The age of randomized clinical trials:

three important aspects of randomized clinical trials in cardiovascular pharmacotherapy with examples from lipid, diabetes, and antithrombotic trials.

Review article #2: Reasons for early stopping of an RCT

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Aims of this review article

This review article aims to explain the important issues that Data Safety Monitoring Boards (DSMB) face when considering early termination of a trial (see Table of Contents) and is specifically addressed to the needs of clinical and research cardiologists. We give an insight into the overall background and then focus on the three principal reasons for stopping trials.

The statistical essentials are also addressed to familiarize clinicians with the key principles. The topic is further highlighted by numerous examples from lipid trials and antithrombotic trials.

This is followed by an overview of regulatory aspects, including an insight into industry-investigator interactions.

To conclude, we summarize the key elements that are the basis for a decision to stop a randomized clinical trial.

Background and challenge

In a recent article published in this Journal [1], we have reviewed the selection of endpoints for RCTs. With the accumulation of recorded endpoints, it is ethically appropriate in every trial to perform interim analyses in order to ensure the safety of investigational treatments. For this purpose, data safety monitoring boards (DSMBs) are a cornerstone of contemporary trials. The aim of the regular meetings of DSMBs is to protect trial participants from harm. Three important challenges may occur that necessitate premature stopping of a trial: overwhelming efficacy, futility, or harm (Figure 1).

A different kind of challenge is the disadvantage of stopping a trial. A huge investment of effort is partly lost in that less evidence is gained when the preplanned size and duration of the trial is reduced.

Responsibilities of the DSMB members

There are many issues to consider when conducting and monitoring a randomized clinical trial. The clinical trial is undertaken to fill gaps in knowledge regarding specific alternative therapeutic interventions. There should be clinical equipoise between alternative treatment

options. With the introduction into a trial of a proposed new treatment (drug, device or strategy), there is an important responsibility on the DSMB and trial management to consider all information being collected, in timely fashion, with predefined criteria and interim analysis plans, to be done by an independent statistician not otherwise involved in the trial.

To reinforce safety concerns, all investigators and all local and national ethics review committees periodically receive (in blinded fashion) a listing of suspected unexpected serious adverse reactions (SUSARS). People involved in the trial may raise issues and refer suspicions of harm to trial management and the DSMB, who will then examine in more detail unexpected signals emerging during the trial.

The DSMB charter

The DSMB charter [2], drawn up at the outset of the trial, should define monitoring procedures including plans for interim or ongoing analytic data. Reports of interim results should be presented to the DSMB in semi-blinded fashion (A vs B). It is then common practice for the DSMB to request the unblinding of the treatment arms. Different thresholds for harm can be applied according to the investigational treatment like in the case where a new treatment may potentially cause a distinct benefit or distinct side effect, as with antithrombotic agents, where bleeding is a potential safety issue. But the general principle is that a DSMB functions better when it is fully aware of the unblinded interim evidence.

Reasons for early stopping of an RCT

With the scope of protecting trial participants from possible harm and not prolonging a trial when the answer is clear, there are threee main reasons for stopping a trial early.

Efficacy

First, upon interim analysis, clear evidence can arise that the new treatment appears superior. In this situation, it is unethical to subject patients of the control group to an inferior treatment. However a trial should only be stopped because of overwhelming evidence of efficacy. Again, it is important to consider specific endpoints that show such efficacy paying particular attention to the pre-defined primary endpoint, which is often a composite of major morbidity and mortality. Some trials are studying softer endpoints e.g. imaging results,

revascularization rates, or surrogate outcomes. In this case, if the prognosis of randomized subjects is not affected, there are no reasons for requesting premature discontinuation.

Futility

Second, the accumulating interim data in a trial may reveal a lack of efficacy, i.e. it looks like there will not be a positive result in terms of a significant difference in endpoints between treatment arms, even if the trial continues to its preplanned end. One can argue that in the interest of participants, the trial should be stopped because they should not be subject to unnecessary investigations. Moreover, for the sponsor stopping is advantageous in this setting because of cost savings.

The paramount level of decision is the predefined primary endpoint of the study. If it is a composite endpoint, then decision-making can be tricky. For instance, if a 3-point MACE endpoint (Major Acute Cardiovascular Event: death, MI or stroke) does not improve, but stroke alone appears to do so, then there may be a case to continue the trial. Also, if clear evidence of lack of efficacy has key implications for future clinical practice, then stopping early for futility may be inappropriate.

