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A Response Adaptive Randomization Platform Trial for Efficient Evaluation of Ebola Virus Treatments: A Model for Pandemic Response

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Abstract

The outbreak of Ebola Virus Disease (EVD) in West Africa is the largest ever recorded. Numerous treatment alternatives for EVD have been considered, including widely available re-purposed drugs, but initiation of enrollment into clinical trials has been limited.

The proposed trial is an adaptive platform design. Multiple agents and combinations will be investigated simultaneously. Additionally, new agents may enter the trial as they become available, and failing agents may be removed. In order to accommodate the many possible agents and combinations, a critical feature of this design is the use of response adaptive randomization to assign treatment regimens. As the trial progresses, the randomization ratio evolves to favor the arms that are performing better, making the design also suitable for all-cause pandemic preparedness planning.

The study was approved by US and Sierra Leone ethics committees, and reviewed by the US FDA. Additionally, data management, drug supply lines, and local sites were prepared. However, in response to the declining epidemic seen in February 2015, the trial was not initiated. Sierra Leone remains ready to rapidly activate the protocol as an emergency response trial in the event of a resurgence of EVD.

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In summary, we have designed a single controlled trial capable of efficiently identifying highly effective or failing regimens among a rapidly evolving list of proposed therapeutic alternatives for EVD and to treat the patients within the trial effectively based on accruing data. Provision of these regimens, if found safe and effective, would have a major impact on future epidemics by providing effective treatment options.

Introduction

The recent outbreak of EVD has since ravaged multiple countries in West Africa,[1,2] spreading to Liberia, Sierra Leone, Nigeria, Senegal, and Mali, with cases exported to the United States,[3,4] Italy,[5] Spain,[6] and the United Kingdom. It is the largest EVD outbreak ever recorded, with greater than 27,000 confirmed cases and more than 11,000 deaths.

At the beginning of the outbreak, there were no licensed therapies for EVD and this remains the case almost two years later. Passive infusion of plasma or concentrated IgG derived from recovered patients may improve survival, and a number of studies were initiated in late 2014 to evaluate convalescent plasma or whole blood infusions.[4,7–11] There are also several products for which there is preclinical evidence of efficacy against Ebola and other filoviruses, including antiviral drugs, monoclonal antibodies and small inhibitory RNAs.[12–20] In addition to the few EVD-specific agents, a number of potential therapeutics not developed for Ebola, but with possible antiviral properties were hoped to improve EVD patient survival. The advantage of such “repurposed” drugs is that they have well-defined safety profiles, and are usually inexpensive and may be widely available in generic formulations. Many of these candidates were identified in large-scale systems biology screens of libraries of existing drugs and were found to have antiviral effects in *in vitro* assays. Several of the candidates are already marketed as antiviral agents,[16,21] while others are marketed for very different purposes (e.g., anti-depressants[12] and anti-neoplastics[22]). Still other candidates, such as statins, have been put forward as candidates based on the suggestion that they may provide physiological support by stabilizing damaged endothelium.[23–25]

Clinical trials for EVD are only possible during an epidemic, when conditions are often not conducive to protocol implementation. As such, protocols should yield results efficiently and rapidly, and they must be acceptable to both those providing and receiving care and to the communities where the studies are implemented. This multi-arm trial was designed to evaluate the efficacy and safety of multiple therapeutic regimens, both as mono-therapy and as combination treatments, in order to identify successful or failing regimens faster than traditional models.

An adaptive design allows the pre-specification of flexible components, such as the treatment arms used (dose, frequency, duration, combinations, etc.), allocation to the different treatment arms, patient population, and sample size. Other adaptive designs have been proposed for use during this outbreak.[26,27] We propose an alternative adaptive platform trial utilizing a response adaptive randomization strategy which learns from the accruing data what the most therapeutic doses or arms are, allowing it to hone in on the best arms. This design can allow the trial to start with a wider range of doses, using a smaller number

of patients. Similar trial designs have been recently used to study diseases such as breast cancer and Alzheimer's.[28]

Methods

Statistical Design

The proposed design is an adaptive platform trial. A platform trial is built with the flexibility to incorporate multiple treatment arms. This trial is built to be perpetual, in that there is no maximum sample size. The platform will run as long as needed. A generic structure allows for any number of available treatment arms. New agents can be added or agents can be removed from the platform seamlessly, according to the protocol. The assignment of the different treatment arms in the trial is controlled by a central statistical model estimating the relative efficacy of each treatment arm based on the accruing data in the platform trial. In this section, we describe the details of the design and the statistical model. The behavior of the trial is investigated using clinical trial simulations. These simulations are described in this section.

