# A Bayesian Sequential Design for COVID-19 Vaccine Trials

## DIA BSWG Series

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# Bayesian Approaches

## Key advantages of Bayesian approaches

- Formally incorporate prior knowledge
- Estimate probability of treatment effect

"*The probabilistic results of Bayesian analysis naturally align with the thought processes of clinicians making treatment decisions at the bedside where the probabilities of various competing benefits and harms must be weighed*" (Golighter et al, JAMA, 2018)

## Growing interest to Bayesian methods

- 10 years experience with confirmatory devices trials (CDRH)
- Bayesian borrowing in Rare Diseases trials
- CDER & NIH collaboration on Bayesian trial during Ebola outbreak
- Use in Early Phase trials and interim decision making
- Increasing number of publications in medical literature

# Clinical research during pandemic

## Needs of clinical research during pandemic

- Adapt quickly to discontinue poorly performing therapies and uncertainties about the course of the disease
- Enable more efficient and informative decision making as early as possible

## Bayesian methods addresses the needs by the use of

- Use of Predictive Probability of Success to answer if a trial is likely to reach a definitive conclusion
- Use complete as well as partial interim information to enable robust interim futility / efficacy decisions
- Sequential learning via interim looks to de-risk incorrect decision about stopping early, etc.

# Challenges of designing trials during pandemic

- Novelty of the diseases and therefor lack of prior data
- Rapidly evolving knowledge on the new diseases
- Evolving standard of care
- Sense of urgency
- Evolving / variable case mix
- Rapidly changing incidence (attack rates)
- Stretched acute care resources

# Case study: Background

- Bacillus Calmette-Guérin (BCG) was developed as a vaccine against tuberculosis (TB)
- Studies have shown that BCG induces substantial protection against other infectious diseases (non-specific effects)

- The innate immune system becomes primed and can react faster and more efficient
- BCG vaccination of infants was associated with reduced neonatal sepsis, respiratory infections, and fever
- BCG re-vaccination of adults was associated with a 70% reduction in acute respiratory infections

nature > nature reviews immunology > comment > article

Comment | Published: 11 May 2020

**BCG-induced trained immunity: can it offer protection against COVID-19?**

Luke A. J. O'Neill ✉ & Mihai G. Netea

*Nature Reviews Immunology* **20**, 335–337(2020) | Cite this article

**84k** Accesses | **29** Citations | **766** Altmetric | Metrics

**Bacillus Calmette–Guérin (BCG) vaccination has been reported to decrease susceptibility to respiratory tract infections, an effect proposed to be mediated by the general long-term boosting of innate immune mechanisms, also termed trained immunity. Here, we discuss the non-specific beneficial effects of BCG against viral infections and whether this vaccine may afford protection to COVID-19.**

# Case study: Trial Objectives

- Objective: Evaluate effectiveness of BCG and MTBVAC (new TB vaccine, nTBV, under development) in preventing symptomatic Covid -19 infection
- Population: Exposed Health Care workers (expected to take care for COVID-19 patients)
- Primary endpoint: Proportion of symptomatic laboratory-confirmed COVID-19 disease within 90 days of after immunization in SARS-CoV-2 seronegative population at the baseline
- Primary Hypothesis: Superiority of BCG and/or nTBV vaccine in preventing symptomatic Covid-19 infection in exposed health care workers.
- Expected Benefit: A reduction of at least 45% in incidence rate, trial powered for 50% reduction, i.e., a vaccine efficacy (VE) of 0.5.
- Secondary endpoints: Any serologically confirmed SARS-CoV-2 infection, WHO severity scale etc.

