# Accepting risk in the acceleration of drug development for rare cancers

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**Rare cancers collectively contribute a disproportionate fraction of the total burden of cancer. The oncology community is increasingly facing small numbers of patients with each cancer subtype, requiring cooperation and collaboration to complete multicentre trials that advance knowledge and patient care. At the same time, new insights into the biology of rare cancers have led to an explosion in knowledge and development of targeted agents. These insights and techniques are set to revolutionise the care of patients with cancer. However, drug development strategies and the availability of new agents for rare cancers are at risk of stalling owing to the ever-increasing complexity and costs of clinical trials. Finding solutions to these problems is imperative to the future of cancer care. We propose that a greater degree of risk sharing is needed than is currently accepted to enable the use of new methods with confidence, and to keep pace with scientific advancement.**

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## Introduction

No internationally agreed definition of rare cancers exists. In Europe, rare diseases are often defined as those with an incidence of fewer than six new cases per 100 000 per year or those that have a prevalence of fewer than 50 per 100 000 people.[1] By comparison, the Orphan Drug Act in the USA defines rare diseases as those affecting fewer than 200 000 individuals.[2] However, a recent analysis of rare cancers in the USA used the definition of fewer than 15 new cases per 100 000 per year.[3] Rare cancers are a burden to society that is difficult to quantify, although they are thought to constitute a major public health problem. As highlighted in the 2010 European Society of Medical Oncology recommendations paper on rare cancers,[4] "Overall health and social costs can be far higher for patients with rare cancers because effective treatments are not always reimbursed, referrals for second opinions within the public health system are not commonplace and many patients must travel long distances to access appropriate care." A 2014 analysis suggested that rare cancers collectively could account for up to 22% of global cancer cases.[5,6] Moreover, the rarest 20% of cancer types by incidence contributes to more than 30% of cancer mortality, perhaps in part owing to the difficulties in the undertaking of research into rare diseases.[7] By virtue of their incidence, childhood cancers fit all definitions of rare cancers and are a substantial source of childhood morbidity and mortality.[8]

New knowledge about the biology of rare cancer enables oncologists to better define subgroups with molecular targets and biomarkers. In doing so, ever-longer lists of so-called rare subtypes of cancer are created. Ultimately, this specialisation might lead to the holy grail of personalised medicine as the rule rather than the exception. In time, a specific drug or course of therapy suitable for administration to an individual patient might be identifiable on the basis of such profiling. As we move toward this ultimate goal of personalised medicine, the profiling of an individual patient's cancer will identify smaller and smaller categories or cohorts for participation in clinical trials of relevant targeted therapies. If present trends continue, this categorisation will become a problem for the entire specialty of oncology. Compounding this complexity is the issue of tumour heterogeneity for such molecular biomarkers. The adult oncology community is facing what paediatric oncologists have had to accommodate for years: small patient numbers with a particular disease necessitating cooperation and collaboration to conduct multicentre trials to advance knowledge and patient care. Indeed, the facilitation of international clinical trials in the academic setting will become increasingly important. As lung cancer has diverged from *ALK*-mutant lung cancer or *ROS1*-mutant lung cancer, the design of clinical trials has had to adapt to take on board new knowledge that changes study populations. Centres that formerly did single-institution trials now need to find sufficient numbers of patients for a biologically driven patient population suitable for a targeted therapy.

## Difficulties in rare cancer research

The successful use of such powerful biological knowledge might lead to more effective biologically driven treatments, fewer (or at least, predictable) side-effects, reduced burden of disease, enhanced quality of productive lives, and hopefully, longevity. Creation of efficient systems that are able to exploit these data to enhance human wellbeing is thus an ethical imperative. Failure to create or adopt such systems would be a failure to avoid foreseeable harm, and would entail moral responsibility for that harm. Such a failure is also contrary to the goal of the reduction of pain and suffering of individuals with cancer.

