

Identifying and retaining subgroups in clinical trials in the context of uncertainty about the external validity of clinical trials

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Characterizing and Communicating Uncertainty
in the Assessment of Benefits and Risks of Pharmaceutical Products:
An Institute of Medicine Workshop
February 12-13, 2014



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Optimizing retention for randomized clinical trials

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Optimizing retention for randomized trials

- Current context and challenges
- Standard retention strategies
- Fresh Start weight management trial
- Innovative retention approaches



Current context and challenges

- Lack of internal validity
 - Follow CONSORT guidelines
 - **Improve quality of reporting of RCTs**
 - Flow diagram & methodological checklist
 - Most medical journals have endorsed
 - **Use to design well-controlled trials at start**
- Lack of external validity
 - Labeled as 'hard-to-reach' or 'hard-to-retain' subgroups
 - Underserved subgroups due to cultural reasons or disparities in access
 - Less successful subgroups

Moher et al. CONSORT 2010 Explanation and elaboration:
Updated guidelines for reporting parallel group randomised
trials. *BMJ*. 2010;340:c869.



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Current context and challenges

- Tension between internal & external validity
 - Heightens ethical considerations
 - Affects (weakens) choice of control groups, equipoise, blinding
 - Affects (restricts) sampling & recruitment goals
 - Exacerbates uncertainty even prior to trial implementation & results



Optimizing retention for randomized trials

- Current context and challenges
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- Fresh Start weight trial example
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Standard retention strategies

HEALTH EDUCATION RESEARCH
Theory & Practice

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Innovative techniques to address retention in a behavioral weight-loss trial

Jennifer H. Goldberg^{1,2} and Michaela Kiernan¹

Abstract

Given that retention rates for weight-loss trials have not significantly improved in the past 20 years, identifying effective techniques to enhance retention is critical. This paper describes a conceptual and practical advance that may have improved retention in a behavioral weight-loss trial—the novel application of motivational interviewing techniques to diffuse ambivalence during interactive group-based orientation sessions prior to randomization. These orientation sessions addressed ambivalence about making eating and exercise behavior changes, ambivalence about joining a randomized controlled trial, and unrealistic weight-loss expectations. During these sessions, overweight and obese men and women learned about the health benefits of modest weight loss as well as trial design, the importance of a control condition, random assignment and the impact of dropouts. Participants were then divided into groups of three or four, and asked to generate two pros and two cons of being assigned to a control condition and an active condition. Participants shared their pros and cons with the larger group, while the investigator asked open-ended questions, engaged in reflective listening and avoided taking a 'pro-change' position. Retention was high, with 96% of the participants ($N = 162$) completing 18-month clinic visits.

Introduction

Based on the 1999–2000 National Health and Nutrition Examination Survey, 64.5% of US adults are overweight or obese (Flegal *et al.*, 2002). To validly test the efficacy of long-term obesity treatments, randomized controlled trials must have minimal participant dropout (Hansen *et al.*, 1985; Ribisl *et al.*, 1996; Ware, 2003). However, retention over time is challenging (Wilson and Brownell, 1980; Brownell and Wadden, 1992). Across behavioral weight-loss treatment studies, 32% of participants drop out (Davis and Addis, 1999). Given that retention rates for behavioral weight-loss trials have not significantly improved in the past 20 years (Wilson and Brownell, 1980; Brownell and Wadden, 1992), identifying novel techniques that improve participant retention is a critical priority (Jeffery *et al.*, 2000).

Ambivalence, defined as 'simultaneous and contradictory attitudes or feelings (as attraction and repulsion) toward an object, person, or action' (Mish, 1990), is thought to undermine behavior change. Motivational interviewing is 'a directive client-centered counseling style for eliciting behavior change by helping clients to explore and resolve ambivalence' (Rollnick and Miller, 1995). One motivational interviewing technique is to build upon a decisional balance exercise (Janis and Mann, 1977; Prochaska and DiClemente, 1983; Miller and Rollnick, 1991; Prochaska *et al.*, 1992, 1994; Miller and Rollnick, 2002) by making any existing ambivalence explicit, and normalizing it using open-ended questions and reflective listening to acknowledge that the pros and cons exist simultaneously and may be contradictory (Miller

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Table III. Additional retention enhancement techniques

- Create 'project identity' that participants can recognize by using similar colors and fonts on trial materials
- Track eligibility status of potential participants on a computer database
- Write protocols to systematically address common participant questions
- Adhere to trial protocols and procedures
- Provide support to all participants
- Offer flexible scheduling
- Attempt to be on time for clinic appointments
- Make multiple attempts to contact participants for complete data by phone and mail
- Encourage participants who move from the area to continue completing questionnaires, and have clinic data (e.g. weight, blood pressure) collected and verified by another health professional
- Send birthday cards to all participants
- Determine two secondary contacts by asking participants to sign letters notifying contacts of trial participation and giving permission to provide forwarding information (letters also served as an *implicit* behavioral commitment to complete the trial)

