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Overcoming Obstacles in the Design of Cancer Anorexia/Weight Loss Trials

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Abstract

Most advanced cancer patients suffer loss of appetite (anorexia) and loss of weight. Despite the fact that cancer anorexia and weight loss are associated with a poor prognosis and detract from quality of life, no interventions have been demonstrated to palliate this syndrome in its entirety, particularly in patients with treatment-refractory malignancies. Recently, two registration trials – one with anamorelin and another with enobosarm -- failed to reach their primary endpoints, thus raising questions. Were both these agents ineffective? Alternatively, did study design issues compromise the ability of these trials to identify effective agents? Thus, this review is timely insofar it serves as an introduction to study design, offers guidance on how to test promising agents for cancer anorexia/weight loss, and provides advice for overcoming trial design obstacles.

Keywords

anorexia; weight loss; cancer; study design

> *Our greatest failing is that we neglect the significance of a question and obsess over the accuracy of the answer* [1].

Such appears to be the case with cancer anorexia/weight loss trials [2]. This syndrome of cancer-associated loss of appetite and weight occurs in patients with advanced, incurable cancer and has been described as a “multifactorial syndrome defined by an ongoing loss of skeletal muscle mass (with or without loss of fat mass), not fully reversed by conventional nutritional support… leading to progressive functional impairment” [3]. Its pathophysiology is characterized by a negative protein and energy balance driven by a variable combination

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of reduced food intake and abnormal metabolism. Despite the fact that, in patients with advanced cancer, loss of appetite (anorexia) and loss of weight are associated with poor survival and quality of life, the question of how best to treat this syndrome remains unanswered [4,5]. A plethora of clinical trials has demonstrated that caloric supplementation is not beneficial for patients with incurable malignancies and, in fact, can be detrimental; indeed, the benefit of nutrition support is confined to a focused group of cancer patients who appear to have highly favorable cancer therapeutic options, as previously reviewed by our group [6]. Furthermore, two recent large registration trials, which together enrolled over 1500 patients, failed to achieve their primary endpoints. Such disappointing results underscore the fact that, to date, no intervention has been demonstrated to improve all aspects of the anorexia/weight loss syndrome, particularly in patients with advanced, treatment-refractory malignancies [7,8].

This therapeutic void has raised concerns that some clinical trials might carry methodological shortcomings that might lead to the premature abandonment of a promising intervention [2]. In an effort to curb this possibility, this review serves as an introduction to trial design, offers guidance on testing promising interventions for the cancer anorexia/weight loss syndrome, and provides advice on overcoming obstacles related to designing and completing a clinical trial.

A DEFINITION

Friedman and others define a clinical trial as a “prospective study comparing the effect and value of intervention(s) against a control in human beings” [9]. This definition emphasizes three obvious but fundamental aspects of a clinical trial. First, a clinical trial is a prospective endeavor. A wealth of important clinical conclusions can be drawn from retrospective studies and even from re-analysis of prospectively-acquired data. However, conducting a study prospectively makes it a clinical trial, and this forward-driven focus serves as an essential design element that helps guard against biased conclusions. Second, a clinical trial tests an intervention that requires a comparative assessment of outcome. Of note, although antineoplastic trials typically involve a drug as the intervention, cancer anorexia/weight loss trials can include non-pharmacologic interventions, such as exercise, dietary modification, or educational programs. All these interventions, no matter what type, entail a comparative assessment when administered within the context of a clinical trial. When referring to a comparative assessment, one often envisions a large phase 3 placebo-controlled trial, which generates the highest level of evidence in support of a change in practice [10]. However, before the investment in an expensive phase 3 trial, smaller scale, proof-of-concept, or translational trials are often performed to reduce the risk of a failed, larger trial (Table 1). For example, early-stage oncology phase 1 studies are designed to assess adverse events associated with a series of drug dose escalations, as prescribed to very small patient cohorts with each cohort sometimes comprised of less than a handful of patients. Such phase 1 clinical trials often rely on patients’ baseline symptoms as the comparative assessment element that serves to determine the final recommended dose of the intervention for future testing. As another example, phase 2 studies, which rely on the dose established in the earlier phase 1 trials, can include one or more study arms and are conducted both to explore the efficacy of an intervention and to further establish the safety of that intervention. Even in

