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Models of Phase 1 vaccine trials: optimization of trial design to minimize risks of multiple serious adverse events

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Abstract

A mathematical model of Phase 1 vaccine trial design was used to investigate strategies for minimizing the number of serious adverse events (SAEs) that could be encountered in the first Phase 1 trials of new vaccine formulations. For a relatively standard dose escalation trial with three dose groups each with 10 subjects, an optimal balanced between risk of more than one serious adverse event and trial design is achieved by splitting each dose group into two subgroups of three and seven. Based on the modeling, for a two vaccination, dose-escalating Phase 1 trial, a design where all subjects receive the first vaccination before any subject receives a second vaccination generally carries a lower risk of multiple serious adverse events than other designs.

Keywords: Trial design; Serious adverse event; Dose; Computer simulation; Mathematical model

1. Introduction

There are a number of dilemmas facing the design of a Phase 1 vaccine trial for the first time a formulation will be tested in humans. Although the formulation will have undergone extensive toxicology and immunogenicity studies in animal models, the required dose and the risk of vaccine related, serious adverse events (SAEs) in humans cannot be known with certainty. Vaccine testing is perhaps more uncertain than most initial human drug trials since the both the desired response and the likely adverse events are both related to the idiosyncrasies of the human immune system and are not readily predicable from animal trials [1].

Although local reactogenicity is common, vaccine related serious adverse events are rare in Phase 1 vaccine trials. However, there is always an unknown risk associated with early stage trials, especially if they involve novel adjuvants. For example, the first time a Montanide ISA720 adjuvanted vaccine was used in humans, many of the subjects developed a painful swelling at the injection site approximately 10 days after the first vaccination [2]. This reaction had not been seen in extensive preclinical animal studies, nor was it seen in human studies with the adjuvant alone [3]. Although this trial followed a commonly used protocol with three groups of 10 subjects, it provided a warning that better trial design could have minimized the risk to subjects: two groups of ten subjects had received their first vaccination before any of these adverse events were seen in the first group. Fortunately, none of these adverse events were serious. Had they been more serious, potentially 20 subjects could have experienced a serious adverse event.

Several strategies can be adopted to minimize the risk, especially the risk of having multiple serious adverse events. These include conservative dose escalation trials that have two potential attractions:

1. At lower doses, the intensity and frequency of adverse events may give a warning that higher doses should not be used.
2. The probability of a serious adverse event is likely to be dose related, so that there is a reasonable chance that a single serious adverse event may be seen at a low dose before

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vaccination of high dose groups in which the frequency results in multiple serious adverse events.

While such steps may minimize risk, for a novel vaccine with unknown risks, it is essentially impossible to prevent at least one serious adverse event from being recorded should the vaccine have an unexpected toxicity or severe reactogenicity.

Phase 1 trials are often described as purely safety studies. However, there is no point in testing the safety unless the dose likely to result in protective, or therapeutic response. As this cannot be known in advance, even in the first Phase 1 study of a new formulation, the aim is to establish a safe balance between adverse events and immunogenicity. It is important to acknowledge this, since the group sizes necessary to determine immunogenicity of the vaccine during the dose escalation are likely to impact the design considerations for safety. For example, power calculations based on the distribution of immune responses in several recent trials of recombinant malaria proteins suggest that 10 subjects per dose are required to give an 80% power of detecting a four-fold difference in immune response between groups [2,4]. Except where stated, the analysis in this paper based on a group size of 10.

Although there has been considerable recent developments in the design of Phase 1 drug trials, particularly for determining the maximum tolerated dose for chemotherapy in cancer patients, there has been surprisingly little discussion on the optimal design for Phase 1 trials of prophylactic vaccines in well subjects [5]. The aim of this paper is to provide a tool to assist in the design of Phase 1 vaccine trials to minimize the risks of having multiple serious adverse events.