Challenges for RCTs

- Despite methodological efforts, abysmal retention rates are the norm
- Likely to affect data quality for other behavioral assessments, e.g., adherence, adverse events, self-report measures
- What about the participant perspective?
 - Walk with their feet, missing something
- Need to develop new approaches that optimize high and non-differential retention of subgroups
 - Via 'preventive medicine'



Challenges for RCTs

- A lot of ambivalence exists
 - Definition ≠ wishy-washy
 - *'Simultaneous and contradictory attitudes or feelings* toward an object, person or action' (Mish, 1990)
- Exists on multiple (and deep) levels
 - In a research trial (can be visceral)
 - Assigned to particular study condition
 - Resent or resist being told what to do re changing target behaviors
 - Contradiction between initial expectations & actual experience



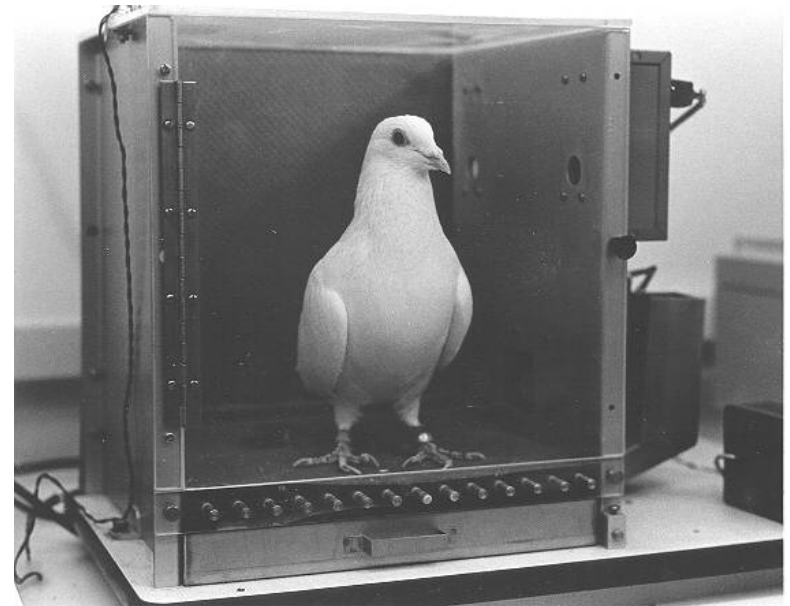
Optimizing retention for randomized trials

- Current context and challenges
- Standard retention strategies
- **Fresh Start weight management trial**
- Innovative retention approaches



Caveats

- Generalizability of weight management trial
- Extensive expertise in field, retention has improved in last 5+ years
- Informed by retention rates, descriptive research, qualitative analysis, & pragmatic experience...
- **Recognize need for randomized experiments of retention strategies**



Fresh Start trial

- Typically, individuals can lose weight but can't maintain – especially after intervention & staff contact are removed
- Tested whether learning **'stability skills first'** improved long-term weight loss maintenance



Fresh Start Weight Loss Study

Learn skills to lose weight!

Researchers at Stanford Medical School are conducting a research study to find out: When is the best time to learn weight maintenance skills? Before or after losing weight?

Interested women will be randomly assigned to one of two 6-month weight-loss programs. In one program, women will learn maintenance skills before losing weight. In the other, women will learn maintenance skills after losing weight. **Our past research shows that women who complete the weight-loss program lose an average of 20 pounds.** There is no charge for the weight-loss programs.

Who is eligible?

This study is seeking **women** who:

- Are 21 years or older
- Have a body weight that falls within the range on the chart at right
- Are free of heart disease
- Do not have diabetes

