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The Use of Biosimulation in the Design of a Novel Multi-level Weight Loss Maintenance Program for Overweight Children

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Abstract

Objective—Weight loss outcomes achieved through conventional behavior change interventions are prone to deterioration over time. Basic learning laboratory studies in the area of behavioral extinction and renewal and multi-level models of weight control offer clues as to why newly acquired weight loss skills are prone to relapse. According to these models, current clinic-based interventions may not be of sufficient duration or scope to allow for the practice of new skills across the multiple community contexts necessary to promote sustainable weight loss. Although longer, more intensive interventions with greater reach may hold the key to improving weight loss outcomes, it is difficult to test these assumptions in a time efficient and cost-effective manner. A research design tool that has been increasingly utilized in other fields (e.g., pharmaceuticals) is the use of biosimulation analyses. The present paper describes our research team's use of computer simulation models to assist in designing a study to test a novel, comprehensive socio-environmental treatment approach to weight loss maintenance in children ages 7 to 12 years.

Methods—Weight outcome data from the weight loss, weight maintenance, and follow-up phases of a recently completed randomized controlled trial (RCT) were used to describe the time

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course of a proposed, extended multi-level treatment program. Simulations were then conducted to project the expected changes in child percent overweight trajectories in the proposed study.

Results—A 12.9% decrease in percent overweight at 30 months was estimated based upon the midway point between models of "best-case" and "worst-case" weight maintenance scenarios.

Conclusions—Preliminary data and further analyses, including biosimulation projections, suggest that our socio-environmental approach to weight loss maintenance treatment is promising and warrants evaluation in a large-scale RCT. Biosimulation techniques may have utility in the design of future community-level interventions for the treatment and prevention of childhood overweight.

Introduction

Weight loss treatments for overweight children have been associated with significant physical and psychosocial health benefits (1-3). However, weight regain after lifestyle change interventions is a common and remarkably robust phenomenon among adults and is a challenge for children as well (4-7). In addition to physiological (8,9) and environmental/cultural (10-12) explanations for why it is difficult to continue weight maintenance behaviors over time, the basic processes by which weight regulating behaviors are acquired (i.e., learned) and sustained (i.e., remembered, retrieved, and practiced) also affect weight regain (12-14). Given the challenges of establishing new eating and activity behaviors, it is not surprising that weight regain follows the end of brief (i.e., four to six months) lifestyle interventions, since little time is available for the intensive practice across contexts that may be necessary for enduring change to occur (15).

Therefore, one approach to improving long-term childhood weight maintenance is to adopt a multi-level perspective to the problem of health behavior change and to lengthen treatment contact to allow for opportunities for the generalization of newly acquired behaviors across contexts (16). Complex, multi-level treatments such as these likely require novel methodologies with which long-term treatment effects and their mediators can be projected, especially prior to investing in large-scale clinical trials.

Despite their status as the "gold standard," RCTs of multi-level interventions with children are costly not only in terms of the financial investment necessary to design and implement a well-controlled trial, but also in terms of time for both investigators and participants (17). For these reasons, investigators and funding agencies alike are cautious in their approach to such endeavors. One method that has been utilized in evaluating the pursuit of high cost clinical trials in other industries is the use of biosimulation and computer modeling techniques (18).

This paper describes the theoretical framework and preliminary data used to inform the design of a treatment study to test a novel, multi-level pediatric obesity intervention aimed at improving the long-term success of weight loss maintenance treatment (7). Potential mechanisms and models for weight regain and general strategies for treatment implementation (i.e., treatment dose, duration, and content) are outlined. Finally, the use of biosimulation to estimate the proposed treatment's impact on weight maintenance is described, and future implications for the application of simulation and computer modeling techniques to multi-level, non-pharmaceutical, clinical trial designs are explored.

