A Bayesian Sequential Design for COVID-19 Vaccine Trials

DIA BSWG Series

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Outline

Topics

BCG as a candidate vaccine for reduction of risk of COVID infection

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.

BCG as a candidate vaccine for reduction of risk of COVID infection

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- In clinical studies, BCG vaccination of infants was associated with lower infant mortality, mainly as a result of reduced neonatal sepsis, respiratory infections and fever.
- A recent placebo controlled study in South Africa showed that BCG revaccination of adults was associated with a 70% reduction in the incidence of acute respiratory infections.

Sponsor's Interest

- Developing a new TB vaccine (similar mechanism of action) but with superior durability of protection - call it nTBV
- Early phase studies have demonstrated the MOA and that nTBV is well tolerated - approval pending on more safety and incidence data over longer follow-ups

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Superiority of BCG and/or nTBV vaccine in preventing symptomatic Covid-19 infection in exposed health care workers.

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Expected Benefit

- A reduction of at least 45% in incidence rate, powered for 50% reduction

Other Trial Details

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- Secondary endpoints include disease severity including the WHO 8-point ordinal scale

Topics

Hypothesis Test

Proportion of subjects getting symptomatic COVID-19 illness within 90 days after immunization:

- BCG arm: π_B; nTBV arm: π_N; Control arm: π_C

Vaccine Efficacy (VE) defined as

$$VE = 1 - \frac{\pi_i}{\pi_C}, \text{ for } i \in (B, N).$$

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Primary Hypothesis:

$$H_0 : \pi_B - \pi_C \geq 0 \quad \cap \quad \pi_N - \pi_C \geq 0$$

VS.

$$H_1 : \pi_B - \pi_C < 0 \quad \cup \quad \pi_N - \pi_C < 0.$$

A Note of Regulatory Requirement

- For vaccine approvals, the point estimate for VE should be at least 0.5 with the lower bound on the alpha-adjusted CI exceeding 0.3 (superiority margin) (Ref: *FDA Guidance, Development and Licensure of Vaccines to Prevent COVID-19, June 2020*)
- This trial is a proof-of-concept trial with limited sample size and follow-up duration - Superiority margin = 0
- Seeking conditional approval based on a successful PoC trial otherwise confirmatory trial to follow if the results are promising.

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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

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- Ability to seamlessly extend PoC trial to confirmatory

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- 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 $\gamma = 1 - 0.025/2 = 0.9875$.

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- 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

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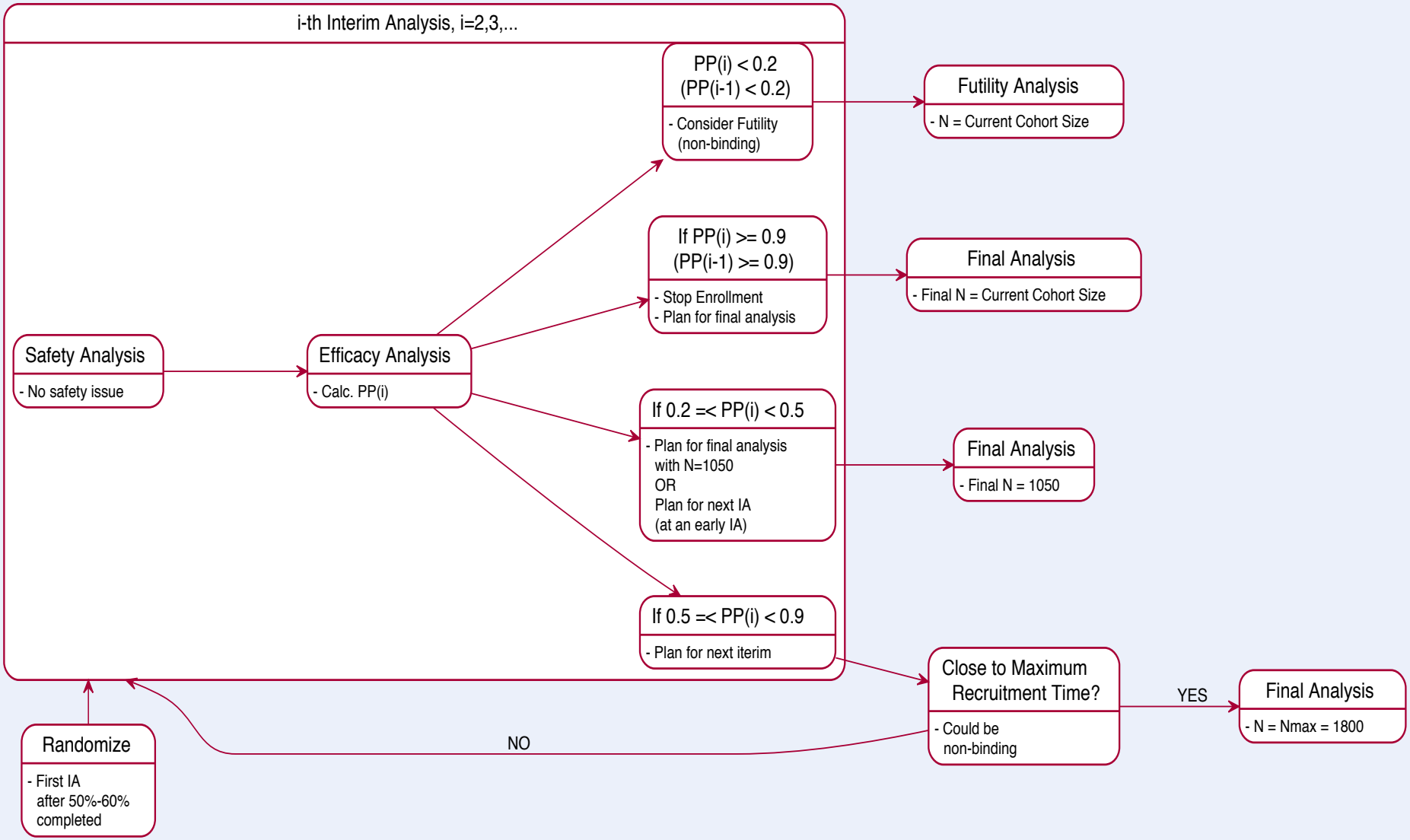
- If current cohort PP is promising then go to next interim or carry out final analysis with maximum 600 per arm
- If current cohort PP exceeds the efficacy threshold (say, 0.9) then stop enrollment and carry out final when the last interim cohort has complete follow-up - this is non-binding - may choose to confirm with at least another interim look.