2. Model

A model of a dose escalating vaccine trial has been generated with the subjects in each group begin vaccinated effectively simultaneously, but the groups separated by sufficient time that any vaccine related serious adverse events from one group would be detected prior to the next group being vaccinated. The model assumes that the trial would be stopped if any SAE are detected. The output of the model is the probability that 0, 1, 2, 3 . . . SAE would be detected. Within a single group, it is assumed that the number of subjects experiencing an SAE will be a binomial distribution with a probability dependent on the vaccine dose and prior vaccination history. Although preclinical trials generally ensure that risk in Phase 1 studies is low, never the less, for the first time a vaccine is used in a human Phase 1 trial, there are several factors that cannot be known. These include

1. The probability per person of an SAE on the first immunization at the lowest dose. In the analysis of this model, a range of probabilities from $<10^{-5}$ to 0.99 has been explored.
2. The function that describes the changing risk with increasing dose. As described in Table 1, a two parameter hyperbolic function has been used to model the dose-risk function. With this function, risk always increases with dose, but the shape of this dose-risk function can be varied from almost flat to a step function. In the analysis of the model, the range of dose- risk functions used is shown in Fig. 1.
3. Where the same subjects are vaccinated more than once (as is usual), the changing risk on subsequent vaccinations. As shown in Table 1, a boosting risk factor has been used to describe the increased or decreased risk on subsequent vaccinations. In this model, the boosting risk factor is independent of the dose. As the probability of an SAE on subsequent vaccinations must have an upper limit of 1, the probability of SAE on subsequent vaccinations cannot be simply the probability on the first vaccination times a constant relative risk. In the function chosen for this model (Table 1), if the first vaccination carries a low risk, then the boosting risk factor for the second injection is the relative risk for that injection compared to the first injection.

Table 1
Definition of parameters in the model

Dose group	All subjects who receive the same dose of vaccine
Dose subgroup	Each dose group may be split into two or more subgroups. All members of a subgroup are vaccinated at the same time. Each subgroup may be vaccinated multiple times, depending on the regimen
Vaccination group	Each time each subgroup is vaccinated, it constitutes a new vaccination group. Thus, the number of vaccination groups in a trial is the number of subgroups times the number of times each are vaccinated
g	A vaccine trial consists of g vaccination groups
n_i	Number of subjects in group i
k	Number of SAE recorded in a trial
P_k	Probability of recording exactly k serious adverse events
s_i	Probability per person of experiencing a serious adverse events on vaccination in group i $s_i = 1 - (1/((a/d_i)^b + 1))^r$
d_i	Vaccine dose for group i
a, b	Parameters that link dose and probability of SAE. b determines the steepness of the relationship between dose and adverse event. As $b \to 0$, probability becomes dose independent. As $b \to 4$ relationship becomes a step function. For $d = a$, the probability per person of an SAE is 0.5
r	Boosting risk factor. $r = 1$ for first vaccination and r', r'', . . . for first and second boost (second or third vaccination). As $s_i \to 0$, $r' \to$ the relative risk of an SAE on the second vaccination compared to the first vaccination

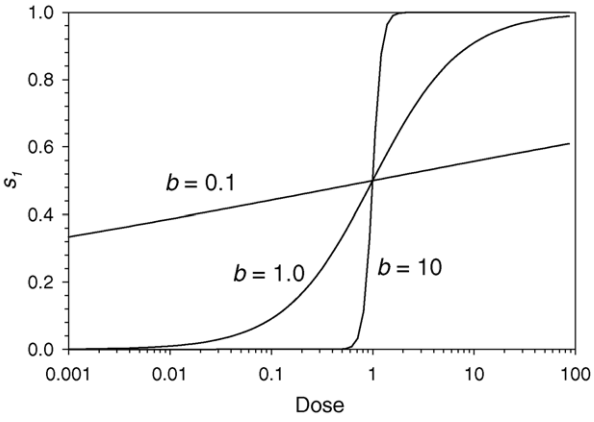

Fig. 1. Relationship between probability an SAE on first vaccination (s_1) and dose for three assumptions ($b = 0.1$, 1.0 and 10) about the increase in risk with dose. Each curves has been plotted for a theoretical vaccine that gives an s_1 of 0.5 at a dose of 1 U (i.e. $a = 1$).

Using the parameters and definitions in Table 1, it is possible to calculate the probability of exactly k SAE occurring before a trial would be stopped as

$$P_k = x_1 + \sum_{i=2}^{g} \left(x_i \prod_{j=1}^{i-1} ((1 - s_j)^{n_j}) \right)$$

where

$$x_i = \frac{n_i!}{k!(n-k)!} s_i^k (1 - s_i)^{(n_i - k)}$$

for $n_i \geq k$ and $x_i = 0$ for $n < k$

The mean number of serious adverse events per trial is

$$\bar{k} = \sum_{i=1}^{m} i P_i$$

where m is the maximum number of subjects in any one group

The probability of having k or fewer SAE is

$$P_{\leq k} = \sum_{i=0}^{k} P_i$$

There is no simple general solution to these equations to find the optimum design that balances risk of multiple SAE against efficient trial design. Consequently, numerical solutions to these equations have been examined over the range of feasible values, using a purpose written Pascal computer program. In determining these numerical solutions, a relative dose of vaccine has been used, rather than an absolute dose. The relative dose has been chosen so that a dose of 1 U at the lowest dose group gives $s_1 = 0.5$, i.e. $a = 1$ for all situations examined.

