PRINCIPLE Platform Trial Design
Treatment for COVID-19 in Primary Care

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Treatment for COVID-19 in Primary Care

- We were contacted Mar 16 by Oxford colleagues for trial design in COVID-19 primary care
- Objective: Compare Hydroxychloroquine vs. Usual Care (open label)
  - In older persons (>65yrs, >50yrs w/ comorbidities) with suspected COVID-19
- Needed a rapidly initiated trial with adaptive features
  - Ability to evaluate treatments quickly (early superiority/futility)
  - Flexibility to add treatments
- Needed a proposal for UKRI, a protocol, adaptive platform trial design, and DMSC quickly!
- First patient was randomized April 3rd (2.5 weeks!)

Key Design Considerations

- Primary endpoint: Ordinal or Binary?
- Interim analyses
  - Timing and frequency
  - Early superiority/futility rules for each treatment
  - Response adaptive randomization
  - Leverage partial information via longitudinal modeling
- Control arm
  - Usual care arm may be replaced
  - Staggered treatment arms with potential population drift (pandemic)
- Simulations to evaluate/calibrate adaptive algorithm
- Quickly transition to trial implementation

Primary Endpoint

- Investigator initially proposed binary endpoint
  - Hospitalization/death for suspected COVID within 28 days
- We immediately steered him to an ordinal endpoint
  1. Home
  2. Hospital admission without ICU/ventilation
  3. Hospital admission with ICU/ventilation
  4. Death
- Expected to see at least 5-10% increase in power, but conducted quick simulation to quantify

Primary Endpoint

- Expect to randomize $\sim$1500 participants per arm
- Expect $\sim$ 20% of participants to have hospital admission
  - Ordinal endpoint adds information to the 20% with hospital admission
- Simulations showed only a 1% power gain for ordinal vs. binary primary endpoint
  - Under proportional odds assumption
  - More power gains expected from ordinal endpoint if we further categorize the 80% home
  - But that's not goal of interventions
  - Objective of interventions: Keep patients alive and out of hospitals
- Additional complexity of ordinal (inferential/operational) not justified for 1% power gain
  - Verdict: Binary endpoint!

Primary Analysis

- Primary endpoint: 28 day hospitalization/death (yes/no)
- Primary analysis: Declare superiority of Hydroxychloroquine to Usual Care if the Bayesian posterior probability of superiority is greater than 0.98
- Primary analysis model: Bayesian logistic regression model to estimate Prob(Hospitalization/Death) by treatment, adjusting for age and comorbidities

Adaptive Platform Design

- Expected accrual: 250 participants/week (after ramp-up)
- First interim occurs after 100 participants have opportunity to complete 28 days
  - Subsequent weekly interim analyses
- Interim: Bayesian model to evaluate arm-specific futility or superiority based on posterior probabilities:
  - Declare treatment superior if Pr(Superiority to Usual Care) > 0.999
  - Stop treatment for futility if Pr(Meaningful Benefit) < 0.01
    - Meaningful benefit effect is 0.05 percentage point decrease
- Control Type I error for each arm at approximately 0.025 (one-sided)
  - Requires simulation
  - Used FACTS for initial calibration in 1:1 setting

Longitudinal Model for Partial Information

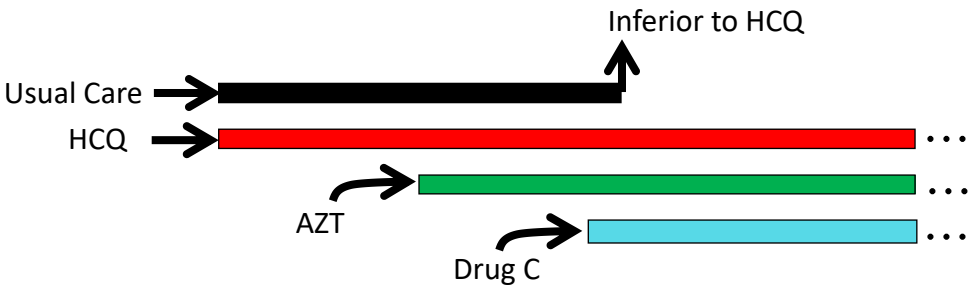
- At interim analyses, many randomized subjects will lack 28-days of follow-up
  - Some will be early hospitalizations
  - How to incorporate without biasing estimates?
- Solution: Capture early hospitalizations with 7-day and 14-day status
  - Daily diary entries, and phone calls at 7 and 14 days
  - 7-day status, among those with opportunity to complete 7 days
  - 14-day status, among those with opportunity to complete 14 days
- Longitudinal model

