Key Statistical Considerations in the design of Phase III COVID-19 Vaccine Trials

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- Key Considerations in Field Efficacy Trials
- Innovative Statistical Design
- Immunogenicity Bridging Studies
- DSMB/IDMC
Pivotal study in vaccine development

- Objective
  - To confirm the efficacy and safety of a vaccine
  - Key evidence to approve a vaccine for regulatory agency

- Field efficacy trial
  - Gold standard to confirm vaccine efficacy
  - Whether the vaccine is able to lower the incidence of target disease?
  - Be required especially to innovative product

- Immunogenicity trial
  - Immunogenicity endpoint is accepted as a surrogate endpoint in replace of efficacy endpoint by regulatory.
  - It is definitive how much antibody level can lead to disease protection
Design of field efficacy trial

• Traditional design
  • a two-arm placebo-controlled trial
  • larger sample size, longer trial duration and higher costs compared with immunogenicity trial

The analysis will be conducted when enough cases are observed.
Design of field efficacy trial

• Key considerations of field efficacy trial
  • Define the primary endpoint
    • Laboratory-confirmed COVID-19 cases occurred after 7/14 days of all-course vaccination
  • Surveillance period of primary endpoint
  • The criteria of COVID-19 case
• Surveillance system of COVID-19 cases
  • Active surveillance vs. Passive surveillance
  • Sensitivity vs. specificity of the system
• Analysis population
  • Modified full analysis set (mFAS), including all-course vaccination is the main population to assess vaccine efficacy, together with per protocol set (PPS).
  • FAS, including at least one dose of vaccination, is to assess the secondary endpoint and may underestimate vaccine efficacy
### Design of field efficacy trial

#### Define the primary endpoint and key secondary endpoint

<table>
<thead>
<tr>
<th>Sponsor Product</th>
<th>Control</th>
<th>Phase</th>
<th>Sample Size</th>
<th>Subject</th>
<th>Location</th>
<th>Register# 3</th>
<th>Primary Endpoint</th>
<th>Key Secondary Endpoint</th>
<th>Timepoint (after the last dose)</th>
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<tbody>
<tr>
<td>BioNtech/Pfizer mRNA</td>
<td>Placebo</td>
<td>1/2/3</td>
<td>32000</td>
<td>18~85y</td>
<td>US</td>
<td>NCT4368728</td>
<td>Virologically confirmed COVID-19 disease (regardless of severity)</td>
<td>• Infection with SARS-CoV-2 (e.g., as determined by serology) • Severe disease including death</td>
<td>from 7d~2y</td>
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<td>1/2</td>
<td>2000</td>
<td>18~65y</td>
<td>South Africa</td>
<td>PACTR202006922165132</td>
<td>Laboratory-confirmed COVID-19 or laboratory-confirmed SARS-CoV-2 infection</td>
<td>• Severe COVID-19 (if not evaluated as a primary endpoint) • SARS-CoV-2 infection (whether or not symptomatic) (if not evaluated as a primary endpoint)</td>
<td>over the course of 6 or 12 months</td>
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<td>18~64y</td>
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<td>30000</td>
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<td>• Infection with SARS-CoV-2 (e.g., as determined by serology) • Severe disease including death</td>
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<td>Sinopharm (2) Inactivated</td>
<td>Placebo</td>
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Design of field efficacy trial

- A case-driven study
  - The required number of COVID-19 cases, not the number of subjects directly related to study power
  - The interim/final analysis will be triggered when pre-specify number of COVID-19 cases are observed

- Sample size determination
  - Step 1: calculate the number of required COVID-19 cases
    - Assumed vaccine efficacy, e.g., at least 50% of point estimate proposed by WHO, US FDA and China regulatory
    - Lower boundary of vaccine efficacy, e.g., 30% in COVID-19 vaccine proposed by WHO, US FDA and China regulatory
    - Significance level (0.05)
    - target power (80%, 85% or 90%)
  - Step 2: estimate the number of enrolled subject from step 1
    - Incidence rate in placebo group
### Design of field efficacy trial

<table>
<thead>
<tr>
<th>Power(%)</th>
<th># of subjects</th>
<th>Incidence rate (1 per 10000 people)</th>
<th>Efficacy</th>
<th>50%</th>
<th>60%</th>
<th>70%</th>
<th>80%</th>
<th>90%</th>
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<td>Required # of cases</td>
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<th>Efficacy</th>
<th>50%</th>
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Lower boundary of 95% CI >30%, alpha=0.05 (two-sided); no drop-out rate is included here.
Design of field efficacy trial

- Other factors that affect sample size
  - Discontinuation rate
  - The proportion of asymptomatic COVID-19 infections
    - Higher incidence rate may have more asymptomatic COVID-19 infections as well.
  - The positive rate of antibody pre-vaccination
    - The threshold of positive antibody still unclear until now.
  - Various vaccine efficacy and incidence because of different age distribution
  - Pre-screening?
  - Sample size requirements of key secondary endpoints, e.g., protection of severe COVID-19 cases
- Sample size “adaptation”
  - Sample size “adaptation” during the trial after blind review of trial data because of varying incidence rate of each region
  - Unblinded sample size re-estimation based on interim analysis is not proposed.
Innovative statistical design

