Animals, Humans, and the Continuity of Evidence: A Study of Clinical Translation

Nominated PI: Jonathan Kimmelman, McGill University
Co-PI: Dean Fergusson, Ottawa Hospital Research Institute

Co-Investigators: Jeremy Grimsaw, Dan Hackam, Greg Knoll, Alex John London, John Marshall, Dave Moher, Tim Ramsay, Margaret Sampson, Duncan Stewart, Charles Weijer

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Lay Abstract:
In the last two decades, researchers have made enormous progress in understanding the causes of human disease. Yet many important discoveries have not yet had an impact on the practice of medicine. This grant aims to understand some of the reasons why therapies that show promise in animals never make it to the clinic. We believe one of the reasons is that animal studies are often not as well designed as they should be. This grant will look at a large group of animal and human studies to see whether this is the case. Our study will further allow us to see whether certain research practices might improve chances that a new drug will have a clinical impact, and whether patients benefit or are harmed by participating in first in human drug studies.

Description:
The present study will examine these questions empirically by performing a systematic analysis of experimental practices and outcomes in studies leading toward clinical translation. Our primary goal is to provide a quantitative description of the degree to which preclinical studies address various threats to valid clinical inference. Our secondary goal is to determine whether addressing certain threats predicts successful clinical translation.

Our specific strategy, depicted in the graphic below, is to identify a large cohort of early phase trials of new drugs or biologics. We will next track down preclinical studies supporting these initial studies, as well as subsequent, later stage clinical studies. Preclinical study outcomes will be recorded, as will be practices along three key axes: internal validity, construct validity, external validity. In the final stages of the grant, we will attempt to relate validity practices in preclinical studies to outcomes in clinical studies.
Our cohort will include a sample of ~200 initial human studies of new, unlicensed agents, 2000-2005, inclusive.

We will identify all available preclinical studies that correspond with each initial human trial, and clinical studies that follow them.

We will develop extraction parameters for study characteristics, validity, and outcomes.

Studies identified in stages 1 and 2 will be extracted and elements entered into a database.

Frequency of practices reducing threats to validity will be measured, and hypotheses about relationship between methods and outcomes will be tested.

Selected Publications from team members supporting grant
(* = team member, † = collaborator)


