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Position Paper

The use of real-world data in cancer drug development

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Abstract Excitement about the dramatic increase in potential successful anticancer medicines in recent years is hampered by the high costs involved as well as the length of time traditional pathways take for regulatory approval. The translation of experimental clinical data into real-world evidence is also problematic. While the randomised controlled trial remains the gold standard for assessing efficacy and safety, there is increasing interest in the use of observational data to enable more rapid, informed and widespread availability and access to important anticancer medicines. Taking real-world evidence into account in regulatory and health technology assessment in a thoughtful and balanced fashion will enrich and justify sound decision-making.

Despite the recent development of many new therapies, advanced cancer is still a largely intractable disease, and the high mortality rate proves the need for better treatment [1]. The regulatory approval of new cancer drugs is built on a benefit–risk paradigm based on objective criteria of efficacy and safety [2]. However, with the advances in genetic and other molecular and clinical subclassification of cancers, the number of patients available for a specific clinical trial may be too small for proper assessment of benefit–risk. Thus, there is a need for rethinking traditional approaches to drug development and approval [1,3]. A potential solution may be to complement results from randomised trials with the wider experience of real-world evidence. This issue was discussed in a CDDF workshop held in collaboration between academia, industry, regulators and health technology assessment (HTA) bodies (www.cddf.org).

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Drug regulatory agencies face the challenge of balancing timely market access to new drugs and the need for comprehensive and valid data on benefits and risks. Some criticise regulatory agencies for allowing drugs on the market too early whereas others call for more comprehensive safety data and more thorough assessment procedures. Although there are obvious advantages to speeding access to efficacious drugs, there are also drawbacks [4]. Any success of early access depends on the extent to which postapproval experiences and follow-up studies are able to confirm clinical benefits.

The main basis for a marketing authorisation (MA) is experimental data, and randomised controlled trials (RCTs) are considered a necessary part of a licence application. It has long been recognised that not all questions may be answered by randomised trials, and there is an increasing interest in using observational data, sometimes termed real-world data (RWD), as part of the drug development process. After promising early phase results, RWD might be used to supplement or adjust traditional requirements for confirmatory trials [5]. HTA bodies are aware of the different experiences both for patients and physicians once a newly licensed medicine is released to the wider general population, in comparison to the selected patients contributing to pivotal licensing trials [6].

After a drug has been granted an MA, a number of countries revisit the relative efficacy and effectiveness of a new treatment in comparison to the standard therapy as part of their decision-making processes for reimbursement and pricing. It is important to know how a new substance compares with existing treatment options, but the assessment of therapeutic benefit is often hampered by the lack of comparative information [7], and decision makers express an increasing demand for data on comparative effectiveness and safety of drugs outside controlled clinical research settings to reduce uncertainty at the time of reimbursement decisions.

The increasing access to administrative databases and electronic health records (EHRs) provides opportunities to conduct observational studies without having to collect new data [8] and could serve two purposes at the same time: help regulators define the benefit–risk balance of a new drug and support HTA bodies in their assessment of the added value outside an experimental situation.

Essentially there are at least three key incentives to add RWD to drug development in oncology [1]: the choice of the right comparator drug is critical when it comes to translate trial results into meaningful treatment scenarios. RWD can guide and inform drug developers to select the most appropriate comparator [2]; we increasingly see single-arm studies in oncology where the comparison is made with historical controls, particularly when a large treatment effect is expected or randomised comparisons are not feasible. RWD can provide natural course of disease data, with and without medical interventions to substantiate such comparisons [3]; most oncology regulatory and (often also) HTA dossiers contain progression-free survival (PFS) and/or overall survival (OS) data. These end-points are considered valid to evaluate efficacy of anticancer drugs but are rather poor in bringing (long-term) safety or quality of life data to the equation. Particularly HTA decision makers have signalled the lack of valid RWD that can be tailored to fill that gap [9,10]. The need for comparative RWD to address the question which therapeutic regimen delivers most clinical benefit for certain well-defined patient populations is increasing in areas where there is a rapid influx of multiple treatment options, such as multiple myeloma. Recently, Luo et al. evaluated both thalidomide and lenalidomide in routine care to compare survival and peripheral neuropathy in an observational cohort study of multiple myeloma patients. The study confirmed early trial results, that is, similar survival outcomes between the two products but differences in neuropathy [11].