Each patient will be randomized to a treatment regimen. A regimen is either a single experimental agent or a combination of two experimental agents. As the trial progresses the available experimental agents and thus available regimens may evolve. Experimental agents will be classified as primary or secondary agents. A primary agent is considered to be potentially beneficial as a single-agent, while a secondary agent is potentially beneficial as an additive to a primary agent. The following rules dictate the design behavior of primary and secondary agents:

1. A primary agent can be assigned as a single-agent regimen.
2. Two primary agents can be combined together to form a regimen.
3. A secondary agent can be added to a primary agent to form a regimen
4. A secondary agent cannot be used as a single-agent, nor be added to a secondary agent to form a regimen.

For example, if there are 4 primary agents and 2 secondary agents then there are 6 combinations of 2 primary agents, 4 single-agent regimens, and 8 combinations of a primary and a secondary, for 18 regimens. Table 1 shows the possible combinations for this scenario (P represents a primary agent and S an secondary).

Additional constraints may be placed on experimental agents that restrict the possible combinations.

Randomization

The trial has two distinct stages of randomization. In the first stage, a fixed randomization scheme is used. Commonly referred to as the 'burn-in stage', the randomization will be 50% to the single primary agents and 50% equally distributed among the combination regimens. If there is a standard of care arm it will be considered a primary agent, and as is explained in the Standard of Care Section will receive a minimum of 20% randomization. When at least

20 patients have passed through the assigned window for determining the primary endpoint (14 days), the trial will enter the perpetual response adaptive randomization stage.

A probability for each of the treatment regimens is created and this randomization is used for all patients during the following week. Every week the full data for the trial on the primary outcome are updated and new randomization probabilities are created for the following week. This cycle continues with new randomization probabilities being created each week until the trial is halted. The probability for each regimen is proportional to the probability that each regimen is optimal, adjusted for the amount of data on that regimen. The details of the response adaptive randomization are presented in the Modeling section.

Adaptive Agent Determination—During the platform trial, individual agents can be determined to be superior or futile. If an agent is found to be superior, the Therapeutic Evaluation Committee will determine the action in the trial. The committee could determine that the trial continues unchanged (where the agent is being given with high probability) or the superior agent could become a basis for all regimens and be given to all patients. If the probability that a single agent is a member of the optimal regimen is at least 0.95, then an agent will be considered superior. The determination of superiority will be reported to the committee and public dissemination of the superiority will be made.

If an agent is found to have a probability of less than 0.01 that it is in the optimal regimen, then the agent will be considered futile. In this case, the committee will determine the action to take. The agent may still be kept in the platform if it is deemed important to be used in combination with other new agents, or the agent may be completely removed from the platform.

Standard of Care—A standard of care arm was felt to be essential to the study design and included in this protocol. The platform can handle a standard of care arm, where the following special rules are adopted. A minimum randomization of 20% for the standard of care arm is adopted for the duration of the study that this arm is included. If one of the comparator regimens has at least a 95% probability of being superior to standard of care, then the standard of care arm will be removed from the platform trial. The steering committee could add a new standard of care arm if deemed needed, otherwise the platform will run without a standard of care arm.

Modeling—The adaptive actions of the trial, both the adaptive randomization and the adaptive decisions on agents, are determined by a single statistical model. This section describes the statistical model used to analyze the constantly accruing results. We label the active agents as t=1,…,k. Without loss of generality, we assume the first p of these agents are primary and the last s are secondary (p+s=k). These experimental agents can be combined together to form a treatment regimen. For ease of notation we refer to the regimen as $\boldsymbol{r_{ij}}$ where this implies the combination of active agents i and j, and $\boldsymbol{r_{ii}}$ refers to using the single active treatment i. Without loss of generality we assume j≥i (r_{ij} *is the same as* r_{ji}).