The Importance of Weight Loss Maintenance

Improving long-term outcomes for pediatric obesity treatment is important in order to reduce the negative medical consequences of overweight for children/adolescents, to improve their psychosocial functioning, and to prevent the tracking of obesity into adulthood

(4,19-22). Family-based behavioral treatment (FBT) programs for pediatric overweight have reliably produced significant short- and long-term weight loss treatment effects (23). The most effective FBT programs show promising results with 30% of children no longer obese at 10-year follow-up (24), and more recent studies of improved versions of FBT have demonstrated almost complete maintenance of effects at two years (25,26). Although these findings are encouraging, weight regain continues to remain a challenge for a number of children following the end of treatment contact (4,7,23,27).

Our previously completed study (7) was the first to target weight maintenance in children through extended contact following FBT, and compared two distinct approaches to behavioral maintenance treatments: 1) Behavioral Skills Maintenance treatment (BSM) and 2) Social Facilitation Maintenance treatment (SFM) to a control group (NTC) which consisted of a personalized, written plan for continuing the healthy behaviors learned in FBT, with no further scheduled contact with treatment staff. While BSM used a cognitive-behavioral approach to teach self-regulation behaviors and relapse prevention strategies for weight maintenance, SFM used an innovative, socially-based behavioral approach developmentally tailored to enhance peer support, increase parental instrumental support, improve body image, and teach effective responses to teasing as strategies for sustaining weight maintenance behaviors beyond the end of treatment contact (6,7,28,29).

Our long-term results indicate that SFM significantly improved children's weight loss maintenance through 2-year follow-up compared to those in NTC. BSM did not differ significantly from NTC, but BSM also did not differ significantly from SFM. Children receiving SFM demonstrated significantly greater improvements in their ability to cope with teasing and to enlist friends to support physical activity over the short- and long-term, compared to both BSM and NTC. There was a moderation effect, suggesting that children with low social problems were more likely to benefit from SFM than NTC. Moreover, at the 2-year follow-up, the SFM-treated children with lower levels of social problems had weight outcomes similar to the optimal weight change outcomes observed immediately after the FBT weight loss intervention. Taken together, these results suggest that SFM, with its focus on the child's social ecology, is a promising treatment approach to sustain weight maintenance. However, improvements are needed to enhance the long-term efficacy of this weight maintenance treatment.

Multi-level Models of Behavior Change

While traditional approaches to lifestyle modification have been criticized for their focus on individual behavior patterns, to the neglect of the familial, peer, and community settings within which these behaviors are fostered or constrained, socio-environmentally based interventions such as SFM are consistent with expert recommendations for taking a “multi-level” approach to health behavior change (30). Multi-level models of health behavior suggest that obesity-related behaviors are the result of reciprocal interactions of the individual with other levels of influence, such as social relationships and environmental factors (30). Each level provides unique challenges for the overweight child, as well as opportunities to intervene to reduce obesity-related behaviors and to improve long-term health (**see** Figure 1).

The Individual Level—Self-regulatory Behaviors—Persistent self-regulation is needed to maintain the long-term adherence to healthy eating behaviors and regular physical activity (energy-balance behaviors) associated with successful weight maintenance in both adults (31,32) and children (24,33-35). Specific self-regulation behaviors for weight *maintenance* are distinct from weight *loss* skills, and include comparing one's current weight with a maintenance weight (through regular self-weighing and using a weight graph), adjusting eating and exercise behaviors, and planning for high-risk situations (7,35). These self-regulation behaviors have consistently been shown to help with weight maintenance both in our previously completed study (7) and in the adult literature (35). Failure to maintain these behaviors is associated with weight regain (36). In our previously completed study, the efficacy of SFM may have been compromised by artificially eliminating key self-regulatory skills (e.g., ongoing weight, diet, and activity monitoring) to minimize procedural overlap with BSM. The efficacy of socio-environmental maintenance treatments such as SFM may be enhanced by having children and parents use self-regulation behaviors, such as monitoring weight, tracking and working towards healthy dietary and activity goals, and pre-planning for high-risk situations.