1. Randomised controlled trials

RCTs are the backbone of an application for the MA of a drug. A large fully blinded RCT incorporating preplanned subgroup analyses is likely to provide the best possible evidence of efficacy. There are, however, circumstances when an RCT is deemed unethical or impossible to conduct for instance in rare diseases owing to small patient populations.

In an era of targeted therapy, it has been questioned whether it is feasible or even necessary to perform randomised phase III trials before a drug is licensed [12], and there is a growing interest in novel clinical trial designs that might improve the efficiency of the drug development process and increase patient access to promising investigational drugs. A major challenge to giving a licence before confirmatory randomised trials are finalised is that there may be less definitive data on safety and efficacy and that postmarketing studies may fail to confirm a positive benefit–risk balance. For ethical or methodological reasons, it may even be impossible to conduct or finalise a confirmatory randomised trial after the drug has been launched, and this may preclude valid estimates of benefit–risk for proper decision-making.

2. Generalisability of trial results

Randomised trials are criticised for operating in an idealised experimental environment, not necessarily focussing on the most relevant comparator, and offering an estimate of the efficacy of a drug rather than a true measure of effectiveness [13]. It has been estimated that only 2–4% of adult cancer patients participate in clinical trials, and it may be questioned whether these patients are, therefore, representative of the population of

patients that might be eligible for treatment in practice. Indeed, the same characteristics that contribute to the high internal validity of RCTs can hamper their external validity [14–16].

A major problem is underrepresentation of the elderly and other disadvantaged groups. As an example, metastatic colorectal cancer (mCRC) survival has improved from 12.6 to 23.9 months over the last decade, but these results should probably not be extrapolated to the general patient population. In an unselected mCRC population, OS was 18 months for those treated with chemotherapy and 21.3 months for participants in chemotherapy trials, whereas OS for all patients was 10.7 months, with short survival for those aged >75 years who were not treated at all (2.8 months) [17]. An obvious explanation to discrepancies between observational studies and randomised trials is that trial patients have better prognostic factors such as younger age, better performance status and less comorbidity than patients not included in clinical trials [18].

Efficacy estimates from randomised and observational studies may differ, and it has been argued that non-randomised trials tend to overestimate efficacy [19,20]. Others find that even though results differ, no method leads to consistently greater effect than another [21–23]. In situations where both randomised and observational studies have been conducted, the main issue is whether efficacy estimates are consistent for patients with a similar risk profile.

3. Pragmatic trials

Pragmatic trials are designed to evaluate the effectiveness of interventions in real life, whereas confirmatory trials aim to test whether an intervention works under optimal conditions [14]. Thus, policy makers have a keen interest in pragmatic trials because these are designed to assess comparative effectiveness. In the regulatory setting, instead of leaning on traditional observational studies to confirm early evidence of efficacy, it has been proposed that when novel cancer drugs meet specific criteria (e.g. conditional approval), a prospectively designed randomised pragmatic trial preagreed with regulatory authorities could provide sufficient evidence for verification of clinical benefit, leading to full approval [24]. Such pragmatic trials would be prospective clinical studies where patients are randomised between two or more interventions and then followed up according to usual practice. The advantages would be that strict adherence to protocol would not be required, patients would be more representative of 'real-world' patients and such trials would also address questions regarding the new drug's value for reimbursement purposes. The downside is potential for bias because such trials are open label, trial end-points are limited by routine care and treatment switching might dilute efficacy estimates. On the other hand, randomised studies embedded in routine care that assess patient outcomes by electronic record databases are cost-effective and may reduce residual imbalances in patient characteristics at the start of a study [25].

4. Real-world data

Observational data or RWD can be defined as any data that do not arise from interventional or experimental studies. In terms of drug development, RWD would mean any data that are not the result of a clinical trial. Instead, data are collected from routine clinical practice, either prospectively or retrospectively. The term would include patient outcomes and data on drug exposure and goes beyond what is normally part of phase III trial programmes in terms of efficacy (and safety).