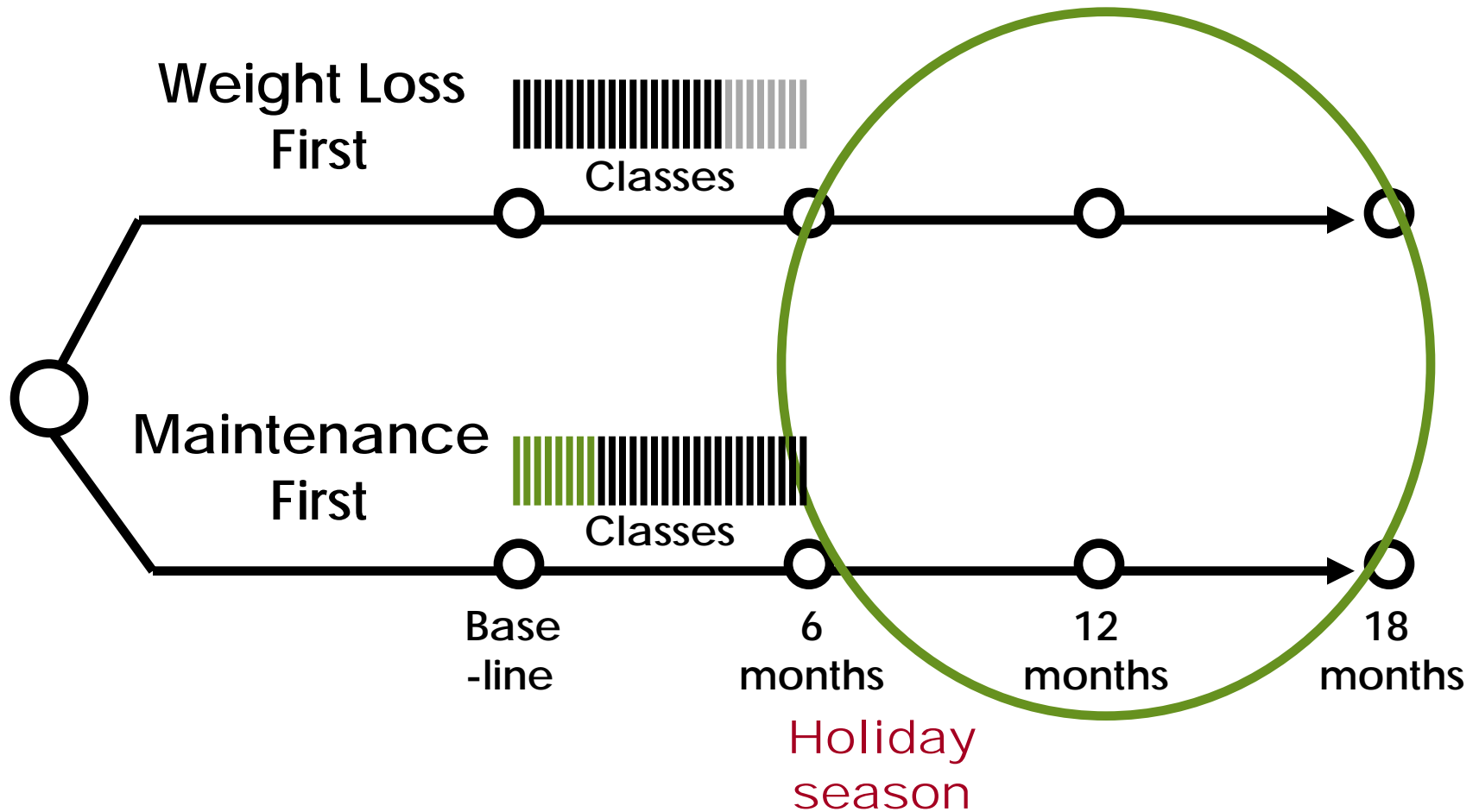
Links

- FAQ's
- Resources
- Contact Us

Does your weight fall within the range for your height?

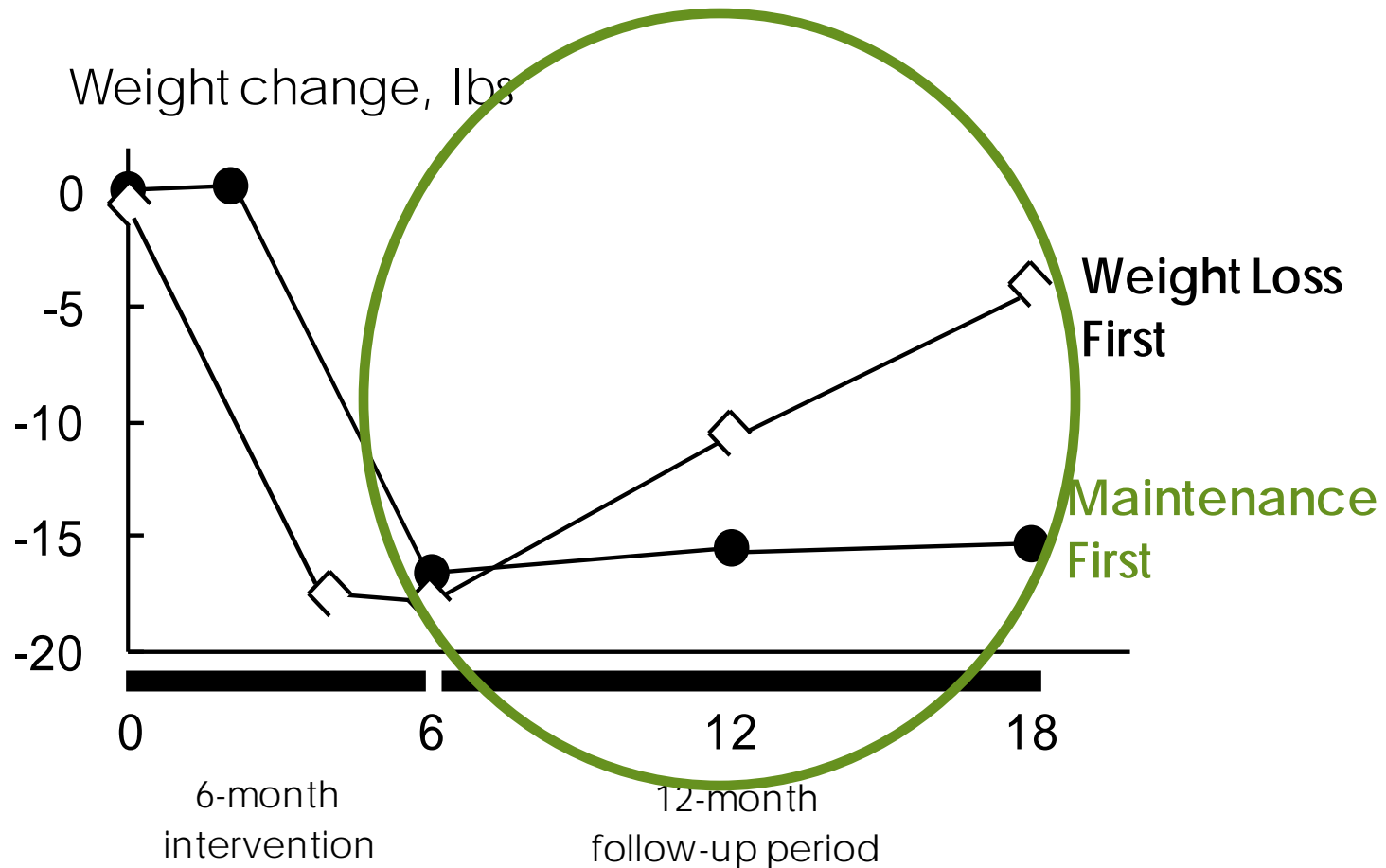
Height/Weight Chart	
Height	Weight
4'8"	120-180 lbs.
4'9"	125-186 lbs.
4'10"	129-193 lbs.

