COVID-19 Efficacy Trial Design Considerations & Early Learnings from Ongoing Studies

September 24, 2020

Agenda

Time (CET)	Topic	Lead Speaker(s)
15:00 – 15:05	Welcome & Meeting Objectives	Melanie Saville
15:05 – 15:10	Introduction	Jakob Cramer
15:10 – 15:20	Vaccine efficacy: The regulators' perspective	Debra Yeskey, Svein Rune Andersen
15:20 – 15:45	Vaccine efficacy: Statistical considerations	Holly Janes
15:45 – 15:55	Vaccine efficacy: Statistical considerations – Novel endpoint approach	Devan Mehrotra
15:55 – 16:05	Vaccine efficacy: Solidarity III Trial	Phil Krause
16:05 – 16:25	Discussion: How to establish vaccine efficacy	Moderated by Jakob Cramer
16:25 – 16:30	*Break*	
16:30 – 16:40	Introduction: Operational Considerations	Peter Dull
16:40 – 17:00	Lessons learned from the field	Mary Marovich, Merlin Robb
17:00 – 17:10	Clinical case workup in efficacy trials: Guidance from community-based surveillance	Amol Chaudhari, Joan Capdevila Pujol
17:10 – 17:50	Panel Discussion: Operational Considerations	Moderated by Peter Dull
17:50 – 18:00	Wrap-up and next steps	Peter Dull

Meeting Norms and Recording Disclaimer

- Throughout the workshop, please ask any questions in the “Chat” function or hold your questions for the discussion sessions.

- In the “Chat” function, you can send your comments and questions to “Panelists only” or “All Panelists and Attendees.”

- During the discussion sessions, please “Raise your Hand” if you want to say something. If called on by the moderator, you will have the ability to unmute yourself.

- This workshop will be recorded. Please be mindful of the diverse audience attending the meeting when participating in open discussions.

Welcome & Meeting Objectives

Melanie Saville, MD

Director of Vaccine Development (CEPI)

Access to COVID-19 tools (ACT) accelerator

ACCESS TO COVID-19 TOOLS (ACT) ACCELERATOR
A Global Collaboration to Accelerate the Development, Production and Equitable Access to New COVID-19 diagnostics, therapeutics and vaccines

DIAGNOSTICS

THERAPEUTICS

VACCINES (COVAX)

CEPI

Development & Manufacturing
Led by CEPI, with industry

Gavi The Vaccine Alliance

Procurement and delivery at scale
Led by Gavi

World Health Organization

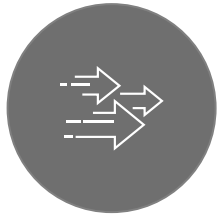
Policy and allocation
Led by WHO

Key players

Bill & Melinda Gates foundation · CEPI · wellcome · Developing Countries Vaccine Manufacturers Network · Gavi The Vaccine Alliance · The Global Fund · IFPMA International Federation of Pharmaceutical Manufacturers & Associations · IGBA International Generic and Biosimilar Medicines Association · Unitaid Innovation in Global Health · World Health Organization

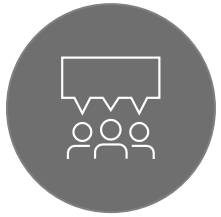
SOURCE: (ACT) ACCELERATOR Commitment and Call to Action 24th April 2020

COVAX SWAT teams are being set up as a joint platform to accelerate COVID-19 Vaccine development and manufacturing by addressing common challenges together



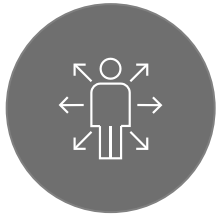
Timely and targeted

Addresses specific cross-developer technical challenges as they are raised and/or identified on an ongoing basis



Multilateral

Establishes a dialogue and global joint effort across different COVID-19 vaccines organizations (incl. industry and other global networks)



Knowledge-based

Identifies and collates most relevant materials and insights across the broader COVID-19 ecosystem to accelerate vaccine development and manufacturing

Resource-efficient

Coordinates between different organizations/ initiatives to limit duplications and ensure expertise is efficiently leveraged

SWAT teams	Enabling sciences	Clinical Development & Operations	Manufacturing

Regulatory Advisory Group

Meeting Objectives

To support COVID-19 vaccine developers with the rapid planning and implementation of pivotal phase 3 vaccine efficacy trials, the aim is to provide developers with

- product-agnostic supportive information and considerations on the assessment of vaccine efficacy
- a forum to communicate and address individual challenges developers may face

In this workshop, we will

- review the regulators positions
- address scientific aspects including but not limited to case definitions and endpoints as well as statistical considerations related to vaccine efficacy
- focus on operational aspects related to the conduct of vaccine efficacy trials
- discuss lessons learnt from the field

Introduction

Jakob Cramer, MD

Head of Clinical Development (CEPI)

Efficacy Trial Design Considerations & Early Learnings from Ongoing Trials

- SARS-CoV-2 (and COVID-19) is approx. 10 months old
- Vaccines are expected to become available at large scale within the next ~6 months
- Limited (no) time for ‘trial and error’
- Phase 3 efficacy studies are complex in “normal times” – these are not normal times
- Yet, no shortcuts allowed to establish vaccine efficacy, safety and trust

Part 1: Vaccine efficacy: scientific considerations for Phase 3 trials

Part 2: Vaccine efficacy: operational considerations for Phase 3 trials

Vaccine Efficacy: The Regulators' Perspective

Debra Yeskey, Pharm.D.

Head of Regulatory Affairs – North America (CEPI)

Svein Rune Andersen, Dr. Sci.

Head of Regulatory Affairs – Europe (CEPI)

Vaccine efficacy: Current regulatory guidance

CEPI

A brief overview

Date (Month + year)

FDA – guidance published June 2020

Vaccine Efficacy - recommendations

Randomised, double-blinded, placebo controlled:

Randomisation : 1:1 – preferred

Observation time – as long as feasible – ideally 1-2 years to assess duration of protection and potential VMED

Efficacy considerations:

Primary end-point:

- Either lab confirmed COVID-19 or SARS-CoV-2
  - Acute COVID-19 cases virologically confirmed
  - SARS-CoV-2 infection, including asymptomatic infection – monitored/confirmed by virological or serological method.

Primary endpoint or a secondary endpoint (with or without formal hypothesis testing) defined as virologically confirmed SARS-CoV-2 infection + one or more symptoms:

- Fever or chills
- Cough
- Shortness of breath or difficulty breathing
- Fatigue
- Muscle or body aches
- Headache
- New loss of taste or smell
- Sore throat
- Congestion or runny nose
- Nausea or vomiting
- Diarrhea

FDA – guidance cont.

Severe COVID-19:

- **Consider** powering efficacy trials for formal hypothesis testing
- If not evaluated as primary, should be evaluated as secondary end-point (with or without hypothesis testing)
- Defined as virologically confirmed SARS-CoV-2 infection with any of the following:
  - At rest: **respiratory rate** ≥ 30 per minute, **heart rate** ≥ 125 per minute, **SpO2** ≤ 93% on room air at sea level or PaO2/FiO2 < 300 mm Hg)
  - **Respiratory failure** (defined as needing high-flow oxygen, non-invasive ventilation, mechanical ventilation or ECMO)
  - **Evidence of shock** (SBP < 90 mm Hg, DBP < 60 mm Hg, or requiring vasopressors)
  - **Significant acute renal, hepatic, or neurologic dysfunction**
  - **Admission to an ICU**
  - **Death**

SARS-CoV-2 infection

- infection (whether or not symptomatic) should be evaluated as a secondary or exploratory endpoint, if not evaluated as a primary endpoint.

CEPI

FDA – guidance cont.

Statistical considerations

- Vaccine efficacy – primary end-point: **≥ 50%, CI LL >30%**
  - The same statistical success criterion should be used for any interim analysis designed for early detection of efficacy.
  - A lower bound ≤30% but >0% may be acceptable as a statistical success criterion for a secondary efficacy endpoint, provided that secondary endpoint hypothesis testing is dependent on success on the primary endpoint.

