

To bias or not to bias in oncology clinical trials: Perspectives on design, endpoint selection, and reporting

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Abstract

Developing drugs for cancer is a process as complex as the disease itself. At the planning stage of a clinical trial for an oncology drug, thorough and careful consideration must be given to choosing the right study design and endpoints/estimands, as any bias introduced at the outset of the clinical trial would cascade down to the analysis and eventually the reporting of the results. The common study designs for oncology drugs, their challenges, the current perspectives (and dilemmas) in the industry on choosing the right endpoints/estimands, design and reporting biases, and the roles of medical writers in facing these challenges are discussed in this article.

Almost 20 million new cancer cases with nearly 10 million deaths were estimated in 2020.¹ Cancer is one of the leading causes of death globally, and consequently, research and development of oncology drugs has never lost its momentum. Between 2009 and 2020, the US FDA approved over 300 oncology drugs (excluding supportive medicines).² Between 2010 and 2019, 85 marketing authorisation applications of oncology drugs in Europe received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP).³ Although Europe appears to be falling behind the US in terms of regulatory approval speed of oncology drugs,⁴ we see a soaring number of approvals in both regions every year. Conducting an oncology clinical trial from

planning to reporting is a painstaking process. The fact that there are multiple guidances dedicated for different tumour types in oncology clinical trials alone shows the magnitude of the complexity of drug development for cancers.

Study designs of oncology trials

Marketing approval of oncology drugs is the culmination of years of research accumulating substantial, confirmatory evidence of efficacy and safety of the investigational drugs acquired from “adequate and well-controlled clinical trials”.⁵ This refers to trials that have a valid control for comparison to quantitatively assess the drug’s effect, appropriate eligibility criteria for the target population, a robust randomisation method, proper masking of participants/observers/data analysts, well-defined and reliable study endpoints, and sound data analytical methods.⁵

For confirmatory studies, proving superiority of an investigational drug to the control on clinically meaningful endpoints in a randomised, controlled, blinded setting is arguably the standard and is considered the most reliable design to demonstrate efficacy.^{6,7} The control used in such studies can be a placebo, active comparator, or both. Data of a superiority study is relatively easy to interpret and for drawing inference of efficacy when superiority of the investigational drug to the control is demonstrated.

When an active control is compared with the investigational drug to establish efficacy, a noninferiority design could be applied to show that the treatment effect difference between the investigational drug and the active control is not beyond a prespecified minimum margin.

Some important considerations, often also considered as challenges, when applying a noninferiority trial design include:⁸

1. The active control must have a well-

characterised effect;

2. The treatment effect size of the active control and the minimum margin are determined from reliable historical data;
3. An appropriately powered sample size should be determined based on the expected treatment effect of the investigational drug and the active control;
4. The noninferiority hypothesis and method of statistical test should be chosen carefully.

In a randomised setting, the cross-over design either allows patients of all treatment arms to be switched over to the opposite arms or patients from one treatment arm to another treatment arm that shows benefit. The latter is typically applied in oncology trials when patients taking placebo experience disease progression, for ethical and patient accrual reasons. Nevertheless, the cross-over design in oncology trials is considered to pose more risks than it does in non-oncology studies, such as symptomatic treatment of chronic diseases and single-dose pharmacokinetic/pharmacodynamic studies, as it often confounds the study endpoints beyond the point of cross-over.^{9,10} Meticulous planning to include cross-over design in an oncology trial

is imperative to avoid misinterpretation of the efficacy data down the line.

Certain circumstances require special attention, such as when no active therapy is available, meaning that using a placebo as control is ethically unfeasible, or when the available patient pool is limited (e.g. for rare diseases), a single-arm study design may be acceptable to assess drug efficacy. Justification, however, is needed for choosing a single-arm design as it presents inherent drawbacks which may limit the validity of the efficacy

data and its generalisability, e.g. difficulties in assessing causality of adverse events, lack of comparison data to ascertain the real effect of the

Confirmatory evidence of efficacy and safety of the investigational drugs must be acquired from “adequate and well-controlled clinical trials”.