3. Vaccine trials modeled

3.1. Effect of splitting each dose group with a single vaccination

The effect of splitting each dose group into two subgroups was modeled for a trial with a single vaccination, with 5–20 subjects per dose and for a four-fold dose escalation for successive dose levels for $b = 0.1$, 1 and 10. The vaccination of the second subgroup was delayed until after any SAEs in the first subgroup could have been observed.

3.2. Vaccine trial strategies for three dose groups each with two vaccinations

Four different trial strategies were modeled as detailed in Table 2 for a two vaccination, dose escalating trial with 10 subjects per dose group, split in to two subgroups and doses escalating by a factor of 4.

Design 1 has all subjects given the first vaccinations before any subject receives the second vaccination. If vaccinations in successive subgroups are delayed by one week then the second vaccinations of the first subgroup cannot occur until week 6.

Design 2 models a trial where the first and second vaccinations separated by 4 weeks, with dose escalating on the first vaccination before escalating on the second vaccination. In this scheme, if a week is allowed between successive vaccinations, it is not possible to escalate though all of the first vaccinations prior to any of the second vaccinations. Therefore, the second vaccination of the first subgroup of the low dose group (i.e. Group 1A, Table 2) takes place at the same time as the first vaccination of the first subgroup of the high dose group (Group 3A). Similarly the second subgroup of the low dose group is vaccinated at the same time as the second subgroup of the high dose group receives their first vaccination (Groups 1B and 3B).

Designs 3 and 4 have all low dose subjects vaccinated with both first and second vaccinations before any of the medium dose group is vaccinated at all. Similarly, both vaccinations of the medium dose group are completed before any of the high dose group is vaccinated. In Design 3, within any dose group, both the first and second subgroups are vaccinated before any of that dose group receives the second vaccination. In model 4, the first subgroup of each dose receives both the first and second vaccination before the second subgroup receives their first vaccination.

The model was used to calculate the probability of 0, 1, 2, ... SAE; the average number of SAE and the 95% upper confidence limit on the number of SAE for each of the four strategies with $b = 0.1$, 0.3, 1, 3 and 10; with $r' = 0.03$, 0.1, 0.3, 1, 3, 10, 30, 100, 300 and 1000; with a range of d so that lowest d test gave $s_i < 10^{-5}$ for the initial injection with the highest dose and the highest d gave $s_1 \geq 0.99$ and using a 10 subjects per dose group split into subgroups of three and seven. The same output parameters were also calculated for

Table 2
Vaccine strategies modeled

Group	No. of subjects	Dose	Vaccination order		Vaccination schedule (weeks)[a]	
			Vaccination 1	Vaccination 2	Vaccination 1	Vaccination 2
Design 1						
1A	3	1×	1	7	0	6
1B	7	1×	2	8	1	7
2A	3	4×	3	9	2	8
2B	7	4×	4	10	3	9
3A	3	16×	5	11	4	10
3B	7	16×	6	12	5	11
Design 2						
1A	3	1×	1	5	0	4
1B	7	1×	2	6	1	5
2A	3	4×	3	7	2	6
2B	7	4×	4	8	3	7
3A	3	16×	5	9	4	8
3B	7	16×	6	10	5	9
Design 3						
1A	3	1×	1	3	0	4
1B	7	1×	2	4	1	5
2A	3	4×	5	7	6	10
2B	7	4×	6	8	7	11
3A	3	16×	9	11	12	16
3B	7	16×	10	12	13	17
Design 4						
1A	3	1×	1	2	0	4
1B	7	1×	3	4	5	9
2A	3	4×	5	6	10	14
2B	7	4×	7	8	15	19
3A	3	16×	9	10	20	24
3B	7	16×	11	12	25	29

[a] Schedule assumes a two vaccination regimen with injections at 0 and 4 weeks.

$b = 0.1$, 1 and 10; $r' = 0.1$, 1 and 10 where each dose group was split into subgroups ranging from 0:10 to 9:1.

