Statistical design challenges of a Phase 2/3 randomized placebo-controlled Ebola vaccine trial

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Contents

Introduction
The PREVAIL I study
Study design
Randomization and blinding
Data Safety Monitoring Board
Current status
Next steps
Bridging efficacy from NHP to humans
Filoviruses

- Enveloped, negative strand RNA viruses (Filoviridae family) of filamentous shape
- 2 family members:
  - Ebola virus (5 subspecies)
    - Zaire ebolavirus (EBOV)
    - Sudan ebolavirus (SUDV)
    - Taï Forest ebolavirus (TAFV)
    - Bundibugyo ebolavirus (BDBV)
    - Reston ebolavirus (RESTV) (not virulent in humans)
  - Marburg virus (MARV)

Ebola virus disease (EVD)

- Incubation 2-21 days, probably function of viral inoculum
- Essentially an aspecific febrile syndrome, with gastrointestinal symptoms. Difficult to diagnose in absence of hemorrhagic symptoms, which are rarely observed (<6%) Unexplained bleeding reported in 18%.
- Interval for onset of symptoms to hospitalization is 5.0 +/- 4.7 days
- Interval for onset of symptoms to hospital discharge is 16.4 +/- 6.5 days
- Interval for onset of symptoms to death is 7.5 +/- 6.8 days
Statistical design challenges in an Ebola vaccine trial

The story so far…

EVD
~28500 cs until Nov, 2015
mortality 40%

Outbreak Distribution Map

http://www.who.org
Developing a vaccine

- Types of vaccines:
  - Prophylactic vaccines: prevent the disease
  - Therapeutic vaccines: cure the disease

- For Ebola we want to develop a prophylactic vaccine
  - Vaccinate “healthy” subjects

Questions in vaccine development

- Is the product safe?

- Does the product induce an immune response?
  - Immunogenicity
  - Persistency of immune response (booster dose needed?)

- Is the product efficacious in preventing the disease?
  - Vaccine efficacy

- Compare to a control group to answer these questions:
  - New Product: Placebo or Vaccine against other disease
  - Existing product: Competitor
  - Control period before vaccination
Phase III Ebola studies

- Liberia: « PREVAIL I » study
  - Double-blind, individually randomized, placebo-controlled

- Guinea: « Ebola ça suffit »
  - Ring vaccination trial (Cluster-randomized, open-label)
  - Immediate versus delayed (21 days) vaccination

- Sierra Leone: « STRIVE » study
  - Open, individually randomized trial with phased introduction of the vaccine (6 months)

Introduction

The PREVAIL I study
  - Study design
  - Randomization and blinding

Contents

- Introduction
- The PREVAIL I study
  - Study design
  - Randomization and blinding
- Data Safety Monitoring Board
- Current status
- Next steps
  - Bridging efficacy from NHP to humans
The PREVAIL I study

- Partnership for Research on Ebola Virus in Liberia
  - NCT02344407
- Phase 2/3
- Randomized, double-blind, placebo-controlled trial
- Two candidate vaccines
  - ChAd3-EBO Z vaccine
  - VSVΔG-ZEBOV vaccine
- Sample size: 28170 subjects
  - ~1500 in a Phase 2 substudy
- Study population: Volunteers ≥ 18 years in West Africa at risk of Ebola infection
- Primary objective: To determine the efficacy and safety of the two vaccines as compared to placebo

Main inclusion/exclusion criteria

- Inclusion criteria
  - Informed consent
  - Age ≥ 18 years
  - Likely to be in the surrounding area of the vaccination center for at least one year

- Exclusion criteria
  - Fever > 38.0º Celsius
  - History of EVD (self-report)
  - Current pregnancy
  - Breast-feeding an infant
  - Any condition which would limit the ability of the participant to meet the requirements of the study protocol (for example, any serious illness)
Study cohort

- Study initiated in existing health facilities in West Africa
- Widespread communication about the trial
  - To encourage volunteers to go to a vaccination center
- Significant outreach efforts
  - Health care workers
  - Other persons likely to have contact with patients with EVD
    - Ambulance drivers
    - Burial crews
  - Efforts will be made to include high risk individuals

Study design overview

Volunteers aged ≥ 18 years
N=26,170

Permuted block randomization

Phase 2 substudy

First 1,500 volunteers at a vaccination center in Monrovia, Liberia
Subsequent 26,670 volunteers

