WHITE PAPER

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Assembling the Right Team for a Successful Nonclinical Program

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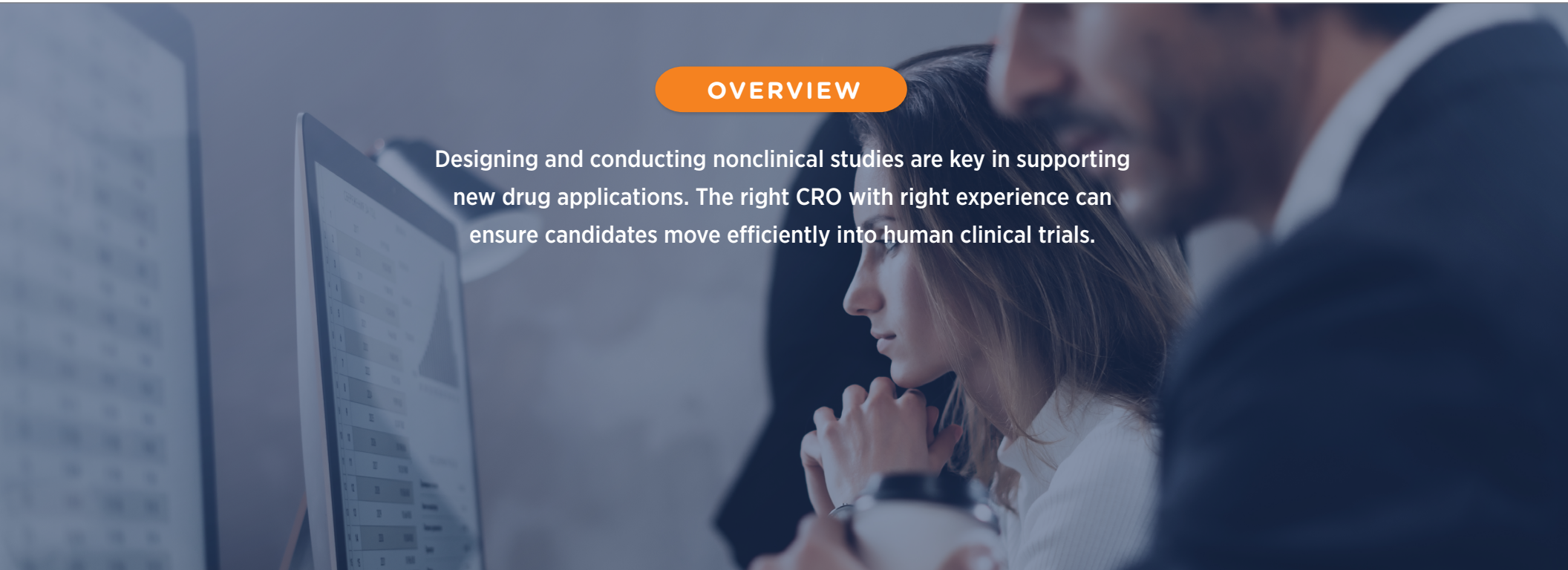
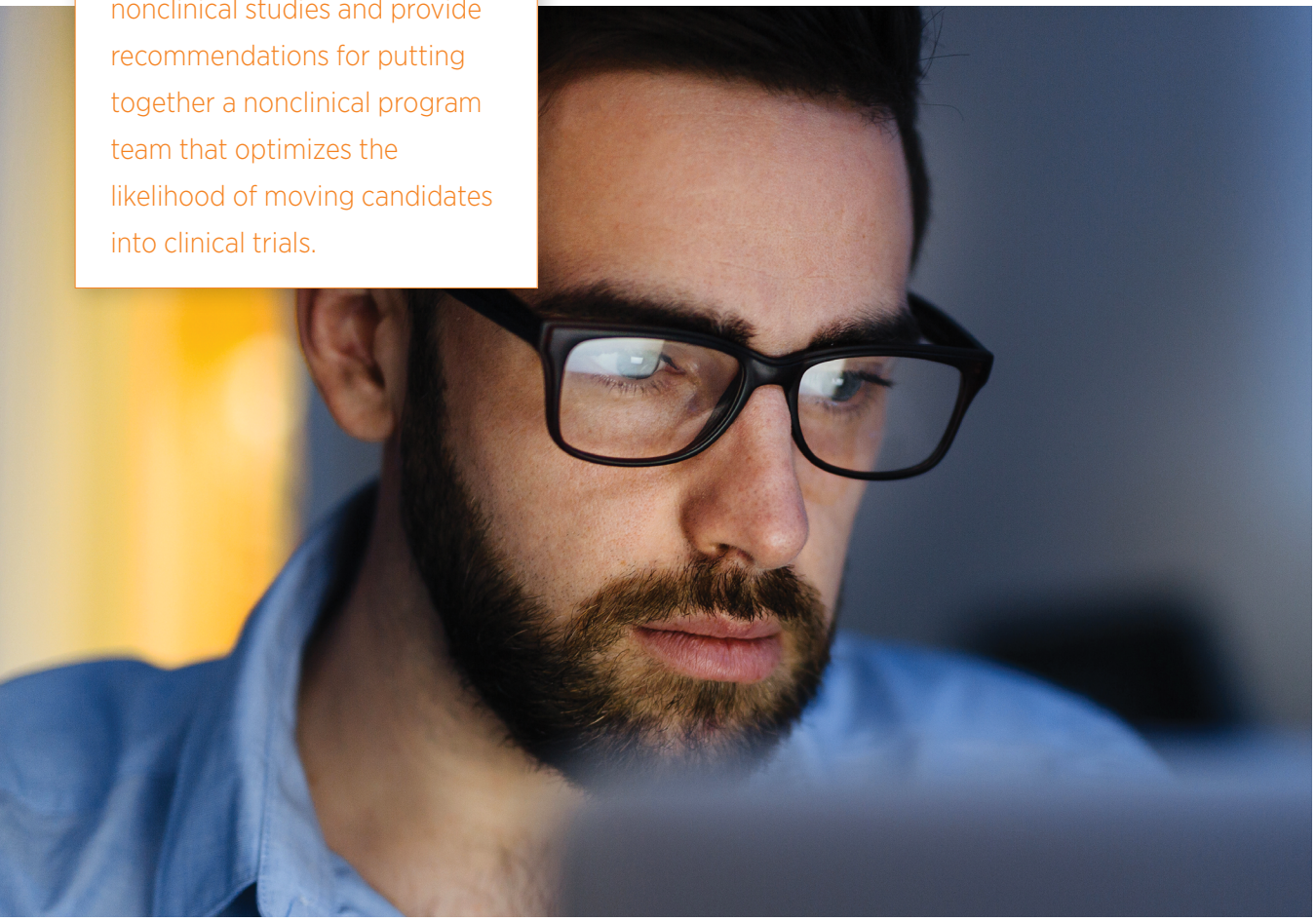


