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'Preproducibility' and Backwards Design: Improving preclinical research reproducibility with reporting guidelines.

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INTRODUCTION. Reproducibility and translation potential of much preclinical animal-based research is poor. Major barriers include substandard methodological quality and reporting. The prerequisite for reproducibility is **'**preproducibility', the clear and complete communication of relevant methodology to allow others to replicate or verify results. Consensus reporting guidelines provide the gold standard to ensure reproducibility. However, methods reporting in the published literature is still critically deficient. In part, this is because investigators do not perform upstream mission-critical methods and so cannot report them.

OBJECTIVES. To review factors contributing to poor reproducibility of preclinical research, familiarize investigators with guidelines ARRIVE 2.0 and PREPARE, and introduce the Backward Design (BD) process for study design.

METHODS. BD is a three-step process focusing first on the desired end results of a study (reproducibility). Quality is built into the study by (1) *identifying* reproducibility standards (Tier 1 of ARRIVE 2.0 guidelines), (2) *determining* necessary performance tasks, followed by (3) study-specific *planning.* The ARRIVE 2.0 "Essential 10" lists all items necessary to ensure reproducibility. ARRIVE 2.0 Tier 2 items and PREPARE provide checklists for identifying logistics, design, and performance tasks. These include study formulation, literature searches, legal and ethical requirements, animal facility interactions, funding, resources, personnel, statistical design and analysis, health and safety, and quality control. Study-specific checklists and SOPs further reduce error and standardize processes. Appropriate up-to-date guidance from veterinarians, information specialists (research librarians, IT), and biostatisticians will require incorporation into the planning process.

CONCLUSION Poorly conducted preclinical studies produce biased and misleading results. When coupled with inadequate reporting, such studies contribute to poor reproducibility and failed translation. These problems could be avoided if experiments are properly planned and designed well before data collection. Poor reproducibility is both an ethical and translational

issue, because animals are wasted in non-informative experiments, with potential harm to human patients. Guidelines such as PREPARE and ARRIVE 2.0 should be used as planning tools to build quality into research protocols. To shift emphasis from “business as usual” to quality reproducible research, substantial investigator cultural change will be required.