a single arm phase 2 trial, a comparative, control element exists, often in the form of historical data. Thus, although the comparative aspect of a clinical trial might not always be readily apparent, it does exist and serves as an inherently important aspect of the trial design. Finally, by virtue of the word “clinical” in “clinical trial,” human beings must be the participants. The evolving role of xenograft or organoid models in clinical research might one day result in a modification of the above definition, but, for now, all high quality, practice-changing evidence requires that human beings be the clinical trial participants [11].

The foregoing definition of clinical trials illustrates the broad-based, incremental approach of drug/intervention development, as reflected in trial design. As noted, clinical trials are categorized as phase 1, 2, and 3 (Table 1). (Phase 4 trials which provide post-marketing data for approved drugs are not discussed here.) Although clinicians await the results of phase 3 trials because of their potential to change clinical practice, the development plan for a therapeutic intervention entails a methodical, stepwise series of clinical trials that often span each of the above development phases, the earlier ones of which often serve to inform the design of the late-stage, phase 3 trial. This effort-intensive approach explains why, for expediency, phases of trials are sometimes merged; for example, phase 1 and 2 trials sometimes take place in sequence within the context of a single, larger clinical trial or, at the very least, an expansion cohort follows the dose escalation cohorts [12,13]. This laborious approach also explains why drug-based interventions can take 10 or more years to establish their efficacy, why many are abandoned prior to phase 3 testing, and why the vast majority are never approved for clinical use [14]

Although the foregoing paradigm of a development plan is drawn from oncology drug trials, this same approach remains relevant to cancer anorexia/weight loss trials. Although some investigators have suggested that trials for the cancer anorexia/weight loss syndrome are distinctly different because of the widely encompassing presentation of this syndrome, we contend that the similarities between the latter and cancer therapeutic trials far outweigh the differences: commonly, cancer therapeutic trials assess tumor response, tumor stability, patient symptomatology, quality of life, patient survival, and biologic endpoints -- in a manner that is analogous to trials aimed at treating the cancer anorexia/weight loss syndrome. Any intervention to treat this syndrome requires scientific justification for the dose of the intervention from a phase 1 trial, further confirmation of the safety of the intervention and preliminary evidence of efficacy within the context of a phase 2 trial, and powerful comparative evidence of efficacy as derived from a phase 3 trial. Exceptions occur. For example, the initial studies which demonstrated that megestrol acetate improves appetite in cancer patients did not rely on previous phase 1 testing but rather on drug dosing that had been used in previous breast cancer antineoplastic trials [15]. Despite such exceptions, the development plan for an intervention to treat the cancer anorexia/weight loss syndrome should consider how the knowledge gleaned from each phase of a trial will be acquired from some source and then incorporated into the overall plan.

COMMENTS ON THE INTERVENTION AND PATIENT POPULATION

This paper makes the assumption that an investigator or group of investigators has carefully considered preclinical data and other preliminary data, has judiciously determined that such

