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Assessing the value of cancer treatments from real world data—Issues, empirical examples and lessons learnt

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ABSTRACT

There is an increasing demand for real world evidence. The shift towards relative effectiveness assessment increasingly based on real world data is a natural consequence of the shift towards new adaptive pathways for development and introduction of new medicines in cancer care. The increasing number of alternative treatment options will further increase the need for outcomes data to help optimize the clinical pathways and resource allocation. In this article the authors explore the opportunities and challenges of real world evidence based on three case studies in cancer care. The central theme is to identify what knowledge gaps can be filled by real world data. Three areas of utility are identified: (1) to validate surrogate endpoints impact against hard endpoints and outcomes over time; (2) to valuate new treatments outside the strict protocol of clinical trials and (3) to optimize the value of new treatments based on regional variations in uptake. The authors also reflect upon how to increase the availability of real-world evidence and ensure sustainable access to needed data. European collaboration could be part of the solution.

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1. Introduction/background

Health care providers and particularly third-party payers in Europe, the US and other developed nations are facing increasing pressure from demographic and structural economic changes. An important challenge lies in ageing populations and increased demand for health care services that will have to match the size of budgets determined by taxpayers' and buyers' of health insurance ability and willingness to pay. In this context it is important that the treatments used give a high value to patients and society.

With an impressive number of new drugs in the development pipeline, the competition and the demand for evidence is high. As many of these treatments will be classified as orphan drugs, the narrow patient population means it will take a long time to develop evidence to support relative effectiveness assessment. Consequently, many products are expected to come to the market

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with limited trial-based data collected during a short time frame combined with epidemiological prognostic data to support a traditional cost effectiveness assessment. This increases the need for post authorisation evaluation and the generation of real world evidence which in turn may take advantage of longer follow-up time. In essence, the shift towards relative effectiveness assessment increasingly based on real world data is a natural consequence of the shift towards new adaptive pathways for development and introduction of new medicines in cancer care. The increasing number of alternative treatment options will further increase the need for outcomes data to help optimize the clinical pathways and resource allocation.

The randomized controlled clinical trial designs sometimes contrast significantly with what happens when new drugs are released into clinical practice. In this article we reflect on some challenges identified in estimating the value of cancer treatments from trial data and the utility of real world data for generating evidence, using three empirical examples.

2. Real world data—which knowledge gaps can they fill?

The randomized controlled clinical trial is the gold-standard trial design to measure safety and efficacy of a treatment. To do so the typical randomized trial apply carefully defined selection criteria and tight research protocols. The primary aim is to achieve high internal validity at this stage. Once evidence is achieved that the medicine works and is safe, the next step is to explore further how the medicine works in clinical practice. In fact, a range of issues relevant to estimating the value of a medicine can only be answered by non-intervention, observational studies, preferably in several settings.

2.1. Challenge 1: when trial data is restricted by surrogate endpoints and short-term follow-up [1]

One challenge is to estimate the benefit of the studied treatment over the relevant period of time, whether the primary outcome of a study is related to morbidity (e.g. disease severity, progression rate or complications) or mortality (gains in overall survival). A short follow-up period, sometimes in combination with surrogate endpoints that cannot readily be translated into patient value (e.g. progression-free survival), pose a challenge for assessing the value of a treatment. In the cancer context, health technology assessments and cost-effectiveness studies need estimates of gains in mean survival, whereas trials are powered to study differences in progression-free or overall median survival. With new cancer drugs that have an opportunity for a long survival for some patients, the difference between median and mean survival can be considerable. Immuno-oncology drugs for treatment of malign melanoma are examples. Yervoy, approved in 2011, has the longest-term data of the three approved drugs, with an eight-year survival rate of about 20 percent. Median survival in the phase 3 trial was 10 months. It is mean survival that is relevant for assessment of value and cost-effectiveness, and early predictions on gains in mean survival may have a high uncertainty [2]. The standard randomized clinical trial format for generation of all evidence may thus be insufficient even if there is evidence on improvements in median survival.

From the research perspective, survival is usually a straightforward outcome to follow in real world. While trial populations would normally be followed also beyond the termination of the trial, a challenge is to extend the compilation of data to include also non-trial patients. To generate high quality real world data and enable evaluation of effectiveness, key information post-launch should be registered on all patients that are clinically eligible for the new medicine. Treatment choice and duration together with mortality is a minimum. Additional variables with individual level information may be valuable and the specific set of real-world data evaluation should be adapted to the needs for each medicine. In countries where population registers allow high-quality follow-up of all-cause mortality, and even information on disease specific mortality, these data should be routinely analysed on a population basis as part of implementation of all new drugs. Non-interventional studies are inherently inferior to the randomized controlled trial in terms of estimating effect size, however, there are a number of methods and study designs that can be utilized to estimate the effectiveness of a treatment in real world. Indeed, it is possible to use even group-level data to explore the value of new treatments as is shown below in section “Exhibit 1: Treatment advances for chronic myeloid leukemia – Using retrospective real-world data to measure value of new technologies”.

An additional, but closely related issue, is that it is not feasible nor can it be economically defended to conduct trials exploring all potentially possible combinations of treatment strategies in all potentially relevant subgroups. With an increasing number of treatments available, the use of combination therapies and the sequencing of treatments are other factors that may affect the value of a given treatment in the real world setting. The challenge lies in finding feasible strategies to make use of the data that can be, but not always are, systematically collected also post-launch.

2.2. Challenge 2: when trial data use selected patients

Discrepancies between patients selected for participation in randomized clinical trials and the full set of patients that may be eligible for treatment in clinical practice is another challenge when assessing the value of a treatment. Randomized clinical trials may exclude patients with certain characteristics, e.g. patients above or below a certain age, patients with certain comorbidities, patients with some types of concomitant treatment or based on measurements of disease severity. While the inclusion/exclusion criteria may be essential for the establishment of internal validity of the trial results, they may affect external validity and questions on whom to treat may remain. Discrepancies between studied and real world patients results in a biased estimate of the value of the treatment in real life if excluded patient groups (within the indication) would have had a different effect size, had they been included. Similarly, rates of adverse events may differ between studied and real world populations. Studies of real world usage of a treatment may therefore have an important role in filling knowledge gaps of risks and benefits of treatment in patient populations (within the indication) that would have been excluded from the controlled trial. In addition, approval of a medicine on one indication does not preclude that the medicine also carries benefits in other patient groups, only that it is not studied within trials yet. Section Exhibit 1 provides an example where new real world evidence complemented previous trial based knowledge and added new findings.

2.3. Challenge 3: when research protocols meets daily clinical practice

The value of a treatment in a real world setting may differ depending on how the health care around the patient is organized. Clinical trials’ strict protocol and careful follow-up are often not representative of real world clinical practice. The benefit of the treatment in clinical practice depends on e.g. the clinics’ adherence to guidelines, routines for follow up or the quality of information given to the patient. The characteristics of patients offered a treatment can vary between health care settings, thereby affecting the value of the treatment. Knowledge of how a treatment is actually used in clinical practice, and whether and how that affects the value cannot be gained from the clinical trial pre-market autho-

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