Safety

Third, and more serious, there can be a signal of harm. If there is the impression that an endpoint increases in the new treatment arm, it is important to distinguish between hard and soft endpoints [2], with increased all-cause mortality representing the hardest indication to stop a trial, followed by disease specific mortality (i.e. cardiovascular) or cardiovascular morbidity (MI, stroke). Next, an important distinction is whether evidence of harm is to be expected (e.g. bleeding events). This aspect is a challenge for a DSMB to act wisely, requiring a judgement based on the totality of evidence that the new treatment is harm. Potential evidence of harm may provoke the needs for more frequent interim reports and DSMB meetings.

Combined reasons for trial stopping

In some instances, a combination of reasons to stop appears appropriate. One example is the HPS2Thrive (Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events) trial [3]. In this trial, nicotinic acid combined with the antiflushing agent

laropiprant on the background of statin-ezetimibe therapy was tested against statin alone. As to efficacy endpoints, futility became evident, and, in addition, cutaneous and gastrointestinal, diabetes incidence, and musculoskeletal side effects increased in the nicotinic acid arm. The decision to stop the trial was based on both these facts.

A further unusual reason led to the premature stopping of the SPIRE 1 and 2 trials [4,5], respectively. The PCSK9 inhibitor bococizumab gave rise to neutralizing antibodies leading to a partial loss of efficacy. The manufacturer decided not to market the drug and thus stopped the two trials that were at different stages, and, consequently to discontinue the whole bococizumab program.

Examples from lipid trials

First evidence for a statin benefit in diabetes mellitus patients had risen from trials where diabetic patients constituted an important minority, like the HPS (Heart Protection Study) trial [6], but the main population (72.5%) was non-diabetic. Therefore, the CARDS (Collaborative Atorvastatin Diabetes Study) [7] study was initiated that included exclusively patients with diabetes. The duration of the trial was planned for 5 years. However, at interim analyses it was evident that the benefits of statin versus placebo were very marked. In order to not expose placebo-treated patients to an unacceptable risk, the trial was stopped prematurely after the second interim analysis showed a significant benefit with treatment.

Another example is JUPITER (Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) [8]. In this primary prevention trial in patients with elevated hsCRP (≥2 mg/L or <2 mg/L) using rosuvastatin versus placebo, an early benefit emerged and led to a premature termination after a median follow-up of 1.9 years rather than the intended 5-year follow-up. This was justified by the observed reduction of hard endpoints, including all-cause mortality. However, later on, the termination was criticized and some experts pointed out that a lot of valuable information was lost by the premature termination of the trial. Interestingly, no increase in the rate of adverse effects was detected in an analysis of participants who continued to receive treatment for 4 or more years [9].

After older studies in the pre-statin era had shown benefit for nicotinic acid to reduce cardiovascular events like in the CDP (Coronary Drug Project) [10] and HATS (HDL-Atheroscloerosis Treatment Study) [11], mostly in monotherapy, the idea was to combine nicotinic acid to statins. Among new trials, ARBITER 6-HALTS (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6-HDL and LDL Treatment Strategies in Atherosclerosis) was designed to test the antiatherogenic potential of the

combination of statins with nicotinic acid [12]. By carotid ultrasound, it appeared that lesions were less fast progressing or even regressing. Because of this level of “efficacy”, the trial was prematurely terminated. The study, although a late breaking trial at the AHA meeting and published amendments in the NEJM, was criticized by the official AHA discussant, John Kastelein. The criticism was mainly that a surrogate endpoint and not a hard endpoint led to early stopping. Later on, large outcome studies with a comparable combination therapy like AIM-HIGH (The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes) [13] and HPS THRIVE (Heart Protection Study 2 – Treatment of HDL to Reduce the Incidence of Vascular Events) [3] failed to demonstrate benefit, proving that it can be misleading to stop a trial based on imaging results.

