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Factors associated with clinical trials that fail and opportunities for improving the likelihood of success: A review

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ABSTRACT

Clinical trials are time consuming, expensive, and often burdensome on patients. Clinical trials can fail for many reasons. This survey reviews many of these reasons and offers insights on opportunities for improving the likelihood of creating and executing successful clinical trials. Literature from the past 30 years was reviewed for relevant data. Common patterns in reported successful trials are identified, including factors regarding the study site, study coordinator/investigator, and the effects on participating patients. Specific instances where artificial intelligence can help improve clinical trials are identified.

1. Background

Clinical trials for pharmaceuticals and medical devices offer many opportunities for failure. Failures can arise from a lack of efficacy, issues with safety, or a lack of funding to complete a trial, as well as other factors such as failing to maintain good manufacturing protocols, failing to follow FDA guidance, or problems with patient recruitment, enrollment, and retention. Generating accurate and sufficient results to determine whether or not there is merit in continuing is important at each stage in the clinical trial process. The investments of resources, time, and funding grow with successive stages, from pre-clinical through phase 3. Thus, the cost of a failed phase 3 trial is not just the cost associated with the trial itself but the cost of all prior trials as well as the cost of lost time pursuing a potentially viable alternative.

It is important to maintain a philosophy of continual improvement with respect to clinical trials broadly and specifically with an aim towards optimizing every aspect of the research and development process. A comprehensive survey of all possible points of failure in clinical trials is beyond the scope of this publication. Still, there are many factors associated with failed trials that can be distilled with evidence, along with recommendations for improving the chances of success.

2. Failing to demonstrate efficacy or safety

The primary source of trial failure has been and remains an inability to demonstrate efficacy. Hwang et al. [58] assessed 640 phase 3 trials with novel therapeutics and found that 54% failed in clinical development, with 57% of those failing due to inadequate efficacy. There are many reasons that potentially efficacious drugs can still fail to demonstrate efficacy, including a flawed study design, an inappropriate statistical endpoint, or simply having an underpowered clinical trial (i.e., sample size too small to reject the null hypothesis), which may result from patient dropouts and insufficient enrollment.

Clinical trials also fail with respect to safety. Hwang et al. [58] found that 17% of the failed phase 3 trials examined were due to safety. Safety is addressed in every clinical trial in every phase, but issues with safety may only become apparent with the larger populations associated with phase 3 studies, or at post-approval (phase 4) or post-market [24]. Identifying safety issues is not always straightforward. Patients have individual concerns about various adverse events that may not match what physicians are concerned about. This can influence which adverse events are reported, particularly if they are mild to moderate in severity.

For example, Henon et al. [49] studied 27 phase 1 trials in diverse settings between 2014 and 2015. Prior to the start of these particular trials, patients most feared adverse events of hematuria, vomiting, and hyperglycemia, and after the trials they feared some of the same events, but also personality change, fever, and dizziness. The physicians in these trials were concerned instead with eye disorders, confusion, and blurred vision. People may have a greater propensity to present for care when they experience an adverse event that is of concern to them, and not necessarily when experiencing an adverse event of less concern to them but greater concern to the physician. Reminding patients of the importance of reporting adverse events, particularly events of special interest, is recommended for improving the likelihood of detecting safety issues earlier rather than later (e.g. [22]).

It is important also to recognize the desire for a sponsor to move a drug or device forward in the clinical trial process. Rushing studies into

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phase 3 after successful phase 2 trials may not provide time for reflection on how best to address safety in phase 3 [107]. Research also has identified that having higher-educated nurses is associated with lower risks of mortality and failure to rescue ([3,121,128]), which may be helpful as a factor to include in study site selection.

It is critical at each stage of clinical development to have safety be a primary concern even if it is not a primary objective. The cost of uncovering a safety issue increases at each stage, including post-approval [118].

3. Financial impact

Hwang et al. [58] noted that 22% of the failed phase 3 studies they examined failed due to lack of funding. The costs required to complete the entire development process from discovery to bringing a drug to market vary, and so do estimates of these costs; however, they have been reported in excess of $2.5 billion [34]. This includes $1.5 billion of hard dollar out-of-pocket costs with the remainder being lost opportunity of investment costs, but does not include additional post-approval clinical trials. Focusing on phase 3 trials, the Pharmaceutical Research and Manufacturers of America estimated the cost at $42,000 per patient in 2013, with $10 billion spent on 1680 phase 3 clinical trials comprising over 600,000 patients.

Certain studies present unique cost considerations. For example, in a study of hospital-acquired bacterial pneumonia, the cost of a 200-site, 1000-patient phase 3 study was $89,600 per patient [112], with screen failures being a principal driver of the cost. Pharmaceutical research and development is a costly endeavor. More generally, particularly in the United States, the cost of complying with an increasing regulatory burden is also impactful, necessitating more staff, storage, and financial outlay [43].

