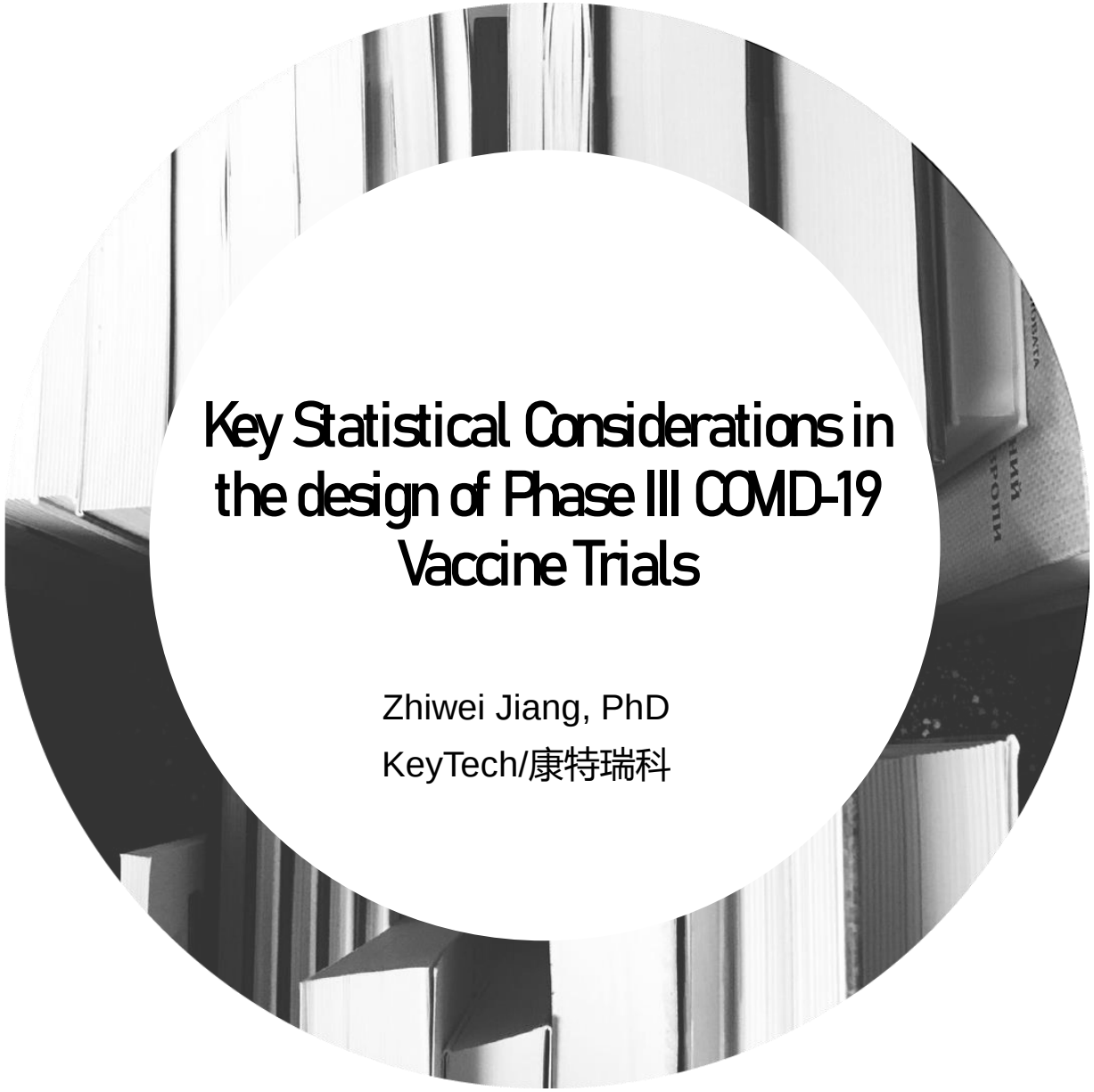


Key Statistical Considerations in the design of Phase III COVID-19 Vaccine Trials