The Interpersonal Level—Parental and Peer Support for Behavior Change— Parents play a critical role in the context of the home environment by supporting, encouraging, and modeling dietary behaviors and levels of physical activity that contribute to weight regulation (37-41). A number of studies show that child outcomes are improved when parents are directly involved in their own weight loss program as well as their child's program (42-44), and that parental weight loss is a consistent predictor of child weight loss in FBT (42). Parental encouragement of their child's healthy eating was also associated with greater reduction in children's percent overweight from baseline to 2-year follow-up in our previously completed study (7).

Peer factors and extra-familial social contexts are also important to support successful weight maintenance behaviors, particularly for children. Peer factors, such as a lack of social support for physical activity/healthy eating (24,45), and teasing related to physical activity (46), are likely to contribute to weight regain. Indeed, recent data suggest that obesity can be “spread” through peer networks (47), likely due to reciprocal modeling of eating and physical activity behavior. However, peers can also reinforce behaviors that prevent weight regain (48). For example, overweight youth make healthier eating and activity choices when in the presence of peers as compared to when they are alone (49). Perceived peer support for physical activity is positively related to children's physical activity (50), with youth reporting that the greatest proportion of exercise occurred with friends (51). Social connectedness (i.e., being satisfied with one's social network) among both children and adolescents is positively correlated with greater physical activity (52) and healthy dietary practices (53). Further, social support from friends as well as family has been shown to predict long-term success in pediatric weight loss maintenance (24,43). While children in SFM significantly increased their ability to enlist peer support for physical activity and healthy dietary intake (7), children with low social problems particularly benefited from the SFM approach of focusing on gaining and maintaining social support for maintenance behaviors. In summary, family and peer support positively influence children's energy intake and physical activity and are critical targets for the treatment of overweight in children, but children with higher levels of social problems may need additional treatment contact to achieve long-term weight loss maintenance, perhaps because these individuals have more associated parental and child psychopathology (54), which may interfere with efficient health behavior change.

The Environmental/Community Level—Broader Influences on Weight Control Behaviors—SFM targeted the home and peer environments, however, environmental features of one's neighborhood have been associated with adult obesity (55) and physical activity rates (56). A similar link between the community environment and both weight and physical activity level has been found in children (55,57). For example, access to parks is a strong predictor of children's physical activity (58) and of increased physical activity when sedentary behaviors are reduced (59). Our previously completed trial demonstrated an association between factors in the families' environments (e.g., access to parks) and children's long-term weight maintenance (54). Since features of a particular home or community environment can help or hinder healthy behaviors, awareness of such environmental features and the targeted use of behavioral prompts and community resources may help to strengthen weight maintenance behaviors over the long-term. Weight loss maintenance treatment would be enhanced by encouraging parents and children to modify, where possible, the stimuli present in the contexts of school, neighborhood, and community that facilitate or constrain their use of newly acquired weight maintenance skills.

Clearly, multi-level, socio-environmentally based approaches to behavior change such as SFM emphasize the important influence of context on behavior change (60). Recent advances in learning theories of extinction and retrieval cues enhance our understanding of why and how context plays such an important role in behavioral relapse and how targeting change across and within multiple contexts may enhance the sustainability of newly learned health behaviors such as weight loss maintenance skills (12).

Context Dependent Learning Theory

According to basic research on the retrieval and extinction of newly learned behaviors (e.g., forming new healthy diet and physical activity habits), old learning or behaviors are not replaced by new learning or behaviors, but rather remain as the original “default” responses (13). This coexistence of new learning with old behavior patterns creates an ambiguous situation for individuals when faced with a behavioral choice, especially in novel contexts. This ambiguity leads to a greater likelihood that the originally learned, obesity-related behaviors (e.g., poor eating habits and sedentary behavior) will be activated. To combat this tendency to revert to old habits, a concerted effort must be made to ensure that the new learning is conducted across as many relevant contexts as possible, that appropriate retrieval cues or behavioral prompts are in place, and that sufficient time is devoted to treatment to master and practice these strategies (12,14).