Visits at week 1, month 1, month 6 and month 12; contact at 2, 4, 6 and 10 months for possible EVD and SAEs

Contact at week 1, month 1, month 2, and then every 2 months for possible EVD and SAEs

Follow-up through a common closing date
Statistical design challenges in an Ebola vaccine trial

Study schedule

<table>
<thead>
<tr>
<th></th>
<th>Phase 2 substudy</th>
<th>All (Phase 2 and 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline (Day 0)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Informed consent / Demographics / Contact information / Indicators of increased risk</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Clinical information / Blood sample / HIV pre-counseling</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td><strong>Week 1 and Month 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical information / Blood sample / AEs / HIV and syphilis post-counseling referral</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td><strong>Days 3, 10 and 14</strong></td>
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<td></td>
</tr>
<tr>
<td>Blood sample for VSV viral RNA measurement (subset)</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td><strong>Week 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interview on targeted symptoms and signs (subset)</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td><strong>Month 6 and Month 12</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood sample for immunogenicity testing</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td><strong>Week 1, Month 1, Month 2 and every 2 months afterwards through study end</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EVD events / SAEs / Deaths</td>
<td></td>
<td>x</td>
</tr>
</tbody>
</table>

Rationale for study design

• Randomization implemented in a practical, simple manner
  – Syringes prepared in a central pharmacy
  – For each comparison: blocks were prepared
    • E.g., blocks of 12: 4 ChAd3; 4 VSV; 2 each Placebo

• Design implementation had to be made as simple as possible
  – Urgency setting: phase I--> III; need to embed a phase II
  – Need to have simple procedures (short timeframe)
  – Epidemic setting with deadly disease
    • Data collection thought to be challenging
    • Limit data collection to absolute needs to avoid burden
Rationale for study design

• Experts at the WHO Consultation on Ebola vaccines
  – These two vaccine candidates be rapidly evaluated for their efficacy and safety
  – Without compromising international standards
  – If feasible, randomized controlled trials (RCT) should be the design of choice
    • They would provide the most robust data
    • In the shortest amount of time

• VRBPAC 12 May 2015
  – RCTs would provide the most direct evidence of VE
  – Additional approaches are available and under consideration

• A lot of debate on RCT in context of Ebola
  – Adebamowo C et al., Lancet 2014; 384:1423-4
  – Cox et al., NEJM 2014; 371: 2350-1

Rationale for study design

• Is randomization ethical in the context of Ebola outbreak?
  – Different perspectives in NEJM and Lancet
  – NEJM: « Evaluating Ebola Therapies — The Case for RCTs »
  – Lancet: « Randomised controlled trials for Ebola: practical and ethical issues »

• In the context of prophylactic vaccines:
  – « Healthy » subjects
  – Before Phase III only limited safety and immunogenicity data
  – No evidence of efficacy in humans, only in animal models
  – “Such randomisation is ethical when there is equipoise”
    • When there is genuine uncertainty about whether an untested treatment has benefits or risks that exceed those of conventional care
Randomization and blinding

- **Randomization**
  - Remove the potential bias in treatment assignment (selection bias)
  - Randomization tends to produce comparable groups

- **Blinding**
  - Increase objectivity (assessment bias)
  - Subjective nature of some of the targeted symptoms

Conventional care to prevent Ebola

1. **Protect yourself**
2. **Protect your family**
3. **Protect your community**

From the Ebola virus

**DO**
- Wash hands with soap and water or an alcohol-based hand rub.
- Cover cough or sneeze with a bent elbow or tissue.
- Clean and disinfect frequently touched objects and surfaces.
- Call for help if you are feeling unwell.

**DO NOT**
- Touch the faces or eyes, nose, or mouth.
- Use tobacco products.
- Touch or shake hands with someone who is unwell.
- Drink untreated water and eat food that has not been properly cooked.

**Additional recommendations**
- Wear protective clothing, including a mask, gloves, and a protective suit.
- Wash hands with soap and water or an alcohol-based hand rub.
- Clean and disinfect frequently touched objects and surfaces.
- Call for help if you are feeling unwell.

Let's stop the spread of Ebola together.
Is there equipoise on risks?