Zhiwei Jiang, PhD

KeyTech/康特瑞科

CONTENTS

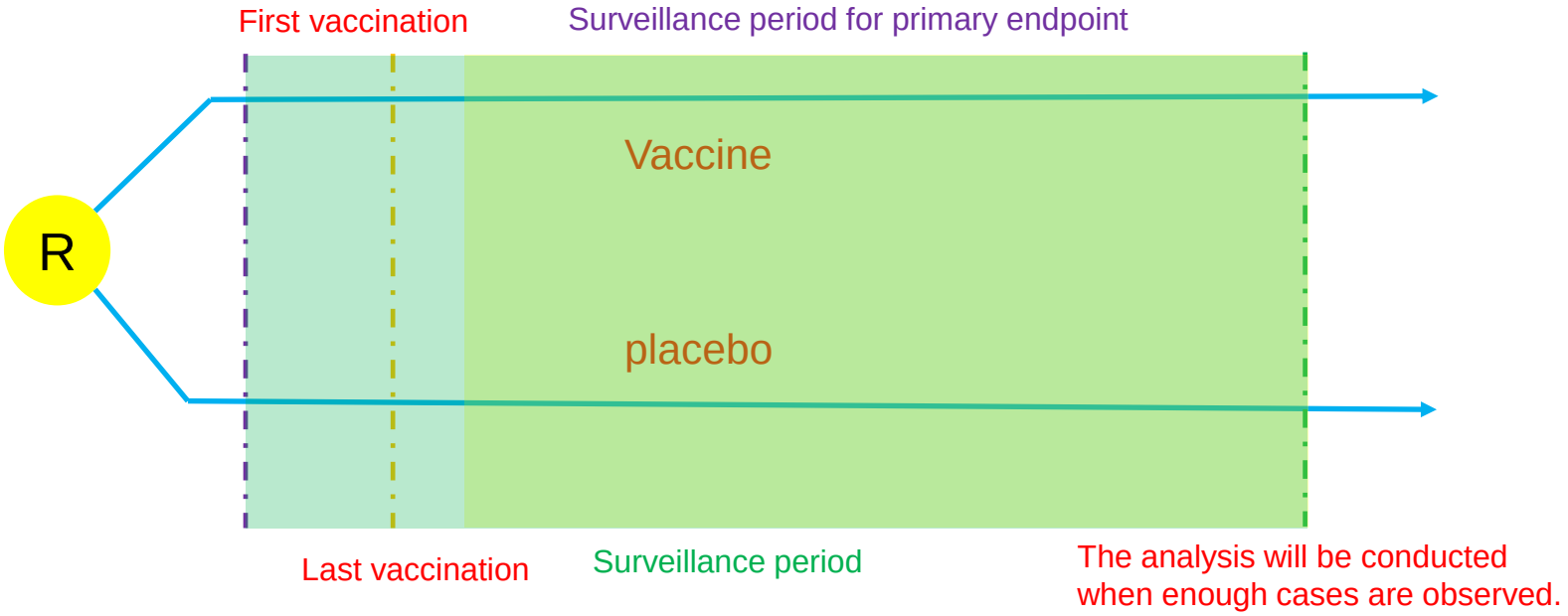
- Key Considerations in Field Efficacy Trials
- Innovative Statistical Design
- Immunogenicity Bridging Studies
- DSMB/IDMC

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



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

	Primary Endpoint	Key Secondary Endpoint
WHO [1]	Virologically confirmed COVID-19 disease (regardless of severity)	• Infection with SARS-CoV-2 (e.g., as determined by serology) • Severe disease including death
FDA Guideline [2]	laboratory-confirmed COVID-19 or laboratory-confirmed SARS-CoV-2 infection	• 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)

