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Beyond *p*-values: A phase II dual-criterion design with statistical significance and clinical relevance

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Abstract

Background: Well-designed phase II trials must have acceptable error rates relative to a pre-specified success criterion, usually a statistically significant *p*-value. Such standard designs may not always suffice from a clinical perspective because clinical relevance may call for more. For example, proof-of-concept in phase II often requires not only statistical significance but also a sufficiently large effect estimate.

Purpose: We propose dual-criterion designs to complement statistical significance with clinical relevance, discuss their methodology, and illustrate their implementation in phase II.

Methods: Clinical relevance requires the effect estimate to pass a clinically motivated threshold (the decision value (DV)). In contrast to standard designs, the required effect estimate is an explicit design input, whereas study power is implicit. The sample size for a dual-criterion design needs careful considerations of the study's operating characteristics (type I error, power).

Results: Dual-criterion designs are discussed for a randomized controlled and a single-arm phase II trial, including decision criteria, sample size calculations, decisions under various data scenarios, and operating characteristics. The designs facilitate GO/NO-GO decisions due to their complementary statistical–clinical criterion.

Limitations: While conceptually simple, implementing a dual-criterion design needs care. The clinical DV must be elicited carefully in collaboration with clinicians, and understanding similarities and differences to a standard design is crucial.

Conclusion: To improve evidence-based decision-making, a formal yet transparent quantitative framework is important. Dual-criterion designs offer an appealing statistical–clinical compromise, which may be preferable to standard designs if evidence against the null hypothesis alone does not suffice for an efficacy claim.

Keywords

Clinical relevance, dual-criterion, evidence, GO/NO-GO, operating characteristics, phase II design, proof-of-concept, statistical significance

Introduction

Making evidence-based decisions is essential in drug development. To conclude activity of a drug, such decisions usually require a statistically significant *p*-value from a well-designed trial. However, statistical significance alone may not suffice if the trial does not deliver a clinically relevant effect estimate.[1] We discuss a simple dual-criterion design that formally combines a statistical (significance) and a clinical (effect size estimate) criterion.

Here we focus on phase II trials, which play a key role in drug development. In particular, proof-of-concept (PoC) is a milestone, the earliest point when the efficacy of an experimental drug is formally investigated. PoC trials typically lead to one of the following decisions: continue further development (GO), stop development (NO-GO), or seek further information.

The consequences of false decisions in phase II can be severe. Therefore, irrespective of the chosen design, understanding statistical error rates is important. For example, false-positive results (type I errors) in PoC

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trials will lead to phase III trials with ineffective experimental drugs and likely cause negative results. On the other hand, false-negative results (type II errors) will often stop the development of a potentially useful drug. Various phase II design options have been proposed, with primary focus on error rate control.[2–13]

GO or NO-GO decisions should always be seen in the context of the clinical needs and the competitive landscape,[14] which requires discussions among clinical teams, governance boards, and key opinion leaders. Consensus is important and easier to reach if trial results meet a pre-defined clinical criterion. A few proposals to formally account for a relevant effect size in clinical and other settings have been discussed.[15–20] Here, we will discuss a simple dual-criterion design, which we have applied in many phase II trials.

We will first review three generic phase II designs: the standard, dual-criterion, and precision designs. We then describe the dual-criterion design in more detail and show a frequentist and Bayesian application.

Design choices for phase II trials

In this section, we introduce the main components of three basic phase II designs: the standard, dual-criterion, and precision designs (Table 1).

The standard design

The standard design is very popular in drug development. For comparative (treatment vs control) trials, it puts forward stringent statistical criteria expressed as error rates:

1. *Type I error control*: If there is no treatment effect (the *null hypothesis*), the probability to declare success at the end of the trial is at most α. Typical values for α (one-sided) are 2.5% for confirmatory trials and 5% or 10% for early-phase trials. Here, success means statistical significance.
2. *Power*: For a selected effect size of interest (the *alternative hypothesis*), the probability of trial success is 80% or 90%.