With such a large financial burden, many trials (in phase 3, but also earlier) are underfunded, and may not have any reasonable opportunity to generate a positive outcome (even if protocols are amended, at additional cost). This leads to ethical issues regarding patient involvement [127]. Patients generally have an expectation that their participation in a trial will lead to an advancement of knowledge based on the trial's successful completion [71]. Underfunded trials are by definition more likely to miss the enrollment needed to demonstrate statistical significance at a predefined level of efficacy.

4. Eligibility criteria

Ideally, inclusion/exclusion criteria should result in a population that matches statistically the intended general patient population [48,124]; however, study designers must account for additional concerns, including whether or not particular segments of a target population may have too many comorbities, leading to additional higher risk of withdrawal and adverse events. For example, Hill et al. [50] noted the heterogeneous nature of pulmonary arterial hypertension (PAH), for which clinical studies have had varied eligibility, but have tended to exclude patients with advanced conditions (New York Heart Association functional class III or IV) and older women, among other categories. The correspondence between the study population and the actual population of concern can become unclear [50].

Inclusion/exclusion criteria also must be chosen in light of the expected effect on recruitment. In the case of patients with PAH, Hill et al. [50] noted the availability of competing therapies, which can suppress enrollment in any one particular study, along with investigators being influenced to recruit patients who will be stable for the duration of the study (3–4 months). Investigators may look for patients who have been stable recently, thus restricting the available population in a way that does not match the general patient population.

Inclusion criteria may vary widely across studies in a specific area, providing little guidance to a prospective sponsor or investigator. For example, in heart failure, Luo et al. [78] reported that there are no uniform diagnostic criteria for heart failure with preserved ejection fraction (HFpEF), with approximately 55% of 121 trials using 50% as the cut-off value for diagnosing HFpEF, leaving 45% choosing another threshold.

Overly specific inclusion criteria can lead to problems in finding suitable participants. This is true particularly for conditions associated with small populations but also it applies generally. Many oncology studies, for example, have exclusions based on prior chemotherapy, having an advanced stage of disease, or not being newly diagnosed. Particularly in oncology, targeted treatments based on specific genetic markers [53] will exacerbate this issue as diagnostics screen out more individuals (hopefully with the benefit of improved efficacy). Making inclusion criteria too narrow may lead to longer recruitment times and also eventually to amending the study protocol in an attempt to recruit additional participants. Getz et al. [44] reported that 16% of protocol amendments are due to changes in inclusion/exclusion criteria, which can lead to differences in the patient populations before and after the amendment [76].

It is clear that the choice of inclusion and exclusion criteria can affect the duration and cost of a clinical trial [4], as well as the likelihood of the trial meeting desired enrollment levels and retaining sufficient participants to have an opportunity to meet a statistical endpoint. Getz et al. [44] noted that across 3400 clinical trials, more than 40% had amended protocols prior to the first subject visit, delaying trials by 4 months. Some protocol amendments cannot be avoided; however, the potential for amendments can be reduced with better planning and anticipation of the consequences from design choices.

Exclusion criteria are often presented without an explicit rationale [104]. Sometimes criteria can be put in place based on an expectation of excluding participants who may not show sufficient improvement against an endpoint, not because their health is too poor but because it is too good. For example, Hill et al. [50] reported on the endpoint of a 6-min walk test for patients with PAH. Patients who could walk more than 400 m prior to being included in trial might not be able to show much improvement (482 m in 6 min is already a 3 mph pace, which would be a moderate pace for a healthy individual). Thus, there would be pressure to exclude patients at this functional level in favor of those who could only walk between 100 and 150 m prior to inclusion. Without background knowledge, someone reviewing exclusion criteria for such a trial might not have explicit motivation to intuit the rationale for this sort of exclusion criterion.

Performing a requisite literature review for related studies remains a labor-intensive task requiring personnel with specific knowledge who can interpret the framework, criteria, and results of prior clinical trials. Future protocol development will benefit from the use of artificial intelligence tools, such as natural language processing [2,17,32,53], which will be able to extract meaningful information across published documents and present systematically organized data to the study designer for consideration. Still, the study designer must think through the implications of different inclusion/exclusion criteria (as well as objectives and endpoints) and the effects they will have on recruitment, enrollment, retention, and ultimately time and cost to completion.

5. Patient recruitment

Patients are often willing to consent to participation in a clinical trial if they believe that they have an opportunity to receive better treatment or if the results can help others [29,45,89]. Still, failing to enroll a sufficient number of subjects in a trial is a long-standing problem [82,101]. A study of 114 trials in the UK [10] indicated that only 31% met enrollment goals. In addition, Campbell et al. [15] reported that one-third of publicly funded trials required a time extension because they failed to meet initial recruitment goals.

Feller [39] reported that 25% of cancer trials failed to enroll a sufficient number of patients, and 18% of trials closed with less than