Approval for reimbursement of cancer drugs is increasingly becoming a public health issue.[9] Along with objective measures of benefit, such as overall survival and the costs per quality-adjusted life-year, internationally regulators, funders, and prescribers are likely to consider many other off-target beneficial effects, including other wellbeing benefits, unmet needs, clinical role, tumour incidence, financial effects in their approval process for funding, and prescription of drugs. For rare cancers, trials are either never done or are likely to be underpowered by comparison with more common cancers, and ultimately will fail to complete accrual or to meet the bar set by

historical standards. The statistical precision of a measurement of a drug's effects is not the same as the magnitude of the benefit being measured. A drug with a lesser benefit than another might be approved because the effect size is conclusively demonstrated in a large population (as, for example, the effect of adjuvant hormonal therapies in early stage breast cancer), whereas a treatment with a much greater benefit might be rejected because the population is so small as to preclude the conduct of an adequately powered trial. Another effect, in which efficacy is achieved but with wide CIs, is that the resulting cost-effect analysis has too great a level of uncertainty attached to it, and marginal results close to the decision threshold (explicit as in the UK or implicit as in Australia) are rejected because of unacceptable levels of uncertainty.

Existing biases in drug licensing and in funding for rare cancer research systematically contribute to poor outcomes for this group of patients. As drug development costs are relatively fixed, sponsors are less willing to invest in a drug that might be used by 500–5000 patients per year, compared with 150 000 patients, as their ability to recover a return on investment is much more restricted with small populations.

The exponential growth in knowledge about cancer offers untold opportunities, but its complexity is amplified by the ever-increasing portfolio of oncology drugs in development. Nearly 1000 new drugs are in the developmental pipeline across the pharmaceutical industry.[10] Many of these agents overlap in their targets, but none is identical, thus complicating future treatment choices for individuals and small cohorts. Furthermore, the likelihood that any individual, multitargeted agent will provide substantial benefit over another agent with a similar but not identical profile will never be tested, leaving myriad unanswered questions about the comparison between agents. Again, this complexity is compounded when combinations of targeted therapies are considered.

The ideal drug development system and scientific design should allow for a balance of acceptable risks, both to research participants and to future populations. Such systems should reduce the costs of new drug development, while at the same time allowing ready access to most of the appropriate population in a safe manner. However, despite consensus in the public sector, academia, and the pharmaceutical industry that drug development should be accelerated, the models for trial design and drug development are adherent to the extremely slow but established pathways developed in the era of cytotoxic drug development.

In that era, drugs were developed as monotherapies, when no alternative treatments were available. Present research approaches evolved from this model and have rarely strayed from it. A recent analysis estimated that 20% of 7776 adult phase 2 and 3 clinical trials in the USA might never be completed, thereby rasing the costs and slowing progress.[11] Similarly, a 2010 report from the Institute of Medicine shows that 40% of trials initiated by the US National Cancer Institute Clinical Trials Cooperative Group Program were not completed.[11] Concomitantly, as the cohorts of people with rare and heterogeneous conditions grow in number, the number of potential participants available for each study becomes smaller and, in turn, the models for trial design and drug development seem increasingly restricted and cumbersome. We are rapidly reaching the point at which studies proceeding through the usual algorithms of dose finding, activity finding, and completion of premarketing development with a randomised comparison against the standard of care simply cannot be done in patients with rare cancers or in small subgroups selected by specific biomarkers. We contend that the rapid development of new technologies has outpaced our ability to fully develop new drugs, and major shifts in approach are required to sustain progress.

## Regulatory requirements

Compounding barriers to fast drug development is the ever-increasing regulatory complexity that burdens drug development.[12] Fundamental to this burden is the risk-averse position of stakeholders at all levels in the drug development process, except perhaps in those patients with lethal conditions.[13]

Some degree of risk is inherent in any research. The central questions are whether that risk is reasonable under the circumstances, and whether the participant or surrogate has been adequately informed of the risk and deems it to be acceptable. Essential to our understanding of "reasonable risk" is the expectation that risk is minimised relevant to the goal, and that continuous surveillance, monitoring, and assessment are essential to ethical drug deployment.

