Health Psychology

ISSN: 0278-6133

2021, Vol. 40, No. 12, 875–880
http://dx.doi.org/10.1037/hea0001024

Adapting Pharmacological Dose-Finding Designs for Early Phase Behavioral Intervention Development Research

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The use of systematic dose-finding designs to develop behavioral health interventions is lacking. In contrast, drug development research consistently follows a prescribed, regulated, and iterative pathway that begins with empirically establishing optimal drug dose. Adapting dose-finding methodologies from the drug development literature offers several advantages to increasing the feasibility, efficiency, and rigor of this important intervention refining step for behavioral intervention development. This article discusses the current state of the science for dose finding within the behavioral intervention development literature. A detailed overview of one drug development dose-finding methodology (the Accelerated Biased Coin Up-and-Down design) is then presented, using our work to adapt the Prevention Plus Intervention for treatment of pediatric obesity for mHealth delivery as an example of how this design can be applied to empirically derive the dose for a behavioral intervention.

Keywords: intervention development, dose finding

Supplemental materials: http://dx.doi.org/10.1037/hea0001024.supp

Empirically deriving dose is an important yet rarely completed step to maximizing the effectiveness of behavioral health interventions and their implementation and dissemination potential. New models for translational research, like the National Institutes of Health (NIH) ORBIT model, specify that dose-finding studies should be included as part of early phase behavioral intervention development to ensure that all components of interventions subjected to efficacy testing are optimized (Czajkowski et al., 2015). In the absence of this refining step, a potentially efficacious intervention may be categorized as ineffective and abandoned when in fact a slightly higher dose may have led to very different results (Kalichman, 2019). Alternatively, an efficacious intervention may not be implemented in real-world settings because it is deemed too expensive, when perhaps a smaller dose would have achieved the same health outcome. Finally, suboptimal dosing may also result in high rates of attrition and therapist burnout (Kalichman, 2019; Voils et al., 2012, 2014).

Instead of conducting empirical investigations, behavioral intervention dosing is typically derived from precedent, anecdotal evidence, clinical experience, and/or asking the targeted population about dosing preferences (Kalichman, 2019; Voils et al., 2012, 2014). Each of these approaches has significant limitations. Insufficient attention to dose has substantial negative effects on attempts to evaluate the literature in a given area. Systematic reviews often include only a small fraction of extant intervention trials because dosing information is not reported (Kalichman, 2019). For example, in their systematic review and metaregression of behavioral prevention and intervention programs for pediatric obesity, Heerman and colleagues (2017) excluded 25% of identified RCTs because publications did not include sufficient information to determine dose. Further, this metaregression only included intended dose because the majority of trials reviewed did not report actual (received) dose. Dose derived from anecdotal evidence may have limited generalizability (e.g., population, provider, or setting-specific). Finally, while asking a targeted population about dosing preferences is important to developing human-centered interventions, individual responses may not be consistent, optimal in terms of efficacy, or cost-effective. Another challenge to empirically establishing dose of behavioral interventions is the absence of systematic and efficient dose-finding methodologies. Instead, multiple and iterative randomized controlled trials (RCTs) are often necessary because design and power limitations restrict the num-

This article was published Online First November 5, 2020.

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This work was supported by an award to Elizabeth Kuhl Towner and April Idalski Carcone from the Grants Boost Program (Office for the Vice President of Research, Wayne State University).

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ber of dosing levels that can be evaluated within a single study (Voils et al., 2014). This increases the already lengthy timeline from intervention development to effectiveness and implementation trials.

In contrast, traditional drug development follows a prescribed, regulated, and iterative pathway. Efficacy trials (Phase III) do not occur until a recommended drug dose is empirically identified (Phase I) and its impact on the desired health outcome is empirically established (Phase II; Voils et al., 2012, 2014). Phase I studies aim to identify either (a) the *maximally tolerated dose* (MTD) or the largest dose of drug that can be administered that minimizes the toxicity rate of the medication to only a small, predetermined proportion of the targeted population (e.g., chemotherapy yielding negative or adverse health outcomes to only 5% of the population) or (b) the *minimally effective dose* (MED) or the smallest dose of the medication that yields the desired health outcome in a large, prespecified proportion of the targeted population (e.g., pain medication providing pain relief in 90% of the population; Pace & Stylianou, 2007). Testing is completed via application of established and efficient dose-finding methodologies. Characteristics of these designs address many of the challenges faced by behavioral scientists and their use could thus improve the rigor of early phase behavioral intervention research.

