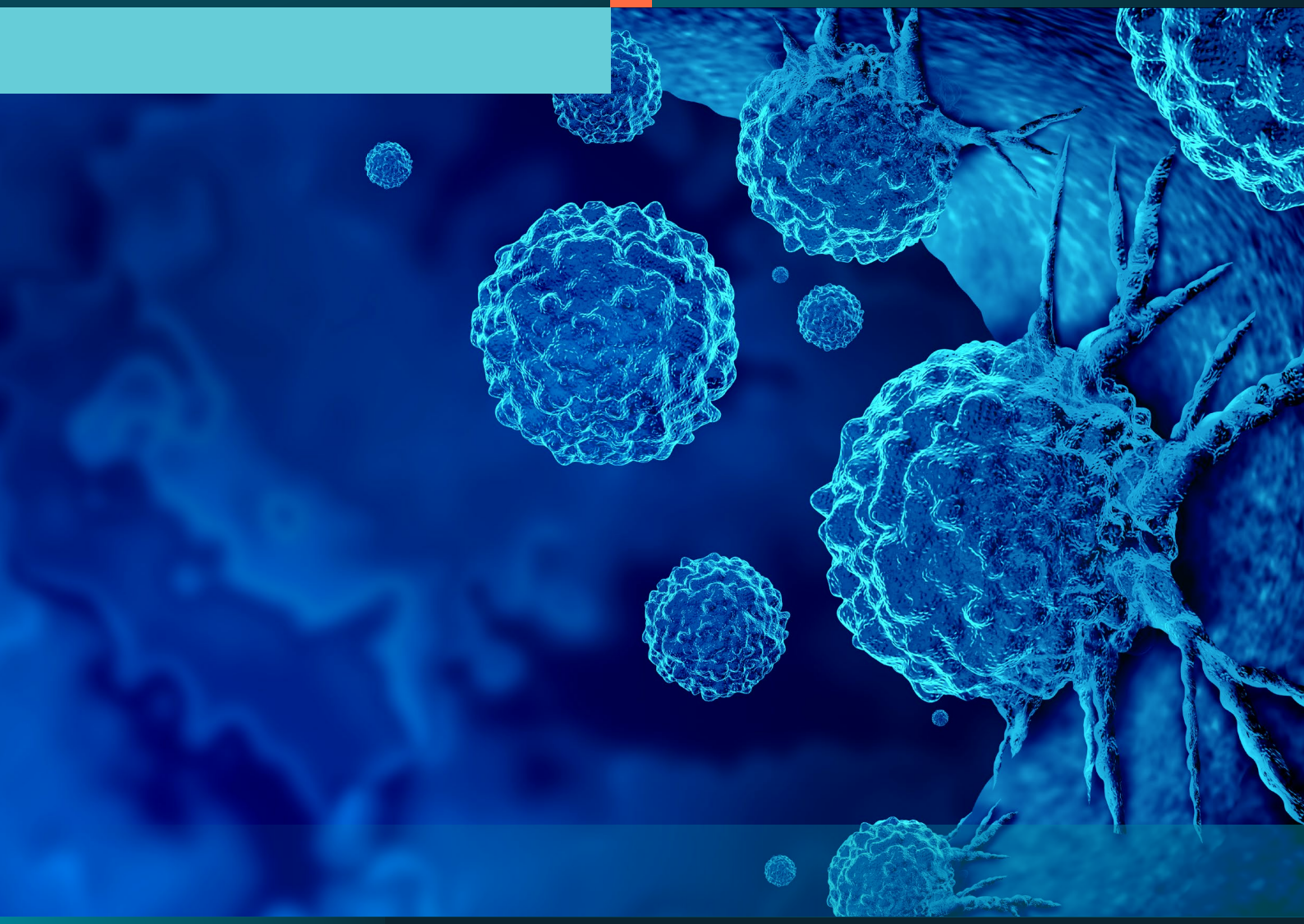
SIMBEC-ORION

Primed for Optimus

Taking a proactive approach to Project Optimus



Introduction: Refining dose optimisation in oncology

In 2021, the U.S. Food and Drug Administration's (FDA) Oncology Center of Excellence (OCE) introduced Project Optimus, a transformative regulatory initiative targeting dose optimisation and selection processes in oncology drug development [1, 2]. Moving away from the traditional early phase oncology development programme based on cytotoxic chemotherapies and the maximum tolerated dose (MTD) concept [3] (Figure 1), this initiative focuses on a comprehensive exploration of the safety, tolerability and efficacy of oncology drug products (DP) to determine the optimal therapeutic dose before approval.