- Phase I data available to quantify possible risks
- Study design should not impact on « Conventional care »
- Blinded trial ensures no assessment bias
  - No false-positive feeling of protection
  - No difference in health seeking behaviour
  - Preventive measures will continue to be applied
  - No difference in disease exposure
  - No difference in risk behaviour
- Blinding versus another control vaccine is difficult
  - Hence the placebo-controlled study

Is there equipoise on benefits?

- No evidence of efficacy in humans, only in animal models
- A prior study of a recombinant adenovirus investigational vaccine for HIV
- Unexpected result that those receiving the vaccine had an increased incidence of infection.
- This was despite evidence of protection in the non-human primate model
- This emphasizes the uncertainty in moving from animal studies to human studies

Duerr et al., J. Infect. Dis. 2012; 206:258-66
Primary efficacy endpoint

- Definite EVD occurring 21 days or more following randomization
  - All Ebola cases reviewed by an Endpoint Review Committee (ERC)
  - Classification in Definite (PCR or ELISA test) or Probable EVD

Randomization

21 days
* to account for incubation period
* to induce immunity

Definite EVD

Follow-up period for EVD

Primary analysis

- Modified intention to treat (mITT) using EVD outcomes that occur 21 days or more following randomization
  - ITT will be a sensitivity analysis

- A Cox model for time to EVD to estimate hazard ratio (HR)

- Vaccine efficacy: \( \text{VE} = (1-\text{HR}) \times 100\% \)

- VE for each pair-wise comparison
  - ChAd3 EBO-Z vaccine versus pooled placebo
  - VSVΔG-ZEBOV vaccine versus pooled placebo
Sample size

- 1:1 randomization ratio for each comparison
  - Pooled placebo group (1ml and 2ml)

- Type I error: 0.025 (2-sided) for each comparison
  - Bonferroni correction

- 90% power to detect VE=50% (HR=0.5)

- Freedman formulae: 112 events

\[ d = \frac{(Z_{\alpha/2} + Z_\beta)^2 (HR + 1)^2}{(HR - 1)^2} \]

Sample size

- 1.0% of volunteers in the pooled placebo group will develop EVD after 12 months
- Enrollment period 4 months
- Follow-up period minimum of 8 months
  - average follow-up is 10 months
  - range is 8 to 12 months
- Deaths unrelated to EVD and losses to follow-up will occur at the rate of 1% per month
- 28170 volunteers need to be enrolled
  - 9390 per active vaccine arm
  - 4695 per each of the two placebo groups
- Sample size re-estimation based on blinded data possible
Group sequential methodology

- Agreement to have several interim analyses

- At each interim analysis
  - Test statistic \( Z_k \)
  - Boundary \( B_k \)

- Lan-DeMets method
  - \( \alpha \)-spending approach

\[
B_1 : P(Z_1 > B_1) = \alpha^*(t_1)
\]

\[
B_2 : P(Z_1 \leq B_1, Z_2 > B_2) = \alpha^*(t_2) - \alpha^*(t_1)
\]

\[
B_k : P(Z_1 \leq B_1, Z_2 \leq B_2, \ldots, Z_{k-1} \leq B_{k-1}, Z_k > B_k) = \alpha^*(t_k) - \alpha^*(t_{k-1})
\]

\[
P(\text{Crossing a bound ever}) = \alpha^*(t_1) + (\alpha^*(t_2) - \alpha^*(t_1))
\]

\[
+ \ldots + (\alpha^*(t_K) - \alpha^*(t_{K-1})) = \alpha^*(1) = \alpha
\]
Group sequential methodology

- Two commonly used spending functions

\[ \begin{align*}
\text{Pocock} & : \quad z_n \leq z_{0.025}, \quad z_n \leq z_{0.15}, \quad z_n \leq z_{0.30}, \quad z_n \leq z_{0.41}, \quad z_n \leq z_{0.49}, \quad z_n \leq z_{0.55}, \quad z_n \leq z_{0.60}, \quad z_n \leq z_{0.64} \smallskip \\
\text{O’Brien-Fleming} & : \quad z_n \leq z_{0.05}, \quad z_n \leq z_{0.10}, \quad z_n \leq z_{0.16}, \quad z_n \leq z_{0.30}, \quad z_n \leq z_{0.41}, \quad z_n \leq z_{0.49}, \quad z_n \leq z_{0.55}, \quad z_n \leq z_{0.60}, \quad z_n \leq z_{0.64}
\end{align*} \]

