Report of a National Institutes of Health–Centers for Disease Control and Prevention workshop on the feasibility of conducting a randomized clinical trial to estimate the long-term health effects of intentional weight loss in obese persons[1,2]

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See corresponding editorial on page 347.

ABSTRACT A workshop was convened in 1997 by the National Institutes of Health and the Centers for Disease Control and Prevention to consider the need for and feasibility of conducting a randomized clinical trial to estimate the long-term health effects of intentional weight loss in obese persons. Although the benefits of weight loss in obese individuals may seem obvious, little information is available showing that intentional weight loss improves long-term health outcomes. Observational studies may be unable to provide convincing answers about the magnitude and direction of the health effects of intentional weight loss. Workshop participants agreed that a well-designed randomized clinical trial could answer several questions necessary for developing a rational clinical and public health policy for treating obesity. Such information will ultimately provide needed guidance on the risks and benefits of weight loss to health care providers and payers, as well as to millions of obese Americans. *Am J Clin Nutr* 1999;69:366–72.

KEY WORDS Obesity, randomized clinical trials, workshop, pharmacotherapy, behavior therapy, weight loss

BACKGROUND

Every year, obesity contributes to substantial morbidity and mortality and is responsible for billions of dollars in medical costs and lost productivity (1, 2). Many physicians recommend weight loss as a therapeutic strategy, but data showing that intentional weight loss improves long-term health status (measured by disability, morbidity, longevity, and overall quality of life) are limited. In fact, a growing number of critics in both the scientific community and the lay press are questioning whether obesity should be treated at all. Many suggest that treatment of obese persons should focus instead on obesity's comorbid conditions, such as type 2 diabetes or dyslipidemia (3). Critics point to numerous observational studies that have found weight loss to be associated with increased morbidity and mortality (4). Most of these observational studies, however, had at least one serious limitation, such as the inability to separate intentional from unintentional weight loss (eg, as a result of illness) or the inability to adequately control for preexisting illness. Among persons trying to lose weight, preexisting illness may confound the association between intentional weight loss and health outcomes by causing unintentional weight loss and contributing to final adverse health outcomes. Some scientists believe that such limitations can be addressed only through interventional studies designed to measure long-term changes in health outcomes that accompany intentional weight loss (5). Only a few studies have examined long-term changes in risk factors and health outcomes resulting from intentional weight loss, however, although numerous clinical trials have shown short-term reductions in physiologic risk factors for disease with weight loss (6).

On April 17 and 18, 1997, a workshop was convened by the National Task Force on Prevention and Treatment of Obesity in Bethesda, MD, in conjunction with the National Institute of Diabetes and Digestive and Kidney Diseases; the National Heart, Lung, and Blood Institute; the National Institute on Aging; and the Centers for Disease Control and Prevention, to consider the need for and feasibility of a randomized clinical trial (RCT) estimating the long-term health effects of intentional weight loss in obese persons. During the workshop, participants reviewed current knowledge of the health effects of both obesity and intentional weight loss, considered economic issues, and discussed study design and the interpretation of study outcomes. Among the participants were representatives from the workshop's sponsoring organizations; distinguished researchers in the fields of obesity, nutrition, physiology, epidemiology, statistics, pharmacology, psychology, and design of clinical trials; and leaders of patient advocacy organizations. The following summary describes the major issues addressed and outlines the conclusions reached by participants during this highly interactive meeting. (A full report of the minutes of the workshop can be

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Received July 2, 1998.

Accepted for publication October 9, 1998.

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CURRENT KNOWLEDGE OF INTENTIONAL WEIGHT LOSS

Animal models

Studies conducted with animal models (eg, Zucker obese rats) have shown that restricting energy intake can dramatically increase longevity. No information, however, was presented at the workshop on the effects of interventions designed to reduce the weight of obese animals on morbidity or mortality.