The TRACE-RA (*Atorvastatin for the Primary Prevention of Cardiovascular Events in Patients with Rheumatoid Arthritis)* trial was designed to assess whether statin therapy is superior to placebo for the primary prevention of cardiovascular events (CVE) in rheumatoid arthritis patients who do not have an indication for statins based on their CV risk [14]. The unexpectedly low CVE rate limited the statistical power to detect an effect during the planned 5 years of follow-up and led to premature termination of the trial after a median of 2.5 years. In hindsight, the non-significant observed relative risk reduction was in line with the significant results from other larger statin RCTs suggesting that such premature stopping was not a wise decision.

Examples from antithrombotic and anticoagulation trials

In the field of antithrombotic and anticoagulant therapy, the AVERROES study compared the efficacy of the factor Xa inhibitor apixaban versus aspirin (then the standard of care) in 5599 patients with atrial fibrillation and low risk for thromboembolic events [15]. At the first planned interim analysis the DSMB, observed a treatment benefit in favor of apixaban for the primary outcome that exceeded 4 SD. After a confirmatory analysis 3 months later (p value 0.000002, z=4.76) the DSMB recommended stopping the study with a shorter than planned mean follow-up time of 1.1 years. Importantly, there was no evidence of any safety concerns. The results were made public and patients in the comparator aspirin arm were given the opportunity to receive apixaban.

COMPASS (*Cardiovascular Outcomes for People Using Anticoagulation Strategies*) was a three-arm trial comparing the combination of low-dose rivaroxaban with aspirin vs aspirin or rivaroxaban alone in secondary prevention of cardiovascular disease events. It was stopped

early for strong evidence of superior efficacy with the combined treatment, even though there was some opposite signal regarding safety, i.e. a marked excess in major bleeding events on rivaroxaban-plus-aspirin compared with aspirin-alone [16–18]. Nonetheless, the executive committee of the trial considered that the net clinical benefit outcome of cardiovascular death, stroke, myocardial infarction, fatal bleeding, or symptomatic bleeding into a critical organ was lower with rivaroxaban plus aspirin than with aspirin alone (HR 0.80; P<0.001) to justify the termination of the trial. However, whether this net benefit applies to all patients is open to debate. That is, are there patients at high risk of bleeding who should avoid such a combined treatment?

RCTs on patients with peripheral artery disease (PAD) are manifold and incorporate interventional, physiotherapeutic (i.e. exercise) and pharmacotherapeutic (mainly antithrombotic) strategies [19]. A common problem is to motivate PAD patients to participate in these RCTs [20,21]. This often leads either to premature termination due to poor recruitment [20] or to stop even before study initiation. This might in part be prevented through amendments to the study protocol. Furthermore, PAD patients appear to be more interested in a specific treatment, rather than willing to be randomized [22].

Altogether, this might be why PAD is rarely studied in a specific RCT, but rather included in a broader group of cardiovascular patients, with the main focus on cardiac patients. Thus, the specific treatment effect on PAD patients is mostly reflected in a subgroup analysis. We intend to pursue the topic of subgroup analyses in a further article currently under preparation.

Notable exceptions are the EUCLID (Examining Use of Ticagrelor In PAD) [23] and the recently published VOYAGER PAD (Vascular Outcomes studY of ASA alonG with rivaroxaban in Endovascular or surgical limb Revascularization for Perpheral Artery Disease) trial [24], which exclusively studied symptomatic PAD patients for the prevention of future cardiovascular risks through antiplatelet agents (ticagrelor vs. clopidogrel [23]) or anticoagulants (rivaroxaban plus aspirin vs. aspirin alone [24]).

Why EUCLID and VOYAGER succeeded is not self-evident. Similar RCTs faced difficulties which then led to their premature termination. One good example is the TI-PAD (Ticagrelor in Peripheral Artery Disease Endovascular Revascularization) trial [25] of antiplatelet monotherapy (i.e. ticagrelor 90 mg twice daily vs. aspirin 100 mg once daily) in patients with PAD. The rationale for TI-PAD was the lack of evidence regarding optimal antiplatelet therapy in endovascular treatment of PAD patients, unlike in cardiology. It was hypothesized that ticagrelor's increased potency for platelet inhibition compared with aspirin would lead to improved patency and better walking performance post procedure. Twenty study sites were