Interim analyses

- 7 interim analyses + final analysis
  - ~12.5%, 25%, 37.5%, 50%, 62.5%, 75% and 87.5%
- Estimated boundaries (HR scale)
Contents

Introduction
The PREVAIL I study
Study design
Randomization and blinding

Data Safety Monitoring Board
Current status
Next steps
Bridging efficacy from NHP to humans

Data monitoring

• Protocol team
  – Blind to interim results by treatment group
  – Monitor enrollment and follow-up of subjects
  – Monitor pooled event rate
    • Make recommendation on sample size re-estimation
    • Request DSMB to convene (e.g., in case of related SAEs)

• Independent Data Safety Monitoring Board (DSMB)
  – DSMB received interim treatment comparisons from unblinded statisticians
  – The protocol team prepared an open report for the DSMB
  – Participated in an open session with the DSMB
Data Safety Monitoring Board

- Will review study design before study initiation
- Will convene every 2-4 weeks
  - Review safety data from substudy
  - Make recommendation of expansion to other sites
  - Review safety throughout the study
  - Review of efficacy data if # cases triggers an analysis
    - Separate for each comparison vaccine versus placebo
    - Flexible Lan-DeMets approach to determine α spent
- DSMB will not communicate whether efficacy data was reviewed
  - Recommend continuing the study as planned
  - or modifying the study
  - or terminating the study

Data Safety Monitoring Board

- Early stopping of one vaccine could impact ability to determine efficacy and safety of other vaccine
  - Pooled placebo group

- E.g., one vaccine is efficacious (boundaries crossed) and the other not
  - DSMB will assess risk/benefit of each vaccine
  - They can recommend to continue the study
    - E.g., increase information on a less effective but safer vaccine
  - Or recommend to stop the study and cross-over to effective vaccine

- Conditional power estimates can be used to guide DSMB
Data Safety Monitoring Board

- Conditional power
  - Probability(Reject $H_0$|data accumulated so far)
- Example: one vaccine has ~30% VE

<table>
<thead>
<tr>
<th>Events</th>
<th>VE</th>
<th>CP_CT</th>
<th>CP_HA</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>0.25</td>
<td>21%</td>
<td>88%</td>
</tr>
<tr>
<td>28</td>
<td>0.25</td>
<td>19%</td>
<td>83%</td>
</tr>
<tr>
<td>42</td>
<td>0.32</td>
<td>38%</td>
<td>83%</td>
</tr>
<tr>
<td>56</td>
<td>0.30303</td>
<td>29%</td>
<td>75%</td>
</tr>
<tr>
<td>70</td>
<td>0.292683</td>
<td>22%</td>
<td>63%</td>
</tr>
<tr>
<td>84</td>
<td>0.285714</td>
<td>14%</td>
<td>44%</td>
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<tr>
<td>98</td>
<td>0.310345</td>
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<td></td>
</tr>
<tr>
<td>112</td>
<td>0.30303</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If CP under alternative (50% VE) < 60%
  - Ask DSMB to recommend stopping study
  - Releasing the data on the efficacious vaccine
  - CP under current trend will also be considered
Data Safety Monitoring Board

- If one vaccine has an unacceptable rate of SAEs or a rate of EVD and/or all-cause mortality greater than placebo
  - Enrollment to that arm will be terminated
  - Allocation will be 1:1 for subsequent enrolments to the other vaccine and placebo

- The DSMB is provided with these guidelines (not rules)

- DSMB will use their expert and independent judgment
  - Concerning early termination of one of the vaccine arms
  - Not every situation can be foreseen
    - Consistency of primary endpoint findings in subgroups
    - Treatment differences for major secondary outcomes
Statistical design challenges in an Ebola vaccine trial

http://www.who.org

Situation over time

http://www.who.org

Latest situation reports

Copyright World Health Organization (WHO), 2014

http://www.who.org
Current status

• Study started 2 February 2015
• Recommendation for expansion on 20 March 2015
• Because of Liberia being ebola-free, no expansion to Phase III part of the study

http://www.nydailynews.com/

Contents

• Introduction
  The PREVAIL I study
    Study design
    Randomization and blinding
  Data Safety Monitoring Board
  Current status