The Declaration of Helsinki, Principle 5 states: "In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society". It informs the central ethical position taken by researchers and research organisations around the world: that research participants must be protected from anything more than the least possible risk of harm. The term 'minimal risk' of harm is often used to describe an acceptable level of risk for any research participant. Indeed, the principle of equipoise articulates that a trial should only be conducted when equipoise exists between existing and novel therapies—that is, when researchers are as confident that one therapy is as effective as the other. If equipoise is even minimally disturbed and a potential for harm exists, a trial should not be started, or it should be terminated if already started when a disturbance of equipoise becomes evident.

Unfortunately, we would contend that in the past three decades many regulatory authorities, funding agencies, and review boards have responded to these sound ethical principles with over-zealous health and financial risk mitigation strategies, and that a sense of balance has been lost. The consequences of this approach have been dire, as

Steensma and Kantarjian have pointed out, "The resulting proliferating complexity and unnecessary formalities involved in developing and testing cancer therapies have stifled innovation, driven up costs, and delayed development of new treatments."[12]

At a personal level, patients and their families are often dismayed when they are told that a new agent will not be available in time for them to participate in a clinical trial due to such formalities. Little evidence supports the view that the increasing regulatory burden and complexity have led to any reduction in harm to patients. Reducing risk to almost zero in any specialty is unrealistic and, in the context of life-threatening illnesses, even if the potential participant gives fully informed consent, can raise the expectations of regulators, insurers, patients, and the community, to the point that new drug development might simply become unsustainable.

## Cost of drug development

One major component of spiralling health-care costs across the globe is the cost of new drugs. Pharmaceutical companies defend the high prices of new drugs as necessary to support investment in research and development. The often-cited cost of bringing anticancer drugs to US FDA approval is at or in excess of US$1 billion per approved agent.[12] However, research and development costs are not unique to the pharmaceutical industry; indeed, all major industries invest in research and development to realise future profits and to remain sustainable. The key question is what the relative reasonable return on investment is, and whether the balance can be shifted for rare diseases. Many would dispute the cost of development, or would argue that, ethically, companies should accept a smaller return on investment for rare cancers than they do at present. The point is that the drivers of the high cost of drug development are actually multifactorial and ultimately these high costs are not sustainable.

## Recommendations

Clinical science is based upon the probability, rather than a certainty, of truth. Thus, probability of truth is routinely accepted as an outcome measure in all clinical trials. The constructs within which data are conventionally provided and the level of certainty that informs our progress through drug development need to be questioned. In the setting of rare cancers, a new balance needs to be made between risk and benefit in securing scientific truth.

The oncology community should consider raising the bar by demanding greater gains in outcome in some settings before accepting new drugs into clinical practice. A proposal that has been well argued by others, and with which we agree, is that drugs that offer only marginal gains to patients should be carefully considered, such as those providing progression-free survival for only 1–2 months, and in particular those with no promise of clear improvement in quality of life and overall wellbeing. Subjecting new drugs to greater scrutiny will reduce—or remove—patients' exposure to drugs with marginal benefit, and will discourage the continued development of copycat drugs that do not offer incremental gains. Developing and marketing a drug that is fourth or fifth in its class offers little benefit, except perhaps for increases in competition that might result in lowering the cost of cancer drugs or improving security of supply.

Conversely, good drugs should not be discarded along with bad ones. Although such small gains might not be enough for a new treatment to be regarded as effective, small, incremental gains that are complementary could translate into large gains overall or in different settings (ie, a 2 month progression-free survival in advanced disease with a hazard ratio of 0·75 might produce a 6 month gain or more in an adjuvant setting). In addition, a drug that is marginally effective in one disease might be extremely effective in another. Allowing clinicians to work out how best to use these new agents in rare cancers will require easier access to drugs for investigation and a flexible approach to studying them.

In cancer research, the reliance on randomised clinical trials and the standards of progression-free survival and overall survival as robust endpoints needs to at least be questioned in some rare diseases. As new targeted agents are produced, clinicians should consider clinically useful endpoints, such as the potential effects of prolonged stability of disease, improvements in quality of life, and non-inferior therapies, that will help patients and might reduce long-term side-effects and secondary complications. These types of alternative outcome measures in a non-randomised format could reduce the required numbers of participants and study costs.