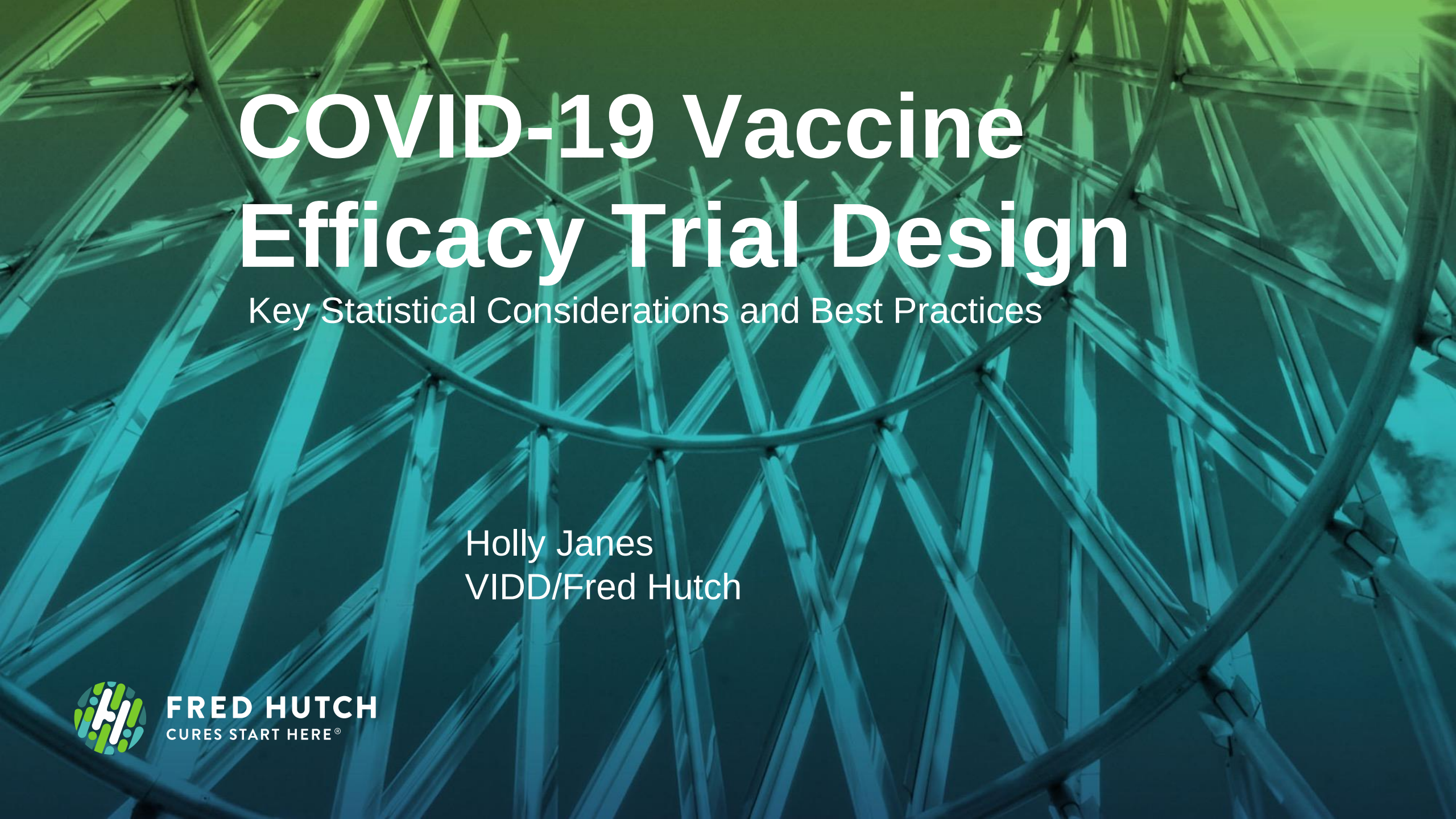
ICMRA

- **Phase 3 clinical trials**
  - **Enrollment of many thousands of participants**, including those with medical comorbidities, to generate relevant data for the **key target populations**.
  - Powered to assess the overall vaccine efficacy across subgroups enrolled
  - Include diverse populations, e.g. race and ethnicity,
  - **Randomized, double-blind and** controlled **either using placebo or active comparator**. Other Phase 3 clinical trials should be discussed with the respective NRA.
  - **Stringent success criteria to ensure** that SARS-CoV-2 vaccines have **adequate efficacy** should be specified in initial clinical efficacy trials:
    - Should include **efficacy point estimates** that reflect the **desired vaccine efficacy** and **specification of the lower bound** of appropriately alpha-adjusted confidence interval around the primary efficacy endpoint point estimate.
    - However, **a specific numeric value to be used for the lower bound and vaccine efficacy point estimate was not agreed** upon at this stage
    - It was also reflected that **efficacy estimates crossing a certain pre-specified lower bound for efficacy**, **due to factors such as epidemiological evolution** of the pandemic, would **not preclude the possibility of a positive benefit risk conclusion** if there also were other data supportive of efficacy.

Vaccine Efficacy: Statistical Considerations

Holly Janes, PhD

Professor, Vaccine and Infectious Disease Division (Fred Hutchinson Cancer Research Center)



COVID-19 Vaccine Efficacy Trial Design

Key Statistical Considerations and Best Practices

Holly Janes
VIDD/Fred Hutch

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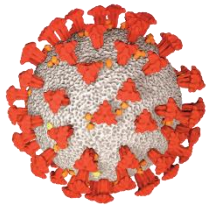
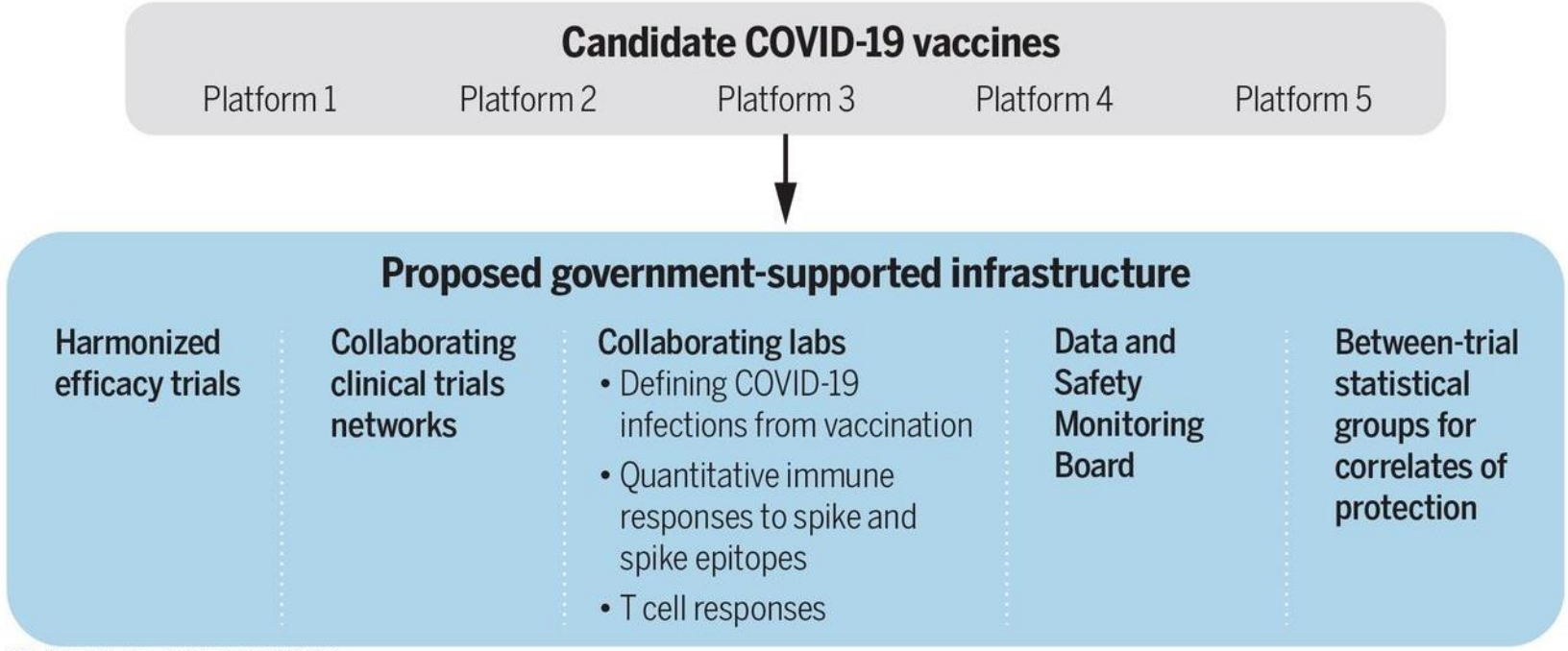
COVID Prevention Network (CoVPN)



COVID-19
Prevention Network

Focal point for USG-sponsored COVID-19 vaccine and mAb trials

Vaccine Trial Leadership: Larry Corey (FHCRC) and Kathleen Neuzil (U Maryland)



GRAPHIC: N. CARY/*SCIENCE*

Laboratory Leadership

Julie McElrath Rafi Ahmed
David Montefiori
Georgia Tomaras Ralph Baric
Mark Dennison Tim Sheahan

Statistical Leadership

Dean Follmann Peter Gilbert
Mike Fay Yunda Huang
Holly Janes Martha Nason

Corey, Mascola, Fauci, Collins. *Science* (2020)

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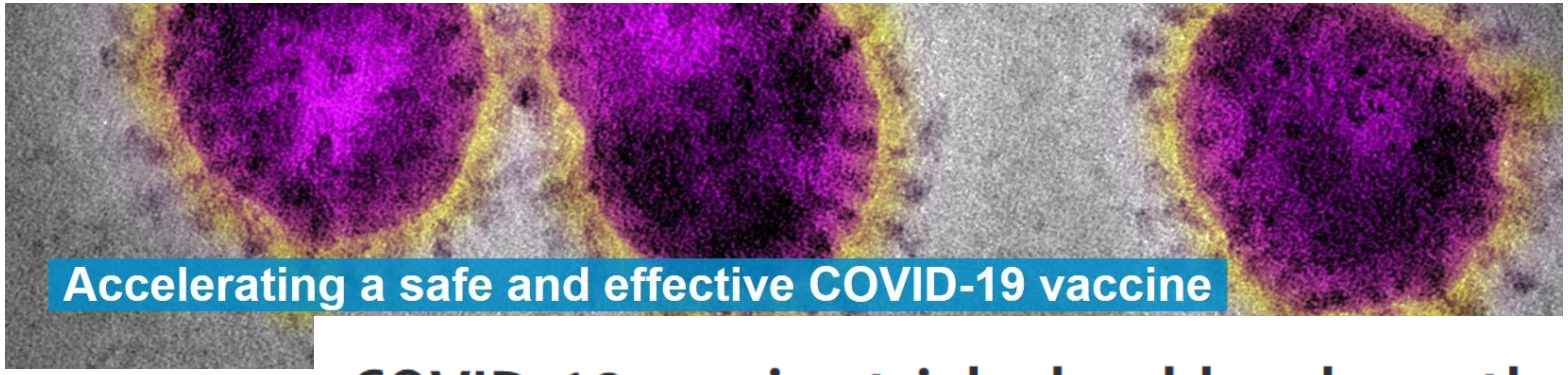
WHO Solidarity III Vaccine Efficacy Trial



COVID-19 vaccine trials should seek worthwhile efficacy

Three issues are crucial in planning COVID-19 vaccine trials: (1) whether to demand not only proof of some vaccine efficacy but also proof of worthwhile efficacy; even weaker vaccine as being non-inferior (so-called bio-creep).[1]

The criteria used to define a successful vaccine in the

Published Online
August 27, 2020
https://doi.org/10.1016/
S0140-6736(20)31821-3

- Key statistical approaches shared between CoVPN and Solidarity III trial designs
- Primary difference is 'platform' trial vs. parallel harmonized trials

An international randomised trial of candidate vaccines against COVID-19. World Health Organization. 09 April 2020

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‘Prototypical’ CoVPN Vaccine Efficacy Trial

Population: ~30,000 adults age 18 and over, at risk of SARS-CoV-2 infection and COVID-19 disease (no screening for prior infection)

- Enriched for high risk based on age, co-morbidities, race/ethnicity
- For U.S., underrepresented minorities enrolled at or above U.S. demographic frequencies

