



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”

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Core design considerations - Arto A. Palmu, FVR – Finnish Vaccine Research, Tampere, Finland

Pragmatic trials are, by definition, randomized trials. This is the most important feature differentiating pragmatic trials from observational studies. Randomization is the most powerful tool to ensure balanced distribution of all baseline risk factors, whether known or unknown, between the treatment groups and will control the healthy vaccinee bias. Randomization can be conducted either by individual participants or by clusters, e.g. by geographical area. Randomization requires minimum two treatment groups, i.e. active vaccination and control. Selection of the control is crucial. Another active vaccination needs to be chosen, if it is available and used for the target group. Placebo or inactive vaccine for the study outcome is very powerful tool, as the comparison would equal “no treatment”. This enables evaluation of absolute benefits and use of the vaccine probe design.

Blinding is needed to ensure that the treatment groups remain comparable during the trial follow-up. Also, in case of misclassification in the outcomes, blinding will guarantee that any misclassification would more likely be non-differential (symmetric), and therefore, the direction of the misclassification bias would be dilution of the effects.

The power of the trial needs to be adequate. Healthy enrollee effect means that the participants in any clinical trial are on average healthier than the general population in the target group. This will usually decrease the outcome incidence in the enrolled trial population and needs to be taken into account. Pragmatic trials are also especially suitable for long-term follow-up, as collection of routine RWD is much less costly compared to active follow-up studies.

High generalizability is also an important feature of pragmatic trials. Permissive eligibility criteria mimicking routine vaccination processes enable straight-forward interpretation of the results. Pragmatic trials can be conducted in late-phase clinical development, i.e. phase 3 and 4. Starting in phase 3 is highly relevant, if the licensure is to be applied using safety and immunogenicity criteria without efficacy data against clinical outcomes. Low-intervention trials in phase 4 are specifically defined in the EU clinical trial regulation and some exemptions to GCP are allowed.

Safety data collection can also be enhanced by RWD, usually in a hybrid fashion with active data collection for related adverse reactions.

In conclusion, pragmatic trials provide a strong study design for post-licensure phase evidence generation, especially in the context of a post-licensure commitment requested by the regulatory authorities.