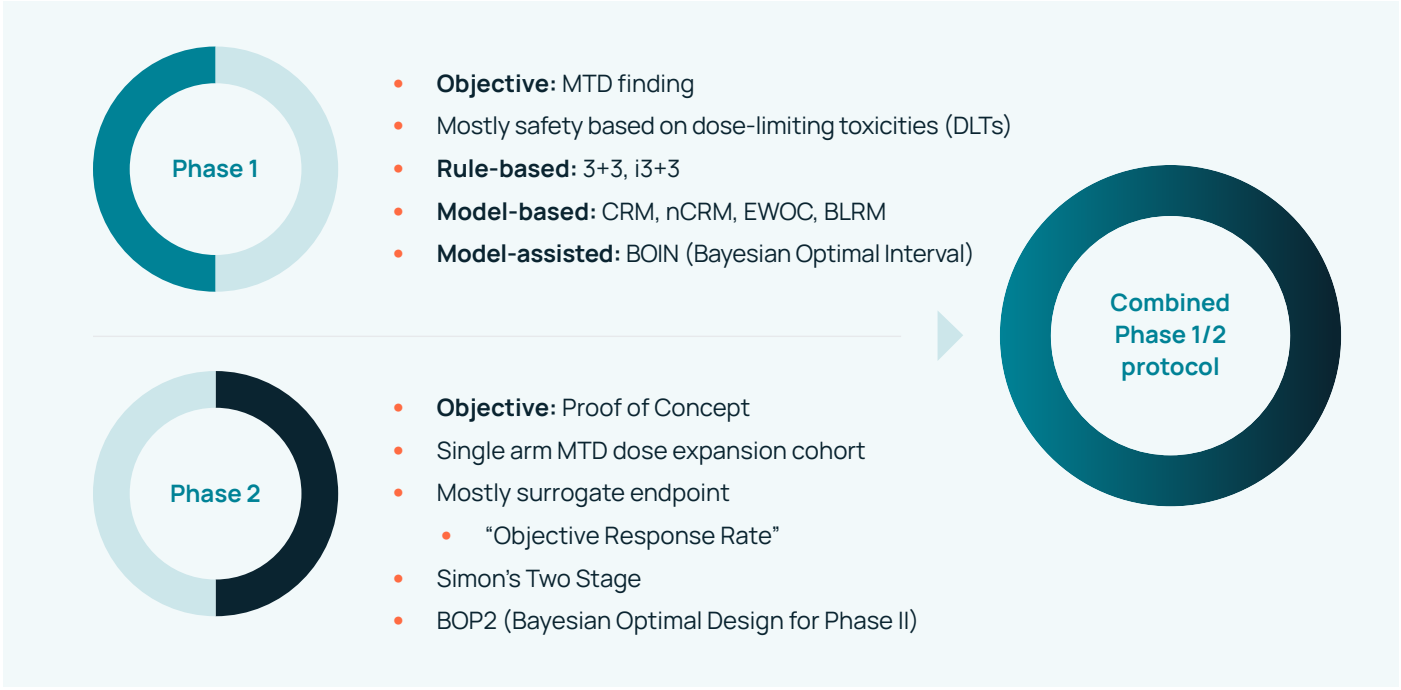


Figure 1: Standard early phase oncology development programme based upon cytotoxic chemotherapies. CRM: Continual reassessment method; nCRM: Nonparametric continual reassessment method; EWOC: Escalation with overdose control; BLRM: Bayesian logistic regression model.

