

## **Bayesian clinical trial designs: Another option for trauma trials?**

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## **ABSTRACT**

Conducting clinical trials in trauma care is challenging. As new treatments become available, we are faced with the dilemma of how to confirm their effectiveness, and strengthen the evidence base. Randomized controlled trials are the gold standard, but target groups in trauma care are often small and specialized, making the classical approach to trial design difficult. Bayesian designs represent an innovative means of increasing trial efficiency, and conducting trials with more realistic sample sizes. This article examines the design of such trials, using the UK-REBOA Trial as an example.

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## **CHALLENGES FACED BY TRAUMA TRIALS**

Randomized controlled trials are considered the gold standard for proving the effectiveness of new treatments. However, clinical trials in trauma care pose a number of challenges. One of the most important is sample size. Clinical trials aim to compare two or more groups of patients, which should be as similar as possible, other than for the treatment under investigation. Trauma patients, however, represent a heterogeneous population. Patients with traumatic brain injuries differ from those who suffer from exsanguinating haemorrhage, and even patients with more closely related diagnoses – for example, those with pelvic fractures – may have very different presentations, needs, and outcomes. As a result, the number of patients with comparable injuries, both in terms of anatomy and physiology, is often small. This can be problematic, because to detect meaningful clinical differences using classical (also known as “frequentist”) statistical approaches to clinical trial design, power calculations often require sample sizes that are not easily achievable given the size of the eligible patient population. This applies particularly when the treatment under investigation is complex, as is the case with many medical device trials, when they are being introduced to highly specific subgroups of patients.

Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) falls into this category. REBOA is a promising and conceptually attractive new intervention, designed to reduce further blood loss, and improve myocardial and cerebral perfusion, albeit at the cost of an ischaemic debt. However, to date, the effectiveness of REBOA has only been evaluated using case series and non-randomised comparisons.<sup>1-5</sup> Importantly, one large study, from Japan, has shown that the technique may in fact be harmful,<sup>6</sup> although the

application of REBOA in the Japanese setting may differ from how it is used in Europe and North America.

Given this uncertainty, a randomized controlled trial would be helpful as any potential confounding variables should be equalized. We have recently designed such a trial, to evaluate the effectiveness, and cost-effectiveness, of REBOA. Given the very specific pool of patients for whom REBOA would be considered appropriate, it became clear that the numbers required for a traditional, frequentist trial design would not be feasible. This prompted us to explore other randomized trial design options, and we eventually adopted a Bayesian group-sequential design. The aim of this special commentary is to describe the deliberations which took place, and the design eventually chosen, in order to illustrate how such methods may be used to overcome the problems posed by small populations such as those seen in trauma care.

### **THE UK-REBOA TRIAL**

The UK-REBOA Trial will compare standard major trauma centre treatment plus REBOA with standard major trauma centre treatment alone, for trauma patients with confirmed or suspected life-threatening torso haemorrhage. Patient recruitment is expected to commence in October 2017. The total duration of the study will be 4 years, including an initial 9-month feasibility assessment phase (figure 3). The trial's entry criteria include adult trauma patients with confirmed or suspected life-threatening torso haemorrhage, which is thought to be amenable to adjunctive treatment with REBOA (zone I or zone III), presenting at major trauma centres. The primary outcome is 90-day mortality, defined as death within 90 days of injury, before or after discharge from

hospital. This outcome is intended to capture any late harmful effects. Cost-effectiveness is also being addressed.

An analysis of national trauma registry data revealed that, per year, an estimated 200 trauma patients in England might benefit from the use of REBOA. Around 125 of these present to major trauma centres.<sup>7</sup> 90-day mortality was 33.5%. A standard sample size calculation for comparing two proportions showed that in order to demonstrate a 5% reduction in mortality (from 33.5% to 28.5%), based on a two-sided  $\alpha$  of 5% and 80% power, a total of 2764 patients would be required (1382 in each arm). This equates to over 20 years' recruitment of all available patients presenting to major trauma centres in England. Given the number of patients who could, even in theory, be recruited, it was clear that a traditional, frequentist design was simply not feasible.

