease progression, overall survival, and quality of life (QoL). Here, we share lessons learned from this experience and provide a starting point for the development of a RWD collection framework for use alongside EAMS and other similar early-access programs in the future.

Development of RWD data collection framework for EAMS

Bristol-Myers Squibb and Evidera designed and implemented a RWD framework within an EAMS program to generate early real-world evidence in support of a promising new therapy (nivolumab) for use in advanced or recurrent gastric or gastroesophageal junction (GEJ) adenocarcinoma after two or more prior systemic therapies. Additional RWD outcomes, including disease progression, overall survival, and health-related QoL [EuroQol 5Dimensions 3-Level (EQ5D-3L)] [9] were incorporated into this EAMS. Given that the premise of EAMS is to provide rapid treatment access to patients with high unmet medical need, the RWD collection approach was designed to avoid hindering or deterring drug access. A flexible approach to incorporating RWD was essential so that patients and sites did not feel that they had to participate in the additional observational research to gain access to nivolumab. Implementation was successful for three reasons: (i) early key stakeholder identification and engagement in EAMS planning; (ii) RWD integration with minimal additional effort for site staff and patients; and (iii) ability for patients to report on their QoL during and beyond treatment.

Although physicians and patients were informed of the benefits of RWD collection, and RWD collection was designed to have minimal burden, participation in the additional observational research with EAMS was optional, and separate consent forms were completed for EAMS and the observational research. The development of a RWD framework was not straightforward, given the general lack of formal guidance and because this was, to our knowledge, the first UK EAMS program to incorporate data collection for clinical effectiveness and QoL outcomes. However, the steps outlined below led to successful ethical approval and implementation of data collection within the EAMS program.

First, a synopsis that outlined plans for additional RWD collection was submitted to the MHRA for review and feedback. Once feedback was received, adjustments were made as needed, and an observational research protocol was developed and submitted to the UK Health Research Authority (UK HRA) following the same pathway that would be used for an observational study. This protocol was submitted in parallel to MHRA for approval of the launch of EAMS. It was essential to engage key stakeholders (MHRA, UK HRA, NHS-England, and NHS-Scotland) to vet the RWD approach and to identify potential uncertainties or hurdles that might have arisen during the ethics submission and RWD collection process. These stakeholders were approached simultaneously to ensure that RWD approvals were in place in parallel with MHRA approval of EAMS scientific opinion.

Second, the observational research component of EAMS was designed to minimize administrative burden for site staff and patients. Combining observational research training with the EAMS training was efficient and well received by clinical staff. Data collection was simplified to include only a few key outcome measures, and physicians entered observational data using the same data collection tool that is required for other aspects of the EAMS program.

Third, patients were asked to report on their QoL during and beyond treatment, which is distinctive given that QoL outcomes outside of a clinical trial before market authorization are rarely collected. Patients completed the EQ-5D-3L questionnaire at baseline and then fortnightly over 24 weeks, in line with trial data collection time points and clinic visits for nivolumab infusion. The timing served as a reminder to complete the questionnaire and probably increased completion rates. This aspect of RWD collection in EAMS was particularly successful, as evidenced by completion of baseline and follow-up data by approximately three-quarters of the patients who initially consented to EQ-5D-3L (to date), with data collection ongoing. The ability to continue data collection beyond the EAMS study period (and beyond market authorization) is an additional advantage of the study design.

Finally, rigorous adverse event monitoring was an integral and important part of the approval of the EAMS scientific opinion and RWD data collection. All sites (and Evidera) were instructed to report all adverse events regardless of the relationship to nivolumab. Additionally, completed EQ-5D-3L questionnaires were submitted to the pharmacovigilance department of Bristol-Myers Squibb to monitor changes in QoL outcomes as a part of safety reporting. These sources provided additional, relevant safety data that help to inform patient care and to ensure that the benefits continue to outweigh the risks during the EAMS period.

Challenges with incorporating observational research in EAMS

It was not possible to select sites in advance because the request for drugs in EAMS is led by physicians. Multiple stakeholders (e.g., drug manufacturer, NICE, MHRA, NHS-England, NHS-Scotland, registered charities, and disease awareness organizations) are involved in ensuring that physicians and patients are aware of drugs available in EAMS. This process contrasts with that of traditional observational studies in which sites, eligibility criteria determining the characteristics of patient population, and sample size are known before study initiation. Therefore, special procedures were required for the set-up of the study at the hospital (to register sites with the UK HRA and to distribute study materials) and for training of clinical staff.