While the standard design prevails in the confirmatory setting, its limitations are well known.[21] The main issue is that statistical significance only guarantees sufficient evidence to reject the null hypothesis (no effect), which may not suffice from a clinical perspective. Importantly, statistical significance does not necessarily support the alternative hypothesis, except when the p-value is highly significant.

The dual-criterion design

The dual-criterion design addresses the limitation of the standard design. It is appealing if one wants to base trial success not only on statistical significance but also on the effect estimate, which is more tangible for clinicians. The design requires the following inputs (Table 1):

1. Like the standard design, type I error control is needed, which requires a null hypothesis and type I error α. Eventually, a significant p-value will provide sufficient evidence for a positive treatment effect.
2. Unlike the standard design, the dual-criterion design requires a DV, which is clinically motivated. The DV is the minimum effect estimate needed for trial success. Estimates superior to this value justify a GO decision, whereas inferior values do not and will usually require additional considerations.

Compared to the standard design, the dual-criterion design combines the rigid statistical criteria (significant p-value, type I error control) with a clinical criterion that guarantees a sufficiently large effect estimate.

The precision design

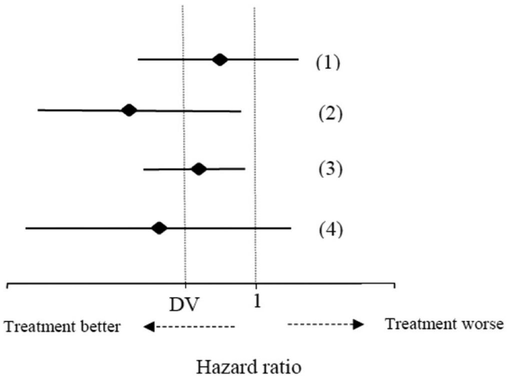
The two previous designs rely on error rates (type I error, power), which require clearly defined criteria for trial success. For the special case where the null hypothesis and other benchmark values (alternative hypothesis or DV) cannot be determined, a precision design may be an option. It requires a sufficiently precise effect estimate, usually defined via the width of the 95% confidence interval.

Table 1. Design components for standard, dual-criterion, and precision designs.

	Standard design	Dual-criterion design	Precision design
Null value	Required	Required	–
Alternative value	Required	–	–
Decision value	(Implied)	Required	–
Type I error	Required	Required	–
Power	Required	(Implied)	–
Precision of estimate	(Implied)	(Implied)	Required
Sample size	(Implied)	(Implied)	(Implied)

Table 2. Outcomes and decisions for a dual-criterion design.

	Not relevant	Relevant
Not significant	(1) **NO-GO** Insufficient evidence of relevant efficacy	(4) **Inconclusive**
Significant	(3) **Inconclusive**	(2) **GO** Evidence of relevant efficacy



Example

We now illustrate the three designs with a simple example. Consider a randomized trial with patients equally randomized to the experimental drug and control. The outcome of interest is the hazard ratio (HR) for progression-free survival (PFS), where the HR is less than one if the experimental drug is better than the control.

The standard design requires a null hypothesis with the corresponding type I error and an alternative parameter with the corresponding power (Table 1). For example, assume a superiority trial (null hypothesis HR = 1), one-sided type I error 2.5%, and 90% power under a 25% hazard reduction (alternative hypothesis HR = 0.75). The number of events to meet these requirements is 508. For this design, statistical significance is achieved if the estimated HR is 0.84, a hazard reduction of 16%. Note that this estimate threshold is implicit, that is, it follows from the design specifications.

The dual-criterion design requires a null hypothesis (with the corresponding one-sided type I error α) and the DV for the effect estimate. As seen above, success for the standard design (with $n = 508$ events) requires an estimated hazard reduction of at least 16%. If clinical considerations require an estimated reduction of at least 20%, the number of events must be at least 309 (see the next section for details). Importantly, the dual-criterion design also controls the type I error at 2.5%, but the power is implicit, that is, it follows from the type I error and the DV criterion. For 309 events, the power is smaller than that for the standard design. The reason is simple: an estimated hazard reduction of 20% (the clinical criterion) is more difficult to achieve than a 16% hazard reduction (considered clinically insufficient) for the standard design.