Randomized to 2:1 (or 1:1) to Vaccine or Placebo, potentially within risk strata

Follow-up for 2 years post-last vaccination

Primary endpoint: virologically-confirmed symptomatic disease

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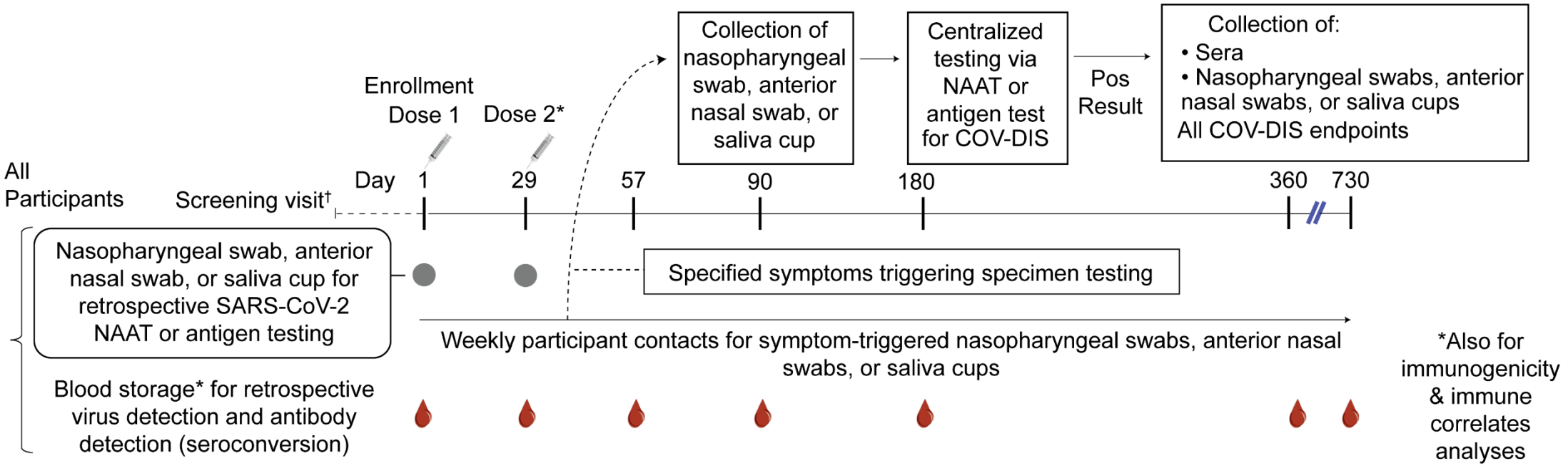
Follow-up and Sampling Schedule



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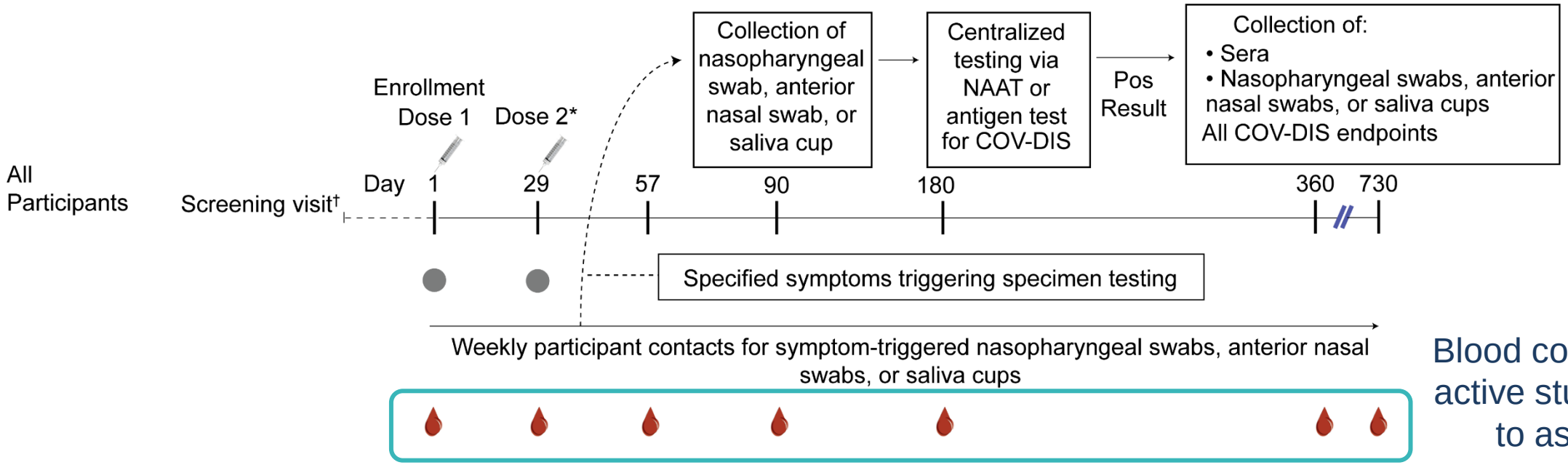
Follow-up and Sampling Schedule

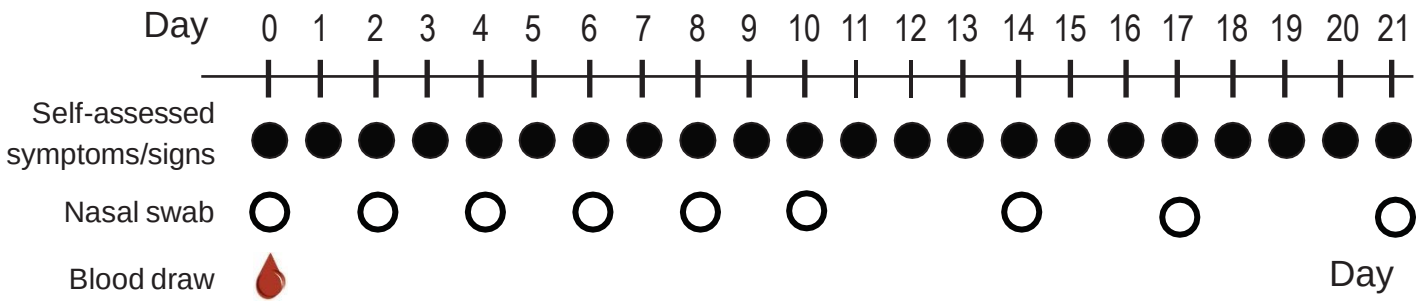


Blood collected at active study visits to assess seroconversion

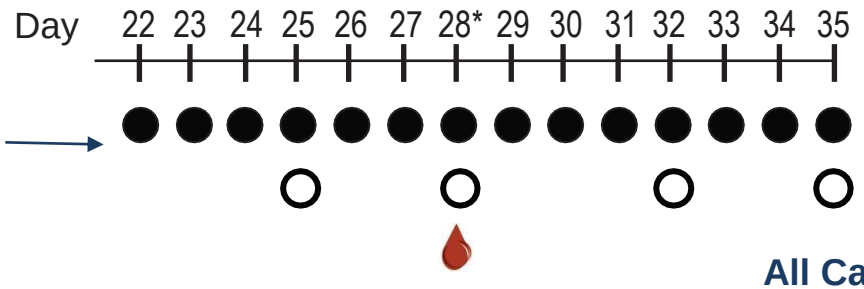
Post-COVID-Diagnosis Follow-Up

To assess vaccine effect on severity and duration of symptoms and viral shedding (2^0 endpoints)

All Cases



If SARS-CoV-2 positive on Day 21



If SARS-CoV-2 negative on Day 21

All Cases:
Continue clinical monitoring and safety f/u through study completion

- Collection of data on disease severity (signs, symptoms) via diary card/mobile app
- Obtain sample (self-collected from nasal swabs) for SARS-CoV-2 detection by PCR (Central lab)
- Blood draw

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Randomization Ratio

Factors mildly in favor of 2:1 vs. 1:1 Vaccine:Placebo

- Fewer primary endpoints required
  - E.g., 150 vs. 170 events to reject H0: VE <=30% in FAS, Day 57+
- Similar time to primary analysis (primary endpoints accrue more slowly)
- Similar performance for evaluating VE (90% power, slightly narrower 95% CI)
- Similar performance for evaluating safety

Major argument in favor of 2:1 vs. 1:1 is increased power for discovering immunological correlates/surrogate endpoints

- 33% increase in breakthrough cases with 2:1 vs. 1:1

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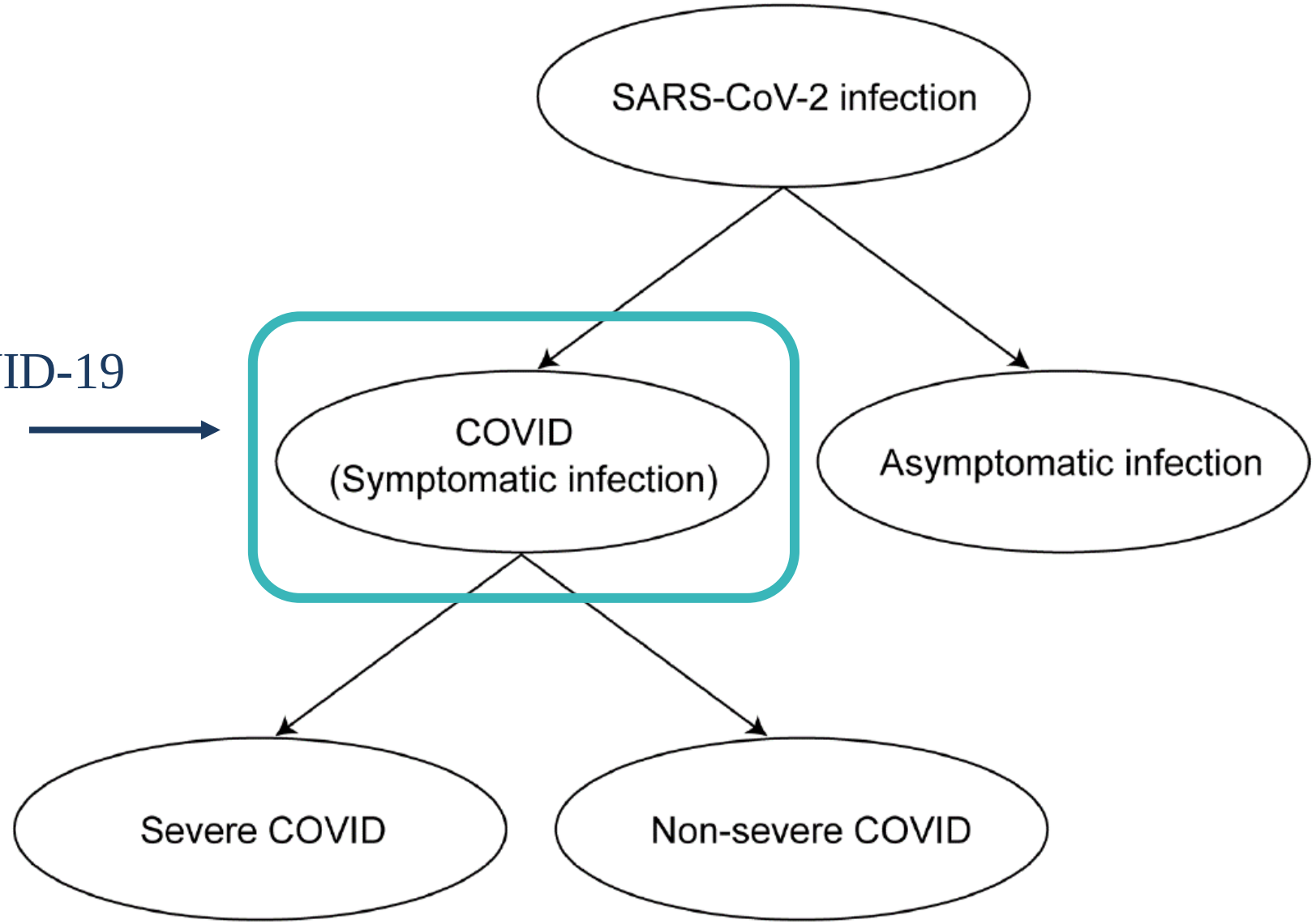
Endpoints