While there are many pharmaceutical dose-finding designs, this article focuses on the Accelerated Biased Coin Up-and-Down Design (ABCD; Stylianou & Follmann, 2004). ABCD is a frequentist method and type of "up-and down" dose-finding design that aims to achieve balance between *tolerability* (defined by toxicity or nonresponse or failure) and *dose response* (defined by the desired outcome of interest or success). Under the assumption of monotonic relationship between drug intensity and toxicity, participants are allocated to a higher or lower drug dose based upon treatment outcome from the previous participant. Intervention dose is thus identified in a systematic and empirical fashion. ABCD is based upon the Biased Coin Up-and Down method, which has better operating characteristics than other up-and-down designs (Pace & Stylianou, 2007; Stylianou & Flournoy, 2002; Stylianou, Proschan, & Flournoy, 2003). ABCD's primary modification to the Biased Coin Up-and Down method is that ABCD allows multiple participants to be enrolled at a given time whereas BCD permits only one participant at a time. The advantages of ABCD to behavioral intervention development are its simplicity to implement compared to other dose-finding designs (e.g., Continual Reassessment Method, see Voils et al., 2012, 2014), its adaptive approach that includes randomization, the fact that it requires a relatively small sample (20–40), and its ability to evaluate multiple dosing levels in the same study.

Adapting ABCD for Use in Behavioral Intervention Development Research

In the sections to follow, we describe the ABCD methodology and use our ongoing work to adapt the Stage I pediatric obesity treatment (the Prevention Plus Intervention [PPI]) for mHealth delivery to illustrate how this method could be applied to empirically derive dose for a behavioral health intervention.

Adapting Stage I Pediatric Obesity Treatment for mHealth Delivery

The Expert Committee for Prevention, Assessment, and Treatment of Child and Adolescent Overweight and Obesity recommends a stepped approach to treating pediatric obesity (Barlow, 2007). As a Stage I intervention, the PPI is intended for delivery to every child who meets criteria for overweight and obesity and by every provider (e.g., pediatricians, nurse practitioners). High scalability, wide reach, and achieving small but significant changes for as many children as possible are aims for population-level interventions such as PPI. When delivering PPI, it is recommended that providers use Motivational Interviewing (MI; Miller & Rollnick, 2012) to collaboratively set goals with families to modify behaviors that may increase a preschooler's obesity risk (e.g., increase fruit and vegetable intake and decrease screen use). Intervention is stepped up (Stage II: Structured Weight Management) if "improved BMI status" is not evident after 3–6 months. Multiple barriers to PPI implementation have been documented. Chief among these are lack of training for providers in MI or pediatric weight management and insufficient time to integrate PPI into already brief well-child visits (e.g., He, Piche, Clarson, Callaghan, & Harris, 2010; Perrin, Flower, Garrett, & Ammerman, 2005; Spivack, Swietlik, Alessandrini, & Faith, 2010).

Currently, we are developing an mHealth Prevention Plus Intervention for Preschoolers (mPPI-P) with two technology-delivered components: (a) two brief, motivational sessions separated by (b) 1 month of automated, MI-tailored text messages. While text messaging is the most common type of mHealth intervention component in the obesity treatment literature (Siopis, Chey, & Allman-Farinelli, 2015; Thomas & Bond, 2014), no study has empirically evaluated what dose (frequency) leads to effective weight control. Further, in contrast to many published mHealth interventions for obesity, the text-message component of mPPI-P is an intervention and all exchanges are two-way. Text-messaging is thus an ideal candidate for a dose-finding study. While we focus on one dimension of dose (frequency), researchers might also select designs to evaluate duration (total length of the intervention) or amount (length of each intervention contact; Voils et al., 2012).

