

Lifestyle Modification in Drug Clinical Trials

By Mark Hochhauser

Many drugs, devices and even surgical procedures require patients to modify their lifestyle or change behaviors. For example, certain diabetes medications must be taken with food, gastric-band implants for obesity are generally prescribed with counseling, and grapefruit juice interferes with the metabolism of many drugs. Those conducting clinical trials of these drugs, devices and procedures should therefore consider incorporating the procedures that will be used in clinical practice to modify behavior or lifestyle (collectively, "behavioral modification procedures"). Clinical trial protocols may specify behavioral modification procedures (e.g., checklists, scripts, handout materials, discussion topics) or may leave the specifics up to individual researchers. Specifying the procedures begs the question of whether those specific procedures will be used in the real world. Not specifying them begs the question of what, if any, procedures will be used.

Protocols use various terms to describe behavioral modification procedures, such as lifestyle modification, lifestyle modification counseling, lifestyle intervention, lifestyle changes, nutritional counseling, and diabetes education. However, this terminology is not standardized in terms of operational definitions, theoretical rationales, modification procedures, or outcomes based on knowledge, attitudes, beliefs or behaviors.

A search for "lifestyle modification" at www.clinicaltrials.gov yielded 134 studies, 40 of which included drug or device interventions. A search for "behavior modification" yielded 1,299 additional studies. A review of some of the lifestyle-modification postings revealed that the descriptions include only minimal information, such as the following:

- Guidance on dietary and lifestyle modifications
- Lifestyle modification advice on physical activity, diet and drug adherence
- Standard advice on lifestyle modification
- Dietary and lifestyle modification counseling

As a psychologist, IRB member, and type 2 diabetic, I'm particularly interested in clinical trials that include such modification strategies. Our IRB has reviewed several clinical trials with behavioral modification. Based on this small sample, I'm concerned that these modifications have not been carefully designed, leading to ambiguous interventions, ineffective one-size-fits-all strategies, confounding variables, ethical concerns, and regulatory and marketing issues.

Research vs. Clinic

If the sponsor includes behavioral modification procedures in a study protocol, it implies that behavioral modification is an important element of therapy. If it specifies non-standard procedures, it implies that those specific procedures are important. As such, they should become part of the "therapeutic package" that clinicians should use. They should thus be examined with the same rigor as the drug or device itself. They should also be included in the drug label or package insert approved by the FDA. However, if the protocol specifies an established standard of care for behavioral modification, that standard can be described in the protocol and referenced in the drug label or package insert.

Undefined Behavioral Modification Strategies

A consent form that came to our IRB said only, "The Study Doctor will provide you guidance on dietary and lifestyle modifications according to the usual clinical routines," but did not define "guidance" or "usual clinical routines." (This study's description at www.clinicaltrials.gov did not mention these behavioral modifications, even though trial subjects would receive diet and lifestyle advice at all 11 visits over five years. Other studies with behavioral modifications may not be identifiable at clinicaltrials.gov.)

Another consent form was so ambiguous that our IRB asked the sponsor for more detailed information about the behavioral modification strategy. The sponsor's reply merely restated information from the consent form and offered no information about the behavioral modification rationale, the theory behind the intervention, how behavior changes would be evaluated, benefits and risks of the behavioral modification, etc.

Unfortunately, such behavioral modifications do not clearly distinguish between knowledge, attitudes, beliefs and behaviors (KABB), each of which requires different interventions. For example, changing subjects' knowledge may have no effect on their behaviors. By relying on biological lab values with no KABB evaluation, there is no way to know whether a particular behavioral modification strategy is effective or ineffective. If it does not change behavior, it is not behavioral modification.

Behavior Change: What Works, What Doesn't

A critical issue is whether a behavioral modification strategy is based on sound scientific evidence. For example, the American Diabetes Association (ADA) has developed national standards for Diabetes Self-Management Education (DSME). In its 2003 report (Mensing, Cypress, Boucher, et al, 2003), the ADA concluded that diabetes instructors should have "specialized diabetes and educational training beyond their basic academic preparation" (p. s150), and that "Evaluation is planned as an essential step in the provision of quality DSME to determine if DSME goals and objectives are met... Monitoring participant progress (medical and behavioral) and best practices are critical to the success of DSME... To measure outcomes effectively, data must be collected over time and data collection instruments administered on multiple occasions" (p. s152).

In the ADA's 2008 report (Funnell, Brown, Childs, et al, 2008, p. s97), the ADA identified five guiding principles for effective DSME:

- Diabetes education can effectively improve short-term clinical outcomes and quality of life.
- DSME has moved from didactic presentations to theory-based empowerment models.
- Better outcomes are obtained in programs incorporating behavioral and psychosocial strategies, cultural and age-appropriate components, and group education.
- Ongoing support is critical to sustain progress.
- Behavioral goal-setting supports DSME.