treatment, and restricted sample size and endpoints selection.⁷

Endpoints selection

In the past, new cancer drugs were typically approved based on tumour assessment outcomes, which are considered surrogate endpoints, such as the tumour objective response rate (ORR), duration of response (DOR), progression free survival (PFS), and time to progression (TTP). For several decades, regulatory authorities across regions have been of the unanimous opinion that Phase 3 confirmatory oncology trials should demonstrate direct evidence of clinical benefit from the investigational drug, that is to extend survival and improve quality of life, and these are intended as the basis for marketing approval.^{6,7,11} Therefore, overall survival (OS) and a selected patient-reported outcome (PRO) such as health-related quality of life (HRQoL) have been the

“gold standard” for efficacy assessment of new oncology therapies.¹²⁻¹⁵ Each clinically meaningful and surrogate endpoint presents its own advantages and disadvantages, which are nicely summarised in the FDA guidance (Table 1).^{6,14}

An estimand framework to underpin any Phase 3 confirmatory trial design, including oncology trial design, is necessary.¹⁶ In the absence of reference to estimands in other oncology trial design guidances, the examples relating to oncology trials within the E9(R1) addendum on estimands and sensitivity analysis are helpful.¹⁶ These include:

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1. A subject switching treatment in an oncology trial as an intercurrent event (ICE) for which the clinical question of interest must be clear and appropriate strategies for addressing this event be applied. Helpfully, Manitz et al.¹⁷ has recently reported an estimand framework for OS in oncology trials with treatment switching.

2. When certain clinical oncology events may represent ICEs of which occurrence or non-occurrence would define different populations of interest. This could occur for time-to-event endpoints. The estimand framework for some of these types of ICEs are elucidated further in recent publications.^{18,19}
3. When an ICE to an original endpoint in itself is informative about the patient’s outcome, for example, treatment discontinuation could be considered part of PFS and incorporated into the definition of PFS. Casey et al.²⁰ have described the estimand framework to support composite outcomes in the oncology setting.

With the emergence of real-world evidence, improved knowledge on the omics of cancer, and new transformative therapeutics that have changed the natural histories of certain cancer types, discussion has ensued in the past decade about reassessing the endpoints in oncology trials for marketing approval.^{21,22} While preserving their standpoint on the importance of clinically meaningful endpoints, regulatory authorities acknowledge the potential benefits of new

Table 1. Advantages and disadvantages of important cancer approval endpoints*

Endpoint	Advantages	Disadvantages
Overall survival	<ul style="list-style-type: none"> Easily and precisely measured Generally based on objective and quantitative assessment 	<ul style="list-style-type: none"> May be affected by switch-over of control to treatment or subsequent therapies Needs longer follow-up Includes noncancer deaths
Symptom endpoints (patient-reported outcomes)	<ul style="list-style-type: none"> Generally assessed earlier and with smaller sample size compared with survival studies 	<ul style="list-style-type: none"> Blinding is important for assessing the endpoint Potentially subject to assessment bias, particularly in open-label studies Lack of validated instruments in many disease areas Definitions vary among studies Balanced timing of assessments among treatment arms is critical
Disease-free survival or event-free survival	<ul style="list-style-type: none"> Generally assessed earlier and with smaller sample size compared with survival studies Generally based on objective and quantitative assessment 	<ul style="list-style-type: none"> Potentially subject to assessment bias, particularly in open-label studies Definitions vary among studies Balanced timing of assessments among treatment arms is critical Includes noncancer deaths
Objective response rate	<ul style="list-style-type: none"> Generally assessed earlier and with smaller sample size compared with survival studies Effect on tumour attributable to drug(s), not natural history Generally based on objective and quantitative assessment 	<ul style="list-style-type: none"> Definitions vary among studies Frequent radiological or other assessments May not always correlate with survival
Complete response	<ul style="list-style-type: none"> Generally assessed earlier and with smaller sample size compared with survival studies Effect on tumour attributable to drug(s), not natural history Generally based on objective and quantitative assessment 	<ul style="list-style-type: none"> Definitions vary among studies Frequent radiological or other assessments May not always correlate with survival
Progression-free survival or time to progression	<ul style="list-style-type: none"> Generally assessed earlier and with smaller sample size compared with survival studies Measurement of stable disease included Generally based on objective and quantitative assessment 	<ul style="list-style-type: none"> Potentially subject to assessment bias, particularly in open-label studies Definitions vary among studies Frequent radiological or other assessments Balanced timing of assessments among treatment arms is critical May not always correlate with survival