Common primary endpoint
Protocol-specified list of COVID-19 symptoms with virological confirmation of SARS-CoV-2 infection (symptom-triggered)



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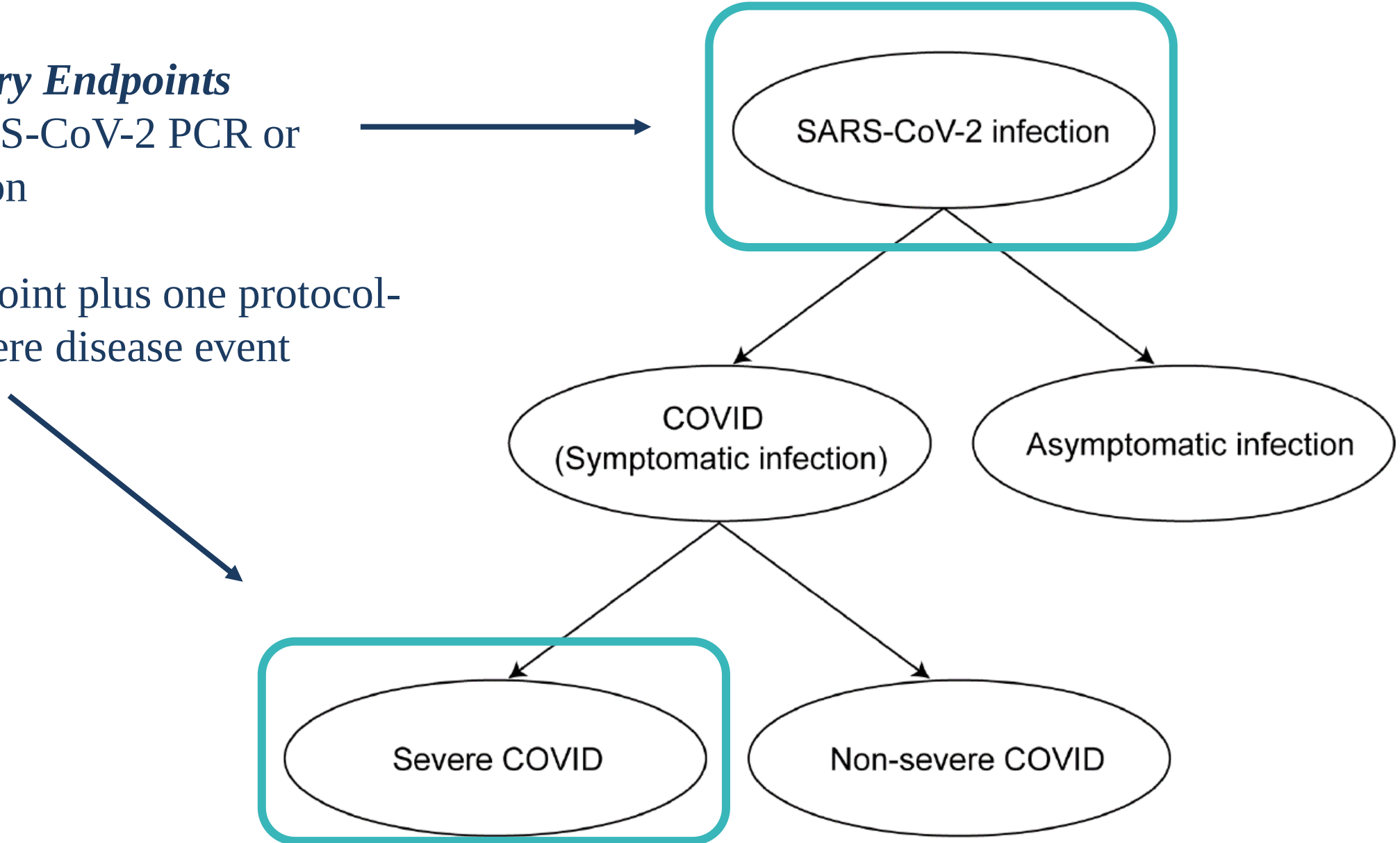
Mehrotra, Gilbert et al. submitted

Endpoints

Key Secondary Endpoints

Positive SARS-CoV-2 PCR or seroconversion

COVID endpoint plus one protocol-specified severe disease event



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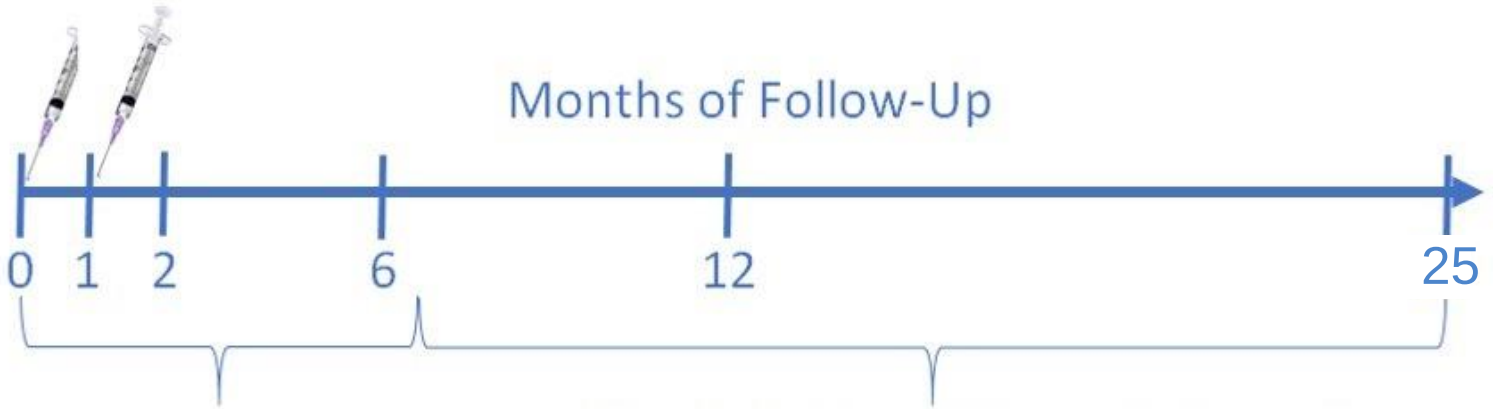
Study Duration and Timing of Primary Analysis



Event-driven primary analysis*
When target number of primary endpoints have accrued:
150 events if 2:1
170 events if 1:1

Continued blinded f/u if positive result at primary analysis

- Trials sized so that under conservative assumptions around COVID-19 incidence, primary analysis likely to occur within ~7 months of trial start
- Continued blinded f/u necessary to evaluate durability of VE (2º objective) and to adequately power VE against severe COVID

* Rationale for target event totals next slides

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Primary Analysis and Success Criteria

Vaccine efficacy, VE = [1 – Endpoint hazard ratio (vaccine/placebo)] x 100%

- Assess by proportional hazards model with separate placebo arm baseline hazard function for each study site x randomization stratum (anticipate heterogeneity in epidemics across sites)

Primary analysis cohort: participants baseline negative for SARS-CoV-2 (PCR/serology) in 'full analysis set' (FAS) [enrolled ppts receiving 1+ dose], counting events 15+ days after last dose*

Success criteria: estimated VE ≥ 50%, and lower bound on 95% confidence interval ≥ 30%

- Per FDA guidance and satisfies WHO Target Product Profile

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* Some trials perform primary analysis among 'per-protocol' participants

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Sample Size and Target Endpoint Total

Success Criteria: **Estimated VE ≥ 50% and LB of 95% CI ≥ 30%**
150 primary endpoints needed for 90% power for VE=60% (2:1 Vaccine:Placebo Allocation)

- Work backwards to identify sample size
  - Specify proportion enrolled baseline SARS-CoV-2 negative
  - Specify 6-month placebo-arm incidence in baseline SARS-CoV-2 negative group
- E.g., 90% baseline SARS-CoV-2 negative and 1% 6-month placebo incidence implies total N = 30,000

Interim Monitoring

Type	Purpose	Methodology and Frequency
Potential harm/enhancement	Stop vaccinations as early as possible if evidence of increased risk associated with the vaccine	Nominal 1-sided 0.05-level exact binomial tests of fraction of endpoints in vaccine arm, *continuously* from 8th primary endpoint to time of primary analysis • COVID and severe COVID
Non-efficacy	Early detection of absent or weak vaccine efficacy, to deliver result to field in a timely manner	Two interim analyses at 35% and 70% of primary endpoint total. Nominal 95% CI monitoring (Friedlin et al.)
Efficacy	Early detection of vaccine efficacy, to permit rapid licensure	Two interim analyses at 35% and 70% of primary endpoint total. O'Brien-Fleming monitoring

Freidlin, Gray, and Korn (2010, *Clin Trials*)

