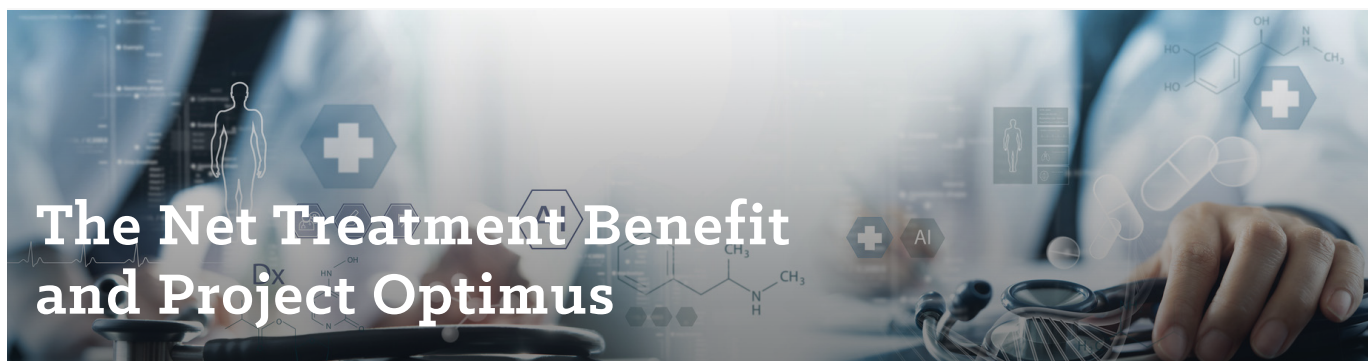




Since the FDA released their Project Optimus guidance for dose optimisation, with the idea to move away from Maximum Tolerated Dose (MTD) designs, many sponsors have very practical questions about how to demonstrate that one dose provides a better overall balance of efficacy, safety and tolerability for patients.

Randomised dose optimisation studies are emerging as an important approach. Net Treatment Benefit (NTB), derived from Generalised Pairwise Comparisons, provides a way to bring these different outcomes together into a single, clinically meaningful overall assessment of benefit and risk.

What is FDA's Project Optimus?

The FDA's Project Optimus is a key step toward improving dose optimisation in oncology. Originally announced in 2021, the guidance aims to move away from traditional dose escalation and maximum tolerated dose (MTD) designs toward approaches that identify the dose that best balances efficacy, safety and tolerability.¹ The traditional approach was developed largely around cytotoxic chemotherapy, where increasing the dose often meant increasing both efficacy and toxicity. The dose was therefore increased until safety became a concern, with the MTD then carried forward into later development. This approach is no longer appropriate for many modern oncology treatments. Higher exposure does not necessarily mean greater efficacy, being able to tolerate a treatment for longer may be more important than a slight boost to efficacy. Therefore, a dose selected at the limit of efficacy and tolerability may expose patients to additional toxicity without providing meaningful additional benefit.^{1,2} Ultimately, the goal is for patients to benefit from treatment doses that maintain strong efficacy while avoiding toxicity that is disproportionate or unacceptable, rather than simply pushing the limit of tolerability.

What Approaches Exist to Answer Project Optimus?

Project Optimus does not prescribe one universal method for identifying the optimal dose. Their guidance recommends randomised, parallel dose-response trials as an approach for comparing multiple dosages when appropriate.³ However, randomised dose optimisation is still not a standard approach for every oncology development programme. Sponsors must decide which doses to evaluate, how many patients are needed, which outcomes should drive the decision and how the resulting efficacy and safety data should be analysed. This is where Net Treatment Benefit can provide a practical approach.

What is Net Treatment Benefit?

Net Treatment Benefit is a measure of treatment effect derived from the Generalised Pairwise Comparisons statistical methodology. Generalised Pairwise Comparisons allow several outcomes to be considered together, while also allowing those outcomes to be prioritised according to their clinical importance.⁴ The principle is relatively straightforward.

Instead of analysing efficacy, toxicity and other outcomes separately, all patients in one treatment group are compared with all patients in the other treatment arm across a predefined hierarchy of outcomes. For example, efficacy might be given the highest priority, followed by serious toxicity, then other clinically relevant measures of tolerability. For each pair of patients, the analysis compares outcomes sequentially according to the hierarchy and determines for each outcome which patient has the more favorable result at. Across all patient pairs, these pairwise classifications are then summarised as the Net Treatment Benefit: the probability that a randomly selected patient receiving one treatment has a better outcome according to the hierarchy than a randomly selected patient receiving the comparator, minus the probability of the opposite situation.^{4,5} This creates a single measure of benefit-risk while retaining the information contained in the individual outcomes.

