



International Alliance for
Biological Standardization

IABS 3rd Real World Evidence Workshop **“Pragmatic Randomized Controlled Vaccine Trials: Toward Global Alignment on Regulatory Framework and Evidence Standards”**

November 18-19, 2026
Leiden, The Netherlands

Outcome Leveraging Integrated Healthcare Systems to Implement Large Pragmatic Randomized Vaccine Trials

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Assessing relative vaccine effectiveness (rVE) of influenza vaccine formulations using traditional randomized vaccine clinical trials can be challenging because of the extremely large numbers of vaccinees required and ethical issues related to use of placebo in populations recommended for routine vaccination. Pragmatic, randomized studies comparing influenza vaccine formulations can overcome these barriers, however, they must be designed and implemented in a way to ensure that the two groups of vaccinees are similar to each other with respect to important cofounders such as underlying medical conditions, access to vaccines, and risk of exposure to influenza virus. We conducted two large, pragmatic, randomized studies to assess the rVE of influenza vaccines against polymerase chain reaction (PCR)-confirmed influenza within Kaiser Permanente Northern California (KPNC). We cluster randomized all KPNC clinical facilities such that approximately half of facilities administered one influenza vaccine and half the other influenza vaccine on the first week of the influenza vaccination season. Thereafter, every facility crossed over and alternated formulations weekly, with the result that every facility administered both vaccines throughout the season on an alternating weekly schedule. This design resulted in individuals in both vaccine groups being well balanced on all measurable confounders. The first study, conducted during 2018-2019 and 2019-2020, compared recombinant influenza vaccine (RIV) with egg-based standard dose influenza vaccines (SD-IIV) among 1,630,328 vaccinees aged 18 to 64 years. Among the primary age group of 50 to 64 years of age, the rVE of RIV vs SD-IIV was 15.3% (95% confidence interval [CI], 5.9 to 23.8; $P = 0.002$), showing that RIV conferred more protection against PCR-confirmed influenza than an egg-based standard-dose vaccine. The second study, which began in 2023-2024 and is currently ongoing, compares adjuvanted influenza vaccine with high-dose influenza vaccine in individuals aged 65 years and older, both of which are preferentially recommended in the US in this age group. We conducted a pre-specified interim analysis for the 2023-2024 season among 429,595 vaccinees which reported an rVE of adjuvanted versus high dose influenza vaccine was 1.5% (95% CI, -8.4% to 10.5%), showing that, in the first season of a large, ongoing study, adjuvanted and high-dose influenza vaccines did not differ in effectiveness against PCR-confirmed influenza in adults 65 years or older. Successful implementation of this design is facilitated by key features of some integrated healthcare systems, including access to large populations, central control of vaccine supply and routine vaccine administration without need for individual informed consent. This design also requires equipoise between vaccine formulations. Real world evidence from such pragmatic trials can contribute to global alignment of vaccine policies.