### **TRADITIONAL APPROACHES TO REDUCING SAMPLE SIZE**

We therefore considered means of reducing the sample size to a more realistic level, while ensuring the scientific integrity of the trial. Parmar et al (2016) have recently described a useful framework for a systematic and constructive examination of the options.<sup>8</sup> Step 1, which is largely intuitive, considers “increasing what is feasible”, including lengthening the accrual time, broadening the eligibility criteria, and extending the collaboration nationally and internationally. Step 2 considers common approaches to reducing sample size, such as using a primary outcome which is more “information-heavy” (usually a continuous outcome), defining a realistic and worthwhile (but larger) target difference, and reducing power by small amounts. Step 3 explores less common approaches to reducing sample size, such as relaxing  $\alpha$ , moving to one-sided significance

tests, and including covariates in the design. Whilst this paper provides a very useful framework, and one that we would recommend is reviewed, when applied to REBOA none of these approaches resulted in a feasible trial design. Instead we decided to use a combination of two other strategies that have occasionally been suggested, but rarely implemented in trauma trials: adaptive (and specifically group-sequential) methods,<sup>9,10</sup> and a shift to the Bayesian paradigm. We will discuss both of these in the following sections.

### **GROUP-SEQUENTIAL DESIGNS**

A group-sequential clinical trial design is a type of adaptive design that allows for one or several interim analyses of the accruing data while recruitment is still ongoing, with the option to terminate the trial early if the intervention under study is found to be ineffective (“stopping for futility”) or even unsafe.<sup>11,12</sup> Some group-sequential designs also permit early stopping for benefit when a clear and convincing treatment effect manifests early on. These methods have the potential to speed up trials and increase the efficiency of clinical research. When using classical (frequentist) statistics, however, repeated interim analyses of accruing data pose a multiplicity problem: the trial’s overall type I error rate  $\alpha$  is inflated, unless statistical adjustments are made, but these again reduce the efficiency of the design.

Bayesian statistics, in contrast, provide a very natural framework for repeated data analyses, without the need for any separate adjustments. Bayesian designs are thus particularly attractive when there are safety concerns, which demand regular analysis of the data. If an intervention is indeed harmful, then the study should be stopped as soon as

possible, to minimise the number of patients exposed. Given the findings of the Japanese study, this was an area of particular concern.

## **BAYESIAN CLINICAL TRIAL DESIGNS**

The Bayesian approach to trial design is fundamentally different.<sup>13</sup> When a clinical trial is being planned, there is usually some existing prior knowledge regarding the effect of the intervention under investigation e.g. from a pilot study or case series. In a Bayesian trial, this existing prior knowledge can be utilized and is represented by the *prior probability distribution* (or, for short, the *prior*). New data is then gathered from the trial itself (and also summarised in the form of a probability distribution, often referred to as *likelihood*), and combined with the prior, using *Bayes' theorem*, yielding the *posterior probability distribution* (or *posterior* for short), which represents the updated knowledge after seeing the trial data. The definitions of these terms are summarised in Table 1, and the combining of probability distributions is shown in Figure 1. In effect, the prior information and the trial results, as they emerge, are viewed as a continuous stream of information, in which inferences can be updated as new data become available. This concept is shown in figure 2.

Although widely used in other fields, the uptake of Bayesian statistics by the medical sciences, and particularly in clinical trial design, has been slow. This may be related to the mathematical complexity of some Bayesian techniques, potentially increased computational cost, and also the concept of a prior. The prior distribution plays a key role in Bayesian analysis, but is often misunderstood. Conceptually, it is easy to comprehend how previous knowledge, when combined into what are known as *strongly informative*

*priors*, could be used to contextualise new data. When good prior information exists, the Bayesian approach allows for such information to be incorporated into the design and analysis of a trial, justifying a smaller or shorter-duration trial, and thus increasing trial efficiency. The major issues lie in how to decide what “good” prior information is, how to determine an informative prior that is acceptable for trialists and stakeholders, and how to “weight” the prior knowledge in comparison to the new trial data. All this is far from straightforward in practice, and even more so when the information available is contradictory, and comes from heterogeneous patient populations. Informative priors, although conceptually attractive, are therefore sometimes regarded as inherently subjective, and viewed with a degree of suspicion. Given the conflicting prior evidence relating to REBOA, and the confirmatory nature of the intended trial, we therefore chose to use *non-informative priors*.

Non-informative priors (which are also known as *flat* or *weak priors*, on account of the shape of their probability distributions) avoid these issues, but cannot make use of existing knowledge. Some regard the term “non-informative” as an unhelpful misnomer (because a completely flat prior suggests that all values of the effect of the intervention are considered equally likely, which is also information), and refer to these priors as “reference” priors instead. They are primarily used when there is no prior information available, when the evidence is conflicting, or for confirmatory trials, where the aim is to “let the data speak for themselves”.