* This table is taken from the US FDA Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics Guidance for Industry. <https://www.fda.gov/media/71195/download>

treatment modalities based on surrogate endpoints and the need to make these treatments rapidly available to cancer patients with serious or life-threatening conditions. The catch is that evidence must be available to justify the ability of the surrogate endpoints to predict clinical benefit.^{23,24} For example, what is the probability that patients showing delayed progression for an

indicated cancer type (prolonged PFS) will also show improved survival (prolonged OS)? Indeed, an increasing number of oncology drugs were approved based on surrogate endpoints and up to half of these were through accelerated approval, with ORR and PFS as the most common primary endpoints.²⁵⁻³⁰ For drugs that obtain accelerated approval, drug companies are

required to fulfil the obligation to continue to provide post-marketing efficacy data to verify the anticipated clinical benefit.

Counterarguments against the overuse of surrogate endpoints for marketing approval are equally extensive. For a start, valid evidence for the chosen surrogate endpoints to predict long-term OS or QoL is generally lacking and if

available, is restricted to a specific tumour type such as advanced colorectal and ovarian cancers.^{31,32} Consequently, most approved oncology drugs based on surrogate endpoints did not prove clinical benefit. Eighty-six percent of identified FDA approvals based on surrogate endpoints from 2008 to 2012 either failed to verify long-term OS or no such data were reported at all;²⁶ 58% of FDA approvals from 1992 to 2019 did not report any post-marketing efficacy data at all, and for new approvals, more than half had no or poor correlation between the surrogate endpoints and OS.³⁰ Similarly, 49% of European Medicines Agency (EMA) approvals from 2009 to 2013 did not show benefit on OS or QoL.³³ These reports prompt a couple of questions: are cancer patients still gaining the clinical benefit that they hope they will gain from their therapies? Are regulatory authorities doing enough in overseeing drugs that are approved based on surrogate endpoints to protect the interest of public health?

To validate a surrogate endpoint, the Institute

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of Medicine Committee proposed a 3-step evaluation process:³⁴

1. Analytical validation – to assess if the surrogate endpoint itself can be accurately measured;
2. Qualification – to assess if the investigational drug affects both surrogate and clinical endpoints in a like manner;
3. Utilisation – to assess the context of the proposed use of the surrogate endpoint.

It is painstaking but crucial to discern a validated surrogate endpoint with robust estimated net effects of a drug on a clinically meaningful endpoint from a mere correlate without any established evidence of clinical benefit.^{32,35,36}

Biased by design

How confident are we to say that a trial is “adequate and well-controlled” when it is claimed to be randomised, controlled, and blinded? We may naturally take the credibility of a randomised, controlled, and blinded trial for granted and miss subtle design details that could bias the trial. Bias can occur at any stage of a randomised clinical trial, from setting of the clinical question at the ideation of the trial, design and conduct, data management and analysis, to final data reporting.³⁷ Bias arising from inappropriate study design at the outset of a clinical trial would cascade all the way down to the outcome of results and therefore the reporting. Eventually, inference of the results in reporting is likely to be misguided by the distorted results and may

Table 2. Common design biases in randomised controlled studies and their impacts on the study outcome

Design characteristics	Types of bias	Impact on outcome
Objective	Multiple primary endpoints, multi-arm	Results in multiple comparison, hence exaggerating the drug effects and increasing the false-positive rate. ⁴²
Treatment allocation	Inappropriate inclusion of cross-over design	Confounding factor for the drug’s effect on survival from the point of cross-over. ³⁷
Randomisation method	Inadequate allocation concealment/ sequence generation (e.g. open random allocation schedule, lack of safeguarding of assignment envelopes)	<ul style="list-style-type: none"> ● Imbalance group sizes and baseline characteristics, hence unequal comparison between treatment arms. ● Drug effect estimates were larger by 10% to 17% in studies with inadequate versus adequate allocation concealment.⁴³⁻⁴⁵ ● Drug effect estimates were larger by 7% in studies with inadequate versus adequate sequence generation.⁴⁵
Blinding	Lack of (double-) blinding	Drug effect estimates were larger by 7% to 13% in unblinded versus blinded studies. ^{43,44}
Choice of control	Use of control with distinct safety profile, dose modification regimen	Unequal comparison between investigational drug and control. ³⁷
Analysis method	<ul style="list-style-type: none"> ● Inappropriate handling of missing data and choice of analysis population ● Excluding patients from analysis 	<ul style="list-style-type: none"> ● Drug effect estimates were larger by 17% when using modified intention-to-treat (mITT) in place of intention-to-treat (ITT).⁴⁶ ● Drug effects were more beneficial in studies with patient exclusion versus no exclusion.⁴⁷

undermine regulatory decision-making. Table 2 describes several common design biases in randomised controlled studies and their impacts on the study outcome, including drug effect estimates.

