



International Alliance for
Biological Standardization

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PHI perspective on value and role of pragmatic RCTs - Nick Andrews, MHRA

Public health institutions (PHIs) routinely undertake post-licensure evaluation of vaccines through vaccine effectiveness, safety, impact, epidemiological, serological, and immunogenicity studies. At the UK Health Security Agency (UKHSA), these activities have supported evidence-based vaccine policy decisions, including assessments of alternative schedules, dose intervals, age groups, and heterologous vaccine regimens. However, despite extensive experience with observational studies and immunogenicity trials, pragmatic randomised controlled trials (RCTs) evaluating vaccine efficacy or safety have not yet been conducted in the UK post-licensure setting.

Several factors have limited the implementation of pragmatic vaccine trials. These include logistical challenges associated with vaccine procurement and deployment systems, ethical concerns regarding unvaccinated comparator groups, the availability of high-quality effectiveness and safety data from both UK and international studies, and the use of immunogenicity data to inform policy decisions. In addition, the costs of large-scale trials, the need for sufficiently important unanswered questions, and expectations that manufacturers should undertake pivotal studies where necessary have reduced the perceived need for PHI-led pragmatic RCTs. Furthermore, a pragmatic trial introduction may miss the opportunity to see wide scale herd immunity.

From a PHI perspective, pragmatic vaccine trials are most appropriate when substantial uncertainty remains regarding vaccine benefits or risks, particularly in populations not currently recommended for vaccination or when comparing alternative vaccines or schedules. Such trials are especially valuable when observational studies are unlikely to provide reliable estimates because of residual confounding or when expected effect sizes are small. In these circumstances, well-designed pragmatic RCTs may offer the most robust evidence for benefit-risk assessment and policy decision-making, provided they can be conducted at an acceptable cost. Looking ahead, potential applications include comparisons between licensed vaccines, randomised step-wedge introductions of new programmes, and evaluation of vaccines approved primarily on immunological correlates of protection or those with potential wider health benefits not captured in pre-licensure studies.