$$Pr(y_{28} = 1) = 1 - \{Pr(y_7 = 0) \times Pr(y_{14} = 0 | y_7 = 0) \times Pr(y_{28} = 0 | y_{14} = 0)\}$$

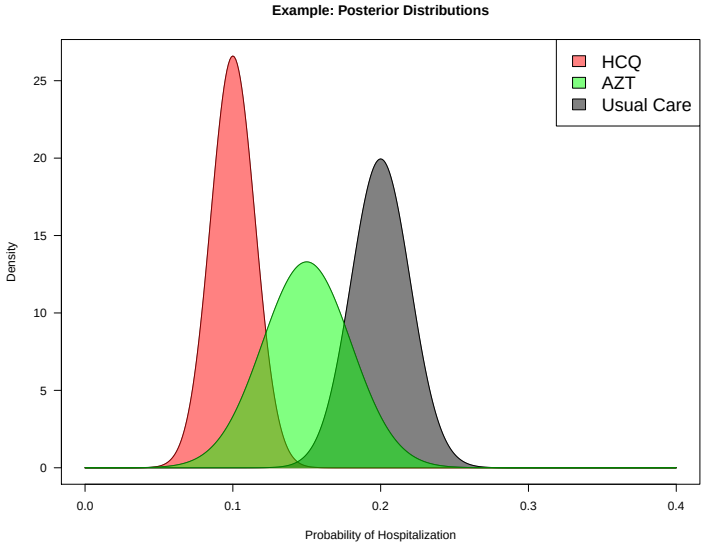
Additional Treatment Arms

- Master protocol allows the addition of new treatment arms
- If at least two interventions, response adaptive randomization allocates subjects to the more promising therapies
  - Use fixed Usual Care allocation (e.g. 1/3)
  - RAR based on Prob(Best Intervention) or Prob(Superior to Usual Care)?
- Superior arm can replace the Usual Care arm as the new standard of care
  - Future comparisons: Non-inferiority to new SOC, or compare to original Usual Care?
  - How do we compare to original Usual Care if no longer randomizing to that arm?

Staggered Entry



Compare to Usual Care



Solution for Staggered Entry

- Primary analysis: Compare each intervention vs. the original Usual Care arm
- RAR based on Prob(Superior to Usual Care)
  - Even if no longer randomizing to Usual Care
- Model the population drift over time

$$\text{logit}\{\Pr(y_{28} = 1)\} = \beta_0 + \boldsymbol{x}_i'\boldsymbol{\beta} + \boldsymbol{z}_i'\boldsymbol{\gamma} + \eta_i(t)$$

- $\boldsymbol{x}_i$ are treatment group indicators, $\boldsymbol{z}_i$ are covariates for subject i
- $\eta_i(t)$ is a function of time: 2nd order normal dynamic linear model (NDLM)
  - Bayesian hierarchical smoothing over 2-week intervals
- Model allows comparison of treatment arms enrolling at different time periods
  - Valid if staggered overlap between arms

*Longitudinal component for interim analyses not shown

Virtual Trial Simulation

- All adaptive decision rules need to be pre-specified
- Simulations have two purposes
  1. Explore/calibrate adaptive algorithm on single example trials
  2. Evaluate/calibrate performance under a wide range of plausible scenarios
- Simulations to be completed and decision rules finalized prior to the first interim analysis

Adaptive Design Execution

- Berry "Execution" team simultaneously prepping to conduct the interim analyses
- Emphasis on timely data collection
- Test data transfers critical
  - Putting programming/validation in place for quick turn-around
  - Interim report generator
- Communication channels for interim analysis results
- Firewalls between design team and execution team effective at first interim analysis

Berry Team

- Nick Berry
- Michelle Detry, Christina Saunders, Mark Fitzgerald