In recent years, the FDA has often requested sponsors to conduct post-marketing trials after approval. These studies or trials have often been completed to obtain additional information on the optimum dosage of a product where the MTD has been used for pivotal trials, in addition to providing further insights into safety and efficacy [4]. These can include:

- **Post-marketing requirements (PMRs):** Completing required studies or trials as per one or more statutes or regulations.
- **Post-marketing commitments (PMCs):** Conducting studies or trials that have been agreed upon but are not required by statutes or regulations.

Recent PMR and PMC data support the need for a change in approach to dose optimisation in oncology in a number of cases (Figure 2 and Figure 3). Therapy types with PMRs/PMCs leading to label changes typically include those with specific molecular targets, such as monoclonal antibodies (mAbs), antibody-drug conjugates (ADCs) and kinase inhibitors [1].

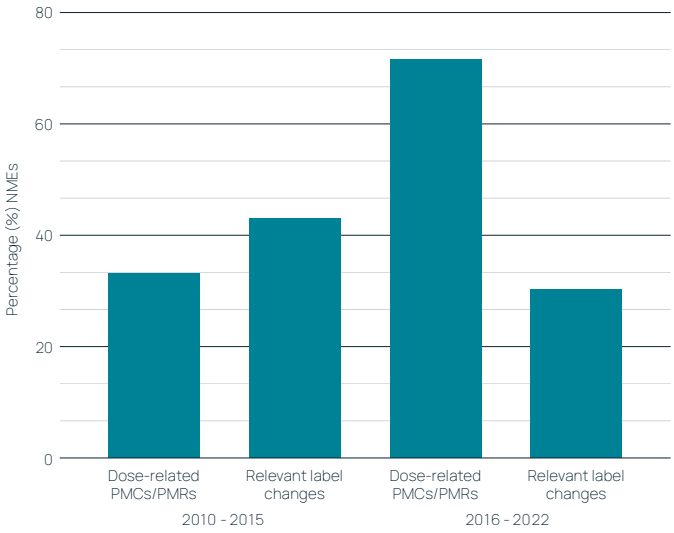


Figure 2: The number of PMRs/PMCs from 2010 to 2022, together with the number leading to label changes. Adapted from Gendy et al., 2024 [1].

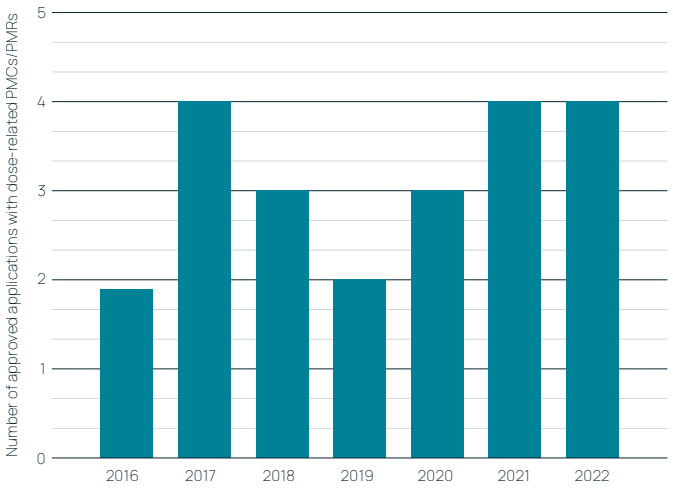


Figure 3: The number of FDA-approved applications with dose-related PMCs/PMRs from 2016 to 2022. Adapted from Gendy et al., 2024 [1].

Project Optimus aims to shift the paradigm from identifying and researching the MTD to dose-finding and dose-optimisation strategies for oncological treatments across the bio/pharmaceutical industry. By educating, innovating and collaborating with industry, academia and regulatory agencies, Project Optimus will provide the necessary framework to advance this transformation. The Project Optimus framework includes communicating dose-finding and dose-optimisation expectations, initiating early engagement and developing efficient dose-finding strategies [5] (Figure 4).