The probability of mortality for a single patient is modeled as a function of the treatment regimen assignment. We model the probability of mortality, $\boldsymbol{\pi_{ij}}$, when assigned to regimen $\boldsymbol{r_{ij}}$ as

$$log\left(\frac{\pi_{ij}}{1-\pi_{ij}}\right)=\begin{cases}\alpha+\beta_i & i=j\\ \alpha+\beta_i+\beta_j+\delta_{ij} & i\neq j\end{cases}$$

The following prior distributions for each of the parameters are used.

$$[\alpha]\sim N(-0.405,2^2),$$

$$[\beta_t]\sim N(0,1^2)\,for\,t=1,\ldots,k$$

and

$$[\delta_{ij}]\sim N(0,0.2^2)\,for\,(i,j)\text{:j>i, i}\leq\text{p.}$$

For any given set of trial results on the number of patients and deaths, the posterior distribution of the model is calculated using standard Markov chain Monte Carlo algorithms. This model is then used to drive the adaptive randomization.

At every interim the posterior probability that each regimen is the optimal regimen is calculated. For each regimen, this is

$$O_{ij}=Pr\,(\pi_{ij}<\pi_{mn}\ for\,all\,(m,n)\neq(i,j))$$

The probability that a single treatment regimen is in the optimal regimen is an important parameter for success. It may be that the single optimal regimen is unknown, but an experimental arm is highly likely to be in the optimal regimen. We calculate the probability that an experimental arm, t, is a part of the optimal regimen:

$$A_t=O_{tt}+\sum_{j=t+1}^{k}O_{tj}+\sum_{i=1}^{t-1}O_{it}.$$

In addition the posterior mean $\boldsymbol{E(\pi_{ij})}$ and variance $\boldsymbol{V(\pi_{ij})}$ of the probability of death for each regimen are calculated. The sample size for a regimen is labeled as $\boldsymbol{n_{ij}}$.

If the platform contains a standard of care arm then we model the probability of mortality under the standard of care, i=0, as

$$log\left(\frac{\pi_0}{1-\pi_0}\right)=\alpha.$$

In this framework, a standard of care arm could be included, seamlessly, with the ability to calculate the probability a regimen is superior to standard of care. The model could easily incorporate different covariates if they emerged during the course of the trial. The expectation is that the rate of death could change during the course of the trial, and hence a prospective model has been set up to treat each month as a covariate and estimate the possible drift over time in mortality rate while allowing the continual balanced estimate of treatment effects even if their randomization rates vary over time.

Simulations—In order to understand the behavior and operating characteristics of this platform trial, clinical trial simulations are conducted. These “in silico” trials allow the calculation of the operating characteristics under different assumptions. The operating characteristics depend on the number of experimental agents, the sample size, the length of the trial, and the true efficacy of each of the possible combinations. In this section, we present a set of these simulations, including the assumptions made, and the scenarios explored. A much larger set of simulated trials was explored in the building of the trial.

In order to simulate the trial, certain assumptions on the trial conduct are made. We assume that the first 30 patients are randomized equally likely to each arm. At this point the model is fit and adaptive randomization begins. Each trial is simulated out to a maximum sample size (varied) to understand the behavior for different sample sizes. It is assumed that there are 10 subjects enrolled each week, and there is always a lag of 20 subjects of data (in the period from randomization until death outcome known). So, every update of the model is done with a lag of 20 patients with unknown results. Results are updated every 10 patients.

The probability of mortality for each regimen is varied to explore the design under different possible truths. For each scenario 5000 simulated trials are conducted and the results of these trials presented.

In this section, we simulate a trial in which there are 4 primary experimental agents and 2 secondary experimental agents. As presented in Table 1 there are 18 treatment regimens available in the trial.

Initially, we present the operating characteristics for a scenario in which there is a 25% absolute advantage in the rate of mortality for a single experimental agent. A maximum sample size of 250 is assumed. Table 2 shows the assumptions that are made about the efficacy of each treatment arm.

Each trial is simulated 5000 times. Table 3 presents the mean sample size for each treatment regimen, the proportion of trials in which an arm is selected as part of the optimal regimen, and the proportion of trials in which an agent is declared superior.