As noted above, the role of context in the expression or modification of obesity-related behaviors is well illustrated by multi-level models of obesity (61,62). As depicted in Figure 1, weight regain occurs following traditional weight loss treatments because the contextual stimuli that set the occasion for the previously learned, unhealthy behaviors to return are not modified, which cue the child and caregiver to engage in their old behaviors (33,43). Predictably, upon discontinuation of treatment, parents no longer model healthy behaviors or negotiate positive peer interactions for the child, resulting in less family and peer support for healthy eating and physical activity. Finally, parents and children cease to be vigilant regarding the constraints of the broader environment and stop coping with its challenges to healthy lifestyle behaviors.

Alternatively (see the right side of Figure 1), during weight loss maintenance treatment with a socio-environmental focus, caregivers are encouraged to persist in modeling healthy behaviors and providing a home environment that fosters healthful eating and activity choices. Likewise, the caregiver is encouraged to help the child select peers who have similar healthy lifestyle goals. At the community level, caregivers are encouraged to help the child practice making healthful choices in a variety of contexts (e.g., various locations and social situations) with the help of supportive peers so that the child (and parent) has the opportunity to “over learn” weight maintaining behaviors rather than returning to the “default” behaviors associated with weight regain.

Despite taking a socio-environmental approach to weight loss maintenance, some people may have difficulties sustaining behavior change after contact with the treatment team is reduced since the treatment setting itself represents a context for learning. Once treatment contact comes to an end, this important contextual cue for engaging in the newly acquired weight maintenance behaviors is also lost. Two methods to combat this tendency toward relapse following the end of treatment contact are suggested by basic learning laboratory and human memory research (13,14,63,64). One method would be to encourage the mastery of new concepts as they are learned and then to practice the retrieval of newly learned skills across as many contexts as possible despite the difficulty of doing so. For example, it is difficult to switch from practicing a skill in the context of the home to practicing a skill in the context of school. However, this process of repeated retrieval of new learning or skills with feedback from the treatment team and supportive others increases the likelihood that these difficult retrieval experiences become valuable opportunities for engaging in new context-dependent learning rather than opportunities for relapse. Through this process, the likelihood that these contexts will also become associated with the desired weight regulating behaviors increases so that weight loss maintenance can be sustained after treatment contact ends (13). Retrieval cues from the treatment setting can also be used to facilitate the practice of new skills in novel settings by allowing the participant to "carry" a reminder of the treatment context associated with the new learning into the novel setting which then prompts the individual to remember to choose the new behavior rather than old just as he or she learned in maintenance treatment sessions (14).

Therefore, building sufficient time into weight loss programs to allow for the mastery of weight regulating behaviors and for the generalization of weight maintenance skills across contexts is imperative to achieving sustainable treatment effects (15). Indeed, weight loss treatment studies with adults that have provided extended contact have demonstrated that participants can achieve and maintain substantial amounts of weight loss for several years (65,66). In one study, 77% of adults who received extended contact maintained their weight for up to 10 years (67). Since childhood obesity follows similar patterns of weight regain following treatment and positive initial responses to a brief, extended maintenance treatment were achieved in our previous study (7), it is reasonable to assume that many obese children in weight loss treatment, like obese adults, would benefit from longer treatment contact to maximize the effectiveness of maintenance interventions (68).

Unfortunately, much of the literature in adult weight loss maintenance interventions is confounded by a simultaneous increase of duration and dose (e.g., ref. 69). Thus, it is impossible to determine whether the critical element in enhancing SFM is to extend the duration of treatment contact or increase the number of sessions within that time (13,14,63,70). On the one hand, spreading maintenance treatment sessions out across time (e.g., 12 months versus 4 months) would permit participants to practice behaviors across more contexts and thus strengthen these behaviors (i.e., "spaced practice" to maximize learning; ref. 63). On the other hand, more frequent sessions (e.g., 32 versus 16) over the same time period would allow for greater therapist reinforcement which may lead to increased utilization of treatment skills and corresponding habit formation (71). In order to tease apart the effects of dose on weight loss maintenance from those of duration, a clinical trial would need to test two treatment conditions, each delivering the same treatment content and occurring for the same duration, but differing with respect to the number of sessions.

