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NARRATIVE REVIEW

A novel framework to assess haematology and oncology registration trials: The THEOREMM project

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Abstract

Background: Methodological limitations affect a significant number of oncology and haematology trials, raising concerns about the applicability of their results. For example, a suboptimal control arm or limited access to best care upon progression may skew the trial results toward a benefit in the experimental arm. Beyond the fact that such limitations do not prevent drugs reaching the market, other assessment tools, such as those developed by professional societies—ESMO-MCBS and ASCO Value Framework—do not integrate these important shortcomings.

Methods: We propose creating a novel framework with the scope of assessing registration cancer clinical trials in haematology and oncology (randomized or single arm)—that is trials leading to a marketing authorization. The main steps of the methods are (1) assembling a scientific board; (2) defining the scope, goal and methods through pre-specified, pre-registered and protocolized methodology; (3) preregistration of the protocol; (4) conducting a scoping review of limitations and biases affecting oncology trials and assessing existing scores or methods; (5) developing a list of features to be included and assessed within the framework; (6) assessing each

John P. A. Ioannidis and Vinay Prasad contributed equally to this work.

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feature through a questionnaire sent to highly cited haematologists and oncologists involved in clinical trials; and (7) finalizing the first version of framework.

Results: Not applicable.

Conclusions: Our proposal emerged in response to the lack of consideration for key limitations in current trial assessments. The goal is to create a framework specifically designed to assess single trials leading to marketing authorization in the field of oncology and haematology.

KEYWORDS

appraisal, framework, haematology, metaresearch, oncology, trials

1 | INTRODUCTION

Patients, healthcare providers, regulators and society face several challenges when approaching novel treatments. Costs—and profits—associated with cancer care are immense, with estimated global costs increasing from 56 billion US dollars in 2011 to 269 billion in 2025.¹ Trial design limitations may hamper the ability of a trial to deliver reliable results and confidence in shared decision-making. While the challenges apply to all medical specialties, haematology and oncology prominently stand out, because the number of regulatory approvals in these specialties is larger than in any other medical specialty and many of those approvals follow accelerated pathways.^{2,3} Furthermore, the number of high-profile trials is larger in haematology/oncology than in any other medical specialty. Among the 600 most-cited trials published in 2019–2022, 260 were on oncology.⁴ Current regulators and health technology assessment (HTA) bodies often grant marketing authorization to drugs with low or questionable value. Scores coming from professional societies like ESMO or ASCO aim to improve upon the existing regulation by focusing more on the potential clinical value. However, those scores do not capture several key features in clinical trials that may influence the perception of clinical value. We will exemplify this based on two important components of randomized clinical trials which are currently not addressed in those scores: the control arms and biases introduced by post-progression therapy. Both features are also not specifically assessed by previously established risk-of-bias tools or the GRADE system, the most widely used system for appraising the strength of evidence toward making recommendations.^{5,6} We aim to incorporate such features into a novel framework in the THEOREMM (Trials in HEmatology and Oncology REviewed by Metaresearch Methods) project.

2 | LIMITATIONS AND BIASES IN ONCOLOGY AND HAEMATOLOGY TRIALS

Over the last three decades, the number of novel approvals in haematology/oncology has grown markedly.⁷ However, an increasing number of approved drugs and biologics does not automatically correlate with improved patients' outcomes. Despite the promise of precision oncology and long-term benefit in a subset of patients receiving immunotherapy, most available advanced cancer therapies offer limited benefits, with an estimated median improvement in overall survival (OS) of 2.5 months for novel cancer drugs approved over the last two decades in advanced or metastatic settings.⁷ More concerning, results from clinical trials may not always be replicated in real-world settings. The 'efficacy-effectiveness gap'⁸ is mainly driven by selective enrolment: A population-based analysis conducted in 125,316 patients in Alberta, Canada, estimated that 38% of them would not have been eligible for enrolment.⁹ Lastly, some 'hard-wired' biases or limitations cannot be corrected after the trial ends. For instance, in randomized controlled trials (RCT), a substandard control arm or suboptimal access to post-progression therapy can hamper the reliability of the results. We will detail those two biases, which, among many others, should be integrated within the novel assessment scheme.