Sponsor Product	Control	Phase	Sample Size	Subject	Location	Register# [3]	Primary Endpoint	Timepoint (after the last dose)
BioNtech/Pfizer mRNA	Placebo	1/2/3	32000	18~85y	US	NCT4368728	• Confirmed COVID-19 in participants without evidence of infection before vaccination • Confirmed COVID-19 in participants with and without evidence of infection before vaccination	from 7d~2y
Oxford/AZ ChAdOx1	Placebo	1/2	2000	18~65y	South Africa	PACTR202006922165132	• Severe and non-severe COVID-19	over the course of 6 or 12 months
	MenACWY	1/2	1112	18~64y	UK	EudraCT2020-001072-15	• Virologically confirmed (PCR positive) symptomatic COVID-19	
	MenACWY	2/3	12330	≥18y	UK	EudraCT2020-001228-32		
	MenACWY	3	2000	18~55y	Brazil	ISRCTN89951424		
Moderna mRNA	Placebo	3	30000	≥18y	US	NCT04470427	• First Occurrence of COVID-19	from 14d~2y
Sinopharm (2) Inactivated	Placebo	3	15000	≥18y	Arab Emirates	ChiCTR2000034780	• COVID-19	from 14d~1y
Sinovac/Butantan Inactivated	Placebo	3	8870	≥18y	Brazil	NCT04456595	• Virologically-confirmed symptomatic COVID-19	from 2w~1y

1. WHO R&D Blueprint. Novel Coronavirus: an international randomized trial of candidate vaccines against COVID-19. Apr 2020.
2. US FDA. Development and licensure of vaccines to prevent COVID-19(Guidance for Industry). Jun 2020.
3. WHO DRAFT landscape of COVID-19 candidate vaccines. 28 July 2020

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

Power(%)		Incidence rate (1 per 10000 people)	Efficacy				
			50%	60%	70%	80%	90%
85%	Required # of case		346	130	61	31	19
	# of subjects	1	4613334	1857094	938462	516668	345456
		5	922668	371430	187694	103334	69092
		10	461334	185716	93848	51668	34546
		50	92268	37144	18770	10334	6910
		100	46134	18572	9386	5168	3456
		500	9228	3716	1878	1034	692
90%	Required # of case		400	154	69	38	19
	# of subjects	1	5333334	2200002	1061540	633334	345456
		5	1066668	440002	212308	126668	69092
		10	533334	220002	106154	63334	34546
		50	106668	44002	21232	12668	6910
		100	53334	22002	10616	6334	3456
		500	10668	4402	2124	1268	692

Lower boundary of 95%CI >30%, alpha=0.05 (two-sided); no drop-out rate is included here.

Design of field efficacy trial

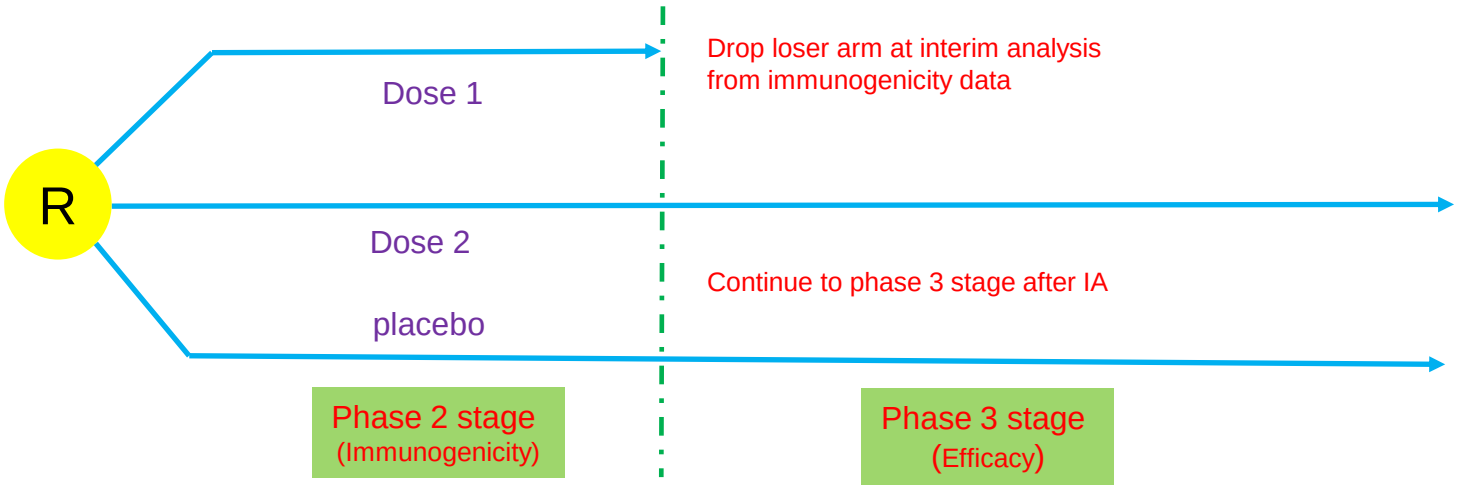
- Other factors that affect sample size
  - Discontinuation rate
  - The proportion of asymptomatic COVID-19 infections
    - Higher incidence rate may have more asymptomatic COVID-19 infections as well.
  - The positive rate of antibody pre-vaccination
    - The threshold of positive antibody still 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).