In the developmental pathway, small trials with greater uncertainty could be accepted because they might lead to improved long-term survival gains when compared with traditional, large trials designed to meet stringent criteria. The conventional approach is often not feasible in rare diseases. For example, a randomised controlled trial in a rare disease setting with a statistical cutoff value of $p<0·05$ and a survival benefit of 5% as the endpoint would require hundreds of patients, and might take 20 years to prove or refute a hypothesis. Meanwhile, patients in the control arm would receive no benefit, the specialty would fail to progress, and future patients would not benefit. If greater uncertainty were acceptable (eg, acceptance of $p<0·1$ as significant), far fewer participants would be needed.

Rapid progress to innovative experimental design is not just desirable, but imperative. Direct evidence of survival gains in randomised controlled trials for rare tumours will be difficult to obtain. Conversely, some evidence on intermediate outcomes of efficacy (such as response and on-target biological effects), combined with evidence of validation of intermediate measures across a range of trials, or combined evidence of the effect of a class of treatments across a range of similar tumour types, might be needed. A satisfactory alternative could be to incorporate previously established evidence with a Bayesian statistical

approach. Available information about the outcome of interest could be quantified as a prior probability distribution when designing the trial. Interpolating trial results with the prior probability could give a posterior distribution from which to draw conclusions. The limitation in this situation might be that, in rare diseases, only indirect or restricted evidence could be drawn on if no direct relevant comparisons are available. In such a context, a reduced set of studies could be proposed in the target population and used to validate data secured for the purposes of extrapolation, such as previous clinical data in the target population, convincing preclinical or other data or, indeed, post-marketing approval data. In addition, novel designs, such as a Bayesian adaptive approach, could assign more patients to the more effective treatments based on the available data at the time via outcome-adaptive designs. More frequent and iterative approaches to interim monitoring would halt the ineffective treatments early for futility. This strategy could be especially effective if, with the caveats described already, stringent demands are placed on outcomes. Final interpretation of the limited data in the target population could be made in the context of the extrapolated data.

## Balancing risk for future generations

In most countries, uncertainty analysis is routine in the economic analysis undertaken towards decisions on drug development. If our proposal is adopted, clinical trial design would require data to be incorporated from multiple sources and an increased level of uncertainty to be accepted. For example, if adaptive designs allow new therapies to be screened more efficiently, there would be a danger these designs alone could be deemed sufficient to inform clinical practice when they may be misleading. The oncology community must also adhere to Principle 11 of the Declaration of Helsinki—that poorly formed research is unethical because it may not benefit people in the future and results may be misleading. Therefore, perhaps most importantly, having accepted alternative outcome measures, designs, and other compromises that could reduce the need for randomised clinical trials in patients with rare cancers, we need to be cautious about placing restrictions on the probability of reaching appropriate conclusions. For this reason, checks and balances need to be in place to ensure the risk of future harm is minimised. Changing the balance and order of regulatory and licensing processes could attain such a state of affairs.

### Search strategy and selection criteria

We searched PubMed for all historical data included in Entrez database, and the proceedings of the American Society of Clinical Oncology, the American Society of Paediatric Haematology/Oncology, and the websites of the European Medicines Agency and US Food and Drug Administration since Jan 1, 1985, with the following terms "rare cancers", "paediatric oncology", "phase 1", "drug development", "paediatric drug", and "drug regulation". Searches were restricted to papers published in English.

In most cases, efficacy testing during drug development is done with an eye on prelicensing or premarketing. Less investment tends to be put into efficacy studies once the drug has reached the marketplace. Present systems place extremely high stringency measures on securing highly selected study populations by requiring adherence to very strict eligibility criteria. Often, these populations and the research environment bear little resemblance to the patients to whom drugs are administered, and the places in which they are treated.

In several countries, including the USA and countries in the European Union, legislations for orphan medicinal products exist. Orphan drugs are intended for the diagnosis, prevention, or treatment of life-threatening or very serious conditions that affect no more than five in 10 000 people. The sponsors responsible for these medicines benefit from incentives such as fee waivers for the regulatory procedures, or periods of market exclusivity. These programmes have been successful and encourage the pharmaceutical and biotechnological industries to carry out research and development of orphan drugs. However, although some statistical burdens are lessened, orphan drugs generally follow the same regulatory developmental pathway as any other pharmaceutical product.