3 | CONTROL ARM AND POST-PROTOCOL THERAPY

The THEOREMM framework proposal is justified by the evidence that key limitations afflicting RCTs are currently not considered in various assessments (See Table 1). We highlight two critical elements: the control

TABLE 1 Existing scores or tools to evaluate trials, with a summarized description and potential shortcomings.

Score/Tool	Summary of main items in the score	Potential shortcomings
ESMO-MCBS	Evaluates clinical benefit, toxicity and quality of life in cancer trials	No assessment of diverse biases
ASCO Value Score	Evaluates clinical benefit, toxicity, quality of life and potential for long-term benefit in cancer trials	No assessment of diverse biases
RoB2 Tool	Designed to assess the risk of bias in randomized trials, focusing on randomization, deviations, missing data and other items	No direct assessment of benefits and harms estimates. Not designed to assess for control arm or post-progression therapy
Indirectness GRADE	Assesses the generalizability and applicability of evidence, looking at population, intervention and outcomes	No built-in items to evaluate key aspects of trials such as the control arm or post-progression therapy

arm and post-progression therapy. These features are emphasized because they demonstrate how a study, even if it appears to have a low risk of bias, can have design limitations that may inherently favour the experimental therapy.

3.1 | Control arm

A suboptimal control arm introduces an inherent bias that remains uncorrectable thereafter. According to the Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects), a new intervention must be ‘tested against those of the best proven intervention(s) (...)’.¹⁰ However, 17% of drugs approved between 2013 and 2018 by the US Food and Drug Administration (FDA) were based on a suboptimal control arm.¹¹

For example, in the first-line setting of patients with metastatic ALK rearranged non-small cell lung cancer, crizotinib was approved by the EMA in 2012 and the FDA in 2013 following the results of a phase 3 trial showing its superiority over chemotherapy.¹² As a result, crizotinib became the standard of care. However, the ASCEND-4 trial, testing ceritinib as the new therapy in the same setting, started to accrue patients after the crizotinib approval, but used chemotherapy—a suboptimal control arm—as the control therapy.¹³

Among randomized trials, an increasing number of trials used control arm therapy defined as ‘physician’s’ or ‘investigator’s choice’. In oncology, 89% of those trials were industry sponsored, and 85% offered a restricted choice.¹⁴ The wording ‘physician’s choice’ gives a false sense of free choice, which therefore sounds optimal. However, a restriction may prevent potentially highly effective options that are part of standard-of-care. In the ASCENT trial, patients with metastatic triple negative breast cancer were randomized between sacituzumab govitecan and the

treatment of physician’s choice.¹⁵ Even though four options were offered, neither platinum-based chemotherapy nor anthracyclines were allowed. These are two important options that 31% and 17%, respectively, of patients in the control arm had not previously received.

The control arm may also be disadvantaged in other subtle ways, for example, dose modification or supportive care rules. Across registration trials leading to marketing authorization of FDA anti-cancer drugs approvals, over a 13-year time period, drug modification rules (which are applied when a patient suffers from toxicity) and supportive care delivery (like medicine preventing febrile neutropenia after chemotherapy) between arms favoured the new therapy in 55% of trials, while they favoured the control arm in only 10%.¹⁶

The REFLECT trial serves as an exemplary case. This phase 3 non-inferiority trial recruited patients with inoperable hepatocellular carcinoma for first-line therapy. Its objective was to establish that lenvatinib (the test drug) was no less effective than sorafenib (the comparator treatment). In patients receiving 12 mg of lenvatinib as a starting dose, three steps of dose reduction were allowed: 67%, 33% and 17% of the initial dose. In contrast, patients receiving the comparator drug could only undergo two dose reductions before stopping the drug, and the dose reductions were more pronounced: 50% and 25% of the starting dose. These rules favoured a higher dose-intensity (i.e., more drug being given) in the experimental arm. Within the REFLECT trial, a similar proportion of patients had a dose reduction in both arms (37% and 38%). However, likely due to the imbalance in dose reduction, the cumulative dose was higher in the lenvatinib group (88%) versus sorafenib (83%).

Overall, the control arm can be inappropriately penalized in different ways: the choice of the control, a restricted choice among several therapies, or drug dosing and supportive care rules. Yet, neither the ESMO score nor the ASCO score include any evaluation of the

control arm in their assessment.¹⁷ In an extreme scenario, a trial may show a spectacular improvement in survival against a poor comparator, yet the disparities in treatment would remain totally uncaptured. Appraising the control arm based on a systematic framework including the features we described will be an important part of the novel THEOREMM framework.

