**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. Whilst 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.

**Key words**: drug development; cancer; clinical trials; real-world data; regulatory approval.

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 sub-classification 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 HTA bodies
([www.cddf.org](http://www.cddf.org) ).

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, 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 post-approval experiences and follow-up studies are able to confirm clinical benefit.

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 utilising observational data, sometimes termed real-world data (RWD), as part of the drug development process. Following promising early phase results, RWD might be used to supplement or adjust traditional requirements for confirmatory trials [5]. Health technology assessment bodies (HTA) 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 marketing authorisation, a number of countries revisit the relative efficacy and effectiveness of a new treatment in comparison to 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 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 in order to reduce uncertainty at the time of reimbursement decisions.

The increasing access to administrative databases and electronic health records 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 as well as 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 PFS and/or OS data. These endpoints 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, like multiple myeloma. Recently, Luo and colleagues 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, i.e. similar survival outcomes between the two products, but differences in neuropathy [11].

**Randomised controlled trials**

Randomised controlled trials (RCTs) are the backbone of an application for marketing authorisation of a drug. A large fully blinded RCT incorporating pre-planned 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 due 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 post marketing 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.

**Generalisability of trial results**

Randomised trials are criticised for operating in an idealised experimental environment, not necessarily focusing 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 under-representation 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, overall survival (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.

**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 since 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 pre-agreed 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 that 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 endpoints 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].

**Real-world Data**

Observational or real-world data 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 as well as data on drug exposure and goes beyond what is normally part of phase III trial programs in terms of efficacy (and safety).

The European Medicines Agency (EMA) considers that real-world data 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, long-term outcomes [27], and to support validation of biomarkers.

*Sources of data*

RWD can be collected from a number of different sources such as databases, patient and population surveys, patient chart reviews, electronic health records, 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.

*Electronic Health Records (EHR)*

The development of electronic health records (EHR) 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 EHRs across member states would be very advantageous both to the research community, to regulators and to health technology assessment. 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 IMI Get Real [28] was planned to develop new methods of RWD collection specifically aimed at early adoption by the pharmaceutical industry and HTAs. Although not primarily focused on cancer the European Medical Information Framework (EMIF) aims to collect available patient level data on up to 40m European patients across 7 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 EHR 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 post approval 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.

*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.

*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 as well as 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 electronic health records. As an example the Norwegian Cancer Registry ([www.kreftregisteret.no](http://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 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 8 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](http://www.flatiron.com)) and UNICANCER’s 14,000 French breast cancer patients ([www.unicancer.fr](http://www.unicancer.fr)).

*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 anti-cancer medicines. It is appreciated that data quality and terminology varies 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 those for efficacy studies and this is of course of particular concern for HTA with potentially expensive new anti-cancer 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 overall survival 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” endpoint like 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.

**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, since 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 post-marketing 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 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]. Figure 1 schematically illustrates handling of confounding.

A strategy to try to overcome 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].

**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. Figure 2 schematically shows the traditional steps in drug development where pre- and post-approval 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 overall survival or progression free 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.

*Conditional approval*

A number of early access tools for medicines addressing unmet medical needs has been available in the EU for a long time. Since 2006, a conditional marketing authorisation 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 marketing authorisations granted by 2010 have later been converted to regular approvals, although some delays in fulfilling the conditions have been reported [39-41].

*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 marketing authorisation. The main aim is to achieve better access to efficacious drugs. It is based on three principles; 1) iterative development which 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 as well as 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 post-authorisation.

Some have argued against adaptive pathways because of the expected lowering of evidence standards leading to funding of poorly tested expensive drugs. If a marketing authorisation 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 like flexible coverage and pricing to reflect changes in the assessment of added value.

**Conclusion**

There is overwhelming interest in adding real-world data, i.e. non-randomised treatment comparisons based on routinely collected data, to RCTs of anticancer drugs in order to increase external validity and to generate evidence on factors determining treatment effects in the real world, e.g. 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 real-world data 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 product, the treatment effects seen during clinical development so far and how alternative treatment approaches have become available as well. So there is no single strategy here. But for sure real-world data will be factored in more and more in weighing the ultimate benefit-risk of such products [45]. There are numerous advantages to collecting 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.

**Disclosure**

The authors have declared no conflicts of interest.

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Table 1 Information recorded in the Norwegian Cancer Registry

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| --- |
| **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 \*)  |
| Date and cause of death |

* Clinical registries; prostate, colorectal, breast, lung, melanoma, lymphoma/lymphatic leukemia, gynecology, childhood.

Figure 1 Handling of confounding



Figure 2 Traditional drug development