Human studies

Information on the long-term health effects of weight loss in humans has come primarily from observational studies, several of which raised concerns about the safety of intentional weight loss or weight variability resulting from unsustained weight loss. Data from both the Framingham Heart Study (7) and the Multiple Risk Factor Intervention Trial (8) suggest that weight loss may be associated with adverse health consequences, but that this may occur primarily in the leanest subjects. In the Framingham study, those who lost weight ultimately had higher mortality rates than those who did not lose weight, even though persons who initially lost weight experienced more favorable changes in blood pressure and serum cholesterol (9). Intentional weight loss was not examined directly in either study. A prospective 12-y study that assessed the intentionality of weight loss, conducted with the American Cancer Society's Cancer Prevention Study I cohort (10), found that intentional weight loss among women with obesity-related comorbidities (such as type 2 diabetes) is associated with increased longevity; among women with no preexisting illness, however, the association was ambiguous. It was noted in the discussion at the workshop that even in those few studies in which losing weight appeared to have a positive effect on health, the relative importance of energy restriction, food substitution, and physical activity was unclear, as was the role of self-selection. All of these factors are difficult to control in observational studies, and workshop participants agreed that current studies do not provide the data necessary to address these questions.

Preliminary data from a long-term research initiative, the Swedish Obese Subjects Study, which is controlled but not randomized, show that obesity-related comorbid conditions were markedly reduced in a cohort of obese men [body mass index (BMI; in kg/m^2) > 38] and women (BMI > 34) who underwent gastric surgery to lose weight. Morbidity and mortality are being studied over a 10-y follow-up period; obesity-associated costs and quality of life are being assessed as well (11). Two-year follow-up data from this study indicated that among those who lost weight, all cardiovascular disease risk factors, with the exception of cholesterol concentrations, improved significantly, whereas most risk factors worsened among those who gained weight (12). Self-selection of participants to the intervention and control groups and restriction of the population to the severely obese are major limitations of the Swedish study. Workshop participants concluded that more information is needed on the long-term health effects of intentional weight loss in persons with lesser degrees of obesity, who constitute the majority of obese individuals for whom weight loss is currently recommended.

THE NEED FOR AN RCT

Is current knowledge of the benefits of losing weight sufficiently compelling to render unnecessary a large and costly RCT of the health effects of intentional weight loss? On the converse issue, the harm of gaining weight, workshop participants generally agreed that the evidence available, such as that from the Nurses' Health Study (13), clearly and consistently shows that weight gain during adulthood corresponds to increased risk of cardiovascular disease and that risk of both cardiovascular disease and type 2 diabetes increases with increasing weight. On the other hand, observational studies do not clearly show that intentional weight loss sustained over the long term reduces health risks. Intentionality has generally not been assessed, and the extent to which weight loss is sustained in the long term is frequently unknown. It is also unclear whether successful, intentional weight loss can reverse established pathology to the degree that disease risk is lowered meaningfully. Finally, variability in obesity-related covariates, such as physical inactivity, can confuse attempts to sort out the effects of weight or weight loss on health because the covariates themselves can cause ill health.

Even when the risks and benefits of an intervention seem obvious, conducting an RCT could reveal unforeseen results. About 2 decades ago, for example, RCTs of 2 scientifically plausible treatments [estrogen treatment to prevent cardiovascular disease in men (14) and clofibrate treatment for hypercholesterolemia (15)] revealed that both caused unexpected, harmful outcomes.

The general use of RCTs to estimate the efficacy of behavioral interventions has been criticized (16). In the case of intentional weight loss, however, workshop participants believed that experimental testing is warranted because efforts by obese persons to lose weight are common; economic costs of implementing effective, sustained weight-loss interventions within the clinical care system are substantial; and concern lingers over the safety of losing weight intentionally.

EFFECT OF AN RCT ON HEALTH CARE POLICY

Estimates derived from an RCT of the health and economic effects of intentional weight loss will allow the clinical and public health communities to better judge the value of investment in obesity treatment. For example, is obesity treatment cost-effective? Such knowledge would help guide resource decisions about clinical and public health programs for obesity treatment, including the development of reimbursement guidelines for managed care organizations and for third-party payers.