Sponsors may be unaware of the behavioral modification literature. Spahn, et al (2010) reviewed almost 90 studies on behavioral modification theories and strategies used in nutrition counseling. They found strong evidence that cognitive behavioral therapy in type 2 diabetic patients effectively improved dietary habits, weight and other cardiovascular and diabetes risk factors. Evidence of benefits was particularly strong for type 2 diabetic patients who participated in an intensive 6-12 month cognitive behavioral modification program. In addition, motivational interviewing (when combined with cognitive behavior therapy) was an effective nutritional counseling strategy.

Another review (Duke, 2009) found only nine studies that evaluated education strategies for adults with type 2 diabetes. The results were generally negative: "In the six studies comparing individual face-to-face education to usual care, individual education did not significantly improve glycemic control...in HbA1c...over a 12 to 18 month period." The only benefits on glycemic control were in three studies involving participants with an HbA1c greater than 8%. The behavioral modification procedures used in a study can thus affect the results of the study.

To be effective, behavioral modification strategies should be grounded in behavior change theory, age, culture, ethnicity, program design and evaluation; otherwise, why would anyone expect the behavioral modification program to work? Behavioral modification strategies require an experimental design (e.g., baseline, post-test, and follow-up) and evaluation strategy (knowledge, attitudes and behaviors) to determine cause-and-effect relationships between interventions and outcomes. For example, although there are numerous behavior change theories (Linden and Roberts, 2004; Linden, Butterworth, Roberts, 2006), none of the materials submitted to our IRB describe the behavior change theory to be used in the studies. This absence does not help the IRB evaluate the studies and suggests that the protocol authors are unfamiliar with the science of behavioral modification. Based on the limited information at clinicaltrials.gov, it is not possible to determine whether behavioral modification procedures in listed clinical trials are based on effective strategies.

One Procedure Fits All

Behavioral modification procedures that are insensitive to age, ethnicity, culture, etc. probably won't successfully modify many unhealthy lifestyles, especially in international clinical trials

Education will probably not be an effective behavioral modification procedure for experienced diabetics. They have probably already received diabetes education from their personal physician, cardiologist, physician's assistant, diabetes educator, nutritionist, pharmacist, etc. Suggestions about diet and exercise will not be the same for 18-year-olds and 80-year-olds. It is not useful to recommend fresh vegetables to inner-city residents without access to fresh vegetables.

Multiple Confounding Variables

Typical behavioral modification procedures can be a confounding variable in clinical trials, especially in studies that have no control group(s) for the modification because all subjects get the same modification intervention. For example, if the experimental drug is designed to lower blood glucose and improve lipids, and if lifestyle modification is designed to lower blood glucose and improve lipids, how will the sponsor know how much of the "improved" blood glucose and lipids scores are due to the drug, how much to behavioral modification procedures in the study, and how much to behavioral impacts outside the study?

With no control group(s) or modification evaluation strategies, researchers cannot statistically evaluate the effectiveness (if any) of the behavioral modification procedures. Some behavioral modification procedures may even worsen subject outcomes.

Ethical Considerations

Given the apparent lack of rigor of behavioral modification procedures in many studies, one has to ask why they are included at all. Are they included because they are an essential part of the therapeutic package? To remind investigators to continue their normal standard of

care? To demonstrate to IRBs that the sponsors are aware that drugs and devices are not panaceas? To increase the likelihood of subject and investigator participation?

If the behavioral modification procedures are specified and do not have published evidence supporting their effectiveness, they should be considered experimental interventions, the same way that drugs are considered experimental. The consent form should describe the benefits and risks of the behavioral modification procedures separately from the benefits and risks of the experimental drug. IRBs should review these benefits and risks. Subjects should not be required to participate in scientifically untested behavioral modification procedures with benefit/risk implications.

Regulatory and Marketing Issues

The FDA approves drugs, not behavioral modification procedures. If a combination of drug and behavioral modification leads to better glycemic control, lower lipids, etc., will the sponsor present information to the FDA that the drug alone is responsible for those changes? Or, will it estimate how much of the improvement is due to the drug and how much is due to behavioral change? How can FDA evaluate a drug's effectiveness if the drug's benefits are a combination of the drug and behavioral modifications?

If the drug receives FDA approval, patients will receive only the drug, not the identical behavioral modification procedures that contributed to the drug's benefits. As a result, the prescribed drug may be less beneficial than the experimental drug plus lifestyle modification was for the study subjects. If clinical trials demonstrated or assumed that behavioral modifications are important, they should be included in the drug label or package insert approved by the FDA.

Summary

Some clinical trials include behavioral modification procedures, for example, to help type 2 diabetes subjects improve their blood glucose, lipids, etc. However, such procedures may be unspecified or have no stated foundation in recognized behavior modification theories or evidence of effectiveness for the study population. Lacking appropriate control groups and program evaluation strategies, sponsors may be unable to statistically separate the test article's benefits from the behavioral modification benefits. As a result, subjects may be participating in scientifically unsound studies. Behavioral modification procedures have been proven to be an important component of healthcare and thus deserve sound scientific treatment in clinical trials.

References

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