The European Medicines Agency (EMA) considers that RWD are a crucial element in the monitoring of drugs [26]. Such data can complement and enhance evidence collected in RCTs and are especially useful to capture rare events and long-term outcomes [27] and to support validation of biomarkers.

4.1. Sources of data

RWD can be collected from a number of different sources such as databases, patient and population surveys, patient chart reviews, EHRs, cohort studies and health registries. Each source has its own potential and challenges, be it data quality, access and linkage with other sources, coverage or information included.

4.2. Electronic health records

The development of EHRs has greatly enhanced the feasibility of collecting RWD, and there are a number of member state and EU-level initiatives trying to increase the quality and value of RWD. In Europe, it is particularly appreciated that harmonisation of process and quality control for each EHR across member states would be very advantageous to the research community, to regulators and to HTA bodies. One example completed in 2015 was the EHR4CR programme to develop tools and services for reusing data from EHR systems used for clinical research. The resulting platform will provide secure access to multiple EHR systems, thus facilitating the assessment for a sponsor of the feasibility of finding eligible patients for candidate clinical trial protocols and to locate the most relevant institutions. The Innovative Medicines Initiative (IMI) GetReal [28] was planned to develop new methods of RWD collection specifically aimed at early adoption by the pharmaceutical industry and HTAs. Although not primarily focussed on cancer, the European Medical Information Framework aims to collect available patient-level data on up to 40 m European patients across seven member states via advanced search and navigation interfaces.

While there may be concerns regarding data quality due to missing information and non-systematic data collection, information gathered from EHRs can lead to information from a very large, possibly unselected patient population without the need to set up a traditional phase IV trial designed to fulfil postapproval commitments. However, significant challenges remain with regard to linking, organising and analysing data from different sources. Many available data currently reside in separate research databases, and there is a need for better methods for extracting patient information from distributed databases without making patients identifiable.

4.3. Patient registries

The value of patient registries is appreciated most particularly for rare diseases and this often includes cancer. EU-level initiatives on patient registries include the PARENT Joint Action and the European Network of Cancer Registries (ENCR) Eurocourse and the EMA initiative on patient registries. The objective of the PARENT Joint Action was to develop interoperable patient registries in fields of importance such as chronic disease and medical technology. A principal concern was to develop cross-border settings for analysis of data both for public health and research purposes. Guidance has been produced on methodology and governance of patient registries in addition to a web-based inventory—the registry of registries. In future, it is important to determine whether such guidelines can be of value to organisations such as the ENCR, learning from the governance principals and the technical guidance provided by the PARENT programme.

4.4. Population-based cancer registries

The primary activity of a population-based (or central) cancer registry is to generate statistics on the incidence of cancer by identifying all cancer cases in a relevant population, but their use has progressively developed to include information on patient survival. In the 21st century, their role has expanded further and includes cancer control activities such as screening projects and detailed information on treatment of individual patients. In 1966, 32 cancer registries reported results on cancer incidence; in 2006, the number of registries had increased to 449 covering 21% of the world population [29]. In most countries, one or more registries provide coverage of a sample of the population, but in some smaller countries, entire national populations are covered.

The Nordic countries are well known for their large number of population-based health registries and access to population based EHRs. As an example, the Norwegian Cancer Registry (www.kreftregisteret.no) has had compulsory, nationwide registration of all cancer patients in Norway since 1952. Table 1 shows the main information recorded for all Norwegian cancer patients. The registry includes coding of primary tumours, patient follow-up and survival and can be linked to other registries and sources of data by the patient's personal identification number. To maximise the use of the data and to understand which patients benefit from diagnosis and treatment, disease-based registries have also been developed, and in 2016, there were eight clinical registries with national status. There is great, unused potential for the use of such data in phase III and IV of cancer drug development. The registry can be used to identify patients, has a system in place for follow-up which would be extremely useful in a pragmatic trial setting and can link with other registries.

Other more recent examples of population-based registries include Flatiron's non–small-cell lung cancer cohort comprising ~26,000 patients from 198 US clinics (www.flatiron.com) and UNICANCER's 14,000 French breast cancer patients (www.unicancer.fr).