4. Results

4.1. Effect of splitting each dose group

The average number of SAEs for a wide range of s_1 is shown in Fig. 1 for a trial with a single vaccination of three escalating doses; $b = 1$; with 10 subjects per dose and where the groups have been split into 0/10, 1/9, 2/8 ... 5/5 subgroups.

For test vaccines that have a very low probability of SAEs, all strategies give similarly low numbers of SAEs. For a vaccine that was unexpectedly very reactogenic (s_1 close to 1), then the number of subjects who experience SAEs will be the number of subjects in the first subgroup to be vaccinated. In this situation, splitting the groups into two subgroups reduces the overall risk of multiple SAEs occurring on the first vaccination.

At intermediate frequencies of SAEs, the modeling predicts that the risk assessment is more complex. For example, at an SAE frequency of 0.6 with a 1:9 split, there is a 40% probability that the first subject will not experience a SAE, but many (about five) of the second group of nine will, and this is reflected in the high average numbers of SAE with this a 1:9 split at this SAE frequency. No single split gives the lowest number of SAEs over the entire range. However, a 3:7 split (shown on Fig. 2, black line) gave the lowest values over most of the range.

The average number of SAEs only gives part of the outcome. In assessing the best compromise, one may also be interested in the probability that the number of SAEs exceeds a certain number (Fig. 3) or the likely upper limit on the number of SAEs that could be experienced (Fig. 4). For a single dose vaccine, these alternative views confirm that splitting each dose into two subgroups with of three and seven, respectively, provides a reduced risk compared to vaccinating single groups of 10.

In simulations for vaccine trials with 10 subjects per dose group, and where the numbers in the subgroup ranged from 6/4 to 9/1, the average number of SAEs progressively increased at all values of s_1 until they approached the number of SAEs predicted for a 0/10 split (data not shown).

These results were similar for all values of b tested ($b = 0.1$, 1 and 10) i.e. regardless of the steepness of the dose-SAE

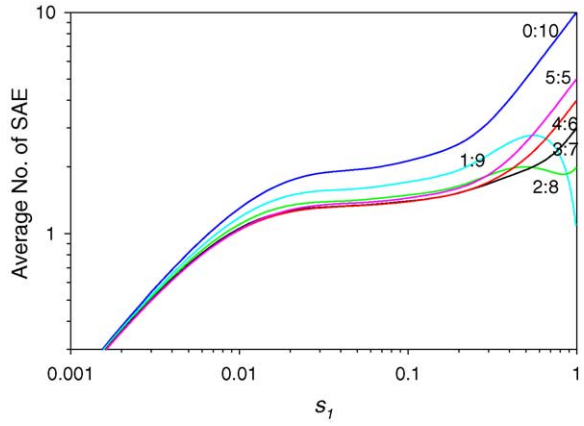

Fig. 2. Effect of splitting a single dose group in to two subgroups on the average number of simultaneously occurring SAEs. Trial is modeled with a single vaccination with three dose groups (relative doses, 1, 4 and 16, respectively, $b = 1$) with 10 subjects per dose. Trial was modeled with each dose group split into subgroups with: 0:10, blue; 1:9, cyan; 2:8, green; 3:7, black; 4:6, red; 5:5 magenta subjects per sub group.

frequency relationship, a 3/7 split gave the lowest number of SAEs over most of the risk range (data not shown).

For trials with 5, 8, 10, or 16 subjects per dose, split into two subgroups, the optimum number in the first subgroup was 2, 2, 3 or 3, respectively. For a study with 20 subjects per group the optimum split is less clear, with trials having three, four or five in the first group giving the lowest number of SAEs. Three would give a lower risk if the vaccine unexpectedly gave a high frequency of SAEs ($s_1 > 0.7$). Five would give lower average number of SAEs if the vaccine had $s_1 < 0.4$. With either strategy, the possible number of SAEs that may be encountered is substantially higher than with smaller numbers of subjects, suggesting that if such large group sizes are required for an initial Phase 1, splitting each dose into three subgroups would be a more conservative strategy.