Out of 250 patients an average of 186.7 (74.7%) of patients are randomized to a regimen that contains P1. If randomization were equally assigned to the 18 cells, then a mean of only 83.3 patients would be assigned to a regimen with P1 (33%). With adaptive randomization, a mean of 53.2 patients die (21.2%), in contrast to an equal randomization schedule in which a mean of 79.2 patients die (31.7%).

At the completion of the trial, a single regimen is labeled as the most likely best regimen. Table 3 presents the proportion of simulated trials that an agent is in the most likely optimal regimen. The effective agent, P1, is in 100% of the most likely optimal regimens (meaning in 100% of the trials it is most likely to be in the optimal regimen). The trial definition of a successful agent (statistically superior) is when there is at least a 95% chance that an agent is part of the optimal regimen. Table 3 presents the proportion of simulated trials that an experimental agent is statistically superior. In the scenario where there is a single experimental agent that has a 25% absolute improvement in the rate of mortality and 250 patients enrolled, there is a 95.8% chance (power) that experimental agent P1 will be identified as effective during the trial.

Range of Effect Sizes—Given the variable sample size of this perpetual platform trial, we simulate the trial with maximum sample sizes ranging from 100 to 400 patients. In addition, we vary the absolute benefit for experimental agent P1 from 0% absolute benefit to 30% absolute benefit. All regimens without P1 are assumed to have a 40% mortality rate. Table 4 presents the power of the platform trial to identify P1 as a statistically superior agent, for the absolute effect size specified in the row, and the trial sample size specified in the column. Figure 1 presents the same power numbers as Table 4 with each color representing an assumed mortality rate for P1 and the x-axis the trial sample size.

When the perpetual platform trial sample size is 200 or larger it would have at least 90% power to identify a single agent as statistically superior when it has a 25% absolute decrease in the case-fatality rate. The power is 79.3% to detect a 20% absolute decrease in the rate of mortality (from a 40% background case-fatality rate) when the sample size is 250 or larger. The likelihood of identifying P1 as statically superior when it is equivalent to all other agents ranges between 1.1% and 2.8% over a sample size range of 100 to 400. This type I error probability for the primary agent is less than 5% over the range of sample sizes. This is illustrated in Figure 1. The appendix to this paper presents additional operating characteristics.

Operational Considerations

Selection of Therapeutic Agents—One of the most complex decisions for the study is the selection of therapeutic agents to be included at the protocol's initiation. Because many of these agents are undergoing evaluation in a variety of *in vivo* models to ascertain efficacy, a Therapeutic Evaluation Committee) was needed to review available *in vitro* and *in vivo* data, available clinical data (if any), supporting pharmacokinetic data, and to deliberate with therapeutic experts. As more data become known, and new therapeutic agents become of interest, the committee makes additional decisions on adding new regimens. Between December 2014 and February 2015, the following agents were considered for possible inclusion into the trial: atorvastatin/irbesartan, azithromycin, brincidofovir, chloroquine, erlotinib/suntinib, and favipiravir.

The study proposed the use of three committees:

- Therapeutic Evaluation Committee, who was tasked with selecting an initial set of treatment, reviewing the algorithm outcome data (i.e., outcome probabilities)

as soon as it is available to assess for regimen failure, and assessing additional treatment agents for inclusion in the study.

- Statistical Analysis Committee, who will oversee the randomization algorithm to ensure it is functioning correctly and appropriately, as well as update it based on the revised randomization probabilities concluded from the weekly analyses.
- Data Safety Monitoring Board, who will meet at least every 4 weeks to assess safety and study data.

Adding New Study Agents—When the therapeutic evaluation committee adds an agent to the trial it must specify whether the agent is a stand-alone (primary) or adjunctive (secondary) agent, and any additional constraints on the possible combinations with other primary or secondary agents. The trial, including the statistical algorithms, is designed generically in order to allow a seamless expansion of the arms available. The new arm will be added to the trial and included in the statistical modeling when available.