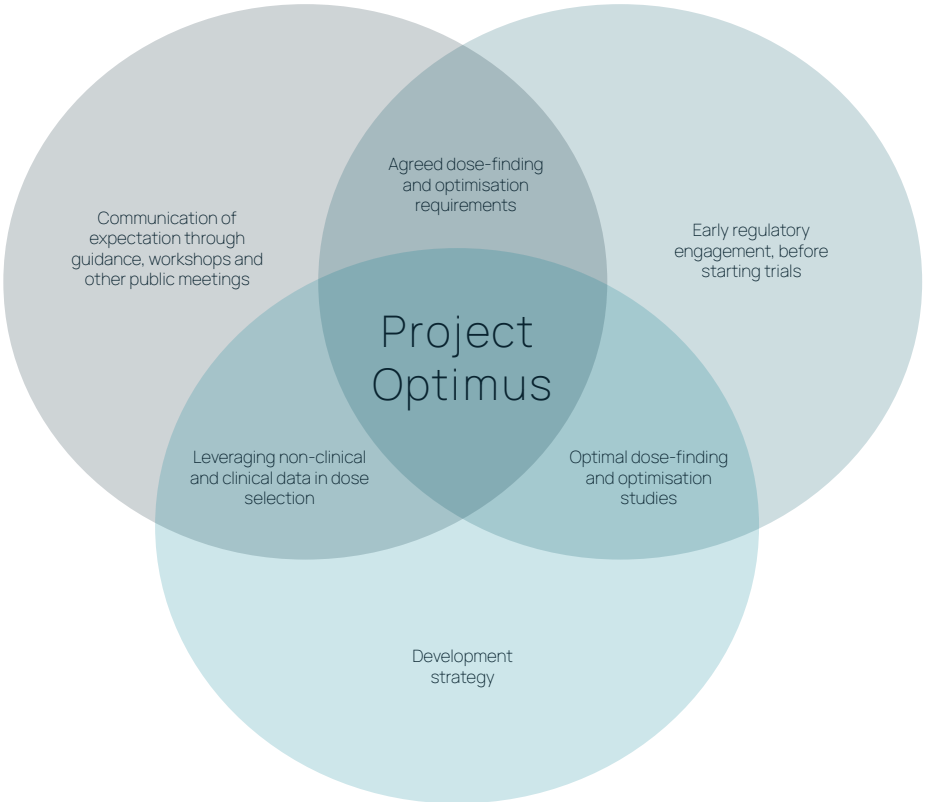


Figure 4: The Project Optimus framework for dose optimisation and selection processes in oncology drug development.

Optimising dosing strategies in oncology aims to improve patient safety and enhance therapeutic efficacy while building on the existing regulatory processes, such as the use of the target product profile (TPP).

The impact of Project Optimus

The shift from the traditional MTD approach will substantially impact oncology drug development, both in terms of redefining how clinical trials are designed and patient numbers. However, with the aim of better optimising oncology drug dosage, implementing Project Optimus should benefit patients by reducing toxicities and side effects, improving tolerability and treatment adherence and improving drug label dose accuracy (Figure 5).

Figure 5: Implementing Project Optimus can improve patient outcomes.

To align with Project Optimus, developers must think of incorporating dose-finding studies (or modules when a modular trial design is selected) into clinical development programmes to better understand the dose-response relationship. This will change how clinical programmes are designed, providing a more in-depth characterisation of drug performance to determine the optimal dose. However, this approach also potentially increases initial costs and prolongs timelines. An example of this is extensive dose-ranging studies causing financial strain.

Successfully preparing for Project Optimus requires a proactive approach and careful planning. The critical steps in Project Optimus can be implemented by undertaking several key actions that support three main objectives (Table 1).

Table 1: Critical steps in implementing Project Optimus.