Ultimately, the goal of the framework will be to determine the relevance of the trial findings to contemporary practices or norms. It is often debated that the standard therapy or control arm might evolve over time, potentially making it challenging for trials to offer the best comparators. However, modifications to the control arm are still feasible and can be effectively executed.¹⁸ Moreover, allowing an entirely flexible control arm, where physicians can select the treatment without any restrictions, could mitigate some of the previously mentioned limitations.

3.2 | Cross-over and post-progression therapy

Cancer therapy typically involves a series of treatments (first-, second- or subsequent 'lines'). Each subsequent line is generally implemented when the disease advances. As such, patients often take a series of drugs, and have a series of breaks in their cancer treatment. The goal of cancer medicine is to maximize survival, while maximizing QoL, and, all else being equal, using the fewest drugs possible for the least amount of time—to minimize toxicity, cost, and therapeutic burden.¹⁹

Crossover to the experimental therapy after progression may be desirable in certain situations, but some types of cross-over and post-progression therapy may introduce substantial bias.²⁰

First, cross-over to the drug being tested may not happen in patients in the control group upon progression, but sometimes it should. For example, in patients with castration-resistant prostate cancer, abiraterone was standard of care before the LATITUDE trial started enrolling patients.²¹ The LATITUDE trial tested abiraterone earlier in patients with metastatic castration-sensitive prostate cancer. However, in LATITUDE, only 24% of control arm patients treated with a subsequent therapy received abiraterone. Because abiraterone was standard of care in later lines, patients should have received it upon progression. As a result, substandard post-protocol therapy in the control arm may have affected the overall trial results. The trial was not able to answer the relevant question: *Is it better to give abiraterone early or limit it to later lines?* Instead, it tested a question with little clinical relevance: *Is some abiraterone better than nothing?*

For pragmatic relevance, cross-over upon progression should use treatments that are known to be effective. If the experimental treatment is not yet documented to be effective when giving it upon progression at a later stage, post-progression cross-over of the control group patients to that treatment may be problematic. Such cross-over may delay the use of other treatments that are known to be effective. Therefore, an ineffective novel treatment may seem to be effective if its use as cross-over in the control group does not allow the control group patients to use other known and effective treatments promptly.

In a third undesirable scenario, the percentage of patients receiving any post-progression treatment within the trial is lower than in real-world conditions in both arms. This may happen when trials enrol globally, including in countries with suboptimal access to best care. The efficacy of ribociclib was evaluated in the MONALEESA-7 trial, primarily among patients receiving initial treatment for hormone-sensitive advanced or metastatic breast cancer.²² The trial compared ribociclib to a placebo, both used in combination with hormonal therapy. Subsequent treatments after disease progression were used in only 73% in the control group and 69% in the ribociclib group. However, real-world data indicates a higher utilization rate of up to 92% after initial hormonal therapy.²³ Would we have observed the same survival benefits if both groups had maximized the use of all available follow-up treatments?

With the three scenarios in mind, the significance of optimal care upon progression becomes more evident. Unfortunately, the post-progression experience of trial participants is often not described in sufficient detail. Across 77 trials that led to FDA approval between 2018 and 2020, 12% (9/77) had available post-progression data assessed as appropriate.²⁰

Regulatory authorities should grant marketing authorization (approvals) based on trials ensuring optimal post-progression treatment in both the experimental and control groups. Rules can be set to assist clinicians in evaluating post-protocol treatment, reflecting the expected standard of care in countries where most approvals are sought.²⁰

4 | CURRENT ASSESSMENTS OF NOVEL DRUGS, NOVEL INDICATIONS AND TRIALS

Having exemplified two key features of oncology clinical trials, it is vital to understand the different levels of current assessments for novel drugs, new indications, or trial results. First, a drug can be marketed after receiving authorization from regulatory bodies. We will detail how

drug regulations vary across countries. Beyond market authorization, clinicians rely on additional assessments to guide their decisions. The GRADE methodology, which evaluates a body of evidence, is one of the most recognized tools in evidence-based medicine. However, because GRADE typically focuses on a body of evidence, oncology professional societies, like ASCO or ESMO, have developed additional tools to assess the value of drugs tested in single trials.