For the precision design, which assumes no comparative benchmarks (null hypothesis, alternative hypothesis, DV), assume that the aim is to estimate the HR with "20% precision": 95% confidence interval = (HR/1.2, HR × 1.2). This requires 462 events. For "25% precision", 95% confidence interval = (HR/1.25, HR × 1.25), and the number of events is 309.

Dual-criterion designs: criteria, outcomes, and decisions

The dual-criterion design is recommended for comparative trials if the required evidence for an effect can be expressed for two benchmarks: the null value (NV; null hypothesis) and the DV for the effect estimate. For a GO decision, the evidence must be sufficiently strong such that the effect is better than the NV and that the effect estimate reaches the clinically relevant DV. The criteria are as follows:

1. *Statistical significance*: The one-sided p-value must be less than α. Equivalently, the one-sided $100(1-\alpha)\%$ confidence interval must exclude the null value.
2. *Clinical relevance*: The estimated effect must reach the DV.

Regarding the statistical criterion, 10%, 5%, and 2.5% are commonly used for the one-sided type I error α, depending on the required strength of evidence to reject the null hypothesis. The clinical criterion must be elicited from clinical experts. Table 2 shows the four possible outcomes of a dual-criterion design:

Case 1: If the trial results fail both criteria, the decision will be a NO-GO.
Case 2: If the statistical and clinical criteria are both met, the decision will be a GO.
Cases 3 and 4: Inconclusive situations arise when only one criterion holds. For example, for large trials or

unexpectedly small variability of the outcome, statistical significance may hold, yet the estimate may miss the DV (Case 3). On the other hand, for small trials or unexpectedly large variability of the outcome, the effect estimate may pass the DV, but statistical significance may not hold (Case 4).

The planning of a dual-criterion trial requires carefully selected decision criteria and sample size. The dual-criterion must be based on clinical input, which necessitates effective collaborations between statisticians and clinicians. Understanding the similarities and differences between a standard and a dual-criterion design is important. Graphs and non-statistical language help explain the main features of a dual-criterion design. In addition, data scenarios with respective decisions may provide further clarification. Finally, operating characteristics (type I error and power) are crucial to justify the design. Details will be discussed in the following sections.

Since decision making in phase II is complex, a final decision in inconclusive situations should account for other relevant information, such as key secondary endpoints, safety, pharmacokinetics/pharmacodynamics (PK/PD), biomarkers, and subgroups.

In summary, recommendations for selecting a design depend on the context, which informs the required design inputs. In the comparative phase II setting, two benchmarks (NV = no effect, DV = minimum effect estimate) will often be available, which suggests a dual-criterion design. In other situations, a standard or precision design may be more appropriate. Irrespective of the chosen design, a clear understanding of the development context is crucial, and a consensus about design inputs and decisions related to possible trial outcomes is important.

Statistical considerations for dual-criterion designs

This section provides the key statistical components of dual-criterion designs. These refer to the formulation of the dual-criterion, the determination of the sample size, and the design's operating characteristics.

Frequentist and Bayesian dual-criteria

The frequentist formulation of the NV and DV has been presented in the previous section. The alternative Bayesian version requires a sufficiently large probability for a positive treatment effect (effect exceeds the NV) and an effect estimate that reaches the DV.

For the first Bayesian criterion, depending on the required strength of evidence for a positive effect, 90%, 95%, or 97.5% are common values for $1 - \alpha$. These values are selected in analogy to their frequentist counterparts (p-value less than one-sided type I error level) and will typically lead to type I errors close to α if prior information is weak. Importantly, despite the approximate equality of p-values and Bayesian threshold probabilities, their meaning is different.[1,22,23] In addition, the DV in a dual-criterion design and the alternative hypothesis in a standard design have entirely different interpretations. It is therefore critical to elicit the DV properly from clinical considerations. Simply taking the alternative hypothesis from a standard design as the DV in a dual-criterion design is unwarranted.