• Interim analysis
  • Two kinds of interim evaluation
    ➢ Blinded interim evaluation: sample size adaptation
    ➢ Unblinded efficacy interim analysis
  • Interim analysis is still triggered by the observed COVID-19 cases
  • Information fraction > 0.5 is proposed to conduct interim analysis
  • O’Brien-Fleming spending function is the gold-standard, and generally acceptable by US FDA and China NMPA to control family-wise type I error, but it is a conservative method.
  • The number of COVID-19 cases and sample size will be inflated because of interim analysis.
  • Interim analysis has to be performed by Independent Data Monitoring Committee (IDMC).
Innovative statistical design

• Seamless phase 2/3 design
  • Combine phase 2 and 3 trials into one to accelerate vaccine development
    • Phase 2 stage: immunogenicity for dose selection
    • Phase 3 stage: confirm vaccine efficacy
    • Only immunogenicity is analyzed at interim analysis, and no vaccine efficacy is involved
    • The subjects from phase 2 stage will be combined to evaluate vaccine efficacy, and sample size is decreased.
  • Interim decision making has to be made by IDMC, which may bring potential risk.
Innovative statistical design

- Platform trial (umbrella)
  - Multi-product shares one placebo control within one trial
  - High efficiency to accelerate vaccine development
  - The concern is to evaluate each product comparing with placebo, not to compare different products.
  - Conflict of interest is a challenge.
Innovative statistical design

• “Master protocol design” for multi-regional clinical trial (MRCT)
  • Background
    • MRCT is more attractive because of varying and indefinite incidence in each region and sample size restriction of participating region.
    • An identical protocol is challenging for an MRCT because of different requirements of regulatory authority from participating regions, which hinders the progress.

Diagram:
- Master protocol
  - Region-1
    - Subprotocol-1
  - Region-2
    - Subprotocol-2
  - Region-3
    - Subprotocol-3
  - Region-…
    - Subprotocol-…
Innovative statistical design

- “Master protocol design” for multi-regional clinical trial (MRCT)
  - “Master protocol” design is a potential solution
    - A master protocol will be written as main protocol for China NMPA submission.
    - “Sub-protocols” will be developed from master protocol according to local regulatory requirements from operational perspectives.
  - Primary analysis will be performed according to master protocol, but includes trial data from all participating regions.
  - The subgroup analysis should also be conducted according to master protocol design, and the analysis based on sub-protocols is only considered as sensitivity analysis.
  - Key elements have to be consistent between master protocol and sub-protocols.
    - Diagnostic criteria of COVID-19 cases
    - Key inclusion/exclusion criteria
    - Key lab test methods
    - ......
**Immunogenicity bridging study**

- **Why?**
  - Field efficacy trial is conducted outside China, but COVID-19 vaccine will be registered in China.
  - Potential ethnical difference between ex-Chinese and Chinese population

- **How?**
  - A immunogenicity study is proposed to bridge vaccine efficacy from ex-Chinese population to Chinese population.
  - A non-inferiority test between ex-Chinese and Chinese population.

- **Key points**
  - Balance of key baseline characteristics, e.g., age, etc.
  - Choice of immunogenicity endpoint.
  - The same lab test method for primary endpoint.
  - ……
Importance of DSMB/IDMC

• Role of DSMB/IDMC
  • Monitor the safety of COVID-19 vaccine during the whole development.
  • Interim analysis for efficacy evaluation has to be done by IDMC.
• A program level DSMB/IDMC is highly proposed to monitor safety information all over the world no matter how many countries/regions are included and how many phase 3 trials are conducted.

• Construction of DSMB/IDMC
  • Clinicians, epidemiologists, statisticians, etc.
  • Members from China are required in an MRCT if it is for China registration.
  • Is a member from local region is necessary according to local regulatory requirements?
Ring vaccination trial

- A design to evaluate vaccine efficacy during disease outbreak.
- An approach to increase vaccine study power to recruit those at highest risk of infection.
Real-world evidence to support conditional approval

- Real-world data from 100,000+ emergency vaccination subjects
  - A retrospective/prospective cohort was built, including vaccinated subjects outside China and unvaccinated subjects under the same exposure
  - Exploratorily evaluate vaccine efficacy and safety
- Data source: Vaccination respiratory + self-report data.
- Analysis methods
  - From the matched vaccinated and unvaccinated subjects based on propensity score, conditional logistic regression will be used to calculate vaccina efficacy.
  - Nested case-control population will be built to evaluate efficacy.
  - The same exposure environment is considered as a cluster effect, negative binomial regression model is employed.
- A supportive evidence for conditional approval and a complementary to phase III pivotal study.
Summary

• COVID-19 phase 3 field efficacy trial
  • It is a case-driven study, and the interim/final analysis is triggered by the number of observed cases.
  • The required number of COVID-19 cases is directly related vaccine efficacy and trial sample size depends on the incidence rate of the disease, too.
  • High incidence rate may be a double-edged sword.
• Innovative statistical design to accelerate COVID-19 vaccine development
  • Seamless Phase 2/3 is able to accelerate the development, but it is not proposed if too much uncertainty is involved in the first stage.
  • Platform trial is a good option to develop multi vaccines at the same time, but the operationality is challenging.
  • “Master protocol design” is a potential solution to initiate an MRCT in a short time.
• It is so important to plan COVID-19 vaccine pivotal studies in a program level.
Acknowledgement

• Thank Reinel Yanping Zhang for her dedication to slide preparation.
• Thank all medical colleagues and vaccine researchers for their discussions from medical perspective and vaccine mechanism.
References

• Howard DR, Broen JM, Todd S, Gregory WM. Recommendations on multiple testing adjustment in multi-arm trials a shared control group. Statistical Methods in Medical Research 2018; 27: 1513–1530.