Several factors were assessed in order to determine whether to include new study agents, including:

- Safety record, to include common side effects
- *In vitro* data and any available *in vivo* efficacy data against Ebola virus
- Assessment of long term availability in Africa
- Cost of treatments
- Availability of study agent(s)
- Storage requirements and expiration time frames
- Possible effects of new study agents to the algorithm
- Potential additive effects of new combination treatments

Dropping a Failing Study Agent—At every interim analysis during the trial, the probability that an agent is a part of the optimal treatment regimen will be calculated. If the probability that an agent is a part of the optimal regimen drops below 1%, the agent will be removed from the trial. When an agent reaches a futility stopping decision it will be presented to the therapeutic evaluation committee for determination of the actual removal.

Discussion

The proposed platform trial provides a single protocol for simultaneous comparison of multiple therapies and their combinations. As demonstrated here, if four primary agents and 2 secondary agents are explored within the platform trial, it would allow an efficient way to find the best of 10 different treatment arms. This occurs in a single experiment, as opposed to trying to perform meta-analyses across heterogeneous trials to compare different treatments. With standard development strategies, this would be accomplished in successive trials, which address only single comparisons. For example, the multiple arms, multiple stages (MAMS) approach[27] runs separate trials and discrete stages. This trial includes all

arms simultaneously, making continuous adaptions throughout the length of the trial. In such a typical scenario, by the time the trial ends, these questions are often no longer relevant. The proposed platform trial provides rapid and relevant conclusions as it runs. In order to be efficient in exploring multiple treatments and combinations, adaptive design strategies are employed. Response adaptive randomization allows the ability to allocate more participants to those arms that are performing more effectively on a specified endpoint, thus increasing the likelihood that a research participant will benefit from the study and affording greater opportunities to differentiate between the best treatments. Conducting frequent interim analyses to update randomization probabilities, while also including evolving treatment arms is critical to efficiently evaluating a wide spectrum of potential effective interventions. The statistical algorithm driving the adaptations is Bayesian in nature. The Bayesian approach is ideal for handling frequent interim analyses and continuous trial adjustments. A key feature of this algorithm is the modeling of the possible drift in the patient distribution over time. Each month is modeled as a separate time bucket, allowing the single trial to utilize all data from the trial in drawing conclusions between arms.

At the time of the outbreak, ethics committees in the affected countries were overwhelmed by study submissions, since many of the committees are composed of physicians who were simultaneously caring for patients, reviewing protocols and trying to uphold ethical and regulatory guidelines. In order to efficiently conduct an emergency preparedness protocol such as this one, the protocol would optimally be reviewed and approved before an outbreak, with engagement with ethics committees and regulatory authorities occurring in a thoughtful and measured setting. Difficult questions around complex study designs or appropriateness of study arms could be discussed well in advance and ideally only minor study modifications would be necessary prior to finalization.

In designing a treatment trial for an infectious disease with no known effective treatment, we felt there was a moral obligation to include possible treatments for a broad population, including vulnerable groups such as children and infants, and pregnant women. This trial design allows for selective randomization safety rules to be programmed into the algorithms, such that children under a specific age or weight, or pregnant women, could be randomized only to regimens that had been deemed safe by previous studies. In this way, we were able to make the study population as broadly encompassing as possible. Similarly, some drugs had known safety concerns in certain populations, (e.g. use of irbesartan in patients with renal failure), and the design has the ability to accommodate this safety restriction.

A major concern during trial design was the lack of consistent infrastructure such as water, phone lines and electricity. This had impact on both randomization procedures, and also data entry. Response adaptive randomization is highly dependent upon rapid feedback of the primary endpoint, and so possible solutions included having multiple methods for completion of randomization procedures, such as provision of satellite phones, online randomization options (when internet was available) and also manual randomization envelopes (to be used when both phone lines and internet were unavailable). Additionally, the team planned that sites would complete paper case report forms by hand and then scan and upload them to a secure file transfer protocol site, where the data would be downloaded by data entry staff in the US, and then manually entered into the study database.

The lack of an available standard of care in many Ebola Treatment Units was also problematic. It would have been unethical to implement the study at a site where the only available standard of care was oral rehydration, whereas enrolled study patients would receive intravenous fluids, laboratory monitoring and medications. For these reasons, the study team agreed that a basic level of standard of care would need to be available to all patients in the unit, regardless of whether they agreed to participate. This would include: intravenous fluids, concomitant medications such as pain relief and anti-emetics, as well as laboratory monitoring. In this scenario, study patients would then only be offered the addition of investigational treatment medications.