For example, for a standard time-to-event design with 80% power at a one-third hazard reduction (HR = 0.667), the implied effect size threshold (minimum effect estimate for success) is 0.754. Using 0.667 as the DV in a dual-criterion trial implies a completely different design. First, the standard design would not fulfill the clinically relevant criterion (estimate threshold 0.754 instead of 0.667). Second, because the dual-criterion is obviously more demanding, the resulting power of the study is less compared to the standard design. For instance, the power at 0.667 is 50% compared to 80% for the standard design.

Sample size

After the design inputs α, NV, and DV have been set, the sample size can be derived. For normally distributed data, the minimum sample size is

$$n_{min} = \frac{\sigma^2 \times z_\alpha{}^2}{(NV - DV)^2}$$

Here, z_α is the $100(1 - \alpha)\%$ quantile of the standard normal distribution and σ is the outcome standard deviation; for example, σ is 2 (under equal randomization) for the standard normal approximation to time-to-event data.

The n_{min} above is the minimum sample size that implies statistical significance if the effect estimate equals the DV. Importantly, the sample size of a dual-criterion design must be at least n_{min}. It can of course be larger than n_{min} if operating characteristics are considered unsatisfactory otherwise.

For non-normal data, a grid search over sample sizes may be needed to determine the minimum sample size. A search over increasing sample sizes is performed until the sample size n_{min} is found so that for all sample sizes equal to or larger than n_{min} the dual-criterion is fulfilled. For an example, see the single-arm trial design in the next section.

Operating characteristics

Operating characteristics (type I error, power) are an integral part of clinical trial designs and should be provided in the study protocol.

For dual-criterion designs, it is important to understand that the power at the DV is (approximately) 50%:

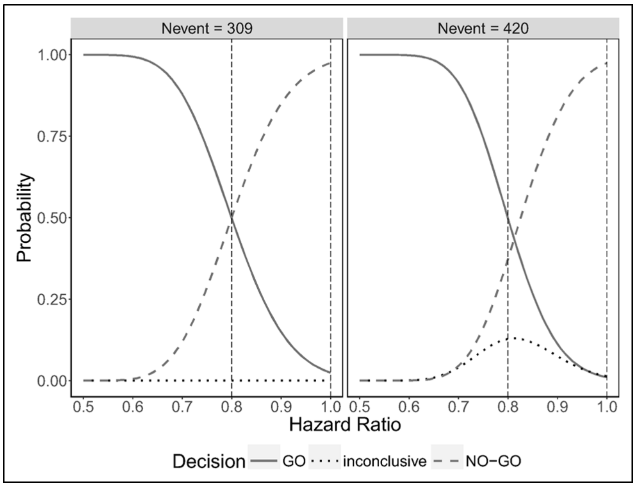


Figure 1. Operating characteristics of dual-criterion designs with 309 and 420 events.

if the true parameter equals the DV, there is a roughly equal chance that the effect estimate lies on either side of the DV. Notingly, increasing the sample size will not change the power at the DV: for parameters superior to the DV the power increases, whereas for inferior values it decreases. This is warranted because superior values justify a GO, whereas inferior values do not. Thus, if the true value equals the DV, a power higher (lower) than 50% would bias decisions toward GO (NO-GO), which is unwarranted. Therefore, having 50% power at the DV does not mean that the study is underpowered. Such a claim fails to understand the difference between the DV of a dual-criterion design and the alternative parameter of a standard design.

For the previous example, the minimum number of events (n_{min}) is 309. The left panel of Figure 1 shows the operating characteristics. If power for larger effects than the DV is considered unsatisfactory, the sample size should be increased. However, for larger sample sizes, the effect estimate may not reach the DV even if statistical significance holds, which is the inconclusive case 3 in Table 2. Moreover, larger sample sizes reduce the type I error below the required α. The right panel of Figure 1 shows the operating characteristics for 420 events: for effect sizes superior to the DV (HR < 0.8), the power increases compared to 309 events, whereas for inferior values it decreases.

In addition to the operating characteristics of a dual-criterion design, data scenarios (effect estimates) with the corresponding decisions may help clarify decisions obtained from a dual-criterion design.