Interim Analysis Plan

Example (used for simulations)



Topics

Predictive Power calculation

Defined as the predictive probability of a successful outcome at the final analysis based on currently enrolled cohort

Current cohort PP

(x, x') is the data of size n from the current cohort, with x the complete data and x' the partial data.

$$PP(n) = \mathbb{E}_{p(x'|x)}\left[\mathcal{I}\left(Pr\{\pi_i - \pi_C < 0 \mid (x, x')\} > \gamma\right)\right],$$

where, the expectation is taken over the posterior predictive distribution of x' given x:

$$p(x'|x) = \int p(\pi|x)L(x', \pi)d\pi.$$

- Actual calculations depend on the nature of interim data (x, x').

PP calc. with binary data only (x' missing)

Algorithm

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- Pros: - Speed, used in simulations
- Cons: - Inefficient use of available data, x' could include partial follow-up times but this is extremely computation heavy for simulations. Could be used for actual interim analysis

PP calc. with partial follow-up info

- Use posterior predictive distribution conditional on partial follow-up times
- Use previous algorithm but to draw x_i' use $BBP(x_i' | x(t_i'), m(t_i'), n(t_i'))$, where, t_i' is the partial follow-up time for x_i',
  $x(t_i')$ is the number of observed cases after time t_i',
  $m(t_i')$ is the number surviving (no COVID illness) till time t_i' and
  $n(t_i') - m(t_i')$ is the number of partial follow-ups greater than t_i'.
- This can still be used for simulations, used for the null case