Selecting MED Versus MTD

An important first step in applying ABCD is to determine whether the design will focus on identifying the MED or MTD. The MED may seem a more intuitive selection for behavioral intervention development research because this design aims to identify the smallest dose that achieves a particular health outcome response. To apply ABCD to identify the MTD, it is first necessary to define what it means for a behavioral intervention to be toxic. A strict translation from drug development cannot be made because behavioral interventions do not yield physiological toxicity as a medication might (Voils et al., 2014). However, adverse or negative outcomes that could occur when dose of a behavioral intervention is too high include "psychosocial toxicity" (e.g., therapist burnout or patient dependency; Kalichman, 2019), excessive costs associated with treatment delivery, and attrition.

In our applied example, we set our ABCD to focus on identifying the MTD of text messages that can be administered

over 1 month and define toxicity as attrition. Our choice of an MTD instead of MED study is because while dose is a suggested moderator of pediatric weight outcomes (Janicke et al., 2014), attrition from pediatric obesity interventions is high (Dhaliwal et al., 2014). Further, while one of the benefits of text messaging is the opportunity for real-time intervention, there is insufficient evidence in the behavioral intervention development literature to conclude what frequency of text messaging (and particularly two-way messaging) individuals will tolerate before it becomes overly burdensome. Given our choice of an MTD study, all subsequent sections we describe design procedures in terms of this type of ABCD design. Readers are referred to Stylianou and Follmann (2004) for more details on designing an ABCD study to identify the MED.

Determining Dosing Levels

As noted above, ABCD evaluates multiple dosing levels in the same study. To the extent possible, dosing levels should be derived from a combination of the strategies commonly used in the behavioral intervention development literature: systematic review of the literature, identifying preferences of the targeted population, and/or anecdotal or clinical experience. From these efforts, researchers need to decide what is the hypothesized target dose. For studies that aim to identify the MTD, the targeted dose is the dose that will produce toxicity or an undesired outcome in a small predetermined percentage of the population. While there is no maximum to the number of doses that can be included in the design, researchers are encouraged to include a minimum of two doses above and below the hypothesized target dose (Liu, Cai, & Ning, 2013).

For mPPI-P, we reviewed the obesity treatment outcome literature, considered the text message dose within an intervention using the same motivational interviewing technology platform as mPPI-P all yielded improvements in motivation, controller medication use, and lung functioning (Kolmodin MacDonell, Naar, Gibson-Scipio, Lam, & Secord, 2016; MacDonell, Gibson-Scipio, Lam, Naar-King, & Chen, 2012), and our formative work with caregivers of young children who exceeded the PPI recommendation for sugar-sweetened beverages. A review of the adult and pediatric obesity treatment outcome literatures revealed a wide range of text messaging doses ranging from once per week up to four times per day (Militello, Melnyk, Hekler, Small, & Jacobson, 2016; Nezami, Ward, Lytle, Ennett, & Tate, 2018; Price et al., 2015; Siopis et al., 2015). The only intervention using the same technology platform to include text messaging found young adults were highly satisfied with receiving messages daily for 30 days between motivational sessions and that this treatment package overall yielded improvements in motivation, medication adherence, and lung functioning (Kolmodin MacDonell et al., 2016; MacDonell et al., 2012). Finally, our formative work revealed most caregivers of the targeted population also preferred daily text messaging. As such, in our example, we identified daily text-messaging as our target dose and set the ABCD to evaluate seven dose (frequency) levels: (a) once weekly, (b) twice weekly, (c) every other day, (d) daily, (e) twice per day, (f) three times per day, and (g) four times per day.

Defining Γ

Prior to initiating the dose-finding study, researchers must define Γ, which in an MTD study is the targeted toxicity level or the proportion of the targeted population expected to experience toxicity. In an MTD study, Γ must be <0.50 (Stylianou & Follmann, 2004). For our example with mPPI-P, we want to identify the MTD of text messaging over 1 month that results in minimal intervention attrition (e.g., 20%), and thus we set $\Gamma = 0.2$.

Determining Sample Size

Extensive simulations considering a large variety of dose–response curves were conducted during development of the ABCD design. These simulations concluded that a sample size of 20–40 is adequate to obtain an estimate of the target dose that is within one dose level of the true dose (Stylianou et al., 2003). Additional information about sample size considerations can be found in the Appendix in the online supplemental materials and in Stylianou and Follmann (2004). There are no formal rules for determining what number in this range is appropriate. Rather, factors such as length of the intervention being tested, timeline, and project budget will have a stronger impact on sample size decisions.