Given that this was the first EAMS to incorporate additional RWD data collection, hospital research and development departments were not familiar with how this research would impact the site. Official confirmation of capacity and capability was not required for sites to participate in EAMS observational research. Nonetheless, some sites chose not to participate in RWD collection because of the uncertainties around time commitment and staff availability.

Typically, within pharmaceutical companies, infrastructure for data collection before market authorization is more focused on clinical trials than on RWD. Programs such as EAMS require a different approach to data collection because they are aiming to understand real-world care as opposed to the controlled clinical trial environment. This means that their capabilities and

standard operating procedures to collect RWD before marketing authorization might be limited and, thus, need to be developed.

Future considerations

The burden of data collection could be further reduced for sites with electronic medical record (EMR) systems that permit direct extraction of the study variables from the EMR system, thus obviating the need to perform manual data entry. However, the ability of sites to directly extract EMR data would need to be assessed in a timely manner because it is not possible to know in advance which sites will participate in EAMS. Alternatively, a common data collection portal for RWD collection in EAMS across NHS Trusts could provide structure to data collection and increase its validity for use in market authorizations. Potentially, this would build upon existing EMR systems, to avoid significant impact on site administrative burden by requiring multiple systems for registering patients, requesting drug supply, and entering RWD. If an NHS Trust-wide system could be used consistently across EAMS programs, this might avoid the need to provide site training in data collection. Additionally, the ability to collect patient-reported outcomes electronically might increase the response rate.

Concluding remarks

In summary, RWD generated during the pre-approval phase could be used to supplement primary clinical trial outcomes in submissions for regulatory market approval and HTA submissions. The number of early-access programs that are being initiated by pharmaceutical companies is increasing to bridge the treatment availability gap between clinical trials and commercial availability. Therefore, knowledge sharing is essential to improve consistency in RWD collection in future EAMS and similar early access programs, which will benefit all stakeholders and, ultimately, patients in the future.

Conflicts of interest

H.P., M.W., C.K., and D.T. are employees and stockholders of Bristol-Myers Squibb Pharmaceuticals Ltd., which provided funding for this work. M.S. and D.S. are employees of Evidera; Evidera received funding from Bristol-Myers Squibb Pharmaceuticals to conduct this work.

Acknowledgements

This work was supported by Bristol-Myers Squibb Pharmaceuticals. We would like to thank Sue Bailey, as well as the MHRA and NHS England for reviewing this article. Editorial support was provided by Kim Poinsett-Holmes and funded by Bristol-Myers Squibb Pharmaceuticals.

References

1 GOV.UK Guidance (2014) *Apply for the Early Access to Medicines Scheme (EAMS).* GOV.UK
2 O'Connor, D.J. *et al.* (2017) Earlier patient access – the UK Early Access to Medicines Scheme (EAMS). *MA@POC* 1, e37–e39
3 Medicines and Healthcare Products Regulatory Agency (2014) *Guidance for Applicants for the Early Access to Medicines Scheme (EAMS) – Step II.* MHRA
4 Agence Nationale de Sécurité du Medicament et des Poduits de Santé (2015) *Notice to Applicants for Marketing for Temporary Authorisation for Use (ATU).* ANSM
5 Italian Ministerial Decree (7th September, 2017): Discipline of the therapeutic use of an investigational medicinal product. *Ital. Off. Gazette* 256, 23 2nd November
6 Academy of Medical Sciences (2018) *Next Steps for Using Real World Evidence: Summary Report of a FORUM Follow-Up Roundtable Held on 24 January 2018.* Academy of Medical Sciences
7 GOV.UK Guidance (2018) *Early Access to Medicines Scheme (EAMS): Task Group and Principles.* GOV.UK
8 Medicines and Healthcare Products Regulatory Agency (2018) *Official Statistics. Scientific Opinion Statistics.* MHRA
9 EuroQol Group (2017) *EQ-5D-3L.* EuroQol Group

Hok Pang[1]
Meng Wang[1]
Christopher Kiff[1]
Mira Soni[2]
Dara Stein[2]
David Tyas[1,*]

[1]*Bristol-Myers Squibb Pharmaceuticals Ltd., London, UK*
[2]*Evidera, London, UK*

**Corresponding author.*