4.1 | Drug regulation and health technology assessment

The two largest regulators, the FDA and the European Medical Agency (EMA), typically do not incorporate the magnitude of added therapeutic value as compared to existing agents.²⁴ As a result, some countries provide such assessment through distinct HTA bodies, allowing for price negotiation and reimbursement decisions.²⁴ Approximately one-third of initial approvals by the FDA and the EMA seem to have high added therapeutic value, with definitions varying according to countries.^{25,26} In supplemental indications—that is, indications in different settings granted after initial approval—the proportion of indications offering high therapeutic value is even lower.²⁴

Therefore, many novel therapies reach the market when their purported benefits may have limited or no benefits in real-life settings, or they may even be harmful.²⁷ The bar for approving cancer drugs has been repeatedly criticized because it has allowed a growing number of low-value and costly drugs to enter the market.²⁸ The accelerated approval pathway, initially designed to allow innovative and promising drugs to be prescribed while awaiting more robust data, has been derailed from its initial goals. Beyond efficacy assessments, similar limitations were described for quality of life (QoL) evaluation within the FDA and EMA assessments.²⁹

4.2 | Risk of bias tools and indirectness issues

GRADE^{5,6} is the most rigorously developed tool for appraising evidence in order to make recommendations and is currently officially utilized by more than 100 organizations worldwide. It is not primarily intended to assess individual trials, but rather to assess a body of evidence regarding a clinical question. The Cochrane Collaboration has developed a ‘risk of bias’ (RoB) tool to systematically assess the risk of specific biases in single trials.³⁰ The updated ‘RoB2’ is most commonly used

currently.³¹ This tool is primarily designed to assess the risk of bias arising from the randomization process, like deviation from intended interventions, missing outcome data, measurement of the outcome and selection of the reported results. This tool does not consider issues related to the choice of the comparator—that is, the control arm.

While being very useful in appraising certain aspects of randomized clinical trials, such tools do not capture other limitations, which may be best assessed as ‘issues of indirectness’ into the GRADE framework.³² Indirectness issues allow one to evaluate the extent in which the included trials are able to answer the clinical question under study. Even though such assessments could theoretically capture limitations such as suboptimal control arm, not all researchers are aware of all indirectness issues that could arise in oncology trials.

Another limitation in applying GRADE to novel drugs in the haematology and oncology fields, is that most novel drugs are currently marketed based on a single trial. The target PICO (which stands for Patients, Interventions, Comparators, Outcomes) is often represented by a single trial. Our proposal does not aim to create another specific risk of bias tool for cancer treatments.

4.3 | Scores emanating from medical societies

Oncology professional societies have developed scores to assess the clinical benefits of new therapies or novel indications. The two main scores are the European Society of Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS) and the American Society of Clinical Oncology Value Framework Net Health Benefit Score (ASCO Value Framework).

Both scores greatly rely on the reported magnitude of benefit in trials (i.e., based on hazard ratio threshold) and the type of endpoints (a survival benefit being most valuable). While these efforts are commendable, the ESMO and ASCO scores sometimes have discrepant results.³³ Fewer than one-third of contemporary randomized trials with significant results met the ESMO or ASCO thresholds for meaningful clinical benefit.^{29,34,35}

Both scores do not take into account some critical limitations in appraising the benefit of drugs, with shortcomings identified by the ESMO-MCBS working group itself.¹⁷ Because they were developed and are supported by organizations which are financially conflicted with the pharmaceutical industry, this may challenge the unfettered independence needed when appraising new products or supplemental indications.^{36–38}

5 | THE THEOREMM PROPOSAL

5.1 | Goals and objectives of the theorem framework

The primary goal of the proposed framework is to increase the awareness of key limitations potentially afflicting clinical trials and to systematically integrate those limitations into a framework to assess novel trials' results. Main goals and secondary objectives are described in [Box 1](#).

The framework scope will aim at systematically assess registration trials (i.e., those supporting marketing authorization). They can be RCTs or non-RCTs and they can be single-arm or multi-arm trials. The project will initially focus on trials leading to marketing authorization in the USA. Companies predominantly seek approvals there before other countries, and the highest number of approvals occur in USA.³⁹

The methods, which are detailed in the protocol-V1—Data [S1](#) (supplemental appendix), will follow a multi-step approach. Those are (1) assembling a group of independent experts—the scientific board; (2) defining the scope, goal and methods of the project through pre-specified, pre-registered, and protocolized methodology (these two first steps constitute the present work); (3) preregistration of the protocol; (4) conducting a scoping review of limitations and biases affecting oncology trials and assessing existing scores or methods; (5) developing a list of features to be included and assessed within the framework; (6) assessing each feature through a questionnaire sent to highly cited haematologists and oncologists involved in clinical trials; and (7) finalizing the first version of the framework.