Fresh Start study design



Fresh Start hypothesized effects

Whether learning 'stability' skills before losing weight improves long-term weight management (2 factors differ)



How is the Stability First
approach different?


Maintenance First maintenance phase

Lifestyle & balance skills	Class & homework activities
<u>Enjoy</u> lifestyle habits	<ul style="list-style-type: none"> • <u>Actively encouraged to eat favorite high-fat/cal foods</u> ...savor & enjoy, mindfully & in moderation (<u>but not a 'slip'</u>) • Find low-fat/cal replacements that taste <u>as good as</u> (also activity)
Make <u>peace</u> w/ the scale	<ul style="list-style-type: none"> • Asked <u>not to lose weight</u> for first 8 weeks • Weigh daily to learn <u>own</u> fluctuations/data • Determine own <u>personalized</u> range (~5 lbs)
<u>Finetune</u> lifestyle habits	<ul style="list-style-type: none"> • Make quick, small, & easy adjustments <u>w/out food records, 'relaxed awareness'</u> • If lose a few lbs, <u>asked to gain it back</u>
Navigate <u>inevitable</u> disruptions	<ul style="list-style-type: none"> • <u>Experience a typical disruption</u> (Vacation Tweak Week & eat 5 high-fat/cal meals)



Are women really willing to do this?

Fresh Start results


Variables	Weight Loss First	Maintenance First	<i>p</i>
N = 267 (15% more than goal)	135	 132	
Weight status, baseline			
BMI, baseline	32.1 ± 3.5	32.1 ± 3.4	
Session attendance, cumulative			
1 st session, mean	97.8	95.5	
Thru 9 sessions, mean	89.7	90.3	
Thru 28 sessions, mean	76.2	80.5	
Retention, clinic visits, 18 months	125 92.6%	124 93.9%	
Weight loss at 6 months, lbs, mean	-17.1 ± 13.4	-16.1 ± 10.9	
% weight loss at 6 months, mean	-9.1 ± 6.9	-8.6 ± 5.7	
Lost ≥ 5% weight loss at 6 months	96 71.1%	97 73.5%	
Weight gain from 6-18 months, lbs, mean			
Lost ≥ 5% at 6 months and gained ≤ 5 lbs at <u>every</u> time point over 18 months			

Kiernan M et al. Promoting healthy weight with 'Stability Skills First':
A randomized trial. *J Consult Clin Psych* 2013;81(2):336-346.