Final analysis

The final analysis of a trial with a dual-criterion design does not differ from other designs. One needs to calculate the respective frequentist or Bayesian metrics:

- The p-value (or one-sided confidence interval) and the parameter estimate (e.g. the unbiased or maximum-likelihood estimate);
- The posterior probability that the parameter is better than the NV and the posterior median (or mean). In addition, plotting the posterior density and cumulative distribution function may be useful.

For phase II trials, the ultimate GO or NO-GO decision is based on these dual-criterion metrics and other possibly relevant information.

Examples

We now discuss two recent implementations of dual-criterion designs in phase II. To illustrate the broad applicability of such designs, we consider a randomized controlled trial with a time-to-event endpoint and a single-arm trial with a binary endpoint. The implementation will be frequentist for the first and Bayesian for the second. We also investigate alternative designs,[9,11] which shows similarities as well as differences in comparison to the dual-criterion design.

A randomized PoC design with time-to-event data

Example 1 was a randomized, double-blind PoC study of an experimental drug in combination with standard of care in patients with non-small-cell lung cancer. Patients were randomized equally to the experimental drug plus standard of care or to standard of care alone. The primary endpoint was progression-free survival (PFS), assessed with a log-rank test and Cox regression with treatment as a covariate.

In addition to the NV of no effect (HR $= 1$), the specification of the DV took into account standard-of-care data, the competitive landscape, and discussions with clinicians, marketing experts, and health authorities. A literature review revealed a median PFS of approximately 5 months. Based on discussions with experts, an estimated improvement of at least 2 months, which corresponds to an approximate HR of 0.7, was deemed necessary to be clinically meaningful. Values larger than 0.7 were judged unsatisfactory to clearly justify further development of the experimental drug. The dual-criterion for further development (GO) of the experimental drug was thus

1. Statistical significance: one-sided p-value of log-rank test ≤ 0.1.
2. Clinical relevance: estimated HR from Cox regression ≤ 0.70.

The sample size calculation used approximate normality of the log HR. From the sample size formula in the previous section, the minimum number of events n_{min} is 52. That is, with at least 52 events, if the estimated HR is 0.7, the one sided p-value is 0.1. To

Table 3. Example 1: operating characteristics for dual-criterion and standard designs; probabilities for GO, NO-GO, and inconclusive decisions given by hazard ratio estimate $\hat{\theta}$.

1. Dual-criterion design: $\alpha = 0.1$, DV = 0.7, $n = 70$

True HR	GO: $\hat{\theta} \leqslant 0.7$	NO-GO: $\hat{\theta} > 0.736$	Inconclusive
0.5	0.920	0.053	0.027
0.6	0.740	0.196	0.064
0.7	0.500	0.417	0.083
0.8	0.288	0.636	0.076
0.9	0.147	0.800	0.054
1.0	0.068	0.900	0.032

2. Dual-criterion design: $\alpha = 0.1$, DV = 0.7, $n = 52$

True HR	GO: $\hat{\theta} \leqslant 0.7$	NO-GO: $\hat{\theta} > 0.7$	Inconclusive
0.5	0.887	0.113	–
0.6	0.711	0.289	–
0.7	0.500	0.500	–
0.8	0.315	0.685	–
0.9	0.182	0.818	–
1.0	0.099	0.901	–

3. Standard design: $\alpha = 0.1,\ \beta = 0.1\ (\theta_A = 0.5),\ n = 55$

True HR	GO: $\hat{\theta} \leqslant 0.708$	NO-GO: $\hat{\theta} > 0.708$	Inconclusive
0.5	0.901	0.099	–
0.6	0.729	0.270	–
0.7	0.516	0.484	–
0.8	0.325	0.675	–
0.9	0.186	0.813	–
1.0	0.100	0.900	–

4. Standard design: $\alpha = 0.1,\ \beta = 0.2\ (\theta_A = 0.5),\ n = 38$

True HR	GO: $\hat{\theta} \leqslant 0.659$	NO-GO: $\hat{\theta} > 0.659$	Inconclusive
0.5	0.804	0.196	–
0.6	0.615	0.385	–
0.7	0.428	0.572	–
0.8	0.276	0.724	–
0.9	0.169	0.831	–
1.0	0.100	0.900	–