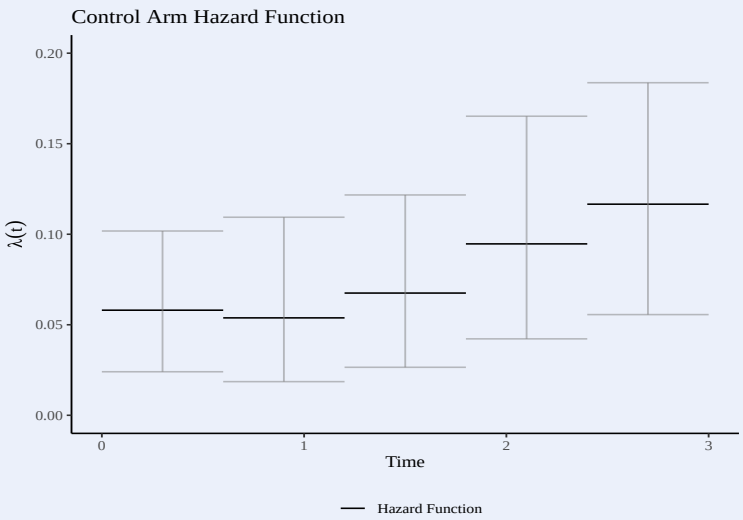
PP calc. with time to event data

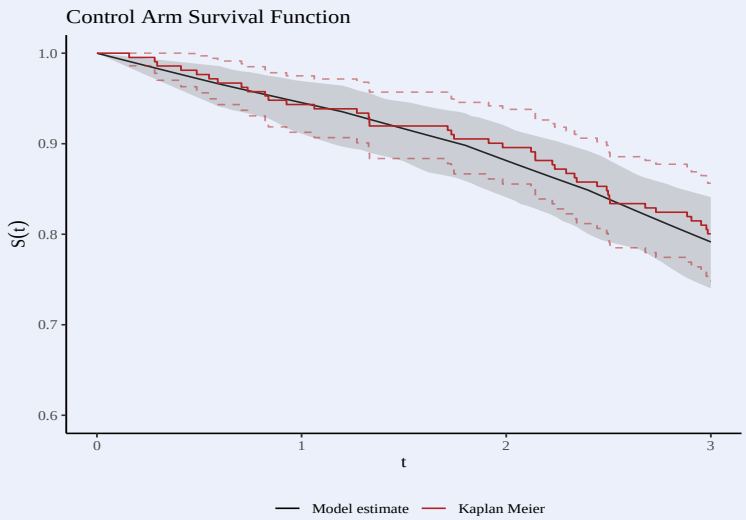
Algorithm (Ref: *Schmidli et al., 2007, Stat. Med.*)

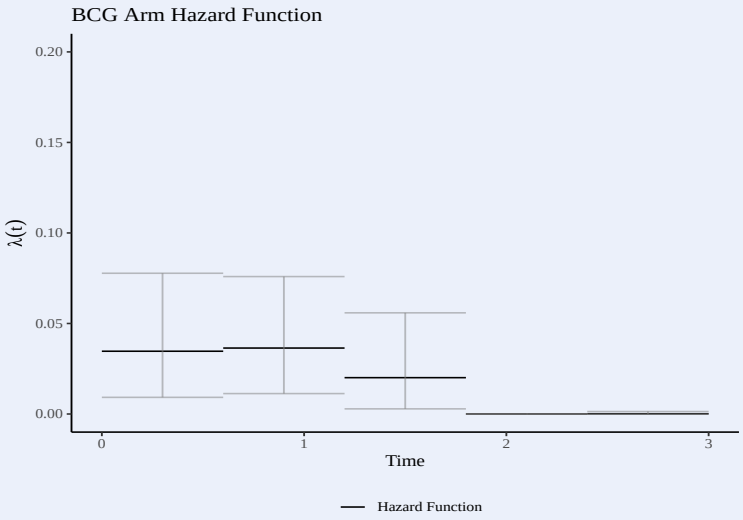
- Model hazard function for each arm using piece-wise exponential distribution.
- Use Gamma-process priors (Ref: *Walker-Barajas, 2002, Sc. J. Stat.*) for the piece-wise constant hazards
- Get the posterior of hazard (or survival) function
- Draw repeatedly (R = 10,000) from this posterior
  - For each draw, predict repeatedly (P = 10,000) infection times (censored at 90 days)
  - Transform predicted data into binary (x') - use (x, x') to compute success indicator
- Average over $R \times P$ draws.

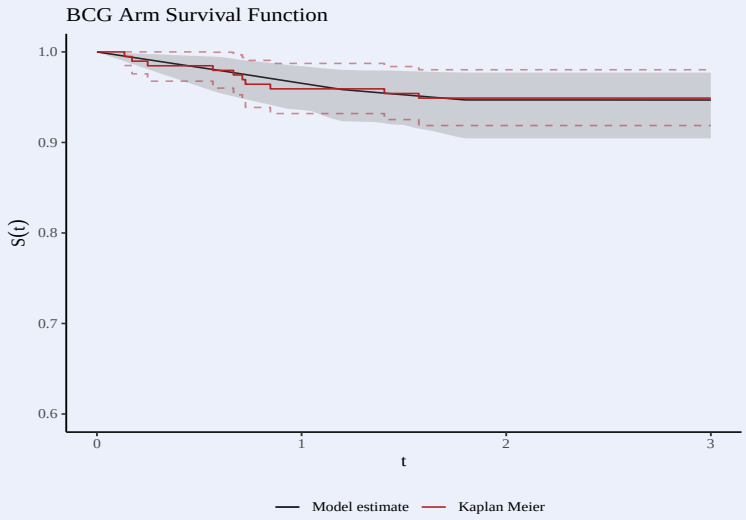
Estimation of Hazard and Survival with Gamma-Process Priors

First Interim Data at 6 months (simulated with mean control arm hazard rate = 0.0637 and HR=0.5), n = 599, n-m = 111 administratively censored, 97 cases









Topics

Simulation Settings

- Recruitment: 100 per month
- Lost-to-follow generated using exponential with rate 1%
- Time to infections generated using piece-wise exponential with average hazard rate 0.067 per-person-month
- First interim look at around 50% information fraction and then every month
- Stopping enrollment early for futility (PP < 0.2) and efficacy (PP ≥ 0.9) based on at two successive PP calculations
- Used $BBP(x'|x, m, n)$ for scenarios under the alternative and $B(x_i'|x(t_i'), m(t_i'), n(t_i'))$ for the null scenario.
- Success criteria: Posterior probability of reduction in incidence proportion compared to control arm > 0.9875.