# Other Trial Details

- Population: Highly exposed healthcare workers
- Recruitment rate: Expected 100 per month
- Randomization: 1:1:1 (BCG:nTBV:Placebo)
- Fixed follow-up of three months

# Sample Size

- Based on a two-sample proportion test with Bonferroni-adjusted significance level of 1.25% for each comparison (BCG vs. Control and nTBV vs. Control). Powering at 90% for an incidence reduction of 50%
- Assumed control arm proportion over 90 days is 20% (quite high)
- Minimal Sample Size: 945 subjects, with 10% dropouts $N = 1050$ (350 per arm)
- Maximal Sample Size: $N_{max} = 1800$ which will provide 90% power if vaccine efficacy is 0.45 (instead of 0.5) or if the control arm rate if 12% (rather than 20%) but VE is at least 50%.

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## Risks Mitigation

- The trial may be under-powered if the control arm incidence (constantly evolving) is lower than assumed
- A Bayesian adaptive design has been proposed

# Rationale for a Bayesian Trial Design

- Constantly evolving attack-rate
- Desire to have a flexible sample size for the PoC trial depending on the control arm rate and VE level ($N_{max} = 1800$ is a guideline), example, if control arm rate is 6% but VE > 55%, the trial could end up with a higher sample size
- Early stopping for futility or dropping one of BCG or nTBV if not efficacious
- Avoid statistical penalty of taking multiple interim looks, using combination test, closed testing procedure, etc. under a frequentist framework
- Use totality of evidence available at interim looks to make interim decisions - Use Bayesian predictive power rather than conditional power (Ref: *Dmitrienko-Wang, 2006, SIM*)
- Ability to incorporate a new SOC arm and borrow from published external control data
- Ability to seamlessly extend PoC trial to confirmatory

# Final Analysis (Bayesian)

- Priors: Non-informative $Beta(1,1)$ priors assumed for $\pi_C, \pi_B$ and $\pi_M$.
- Likelihood: Binomial
- Success criteria at final analysis: The hypothesis test will be carried out only once at the final analysis using posterior distributions for $\pi_i$. The success criteria for the $i^{th}$ ($i \in (B, N)$) vaccine arm being

$$Pr\{\pi_i - \pi_C < 0 | \text{ data } \} > \gamma.$$

- Under the Beta-Binomial (conjugate) model the posteriors are also Beta distribution. The posterior probability on differences are calculated using the convolution formula.
- The success threshold is set to $\gamma = 1 - 0.025/2 = 0.9875$.

