March 16, 2023

Dear Dr. Sax,

We write to submit our manuscript “**First Do No Harm? Modeling risks and benefits of challenge trials for hepatitis C vaccine development”** for consideration at *Clinical Infectious Diseases*.

Hepatitis C virus (HCV) is a substantial and growing cause of global morbidity and mortality, and there is currently no vaccine available to prevent chronic infection. Because prior HCV vaccine trials have required long follow-up and therapeutics are available to treat infection, some experts have proposed challenge trials for HCV vaccine development. We develop a decision-analytic model to evaluate the benefits and risks of a challenge approach to HCV vaccine development, compared to a traditional approach. We find that even with conservative assumptions, the benefits of a challenge approach are potentially significant relative to risks and that policies focused on streamlining the regulatory process and ensuring vaccine availability once approved can maximize potential benefits.

All authors have seen and approved the manuscript and contributed significantly to the work, and the manuscript has not been previously published nor is not being considered for publication elsewhere. Some potential reviewers for this work include:

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Thank you for your consideration.

Sincerely,

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