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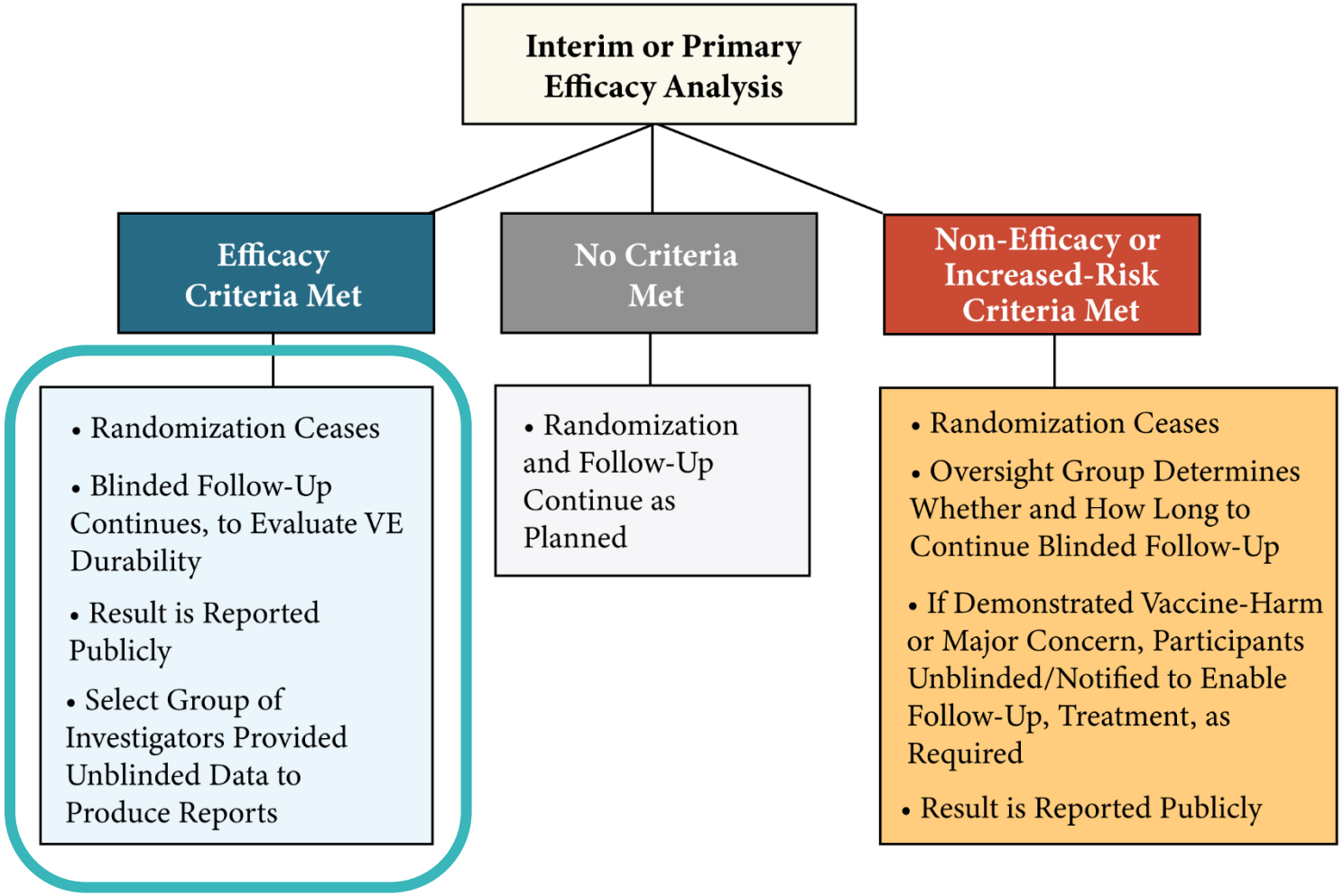
Potential Outcomes of Interim and Primary Analysis



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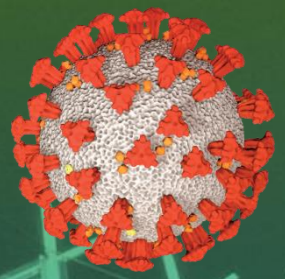

COVID-19
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Leadership and Operations
Larry Corey and Kathy Neuzil
Jim Kublin

Laboratory
Julie McElrath
John Hural

Statistics and Data Management
Dean Follmann
Jessica Andriesen
Lindsay Carpp
Youyi Fong
Ollivier Hurien
Alex Luedtke
Ying Huang
April Randhawa
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Martha Nason
Yunda Huang

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Vaccine Efficacy: Statistical Considerations – Novel Endpoint Approach

Devan Mehrotra, PhD

VP, Biostatistics (Merck)

COVID-19 Vaccine Efficacy Evaluation

***Focus*: Burden of Disease Endpoint and Asymptomatic SARS-CoV-2 Infections**

Devan V. Mehrotra, PhD*
Peter B. Gilbert, PhD

(on behalf of a team of biostatisticians, clinicians and infectious disease specialists from academic centers, industry and US government)

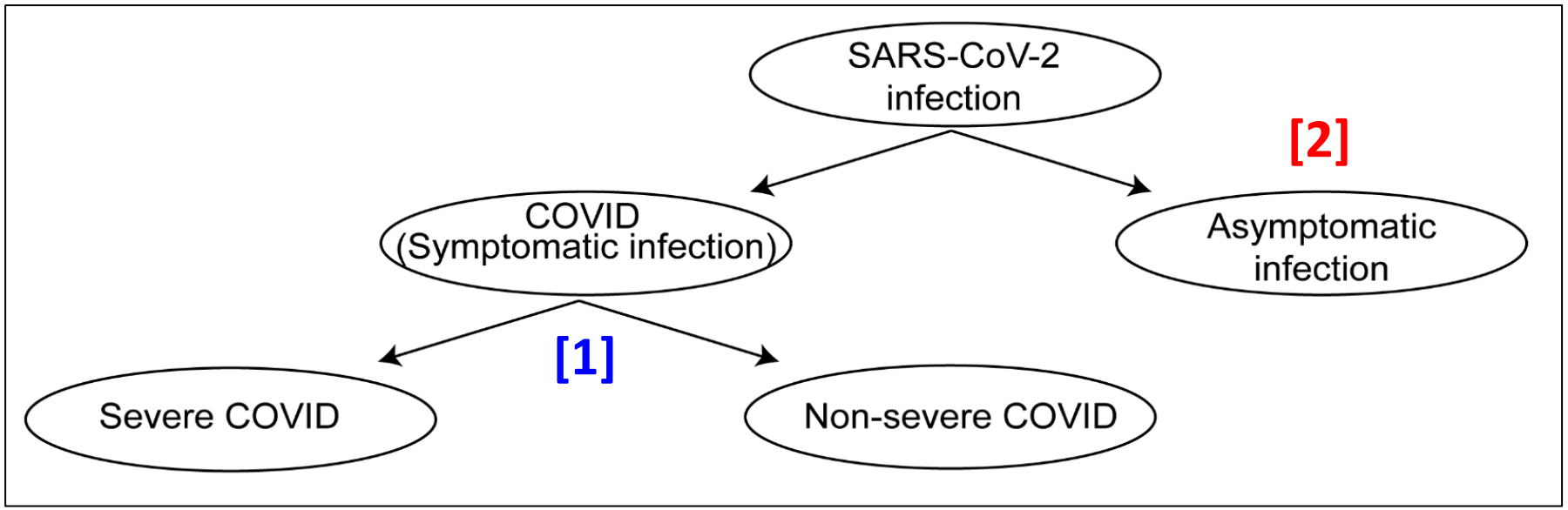
COVAX Clinical SWAT Team Workshop
Sep 24, 2020

**devan_mehrotra@merck.com*

Two Goals of Today's Presentation

[1] Propose a burden of disease (BOD) endpoint as part of a harmonized evaluation and comparison of the efficacy of candidate COVID-19 vaccines

[2] Draw attention to a potential shift towards more SARS-CoV-2 infections that are asymptomatic if the vaccine prevents COVID (below) but not infection



Endpoints and Vaccine Efficacy (VE) Definitions

Participant-level Clinical Outcome	Binary Efficacy Endpoint **Scores**			**BOD score**
	SARS-CoV-2 infection? no=0, yes=1	COVID disease? no=0, yes=1	Severe COVID disease? no=0, yes=1	
Not infected (negative SARS-CoV-2 tests)	0	0	0	0
Infected, no COVID (asymptomatic)	1	0	0	0
Infected, non-severe COVID	1	1	0	1
Infected, severe COVID	1	1	1	2

$$VE_{COVID}\,(\%) = 100 \times \left(1 - \frac{mean\ COVID\ score\ for\ Vaccine}{mean\ COVID\ score\ for\ Placebo}\right)$$

$$VE_{BOD}\,(\%) = 100 \times \left(1 - \frac{mean\ BOD\ score\ for\ Vaccine}{mean\ BOD\ score\ for\ Placebo}\right)$$

Similar VE definitions for other efficacy endpoints

Burden of disease (BOD) endpoint scores severe COVID as a worse clinical outcome than non-severe COVID

Power based on choice of primary efficacy endpoint(s)

Simulated design with V:P=2:1, n=147 disease cases (fixed), α=2.50% (1-tailed)

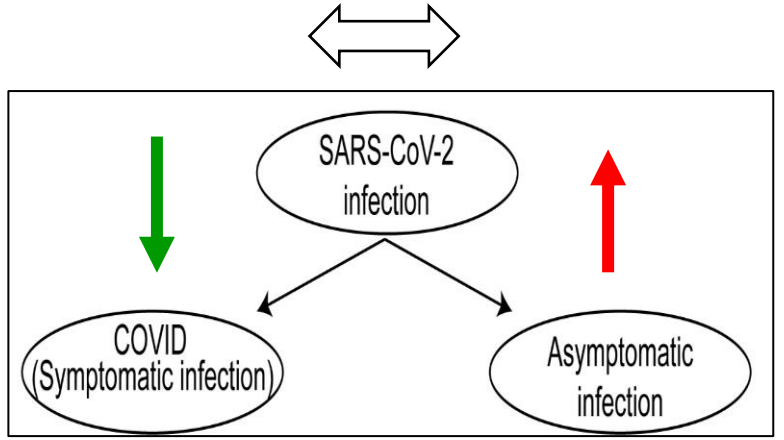
Assumed VE (%)		Implied VE (%)	Power (%) with chosen primary or dual primary endpoint(s)			
COVID	Severe COVID	Non-Severe COVID	Severe COVID	COVID	BOD	COVID, BOD*
55	60	54	26	74	75	77
55	70	51	47	74	82	80
55	80	49	73	74	87	85
55	90	46	94	74	92	90
60	60	60	27	91	89	92
60	70	57	50	91	93	93
60	80	55	76	91	96	95
60	90	52	95	91	98	97

VE = vaccine efficacy; assuming 20% of disease cases in placebo arm will be severe (Clark et al 2020 Lancet Global Health), VE(COVID)=0.8 x VE(non-severe COVID) + 0.2 x VE(severe COVID); power based on statistical success defined as point estimate of VE at least 50% with lower bound of corresponding 95% CI greater than 30% (2020 FDA guidance); COVID scoring is 0=no disease, 1=disease and BOD scoring is 0=no disease, 1=non-severe disease, 2=severe disease; * dual primary endpoints analysis uses novel multiplicity adjustment that leverages the strong correlation between the COVID and BOD endpoints (success = win on at least one after multiplicity adjustment)