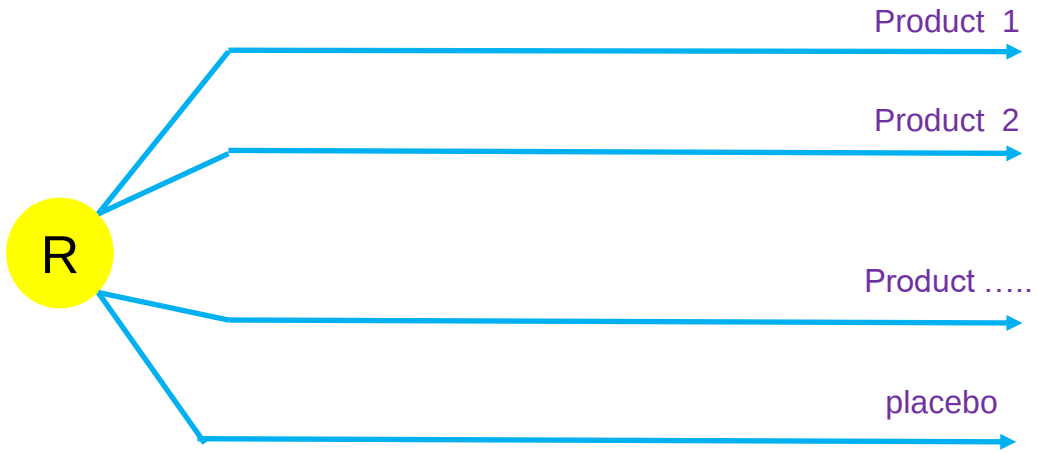
Innovative statistical design

- 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.