OVERVIEW

Designing and conducting nonclinical studies are key in supporting new drug applications. The right CRO with right experience can ensure candidates move efficiently into human clinical trials.

In this paper, we offer insight into the importance of – and requirements for – nonclinical studies and provide recommendations for putting together a nonclinical program team that optimizes the likelihood of moving candidates into clinical trials.



Introduction

In drug development, nonclinical studies are essential for establishing the safety of a new potential drug product and determining a safe starting dose for human clinical trials. The key to success lies in designing and conducting the appropriate nonclinical studies to support an investigational new drug (IND) application in the most efficient and cost-effective manner.

In this paper, we offer insight into the importance of – and requirements for – nonclinical studies and provide recommendations for putting together a nonclinical program team that optimizes the likelihood of moving candidates into clinical trials.

Determining which nonclinical studies are needed

Every drug development program is unique, and the nonclinical studies required for each program will vary. Generally, nonclinical studies are necessary for:

- Providing information on potential toxicity
- Determining safety margins that allow for the selection of clinical doses
- Identifying potential biomarkers for monitoring treatment response in clinical trials

Sponsors should consider the type of drug – small molecule versus biologic – in order to understand the applicable regulatory guidelines.

Non-oncology products

For non-oncology new chemical entity (NCE) or new molecular entity (NME) programs, the first nonclinical studies typically evaluate efficacy and pharmacokinetics (PK). These evaluations are generally followed by:

- Toxicology studies, which are usually conducted in both rodent and non-rodent species
- Safety pharmacology studies, using rodents to assess effects on the central nervous and respiratory systems and non-rodents to assess effects on the cardiovascular system

In most cases, absorption, distribution, metabolism, and excretion (ADME) studies are needed before an IND is filed. Some genotoxicity studies – including in vitro mutagenesis and chromosomal aberration studies – need to be initiated prior to IND filing, while others are required to be completed before Phase 2 clinical trials. Long-term and chronic toxicology, carcinogenicity, and reproductive studies must all be conducted before filing a new drug application (NDA).

Oncology products and biologics

For oncology NCEs, safety pharmacology endpoints may be included in pivotal Good Laboratory Practices (GLP) studies, eliminating the need for stand-alone studies. Carcinogenicity and certain toxicology studies may not be required at all, and genetic toxicology studies are not needed until NDA filing.

Special considerations for biologics include attention to immunological endpoints and the selection of an appropriate species for nonclinical studies. Genetic toxicology studies are not needed, and the requirement for carcinogenicity studies is determined on a case-by-case basis.

Other products

Below are a few scenarios wherein the nonclinical study requirements differ from those of more common small molecules and biopharmaceuticals.