involved with 90% open within 4 months. However, study enrollment was lower than anticipated with 0.04 patients per site per month. The reasons for this were manifold: a 4-week washout period for concomitant medication, logistic difficulties related to multiple study visits over a short period of time. Also peak walking time being the major endpoint, required a treadmill test as an inclusion criterion but scheduling and performance was not possible for all eligible subjects at every study site. Most important, the antiplatelet monotherapy after intervention was not well received: dual antiplatelet therapy (DAPT) was simply favored over the required monotherapy in the protocol, despite its lack of justification [26]. Despite appropriate protocol amendments, recruitment remained low over 13 months with 0.29 patients per site per months (less than half what was initially anticipated). Hence the trial was prematurely terminated. The rationale for the study of antiplatelet monotherapy after revascularization was more than justified but the protocol might have been too ambitious. The decision to terminate the trial was inevitable.

Statistical considerations

The decision to prematurely terminate a clinical trial depends on a multitude of factors, and besides advantages carries important risks (Figure 2). Whatsoever, it is always founded on statistical considerations. Statistical methods used in clinical trials are numerous, are laid out in the SAP (statistical analysis plan) of the trial and conform to the FDA and EMA guidelines of statistical principles of clinical trials.

The statistical stopping guidelines will be trial-specific and should be documented in the DSMB charter. They should cover several potential reasons for terminating the trial i.e. for superiority, harm or futility as mentioned previously. The guidelines mainly focus on the primary endpoint for stopping.

A clinical trial by definition compares interventions in a limited number of patients in order to extrapolate to the much larger number of subjects with the same condition who may subsequently benefit from the knowledge gained. This extrapolation is a challenge. When differences between treatment arms are found in the trial, they may be simply due to chance. The probability for such an error, the so-called type I or alpha error, is given as the p-value; conventionally, p-values <0.05 (indicating that the probability of a false positive result is below 5%) are considered statistically significant.

However, while the chances for a false positive result is low (as is reflected by a statistically significant, low p-value) for any single analysis, the chance to obtain a false positive result increases with the number of interim analyses, just as the chance of winning a gamble

increases with multiple tries. Hence, the naïve use of a p<0.05 in interim analyses with subsequent early termination of a trial would strongly increase the likelihood of false positive results and therefore is clearly not recommended.

To overcome this problem statistical stopping boundaries may be used which require P-values much smaller than 0.05 in order to stop a trial for efficacy [27,28].

One such example is the O'Brien and Fleming rule [29]. However, this requires a fixed number of planned interim-analyses. The Peto-Haybittle rule [30] is more flexible in that it specifies a fixed low p-vale such as <0.001 for the early termination of a trial, independently of the number of interim analyses. Alpha-Spending Functions (Lan, Kim and DeMets) can be used which allow flexibility when interim analyses happen, while controlling Type I error [31,32].

The term "rule" is misleading, because these are not true rules, but rather objective guidelines to help data monitoring committees (DMCs) make recommendations based on the totality of evidence. Importantly, however, even when these rules are applied, early termination for efficacy biases results towards an exaggeration of the true treatment effect [33]. This is due to the fact that overwhelming efficacy at one point may well reflect a random high, and subsequent longer observation (if allowed to happen) would on average show regression to the truth, i.e. a more moderate effect.

It is generally recommended that stopping a trial for efficacy requires proof beyond reasonable doubt of a treatment benefit that will change clinical practice (e.g. the RECOVERY trial of dexamethasone for COVID [34]).

The "rules" mentioned above deal with the issue of stopping trials early for the unequivocal benefit of one intervention. But when evaluating whether to stop a trial early for safety problems or for lack of efficacy, other considerations become important. One statistical method used when stopping for futility is conditional power whereby one calculates the probability of achieveing a statistically significant treatment benefit at the end of the trial given the data so far. If this is unacceptably low one may consider stopping early for futility. However, with an early termination for lack of efficacy other advantages of the studied intervention may be lost and the value of the trial for potential future meta-analyses is decreased.

Usually, for ethical reasons, somewhat weaker evidence is required to stop a trial because of potential harm of a new treatment. While one still has to be cautious in not over-reacting to potentially false safety signals, there is an ethical need to protect patients from being randomized to any new treatment that turns out to be harmful. Even more than stopping a trial

early for efficacy, stopping a trial early for potential harm or for lack of efficacy cannot be solely based on statistical rules. The whole body of existing evidence will influence this decision.

To further illustrate these issues some examples are given below.