These priors carry very little information and have thus only minimal influence on the posterior (figure 1a). Despite not incorporating (much) prior knowledge, these types of trials are often more efficient and appealing than frequentist designs. The reason is that

the Bayesian concept can be used for iterative updating of the state of knowledge: starting with a completely flat prior and adding data from the first patient (or cohort of patients), the posterior is the same as the likelihood. This posterior – which is now “informative” – then becomes the prior for the next updating step when data from the next patient (or cohort of patients) is added, and so on (figure 2).

Another major advantage of Bayesian methods is that they provide intuitively comprehensible answers. One of the problems with frequentist statistics is that p-values and confidence intervals are easy to misinterpret,<sup>14-16</sup> and when correctly interpreted often do not give a useful answer to the question asked: a Bayesian analysis yields the probability of a specific treatment effect given the data, whereas a frequentist p-value is the probability of a specific or more extreme treatment effect given the assumption of a null hypothesis of no effect being true, which is convoluted and hard to appreciate. And unlike frequentist confidence intervals, Bayesian credible intervals are also straightforward to understand: there is a 95% probability that the true value of the treatment effect falls within the 95% credible interval, given the observed data. Moreover, Bayesian designs can offer great flexibility when it comes to formulating meaningful decision criteria e.g. for declaring the success of a trial, or for stopping a sequential trial early.

## **SPECIFIC CONSIDERATIONS**

In a Bayesian trial, we often present how a Bayesian analysis will perform given a set sample size. We therefore estimated the number of patients whom we felt we would be able to recruit for the UK-REBOA Trial, in a reasonable number of centres, in a

reasonable time. We calculated this number as 120, based on a pilot phase comprising five major trauma centres, recruiting over a period of 9 months, and a full trial phase comprising ten major trauma centres, recruiting for 24 months (figure 3), based on our registry analysis. 120, therefore, became our set sample size on which the expected performance of the Bayesian design was assessed.

We adopted a group-sequential Bayesian design<sup>17</sup> with three stages, of 40 patients each, and two interim analyses after 40 and 80 randomised participants, and a final analysis after a maximum of 120 randomised participants. We decided that the trial should be stopped early if there is a high (posterior) probability (90% or greater) that the 90-day survival odds ratio (OR) falls below 1 (i.e. REBOA is harmful) at the first or second interim analysis. REBOA will be declared “successful” if the probability that the 90-day survival OR exceeds 1 at the final analysis is 95% or greater.

We explored the trial’s operating characteristics based on the data obtained from our registry analysis, and assumed a control group (standard major trauma centre treatment alone) 90-day survival rate of 66.5%.<sup>7</sup> The design’s properties in terms of the probabilities of stopping for futility, at each interim look, and declaring success, for potential effect sizes from an odds ratio of 0.7 (equating to a reduction in 90-day survival from 66.5% to 58.2%, ie. REBOA causing harm) through to 1.3 (equating to an increase in 90-day survival from 66.5% to 72.1%), and the expected sample size (the number of patients expected to be randomized under this scenario), are shown in table 1. The probabilities were computed using the R package `gsbDesign`.<sup>18</sup>

The probabilities of early stopping are high if REBOA results in markedly decreased 90-day survival, roughly 19% if there is no difference to standard care (table 1, highlighted

blue), and below 10% if REBOA is a success with  $OR \geq 1.05$  (highlighted yellow). The probability that success is declared is less than 1.5% if REBOA is harmful with  $OR \leq 0.95$ , exactly 5% if both treatments are equal (as specified in our success criterion), over 60% if REBOA does well ( $OR \geq 1.2$ , highlighted light green), and over 90% if it does exceptionally well ( $OR \geq 1.3$ , highlighted dark green). The expected sample size is directly related to the probability of early stopping.

## **DISCUSSION**

Conducting clinical trials in trauma care is challenging. As new treatments become available, we are faced with the dilemma of how to confirm their effectiveness, and strengthen the evidence base. Target groups in trauma care are often small and specialized, making the classical approach to trial design difficult. As a result, studies may not happen at all, often because of infeasible sample sizes, or may be underpowered. One possible solution is to combine the results of such studies, if available, in meta-analyses. However, meta-analyses have their own limitations – they require a sufficient number of primary studies to be available, and heterogeneity may be problematic. An alternative solution is a complete shift in statistical paradigm, from traditional frequentist to Bayesian designs, using innovative methods such as the Bayesian group-sequential design that we implemented for UK-REBOA.