data are encouraging, and then has decided to formulate and embark upon a development plan to test that promising intervention within a clinical setting. This process is perhaps the most challenging aspect of clinical trial investigation and has resulted in many important but negative clinical trials. For example, on Christmas Day 1996, Clark and others reported on a 1321-patient, double-blind, randomized, placebo-controlled trial that showed that the micronutrient, selenium, when taken as a supplement, did not protect against skin cancer [16]. However, in the analysis of secondary outcomes, this study reported that selenium appeared to reduce the incidence of lung and prostate cancer. Years later, three double-blind, randomized, placebo-controlled studies showed that selenium did not prevent prostate cancer, did not prevent lung cancer, and might even have detrimental effects [17–19]. In short, it took many years, almost 38,000 subjects/patients, and close to $100 million to disprove these earlier-reported secondary observations [17–19]. The three, above-referenced, studies are landmark trials and illustrate the point that the decision to test any intervention for any indication, including for treating the cancer anorexia/ weight loss syndrome, should be well grounded in solid data and thoughtfully considered prior to the initiation of a clinical trial or a series of clinical trials. Yet, to justify the conduct of a trial from a scientific, ethical, and financial standpoint, the chance that an intervention will be effective must be deemed equal to the chance that it will not – in effect, equipoise must exist at the outset [20]. Chan and others cite several factors that predict the success of a phase 3 trial that followed a phase 2 trial with a targeted cancer agent -- such as multi-site phase 2 trial participation, pharmaceutical company sponsorship, and, of course, a favorable outcome from the phase 2 trial [21]. We can only speculate on why pharmaceutical company-sponsorship is associated with success; this positive association may hinge on a desire to seek more pragmatic outcomes that drive a business model or perhaps on better financial support for the development plan. In the absence of compelling phase 2 data, the success of phase 3 trials in cancer therapeutics with targeted agents is much lower [22]. Similar findings as those from Chan and others have been reported by others, although the clinical value of the endpoint that defined the success of the phase 3 trials at times seems debatable [21]. Nonetheless, taken together, such findings raise hope that scrutiny of phase 2 data and consideration of the other points raised by Chan and others will eventually lead to therapeutically positive phase 3 trials for the cancer anorexia/weight loss syndrome as well.

It stands to reason that a specific intervention for the cancer anorexia/weight loss syndrome might work better for some patients than for others. Fearon and others provided a thoughtful exposition of the stages of the cancer anorexia/weight loss syndrome based on degree of weight loss and other clinical factors. These investigators outline three categories of cancer anorexia/weight loss, thereby enabling clinical trialists to select a target population for a clinical trial. Some investigators have voiced that the less severe category of cancer anorexia/ weight loss comprises the ideal patient population for clinical trial recruitment (Table 2) [3]. Despite the importance of the work from Fearon and others, we believe that patient trial selection should be based on the mechanism of action of the intervention, pharmacokinetics, or other scientific aspects of the intervention itself. For example, if a candidate drug is likely to take several weeks *in vivo* to reach a steady state, such a drug is unlikely to be effective for treating cancer patients with rapid, severe weight loss; a different patient population with perhaps a more indolent course should be targeted for a clinical trial with that agent.

In concert with the preceding point, several investigators have advocated for focusing on cancer patients who have a more indolent clinical course with a slower pace of weight loss. These investigators have described how some cancer patients with rapid and severe weight loss may have reached a point after which even the most effective of interventions is unable to yield a favorable impact. In fact, the recruitment of patients with rapid, severe weight loss results in high patient dropout rates, which in turn results in a need to design a trial with a very large sample size or, worse yet, leads to biased conclusions when patient dropout is not handled appropriately in the analysis. Short-term endpoints may more accurately capture the effect of an intervention that targets this patient population at risk for dropping out. Although a source of frustration for some investigators, these high dropout rates speak directly to the need to pursue clinical investigation in this field in general. Early patient demise is an unfortunate but seminal feature of the cancer anorexia/weight loss syndrome; to ignore the lethal nature of this syndrome is to ignore the urgent, fundamental impetus for conducting clinical research in this field [4,5].

KEY TACTICS TO CIRCUMVENT BIAS: RANDOMIZATION AND BLINDING

Randomization and blinding are key tactics that reduce the risk of bias in clinical trial results. Both are elementary concepts but are important to grasp prior to designing a clinical trial. Although randomization and blinding are more commonly employed in phase 3 studies, they can also be used in earlier phase studies to benchmark comparative outcomes.

The National Cancer Institute in the United States defines randomized trial as follows [23]:

> *A study in which the participants are assigned by chance to separate groups that compare different treatments; neither the researchers nor the participants can choose which group. Using chance to assign people to groups means that the groups will be similar and that the treatments they receive can be compared objectively. At the time of the trial, it is not known which treatment is best.*

Because baseline and other differences between groups can potentially confound study results, randomization is a powerful tool that equalizes confounding factors and helps to ensure that study results capture the true effect of the intervention. Bias can be viewed as an insidious threat in clinical trials, and randomization is an important tool that, by default, eliminates bias caused by treatment selection.