Dosing Procedures

ABCD uses a two-step approach to promote faster arrival at the MTD (see Figure 1). Step 1 begins with the first participant allocated to the hypothesized target dose or dose expected to yield toxicity. If the participant has a nontoxic response, then Step 1 continues with the next participant allocated to the next highest dose. This pattern of one participant in active intervention at a time and each subsequent participant being allocated to the next higher dose repeats until a participant meets criteria for "toxicity," at which time the study moves to Step 2.

Figure 2 presents a hypothetical example of dosing flow for the first seven families to participate in the dose-finding study. In Step 1, the first family (Family A) is allocated to the hypothesized target dose of daily text messaging and meets the criterion for a nontoxic response (retention) on Day 30 because the family has replied to all messages in the allocated dose. Since Family A did not experience toxicity, the study remains in Step 1. On Day 32 Family B is allocated to the next highest dose of text messages (twice daily). On Day 40, Family B did not respond to a text message, so they are considered to have a toxic response and the study moves to Step 2.

Per ABCD methodology, the first participant in Step 2 is allocated to the next lower dose than the dose that yielded a toxic response in Step 1. Dosing procedures depend upon three factors: (a) Γ or the desired target toxicity level for the intervention, (b) dose response of the previous participant, and (c) biased coin flip based upon a predefined probability of success (Stylianou & Follmann, 2004). As noted in Figure 1, if the previous participant meets the criterion for toxicity, then the next participant is allocated to the next lower dose. If the previous participant meets the criterion for nontoxicity, then the next participant is randomized based upon probability $b = \Gamma/1-\Gamma$ to the next higher dose and with probability $1-b$ to the same dose. In Step 2, a response is counted as complete either once a participant reaches the end of his or her evaluation period (the length of the intervention) or as soon

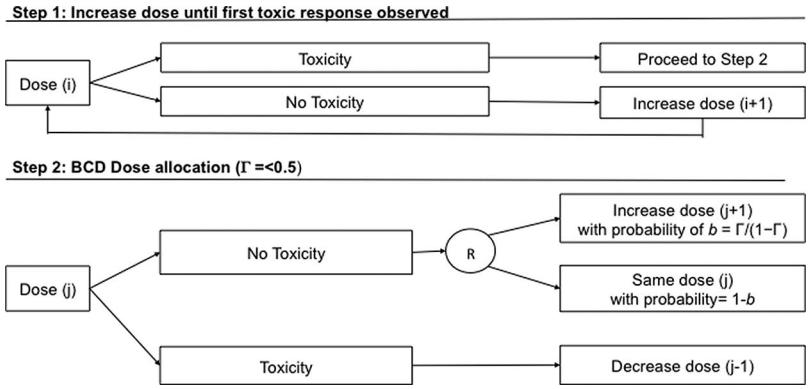

Figure 1. Dosing procedures for Two-Step Biased-Coin Design Dose-Finding study to identify the maximally tolerated dose. MTD = maximally tolerated dose; i = hypothesized target dose; j = dose yielding a toxic response in Step 1; b = beta; Γ = the desired toxicity level for the intervention (percent expected to have a toxic response); R = randomization.

as the criterion for toxicity is met. As such, dose allocation for newly enrolled participants may not be (and usually is not) based upon the last participant to enroll in the study. In efforts to minimize bias that might occur from a burst in recruitment and to ensure the sample is not exhausted on any one dose, ABCD also limits the number of participants that can be enrolled at a particular dose at the same time to three (Stylianou & Follmann, 2004).