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Lost ≥ 5% weight loss at 6 months	96 71.1%	97 73.5%	
Weight gain from 6-18 months, lbs, mean	7.3 ± 9.9	3.2 ± 10.4	.001
Lost ≥ 5% at 6 months and gained ≤ 5 lbs at <u>every</u> time point over 18 months	24 17.8%	44 33.3%	.004

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- Fresh Start weight management trial
- **Innovative retention approaches**



Philosophy of group-based orientation sessions

- In-person small groups, alternatives likely online via social media
- Not just 'info' session, not a 'meet & greet'
- Rationale for study conditions explicit & **transparent**
 - Explicitly acknowledges study challenges
 - **People are not dumb**
 - Manage expectations, don't ignore
 - **Think partnership**, informed by CBPR perspective esp. with underserved/vulnerable communities
 - Clinicaltrials.gov lists types ('active comparator', 'sham control'), ethics, look in the eye
- Principal investigator hosts, not research assistant
 - Approachable, **interactive**, conversational, no Qs off limits
 - **Opposite of 'hard sell'** at group & individual levels
- Also, people 'like me', adult learning, behavioral commitment



Innovative retention approaches

- Introduce potential participants to new value, i.e., the scientific quality of the trial
 - Independent of their own experience (success or failure) AND if trial 'works'
- Acknowledge & diffuse ambivalence on multiple (and deep) levels
- Separates commitments to self & trial quality
- Prior to randomization (not post hoc)
 - Sets tone early = no coercion
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Scientific quality = Research Methods 101

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Introduction

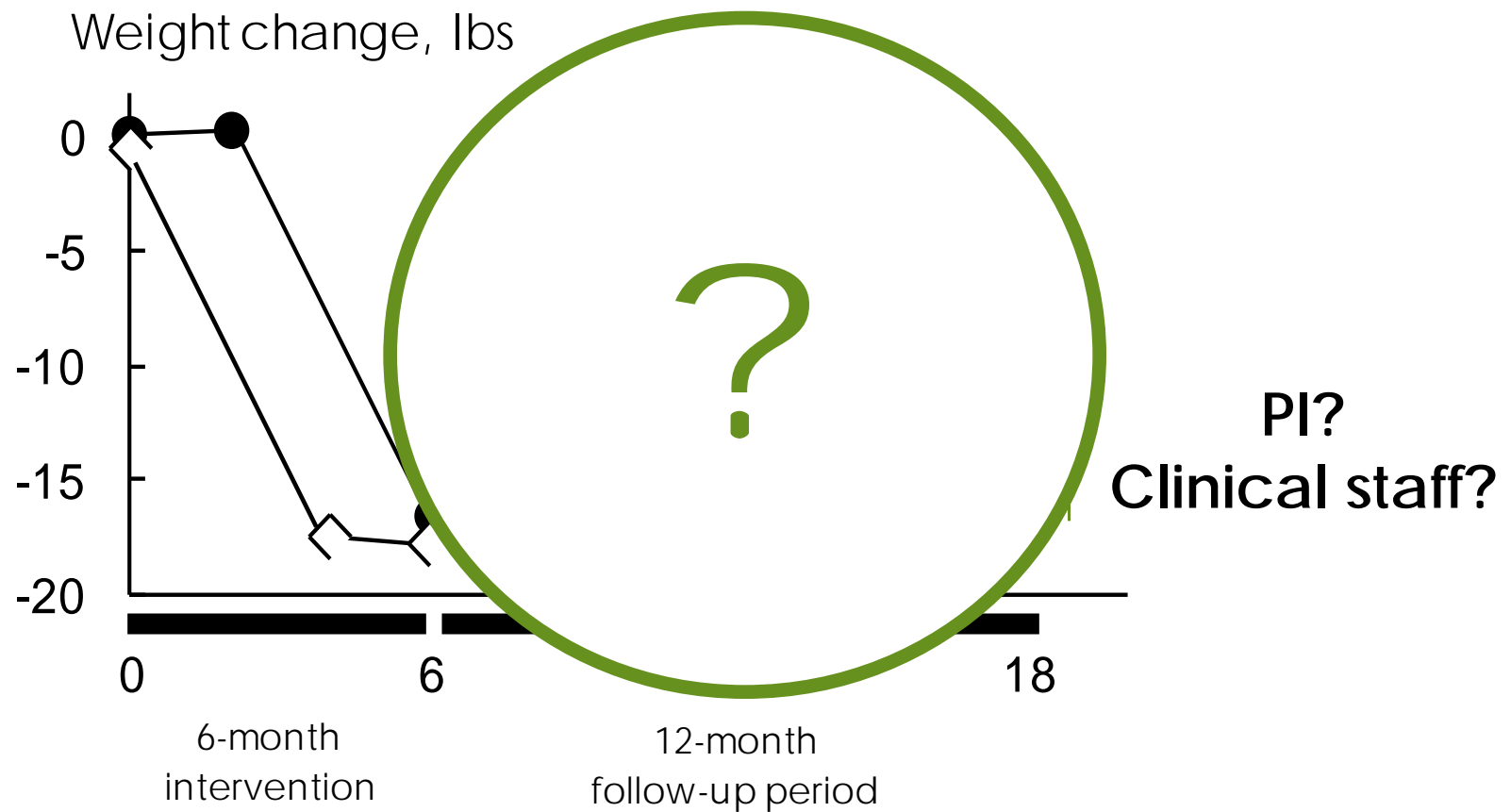
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During these orientation sessions...participants learned about trial design, the importance of a control condition, random assignment, and the impact of dropouts.