Conceptually, meta-analysis and Bayesian updating share similarities: Both techniques combine information in order to obtain the current best estimate about the treatment effect of interest. Under a Bayesian framework one could – at least in theory – construct a prior that captures and represents all available information about the treatment effect

(such as estimates from previous trials) and update it with new trial data so that the posterior would be broadly equivalent to an updated meta-analysis, but of course it would pose challenges such as how to weight the prior information in relation to the emerging trial data. Bayesian updating does not make meta-analysis obsolete, as the goal of the latter is not only to aggregate evidence and estimate a treatment effect but also to assess consistency or heterogeneity between single trials. Furthermore, meta-analysis can be conducted with Bayesian methods as they are well suited to flexibly modelling complex hierarchical relationships.<sup>19</sup>

When considering the design of primary research, Bayesian clinical trial designs represent an innovative means of increasing trial efficiency, and conducting trials with more realistic sample sizes, especially when the conduct of a trial would otherwise be infeasible, along with other benefit such as straightforward interpretability. The use of these designs is increasing, and both the Food and Drug Administration and the European Medicines Agency have released guidance relating to the use of Bayesian clinical trials,<sup>20,21</sup> but despite such endorsements, Bayesian designs are often still viewed as too unconventional or difficult. Medical devices are unusual in that regulatory approval does not require proof of effectiveness, resulting in their rapid proliferation. Buxton's law of the evaluation of new technologies and devices – which states that “it is always too early [for rigorous evaluation] until, unfortunately, it's suddenly too late”<sup>22</sup> – unfortunately often applies in trauma care. Bayesian clinical trial designs are an attractive alternative to case series and poorly controlled retrospective comparisons.

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## **AUTHOR CONTRIBUTION STATEMENT**

The idea for this article was conceived by JOJ, GM and MKC. The first draft was written by JOJ, GM and MKC, and subsequently revised and added to by PP. The UK-REBOA Trial was designed by the UK-REBOA Trial Investigators, who contributed to the writing and revision of the manuscript.

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## LEGENDS TO FIGURES

Figure 1. Bayesian data analysis in action: the posterior is obtained by combining the prior with the likelihood. In this example, all prior, likelihood, and posterior are normal distributions. The influence of the weak prior (left hand panel) with variance 2 is minimal, hence the likelihood and posterior are very similar, whereas the strong prior (right hand panel) with variance 0.1 has notable influence on the posterior. In both cases the likelihood is based on a sample of data with  $n=10$ , mean 0.5, and (known) variance 1. The prior means are 0 in both cases, and the posterior means are 0.476 and 0.25, respectively.

Figure 2. Illustrative example of the iterative nature of a Bayesian sequential trial, with updating after every single patient. All prior, likelihood, and posterior are normal distributions. After each patient, the prior and the data are combined, yielding the posterior, which then becomes the prior for the next iteration. The initial prior is weak with variance  $\sigma^2=2$ . The patient data were randomly drawn from a normal distribution with mean 0.5 and (known) variance 1.