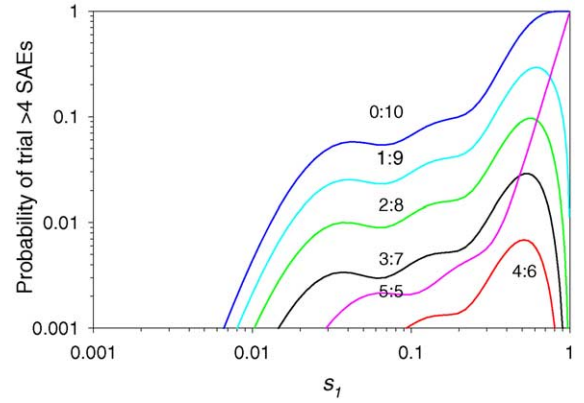

Fig. 3. Effect of splitting each dose group in to two subgroups on the proportion of trials that have 5 or more simultaneously occurring SAEs. Trial is modeled with a single vaccination with three dose groups (relative doses, 1, 4 and 16, respectively, $b = 1$) with 10 subjects per dose. Trial was modeled with groups split into subgroups with: 0:10, blue; 1:9, cyan; 2:8, green; 3:7, black; 4:6, red; 5:5 magenta subjects per sub group.

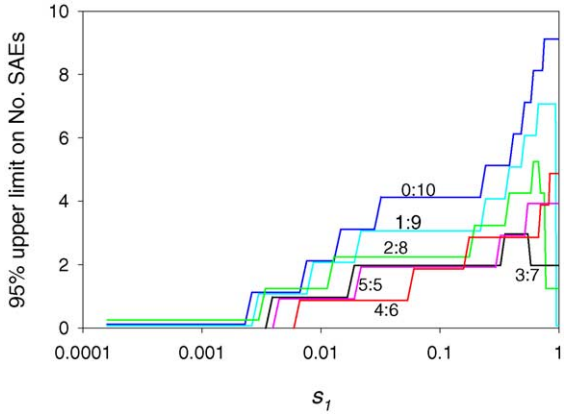

Fig. 4. Effect of splitting each dose group in to two subgroups on the 95% upper limit on the number simultaneously occurring SAEs. Trial is modeled with a single vaccination with three dose groups (relative doses, 1, 4 and 16, respectively, $b = 1$) with 10 subjects per dose. Trial was modeled with groups split into subgroups with: 0:10, blue; 1:9, cyan; 2:8, green; 3:7, black; 4:6, red; 5:5 magenta subjects per sub group. All values at the 95% limit are integral; successive horizontal lines have been given a small vertical offset to enable the curves to be distinguished.

4.2. Two vaccination schedule

For a dose escalation trial involving two vaccinations, the number of choices becomes much greater. Not only are there several choices in the timing of the vaccinations for the different groups, but also the relative risk of the first and second vaccination may be substantially different.

The average number of SAE for the four vaccination models described in Table 2 are shown in Fig. 5 for r' of 0.03, 1, 30 and 1000 and for $b = 1$.

Where the risk of SAE on the second vaccination is lower than the first vaccination, the four trial design models tested all have similar risks of multiple SAE over the full range of s_1 and b tested i.e. there was no situation found in which the order of vaccination altered the average number of SAE observed before a trial was stopped.

Where the risk of SAE on the second vaccination was similar to the first vaccination ($r' = 1$), there was a small but consistent difference in the average number of SAEs for the different models over a range of moderately high s_1 values and for the range of b from 0.1 to 10 (i.e. from a nearly flat dose-risk relationship to close to a step function (Fig. 1)). The trial designs for which all low dose subjects received both vaccinations prior to the medium dose receiving their first vaccinations (Designs 3 and 4) gave slightly lower average numbers of SAE. This is as expected, since in Designs 1 and 2, there are a total of ten vaccinations before the first three subjects received a medium dose, and for designs 3 and 4 there are a total of 20 vaccinations of similar risk, before the first three subjects receive a medium dose. Although this difference can be detected, it was usually very small (e.g. less than 10% difference in average numbers of SAE for $r' = 1$ and $b = 1$). The differences were greatest for scenarios with a moderately steep dose-risk relationship ($b = 3$ and for a mod-