Asymptomatic SARS-CoV-2 Infections

- The latest CDC estimate is that **40% of SARS-CoV-2 infections are asymptomatic**. Given that, the following table is instructive:

Assumed Vaccine Efficacy (VE)		**Implied VE**
SARS-CoV-2 Infection	Symptomatic Infection (COVID)	Asymptomatic Infection (No COVID)
10%	60%	-65%
10%	70%	-80%
20%	60%	-40%
20%	70%	-55%
40%	60%	10%
40%	70%	-5%



VE(infection)=0.4xVE(asymptomatic infection) + 0.6xVE(disease)

- A vaccine with strong efficacy for reducing symptomatic COVID but weak efficacy for reducing SARS-CoV-2 infections has the potential to prolong the pandemic if the increased asymptomatic carriers transmit infective virus (unknown)

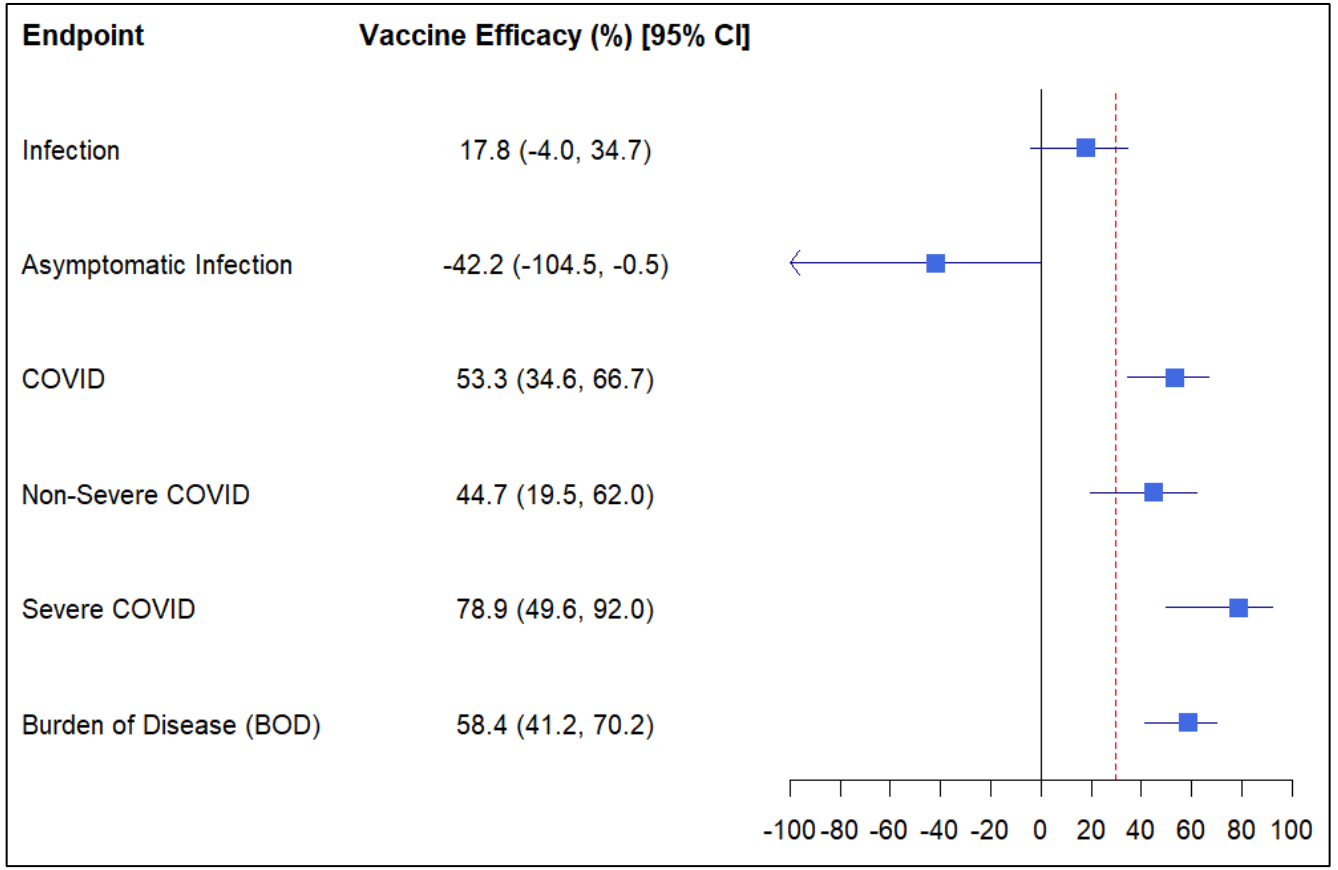
Hypothetical Example

2:1 (V:P) randomization, analysis at 147 COVID cases

			Among participants that become infected		
Arm	N	SARS-CoV-2 Infected	*Asymptomatic No COVID*	*Symptomatic Non-Severe COVID*	*Symptomatic Severe COVID*
Placebo	10,000	121 (1.21%)	*45 (37.2%)*	*57 (47.1%)*	*19 (15.7%)*
Vaccine	20,000	199 (1.00%)	*128 (64.3%)*	*63 (31.7%)*	*8 (4.0%)*

FDA success criteria:

1) Estimated vaccine efficacy (VE) > 50%
2) 95% CI lower bound (LB) for VE > 30%



concern?

VE > 50%, LB > 30%

VE > 50%, LB > 30%

Summary

- ***Burden of Disease (BOD) Endpoint***
  - The proposed burden of disease (BOD) endpoint explicitly recognizes severe COVID as being a worse clinical outcome than non-severe COVID; it modifies the 2-level disease score endpoint (0=no COVID, 1=COVID) to a 3-level disease score endpoint (0=no COVID, 1=non-severe COVID, 2=severe COVID)
  - COVID-19 vaccines in development are expected to reduce the incidence of COVID, particularly severe COVID; this (in support with simulation results) makes BOD a promising primary, dual primary or key secondary endpoint

- ***Asymptomatic SARS-CoV-2 Infections***
  - If vaccines under development do not materially reduce the risk of SARS-CoV-2 infection, a reduction in the incidence of symptomatic COVID-19 disease may be accompanied by a shift towards more infections that are asymptomatic
  - A thoughtful consideration of this issue and design implications is warranted

Vaccine Efficacy: Solidarity III Trial

Phil Krause, MD

Chairperson (WHO Vaccines Expert Group / US FDA)

World Health Organization

Statistical and endpoint considerations for COVID-19 vaccines, in the context of WHO's Solidarity Vaccines Trial

Phil Krause

Chair WHO COVID vaccines Expert Group

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What is the most appropriate endpoint?

Vaccines are almost always more successful in preventing severe disease than mild disease.

If the endpoint is tilted towards mild disease, there may be a risk of study failure if vaccine only is effective against severe disease; however, a 50% point estimate gives a lot of room for success. On long term follow-up, a vaccine that is effective against severe but not mild disease will still become apparent.

If the endpoint is tilted towards rarer severe disease, it may be difficult to adequately power the study. Also, if a vaccine prevents severe but not mild disease, it is less likely to be useful in controlling transmission.

If the endpoint misses some cases, as long as this does not bias the results, the consequences only influence study power. Thus, there is no requirement to capture every single case of disease.

Key principles for endpoint selection

Should not be so rare as to render the trial infeasible

Simplicity of endpoints is valued, otherwise an adjudication committee may be required which complicates interpretation of interim results

In most trial locations, clinicians will follow WHO evaluation and testing recommendations whether participants are in trials or are not

WHO Solidarity Vaccines Trial assumes that trial participants are likely to be referred for testing based on **WHO case definition criteria** but considers anyone with a positive test as a case for purposes of evaluating trial endpoints (as also WHO criteria states). WHO Clinical criteria are used to define severity

This avoids the complexity of having substantially different trial criteria vs. surveillance clinical criteria used in most communities.

Disadvantages of COVID-19 burden of illness endpoints

Not validated or standardized

- Definition of severe disease puts a lot at stake, and outcome may be influenced by antivirals, steroids, etc.
- Chance differences in incidence of the less common severe disease endpoint would have amplified effects

Difficult to explain what BOI endpoints mean

May have minimal advantages, given relatively low incidence of severe disease

There is general agreement on appropriate success criteria

>50% point estimate with >30% LB

(on alpha-adjusted confidence interval) endorsed by WHO, USFDA, India, China, HC

This assures that weakly effective vaccines will not meet criteria for wide distribution, potentially doing more harm than good

This also assures studies of sufficient size to evaluate safety and other important endpoints

Lancet. 2020 Sep 12;396(10253):741-743. doi: 10.1016/S0140-6736(20)31821-3.

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Interim analyses

Interim analyses may be performed using the same criteria as used for the primary endpoint

Alpha must be appropriately adjusted for interim analyses.

- The WHO Solidarity Vaccines Trial uses the conservative O'Brien-Fleming approach, which requires stronger evidence of efficacy at early interim analyses than others do

Just because a trial meets success criteria at an interim analysis does not mean that it will meet criteria for EUA/EUL or licensure.

- These decisions will likely also depend on accumulation of safety data and data relevant to secondary endpoints, and sufficient follow-up to infer that vaccine efficacy is not extremely short-lived.

Even if interim success criteria are met, trials should continue in order to accumulate more data

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What does an EUA/EUL mean?

Any vaccine authorized/listed under EUA/EUL is still investigational

Studies that have already begun should continue, yielding more data about efficacy against severe disease, more safety data, more data about duration of efficacy, and better assessments about potential for enhanced disease

The Solidarity Vaccines trial contemplates formal statistical evaluation of duration of efficacy and efficacy against severe disease as secondary endpoints, which could happen after a vaccine is made available under EUA/EUL

Additional safety studies may be initiated to accumulate sufficient safety data to support widespread confidence in the vaccine

What if a vaccine is licensed?