Figure 3. Summary of UK-REBOA Trial design

**Figure 1**

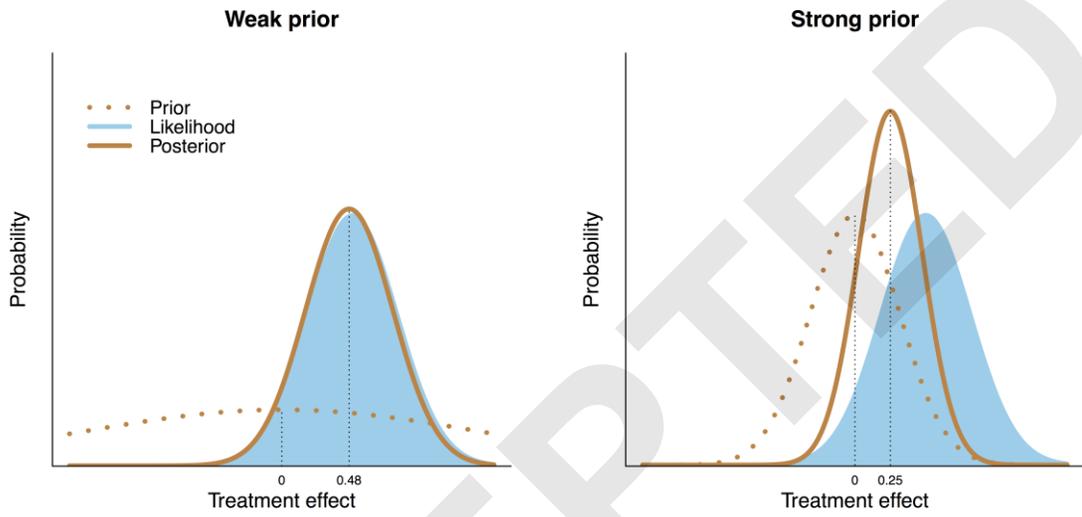
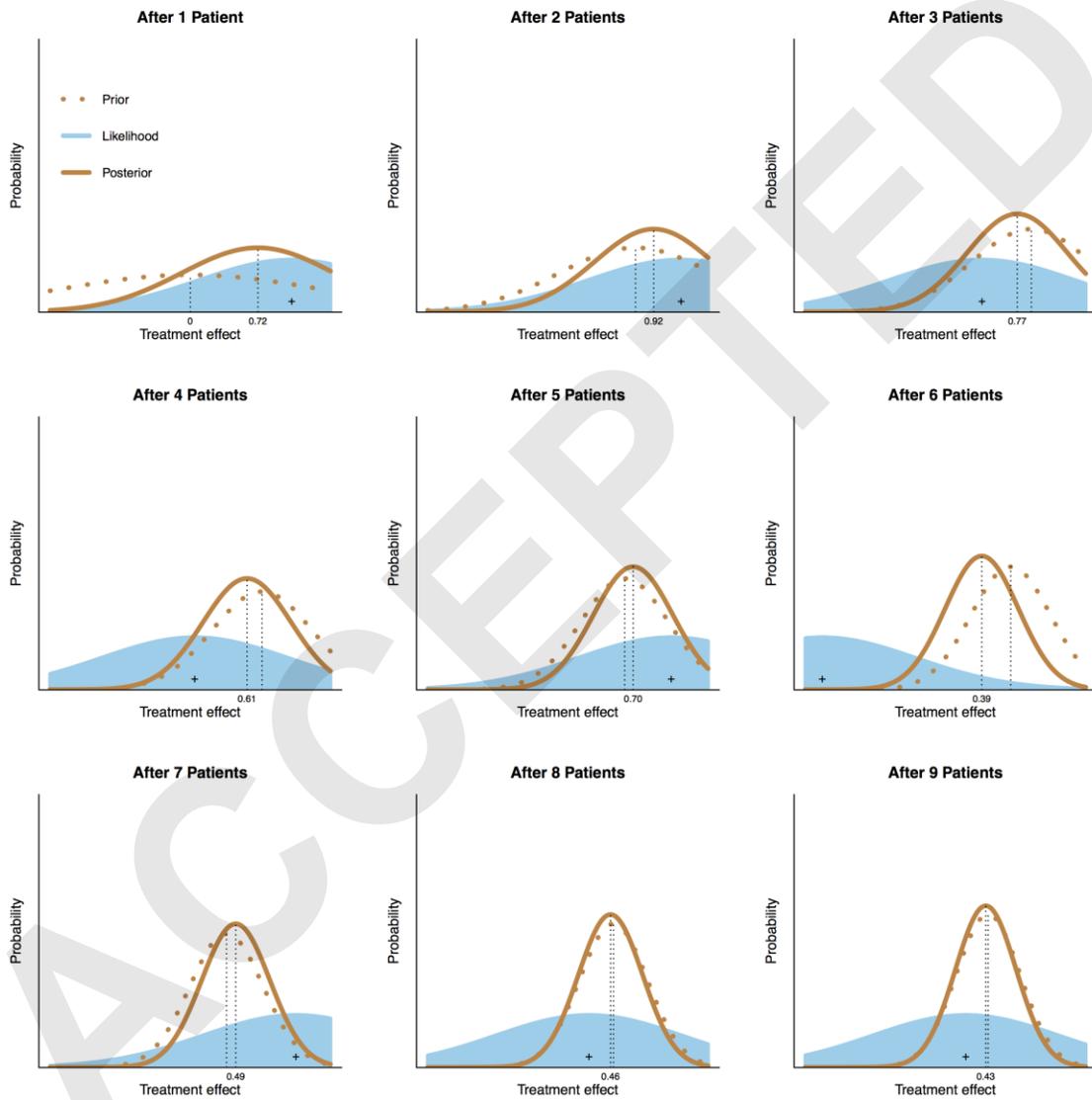