Along similar lines, the National Cancer Institute in the United States defines a blinded trial as follows [24]:

> *A type of study in which the patients (single-blinded) or the patients and their doctors (double-blinded) do not know which drug or treatment is being given. The opposite of a blinded study is an open label study.*

A double-blinded study, as opposed to a single-blinded study, gives rise to the more reliable study results. Again bias is insidious, and both patients and healthcare providers can inadvertently inject bias into trial results. Blinding minimizes this injection of bias, thereby enabling the benefits and detriments of a therapeutic intervention to become more accurately manifest.

A placebo-controlled, randomized, double-blinded clinical trial provides a rigorous trial design for learning the benefits and detriments of an intervention. Admittedly, at times, the inclusion of a placebo, or an inert substance, is viewed as unethical, particularly if a standard therapeutic intervention with proven efficacy already exists. Daugherty and others have generated an algorithm that relies on ethical and scientific parameters to decide whether the incorporation of a placebo into a clinical trial is appropriate; for the cancer anorexia/weight loss syndrome, it appears to be appropriate [25]. Moreover, given that as many as 40% of placebo-exposed patients enrolled in cancer anorexia/weight loss trials have described an improvement in appetite, one might view the inclusion of a placebo arm as essential for interpreting study findings and for understanding the true, unbiased effect of an intervention [15]. Importantly, a placebo effect can also be seen with more objective parameters such as improvement in weight, thus reflecting the possibility that other, non-study interventions are influencing outcomes and thus demonstrating the need to incorporate a placebo into the study design to gauge true benefits and toxicity of the putatively active intervention [15].

In this context, where multiple placebo-controlled trials have already been completed, one might, however, further question the value of a placebo. Might one assume that the placebo effect for specific endpoints, such as perhaps appetite, has already been established and anticipate -- but not re-measure -- this effect in future cancer anorexia/weight loss trials? The answer is “no” [26–30]. The placebo effect can vary markedly from trial to trial for unapparent reasons. For example, an intramuscularly administered placebo for pain yields a higher placebo effect than one that is oral, although an oral placebo can yield a greater effect for treating a symptom such as insomnia. Frequent daily dosing appears to yield a higher placebo effect than once a day dosing. A multi-arm study with an embedded placebo arm yields a higher placebo effect than a two arm study with a placebo arm. And conceivably, the well-intentioned, enthusiastic clinical investigator who speaks of his research with great passion to audiences who include potential trial candidates or current trial recruits is likely to escalate the placebo effect as a result of his actions. In essence, the placebo effect is influenced by a variety of factors that vary over time and that may even be unique to a specific trial. Capturing this placebo effect requires a reassessment within the context of each specific, phase 3 trial. Indeed, the placebo effect goes beyond patient-reported outcomes, such as appetite. It can also modulate the so-called “hard endpoints,” such as body composition or weight itself. For example, in the placebo-controlled ROMANA trials that tested the oral ghrelin agonist, anamorelin, some patients who were assigned to the placebo arm gained weight over time [31]. Whether this weight gain was the result of effective antineoplastic therapy or some other intervention partaken by a subgroup of patients remains unknown; nonetheless, this observation of weight gain tells of the importance of a placebo in capturing unexpected clinical outcomes and benchmarking these outcomes against those observed in the active intervention arm. Of relevance, not just patients but also healthcare providers report favorable outcomes among placebo-exposed patients, and sometimes healthcare providers who know the treatment assignment can inadvertently influence patients’ reporting of outcomes, realities that further emphasize the importance of double-blinding [26–30].