Biosimulation to Project Long-Term Weight Outcomes

In order to make informed decisions regarding the design of complex, multi-level clinical treatment trials such as the one proposed above, investigators may need novel methods for projecting long-term treatment effects and their mediators given the costs of large-scale clinical trials in terms of time and money, as well as in terms of participant burden (17). One method that has been utilized in evaluating the pursuit of high cost clinical trials is biosimulation. This method involves two main steps: 1) building of a model and 2) simulation from the model

The modeling step provides a description of the relationship between outcomes (e.g., relative body weight) and covariates (i.e. the range of characteristics in the prospective sample, such as age and sex, and the physiological and behavioral modifications of interest). The impact of changes in one covariate or a combination of covariates on outcome can be evaluated. Choice of covariate values can be made based on experience with prior trials and/or from what is known of the literature. Influence of drop out rates and impact of design conditions and trial settings on power considerations can be explored under alternative scenarios, aiming at minimizing sample size and trial duration. The simulation step allows investigators to make quantifiable projections of outcome, sample size calculation for sufficient power, and the assessment of influence of various design modifications and trial conditions. This approach, unlike standard power calculation, provides a more realistic power estimation by virtue of integrating the various sources of variance together with trial assumptions. It thus permits simulating clinical trials on “virtual patients,” allowing treatment developers to perform various “what if” experiments about study modifications (e.g., extending duration, increasing intensity, or manipulating content) in a controlled setting without unnecessary participant burden (18)

These techniques have been used in high-risk industries such as aerospace and pharmaceuticals in their research and development processes (18), but until recently, these methods have not been applied to the development of large clinical trials in most areas of the social sciences (i.e., that do not involve the testing of medications). As discussed above, childhood overweight is a complex problem necessitating a multi-level treatment approach. Biosimulation includes state-of-the-art methodology, which can incorporate multifaceted intervention and participant characteristics, with which to evaluate these programs.

To provide further support for our predicted weight outcome trajectories of children in a high dose, extended duration weight loss maintenance treatment, analyses were performed in collaboration with a company specializing in model-based drug development.[1] Using weight and height data from participants in our previously completed trial, a model was created to project the relative weight outcomes of the high dose treatment over time under various assumptions.

Building the model—The data used to build our model comprised weekly body weight measurements taken during FBT (Months 0-5) and during weight loss maintenance (Months 5-9) for both BSM and SFM. The combined BSM and SFM groups contained 100 subjects and provided 2871 weight observations. Based on the overall time course of the percent overweight (POW) response, an Inhibitory Emax model was considered appropriate. Emax represents the maximal effect when time is sufficiently long (see equation in Table 1). The parameter ET50 represents the time required to reach 50% of Emax, and H, commonly known as the Hill parameter, captures the sigmoidicity in the time profile. Due to the longitudinal nature of the data, and potential correlation between observations made on individual subjects, a mixed effects model was used. Subject random effects were found necessary for Intercept (or baseline) and for Emax. The analyses revealed no significant difference between BSM and SFM; thus the model would be equally applicable for either treatment. Summary of the model fit is shown in Table 1.

The follow-up data at Months 17 and 29, together with Month 9 observations (considered as the baseline of the follow-up phase) provided information that helped determine weight regain since the cessation of maintenance at Month 9. A linear mixed effects model was

[1]Biosimulation analyses were conducted by Pharsight, Corporation, a Certara Company (Mountain View, CA), with whom we collaborated for the present manuscript. Other such biosimulation companies include Entelos, Inc. and Archimedes, Inc.

successfully fitted to the data, and estimated a regain in POW equal to 0.41% per month (see Table 2).