5. Standard design: $\alpha = 0.2,\ \beta = 0.1\ (\theta_A = 0.5),\ n = 38$

True HR	GO: $\hat{\theta} \leqslant 0.761$	NO-GO: $\hat{\theta} > 0.761$	Inconclusive
0.5	0.902	0.098	–
0.6	0.768	0.232	–
0.7	0.602	0.398	–
0.8	0.439	0.561	–
0.9	0.303	0.697	–
1.0	0.200	0.800	–

DV: decision value; HR: hazard ratio.

improve the power of the study for effect sizes better than 0.7 (DV), the number of PFS events was increased to 70. To reach 70 events, approximately 200 patients (100 per arm) were expected to be enrolled.

Table 3 shows the operating characteristics of the design, that is, the probability for a GO, NO-GO, or inconclusive outcome. Design 1 was the actually used design. Since 70 exceeds the minimal number of events (52), an inconclusive decision (significant p-value with an estimate inferior to the estimate threshold 0.7) may occur. However, this probability is less than 0.1 for all HR scenarios. The type I error is 0.032, considerably less than the required 0.1, and the power is reasonably large for convincing HRs (0.92 for HR 0.5, 0.74 for HR 0.6).

The second design considers the case of 52 events, the minimum number such that statistical significance implies clinical relevance (HR estimate = 0.7). As can be seen, inconclusive decisions cannot arise. Compared to the first design, the type I error is now the postulated 0.1 and the power is smaller (compared to design 1) for HRs superior to the 0.7 threshold. The probability that the study fails is larger for HRs inferior to 0.7.

For comparison, we now look at three more classical designs with different choices for type I error and power at an alternative HR of 0.5, referred to as *Randomized Screening Designs* by Rubinstein et al.[11] Design 3 is the most demanding, with one-sided type I error of 0.1 and power of 0.9. The number of events is 55 and statistical significance is achieved if the HR estimate is better than 0.708; in the actual trial, such an estimate would have been insufficient for a GO decision. The sample size and estimate threshold are similar to design 2, so type I error and power are similar too. Power is slightly higher due to the larger number of events and the weaker estimate threshold (0.708 compared to 0.7). However, design 1 differs in two aspects: if the sample size is larger than n_{min}, inconclusive decisions may arise (statistical significance but clinical irrelevance), and the type I error will be smaller than α.

Design 4 shows an example with the same type I error (0.1) but decreased power (0.8). The implied required HR estimate is now 0.659, which is clearly more aggressive than the explicitly postulated 0.7 in the dual-criterion design.

Finally, design 5 uses a type I error of 0.2 and a power of 0.9. This allows for more GO decisions: the required HR estimate is now only 0.761, which is in stark contrast to the clinically relevant value of 0.7. If an estimated 24% hazard reduction had been considered sufficient for a clear GO, a dual-criterion design with a DV of 0.76 would have been an alternative to design 5.

A single-arm PoC design with binary data

Example 2 was a single-arm PoC trial of an experimental drug in Chinese patients with non-small-cell lung cancer. This type of study is common in early-phase oncology trials, for example, in the expansion phase of a dose-escalation trial. The primary endpoint was objective response rate (ORR), which quantifies the preliminary efficacy of the experimental drug. The final analysis, which was Bayesian in this example, used a binomial sampling and a minimally informative unimodal beta prior distribution with mean 0.075, that is, a Beta(0.0811,1) distribution.

While the NV is usually clear (no effect) in randomized trials, selecting it is more challenging in single-arm trials due to the absence of a comparator. Based on a literature review and clinical discussions, the NV for the ORR was set to 7.5%. Moreover, a minimum improvement of 10% was considered necessary to justify further development. The dual-criterion was thus defined as

1. Bayesian statistical significance: pr(ORR $\geq$ 7.5% | data) $\geq$ 0.95.
2. Clinical relevance: posterior median $\geq$ 17.5%.