This will make continuation of placebo in places where a vaccine is licensed and available infeasible

The trial can then be **switched to a non-inferiority design**, where non-inferiority criteria may depend on the estimated efficacy of the licensed vaccine

Continued use of **clinical endpoint efficacy endpoints is preferable** to other approaches, which are less reliable and may be biased

The Solidarity Vaccines Trial contemplates this, and this is simpler in a multi-vaccine trial format

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Discussion: How to Establish Vaccine Efficacy

Moderated by Jakob Cramer

Discussion Panel Members and Potential Questions

Panel Members

- **Holly Janes, PhD**, Professor, Vaccine and Infectious Disease Division (Fred Hutchinson Cancer Research Center)
- **Devan Mehrotra, PhD**, VP, Biostatistics (Merck)
- **Phil Krause, MD,** Chairperson (WHO Vaccines Expert Group / US FDA)

Potential Discussion Questions

- What are strategies to de-risk the selection of an ‘inappropriate’ primary endpoint (e.g. dual / multiple primary endpoints; key secondary endpoint)?
- BOD endpoint to better reflect protection against disease severity: Consider as one of several primary endpoints or key secondary endpoint?
- Dual / multiple primary endpoints as well as pre-defined IAs in case-driven trial design: How to address the multiplicity problem and spending alpha?
- Statistical approaches to assess vaccine efficacy for the primary objective: will different methods provide comparable results?
- Disease versus infection & transmission: How should the latter objectives be addressed?

Break

5 minutes

Introduction: Operational Considerations

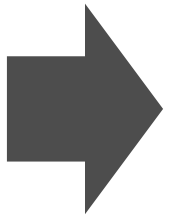
Peter Dull, MD

Deputy Director, Integrated Clinical Vaccine Development (BMGF)

Introduction: Operational Considerations for Phase III Trials

Context

- This unprecedented novel respiratory virus outbreak requires unprecedented vaccine development efforts
- We all have a common goal – a global supply of safe and effective vaccines
- Distrust of one vaccine will not be siloed; all developers will be negatively affected
- Multiple Phase III studies have initiated with tens of thousands enrolled



Implications

- All developers will benefit if all studies are conducted with high quality and answer the right questions
- It is critical to continue collaborating and communicating across developers, especially as those already in Phase III trials have already learned critical operational lessons along the way

Primary Objectives (Efficacy)

Developers – publicly available efficacy trial protocols

Element	Moderna	BNT/Pfizer	AZ (US trial)	Janssen**
Primary efficacy objective/ endpoint	**First occurrence of COVID-19:** a. Positive RT-PCR **AND** **b. At least 1 of**: cough, SOB, or clinical/ radiographic pneumonia **OR** **c. At least 2 of**: fever, chills, myalgia, headache, sore throat, olfactory & taste disorder	**Confirmed COVID-19** : a. Positive RT-PCR or other NAAT# **AND** **b. At least 1 of**: fever, cough, SOB, chills, muscle pain, sore throat, anosmia/ageusia, diarrhea & vomiting A **2nd definition** with extra symptoms: fatigue, headache, congested/runny nose & nausea	**First occurrence of COVID-19:** a. Positive RT-PCR **b. At least 1 of**: Pneumonia (CXR/ CT); SPO2 ≤ 94% or need for O2; SOB **OR** **c. At least 2 of** fever; cough; myalgia; fatigue; vomiting/diarrhea*; anosmia/ageusia*	**First occurrence of COVID-19:** a. Positive RT-PCR **AND** **b. Any 1 of:** RR ≥ 20 breaths/min, abnormal SpO2 but still >93%, clinical/radiologic pneumonia, radiologic DVT, shortness of breath **OR** **c. Any 2 of:** fever, HR ≥ 90 BPM, shaking chills/rigors, sore throat, cough, malaise, headache, myalgia, GI symptoms, olfactory/ taste disorder, red/bruised feet/toes
VE from	14 days post dose 2 onwards	7 days post dose 2 onwards	15 days post dose 2 onwards	15 days post single dose onwards
Stratification on baseline serostatus	Only seronegatives in primary VE analysis; Separate analysis for seropositives	2 primary endpoints – a. without evidence of past infection & b. with or without evidence of past infection	Only seronegatives in primary VE analysis; Separate analysis for seropositives	Only seronegatives in primary VE analysis; Secondary efficacy analyses include all regardless of serostatus
Age range	Age-based analysis: 18-64 & ≥ 65; age-based stratification: (25-40% of enrollment either ≥ 65 or <65 and at risk at screening)	Age-based stratification: 16-55 & > 55 (~40% of total enrollment)	Stratified randomisation: 18-55; 56-69 & ≥ 70; age-based analysis planned, no details	Age-based stratification: 18-60 & >60 (~30% of total enrollment ≥ 60, 20% between 18-40)

 # - nucleic acid amplification test
**** - only one finding to be counted toward endpoint definition***
***** - moderate, not severe COVID-19 case endpoint listed; all moderate to severe/critical cases will be considered for primary objective***

Primary Objectives (Efficacy)

Developers – publicly available efficacy trial protocols

Element	Moderna	BNT/Pfizer	AZ (US trial)	Janssen
Target VE & LB 95% CI	≥ 50% & >30%	≥ 50% & >30%	≥ 50% & >30%	≥ 60% & > 30%
Maximum n (V:P)	30,000 (1:1)	43,998 (1:1)	30,000 (2:1)	60,000 (1:1)
Analysis population for primary endpoint	• All doses received • No significant PDs • No evidence of infection or COVID-19 at baseline	• All doses received • No significant PDs All-available efficacy: All eligible randomised subjects 1. Received at least 1 dose; 2. Received both doses	• At least one dose received • Not seropositive • Not withdrawn or no COVID-19 before Day 15 post dose 2	• Receive study vaccine • Seronegative at time of vaccination • No other major PDs
VE analysis method	Cox-proportional hazard	Beta-binomial model	Poisson regression model	Sequential probability ratio test
Cases needed for VE	151	164	150	154
No. of IAs planned	2	4	1	1+
IAs planned at no. of cases	First: 53 Second: 106	First: 32; Second: 62; Third : 92; Fourth: 120	First: 75	First: 20; at least once a week after**

 # - nucleic acid amplification test
**** - only one finding to be counted toward endpoint definition***
***** - 4 conditions must be met: first 50% of planned participants had at least 2 months of follow-up after vaccination, ≥ 6 COVID-19 cases for ≥ 60 years age group, ≥20 cases meeting primary endpoint definition of moderate to severe/critical COVID-19, subset of ≥5 cases meeting primary endpoint definition of severe/critical COVID-19***

Triggers for COVID-19 case work up

Triggers[4]	Moderna[1]	BNT/Pfizer	AZ (US trial)[2]	Janssen[5]
Fever	Yes	Yes	Yes	Yes
Cough	Yes	Yes	Yes	Yes
Dyspnoea	Yes	Yes	Yes	Yes
Anosmia/ageusia	Yes	Yes	Yes	Yes
Chills	Yes	Yes	Yes[3]	Yes
Myalgia	Yes	Yes	Yes	Yes
Fatigue	Yes[3]	No	Yes	Yes
Sore throat	Yes	Yes	Yes[3]	Yes
Diarrhoea	Yes[3]	Yes	Yes	Yes
Nausea	Yes[3]	No	Yes[3]	Yes
Vomiting	Yes[3]	Yes	Yes	Yes
Headache	Yes[3]	No	Yes[3]	Yes
Congested/runny nose	Yes[3]	No	Yes[3]	Yes
Diagnosis of COVID-19	No	Yes	No	No

1 – Fever, chills, cough dyspnoea & difficulty breathing of any duration; other symptoms should be present for at least 48 hours;
2 – Fever, dyspnoea & difficulty breathing of any duration; other symptoms should be present for at least 48 hours
3 – These symptoms are only part of the secondary efficacy endpoint definition
4 – During first 7 days post vaccination, swab collection will be based on PI judgement for symptoms that overlap solicited reactions.
5 – Other symptoms to trigger work up for Janssen include: chest congestion, general malaise, wheezing, eye irritation/discharge, SpO2 ≤95%, HR ≥ 90 bpm, abdominal pain, neurologic symptoms, red/bruised looking toes, skin rash, symptoms of blood clots, confusion, bluish lips/face

Primary Objectives (Efficacy)

Developers – publicly available records on clinical trial registries for Phase 2b/3 efficacy trials

Element	CanSino Bio./BIB	Oxford Univ. [UK only]	Gamaleya Research Institute	Butantan /Sinovac	CNBG/Wuhan IBP /Sinopharm
Primary efficacy outcome	Incidence of PCR positive COVID-19	COVID-19 confirmed virologically (RT-PCR)	Incidence of COVID-19 (PCR positive)	Incidence of COVID-19	Protective efficacy against COVID-19
VE from	Day 28 after vaccine	Information unavailable	Information unavailable	14 days post dose 2 onwards	14 days post dose 2 onwards
Baseline serostatus	Information unavailable	Either	Only seronegatives	Only seronegatives	Unclear
Age range	≥ 18 YO	Stratified enrolment: 5-12 YO; 18-55; 56-69 & ≥ 70	18-111 YO	≥ 18 YO	≥ 18 YO
Samples size	40,000	12,330	40,000	8,870	15,000

Lessons Learned from the Field

Mary Marovich, MD

Director, Vaccine Research Program (NIH, NIAID)

Merlin Robb, MD

Chief Medical Advisor (Henry M. Jackson Foundation for the Advancement of Military Medicine)

Lessons Learned:
Phase 3 COVID-19 Vaccine Efficacy Trials

Mary Marovich and Merlin Robb

24 September 2020

Operational Considerations and Impact on Design

- Enrollment strategies
- Case ascertainment and management
  - Monitoring frequency and process
  - Triggers for testing
  - Confirmatory testing process
  - Case management
- Need for space and personnel in view of COVID-19 generally and medical visits for COVID-19 cases

Enrollment strategy considerations

- Early community engagement
  - African American enrollment is notably less efficient than other ethnic and racial groups
  - It is possible that both media focus on moving vaccine discovery forward quickly and safety issue coverage may be impacting enrollment
  - Community engagement activities have built on tools and platforms used in HIV research for many years

Case ascertainment and management

- General consensus that there should be a medically attended initial visit early in entry into COVID-19 case evaluation
  - Allowing some clinical judgement probably helpful to exclude
    - Allergies with usual pattern and severity of symptoms
    - Expected reactogenicity following vaccination
    - Assess the ability of the participant to adhere to self monitoring activities
  - Permit use of a locally resourced but qualified assay for case ascertainment
    - Participants on quarantine pending central RNA test and TAT can take a week
    - Anxiety provoking for participants
    - Impacts the participant behavior, i.e. quarantine, inability to work, financial implications
    - Some have access to testing which excluded SARS CoV-2 diagnosis yet must continue the monitoring as if COVID-19 positive