An adaption of the Peto stopping criteria were used in the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) trial, evaluating eplenerone against placebo in patients with chronic systolic heart failure and mild symptoms [35]. Two interim analyses were planned: at the second one after 542 primary end points had accrued, the trial could be recommended to stop if it reached $p < 0.001$ for reduction of CV death and HF hospitalization. The trial was indeed stopped early due to such superiority after a median follow-up period of 21 months and the HF guidelines revised to include the effect of eplerenone.

The COMPASS trial evaluated 27.395 patients with chronic coronary artery disease to rivaroxaban plus aspirin vs aspirin alone vs rivaroxaban alone [16]. The trial was stopped after just 23 months on recommendation of the DSMB for superiority of rivaroxaban plus aspirin ($P<0.0001$). Rivaroxaban alone also showed marginally positive results ($P<0.05$) initially compared to aspirin alone. However, between stopping the trial and publication of the final data, the difference between rivaroxaban alone and aspirin alone had attenuated to non-significance indicating some regression to the truth.

In the GALILEO trial 1520 patients were randomized to Rivaroxaban 10mg plus aspirin vs aspirin plus clopidogrel after transcatheter aortic-valve replacement (TAVR) [36]. In March 2018 the DSMB noted excess of bleeds in the rivaroxaban arm and a negative trend for the primary end point, death or thrombotic event. In August 2018 there was firm evidence that rivaroxaban resulted in an excess of death or any thrombotic event after TAVR as well as major bleeds and the trial was stopped early for safety reasons.

The publication of a trial that stops early claiming superiority needs to recognize that less information is available than if the trial had continued to its originally intended conclusion. Specifically, a trial that stops early is prone to exaggerate treatment efficacy, and had it continued longer some regression to the truth might be expected. These issues indicate the need for interim results of a trial to demonstrate proof beyond reasonable doubt of treatment superiority in order to consider early stopping.

Pharmaceutical companies and regulatory aspects

The primary goal of pharmaceutical companies that invest in drug development is to achieve a label for the compound. A label is a marketing license indication issued by a Regulatory Agency - most importantly by the US Food and Drug Administration (FDA) or the European Medicines Agency (EMA) - preferably both - as a result of RCTs. A label allows marketing and advertisement of a drug, and thus profits ensue.

To achieve success, big pharma companies organize work in several departments: typically, the Marketing Department, the Research and Development Department, the Clinical Operations Department and Regulatory Affairs. Hence, the Marketing Department sets the company goal of RCTs to evaluate medical need and consequent profitability. The Research and Development Department figures out the path to achieve the goal set by the Marketing Department and produces the trial protocol to do so, often in collaboration with independent clinical and statistical experts who may form a Trial Executive Committee. The Clinical Operations Department makes it possible to conduct the RCT on a practical level, i.e. organizes sites, site monitoring, database management etc.; and Regulatory Affairs assesses the outcome goals required for a label and interacts with FDA and EMA.

The key aspects of stopping a trial prematurely are as discussed above efficacy, futility and harm. In general terms stopping a trial prematurely for efficacy and futility is based upon statistical considerations of predetermined significance. However, harm does not need to reach a conventional level of statistical significance, for a signal of harm to stop even an entire drug development program. An example of this was seen in the F7CARD-1610 trial in which recombinant Factor VIIa significantly decreased reoperation rate for bleeding following coronary artery bypass grafting (CABG), but also showed a trend of thromboembolic events in the active drug group. This stopped the development of recombinant Factor VIIa in critical bleeding, although the use of recombinant Factor VIIa to certain degree continues even today off-label [37].

As for efficacy assessments, interim analysis plans may be allowed in pivotal registration RCTs under the aegis of an independent DSMB that has no other connections to the trial. It is essential that we have pre-defined statistical stopping guidelines with strict preservation of the overall type I error.

From a regulatory point, it may not be acceptable to stop a trial early during its execution, even in spite of apparent convincing efficacy results, because of insufficient data on safety and secondary endpoints may be available. Furthermore, cutting a trial short for efficacy may

be compared to stopping a football match at half time when the team you favor is ahead. Your team could or might still lose after completion of the second half.