Figure 2



**Figure 3**

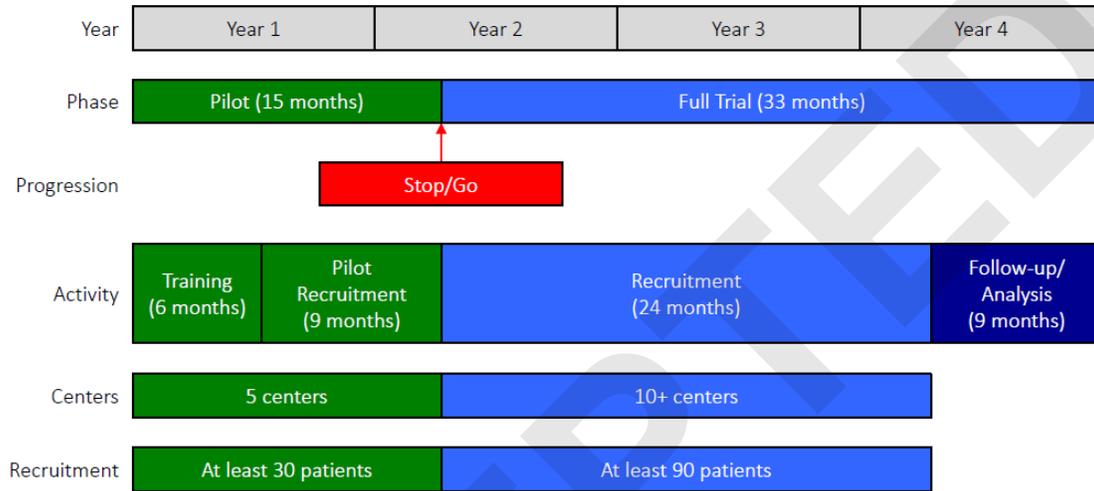


Table 1. Definitions

Term	Definition	
Prior (probability distribution)	$P(H)$	Probability that hypothesis H is true before observing data D
Posterior (probability distribution)	$P(H D)$	Probability that hypothesis H is true given the observed data D
Likelihood	$P(D H)$	Probability of observing this data D when hypothesis H is true
Marginal	$P(D)$	$P(H D)=PH*P(D H)$ Probability of observing this data D under all possible hypotheses
Bayes' theorem	$= \frac{P(H D) \cdot P(D H)}{P(D)}$	Posterior = $\frac{\text{Prior} * \text{Likelihood}}{\text{Marginal}}$

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Table 2. Stopping and success probabilities and expected sample sizes in UK-REBOA

Odds Ratio	Survival	Probability of declaring				Success	Expected sample size
		Futility (1st)	Futility (2nd)	Futility (final)	Futility (total)		
0.70	58.2%	85.3%	13.0%	1.6%	99.8%	0%	46.6
0.75	59.8%	72.5%	20.6%	5.2%	98.3%	0%	53.8
0.80	61.4%	57.0%	24.7%	10.5%	92.2%	0%	64.5
0.85	62.8%	41.3%	23.0%	13.5%	77.8%	0%	77.8
0.90	64.1%	27.7%	17.1%	11.8%	56.5%	0.2%	91.0
0.95	65.3%	17.2%	10.4%	7.4%	35.0%	1.3%	102.1
1.00	66.5%	10.0%	5.3%	3.5%	18.7%	5.0%	109.9
1.05	67.6%	5.5%	2.3%	1.3%	9.0%	13.7%	114.7
1.10	68.6%	2.9%	0.9%	0.4%	4.1%	28.5%	117.4
1.15	69.5%	1.4%	0.3%	0.1%	1.8%	47.4%	118.8
1.20	70.4%	0.7%	0.1%	0%	0.8%	66.1%	119.4
1.25	71.3%	0.3%	0%	0%	0.3%	80.9%	119.7
1.30	72.1%	0.1%	0%	0%	0.1%	90.6%	119.9