Case ascertainment and management

- An emphasis on frequent monitoring
    - to advance severe cases quickly to higher levels of care
    - Ensure we capture COVID-19 cases comprehensively to
        - Assess severity
        - Identify enhanced or atypical disease
- Oximetry included routinely for case management
    - Variable oximeter platforms
        - Some with continuous monitoring and telemetry
    - Daily evaluation in AM, PM and before bed
    - Entered into an eDiary but ability to call for direction

- Technology challenged participants or participants with limitations for access
    - Retain a paper documentation system as a back-up

Personnel and Space Management

- Resource intensive trials in pandemic setting
- One site with about n=500 participants enrolled
  - N=90 staff required
  - Incorporate COVID-19 case visits with regular COVID-19 care clinic
  - Expand research clinic space to accommodate segregated follow-up for possible cases versus screening/enrollment etc
    - External semi-permanent trailers
    - Re-purpose office space
    - Dedicated rooms special air handling or open air

Clinical Case Workup in Efficacy Trials: Guidance from Community-Based Surveillance

Amol Chaudhari, MD

Clinical Development Lead

Joan Capedevila Pujol, PhD

Data Scientist at ZOE

COVID Symptom Study

Symptom analysis on a prospective, community-based cohort from the COVID Symptom Study

Interim analysis by a joint team from CEPI & ZOE

24 Sep 2020

CEPI ZOE

Rationale

- In subjects enrolled in vaccine efficacy trials, ideally, all C-19 symptoms should trigger case work-up, including PCR testing for SARS-CoV-2
    - Indiscriminate PCR testing all possible symptoms may overwhelm laboratory capacity
- The present study is conducted to quantify how individual COVID-19 (C-19) symptoms contribute to C-19 ‘case’ finding

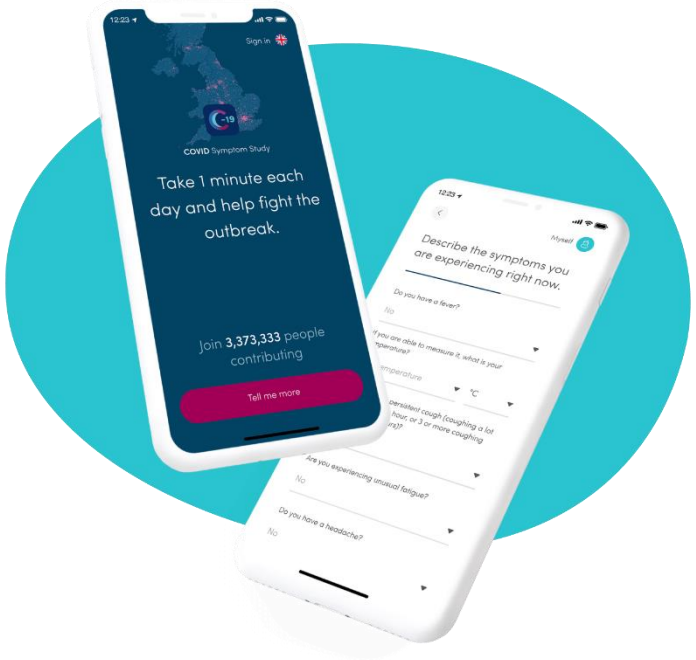
CEPI ZOE

Rationale

- The concept is to simulate C19-case-finding in a community-based, prospective, observational cohort study
    - The cohort must be a community-based to reflect the vaccine efficacy trial setting
    - The cohort must collect C-19 symptoms in a structured manner, and include PCR tests results in symptomatic people - both positive and negative
- It is assumed that PCR will *always* be triggered by the following 'classic' symptoms
    - New onset persistent cough, dyspnea, tachypnea, and fever: these symptoms point towards moderate or severe C-19 with lower respiratory tract involvement
    - Anosmia and/or ageusia should: these symptoms have been shown to have the highest specificity for predicting PCR positivity.

Background

- The *COVID Symptom Study App* was launched in the UK on the 24th of March, and in the US and Sweden on the following weeks together with *KCL*, *MGH Harvard* and *Lund University*
- Users can log up to 20 distinct symptoms on a daily basis and enter COVID test results
- **4+ million users** have joined, **170+ millions health reports** have been logged and **1+ million test results** have been entered
- **800,000+ users** have signed up to the **vaccine registry** allowing us to contact them about potential studies involving vaccines and other preventive treatments



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Inclusion criteria

- UK 18+ users active from 24th of March to 15th of September 2020
    - Users who have regularly logged feeling healthy and then got sick *(i.e. newly symptomatic)* or kept feeling healthy *(i.e. healthy)*.
- Included health reports that were logged any time after they got sick *(i.e. symptoms onset)* until 14 days after the onset - regular analysis - or until 3 days after the onset - 72 hours analysis.
- Included PCR test results that were logged any time from symptoms onset to 7 days after the onset.
- Included only first episode of PCR positive.
- Excluded users who signed up in the App and had already had COVID-19.

Data summary

- 1,404,740 users in the UK cohort meeting the inclusion criteria
- 468,263 users in the UK cohort have reported symptoms at some point - *newly symptomatic*
- 105,123 *newly symptomatic* users have entered valid PCR results - *positive or negative*
  - 55% aged 18 - 49, 34% aged 50 - 65 and 11% aged 65+
  - 75% female and 25% male
- 121,347 *negative* tests from *newly symptomatic* users
- 1,272 *positive* tests from *newly symptomatic* users

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Terminology

- **Recall or Sensitivity:** % of C-19 positive users who are correctly identified by a symptom or a combination of symptoms.
- **Precision or PPV:** % of users identified by a symptom or a combination of symptoms who are C-19 positive.

14% of the positive cases showed no classic symptom during the two first weeks

Symptoms	Tested positive	Recall (or Sensitivity)	Tested negative	Precision (or PPV)
Fatigue	1068	84.0	63138	1.7
Headache	1021	80.3	65038	1.5
Sore throat	744	58.5	55383	1.3
Loss of taste and smell *	730	57.4	5856	11.1
Persistent cough *	671	52.8	16648	3.9
Fever *	618	48.6	19576	3.1
Unusual muscle pains	592	46.5	20253	2.8
Shortness of breath *	527	41.4	15441	3.3
Chest pain	522	41.0	16274	3.1
Skipped meals	513	40.3	16017	3.1

Total num positive tests	1272
Total num negative tests	121347

Symptoms	Tested positive	Recall (or Sensitivity)	Tested negative	Precision (or PPV)
* Any classic symptom	1092	85.8	42292	2.5

Total number of tests
43,384

This percentage reduces to 3% if we include fatigue and headache into the triggering symptoms

Symptoms	Tested positive	Recall (or Sensitivity)	Tested negative	Precision (or PPV)
Fatigue	111	61.7	34243	0.32
Headache	106	58.9	39391	0.27
Sore throat	83	46.1	33685	0.25
Diarrhoea	44	24.4	15588	0.28
Unusual muscle pains	43	23.9	9483	0.45
Dizzy light headed	43	23.9	16695	0.26
Typical hayfever	43	23.9	18917	0.23
Nausea	42	23.3	16683	0.25
Abdominal pain	36	20.0	14371	0.25
Eye soreness	33	18.3	11732	0.28

Total num positive tests	180
Total num negative tests	79055

Extended symptoms = classic symptoms + fatigue + headache

Symptoms	Tested positive	Recall (or Sensitivity)	Tested negative	Precision (or PPV)
Any extended symptom	1236	97.2	95073	1.3

Total number of tests
96,309

Classic symptoms are less likely to occur in the first 72 hours, but fatigue+headache might help case finding

Symptoms	Tested positive	Recall (or Sensitivity)	Tested negative	Precision (or PPV)
Headache	845	66.4	57798	1.4
Fatigue	828	65.1	56176	1.5
Sore throat	598	47.0	49526	1.2
Persistent cough *	469	36.9	13411	3.4
Fever *	467	36.7	16567	2.7
Unusual muscle pains	374	29.4	16737	2.2
Hoarse voice	311	24.4	12126	2.5
Skipped meals	293	23.0	13386	2.1
Chest pain	293	23.0	13248	2.2
Loss of taste and smell	284	22.3	4673	5.7

Total num positive tests	1272
Total num negative tests	121340

Extended symptoms = classic symptoms + fatigue + headache

Symptoms	Tested positive	Recall (or Sensitivity)	Tested negative	Precision (or PPV)	Total number of tests
Any classic symptom *	865	68.2	36523	2.3	37,388
Any extended symptom	1160	91.2	89725	1.3	90,885

Summary

Based on data from the *COVID Symptom Study App,* we showed that:

		Recall	**Tests per positive case**
14 days	Classic symptoms	85.8%	40
	Extended symptoms	97.2%	77
3 days	Classic symptoms	68.2%	43
	Extended symptoms	91.2%	78

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Limitations

- This is work in progress - data analysis is not yet final
- This is based on self-reported data
- Setting is UK specific; i.e., no malaria, dengue, etc.
- Seasonality: study was conducted during the northern hemisphere summer; i.e., few concurrent respiratory pathogens, influenza, common cold etc.
- Study population biased towards people with smartphones and high socioeconomic status.

Conclusions

- The *COVID Symptom Study App* has created a large prospective community-based cohort to understand how symptoms that may trigger PCR contribute to case finding.

Based on data from the COVID Symptom Study App:

- 14% of the positive cases show no classic symptoms (Fever, cough, dyspnea, tachypnea, anosmia & ageusia) during the first two weeks of symptoms.
- By including fatigue and headache to the triggering symptoms, one would double the number of tests performed but 97.2% of the positive cases could be found.
- This is even more important during the first three days of symptoms, in which classic symptoms would only find 68.2% of the positive cases and the extended symptoms, 91.2%

Discussion: Operational Considerations

Moderated by Peter Dull

Discussion Panel Members

- **Ricardo Palacios, MD, PhD**, Clinical Research Medical Director (Instituto Butantan / Sinovac)
- **Jacqueline Miller, MD**, SVP Therapeutic Area Head, Infectious Diseases (Moderna)
- **Shabir Madhi, PhD**, Professor of Vaccinology, Director of the MRC Respiratory and Meningeal Pathogens Research Unit (ChAdOx-Novavax)

Wrap Up and Next Steps

Peter Dull

Closing remarks

- Thank you all for your participation and engagement today
- The COVAX Clinical SWAT Team plans to continue sharing learnings across developers as we pursue our common goal – a global supply of safe and effective vaccines
- We will continue to share resources at the website here: https://epi.tghn.org/covax-overview/clinical/
- We will be sharing a post-workshop survey to capture any remaining questions or comments
- We will distribute a workshop report to summarize today's conversation; for any outstanding questions, we will do our best to direct you to the appropriate resource


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