In continuing with our applied example (see Figure 2), Step 2 begins by allocating the next family (Family C) to a dose of daily text messaging because this dose is the next lower dose that achieved toxicity in Step 1. Family D begins on Day 50 and, since Family C has not met the criterion for toxicity or nontoxicity, is also allocated to the dose of daily text messaging. Family E begins on Day 52 and, since neither Family C nor Family D has met criterion for toxicity, they are also allocated to the dose of daily text messaging. Family F arrives on Day 53 but, because we have three families at the dose of daily text messaging already, we must wait to start Family F until one of the families currently amid the intervention (C, D, or E) meets criterion for toxicity (attrition) or nontoxicity (retention). This occurs on Day 60, when Family D fails to respond to a text message and thus meets criterion for toxicity (attrition). Family F begins the intervention the next day and because Family D had a toxic response (attrition) is allocated to the next lower dose (every other day text messaging). Family G enrolls on Day 72 and because the last family to complete (Family C on Day 71) had a nontoxic response, is allocated at a probability of b = 0.2/(1–0.2) = 0.25 to the next higher dose and 1–0.25 = 0.75 to the same dose. In our example, the outcome of the randomization is that Family G receives the same dose (daily text messaging). The study would continue in this manner until the desired sample size (n = 20–40) is achieved.

Stopping Rules

If the target dose is not within the levels being tested, then participants will keep being allocated to the lowest dose (if the target dose is actually lower than the minimum dose included in the design) or the highest dose (if the target dose is actually higher than the maximum dose included in the design). If allocation to the minimum or maximum dose occurs for more than three to four

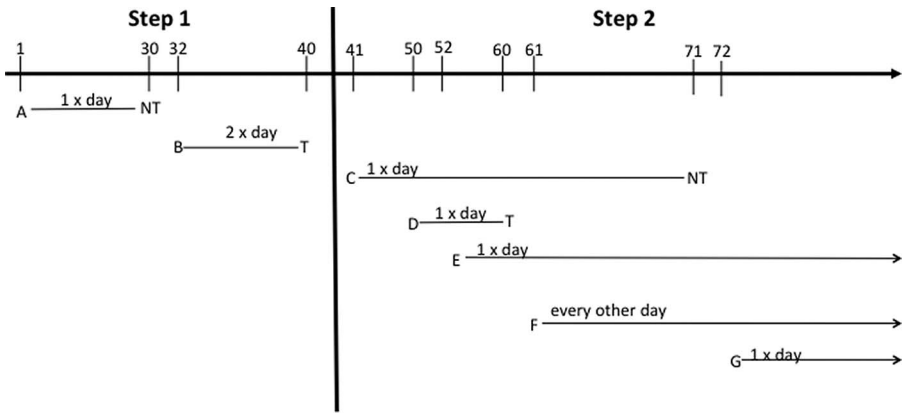

Figure 2. Dosing pattern for hypothetical ABCD to determine MED of text messaging. ABCD = accelerated biased-coin up-and-down design; MED = minimally effective dose; T = toxic response (attrition) to allocated dose; NT = nontoxic response (retention) to allocated dose.

consecutive participants, then it is reasonable to stop the study, reassess the specified dose range, and initiate a new study with a different dosing range informed by the previous study.

Determining the MTD

The estimation of the recommended dose is determined by assuming the probability of toxicity increases with increasing dose. Isotonic regression using a pooled adjacent violators algorithm (PAVA; Robertson, Wright, & Dykstra, 1998) is a natural way to estimate the probability of toxicity for each dose level tested. Isotonic estimates of the probability of toxicity are used to produce an estimator of the target dose. An R code is available to produce these estimates along with the confidence intervals (contact author MS).

Conclusions

Despite its importance to treatment optimization and improving the translational process (Czajkowski et al., 2015), most early phase work to develop behavioral interventions does not include studies to empirically determine dose. Identification of systematic and efficient dose-finding designs may help to address this gap. Methodologies from drug development, such as ABCD, can be adapted for use by behavioral researchers and provide several advantages to increasing the feasibility and rigor of dose finding in early phase intervention development research including that many are adaptive, include randomization, and require a range of doses be tested. Designs are also implemented with small samples without compromising power, making them ideal for grant mechanisms specific to early phase research (e.g., NIH R21 and R03) that often have shorter timelines and smaller budgets.

As with any intervention development, consideration must be given to variables that may impact dosing. Examples include sociodemographic characteristics, time since diagnosis and disease severity, neurocognitive and emotional states, content, and also context if the intervention includes text messaging like the example presented in this article. Some variables might be addressed in work that informs the dose-finding design and others at a later point in the developmental trajectory when sample sizes are larger and there is sufficient power to explore mediation and moderation.

