Ecological validity of biomarkers in drug research

Koopmans, I.W.

APPENDICES

ENGLISH SUMMARY

This thesis explores the integration of ecological validity in biomarkers used in early-phase clinical drug development. Ecological validity refers to the extent to which a biomarker reflects real-world clinical outcomes and patient-relevant functional capacities. While early clinical trials primarily assess safety and pharmacokinetics in healthy volunteers, the progression toward registration trials requires outcome measures that are both scientifically robust and clinically meaningful. Traditional biomarkers often lack the ability to predict clinical outcome assessments (COAs) needed for registration, creating a translational gap between proof-of-concept studies and real-world efficacy.

To bridge this gap, this research introduces a novel tiered framework named the Ecological Validity of Biomarkers (EVIB). This framework categorizes biomarkers based on their relevance and predictive value for real-world outcomes. The framework consists of six tiers, ranging from pharmacological proof (Tier 1) to real-world evidence (Tier 6). This provides a structured method for assessing biomarkers' applicability throughout the clinical development pipeline.

Besides the introduction, this thesis applies the framework across multiple case studies, each involving different functional domains: driving behaviour, fall risk, grip strength, and pain perception. These studies demonstrate that while high-tier biomarkers (e.g., on-the-road driving tests or real-life gait assessments) offer higher ecological validity, they are often costly, time-consuming, or logistically challenging. Intermediate biomarkers, such as those derived from driving simulators or dynamic walking tasks, can offer a balance between feasibility and real-world relevance. Similarly, novel tools like the PowerJar device and VR-PainCart show potential for increasing ecological validity when conventional measures fall short.

Biomarker selection for clinical trials should account not only for technical rigor but also for contextual relevance to daily life activities. Ecological validity, though dynamic and influenced by evolving scientific evidence, is essential for enhancing the predictive power of early-phase studies and optimizing drug development efficiency. By structuring the assessment of ecological validity, this work offers a practical strategy to improve translational reliability and reduce late-stage clinical trial failures.