Not considering estimands in the study design would also amount to a design bias. For Phase 3 confirmatory oncology trials, ICEs should be defined and the appropriate strategies for addressing these ICEs should be determined according to the clinical questions of interest at the outset. One should be aware that using different strategies for the same ICE would address different questions.²⁰ A well-designed estimand framework will reduce the risks of missing data, help address the right question, ensure appropriate analyses, and eventually support the interpretation of the results.

Reporting bias

In addition to “passive” reporting bias due to biases in the design choices, “active” reporting bias has been the kind of bias that medical writers would consciously avoid, albeit not always successfully. The most common reporting biases include:³⁸⁻⁴⁰

1. Publication bias – not publishing clinical trials with negative outcomes;
2. Outcome reporting bias – reporting only the favourable data or a subset of data, or even changing the primary endpoint in reporting;
3. “Spin” – strategising the reporting to emphasise the benefit of the investigational drug even though it is not supported by the hypothesis testing.

In an analysis of the reporting of randomised controlled studies for breast cancer, one fifth of studies reported in ClinicalTrials.gov had the primary endpoint altered in the final report; one-third of the studies were reported to have positive outcome by “spinning” the results to focus on other endpoints; and half of the studies were reported to have a positive outcome based on a non-statistically significant test result for the primary endpoint.³⁹ These staggering statistics may only represent the tip of the iceberg.

The implications of reporting bias, passive or active, could be profound for the oncology drug development industry and public health sector. Incomplete and skewed reporting of outcome results could mislead policymakers in drug approval decision-making, thereby misinforming

medical service providers, and potentially jeopardising access to effective treatments for cancer patients.

Bias can occur at any stage of a randomised clinical trial.

What can we do as medical writers?

- **Be proactive and do it the right way from start to finish.** Myriad guidelines, for generic study types and oncology trials alike, are available to help us from planning and design all the way to accurate and transparent reporting.⁴¹ If we are involved in planning the research strategy, be encouraged to engage with the regulatory authorities to discuss the best study design based on the nature of the disease, availability of comparators, known benefit-risk of the investigational drug, and the long-term plan for collecting data on the clinical benefit of the drug.

- **Equip ourselves with the right knowledge.** Be vigilant and learn where to look. Is the comparator appropriate? Do the study endpoints fit the study design and answer the clinical question?

What is the expected magnitude of clinical benefit? Does a Phase 3 confirmatory trial design include some kind of estimand framework? If not, open discussions with the medical expert and biostatistician. Being able to identify biases throughout the entire clinical trial will help us report the trial critically and clearly.

- **Remember that responsibility for appropriate trial design does not rest solely with the medical writer.** We may need to raise awareness where it might otherwise be lacking, but ultimately, design considerations and responsibilities lie with the sponsor, medical expert, and biostatistician.
- **Be aware of the different types of reporting biases.** Understanding the types of reporting biases, under what circumstances they may happen, and their implications in clinical research will help us all to become more “conscious” writers.

Conclusion

Writing for oncology trials is never an easy task. Challenges await at every stage of a clinical trial, from ideation to reporting. Medical writers need to equip themselves with solid knowledge of the oncology drug development process, be attentive to new treatment modalities in oncology, be conscious of the current trends in oncology trial designs, be aware of the possible biases in all aspects of a trial, and be skilled to tackle the biases, all of which are essential for clear and transparent writing. Appropriate oncology trial design can and should be advocated for by a well-informed medical writer, but must be a cross-functional endeavour, at a minimum involving

the sponsor, medical expert, and biostatistician. Fortunately, myriad resources exist to help medical writers at every stage of the writing process – perhaps that is yet another challenge to locate the right resource for the right purpose.

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The most common reporting biases include publication bias, outcome reporting bias, and “spin”.

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The opinions expressed in this article are the author’s own and not necessarily shared by her employer or EMWA.

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