Drug development dose-finding methodologies may not be suitable for all behavioral interventions, however. For example, defining *response* for a study that aims to identify the minimally effective dose of a behavioral intervention is more intuitive as the majority of behavioral interventions target specific behaviors or health outcomes (e.g., weight loss or adherence). However, defining *toxicity* is more difficult. Kalichman (2019) suggests the term *psychosocial toxicity* to describe unintended outcomes of behavioral interventions like therapist dependency and exhausting emotions. Additional toxic outcomes might include attrition and therapist burnout. Whether and how to explore toxicity of behavioral interventions warrants additional thought and exploration. Another consideration is that drug development dose-finding designs are intended to evaluate interventions and treatments delivered at the individual level, so they may not be appropriate for behavioral interventions delivered at the group level.

In summary, empirically deriving dose is imperative to optimizing behavioral health interventions. However, systematic designs for completing this step in the behavioral literature are lacking. The drug development literature offers several designs that can be adapted for use in behavioral intervention development to address this critical gap.

References

Barlow, S. E. (2007). Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: Summary report. *Pediatrics, 120*(Suppl. 4), S164–S192. http://dx.doi.org/10.1542/peds.2007-2329C

Czajkowski, S. M., Powell, L. H., Adler, N., Naar-King, S., Reynolds, K. D., Hunter, C. M., . . . Charlson, M. E. (2015). From ideas to efficacy: The ORBIT model for developing behavioral treatments for chronic diseases. *Health Psychology, 34,* 971–982. http://dx.doi.org/10.1037/hea0000161

Dhaliwal, J., Nosworthy, N. M., Holt, N. L., Zwaigenbaum, L., Avis, J. L., Rasquinha, A., & Ball, G. D. (2014). Attrition and the management of pediatric obesity: An integrative review. *Childhood Obesity, 10,* 461–473. http://dx.doi.org/10.1089/chi.2014.0060

He, M., Piche, L., Clarson, C. L., Callaghan, C., & Harris, S. B. (2010). Childhood overweight and obesity management: A national perspective of primary health care providers' views, practices, perceived barriers and needs. *Paediatrics & Child Health, 15,* 419–426. http://dx.doi.org/10.1093/pch/15.7.419

Heerman, W. J., JaKa, M. M., Berge, J. M., Trapl, E. S., Sommer, E. C., Samuels, L. R., . . . Barkin, S. L. (2017). The dose of behavioral interventions to prevent and treat childhood obesity: A systematic review and meta-regression. *The International Journal of Behavioral Nutrition and Physical Activity, 14,* Article 157. http://dx.doi.org/10.1186/s12966-017-0615-7

Janicke, D. M., Steele, R. G., Gayes, L. A., Lim, C. S., Clifford, L. M., Schneider, E. M., . . . Westen, S. (2014). Systematic review and meta-analysis of comprehensive behavioral family lifestyle interventions addressing pediatric obesity. *Journal of Pediatric Psychology, 39,* 809–825. http://dx.doi.org/10.1093/jpepsy/jsu023

Kalichman, S. C. (2019). When is enough, enough? How the absence of dose-determination trials impedes implementation of HIV behavioral interventions. *AIDS and Behavior, 23,* 2219–2225. http://dx.doi.org/10.1007/s10461-019-02650-1

Kolmodin MacDonell, K., Naar, S., Gibson-Scipio, W., Lam, P., & Secord, E. (2016). The Detroit Young Adult Asthma Project: Pilot of a technology-based medication adherence intervention for African-American emerging adults. *Journal of Adolescent Health, 59,* 465–471. http://dx.doi.org/10.1016/j.jadohealth.2016.05.016

Liu, S., Cai, C., & Ning, J. (2013). Up-and-down designs for Phase I clinical trials. *Contemporary Clinical Trials, 36,* 218–227. http://dx.doi.org/10.1016/j.cct.2013.07.002

MacDonell, K., Gibson-Scipio, W., Lam, P., Naar-King, S., & Chen, X. (2012). Text messaging to measure asthma medication use and symptoms in urban African American emerging adults: A feasibility study. *The Journal of Asthma, 49,* 1092–1096. http://dx.doi.org/10.3109/02770903.2012.733993

Militello, L., Melnyk, B. M., Hekler, E. B., Small, L., & Jacobson, D. (2016). Automated behavioral text messaging and face-to-face intervention for parents of overweight or obese preschool children: Results from a pilot study. *JMIR mHealth and uHealth, 4*(1), e21. http://dx.doi.org/10.2196/mhealth.4398

Miller, W. R., & Rollnick, S. (2012). *Motivational interviewing: Helping people change* (3rd ed.). New York, NY: The Guilford Press.