The ability to use newly discovered Ebola therapeutics for compassionate use provided the option of bringing new compounds into the study. Supply and demand was more of a concern for new therapeutics since manufacturing is often not scaled up until there is solid evidence that the drug is efficacious, and in some instances is simply process dependent (e.g. Zmapp). Lack of supply may therefore require closure or suspension of specific randomization arms, but this contingency is both operationally and statistically viable within this study design. Notably, manufacturers with new drugs or those seeking an indication change, often require more information than would be otherwise collected during an emergency use trial, including gradual increases in dosing, more extensive lab testing and pharmacokinetic sampling. Depending on the severity of the disease and the tempo of the outbreak, the adaptive design could easily accommodate either type of trial (registrational or emergency treatment), and would still be more efficient than the usual fixed randomization approach.

Finally, we considered other important ethical and operational concerns in designing this trial, specifically related to evaluation of new therapies during an outbreak:

- Quality drug supply. The apparent high number of counterfeit drugs sold in West Africa. The study team researched sources from multiple countries in order to be able to cost effectively obtain each of the regimens.
- Ability to obtain informed consent. It is often the most severely ill patients that such a trial would seek to enroll, yet these patients are often unable to provide consent. Appropriate national and/or local IRB review and approval of the protocol and informed consent form is crucial for ensuring consistency with community values and internationally accepted ethical principles.
- Adverse event reporting. Given that EVD is a multisystem, complex and frequently fatal infectious disease, recording of individual adverse events might be required by regulatory authorities if the trial was used to support an IND, and this approach would place significant added time and personnel burdens on the enrolling sites. For all these reasons, risks and benefits of the decision to include new therapeutics (especially those requiring operational changes) should be carefully considered, and ideally discussions with manufacturers would occur well in advance of an outbreak.

Application for Pandemic Situations

The platform trial design presented here was optimized for the Ebola outbreak, but has much larger applications as a general purpose trial design for the next pandemic. Such a trial can be constructed ahead of time, with pre-prepared protocol, algorithms, and infrastructure ready for an outbreak. This would enable rapid deployment of a very flexible trial design, with the ability to study multiple agents and combinations effectively and efficiently. The design can also be tailored very quickly to the unique requirements of an individual outbreak. For example, combinations can be excluded if needed, a standard of care could be included or not, and the decision points of the trial can be selected based on the pre-existing science. Pre-created software can be created in order to simulate the trial under different scenarios for a new outbreak to quickly optimize the trial design.

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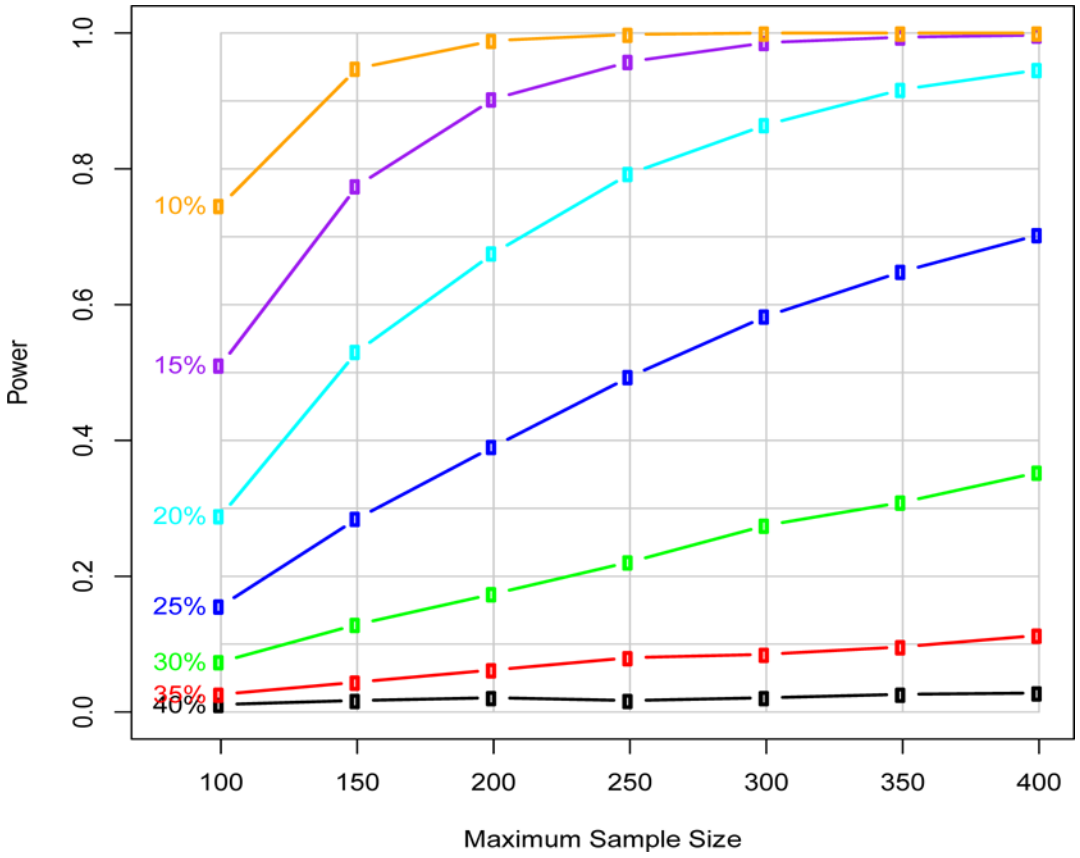