Operating Characteristics

Simulation Results with Non-binding Futility, at least 2 IAs

Scenario	No. Sims	No. of Interim Mean (SD)	Sample Size Min. Mean (SD) Max.	Duration Min. Mean (SD) Max.	Power/Type-I
null	50000	2.14 (0.68)	622 1043.54 (49.88) 1800	9.22 13.44 (0.5) 21	0.0276
alt.5.5	10000	2.52 (1.14)	619 806.03 (154.78) 1800	9.19 11.06 (1.55) 21	0.9304
alt.5.1	10000	2.63 (1.25)	629 865.18 (170.68) 1800	9.29 11.65 (1.71) 21	0.8444
alt.55.55	5000	2.67 (1.34)	629 847.22 (173.91) 1708	9.29 11.47 (1.74) 20.08	0.8702

- The success threshold can be slightly increased to get type-I error < 0.025.

Topics

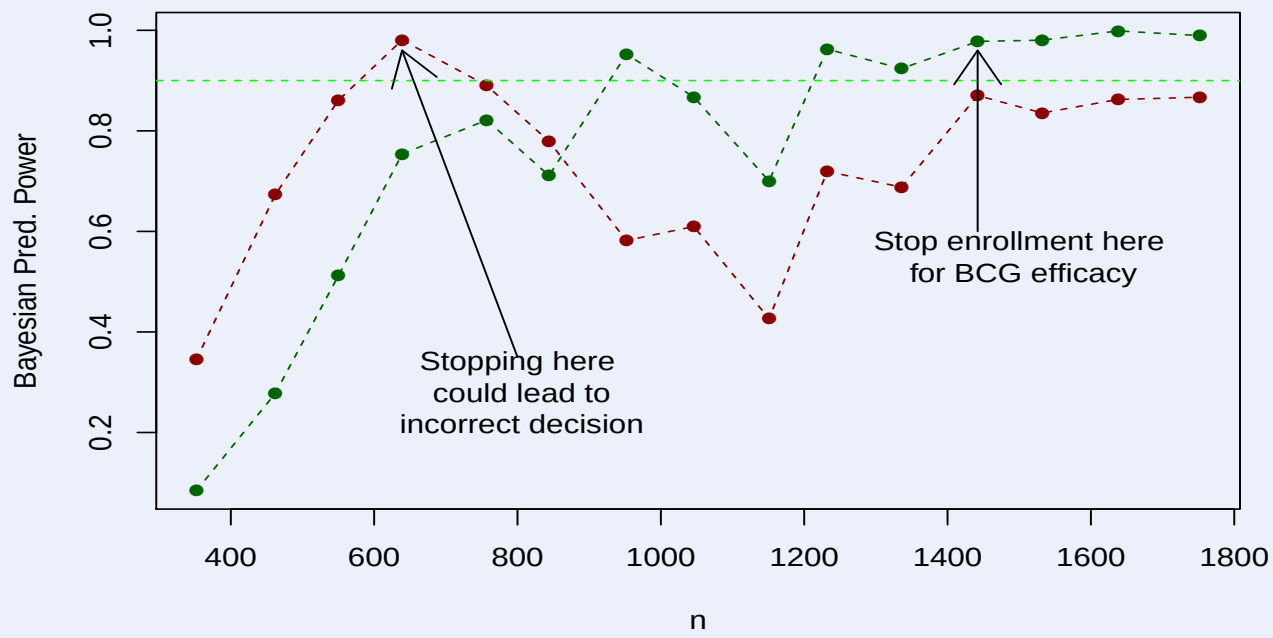
Extension to a Confirmatory Trial

- 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.
- 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. This will lead to prior-data conflicts
- Options to resolve prior-data conflict must be considered
  - Robust Informative Priors: Adding a weakly-informative mixture component to the informative prior (Ref: *Schmidli et al., 2014, Biometrics*)
  - Use of power prior methodology (Ref: *Ibrahim et al., 2015, SIM*) along with commensurate priors (Ref: *Hobbs et al., 2012, Bayesian Anal.*)

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 HR.BCG = 0.5 and HR.nTBV = 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
- The predictive power approach can also be used for interim decisions only while the final analysis is carried out using a frequentist test (hybrid design)
- 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!

Email: rajat.mukherjee@cytel.com