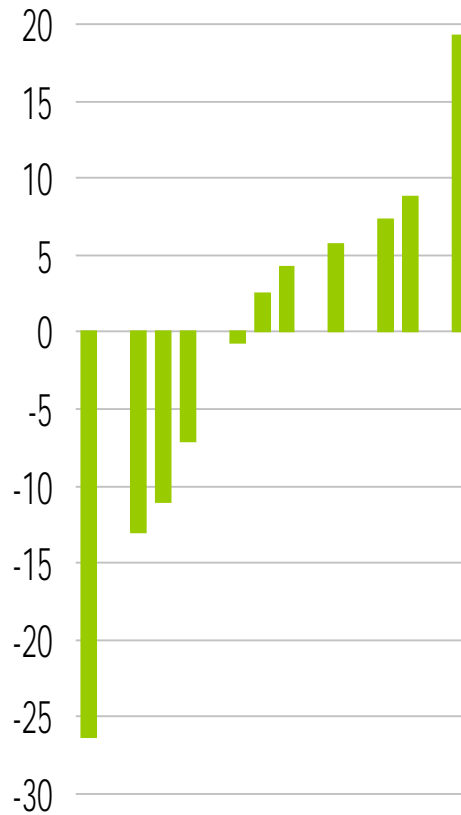
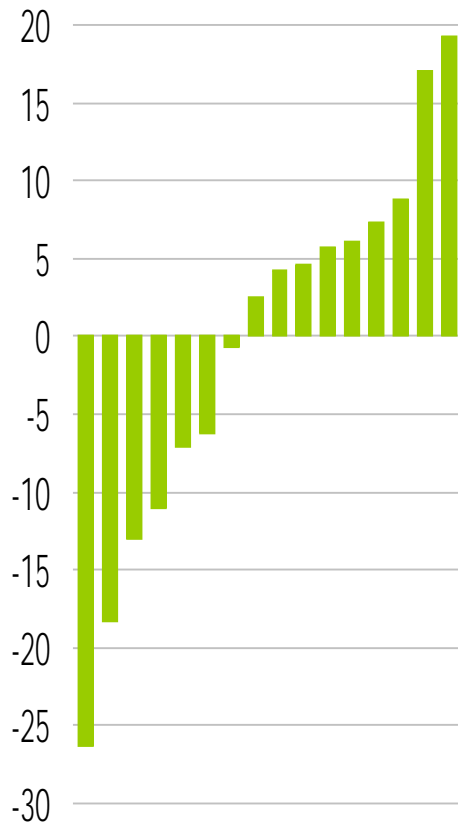
Fresh Start clinic visits & results session





What would scientists conclude if some participants didn't come back?