BOX 1 Goals of the THEOREMM Framework

1. Primary objective: increase awareness of key limitations potentially affecting clinical trials and to systematically integrate such limitations into a novel framework evaluating trials' results.
2. Enable clinicians to make better-informed clinical decisions. This could improve patients' outcomes and satisfaction.
3. Provide an educational platform for medical professionals, fostering an improved understanding of research methods.
4. Be integrated in various aspects of current regulatory processes. Better-informed healthcare policies may justify resource allocation.
5. Build trust and ensure relevance by patient and public involvement, as well as high-profile clinicians and trialists.

6 | GENERAL PRINCIPLES IN DEVELOPING THE FRAMEWORK

Our proposal also incorporates key principles: patient-centredness, independence, multidimensionality, transparency and open-science.

The concept of patient-centredness has no unique definition.⁴⁰ Patient-centredness holds on the belief that patients have unique perspectives.⁴¹ To ensure patient-centredness, patient and public involvement will be integrated throughout different steps of the project.

The new framework should be unbiased and unaffected by any form of undue influence, manipulation, or conflicts of interest that could potentially arise from pharmaceutical or commercial enterprises. To mitigate these risks in our proposal, we aim to ensure that the experts who will directly develop the framework and provide the accompanying reviews are free from any conflict of interest with the industry. Similarly, for patients and the public who wish to directly participate in the project, independence regarding financial conflict of interest with the industry will be required.⁴²

Relying on a single indicator would not do justice to what is a multi-factorial conglomerate of strengths, biases, and limitations. Quality scales have shown lack of reproducibility and are discouraged when assessing a trial.^{30,43} We propose a multi-dimensional framework which will incorporate various features or items.

The protocol is pre-registered. Additionally, as part of the project, reviews of trials being assessed will be made publicly available online. The THEOREMM project will be conducted following the principles of open-science.⁴⁴

7 | CONCLUSION

The THEOREMM project emerged naturally in response to the lack of consideration for key limitations in current trial assessments, such as the adequacy of control arms and post-progression therapy. Its goal is to create a framework specifically designed to assess individual trials leading to marketing authorization—registration trials—in the field of oncology and haematology. The framework will systematically incorporate elements and features that are not consistently assessed by other frameworks or scores. The project will be guided by the involvement of clinicians, patients and the public, independence from industrial conflict of interests, transparency and open-science principles.

AUTHOR CONTRIBUTIONS

All authors have contributed substantially to the design, performance, analysis, or reporting of the work. Specifically: TO contributed to the study's original concept and design. TO wrote the first draft of the manuscript and the protocol.

Searches was done by TO, AH and VP. The protocol was discussed and conceived by JPAI, VP, FN, IB, AH, and TO. All authors contributed to the drafting and revising of the manuscript, provided critical revisions for important intellectual content, and gave their final approval of the version to be published. Furthermore, all authors agree to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST STATEMENT

There are no conflicts of interest related to the study design or its results. Dr Vinay Prasad reported receiving research funding from Arnold Ventures LLC through a grant made to UCSF; royalties for books and writing from Johns Hopkins Press, MedPage, and the Free Press; and consulting fees from UnitedHealthcare and OptumRX. He also reported receiving revenue from Patreon, YouTube, and Substack for the podcasts Plenary Session, VPZD, and Sensible Medicine; for the newsletters Sensible Medicine, The Drug Development Letter, and VP's Observations and Thoughts; and for the YouTube channel Vinay Prasad MD MPH. Dr Isabelle Boutron is a member of the SPIRIT-CONSORT steering committee. Other authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

Reviews of trials being assessed by the novel framework will be made publicly available online. The THEOREMM project will be conducted following principles of open-science. The research protocol is preregistered on the Open Science Framework (OSF) (available at <https://osf.io/q3upe/>), the data generated during the project will be openly available through website repository, and all peer-review publications will be open-access.

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