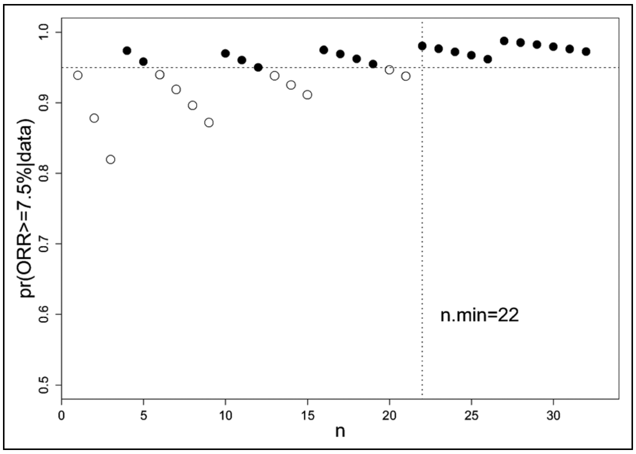


Figure 2. Example 2: grid search for minimum sample size.

For this dual-criterion, the minimally required sample size n_{min} is 22; that is, for $n \geq 22$, clinical relevance (criterion 2) ensures statistical significance (criterion 1). The final sample size of the trial was set to 25. Figure 2 shows the posterior probability that the ORR exceeds 7.5% as a function of n, assuming that the number of responders is the smallest r such that the posterior median exceeds the DV of 17.5%.

For $n = 25$, the minimum number of responders required for a GO is 5, with the respective estimate of 18.7% (posterior median) and the posterior probability for a positive effect (ORR > 7.5%) of 0.967. If the number of responders is less than 5, both criteria are missed (NO-GO): for four responders, the posterior median is 14.8% and the probability of a positive effect is 0.895. Thus, in contrast to example 1, there will be no inconclusive outcome here.

Table 4 shows the designs's probabilities of GO or NO-GO (design 1). The type I error is 0.036 and the power was considered reasonably large.

For comparison, we consider a three-outcome design with H_0: ORR $\leq$ 7.5%, H_1: ORR $\geq$ 27.5%, $\alpha = 0.05$, $\beta = 0.1$, $\eta = 0.8$, and $\pi = 0.9$, which requires 27 patients.[9] The decisions are as follows: NO-GO for zero to three responders, GO for five or more responders, and inconclusive for four responders.

For comparison to the three-outcome design, assume a larger size ($n = 36$). Now, to meet the dual-criterion, seven responders are necessary: for this, the posterior median is 18.5% and the probability of a positive effect is 0.985. An inconclusive outcome would occur for six responders: the posterior median is 15.8% (missing clinical relevance), yet the posterior probability of a positive effect is 0.954, reaching the 0.95 threshold. The operating characteristics for this design are also shown

Table 4. Example 2: operating characteristics for dual-criterion and three-outcome designs; probabilities for GO, NO-GO, and inconclusive decisions given by the number of responders (r).

1. Dual-criterion design: α = 0.05, DV = 0.175, n = 25

True ORR (%)	GO: $r \geq 5$	NO-GO: $r<5$	Inconclusive
7.5	0.036	0.964	–
12.5	0.195	0.805	–
17.5	0.451	0.549	–
22.5	0.693	0.307	–
27.5	0.858	0.142	–

2. Dual-criterion design: α = 0.05, DV = 0.175, n = 36

True ORR (%)	GO: $r \geq 7$	NO-GO: $r \leqslant 5$	Inconclusive: $r = 6$
7.5	0.016	0.950	0.033
12.5	0.156	0.709	0.135
17.5	0.446	0.380	0.174
22.5	0.731	0.149	0.121
27.5	0.902	0.044	0.054

3. Three-outcome design: n = 27

True ORR (%)	GO: $r \geq 5$	NO-GO: $r \leqslant 3$	Inconclusive: $r = 4$
7.5	0.048	0.860	0.092
12.5	0.243	0.558	0.199
17.5	0.523	0.280	0.197
22.5	0.759	0.113	0.128
27.5	0.901	0.038	0.062

DV: decision value; ORR: objective response rate.

in Table 4 (design 2). The comparison to the three-outcome design is interesting. The type I error α and type II error (for a response rate 0.275) are both small (0.016 and 0.044). In addition, the probability for NO-GO under the null hypothesis is 0.95 and the probability for GO is 0.902 for a response rate of 0.275. Both exceed 0.8, as suggested by Sargent et al.[9] This shows that this dual-criterion design is a three-outcome design with desirable properties.