Objective	Actions
Characterisation of the exposure-response relationship	**PK/PD modelling:** Enhance drug development by establishing correlations between drug concentrations and treatment outcomes (including biomarkers and clinical endpoints such as best overall response (BOR)) through comprehensive PK/PD modelling, thereby guiding optimal dose selection. **Identification of exposure-response drivers:** By analysing PK/PD data, the key factors influencing the exposure-response relationship can be identified, such as patient characteristics, concomitant medications and disease stage. This helps to tailor dosing strategies to patients, minimising adverse effects.
Characterisation of the dose-response relationship	**Safety assessment:** Evaluate the safety profile of the drug across different dose levels, monitoring any adverse effects. **PK/PD analysis:** PK/PD modelling will assess the dose-dependent drug exposure and efficacy changes. **Biomarker evaluation:** Explore the relationship between dose and biomarker levels to identify potential dose-dependent changes in biomarkers that correlate with efficacy or safety. **Efficacy assessment:** Analyse the drug's efficacy at different dose levels based on defined clinical endpoints.
Selection of the recommended phase II dose(s) (RP2R) and the recommended phase III dose (RP3D)	**Comprehensive analysis:** Conduct a thorough evaluation of exposure-response, dose-response and safety assessments. Consider efficacy, safety and tolerability to optimally select the RP2R and RP3D. **Statistical analysis and models:** Utilise statistical approaches such as Multiple Comparisons Procedures and Modeling (MCP-Mod) methodologies to identify the optimal drug dose. This methodology merges several procedures of multiple comparisons (MCP) with model-based approaches (MOD) to create a more thorough and effective analysis of dose-response relationships [6]. Bayesian hierarchical models or mixed Bayesian-frequentist models can also be used to produce flexible modelling frameworks for dose-response modelling.

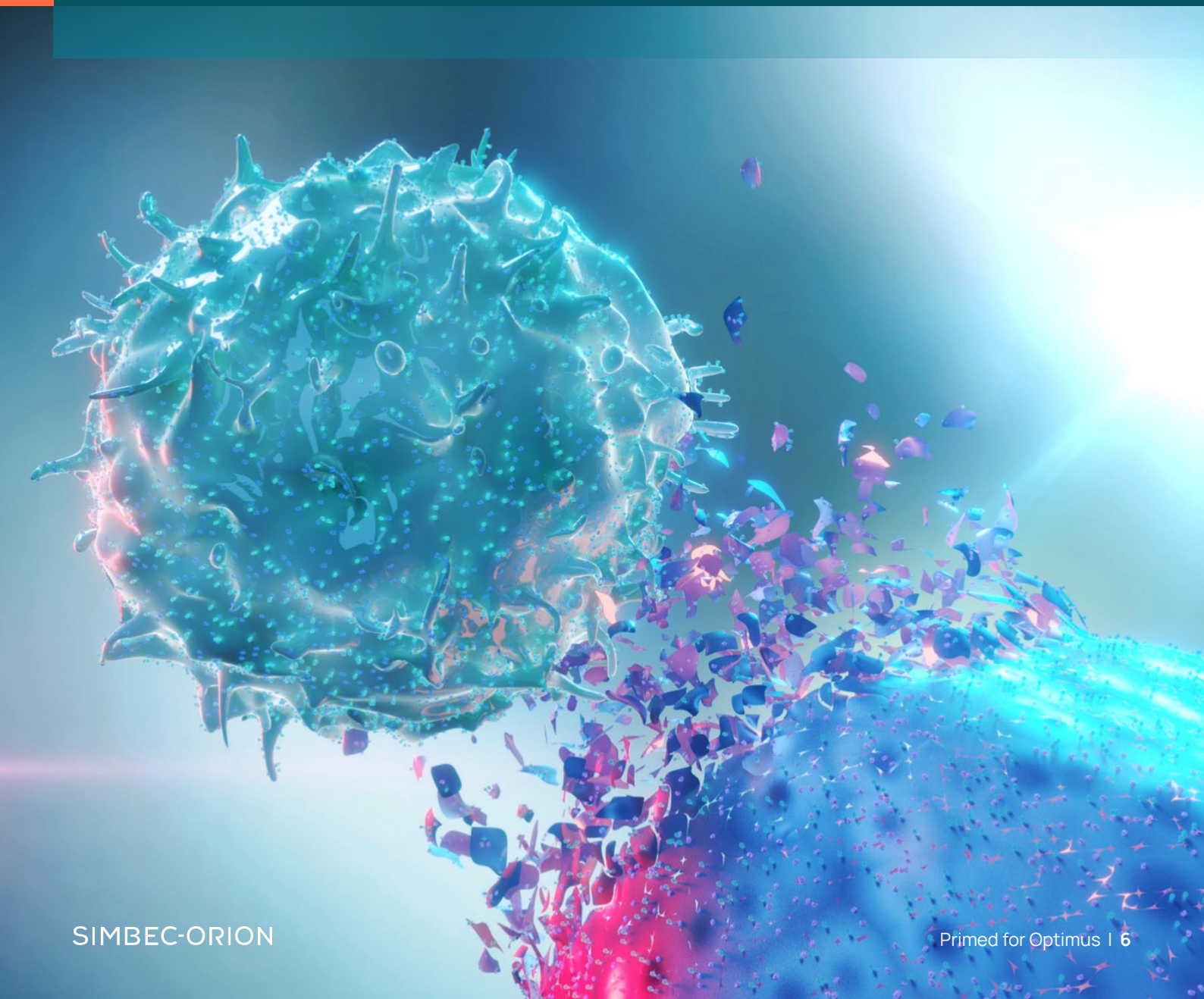
This initial investment may prevent costly delays later in the development process by avoiding PMCs and PMRs, which often need to be discussed. Moreover, there is an expected reduction in dose-related label changes post-approval, which can ultimately benefit patients and the industry.