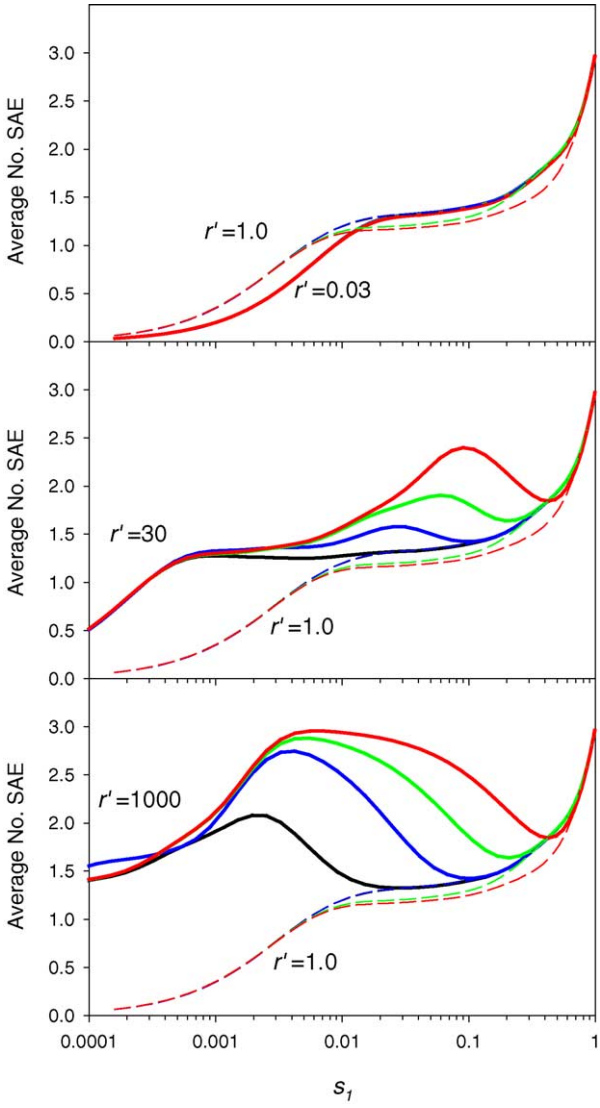

Fig. 5. Average number of simultaneously occurring SAE for four trial designs for a three dose escalating, two vaccination trial. The four trial designs (Design 1, black; Design 2, blue; Design 3, green; Design 4, red) are specified in the text and in Table 2. Each design uses two subgroups for each dose with a three and seven subjects per group; $b = 1$. Top panel: second vaccination lower risk than first vaccination ($r' = 0.03$), solid curves. Middle panel: second vaccination higher risk than first vaccination ($r' = 30.0$), solid curves. Lower panel: second vaccination much higher risk than first vaccination ($r' = 1000$), solid curves. Each panel has same data plotted for the second vaccination having equal risk as the first vaccination ($r' = 1$), dashed curves.

