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What's New in GCP?
Investigator Brochures in Early Trials Found Wanting

German and Canadian researchers found most investigator brochures for early-phase human research "lack sufficient information to systematically appraise the strength of the supporting preclinical findings."

The analysis published in PLOS Biology also found that the very rare reporting of preclinical efficacy studies that demonstrated no effect "raises concerns about potential design and/or reporting biases. The poor preclinical study design and reporting thwarts risk–benefit evaluation during ethical review of early human research."

The researchers from the Hannover Medical School and McGill University recommended regulators develop standards for the design and reporting of preclinical efficacy studies to support ethical clinical trials.

The article noted that evidence for risk-benefit judgments in Phase 1 and 2 trials often stems from preclinical efficacy studies (PCESs). The researchers conducted a systematic investigation of investigator brochures (IBs) presented to three German institutional review boards between 2010 and 2016. The researchers examined 109 IBs and identified 708 unique PCESs.

The researchers rated the PCESs for their reporting on study elements that help to address validity threats, whether they referenced published reports, and whether they offered positive or negative results. They found less than 5% of the PCESs described elements essential for reducing validity threats, such as randomization, sample size calculation, and blinded outcome assessment, and 89% had no reference to a published report. "While it is possible that sponsors maintain internal review mechanisms for PCESs, members of IRBs or regulatory agencies reviewing IBs have no way of knowing whether preclinical efficacy data have been subject to critical and independent evaluation," the article said. "Further, IRBs and regulatory sponsors have no way of directly accessing preclinical reports if they are not published. Such commonplace nonpublication of preclinical evidence is potentially inconsistent with numerous scientific and ethical guidelines on early-phase trial launch."

In addition, only 6% of the PCESs reported an outcome demonstrating no effect and 82% reported positive findings. "Several nonexclusive explanations for this imbalance of outcomes in PCESs can be envisioned. One is biased study design. It is possible that, in the absence of prespecifying end points or the limited use of techniques like blinded outcome assessment, PCESs consistently show large effects. A second explanation is biased inclusion of PCESs in IBs," the article said. "A third explanation is that only those treatments that show consistently positive effects in PCES were selected for early-phase trials. Though our study does not allow us to discriminate between these explanations, we think the latter explanation is improbable. Studies demonstrating no effect are crucial for demarcating the boundaries of dosing, diagnostic eligibility, or treatment timing for a new treatment."

"Our results show that most IBs for Phase 1/2 studies did not allow evaluators to systematically appraise the strength of the supporting preclinical findings," the article said, adding the IBs contained "very little information that would enable reviewers to evaluate the risk of bias in these individual studies. For example, less than 20% of PCESs reported baseline characterization, exclusion of data from analysis, or randomization. Sample size calculation and blinding for outcome assessment were never reported," the article said.

To improve the effective use of preclinical information for risk–benefit assessment in Phase 1/2 trials, the researchers recommended that IBs should describe measures taken in PCESs to support clinical generalizability. "To facilitate efficient evaluation of IBs, it might be helpful to present relevant practices, like use of randomization or choice of endpoints, in tabular form. Furthermore, explicit remarks on the 'level of evidence' for each preclinical study might be presented in such tables, with studies designated as 'confirmatory' when they had prespecified hypotheses and protocols or 'exploratory' when their hypotheses and and protocols were not established prospectively."

In addition, confirmatory studies should employ methods that would enhance internal and construct validity, such as a priori sample size calculation, concealed allocation, or blinded outcome assessment, and use of clinically relevant endpoints. "Information on the reproducibility of confirmatory preclinical studies and meta-analysis of sufficiently similar studies might further improve the level of evidence," the article added.

A stepwise presentation of preclinical evidence could further help evaluators navigate the most important questions to assess clinical promise and safety: Have effects been reproduced in different models and/or in independent laboratories? Do the conditions of the experiment (for instance, age of animal models, timing of treatments, and outcomes) match clinical scenarios?

Second, the researchers recommended that IBs should state whether they are presenting the totality of preclinical evidence, and if not, how data were selected for inclusion in the IB. One option would be to present only preclinical studies that have been preregistered, the article said. "This increased transparency might help with preventing selective outcome reporting," and would allow evaluators to check whether other relevant preclinical studies exist.

In addition, future studies are needed to evaluate how improved reporting for preclinical data presented in IBs influences risk-benefit analysis during ethical review. "However, better reporting alone is unlikely to solve problems related to risk of bias in preclinical evidence," the article said. "Regulatory bodies like the FDA and the EMA offer specific recommendations for the design of preclinical safety studies. To our knowledge, there are no regulatory guidelines offering standards for the design and reporting of PCESs."

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