Despite the benefits, Project Optimus adoption has been slow to be embraced as developers face many obstacles. These challenges must be overcome to effectively meet the goals of Project Optimus and optimise oncological drug doses.

What makes Project Optimus challenging?

- **Varying awareness:** Awareness and understanding of Project Optimus differ widely across the industry, which has impacted successful uptake. Most organisations are unclear when to actively incorporate Project Optimus into their research programmes.
- **Complex clinical trial designs:** Transitioning from the traditional '3+3' dose-escalation design to more advanced designs requires sophisticated statistical methodologies, representative models and clinical outcome evaluation, which are available but have not been widely adopted by the research community.
- **Evolving guidance:** Project Optimus is still evolving, and guidance related to certain aspects continues to evolve, such as Bayesian Optimal Interval (BOIN) boundaries and its application in combination treatments. At present, this necessitates case-by-case decisions and highlights the need for further collaboration among stakeholders.
- **Need for collaboration:** Overcoming these challenges requires open collaboration across the industry. Stakeholders must share experiences and insights to refine guidelines and implementation strategies, ultimately improving patient outcomes.

Despite the challenges, Project Optimus is here to stay. It holds promising long-term benefits in improving the quality and safety of oncology treatments. Moving forward, international approvals will demand close alignment with Project Optimus, necessitating widespread adoption across the industry — from academic units and small biotech companies to big pharma. The bio/pharmaceutical industry must work together to to ensure successful implementation.