4.5. Data quality

It is appreciated that there are significant challenges to realising the potential of RWD across Europe; these include the fact that not all member states have extensive use of EHRs and in some member states, it is the insurance market that is responsible for this. It is, therefore, commercially owned data—which may not be freely available. This is a particular concern to the long-term follow-up of cancer patients, especially in the situation of records being anonymised if individuals leave one healthcare system for another. A further point particularly concerning cancer is that eHealth records are often of better quality in the community than in the hospital setting, and this could be of specific concern for the introduction of new anticancer medicines. It is appreciated that data quality and terminology vary in different languages and different member states and that work may be required to improve the retrieval of eHealth data of an appropriate standard. In general, methods for monitoring safety are better developed than

Table 1
Information recorded in the Norwegian Cancer Registry.

Information recorded
Name and personal identity number (age and sex)
Address and municipality of residence
Site of origin of cancer
Morphological diagnosis
Spread at the time of diagnosis
Metastases
Relapses
Diagnostics
Treatment (including complications or adverse events[a])
Date and cause of death

[a] Clinical registries; prostate, colorectal, breast, lung, melanoma, lymphoma/lymphatic leukaemia, gynaecology and childhood.

those for efficacy studies, and this is, of course, of particular concern for HTA with potentially expensive new anticancer medicines. The problem of obtaining sustainable funding for routine health monitoring is universal.

A crucial issue is to what degree data can be trusted. Different sources undergo very different types of quality assurance, and potentially no source is as closely monitored and quality assured as an RCT intended to be part of a licensing application. Although certainly not a rule, is likely that the risk of measurement error and misclassification of either outcome or exposure (or both), and perhaps also missing values on certain variables is larger with observational data from different kinds of registries. That might in turn affect estimates of efficacy and safety of cancer treatment. The value of large studies that use low-quality data may on occasion be limited by their tendency to produce precise but biased estimates [8].

If OS is the outcome of interest, the degree of misclassification is expected to be small, but cause of death registers will never be fully up to date and tend to have a potentially large lag time. If a 'softer' end-point such as progression-free survival is the main focus, the risk of bias increases with observational data. Assessment bias can only be truly avoided if the assessment is blinded.

5. Methodological challenges

The main threat to valid conclusions on efficacy based on observational data is confounding. Inferences about the effect of treatment may be invalidated because the data are observational rather than experimental [30] and it is necessary to control for systematic differences to ensure a fair and valid comparison.

From a scientific point of view, the larger the database both in terms of number of patients and in terms of number of patient characteristics registered the better. The problem of confounding is, however, unfortunately by no means precluded by access to high-quality data because patients who are exposed to a certain treatment will usually differ with regard to characteristics other than treatment and a direct comparison of exposed and unexposed is likely to be unfair or biased. Who are the patients not using an innovative agent, despite its expected benefit?

The choice of treatment usually depends on disease severity and duration and the challenge is how to avoid or reduce confounding by indication [31], which is a serious threat to valid conclusions in observational studies. Even if one tries to control such bias by including confounding factors in the statistical model, the risk of misinterpretation without randomised drug allocation remains high. Patient characteristics that drive new drug decisions can vary from drug to drug, and in the extreme case, patient populations receiving different drugs are simply not comparable, especially in the immediate postmarketing period [32]. The approaches to control for confounding by indication are the same as for confounding by other factors: adjustment in multivariable models, stratification or matching.

Even if proper adjustment for known confounding factors has been performed, uncontrolled or residual confounding may occur as some factors may not have been measured. The possibility of residual confounding from known or unknown factors is difficult to exclude. Unfortunately, confounding variables are rarely the only important source for uncertainty [33]. Residual confounding may also be due to measurement error or misclassification of the confounding factor.

A possible solution to the problem of unbalance in patient characteristics between the treatment and control group is to use propensity scores. The basic idea of propensity score methods is to replace the confounding variables with a function of these—the propensity to receive treatment A rather than B. This score is then used as if it were the only confounding variable. Treatment group membership is predicted for example by logistic regression involving all covariates but not the outcome of interest. Each patient's propensity score is then the estimated probability of being exposed to treatment A rather than B and reflects the likelihood of exposure rather than the fact, given all measured characteristics. The main advantage of using a propensity score instead of traditional adjustment for confounding factors is that a large number of covariates can be included simultaneously without the risk of overfitting the model. It is important to remember, however, that even propensity score methods can only adjust for observed confounding variables and not for unmeasured ones [30]. Fig. 1 schematically illustrates handling of confounding.