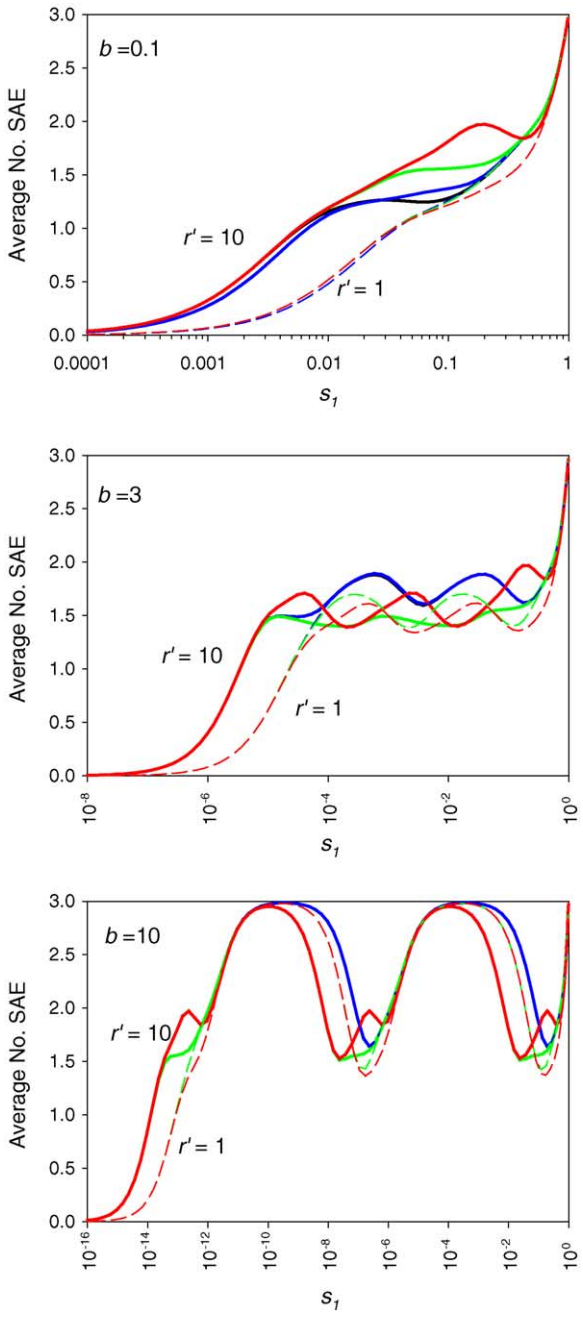

Fig. 6. Average number of simultaneously occurring SAEs for four trial designs for a 3 dose escalating, two vaccination trial for a shallow SAE frequency/dose relationship ($b = 0.1$), top panel, or a steep SAE frequency/dose relationship ($b = 3$), middle panel or very steep ($b = 10$) *lower* panel. The four trial designs (Design 1, black; Design 2, blue; Design 3, green; Design 4, red) are specified in the text and in Table 2. Each design uses two subgroups for each dose with three and seven subjects, respectively; For each panels, second vaccination: higher risk than first vaccination ($r' = 30.0$), solid curves; equal risk as the first vaccination ($r' = 1$), dashed curves. In the middle and lower panels, the curves for Design 1 (black) and Design 2 (blue) coincide over the entire range modeled and only the Design 2 (blue) lines are visible. At $s_1 < 10^{-4}$ (middle panel) or 10^{-12} (lower panel), curves for Designs 1–3 (black, blue and green dashed lines) for $r' = 1$ coincide. Above these values, curves for Designs 1–2 for $r' = 1$ (black and blue dashed) and for $r' = 10$ (black and blue solid) coincide. In this range, only the Design 2, $r' = 10$ solid blue line is visible.

erately higher risk, Fig. 6 middle panel; maximum difference 25% in number of SAEs). At steeper dose-risk relationships ($b = 10$) the differences in number of SAE was smaller (Fig. 6 lower panel).

Where the risk on the second injection is higher than on the first, the number of SAE increased in the order of Design 1, Design 2, Design 3 and Design 4 (Fig. 5 middle and lower panels and Fig. 6 upper panel). Under these conditions, not only did Design 1 have a substantially lower average number of SAEs (Fig. 5) it also had a substantially lower 95%

upper limit on the number of SAEs (not shown). Again this is consistent with a qualitative analysis: with Design 1, 30 people are vaccinated with a vaccine before the first three are vaccinated with a substantially higher risk vaccine. In Design 4, by contrast, only three people have been vaccinated before the first three receive a higher risk vaccine, and those first three will have received only the lowest dose.

For steep dose-risk relationships ($b > 3$) and where the second vaccination was of equal or greater risk to the first, the relationship between number of SAE and design was more complex. No single strategy gave the lowest number of SAE over the entire range of s_1 values modeled. However, a number of generalizations can be made.

1. There is a balance between b and r'. For vaccines where the second vaccine has a much higher risk that the first vaccination ($r' \geq 30$ for $b = 3$), then the best strategy is Design 1 followed by Design 2, Design 3 and Design 4 in that order (data not shown).
2. For vaccines where the second vaccination caries moderately more risk than the first ($r' = 10$, Fig. 6), then there is no difference between Design 1 and Design 2, and Design 3 is better than or equivalent to Design 4.

Over the range of conditions tested for a two vaccine, 3 dose escalating trial, a split of each dose group in to two subgroups of three and seven gave the minimum number of SAE over a wide range of s_1 and b (data not shown).

5. Discussion

There are uncertainties associated with the nature of the risks, the way in which these risks increase with vaccine dose and the relative risks of first and subsequent injections. Never the less, the sensitivity analysis shows that there are several generalities that can guide vaccine trial design.

First, regardless of the dose-risk relationship or of the increasing or decreasing risk on the second vaccination, splitting each dose group into subgroups and delaying the vaccination of the second subgroup until adverse events in the first subgroup could have been seen, substantially reduces both the average and the maximum number of SAEs that would be observed. For the group sizes likely in Phase 1 vaccine trials, the optimum number in the first subgroups will be either two or three. Less than this number, the chances of not observing a SAE in the first subgroup, but still having multiple SAE in the second subgroup is substantial. A larger initial subgroup, puts more subjects in this group at unnecessary risk.