ISSUES RELATED TO THE INTERPRETATION OF AN RCT

Can an RCT separate the effects on health outcomes of weight loss per se from the effects of the weight-loss interventions? What is the efficacy of currently available weight-loss interventions? Is it appropriate to have a control group, and how might this group be "treated?" These issues were discussed at some length.

Treatment effects compared with weight-loss effects

Subjects in an RCT could not be randomly assigned to lose or not lose weight; they could only be randomly assigned to receive or not receive interventions that might result in weight loss. These interventions, however, might well produce changes in

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health status that are not due to weight loss. Promotion and maintenance of weight loss through increased physical activity, reduced saturated fat intake, and consumption of large amounts of fruit and vegetables are examples of such interventions. It may appear that one could never infer that weight loss itself caused the changes in health status. However, if participants in an RCT were randomly assigned to several interventions that produce weight loss through different mechanisms and these interventions yielded similar improvements in health status, then the conclusion that weight loss was responsible for the improvements in health outcomes may be justified.

Efficacy of current weight-loss treatments

In experimental studies of weight loss, well-executed studies using currently available pharmacologic or behavioral interventions rarely result in more than 8–10% average reductions in body weight (17). The lowest weight is generally reached ≈6 mo after the intervention begins and is rarely maintained by the average participant for longer than another 12 mo, at which time the participant's body weight begins to increase back toward its preintervention level (18). Even such relatively brief reductions in weight have produced clinically meaningful changes in intermediate physiologic risk factors (such as blood pressure or cholesterol) for morbidity and mortality in the short-to-medium term. On the other hand, although a large proportion of the US population reports intentionally losing weight (19), the value, and even the safety, of intentional weight loss on long-term health is being seriously questioned (3). Thus, a valid and useful function of the RCT would be to specifically evaluate the efficacy (in terms of both risk and benefits) of current weight-loss practices.

Control group

Theoretically, the control group should include obese persons who do not intentionally lose weight during the entire study, and the health status and health outcomes of these participants should be monitored in the same way as the health status and health outcomes of participants randomly assigned to the intervention groups. Good RCT practice also dictates that participants and investigators in all treatment groups, including the control group, be blinded to treatment status. Because obese persons in our society are likely to try to lose weight, especially through self-treatment, it is possible that any control group would try to lose weight in parallel with the treatment groups, which might bias results of the trial toward showing no difference. In addition, neither participants nor study providers in any of the control or intervention groups could be blinded to their status. On the other hand, it may be feasible to maintain control groups who do not lose weight in long-term studies by providing them with a minimal intervention of a self-help manual on weight loss and healthy eating (20). Obese control groups often have greater retention rates than do treatment groups. This result is believed to be attributable to the control group members feeling less embarrassed than their intervention group counterparts if they do not lose weight or if they regain lost weight.

In the workshop discussion, the issue was also raised of whether it is ethical to have a control group in which participants do not receive weight-loss treatment, even though we do not currently know how beneficial weight loss is in terms of changes in long-term health status. It was pointed out that even a minimal control intervention provided by a study is more than many obese persons ever receive from their own physicians. Viewed in this light, having a control group might not be seen as creating an ethical problem of withholding beneficial treatment. Furthermore, questions raised regarding the putative harmful associations between weight loss and long-term health argue that not providing weight-loss treatment to obese persons in a clinical trial may be appropriate.

DESIGNING AN RCT

Study population

The 2 key issues in identifying study populations are the statistical power of the study and the generalizability of the findings. Age, sex, race-ethnicity, degree of obesity, and presence of comorbid conditions should be considered in choosing the study population. Because the RCT should address the public health effect of weight loss, the study population should reflect the distribution of obesity in the United States. Including men and women of various socioethnic backgrounds is important because of the adverse secular trends toward increased weight among racial and ethnic minority populations (21). In addition, the relation between obesity and health may differ by sex or ethnicity. Older adults should be included because both the risks and benefits of weight loss are less clear in this population. Younger adults should be included as well; a study by Stevens et al (22) suggested that the risk of obesity-related mortality is higher in younger subjects.