Nezami, B. T., Ward, D. S., Lytle, L. A., Ennett, S. T., & Tate, D. F. (2018). A mHealth randomized controlled trial to reduce sugar-sweetened beverage intake in preschool-aged children. *Pediatric Obesity, 13,* 668–676. http://dx.doi.org/10.1111/ijpo.12258

Pace, N. L., & Stylianou, M. P. (2007). Advances in and limitations of up-and-down methodology: A precis of clinical use, study design, and dose estimation in anesthesia research. *Anesthesiology, 107,* 144–152. http://dx.doi.org/10.1097/01.anes.0000267514.42592.2a

Perrin, E. M., Flower, K. B., Garrett, J., & Ammerman, A. S. (2005). Preventing and treating obesity: Pediatricians' self-efficacy, barriers, resources, and advocacy. *Ambulatory Pediatrics, 5,* 150–156. http://dx.doi.org/10.1367/A04-104R.1

Price, S., Ferisin, S., Sharifi, M., Steinberg, D., Bennett, G., Wolin, K. Y., . . . Taveras, E. M. (2015). Development and implementation of an interactive text messaging campaign to support behavior change in a childhood obesity randomized controlled trial. *Journal of Health Communication, 20,* 843–850. http://dx.doi.org/10.1080/10810730.2015.1018582

Robertson, T. L., Wright, F. T., & Dykstra, R. L. (1998). *Order restricted statistical influence*. New York, NY: Wiley.

Siopis, G., Chey, T., & Allman-Farinelli, M. (2015). A systematic review and meta-analysis of interventions for weight management using text messaging. *Journal of Human Nutrition and Dietetics, 28*(Suppl. 2), 1–15. http://dx.doi.org/10.1111/jhn.12207

Spivack, J. G., Swietlik, M., Alessandrini, E., & Faith, M. S. (2010). Primary care providers' knowledge, practices, and perceived barriers to the treatment and prevention of childhood obesity. *Obesity, 18,* 1341–1347. http://dx.doi.org/10.1038/oby.2009.410

Stylianou, M., & Flournoy, N. (2002). Dose finding using the biased coin up-and-down design and isotonic regression. *Biometrics, 58,* 171–177. http://dx.doi.org/10.1111/j.0006-341X.2002.00171.x

Stylianou, M., & Follmann, D. A. (2004). The accelerated biased coin up-and-down design in phase I trials. *Journal of Biopharmaceutical Statistics, 14,* 249–260. http://dx.doi.org/10.1081/BIP-120028518

Stylianou, M., Proschan, M., & Flournoy, N. (2003). Estimating the probability of toxicity at the target dose following an up-and-down design. *Statistics in Medicine, 22,* 535–543. http://dx.doi.org/10.1002/sim.1351

Thomas, J. G., & Bond, D. S. (2014). Review of innovations in digital health technology to promote weight control. *Current Diabetes Reports, 14,* Article 485. http://dx.doi.org/10.1007/s11892-014-0485-1

Voils, C. I., Chang, Y., Crandell, J., Leeman, J., Sandelowski, M., & Maciejewski, M. L. (2012). Informing the dosing of interventions in randomized trials. *Contemporary Clinical Trials, 33,* 1225–1230. http://dx.doi.org/10.1016/j.cct.2012.07.011

Voils, C. I., King, H. A., Maciejewski, M. L., Allen, K. D., Yancy, W. S., Jr., & Shaffer, J. A. (2014). Approaches for informing optimal dose of behavioral interventions. *Annals of Behavioral Medicine, 48,* 392–401. http://dx.doi.org/10.1007/s12160-014-9618-7

Received October 13, 2019
Revision received May 7, 2020
Accepted June 24, 2020 ■