Importantly, the incorporation of an inert, comparative arm is essential even for non-drug trials, but defining and incorporating such an arm and analyzing and interpreting trial results

can be especially challenging when blinding is not feasible. For example, the mere mention of testing exercise in a cancer anorexia/weight loss trial is likely to attract a group of patients who are more interested in exercise and therefore perhaps are inadvertently likely to begin to exercise even if not assigned to the interventional exercise arm of the trial. In effect, the non-exercise, control arm becomes “contaminated” with exercise. Circumventing this bias from contamination can be challenging but remains achievable by means of several approaches. First, defining the clinical intervention with great specificity and incorporating a comparative arm that clearly does not include this same specific intervention partially attenuates this risk of contamination between arms. Second, if adherence to exercise can be checked with a marker –a blood- or urine-based biomarker, such as, for example, urine creatine which provides an important estimate of total body skeletal muscle mass -- then that marker can enable the investigators to adjust for possible contamination when analyzing the final trial results [32]. Third, increasing the sample size to enable the trial to detect a smaller effect size as a result of contamination between study arms is yet another approach that enables a controlled, non-pharmacological trial to be meaningfully interpreted. Fourth, relying on data from a meta-analysis, Steins Bisschop and others describe how using a crossover design and offering an intervention to the control arm following an intervention of limited duration reduces both contamination and dropout rates [33]. Of note, this approach may be challenging to implement in cancer anorexia/weight loss trials because untreated patients with this syndrome are likely to manifest a decline over time and thereby become ineligible for the crossover; nonetheless, this approach is important to mention. Similarly, a waitlist trial design might also be considered because of its ability to enhance power; however, although this trial design is optimal for assessing an intervention that potentially provides a short-term favorable impact within the context of a static clinical situation, it appears to be less fitting for cancer anorexia/weight loss trials because of this syndrome’s non-static nature and because this design appears to increase the possibility of yielding exaggerated treatment effects [34]. In general, intervention contamination shifts outcomes in trial arms toward equivalence, hence making trials that report a major difference in outcomes between arms particularly noteworthy.

ENDPOINTS

The choice of primary endpoint is one of the most challenging decisions of trial design and merits considerable thought, as outlined below. First, the endpoint(s) of a trial will likely vary based on the phase of the trial. For example, a phase 1 study may examine toxicity or preliminary evidence of biological effect whereas a phase 3 study will likely incorporate a clinically relevant primary endpoint into its study design. Moreover, endpoints in an early-phase trial often will determine the choice of primary endpoint in a later phase trial; in other words, endpoints are often not determined at the very outset when an overarching drug/intervention development plan is being pondered and constructed. However, sometimes this evolution of thought on endpoints does not work out as planned. For example, the phase 3 studies with anamorelin used hand grip strength as a co-primary endpoint to assess whether any derived increments in lean tissue led to functional lean tissue [31]. Although phase 2 data had shown that hand grip strength resulted in a statistically significant improvement in anamorelin-treated patients compared to placebo-exposed patients at 8 weeks (p=0.011), in

the phase 3 trial, comparative improvement in hand grip strength was not observed. In fact, using a co-primary efficacy endpoint of hand grip strength coupled with median change in lean body mass as assessed by dual x-ray absorptiometry, this 900+ patient phase 3 trial generated negative/neutral findings: “We noted no difference in handgrip strength….” Second, this last point underscores the obvious: the choice of the primary endpoint perhaps merits more thought than any other aspect of the trial design. The choice of the primary endpoint should be congruent with expectations of the drug/intervention and should be based on solid scientific rationale. In other words, if the efficacy of an agent is thought to revolve around its orexigenic effects, then seeking a primary endpoint that focuses on augmentation of lean tissue is illogical and should not be incorporated into the trial. Similarly, the optimal timing of the assessment will vary based on the half-life and mechanism of action of a specific agent and, therefore, will differ from trial to trial. Third, at least two recent phase 3 studies in this field have been viewed as negative/neutral in part because of their use of a co-primary endpoint [31,35,36]. These studies were apparently designed with input from regulatory agencies and relied on both augmentation of lean tissue and functionality of lean tissue as definitions of success with regard to drug approval for the indication of “cachexia” [31,35,36]. Obviously, seeking success in two outcomes sets a higher bar than seeking success in only one. Other important endpoints can be ranked as secondary, do not determine the success of the trial, but can be critically measured and reported. When possible, the primary endpoint should be sharply focused, clean, and clinically relevant. Indeed, the American Society of Clinical Oncology (ASCO) noted that the two most meaningful endpoints in cancer treatment are survival and quality of life [37]. Although cancer anorexia/weight loss trials pose a special challenge because no approved agent yet exists to treat this syndrome and because this syndrome is far-reaching with loss of appetite, changes in body composition, and a negative impact on both survival and quality of life, the above comments from ASCO perhaps remain germane to all cancer patients and are important for establishing future precedent in this area of clinical research.