Simulation from the model—This estimated regain, together with the Emax model, was used to project outcome under alternative scenarios. The projections were calculated incorporating model parameters and uncertainty in their estimates. Specifically, realizations of the vector of parameter estimates are drawn from a multivariate normal distribution with mean=μ and variance=Σ. The mean is the vector of estimates shown in Table 1, while Σ is the variance-covariance matrix of the estimates determined by the fitting algorithm. Applying one realization to the model equation, a response value is obtained. Repetition of this process a large number of times (e.g., 10,000) will provide a range of response values at time points of interest. At each time point the 5^{th} and 95^{th} percentile are determined, providing 90% confidence or uncertainty limits (Figures 2a and 2b).

Specifically, a “best case” scenario assuming successful maintenance (**see** Figure 2a; i.e., assuming no relapse following maintenance cessation) and a “worst case scenario” assuming no additional effect of the improved maintenance intervention beyond our original SFM (**see** Figure 2b; i.e., assuming the rate of relapse of 0.41% per month estimated in our previous study following maintenance cessation) were projected. The 90% interval represents confidence in the estimates due to imprecision in model estimates. With high confidence that the true value will be between these two extreme scenarios, we believe it will be at midway (i.e., an approximately 12.9% decrease in percent overweight at 30 months). This -12.9% value was also considered reasonable, supported by data from adult studies indicating that the longer individuals are successful in maintaining their weight loss, the greater their chance of continuing to maintain over the long-term (36, 67, 72). Thus, we anticipated that an extended and intensive course of treatment such as the one proposed would result in further reductions in the rate of regain following the end of treatment contact than observed in our previous trial (7).

In sum, the biosimulation results confirm the appropriateness of our selected effect size. One of the advantages to receiving this form of confirmation early in the treatment design process is that it allows for setting reasonable recruitment and staffing estimates, potentially minimizing costs of understaffing or of underpowering this extensive clinical trial.

Conclusion and Future Directions

The development of efficacious weight loss and weight maintenance interventions is a crucial step towards combating childhood obesity. The varied factors that contribute to obesity in youth, which tend to continue into adulthood, require a correspondingly multi-level, socio-environmental treatment approach that addresses both the individual learning level, as well as the multiple contexts in which newly learned behaviors occur (e.g., the peer, family, and community contexts). The weight control interventions available to date may not be of a sufficient duration, dose, or breadth of content to create sustainable behavior change in the long-term.

Multi-level interventions, which are being recommended for their potential to promote sustainable changes in health behaviors, require significant resources if well designed RCTs are to be conducted using these approaches, and biosimulation offers a cost-effective method for estimating treatment effects prior to a trial's inception. Furthermore, this model-based biosimulation approach may also be utilized iteratively throughout the course of an investigation as new data become available. Updated models and revised simulations should give further insight as the likely success of the investigation. Our preliminary simulation analyses, which examined and modeled data from our previously completed trial (7), suggest that our socio-environmental approach to weight loss maintenance treatment is promising, and enhancements of it warrant evaluation in a large-scale RCT. As such, biosimulation may be useful in the development of future community-level treatments and prevention programs for overweight children.