A strategy to try overcoming the inability to control for residual confounding and enable unbiased estimates of efficacy in non-randomised studies is the use of instrumental variables which substitute the actual treatment status, an idea adopted from econometrics [34,35]. However, it may in practice prove hard to find valid instruments, and estimates from IV analyses may be biased, especially if the instrument is weak [36].

6. When do we have sufficient information on efficacy and safety for regulatory decisions?

An important goal of the drug development process is to establish efficacy and safety and to demonstrate that the benefit of a substance is large enough to outweigh its risk. Fig. 2 schematically shows the traditional steps in drug development where preapproval and postapproval periods are clearly separated. When developing cancer treatments, the primary focus is usually efficacy. 'Blockbusters' are rare, and unfortunately, the benefit of new drugs, be it in terms of OS or progression-free

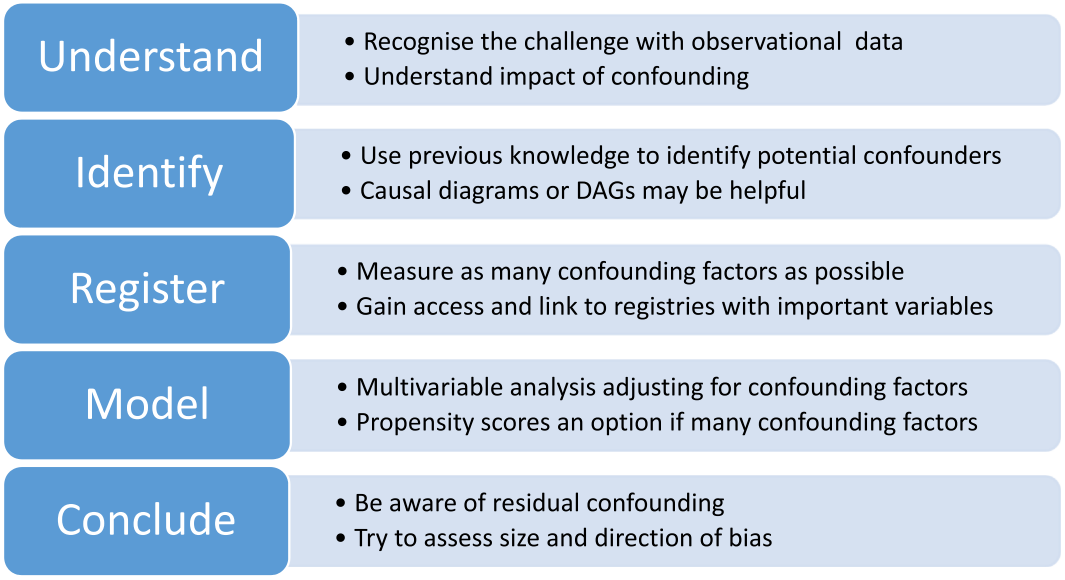

Fig. 1. Handling of confounding.

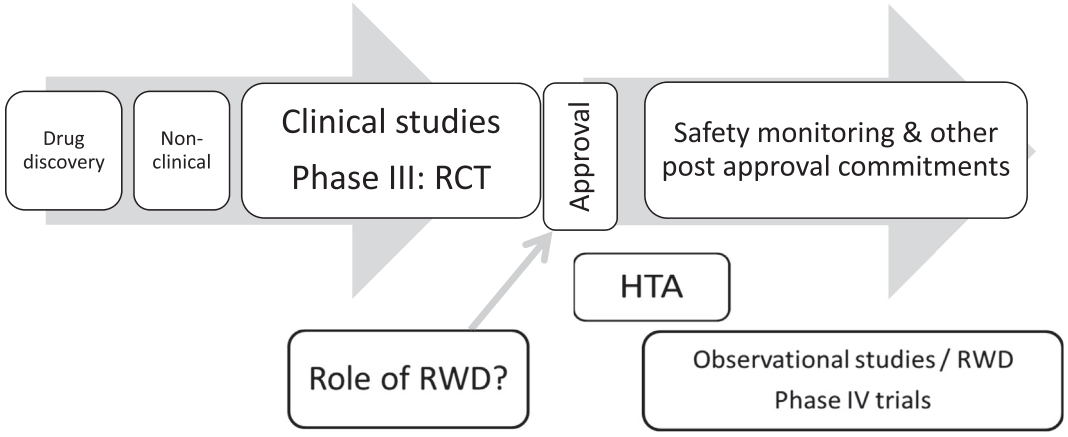

Fig. 2. Traditional drug development.