# Interim Adaptations

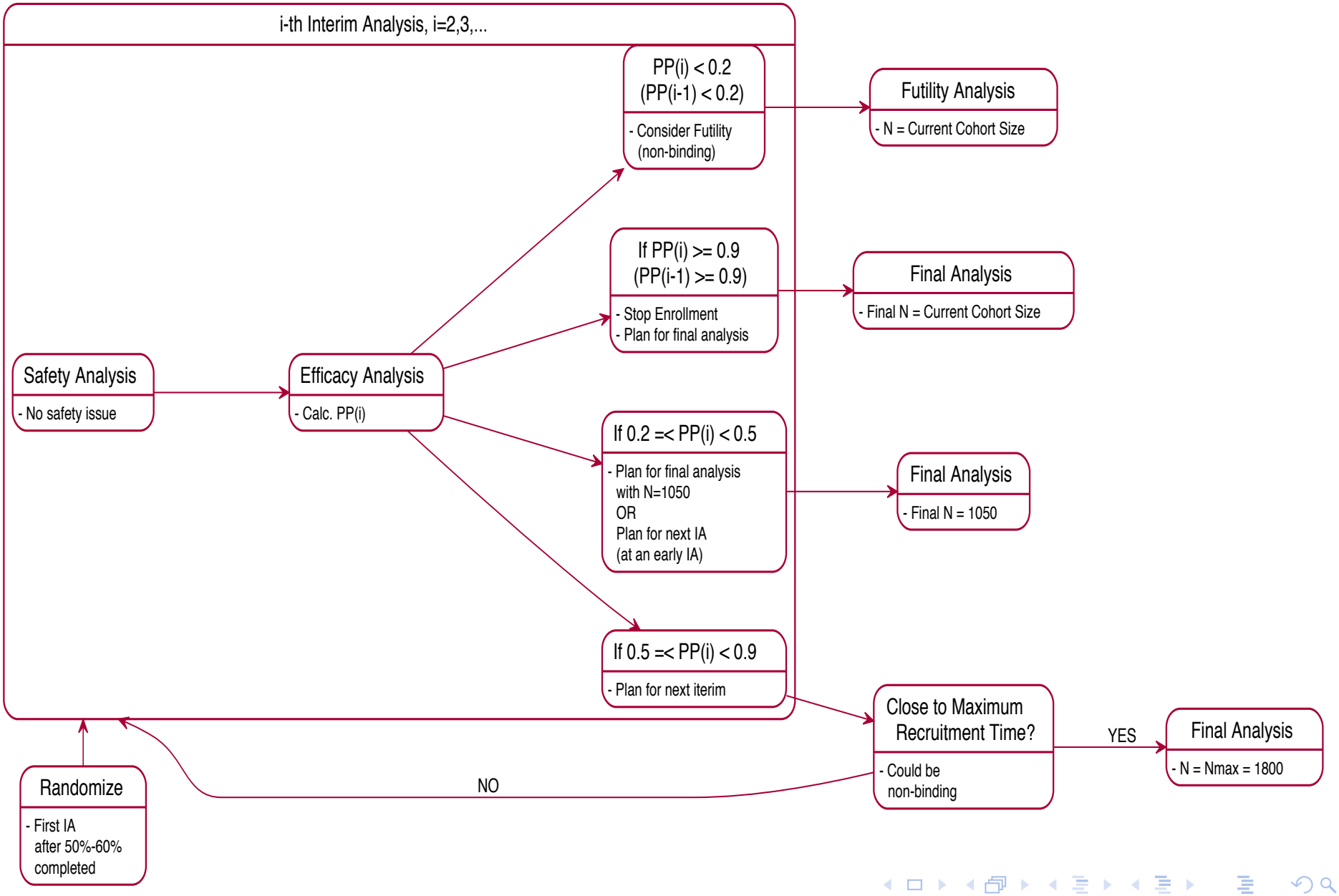
- Multiple interim analyses have been planned with the first interim at around 50% information fraction ($\approx$ 500 completed) with each subsequent interim analysis with 100 additional subjects
- At each interim analysis, Bayesian predictive power (Ref: *Spiegelhalter et al., 2004, Wiley*) with the current cohort will be computed based on the predictive distribution of the binary response conditional on the interim data. This will be done separately for the two vaccine arms

# Guidelines for Interim Decision based on PP

Based on the calculated PP the following mutually exclusive interim decisions will be made by the iDMC:

- Stop trial for safety issues; or
- Stop trial for futility or drop an arm if PP with planned N (350 per arm) is consistently low
- If current cohort PP is moderate then either continue to the next interim (if increasing trend) or go to planned end (350 per arm)
- If current cohort PP is promising then go to next interim or carry out final analysis with maximum 600 per arm
- If current cohort PP exceeds the efficacy threshold (say, 0.9) then stop enrollment and carry out final when the last interim cohort has complete follow-up - this is non-binding - may choose to confirm with at least another interim look.

# Design Schematic



# Main Design Characteristics

- Simulation studies to establish operating characteristics show that if the null hypothesis is true, with a minimum of two interim looks and $\gamma = 0.9875$, the type-I error probability is 2.7%. With a higher threshold $\gamma = 0.99$ it reduces to 2.3%.
- Under the alternative, with VE = 0.5 for both vaccine arms, with at least two interim looks, the power is 93% with an expected sample size of 810 and a study duration of 10 months.
- The power reduces to 84% if only one of the two vaccines are efficacious