How Can Net Treatment Benefit Support Dose Optimisation for FDA's Project Optimus?

Imagine a randomised dose optimisation study comparing 2 doses of an oncology treatment. The highest dose may produce a slightly higher response rate, but also more grade 3 or 4 toxicities and more treatment discontinuations. The lower dose may produce a similar response rate, while substantially improving tolerability. Looking at each outcome independently can make the final decision difficult. Net Treatment Benefit allows efficacy, toxicity and tolerability outcomes to be considered together. A possible hierarchy could prioritise Overall Survival or another efficacy outcome first, followed by clinically important toxicities and then treatment discontinuation or patient-reported tolerability. The hierarchy should be defined prospectively and should reflect the clinical objectives of the trial. NTB does not need to replace individual analyses on each outcome. Instead, it can provide an additional integrated analysis that helps to interpret them together, and to make a decision. It can also make the result easier to communicate. Rather than presenting a series of efficacy and safety tables and asking decision-makers to determine how they should be balanced, NTB provides a quantitative estimate of the overall difference between doses. For example, an NTB of 10% means that the probability that a randomly selected patient receiving one dose has a more favorable outcome than a randomly selected patient receiving the comparator exceeds the probability of the reverse outcome by 10 percentage points, according to the prespecified outcome hierarchy. In most cases this does not make a dose selection decision automatic and clinical judgement remains essential, but NTB provides a statistically rigorous framework for making the benefit-risk trade-off more explicit.

What Happens After the Dose Has Been Selected?

If the treatment is ultimately approved, the same evidence used to select the best dose continues to have value. It can provide a transparent scientific rationale for why the selected dose was taken forward into Phase III and ultimately to patients. A robust benefit and risk analysis can also help to communicate the reason behind



dose selection to regulators, HTA bodies, and clinicians, who want to better understand the overall benefit-risk profile of a treatment.⁷ Since Project Optimus was first launched, the positive trajectory is clear. Still, there is work to be done to ensure that approved doses are the ones that provide the greatest overall benefit to patients. Randomised dose optimisation studies provide the evidence needed to make that decision. Net Treatment Benefit provides one practical framework for bringing efficacy, safety and tolerability together into a single analysis, helping sponsors select the right dose with confidence and supporting that decision from Phase II through regulatory review and into clinical practice.

REFERENCES

1. U.S. Food and Drug Administration. Project Optimus: Reforming the dose optimization and dose selection paradigm in oncology. FDA Oncology Center of Excellence. Available at: www.fda.gov/about-fda/oncology-center-excellence/project-optimus, visited on 13 Aug 2026.
2. Shah, M., Rahman, A., Theoret, M. R. & Pazdur, R. The Drug-Dosing Conundrum in Oncology: When Less Is More. *N Engl J Med* 385, 1445–1447 (2021).
3. U.S. Food and Drug Administration. Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases: Guidance for Industry. August 2024.
4. Buyse, M. Generalized pairwise comparisons of prioritized outcomes in the two-sample problem. *Stat Med* 29, 3245–3257 (2010).
5. Gai, J. et al. Net benefit in the presence of correlated prioritized outcomes using generalized pairwise comparisons: A simulation study. *Stat Med* 40, 553–565 (2021).
6. Peron, J. et al. Restricted Net Treatment Benefit in oncology. *J Clin Epidemiol* 168, 111340 (2024).
7. U.S. Food and Drug Administration. Benefit-Risk Assessment for New Drug and Biological Products: Guidance for Industry. FDA, 2023.

Pascal Piedbois



Pascal Piedbois, professor of medical oncology, offers considerable experience from both the academic and industry sectors. In academia, he served as the Head of Medical Oncology at Paris University and was the General Director of the Comprehensive Cancer Centre of the Alsace Region, based in Strasbourg, until 2015. In the industry, Pascal has held several prominent leadership roles, including Vice President, Head of Global Oncology and Infectious Diseases at AstraZeneca, Senior Vice President, Head of Medical Europe, Canada, and Japan, and Senior Vice President, Head of Medical Go to Market Strategy for Bristol Myers Squibb. Additionally, he has served as the General Manager of Boehringer-Ingelheim Belgium. Pascal's passion and commitment to combining digital innovation with medical relevance is set to enable the incorporation of patient preferences and needs into the development and market access of new treatments.