- **Vaccines.** Since vaccines are not intended for chronic administration, they have distinct nonclinical study requirements. Nonclinical assessment of vaccines should be performed in a single relevant species in which there is a demonstrated immune response. Toxicokinetic evaluations may not be required, but parameters such as body temperature and injection site reaction will likely need to be incorporated into nonclinical study evaluation.
- **Drugs containing novel excipients**. Most excipients used in drug development are considered Generally Regarded as Safe (GRAS) and do not require testing. If, however, a drug requires a novel excipient, nonclinical studies similar to those required for small molecules are necessary.
- **Repurposed or reformulated drugs.** For previously approved drugs with new formulations, new routes of administration, or other changes, sponsors may be able to use the 505(b)(2) pathway and leverage existing data on the previously approved drug to minimize the nonclinical studies required.
- **Drugs with pediatric indications.** If the clinical trial target population includes children, nonclinical studies must be performed in a species that reflects the pediatric population and should be designed to evaluate effects on growth and organ systems that develop after birth.
- **Cell and gene therapies.** The nonclinical study guidelines for these therapeutics are similar to those for biologics but may also require non-traditional endpoints and stricter chemistry, manufacturing, and controls (CMC) standards.

Designing nonclinical studies

Proper design of a nonclinical program reduces the risk of having to repeat nonclinical studies or even redesign clinical trials. When designing nonclinical studies, it is important to start with the end in mind by defining the scientific objectives – the data and endpoints needed to inform and advance development. Understanding what background information is available and what previous or similar work has been done can help sponsors select the right species and dose ranges.

Species selection is critical, as the FDA requires sponsors to conduct nonclinical studies in the most relevant species based on the pharmacological activity of the drug. Many biopharmaceuticals that do not exert a pharmacological effect in rodent models may therefore require the use of non-human primates (NHPs) for nonclinical studies. Of note, there is currently a global shortage of NHPs, predating but exacerbated by the COVID-19 pandemic and China's ban on the export of NHPs. This shortage may require sponsors to consider alternative species, adjust their development priorities, or reevaluate program timelines.

Given that nonclinical studies are intended to support downstream clinical studies, understanding the proposed clinical trial design is crucial. For instance, if the intent is to dose for 21 days in a clinical trial, the nonclinical study would need to involve 21 days of dosing. To properly design a nonclinical program, sponsors should define, at a minimum, the intended clinical trial dosing regimen, route of administration, anticipated dose range, and study population. If GLP studies are needed, sponsors will need to ascertain if proposed analytical methods need to be developed. In addition, assay development and validation can cause significant delays in nonclinical programs, so planning for them early in the development process can help to keep programs on track.

Mitigating potential challenges encountered during nonclinical studies

Common obstacles that sponsors may encounter while conducting nonclinical studies include:

- Insufficient supply of the test item or animal model
- Poor animal species choice or dose selection due to a lack of prior knowledge of the test item
- Delays or unrealistic timelines
- Unexpected outcomes
- Logistical issues

Sponsors can help mitigate the risk of encountering these challenges by performing a thorough assessment and gap analysis of their study plans. Working with a partner who has deep experience in the execution of nonclinical studies may help sponsors avoid common pitfalls encountered during the drug development process.

When sponsors have access to the right nonclinical expertise, they are better-equipped to perform only studies that are necessary and to conduct those studies in the right order so that data is available at the right time to inform decision making and support regulatory submissions. Experienced nonclinical partners can also help sponsors identify meaningful study outcomes and find ways to address unexpected issues that arise, such as non-ideal PK profiles.

Finding the right partner

Partnering with a cross-functional team that can provide integrated strategy, regulatory, and development support is valuable for navigating the complexities of the drug development process and identifying an efficient, streamlined path to better outcomes. Seeking input from regulatory agencies along the entire product development pathway is also essential, and finding a partner that has experience interacting with the FDA allows for productive engagement.

When evaluating potential partners for nonclinical studies, consider their development planning, oversight, and execution capabilities.

In particular, sponsors should look for partners with deep experience in CRO qualification, selection, and management. A partner that has existing relationships with specific CROs, as well as a long history of working with their study directors and other personnel, can significantly mitigate the risk involved in conducting a nonclinical program. This familiarity with particular sites can also ensure that the right CRO is selected for a sponsor's program.

Working with a nonclinical CRO that has experience in the therapeutic area of interest, the type of drug, and the route of administration helps ensure the necessary depth of regulatory knowledge and breadth of functional expertise. Performing a comprehensive review of the CRO's regulatory inspections, including the frequency of inspections and the number and nature of any 483s issued, is advisable. It may also be useful to understand the organization's history of interactions with the FDA and its track record of approvals and first-pass approval rate.

Development Planning	Development Execution
Nonclinical strategy	Contract research organization (CRO) vendor qualification, selection, and management
Nonclinical study design	CRO auditing to ensure GLP compliance
PK/pharmacodynamics expertise	Study monitoring capabilities
	Study analysis and reporting experience
	Project management

About Premier Consulting

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Our end-to-end solutions in strategy, regulatory, nonclinical, clinical, CMC, quality, and commercial help sponsors build and execute development plans that meet regulatory requirements and deliver results for sponsors and the patients they serve.

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