The issue of the degree of obesity of study subjects sparked considerable controversy. Some workshop participants suggested including persons who are mildly obese because these persons are more prevalent in the population than the severely obese and because there is less certainty about the health benefits of weight loss in this group. Others asserted that persons with more severe obesity should be the focus of study, particularly those with obesity-related comorbid conditions, to ensure an adequate rate of development of clinical events, such as cardiovascular endpoints. In absolute terms, most obesity-associated disease risk occurs among moderately overweight persons because of their number in the general population. Furthermore, the distribution of abnormalities that influence risk in moderately overweight persons does not differ substantially from the distribution in higher weight groups, suggesting that an adequate number of clinical events could be obtained in this population. On the other hand, very large persons (ie, those with a BMI > 40) should not be excluded from any study because few data are available for this population.

Interventions

Interventions in an RCT can be behavioral, pharmacologic, or both.

Behavioral interventions

Effective behavioral interventions generally include a hypoenergetic diet, moderate-intensity physical activity, and behavioral techniques such as self-monitoring, stimulus control (for example, restricting the places in which food is consumed), and relapse prevention. Treatment is often provided in groups, with meetings initially held weekly and then less often. Results from recent treatment studies show that weight loss averages ≈8–10% over 26 wk, with some regain typical after treatment. Average weight loss 1 y after treatment is 6% of initial body

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weight (23). There is some indication that modest weight loss can be sustained over the long term. The Trial of Nonpharmacologic Interventions in the Elderly (24) recently reported a mean weight loss of >4.5 kg at 30 mo in overweight, older adults who received instruction in diet, physical activity, and behavioral skills, compared with a mean weight loss of <1 kg in those not assigned to weight-loss intervention. Data from other behavioral studies show even more impressive results with long-term, intensive behavioral therapy, with weight loss equal to or exceeding that in trials of pharmacologic agents (25, 26). Treatments including moderate energy restriction (4180–6280 kJ/d), behavioral techniques, and ongoing support can be effective in producing substantial weight loss at 1 y; the best results are achieved with more intensive programs. When patient contact decreases or is stopped, weight is regained.

Pharmacologic treatment

(Note that this workshop was held before the release of information on the association between valvular heart disease and fenfluramine-dexfenfluramine and the subsequent withdrawal of these medications from the market.)

Numerous studies have found that pharmacologic treatment confers a modest but significant increase in weight loss compared with that obtainable by behavioral treatment alone (17). Weight generally decreases for the first 6 mo of pharmacologic treatment and this loss is generally maintained while drug therapy continues over the ensuing 6 mo. Some patients, however, do regain weight despite continuing treatment (17). In general, obesity-related risk factors such as blood pressure and hyperlipidemia decrease commensurately with weight loss; however, this reduction may be medication specific (17). Both controlled (27) and uncontrolled (28) studies have suggested that weight loss can be sustained over longer terms (ie, >2 y), but few studies have evaluated the safety or efficacy of weight-loss medications for >12 mo (17).

As additional weight-loss medications become available for long-term use, assessing their risks and benefits as an adjunct to behavioral weight-loss treatment becomes critical. Because an RCT evaluating the health effect of sustained, intentional weight loss requires the ability to assist subjects in maintaining weight loss over the long term and because the primary benefit of pharmacotherapy appears to be in enhancing weight maintenance, one or more medication interventions should be included in the RCT if safe and effective drugs are available. Medication should be combined with behavioral treatment because studies suggest that these treatments interact beneficially (17). It is anticipated that, as with behavioral treatment, medication effects will not be sustained when the drug is discontinued; therefore, any drug treatment should be continued throughout the trial.