survival, is usually marginal. There is, however, an obvious need for better cancer therapy, and cancer patients, oncologists, pharmaceutical companies and regulators all see the need for access to efficacious drugs. With this in mind, new pathways to early access are being developed and several initiatives are ongoing.

6.1. Conditional approval

A number of early access tools for medicines addressing unmet medical needs have been available in the EU for a long time. Since 2006, a conditional MA can be granted to drugs intended for orphan, seriously debilitating or life-threatening diseases, or public health emergencies accepting less comprehensive evidence. A positive benefit–risk balance must, however, be documented, and confirmatory data must be provided within a reasonable timeframe [37]. Typically, results from interim analyses regarded as reasonably robust evidence of efficacy may be accepted for early approval, but at the same time, regulators are presented with additional uncertainty in the assessment and decision-making process [38]. It has been shown that all conditional MAs granted by 2010 have later been converted to regular approvals, although some delays in fulfilling the conditions have been reported [39–41].

6.2. Adaptive licensing/adaptive pathways

Adaptive licensing was proposed in 2012 and was later renamed adaptive pathways to better reflect the focus on development rather than authorisation [42,43]. The adaptive pathways approach is a scientific concept for drug development and data generation, which allows for early patient access, making use of existing approval tools such as conditional MA. The main aim is to achieve better access to efficacious drugs. It is based on three principles: (1) iterative development that implies

starting with a well-defined restricted patient population followed by iterative phases of evidence gathering and progressive licensing expanding to a wider patient population, (2) gathering evidence through real-life use to supplement clinical trial data and (3) early involvement of patients and HTA bodies in discussions on product development [44]. The concept applies primarily to treatment of high medical need where it is difficult to collect data via traditional routes.

A pilot project of which oncology development plans accounted for a third of the total submissions showed that adaptive pathways can bring multiple stakeholders together to discuss product development [26]. However, it is still a developing concept, and further work is needed to identify methodologically sound strategies for real-world evidence collection to support assessment of efficacy and effectiveness. The quality of data and control of bias are key elements, and for the adaptive pathways approach to succeed, submitted plans must be clear with regard to the purpose of collection of RWD to support RCT results. It must also be justified how efficacy and safety can be confirmed after authorisation.

Some have argued against adaptive pathways because of the expected lowering of evidence standards, leading to funding of poorly tested expensive drugs. If an MA is based on a small RCT, it could leave HTA decision makers with considerable uncertainty regarding a product's added value. However, this evidence gap exists already today [45]. The political willingness to stop reimbursement if follow-up data indicate lower than expected effectiveness has been questioned, and some suggest alternative procedures such as flexible coverage and pricing to reflect changes in the assessment of added value.

7. Conclusion

There is overwhelming interest in adding RWD, that is, non-randomised treatment comparisons based on routinely collected data, to RCTs of anticancer drugs to increase external validity and to generate evidence on factors determining treatment effects in the real world, for example, health systems, pharmaceutical policies, doctor–patient relationship or patient preferences [13,21].

Observational studies may certainly fill a critical gap [43], especially with regard to HTA, but many challenges remain before real-world evidence may become an integrated part of decision-making in drug development. To translate RWD into real-world evidence remains a critical challenge, even with advanced (statistical) strategies to adjust for confounding factors and the various biases that my occur [22,46]. This translation is of course very much dependent on the kind of products, the treatment effects seen during clinical development so far and how alternative treatment approaches have become available as well. Therefore, there is no single strategy here. But for sure, RWD will be factored in more and more in weighing the ultimate benefit–risk of such products [45]. There are numerous advantages to collect RWD as part of cancer drug development, including reduction of timelines and costs, minimising the number of patients in randomised trials and supplementing or confirming results from RCTs.

Conflict of interest statement

None declared.

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