Second, there is a set of circumstances where the design for a dose escalating trial can make a substantial difference to the likelihood of multiple SAE. Specifically where a subsequent vaccination is more likely to result in SAEs, and the dose-risk relationship is not extremely steep (i.e. $b \leq 1$), then a trial design that escalates dose in all of the initial vaccinations before any group receives a second vaccination is clearly superior to a design where initial and second vaccinations are administered to one dose group before vaccination any of the second and subsequent dose groups. There is no situation modeled where this strategy is csubstantially worst than the alternative of only escalating dose after both vaccinations at a lower dose have been given. For example, where the subsequent vaccination is less risky than the initial vaccination, then provided dose groups are split into subgroups, the actual trial design is not critical. Where each vaccination carries similar probabilities of a SAE, then there are differences in risks in the trial design, but these are small compared to the effects observed with an increasing SAE probability on subsequent vaccinations.

Thus, for early Phase 1 studies, where the risks are unknown, the best strategy for dose escalation design is to escalate dose following the first vaccination.

Note that the model makes no assumptions about the nature of the risk. The same result would be obtained if the nature of the risk was the same or different in the two vaccinations, e.g. if the main concerns were sterile abscesses on the first vaccinations and anaphylaxis on the second vaccination would give the same curves and if the major concern was for sterile abscesses on both vaccinations. The only requirement for Design 1 to be a better strategy than Designs 3 or 4 is a higher risk on the second vaccination than on the first.

There are theoretical and some experimental data to suggest that in some vaccine trial risks on a second vaccination may be lower than on the first vaccination. For example, subjects display a pre-existing hypersensitivity reaction to components in the vaccine such as aluminum or contaminating proteins originating from the production of antigen (e.g. egg proteins). Since the hypersensitive subjects are likely to be identified on the first vaccination and are unlikely to be vaccinated again, the overall risk of the vaccine may actually decrease for second and subsequent vaccinations. In the Montanide ISA720 trial with malaria antigens quoted above, the incidence of the delayed swelling and pain at the injection site was lower on the second injection [2].

However, in many cases it is likely that the risk of SAEs may be greater on the second vaccination, and especially greater on a third vaccination. Particularly for alum-based vaccines with poorly bound or free antigen, the risk of inducing a systemic hypersensitivity reaction is significant. Recently, several first time in humans, Phase 1 vaccine trials have been prematurely terminated for this reason [6–8].

In any Phase 1 trial design, there has to be a balance between the practicalities of undertaking the trial and the risk to the subjects. If there was no other factors, the safest trial would be to vaccinate a single subject at the lowest dose, wait a long time, vaccinate the second subject etc. However, the inordinate time this trial would require makes this impracticable. Even with the designs considered in this paper, the longer times associated with Design 4, and to a lesser extent with Design 3 can compromise analysis or even the ability to complete such trials. For example, for the first time a vaccine is used in a Phase 1 trial, it is likely that long term stability

of the vaccine under investigation will not be known. This leads to an ethical dilemma in extended trial designs: balancing the lowered risk of an SAE in an individual subject against the probability of exposing a group of subject to adverse events ranging from mild to serious with a risk of no useful outcome. In some diseases, e.g. HIV or malaria, this ethical issues is further clouded by the literally millions of additional deaths that could occur should the development of an ultimately successful vaccine be unnecessarily delayed.

Fortunately, over a wide range of modeled conditions, Design 1 (Table 2), where doses are escalated following the first vaccination not only leads to a lower or similar risk of multiple SAE to other designs, but also leads to much shorter trial designs than trial designs where a primary vaccination and a booster vaccination is given before escalating.

Although attractive from both the decreased risk of SAE under some conditions and the decreased time the trial takes compared to Designs 3 and 4, there can be practical difficulties in implementing Design 1. There may be immunological or operational reasons (e.g. compatibility with the EPI vaccine timetable) for choosing a particular time between a first and second vaccination and this may preclude a complete dose escalation of the first vaccine prior to the low dose group receiving the second vaccinations e.g. Design 2 (Table 2). Design 1 requires close coordination between safety monitoring committees and investigators. Scheduled reviews of safety data prior to dose escalation requires rapid response from review committees in order to maintain the planned timetable. Unplanned delays in approval to proceed with dose escalation (e.g. while the relationship between an observed adverse event and vaccination are being investigated) may inadvertently convert the trial into a Design 2 or even a Design 3 implementation.

This study only examined trial design for a two vaccination regimen and where all subjects within a group had the same risk. Many Phase 1 vaccine trial designs will be more complex than the designs considered in this publication. However, the approach used in this study should be readily extended to these situations on a case by case basis. Programs written in Pascal and compiled for use on IBM personal computers are available on request from the author as an aid optimizing more complex Phase 1 vaccine designs involving multiple vaccinations and where some subjects within each group may be at substantially higher risk than others.

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