Several workshop participants contended that the RCT should address the question of whether weight loss improves people's lives in the longer term and not focus more narrowly on the efficacy of a particular drug. It was noted that no drug currently used for weight loss has safety or efficacy data available for ≥5 y, the time some participants thought would be necessary for determining relevant clinical events. Combining medications (as in a stepped-care approach for hypertension) was suggested as being of possible value. Concern was also expressed that negative outcomes from a drug-only treatment could lead to the mistaken conclusion that weight loss is bad rather than that the medication caused the negative result. This concern could be ameliorated by comparing any drug treatments with behavioral treatment alone (with or without placebo), so that any added benefit or deleterious effect of the drug treatment could be determined.

Relevant health outcomes

Choosing outcome measurements for an RCT is extremely important because these measurements affect nearly all decisions made about the other key attributes of the trial, including the target population, the length of the study, and the sample size. Trial outcomes must be clinically relevant and compelling and they must be biologically responsive to the treatments being studied. They also must be measured reliably, accurately, and identically across the treatment and control groups. RCT health outcomes can be classified as functional outcomes (eg, serum glucose concentrations), severity-stage outcomes (eg, progression of cardiovascular disease or onset of diabetes), and ultimate outcomes (eg, total or cardiovascular mortality). Because the RCT literature on the effect of weight loss on functional outcomes is well established, the primary outcome measurements for an RCT of weight loss and long-term health should include severity-stage and ultimate outcomes.

Mortality

Total mortality is perhaps the most useful health outcome, especially if a target population is chosen of obese young and middle-aged adults, both because observational data suggest that the relative risk of obesity for mortality is most elevated in this group (22) and because this population potentially has many years of life remaining. The demographic realities, however, mean that an RCT of weight loss and mortality carried out in this population would likely require an extremely long follow-up to find meaningful differences in mortality across treatment groups. Such a trial might be prohibitively expensive, and using cause-specific mortality as the primary outcome would be even less feasible. A better approach might be to study those who have established comorbidities, such as type 2 diabetes, because their risk of death is elevated. There was consensus among the workshop participants that total and cause-specific mortality may not be feasible primary health outcomes in an RCT, but there was concern about not monitoring mortality. If mortality differences are not compared across treatment groups, adverse associations of weight loss and mortality, which have been found in some observational studies, would be missed.

Morbidity

After mortality, morbidity (or disease incidence) was considered to be the most relevant health outcome. Cardiovascular disease incidence (eg, development of myocardial infarction, stroke, or angina) would be a primary candidate because of the well-established relations between obesity, weight loss, and physiologic risk factors for cardiovascular disease. Furthermore, cardiovascular disease is common in the US adult population and imposes high social and economic costs.

In addition to cardiovascular disease, obesity is strongly associated with the incidence of other important health outcomes, including type 2 diabetes, sleep apnea, osteoarthritis, gall bladder disease, and some cancers. Consideration should be given to monitoring these other morbid outcomes. In practice, because of statistical power considerations, these outcomes would likely need to be combined into a summary outcome. Consideration should also be given to combining morbidity and mortality end-

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points within a specific disease category, such as cardiovascular disease, for which this is a well-established tradition (29–31).

Quality of life

For many patients, overall quality of life is significantly affected by obesity. Improvements in quality of life have been reported in association with weight loss (32) and these may vary significantly with the type of weight-loss treatment and the subsequent maintenance regimen used. In addition, if one conducts a formal assessment of the differences in cost-effectiveness of treatments, adjustments for various quality-of-life components related to both the health outcomes and the treatments are required (33). Although assessment of quality of life would be essential to conducting a modern, high-quality RCT, it was generally agreed that this variable should not be a primary health outcome.

Adverse events

Adverse events will need to be monitored, especially if the RCT includes one or more drug treatments. If investigational drugs are used, formal adverse event reporting will be mandated by federal regulatory requirements and good clinical practice guidelines. In addition to the safety and ethical considerations that dictate monitoring adverse events, the treatment costs of adverse events and associated changes in quality of life need to be accurately assessed in any cost-effectiveness analysis comparing the efficacy of treatments.

