Practical considerations for vaccine pragmatic trials to study safety and efficacy

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Could we use observational trials to confirm efficacy in accelerated/animal rule/conditional approvals?

There is a regulatory requirement to confirm/study efficacy

RCTs are the gold standard, but it becomes very difficult to use placebo after a product is licensed; trials are ideally underway at the time of licensure (though this may not always be feasible)

Disease epidemiology is constantly evolving and “feasibility” of generating randomized evidence evolves too, so it’s important to really rule out getting randomized clinical endpoint data

There is substantial concern about bias in many observational studies

Non-randomized observational studies

There is always a risk of bias or mistaken conclusions

- Confounding; Healthy vaccinee bias; Misclassfication bias; Selection bias; Biases specific to test negative designs; Differential depletion of susceptibles; Waning immunity

Type I error is nearly impossible to control

Absence of randomization and potential for unmeasured biases mean that statistical significance does not guarantee a true association

Ways to reduce (but not eliminate) the risk:

- Prospective protocol
- Internal controls
- Falsification outcomes
- Require high efficacy
- Multiple studies or verify results of randomized trials
- Better matching of groups

https://www.who.int/news-room/events/detail/2023/09/14/default-calendar/improving-vaccine-effectiveness-studies--a-vital-step-before-the-next-pandemic

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Better matching of groups

Test negative design case control study: by taking as controls people with symptoms similar enough to provoke testing, but negative test results, attempt to control for health-seeking behavior (didn't work very well for COVID)

Attempt to identify similar controls (e.g., in cohort studies)

Randomization

Pragmatic trials: Randomization during deployment

When FDA licensed the first COVID mRNA vaccines, reviewers suggested pragmatic trials of vaccine safety to gain confidence in the vaccines

Since (at least initially) demand greatly outstripped supply, it would have been ethical to randomize within risk groups between immediate vs. delayed vaccination

- (instead of allowing immunization managers to decide the order in which people get vaccinated, use randomization to decide it)

This could have allowed earlier and more confident detection of vaccine-associated adverse events

This same idea can be applied to collecting observational (real world) efficacy data

Considerations: Randomization

Individual

- Randomize vs. placebo
- Randomize appointment times

Clusters

- Randomize by location or sublocation

It’s important to enumerate groups and randomize before vaccine is delivered

Considerations: Ethics

When can you randomize in favor of/against getting a recommended treatment or vaccine?

Non-placebo control (such as high vs low dose vaccine)

Limited supply of vaccine or delivery capacity, as is often the case at product launch:

- Randomization (within priority groups) is the fairest way to distribute
- Immediate vs delayed vaccination assures that everybody receives vaccine, though where feasible, inclusion of placebos is desirable

Copious supply:

- If vaccine is available outside the study, can make randomization more difficult, though not impossible
- Informed consent

Pragmatic trials: one possible design

POPULATION. All who are anyway eligible for deployment. These can be large studies.

The enumeration/registration of those to be included (a given risk group) is defined in advance (e.g. in context where electronic vaccine registration is used).

RANDOMIZATION People who are in the registry or have signed up by a cutoff date receive randomized appointment times. All are randomized at the start.

Those randomized but not yet vaccinated can serve as controls for those who were.

DELIVERY Vaccination occurs via normal deployment using regular vaccination teams in the order determined by the randomized vaccination appointments.

All available doses are used up!

ENDPOINTS All cases are detected independently by "routine surveillance and lab systems" using methods analogous to observational studies. Endpoints need to be severe enough to mitigate any bias from unblinded nature of study

INTERVAL Needs to be wide enough to allow comparisons in disease incidence between those vaccinated first and those vaccinated later. For multi dose vaccines, the delay would need to be lengthened by the time between vaccinations.

Topics for panel

What are practical hurdles to designing and implementing pragmatic trials of vaccine efficacy and/or safety?

Do pragmatic trials fit into the current regulatory paradigm? Could changes facilitate the conduct of pragmatic trials?

Could informed consent be simplified for pragmatic trials? How?

What obstacles does the panel see to implementing pragmatic trials more broadly? How could they be addressed?