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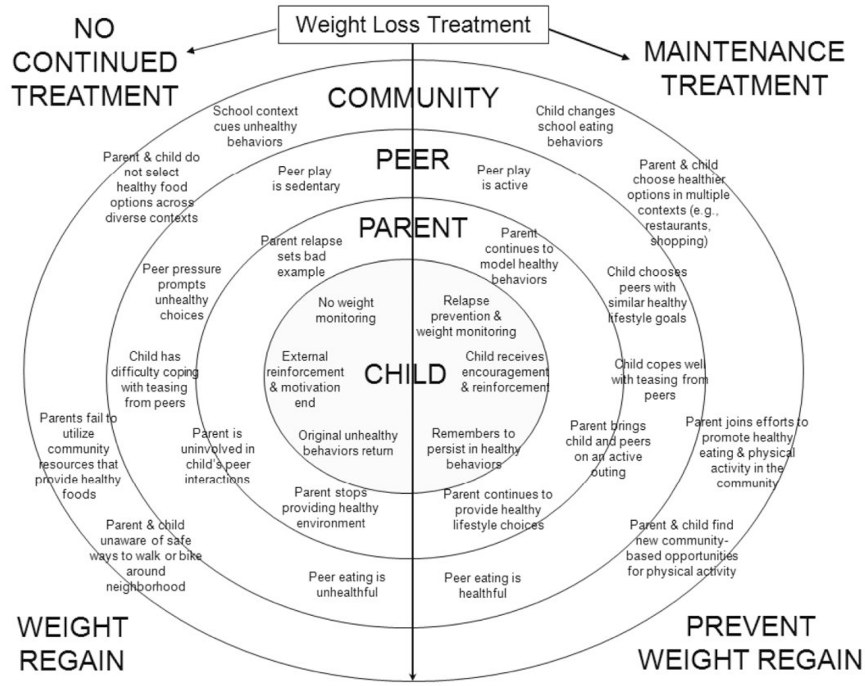

Figure 1. A socio-environmental model of weight regain and weight maintenance

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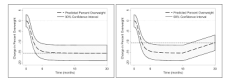

Figure 2. Biosimulation to project long-term weight outcome

Figure 2a. Biosimulation analyses estimated a 15.4% decrease in child percent overweight at 30 months under a “best case scenario” assuming no relapse following maintenance cessation. (Pharsight Corp. © 2008)

Figure 2b. Biosimulation analyses estimated a 10.4% decrease in child percent overweight at 30 months under a “worst case scenario” assuming the rate of relapse seen in our previous study following maintenance cessation. (Pharsight Corp. © 2008)

Table 1

Biosimulation Emax model

Parameter	Value	Std. Error	DF	t-value	p-value
Intercept	63.8	1.8	2768	35.3	< 0.0001
Emax	11.9	1.1	2768	10.8	< 0.0001
Ln(ET50) (week)	2.3	0	2768	93	< 0.0001
Ln(H)	1	0.1	2768	16	< 0.0001
SD RE Intercept	18	-	-	-	-
SD RE Emax	10.5	-	-	-	-
SD Error	4.5	-	-	-	-

Families = 100; # observations = 2871; Log Lik. = -8856.11; RE = Random Effect

$$POW_{i,t}=Intercept_i+Emax_i\ \frac{t^H}{t^H+ET_{50}^H}+\varepsilon_{i,t}$$

i = i th family

t = time (in weeks)

$Emax_i$ = Emax + η_{2i}

$\eta_{ji} \sim N(0,\sigma^2_{\eta j})$, j = 1,2

$\varepsilon_{i,t} \sim N(0,\sigma^2_{\varepsilon})$; $Intercept_i$ = Intercept + η_{1i}

The model estimates a maximal reduction (Emax) of 11.94%. The time to reach 50% of maximum effect is exp(2.3) = 10 weeks. (Pharsight Corp.)

Table 2

Biosimulation linear effects model

Parameter	Value	Std. Error	DF	t-value	p-value
Intercept	50.44	0.91	260	55.6	< 0.0001
POW Month 5	1.05	0.03	142	35.8	< 0.0001
% Gain/month	0.41	0.06	260	3.8	< 0.0001
Control - BSM or SFM	4.4	1.17	142	3.8	< 0.0001
SD RE Intercept	3.98	-	-	-	-
SD RE % Gain	0.59	-	-	-	-
SD Error	6.1	-	-	-	-

Families = 145; # observations = 406; Log Lik. = -1461.17; RE = Random Effect

A linear mixed effects model was fitted to the Month 9, 17, and 29 data from our previously completed trial, in order to estimate weight gain and subsequently to help project outcome under alternate scenarios. (Pharsight Corp)