Statistical considerations

Determination of sample size should take into account *1*) the number and configuration of the control group and the intervention group or groups, *2*) the duration of participant follow-up, *3*) the control group's rate of developing the primary outcome, *4*) the minimum detectable difference between the intervention group or groups and the control group, *5*) statistical power, and *6*) the rate of losses to follow-up. Workshop participants proposed several research designs, with various numbers and configurations of intervention groups. Rather than review each of these at length, we discuss as an example how sample size is determined in a 2-group design given certain assumptions.

Assume that the RCT will test the effectiveness of a single intervention on the cumulative incidence of the primary outcome with use of a control group for comparison. Half of the eligible participants are randomly assigned to the intervention group (pharmacologic or nonpharmacologic treatment or both) and half are randomly assigned to the control group. Participants are randomly assigned during a fixed time and followed up for the remainder of that randomization period and an additional fixed time after the last participant is assigned. We consider scenarios with maximum durations of 5 and 10 y. In the first scenario, participants are randomly assigned during a 2-y period and are followed up for an additional 3 y after recruitment closes (follow-up time in years: minimum, 3; maximum, 5; average, 4). In the second scenario, participants are randomly assigned during a 2-y period and are followed up for an additional 8 y after recruitment closes (follow-up time in years: minimum, 8; maximum, 10; average, 9).

The principal outcome in this example is the time to a specified primary outcome (eg, death, cardiovascular morbidity, noncardiovascular morbidity, or some combination of these). A key feature in sample size determination will be the control group's rate of reaching the primary outcome during the follow-up period (λ_c). For the proposed clinical trial, we assume that the control group's time (t) to the primary outcome is exponentially distributed (ie, cumulative incidence = $1 - e^{-\lambda t}$). The sample size scenarios consider 3 primary outcome hazard rates for the control group: 2.5%/y (eg, fatal or nonfatal myocardial infarction), 5.0%/y, and 7.5%/y (eg, clinical progression to diabetes).

In determining sample size, a clinically important difference must be specified between the control group and the intervention group. This difference may be specified in terms of the relative hazard rate, λ_i/λ_c, where λ_i is the primary outcome hazard rate in the intervention group. We consider 3 values of λ_i/λ_c: 0.75 (25% reduction in λ_c experienced by the intervention group), 0.67 (33% reduction), and 0.60 (40% reduction).

In selecting a sample size, one should try to maximize statistical power and minimize type I error. In the present scenario, the type I error rate is the probability of rejecting the hypothesis that the control group and the intervention group are equivalent when the true cumulative incidence of the primary outcome over time is the same for the 2 groups (ie, the intervention is not effective). Statistical power is the probability of rejecting the hypothesis that the control and intervention groups are equivalent when the true cumulative incidence of the primary outcome over time differs for the 2 groups. For the present illustration, we set the type I error rate at 5% (two-sided) and the statistical power at 90%.

Loss to follow-up is defined as the cessation by a randomly assigned participant of scheduled follow-up visits before the scheduled end of the study. The number of randomly assigned participants must be large enough to achieve the statistical power even with losses to follow-up. We assumed that losses to follow-up are exponentially distributed and set the loss hazard rate at 5%/y.

To calculate sample sizes we used the formula of Lachin and Foulkes (equation 6.2 in reference 34). Alternative sample size goals per group (intervention or control) as a function of λ_c and the percentage reduction in λ_c experienced by the intervention group are presented in **Table 1** for a maximum study duration of 5 y (average: 4 y). For example, the total sample size required to ensure 90% power of detecting a ≥33% reduction in the intervention group of a λ_c = 0.050/y (ie, a λ_i of 0.033/y) is 967 per group, based on a level of significance of 5% (two-sided) and a loss hazard rate of 5%/y.