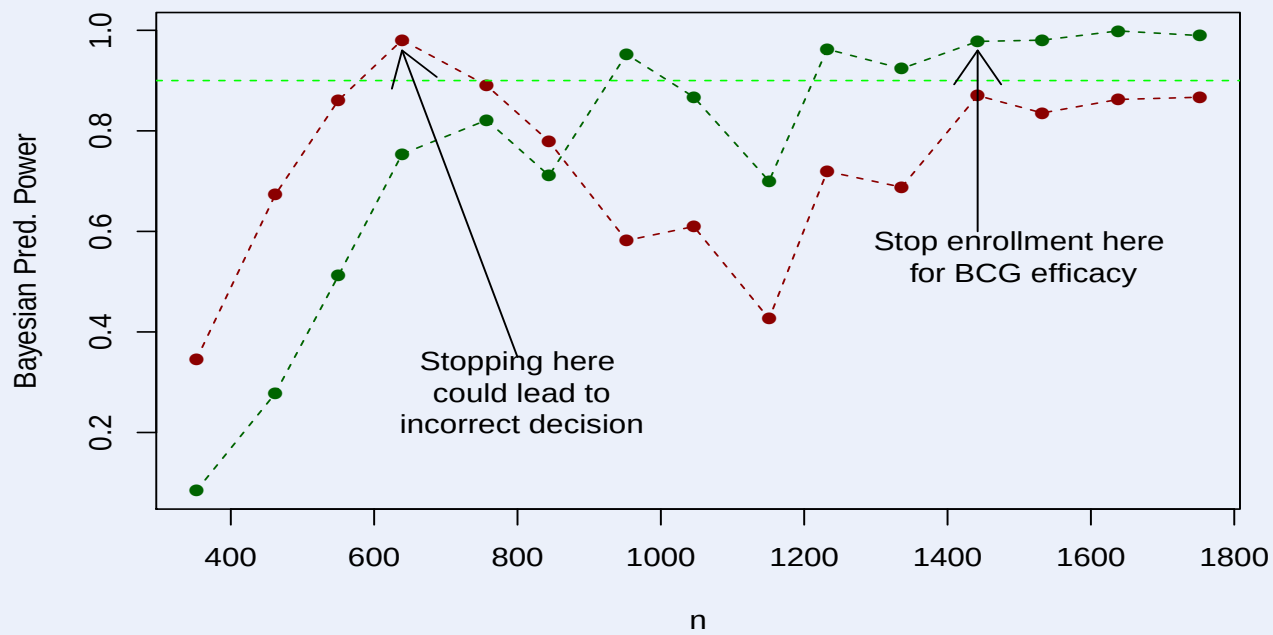
# Extension to a Confirmatory Trial

- If the results of this PoC study are promising then the study can be seamlessly (operationally) extended to a confirmatory study with longer follow-up ($\geq$ 24 months) and powered with a superiority margin of 0.3 for VE (Ref: *FDA Guidance, Development and Licensure of Vaccines to Prevent COVID-19, June 2020*).
- Inferential seamless option can be also be considered by using the PoC data to construct informative priors.
- However, attack-rates may be different in 10-12 months time. Also the follow-up time will be longer.
- Methods to resolve Prior-data conflicts will be needed

# Note on Interim Monitoring

- PP can be calculated at any time during the course of the trial, however, early stopping decision (for efficacy or futility) should be avoided based on early looks (< 50% info. frac.)
- Under the proposed design, it is possible to carry out stopping decisions based on PPs calculated at multiple looks

Fluctuating PPs, simulated data with BCG VE = 0.5 and nTBV VE = 0.6



# Summary

- Discussed a flexible sequential and adaptive design ideal for rapid establishment of proof-of-concept under uncertainties and logistical constraints
- The design is aimed at facilitating flexible and robust interim decisions
- We used non-informative priors here, however, informative priors could be incorporated if historical data is available
- Careful planning and appropriate use of firewalls will reduce operational burden and the chance for operational bias

Thank You!

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