Next steps
  Bridging efficacy from NHP to humans
**Next steps**

- December 2014 FDA Workshop
- VRBPAC May 2015
  - If phase 3 clinical trials yield inconclusive results (due to low Ebola virus attack rates or other factors), the FDA may need to consider other approaches to demonstrating effectiveness for licensure
  - Preliminary results of Ebola vaccines suggest the vaccines can induce human immune responses at levels comparable to protective responses in NHPs
  - NHP studies are important for evaluating mechanisms of protection and for mimicking human infections

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**Guinea trial showed efficacy**

Efficacy and effectiveness of an rVSV-vectored vaccine expressing Ebola surface glycoprotein: interim results from the Guinea ring vaccination cluster-randomised trial

Anonymous authors

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Statistical design challenges in an Ebola vaccine trial
Bridging NHP to human efficacy

- Logistic regression in NHP
- Average predicted protection level in humans (%)

Fig. 5. Graphical representation of first row in Table 3: Orange logistic line is the predicted survival based on setting 3 (rabbits). The lines going from the horizontal axis to the logistic curve, then to the vertical axis represent the TNA values for the 29 cyna monkeys in setting 5. Random noise was added to the lines close to TNA = 1.5 half the limit of detections, and those lines represent eight monkeys, five that died and three that survived. The dark blue tick on the vertical axis represents the mean predicted survival (95%) for cyna monkeys based on rabit efficacy data.

Statistical design challenges in an Ebola vaccine trial

Bridging NHP to human efficacy

- Challenges
  - Humans and NHP may need different vaccine doses to reach comparable immune response
  - Generate a relatively wide range of antibody titers
  - Avoid that all NHP survive or die

- A Bayesian adaptive design was implemented to overcome these challenges
Statistical design challenges in an Ebola vaccine trial

- 4-step Bayesian adaptive design

- After each step:
  - Evaluate survival rate
  - Evaluate antibody titers
  - Adapt #NHP/dose for next step
    - Standard error of the slope
    - Survival rate

Bridging NHP to human efficacy

- Logistic regression
  \[ \log\left(\frac{\pi}{1-\pi}\right) = \alpha + \beta \log(\text{titer}) \]
  \[ \alpha \sim N(\theta_0, \alpha, \theta_1, \alpha) \]
  \[ \beta \sim N(\theta_0, \beta, \theta_1, \beta) \]

- ANOVA model
  \[ \log(\text{titer})|\text{dose} \sim N(\mu_{\text{dose}}, \sigma^2_{\text{dose}}) \]
  \[ \mu_{\text{dose}} \sim N(\theta_0, \mu, \theta_1, \mu) \]
  \[ \sigma^2_{\text{dose}} \sim \Gamma(\theta_0, \sigma^2, \theta_1, \sigma^2) \]
Bridging NHP to human efficacy

- Desirability approach

![Graph showing survival rate and precision slope]

- Overall desirability used to determine dose allocation

Next dose allocation

- Simulate next step based on what we know
- The scenarios are:

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Dose 1</th>
<th>Dose 2</th>
<th>Dose 3</th>
<th>Relationship</th>
<th>Survival</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
<td>11</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>2</td>
<td>10</td>
<td>?</td>
<td>?</td>
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<tr>
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<td>1</td>
<td>3</td>
<td>9</td>
<td>?</td>
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<td>...</td>
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</tbody>
</table>

- Select the one that would give the best compromise between quality of the fit and a survival rate close to 50%
Conclusion

- PREVAIL I Phase 2/3 study
- Phase 3 part not yet started due to Liberia ebola-free
- One vaccine shown to be efficacious in another Phase III
- Other vaccine bridging from NHP to human efficacy

Acknowledgements

- Liberian partners and collaborators
  - Ministry of Health
  - Liberia Institute for Biomedical Research
  - University of Liberia
  - Residents and community leaders of New Kru Town/Monrovia
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  - NIH/NIAID
  - University of Minnesota
  - Leidos Biomedical Research
  - Centers for Disease Control
  - US Public Health Service
  - Volunteers from throughout NIH Institutes and Centers
  - US Department of State
  - US Department of Defense
  - Vaccine Research Center
- Industry partners and collaborators
  - GSK
  - NewLink/Merck
- FDA CBER for guidance and discussions