In any case, interim analyses without realistic objectives should be avoided during the course of the study. Primary efficacy data should be complemented by a demonstration of consistency of trial results. However, if a trial is to be terminated early as a result of an interim analysis it is always important to perform additional analyses on the final trial database including all patient follow up that did not contribute to the interim analysis, and independent adjudication of all primary endpoints.

Conclusions

Stopping a trial early is an important contemporary issue that is of interest to every cardiologist in order to interpret trial findings and to make a subsequent wise choice in therapeutic management. This particularly holds true for cardiovascular pharmacotherapy.

To ensure that investigational treatments are as safe as possible for the participating individuals, DSMBs are a cornerstone of each trial. Their challenges are to interpret data correctly and look for evidence of efficacy, futility, or harm that becomes gradually evident along with accruing endpoints. The DSMB receives interim endpoint data usually in a semi-blinded fashion (A vs B) but it is common practice for the DSMB to confidentially unblind the treatment code when necessary.

With appropriate priority, reasons for stopping are evidence of efficacy, futility, or safety at interim analysis. The a priori selection of key endpoints with an emphasis on the pre-defined primary endpoint is mandatory. We strongly suggest relying on hard endpoints when considering efficacy or safety as a reason for termination; and not on findings that do not affect the prognosis of randomized subjects. These principles are underlined by multiple examples of lipid and antithrombotic trials in this article.

Statistical considerations are the main basis for decisions by the DSMB. The principal methods and examples are outlined, with the recognition that all DSMB recommendations rest on their wise judgement based on the totality of evidence.

Finally, we highlight regulatory aspects, shedding light on the differing and sometimes contrasting interests of the various parties involved. The winner of the compromise of these

interests should always be and mostly is the patient, taking into account the needs of both, patients in the trial and the larger population of future patients.

The 3rd part of this series will be dedicated to subgroup analysis in RCTs.

Conflict of interest

Drexel H, Dopheide JF, Kaski JK, Niessner A, Pocock S, Tamargo J, Mader A, Tautermann G, Huber K, Semb A, Wassmann S, Schmidt TA, Kjeldsen KP, Rosano G

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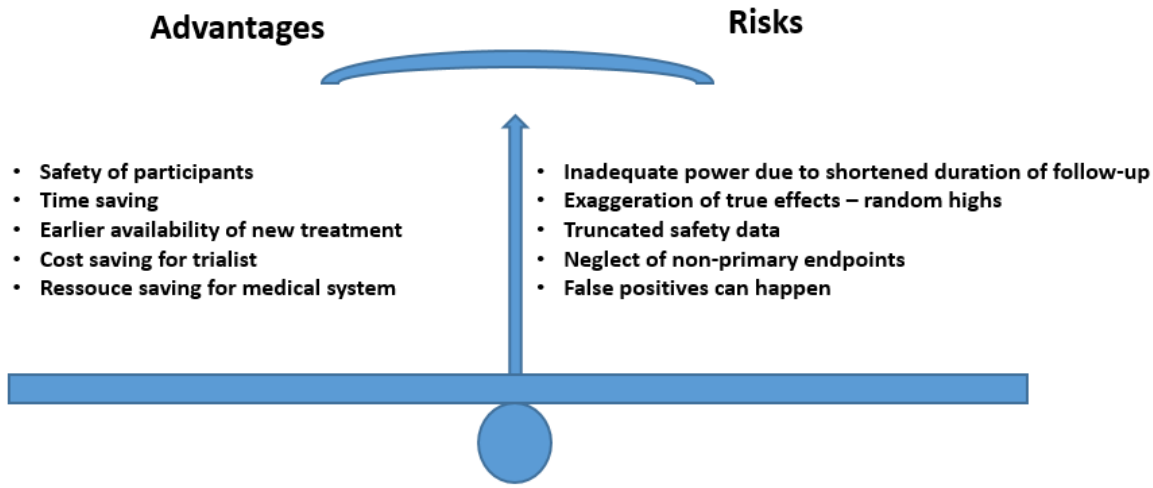
Figure 1: Reasons for early stopping of an RCT

Figure 2: Advantages and Risks for early stopping of an RCT



The age of randomized clinical trials

Three important aspects of randomized clinical trials in cardiovascular pharmacotherapy with examples from lipid diabetes, and antithrombotic trials.

Review Article #2: Reasons for early stopping of an RCT

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