Of incidental note, although quality of life is sometimes viewed as a “soft endpoint,” it is important to acknowledge that quality of life – as well as all symptoms -- can be measured. Although quality of life endpoints often introduce greater variability of measurement than other endpoints, quality of life can nonetheless be reliably and scientifically measured by means of questionnaires which have been validated both for accuracy and precision [38–41]. Thus, when appropriate, the assessment and measurement of quality of life is feasible and important in cancer anorexia/weight loss trials.

Fourth, the choice of primary endpoint and the calculation of sample size are intricately tied together (Table 3). For a phase 3 trial, sample size should be based on a clinically meaningful and realistic treatment effect size. During these days of cost containment, it is easy to settle for a smaller sample size and generate inconclusive trial results. Tension exists between realistic expectations surrounding trial accrual (“if we can’t accrue the designated large sample size, we will not have given the agent a chance to work”) and seeking a sample size based on a clinically meaningful effect size (“if we settle on a smaller sample size that does not allow us to truly assess the efficacy of an agent, we will have prematurely discarded a potentially effective agent”). In essence, mounting a definitive trial requires that a team of investigators acknowledge that clinical research is expensive and that conducting a clinical

trial entails an ethical responsibility to find definitive answers – regardless of whether positive or negative -- to address the needs of cancer patients. In our opinion, the larger sample size -- if needed to prove or refute the efficacy of an intervention -- should be incorporated into the trial design.

Finally, definitive phase 3 trials in cancer anorexia/weight loss clearly call for large sample sizes. The risk of too large a sample size that detects a treatment effect that is too small to be clinically meaningful tends to be a lesser concern in phase 3 cancer anorexia/weight loss trials. Of parenthetical note, investigators sometimes query whether an interim analysis might help reduce sample size – particularly in the off chance that a statistically significant difference in treatment arms might emerge and thereby result in early study closure and early reporting of results. Ironically, this approach can result in the need for an even larger sample size; each planned look at the data for efficacy detracts from power and thereby requires an even larger sample size. Similarly, other factors that increase the calculated sample size, sometimes to the surprise of clinical investigators, include the following: an incidence rate of the endpoint of interest that hovers close to 50%, a small anticipated effect size, an anticipated few number of events of interest (Table 3), a randomization ratio other than 1, and a responder analysis where a continuous primary outcome variable is dichotomized into responder versus non-responder categories [42,43]. These factors should be considered carefully in designing a clinical trial, particularly if feasibility concerns point to the need to deliberate about a smaller but clinically reasonable sample size.

In general, however, this requirement for a large sample size in cancer anorexia/weight loss trials reflects high dropout rates and rigorous analysis plans that call for an intention-to-treat analysis. In other words, patients who have dropped out of the trial must be included and reported in the primary analyses. For example, previous, well-conducted studies have reported, in the numerator, the number of patient who have achieved a specific, clinically meaningful outcome and, in the denominator, all the patients enrolled in the trial – regardless of when or whether that patient had dropped out of the study [15]. The decision to study and attempt to help patients with this syndrome inevitably entails a willingness on the part of investigators to conduct large phase 3 trials, to analyze the resulting data in an unbiased fashion with an intention-to-treat analysis, and then also to evaluate the patterns of dropout and conduct a sensitivity analysis to provide assurance that patient drop outs do not reflect bias within the trial.