Figure 1.

Table 1

The possible combinations assuming a hypothetical state of the trial with 4 primary agents (P) and 2 secondary agents (S). The green squares are single agent combinations, the yellow are two-paired primary agent, and the blue are a primary and a secondary agent.

Regimens		Treatments					
		P1	P2	P3	P4	S1	S2
Treatments	P1						
	P2						
	P3						
	P4						

Table 2

The assumed rate of mortality for each primary (P) or secondary (S) treatment regimen is reported in each cell. Each cell represents the combination of two agents (or a single-agent when the row and columns are identical (for example, P1, P1).

Assumed Rates of Mortality		Treatments					
		P1	**P2**	**P3**	**P4**	**S1**	**S2**
Treatments	P1	0.15	0.15	0.15	0.15	0.15	0.15
	P2		0.40	0.40	0.40	0.40	0.40
	P3			0.40	0.40	0.40	0.40
	P4				0.40	0.40	0.40

Table 3

The mean sample size for each treatment regimen based on 250 total patients. The Optimal Regimen row presents the proportion of trials in which the agent is part of the most likely optimal regimen. The last row, Statistical Success, reports the proportion of trials in which the experimental agent was found statistically superior.

Operating Characteristics		Treatments					
		P1	**P2**	**P3**	**P4**	**S1**	**S2**
Treatments	P1	26.7	31.3	32.0	31.9	32.4	32.5
	P2		5.6	5.7	5.7	4.8	4.8
	P3			5.7	5.7	4.9	4.8
	P4				5.7	4.9	4.9
Arm Total		186.7	57.9	58.8	58.8	46.9	47.1
Optimal Regimen		1.00	0.167	0.175	0.173	0.198	0.191
Statistical Success		0.958	0.001	0.003	0.002	0.002	0.002

Table 4

The proportion of trials in which the experimental agent P1 is found to be statistically superior for the assumed mortality rates (absolute benefits from 0 to 30%) and trial sample sizes from 100 to 400. Figure 1 presents the same power numbers as this table.

Mortality Rate		Trial Sample Size						
Regimen with P1	**All other regimens**	**100**	**150**	**200**	**250**	**300**	**350**	**400**
40%	40%	0.011	0.017	0.021	0.017	0.021	0.026	0.028
35%	40%	0.026	0.044	0.062	0.080	0.085	0.096	0.113
30%	40%	0.074	0.129	0.174	0.221	0.275	0.309	0.353
25%	40%	0.156	0.285	0.391	0.494	0.583	0.649	0.703
20%	40%	0.289	0.531	0.676	0.793	0.865	0.917	0.946
15%	40%	0.511	0.775	0.903	0.958	0.986	0.994	0.997
10%	40%	0.746	0.948	0.989	0.998	1	1	1