For a maximum duration of 10 y (average: 9 y) and the same assumptions, a different set of sample sizes would be calculated (**Table 2**). For example, the total sample size required to ensure 90% power of detecting a ≥33% reduction in the intervention group of a λ_c = 0.050/y (ie, λ_i of 0.033/y) is 528 per group.

Note that the sample size per group increases as λ_c decreases, as the percentage reduction in λ_c experienced by the intervention group decreases, and as the duration of follow-up decreases. Adding a second intervention group would increase the sample

TABLE 1
Required sample per group for a maximum study duration of 5 y[1]

Control group hazard rate (%/y)[2]	Percentage reduction[3]		
	25	33	40
		%	
2.5	3395	1857	1209
5.0	1771	967	629
7.5	1231	671	436

[1] Average follow-up of 4 y (range: 3–5 y).
[2] Primary outcome rate.
[3] Reduction among the intervention group in the control group hazard rate.

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TABLE 2
Required sample per group for a maximum study duration of 10 y[1]

Control group hazard rate (%/y)[2]	Percentage reduction[3]		
	25	33	40
		%	
2.5	1779	971	632
5.0	971	528	343
7.5	704	382	247

[1] Average follow-up of 9 y (range: 8–10 y).
[2] Primary outcome rate.
[3] Reduction among the intervention group in the control group hazard rate.

per group to allow for multiple comparisons of the 3 groups (35). Other considerations in calculating required sample size include noncompliance with the assigned intervention, nonuniform enrollment of participants over time, and stratification of the eligible participants (eg, by sex or ethnicity) before they are randomly assigned.

SUMMARY AND CONCLUSIONS

The primary prevention of obesity is seen as the cornerstone of any public health approach to decreasing the high prevalence of obesity in the United States. Even so, workshop participants agreed that we need to better understand the health effects of intentional weight loss on the millions of Americans who are already overweight and are currently treating their obesity with weight loss. The consensus of the participants was that a well-designed RCT might answer several questions of clinical and public health importance.

Two key study questions that emerged from the workshop were the following: What is the health value of getting overweight persons to intentionally lose weight and maintain weight loss? and Can the effects of sustained weight reduction on morbidity and quality of life be shown? It was agreed that mortality, although important to monitor, is not likely to be a feasible primary outcome measure for the trial proposed.

It was also agreed that an RCT should include racial and ethnic minorities and older adults. Most workshop participants thought that the study should focus on persons with moderate obesity (eg, BMI ≥30–39.9), but that those with greater degrees of obesity should be included. Persons with or at high risk for obesity-related comorbid conditions would be a useful target population because their relatively higher event rate would enhance the possibility of having an adequately powered study. Behavioral treatment, dietary intervention, and physical activity must all be included and monitored in the RCT. If a treatment involves dietary modification, the regimen should meet current nutrition guidelines established by national organizations in the public or private sector. It is imperative to determine what benefits, if any, accrue from the addition of weight-loss medications to behavioral treatment for obesity.

Other issues that could be addressed by an RCT include determining the long-term health outcomes of an intervention effect that is sustained only in the short term (weight cycling) and finding out where the thresholds are in terms of amount or duration of weight loss that affect risk factors or comorbid conditions. Potential study designs were proposed, including factorial designs that included drug and lifestyle interventions and stepped-care designs in which interventions would be progressively added to achieve the weight-loss goals. The option of conducting several small studies rather than a single large clinical trial was also introduced. Adding a weight-reduction component with pharmacologic treatment to the ongoing Diabetes Prevention Program (36) was also proposed as a potentially cost-effective option.

Continued interactions among the staffs of the National Institutes of Health and the Centers for Disease Control and Prevention, the National Task Force on Prevention and Treatment of Obesity, the National Institute of Diabetes and Digestive and Kidney Diseases Scientific Advisory Council, and other experts will determine the optimal research design characteristics for obtaining valid scientific data on the long-term health effects of intentional weight loss. Such information will ultimately provide millions of obese Americans with guidance on the risks and benefits of weight loss.

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