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
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

Current context and challenges

• Tension between internal & external validity
  - Heightens ethical considerations
  - Affects (weaken) 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
- **Standard retention strategies**
- Fresh Start weight trial example
- Innovative retention approaches
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
  - Contradiction between initial expectations & actual experience

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- 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**
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 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

<table>
<thead>
<tr>
<th>Lifestyle &amp; balance skills</th>
<th>Class &amp; homework activities</th>
</tr>
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</table>
| **Enjoy** lifestyle habits | • Actively encouraged to eat favorite high-fat/cal foods ...savor & enjoy, mindfully & in moderation (but not a ‘slip’)  
  • Find low-fat/cal replacements that taste as good as (also an activity) |
| Make **peace** w/ the scale | • Asked not to lose weight for first 8 weeks  
  • Weigh daily to learn own fluctuations/data  
  • Determine own personalized range (~5 lbs) |
| **Finetune** lifestyle habits | • Make quick, small, & easy adjustments w/out food records, ‘relaxed awareness’  
  • If lose a few lbs, asked to gain it back |
| Navigate **inevitable** disruptions | • Experience a typical disruption (Vacation Tweak Week & eat 5 high-fat/cal meals) |

Are women really willing to do this?
## Fresh Start Results

<table>
<thead>
<tr>
<th>Variables</th>
<th>Weight Loss First</th>
<th>Maintenance First</th>
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<tbody>
<tr>
<td>N = 267 (15% more than goal)</td>
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<td>132</td>
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<td>Weight status, baseline</td>
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<td>Retention, clinic visits, 18 months</td>
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<td>92.6%</td>
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<tr>
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<td>7.3 ± 9.9</td>
<td>3.2 ± 10.4</td>
<td>.001</td>
</tr>
<tr>
<td>Lost ≥ 5% at 6 months and gained ≤ 5 lbs at every time point over 18 months</td>
<td>44</td>
<td>33.3%</td>
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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
  – Sets context/stage for future discussion

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

Weight change, lbs

-20
-15
-10
-5
0
6-month intervention
12-month follow-up period

PI?
Clinical staff?
What would scientists conclude if some participants didn’t come back?

Change in weight, lbs

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

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

Retention letter experiment (ongoing)

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<th>Computer-tailored personalized online interventions to increase FV intake</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>MENU</td>
</tr>
<tr>
<td>Methods letter</td>
<td></td>
</tr>
<tr>
<td>Control letter</td>
<td></td>
</tr>
</tbody>
</table>

- Collaboration among M. Kieman, 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
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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

Pros & cons of participating in a scientific trial

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<tbody>
<tr>
<td></td>
<td>3</td>
<td>2</td>
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- Cons

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<tr>
<td></td>
<td>4</td>
<td>1</td>
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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

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