Change in weight, lbs



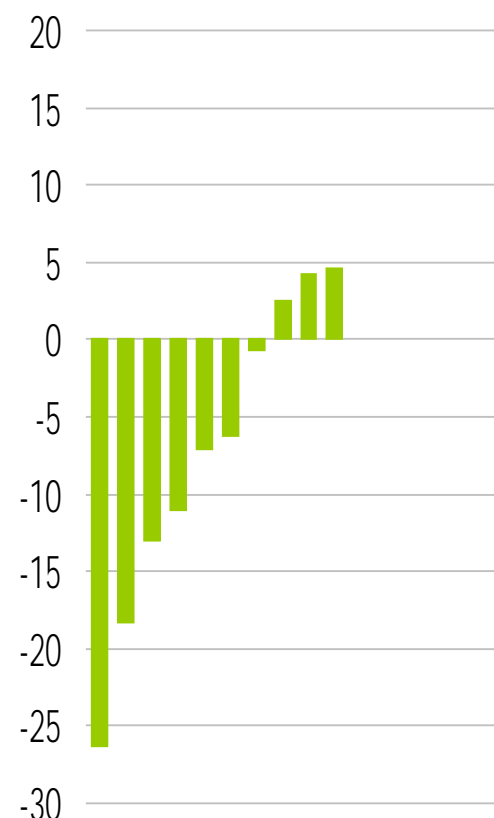
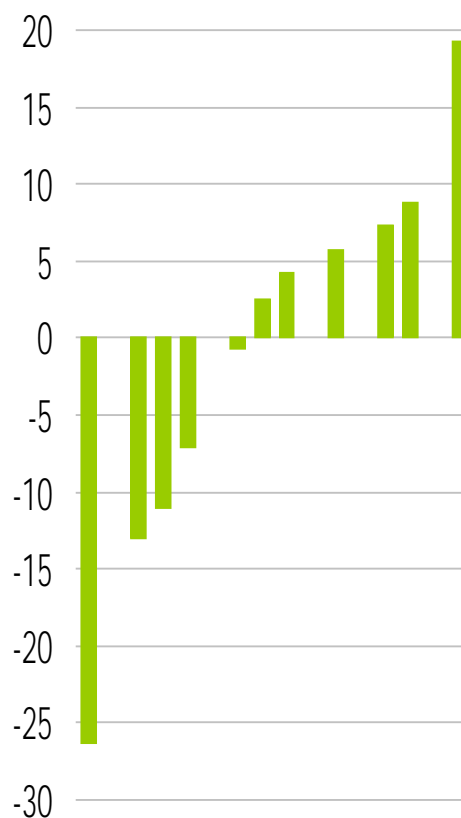
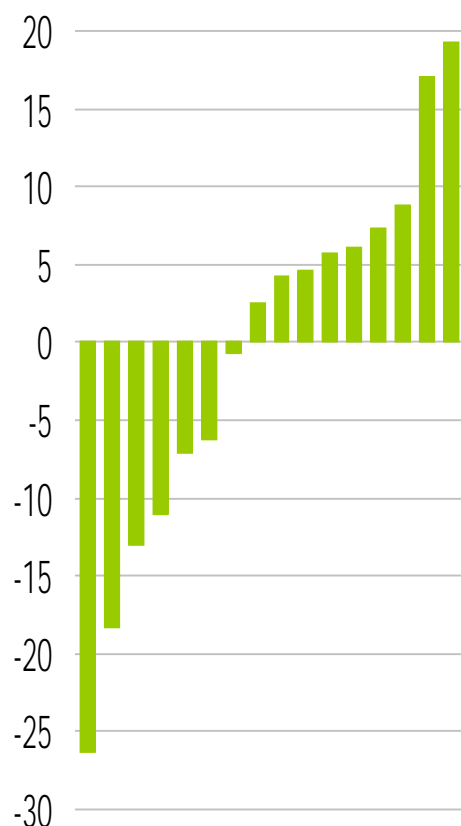
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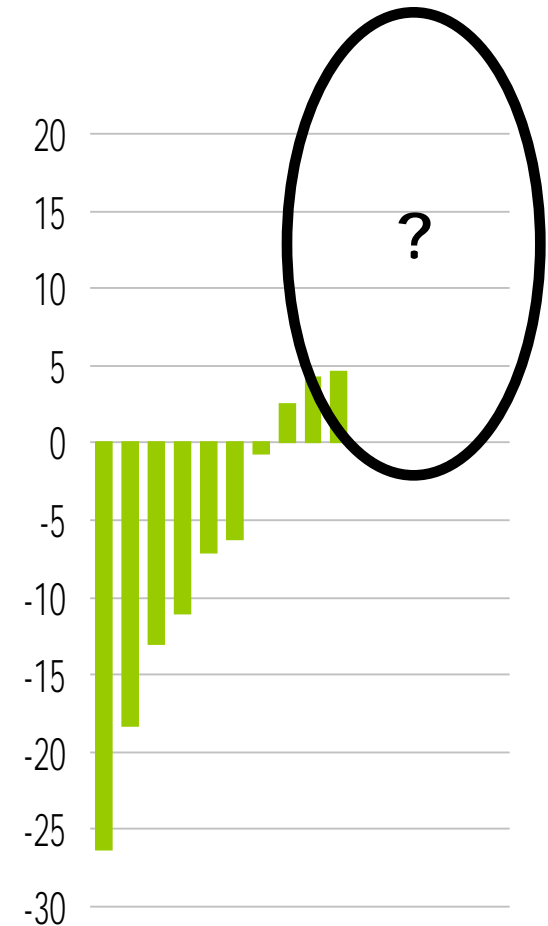
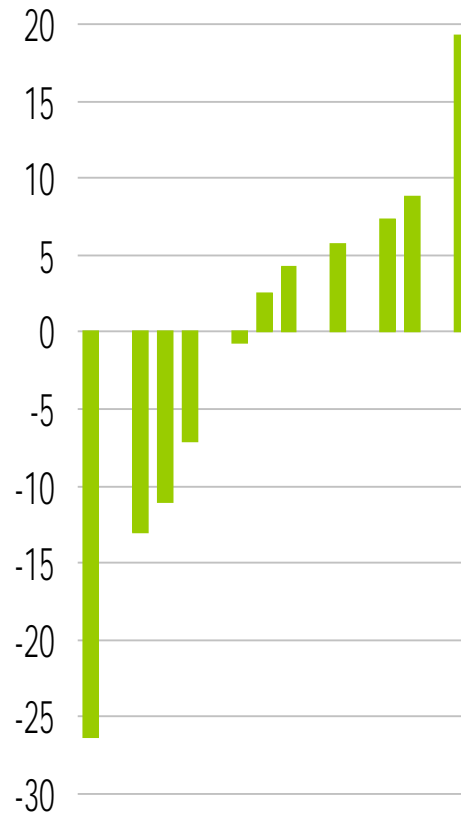
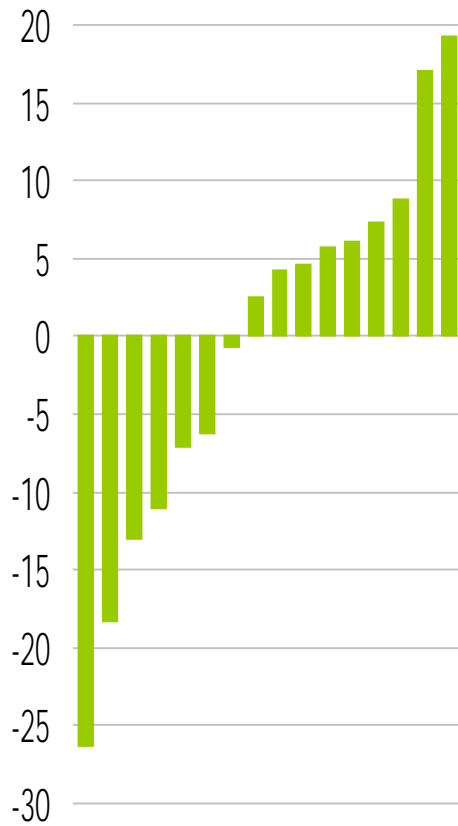
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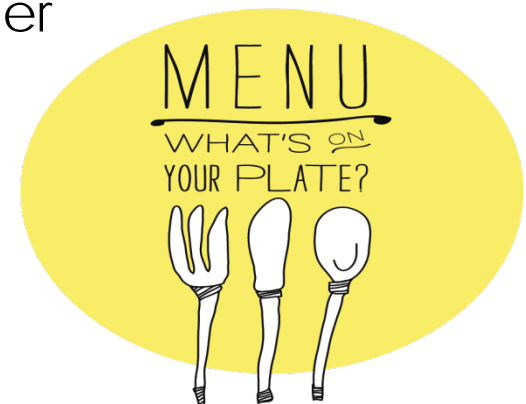