In the case of rare cancers, we propose that regulators should consider allowing drug manufacturers the opportunity to obtain an early commercial return on investment by providing a license for sale with less-stringent criteria. However, freedom to commercialise a drug would be conditional on postlicensing data and funding agreements designed to confirm the limited upfront developmental data. Internationally, precedents exist for this type of coverage with the evidence-development approach. An example is in the Accelerated Approval and Fast Track programmes of the US FDA. The accelerated approval system grew from the desire to make potential drugs that appear to offer hope to otherwise untreatable disorders available as early as possible. In the early 1990s, HIV/AIDS activists demanded a shortcut regulation to make promising drugs available, even if the data were incomplete. In 1992, the FDA responded by revamping a little-used compassionate care programme into an official, accelerated approval system. Underpinning this accelerated approval is a requirement for phase 3/4 studies to be completed at the risk of the drug losing its license.

The use of many new agents needs to be accompanied by companion biomarkers if an understanding of factors influencing good responses is to be understood. As such, postlicensing studies would require the collection of data on biomarkers, such as the molecular characterisation of tumours. This requirement will mandate methods for de-identification of tumour subtype to protect the privacy of individuals. Such data collection and protection of privacy is logistically feasible on a large scale in a postlicensing setting, and is already in operation in countries such as Australia, which has a national prescribing and drug

reimbursement system. In this type of system, funding for the drug is only approved and provided after such data are submitted centrally for review.

We propose that, for rare cancers, regulators should consider not requiring stringent randomised controlled trial-based evidence, but rather an accumulation of data with the Bayesian statistical approaches and others previously described. Furthermore, if the drugs are adopted, then manufacturers will have to accept that some percentage of approvals might be rescinded at a later date if they are found to lack efficacy or have increased toxicity with long-term use.

Such an approach to drug development could have broad-ranging effects: it would reduce the burden of upfront costs and reduce the numbers of research participants; potentially, it could refute the argument that developmental costs are driving up drug costs; and would ensure the study of new drugs in unselected patient populations with rare cancers.

## Conclusion

Recent insights into the biology of rare cancers have led to a rapid increase in new knowledge and the development of targeted agents. These insights and techniques are set to revolutionise the care of patients with cancer. However, drug development methods and the availability of agents tested in rare cancers are at risk of stalling owing to the ever-increasing complexity and costs of clinical trials with present approaches. Finding solutions to these problems is imperative to future cancer research. Personalised care might represent the optimum strategy for treatment of all diseases. Although all parties are striving for better clinical outcomes, each of the stakeholders in the drug development arena—patients, families, academics, industry, and regulators—is subject to vastly different drivers, ranging from commercial imperatives to scholarly and scientific interests, to a desire for the greater good and making best available use of government funding. However, we propose that a greater degree of risk sharing is necessary to enable the use of new methods with confidence, and to keep pace with scientific advancement.

Arguably, in the 21st century, individuals and society live with more and greater risks than ever before. An approach to drug research and development that is well adapted to risk speaks in favour of patient autonomy—a feature of contemporary society in the developed world, at least. Policy makers, regulators, and insurers are increasingly risk-averse, demanding ever-decreasing risks in health care and drug development. For rare cancers, most patients would accept increased levels of risk for higher levels of innovation.

**Contributors**

DA did the literature searches, provided conceptual discussions, drafted the initial report, and contributed to revision and editing. DT was involved in the conception, design, and writing of the report. LG did literature searches, provided conceptual and organisational discussions, assisted with data analysis, report writing and editing of the submission. RC's role involved contributing to the arguments presented in the article, particularly from a health economics (pharmacoeconomics) perspective and his experience as a former member of the Pharmaceutical Benefits Advisory Committee (PBAC) and its Economic SubCommittee (ESC) in Australia. JZ was involved in the data interpretation and writing of this report. RO did literature searches, provided conceptual discussions, and assisted with report writing and editing of the submission. JS was involved in conceptualisation, including the association to personalised medicine and requirement for new models of evaluation; he also drafted sections and involved in all revisions. All authors approved the final version of the paper.

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