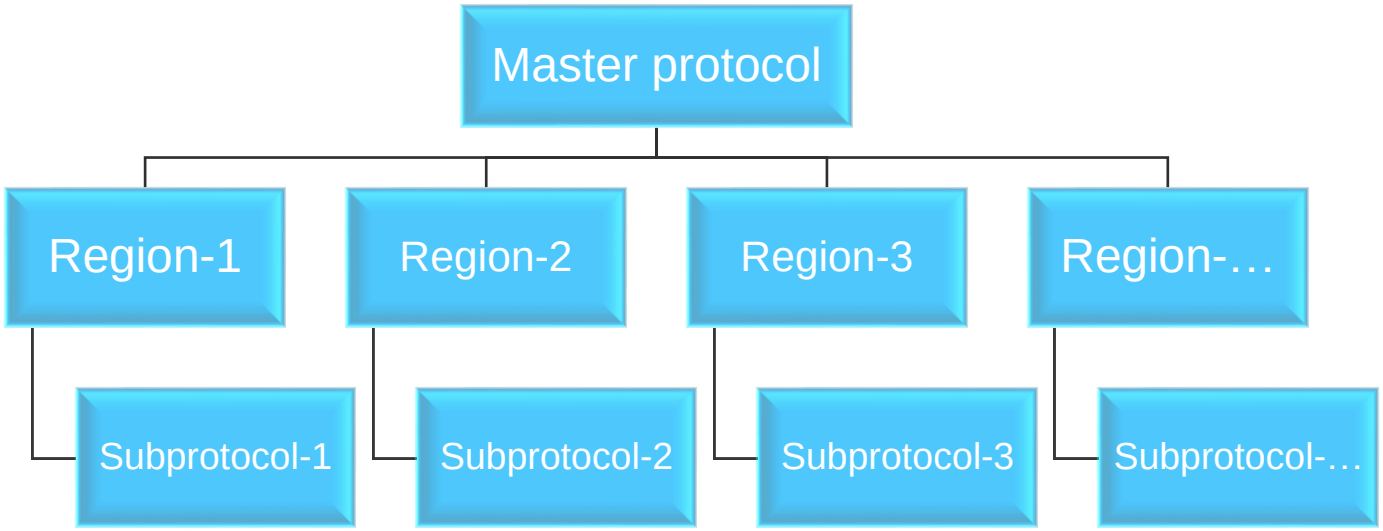
Innovative statistical design

- 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.



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
    - ……

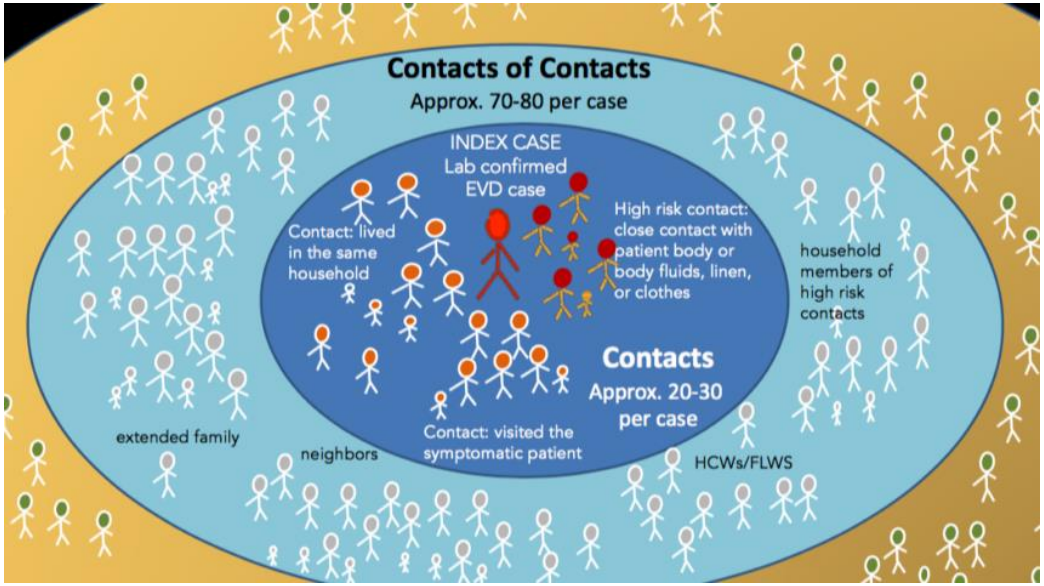
Immunogenicity bridging study

- 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

- US FDA. Development and licensure of vaccines to prevent COVID-19(Guidance for Industry). 2020.
- WHO R&D Blueprint. Novel Coronavirus: an international randomized trial of candidate vaccines against COVID-19. 2020.
- 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.
- Jiang Z, Wang X, Xia J. The Considerations in the Clinical Development of COVID-19 Vaccine from Trial Design Perspectives. Human Vaccines & Immunotherapeutics, 2020. (*in print*)