This last point of conducting a sensitivity analysis to further establish the validity of trial findings is an important one [44,45]. A sensitivity analysis is “a method to determine the robustness of an assessment by examining the extent to which results are affected by changes in methods, models, values of unmeasured variables, or assumptions” [38]. In effect, if multiple different analyses of the same data set – for example, including and then omitting patients who dropped out of the trial; including and then omitting outliers; and omitting and then including patients who were enrolled inadvertently despite their failure to meet the trial’s eligibility criteria -- point to the same conclusion as the primary analysis, the trial results can be reported with greater confidence. Described in fewer than 30% of reported clinical trials, a sensitivity analysis is a powerful and cost-effective tool that examines consistency within the data set but that appears to be grossly underutilized [46].

THE CLINICAL PROTOCOL: A STANDARD OPERATING PROCEDURE (SOP) MANUAL

Some journals have now begun to ask for the original clinical trial protocol when reviewing and publishing the manuscript that reports the clinical trial's primary endpoint [47]. This document outlines the SOP for conducting the clinical trial and includes multiple components: background/rationale, objectives/endpoints, patient eligibility and exclusion criteria, details about the protocol intervention, a patient follow up schedule, and an in depth data analysis plan during the conduct of the trial and after its completion (Table 4). Although this document often needs to be revised over time, in general, it acquires "a life of its own" during the conduct of the trial and remains immutable unless modifications occur by means of a consensus that, at times, relies on input external to the study team. This document must be adhered to up until publication of the report of the trial's primary endpoint,

The main reason that journals now ask for the clinical trial protocol rests in the fact that lack of adherence to the protocol SOP gives rise to compromised trial results. This lack of adherence – for example, enrolling patients who do not meet trial eligibility criteria or for example, reporting a secondary endpoint as the primary endpoint -- can also increase the likelihood of generating findings that are irrelevant to the patient population of interest or spurious and unable to be replicated. Thus, using the clinical protocol document as a SOP throughout the conduct of the trial adds rigor and credibility to study results.

INVOLVE A STATISTICIAN EARLY AND THROUGHOUT THE TRIAL PROCESS

Ioannidis published an essay entitled, "Why most published research findings are false." The published literature is apparently fraught with studies that are unable to be replicated [48]. Importantly, the most reliable predictor of success in replication is the strength of the original evidence [48]. Although we began this paper with a quote that downplays obsessing over the "accuracy of the answer," we believe that rigorous clinical trial design not only makes it easier to acknowledge the importance of the question but also makes the accuracy of the answer a foregone conclusion.

To this end, we believe a special plea can be made for engaging a statistician early and throughout the clinical trial process – particularly for cancer anorexia/weight loss trials. Statistical models are valid under only certain assumptions. A study statistician can help ensure that the trial is designed so that the data obtained at the end meet these assumptions and that the appropriate analysis will be conducted to ensure the validity of the results. Given the high morbidity and high mortality of cancer anorexia/weight loss, it is only humane to convey to patients, their families, and their healthcare providers information that can honestly be relied upon. It also appears only humane to make the original evidence of efficacy – or of lack of efficacy – as strong as it can possibly be. We believe these goals can only be achieved with the inclusion of a statistician as a member of the study team. Such a team approach is essential for the generation of meaningful, trustworthy results.

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Biographies

Dr. Le-Rademacher is the lead statistician within the Cancer Control Program at the Mayo Clinic and holds a long track record of designing and overseeing clinical trials in cancer patients. She holds special interest in understanding methodological issues in clinical trials.

Dr. Crawford is a practicing medical oncologist with an interest in lung cancer therapeutics. He has been involved in multiple clinical trials, including multi-institutional clinical trials.

Dr. Evans holds interests in geriatrics and functional reserve and has published extensively in these areas. He has special interests in understanding issues as relevant to resilience in older individuals.

Dr. Jatoi is a practicing medical oncologist with interests in supportive care issues, including cancer-associated weight loss. She has conducted numerous clinical trials in cancer-associated weight loss.

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Highlights

- To date, no intervention has been demonstrated to improve all outcomes in patients who suffer from cancer-associated anorexia and weight loss.
- The design of high-quality clinical trials may lead to improved clinical outcomes in patients with advanced cancer.
- In designing clinical trials for patients suffering from cancer-associated anorexia and weight loss, multiple design issues should be carefully considered, as reviewed here.

