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TITLE: Data-driven classification of endpoints patterns in toxicology studies: toward innovative study design using virtual control groups

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ABSTRACT: Preclinical toxicology study involves complex decisions about which endpoints to measure, and when. Although respective OECD, EPA and ICH guidelines specify core requirements, actual measurement protocols may vary substantially between organizations and across development phases. This heterogeneity makes it difficult to use historical control data as virtual control groups (VCG) and reduces the effectiveness of data imputation or synthetic data generation. We hypothesized that patterns of measured endpoints across studies reflect underlying scientific principles and study objectives, which can be leveraged to classify studies using data-driven methods. Within such innovative study designs classes, more robust data imputation and reliable virtual control groups could be established.

SEND-formatted toxicology studies from the IHI VICT3R project were assessed for the presence or absence of endpoints and observations. Clustering was combined with bipartite network analysis and community detection algorithms, revealing consistent patterns of co-occurring measurements ("endpoint signatures") among studies, corresponding to recognizable study "types", while being defined by data (detected communities) rather than labels. Our analysis distinguished between: i) standard repeat-dose communities characterized by broad laboratory panels, multi-organ histopathology, and cardiac monitoring; ii) biomarker-intensive communities, typical of early development, featuring extensive clinical chemistry but reduced histopathology; iii) specialized communities aligned with dedicated organ toxicity (e.g., neuro- or immuno-toxicology) or bespoke, hypothesis-driven designs.

We found that tests within these communities form recognizable panels (e.g., hepatic markers like ALT/AST/ALP) and follow expected pathophysiological relationships (e.g., renal function paired with urinalysis). The findings suggest that endpoint signatures are shaped by mechanistic and regulatory influences, offering a strong statistical foundation for data imputation. By identifying these signatures and incorporating them into innovative VCG based study designs enables researchers to improve animal matching and create more reliable datasets, especially when endpoints are missing at random across studies. This framework suggests a new practical pathway for VCG generation and aims to optimize future study design, aligning with the evolution of regulatory science toward a data-driven paradigm.