Overcoming challenges and implementing Project Optimus

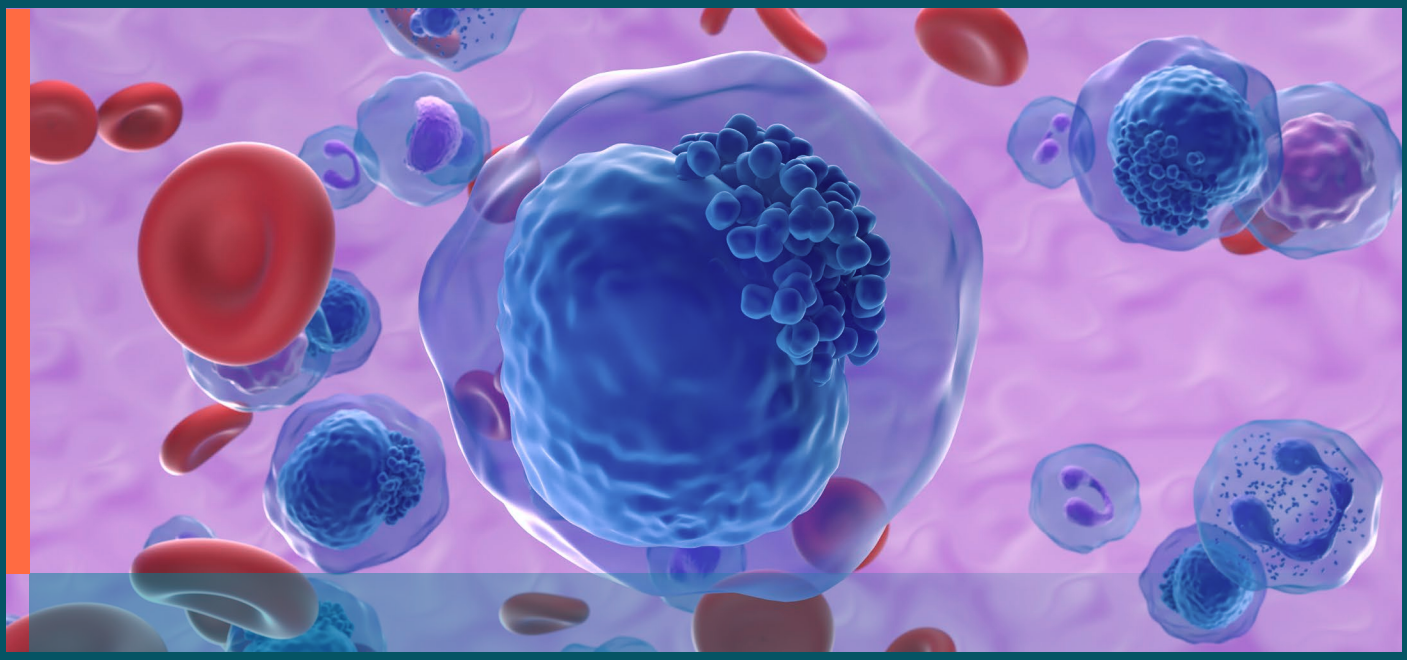
The role of CROs in the success of Project Optimus

Partnering with a contract research organisation (CRO) provides the expertise and experience to effectively navigate the drug development changes required for aligning with Project Optimus. However, choosing the right CRO to partner with is critical, and the following should be considered to navigate Project Optimus successfully:

- **Clinical trial management:** Expertise in designing and managing adaptive and complex dose-finding trials.
- **Central laboratory services:** Supporting biomarker development and PK/PD modelling.
- **Clinical pharmacology:** Providing advanced methodologies for dose optimisation studies.
- **Regulatory affairs:** Guiding compliance with Project Optimus requirements, ensuring all dose optimisation data and justifications are well-documented for robust regulatory submissions.
- **Medical writing:** Providing medical writing services ensures effective communication of dose optimisation strategies and outcomes to regulatory agencies and stakeholders by developing comprehensive documentation and justifications for dose selection with the support of scientific and statistical experts.
- **Drug development advisory board:** Offering strategic scientific and statistical insights and expert guidance to sponsors helps ensure clinical trials are designed and conducted in alignment with Project Optimus principles. Advisory boards also help navigate complex regulatory landscapes and optimise therapeutic dosing strategies.

Choosing a specialist CRO with the understanding and insight to guide customers through the Project Optimus transformative period is essential. Adjusting clinical trial design and harnessing innovative study designs and methodologies demonstrates the capability to navigate Project Optimus and the journey to optimal dose selection for oncological therapies. In addition, by forming an early-phase oncology centre of excellence, a CRO that prioritises Project Optimus can help provide customised solutions tailored to each client's needs and address the unique challenges of dose optimisation in oncology drug development.

Looking ahead with Project Optimus



Project Optimus represents a significant shift in oncology drug development, emphasising the importance of dose optimisation for improving patient outcomes and therapeutic efficacy. Its implementation offers significant benefits for patients, including reduced toxicity and side effects and improved safety and tolerability of critical oncological treatments. Improved dose optimisation enhances drug product labelling by ensuring patients do not receive unnecessarily high dosages.

Simbec-Orion is a full-service CRO with a wide range of therapeutic experience and specialist services including clinical pharmacology, oncology and rare disease clinical trial design. With a wealth of experience in complex study designs and comprehensive dose-finding studies, Simbec-Orion is ready to help guide you through the opportunities and challenges associated with Project Optimus.

For more information and to discover how Simbec-Orion can help you prepare for Project Optimus, **contact us today.**

References

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