Table 1

United States' National Cancer Institute Clinical Trial Definitions*

TYPE OF TRIAL	QUOTED DEFINITION
Phase 1	The first step in testing a new treatment in humans. A phase I study tests the safety, side effects, best dose, and timing of a new treatment. It may also test the best way to give a new treatment (for example, by mouth, infusion into a vein, or injection) and how the treatment affects the body. The dose is usually increased a little at a time in order to find the highest dose that does not cause harmful side effects. Phase I clinical trials usually include only a small number of patients who have not been helped by other treatments. Sometimes they include healthy volunteers.
Phase 2	A study that tests whether a new treatment works for a certain type of cancer or other disease (for example, whether it shrinks a tumor or improves blood test results). Phase II clinical trials may also provide more information about the safety of the new treatment and how the treatment affects the body.
Phase 3	A study that tests the safety and how well a new treatment works compared with a standard treatment. For example, phase III clinical trials may compare which group of patients has better survival rates or fewer side effects. In most cases, treatments move into phase III trials only after they meet the goals of phase I and II trials. Phase III clinical trials may include hundreds of people.
Phase 4	A type of clinical trial that studies the side effects caused over time by a new treatment after it has been approved and is on the market. These trials look for side effects that were not seen in earlier trials and may also study how well a new treatment works over a long period of time. Phase IV clinical trials may include thousands of people. Also called post-marketing surveillance trial.

* All definitions are quoted from the NCI Dictionary of Cancer Terms (https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45835; last accessed January 14, 2017).

Table 2

Stages of the Cancer Anorexia/Weight Loss Syndrome, or “Cachexia”

NORMAL	PRECACHEXIA	CACHEXIA	REFRACTORY CACHEXIA	DEATH
	Weight loss </= 5%; anorexia and metabolic changes	Weight loss > 5% OR body mass index (BMI) < 20 and weight loss >2% OR sarcopenia and weight loss > 2%. Often reduced food intake/systemic inflammation	Variable degree of cachexia. Cancer disease is both procatabolic and not responsive to anticancer treatment. Low performance score. < 3 months expected survival.	

Modified from: Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol 2011; 12:489–95.

Table 3

Trial Factors that Modify Sample Size

FACTOR	DIRECTION OF CHANGE IN SIZE OF FACTOR*	CHANGE IN SAMPLE SIZE
Type 1 error	decrease	larger
Power	increase	larger
Effect size	decrease	larger
discrete	close to 0.5	larger
time-to-event	fewer events	larger

*Assumes that only one factor changes at a time.

Table 4

Protocol Elements

PROTOCOL ELEMENT	PURPOSE	INFORMATION PROVIDED	AFFECTED DESIGN ELEMENT
Background	• Provides summary of previous work • Justifies trial	• Rationale for outcome estimates (patient population) • Rationale for anticipated treatment effect(s)	• Phase • Number of arms • Randomization • Blinding • Interim analysis • Sample size • Trial duration
Objectives/Endpoints	Defines objectives and endpoints	• Type of intervention response • Response time point	• Phase • Number of arms • Randomization • Sample size (methodology) • Trial duration (timing of response)
Eligibility (includes both inclusion and exclusion criteria)	Sets criteria required for legitimate patient enrollment	Specific parameters that result in inclusion or exclusion of patients to the trial	Sample size (due to outcome estimate, adherence, withdrawal, drop-out)
Protocol Intervention(s)	Describes how treatment(s) are delivered	Treatment • Mode • Dose • Frequency • Duration	• Blinding • Sample size (adherence, withdrawal, dropout) • Trial duration
Patient Follow-up Schedule	Describes how patients will be followed after treatment	Follow-up • Frequency • Duration	• Sample size (loss to follow-up) • Trial duration (follow-up duration)
Analysis Plan	Describes how all aspects of the data will be presented and analyzed	• Rationale for analysis plan • Definition of primary and secondary analyses • Description of handling of missing data • Description of sensitivity analyses	