Finally, design 3 in Table 4 shows possible differences between a dual-criterion and a three-outcome design. First, note that the operating characteristics reveal small error rates and reasonably large power, implying a three-outcome design with acceptable properties. Of special interest is the inconclusive outcome (four responders in 27 patients): the posterior median is 13.7% and the probability of a positive effect (ORR $\geq$ 7.5%) is 0.869. Thus, the dual-criterion fails for both (Bayesian) statistical significance and clinical relevance (NO-GO), whereas the three-outcome design results in an inconclusive outcome.

The computations for the two examples of this section were done with R 3.2.[24] Code is available from the main author upon request.

Discussion

The development plan of each experimental drug is unique, for which phase II trials are an important screening or early examination step. A good phase II design should be based on clinical needs, already available information about the drug, and the competitive landscape. In addition, it must have acceptable error rates for well-defined success criteria. For comparative efficacy trials, standard designs aim for a statistically significant p-value under type I error control and sufficiently large power. However, statistical significance only guarantees sufficient evidence that the drug has an effect. It does not guarantee clinical relevance.

We have discussed a dual success criterion that goes beyond a single null-metric, a p-value[1] or posterior threshold probability. The criterion complements statistical significance by a sufficiently large effect estimate. The latter is easily interpretable, ensuring clinical relevance if success is declared. Whether a frequentist or Bayesian design is chosen is rather unimportant in the absence of prior information. Otherwise, a Bayesian implementation is preferred.

There are similarities for dual-criterion and standard designs. Type I error α and power $(1-\beta)$ are important for both. For standard designs, they define the design, leading to an implicit success threshold for the effect estimate. To guarantee clinical relevance (a sufficiently large effect estimate), the effect threshold can be changed by changing α and β. Alternatively, and more directly, a dual-criterion can be used. This, however, has no explicit power requirements and power should therefore be assessed. Irrespective of the chosen design, the three main metrics (type I error, power, estimation threshold for success) must be understood to ensure a sensible balance of statistical and clinical requirements.

Beyond these similarities, differences between the two designs should be kept in mind. First, standard designs always result in success (statistical significance) or failure. Dual-criterion designs may lead to a statistically significant but clinically irrelevant result. As we have shown, such inconclusive outcomes are possible if the sample size is larger than the minimum sample size that implies statistical significance if the estimate reaches the clinical success threshold. Second, for standard designs, increasing the sample size increases the power for effects better than the null. For dual-criterion designs, power is only increased for values superior to the DV since inferior values are clinically irrelevant.

The specification of a dual-criterion should be tailored to the development plan. While conceptually simple, its implementation requires care. We have experienced two related challenges: First, the elicitation of the DV, the threshold for the effect estimate, is sometimes considered challenging. However, if carefully done, elicitation of the DV is often easier for clinicians compared to an alternative hypothesis with respective power. Second, the fact that study power is 50% at the DV has let some reviewers conclude that the study is underpowered. This concern can be alleviated in the protocol by precisely defining the dual-criterion, clarifying that the DV differs from the alternative hypothesis in a standard design, and providing the power for effect parameters considerably better than the DV.

We have only discussed the dual-criterion design for two simple phase II examples. A dual-criterion can of course be applied in other settings too because requirements of statistical significance and a reasonably large effect estimate are generally applicable. Examples include non-inferiority,[18] bridging, and dose-finding studies, as well as multiple endpoints. In addition, dual-criterion designs may include interim analyses for futility for which we often use probability of success for interim decisions.[25]

Finally, our experience so far has been confined to non-confirmatory trials. In the confirmatory setting, the size of effect estimates matters but is usually not part of the success criterion. However, a formal criterion may help avoid negative surprises, in particular for large trials: rather than questioning the relevance of a significant phase III trial with an unconvincing effect estimate, formally introducing the minimum effect estimate in the success criterion may be a better option.

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