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Retention letter experiment (ongoing)

Retention letter intervention condition	Computer-tailored personalized online interventions to increase FV intake		
	MENU	MENU-GenY	MENU-GenY + e-Coach
Methods letter			
Control letter			

- Collaboration among M. Kiernan, G. Alexander, K. Resnicow
- 1624 young adults (21-30 years), 2 sites, minority recruitment
- Trial tests whether online interventions increase fruit & vegetable intake at 12 months
- Retention letter sent w/ incentive payment after baseline
- Retention experiment tests effect of letter on 3 month retention
- **Used a different graphic**
- Initial psychometrics of proposed moderators & mediators (scale items)
- If works, easily disseminated



Innovative retention approaches

- Introduce potential participants to new value, i.e., the scientific quality of the trial
 - Independent of their own experience (success or failure) AND if trial 'works'
- Acknowledge & diffuse ambivalence on multiple (and deep) levels
- Separates commitments to self & trial quality
- Prior to randomization (not post hoc)
 - Sets tone early = no coercion
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Theoretical rationale

- **Motivational interviewing**
 - ‘Directive client-centered counseling style for eliciting behavior change by helping clients to explore and resolve ambivalence’ (Rollnick & Miller, 1995)
 - Build on decisional balance exercise (pros & cons)
- **Make any existing ambivalence explicit**
- Normalize using open-ended questions & reflective listening
- **Acknowledge pros & cons exist *simultaneously* & *may contradict***
- Especially effective when counselor **avoids taking or defending ‘pro-change’ position** (Miller & Rollnick, 1991), no hard sell

Pros & cons of participating in a scientific trial

- Break into small groups of 3-4 & generate 2 pros & 2 cons, PI leaves room
- Then lead discussion w/ whole group (n=20+)
- Avoid 'pro-change' position
 - Discuss cells in particular order
 - Focus on two critical cells
 - Elicit equal # of responses
- Finish w/ big picture
 - Two commitments
 - Their decision

	In the trial	Not in the trial/ On your own
Pros	3	2
Cons	4	1



Final things to think about

- Results session when trial is over
- Takes work to be in a research trial
- Treat yourself to a Fresh Start
- Will be asked to make two commitments:
 - To **yourself**
 - What will you do less of to make time to participate?
 - Is this a good time for me?
 - To the **scientific quality** of the trial
 - Complete all assessments regardless of whether you lose & maintain weight



Optimizing retention for randomized trials

- Current context and challenges
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- Fresh Start weight management trial
- **Innovative retention approaches**
 - Introduce potential participants to new value, i.e., the **scientific quality** of the trial independent of their own experience (success or failure) AND if trial 'works'
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