Mitigating the Effects of Nonadherence in Clinical Trials

Findings of the ISCTM Working Group
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Mitigating the Effects of Nonadherence in Clinical Trials

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Abstract

Accounting for subject nonadherence and eliminating inappropriate subjects in clinical trials are critical elements of a successful study. Nonadherence can increase variance, lower study power, and reduce the magnitude of treatment effects. Inappropriate subjects (including those who do not have the illness under study, fail to report exclusionary conditions, falsely report medication adherence, or participate in concurrent trials) confound safety and efficacy signals. This paper, a product of the International Society for CNS Clinical Trial Methodology (ISCTM) Working Group on Nonadherence in Clinical Trials, explores and models nonadherence in clinical trials and puts forth specific recommendations to identify and mitigate its negative effects. These include statistical analyses of nonadherence data, novel protocol design, and the use of biomarkers, subject registries, and/or medication adherence technologies.

Keywords

nonadherence, professional subjects, duplicate subjects, adherence, clinical trials
Mitigating Nonadherence
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Potential Conflict of Interest: Dr. Shiovitz is owner and President of the CTSdatabase subject registry
Noncompliance or Nonadherence?

“It was worse than guilty! — The jury found me noncompliant!”
Nonadherence: Definitions

- We will refer to adherence, not compliance: compliance is passive, adherence is a partnership.
- Nonadherence is the extent to which patients do not take medications and/or follow treatment recommendations as prescribed by their health care providers.
- Clinical trial nonadherence is the extent to which subjects do not take study medications and/or follow protocol requirements.
- Clinical Trial nonadherence may be real-world or artifactual.
- Artifactual nonadherence is the unique type of nonadherence found only in clinical trials.
Artifactual Nonadherence:
Inappropriate behavior specific to the clinical trial setting

Deceptive/misleading subject behavior producing data which is noninformative (or worse) with respect to the study hypotheses being tested
Nonadherence

Artifactual Nonadherence
(occurs only in clinical trials)

Medication nonadherence
- Professionals w/no intention to take meds
- Non-professionals who stop IP but report perfect compliance
- CATIE: 74% D/C meds prematurely

Protocol nonadherence
- e.g. NA with lifestyle guidelines, diaries, ratings, missed visits, I/E, don’t have the condition
- Subject or site, unintentional or fraud,
- May actually be IP adherent
- Incr. with incr. study complexity

Real-world nonadherence
Patient and clinician factors, cultural, socioeconomic and illness factors

Real-world nonadherence
(outside clinical trials)
- Medication nonadherence rates as high as 50% (e.g. stop antibiotics early)
- Nonadherence with Tx recommendations common, e.g. lose weight and exercise; check RBS

Real-world nonadherence
(w/in clinical trials)
- e.g. Stop meds due to AE, forgetting or social factors
Sources of Real-World Nonadherence*

- **General Factors**: NA incr. with incr. cost, complexity and duration of the regimen; disruption of lifestyle; pt. perception of benefits and risks; poor communication between doctor and patient
- **Treatment factors**, particularly side effects like weight gain or sexual dysfunction
- **Patient factors**, like the desire to be independent and eschew the healthcare system
- **Illness factors**, like psychosis, depression or cognitive impairment

*Partial NA more common than complete NA*

*from Mitchell and Selmes, 2007*
Real-world Nonadherence*

Many patients stop taking their medications
Adherence rates plummet in just a few months

<table>
<thead>
<tr>
<th>Treatment area</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td>60%</td>
<td>52%</td>
<td>41%*</td>
</tr>
<tr>
<td>Diabetes (type 2)</td>
<td>53%</td>
<td>43%</td>
<td>38%</td>
</tr>
<tr>
<td>Obesity</td>
<td>48%</td>
<td>41%*</td>
<td>35%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>47%</td>
<td>43%</td>
<td>41%</td>
</tr>
<tr>
<td>Depression</td>
<td>30%</td>
<td>20%</td>
<td>10%</td>
</tr>
</tbody>
</table>

By the end of the first year of treatment, 50 to 90% of patients stop taking their prescribed therapies.

* Adherence rate ranges were averaged. Source: Various sources; A.T. Kearney analysis

Sources of Artifactual Nonadherence (1)
Subject behavior that provides false/misleading data

- Incentives to not always be 100% truthful: Want to please/participate/not be rejected/be compensated
- 93% reported compliance by pill count (43-78% actually measured with PK)
- Inclusionary conditions magnified, exclusionary conditions denied, ratings inflated
- The worst subjects may be the easiest on sites, monitors, data managers, statisticians (no med hx, no AEs, 100% compliance: don’t ask / don’t tell?)
Case example: Seeing double

• A psychiatrist and his spouse work together as investigator and rater at a site doing a rTMS study and the spouse also works separately as a rater at a CNS site about a mile away.

• The rater arrived at the second site to find the subject she had just rated at the rTMS site in the waiting room filling out paperwork. “I didn’t know you’d be here too”, the subject laughed.
Dan Ariely on Why People Cheat

TED Talk
Dishonesty
From The Honest Truth About Dishonesty, Dan Ariely, 2012

• The vast majority of people cheat, but just by a little bit
• We cheat up to the level that allows us to retain our self-image as reasonably honest individuals
• Biased incentives can lead even the most upstanding professionals astray
• Moral reminders and monitoring reduce dishonesty
• The more taxing/depleting the task the more participants cheat
Case example:
* Lose the exclusion and try again *

• A PI in the Midwest was frustrated to learn his subject was excluded by the medical monitor (on the basis of his pre-baseline form due to a brief LOC as a child), and he told the subject that he would be SF due to this condition.

• Later he learned that the subject was accepted for the same protocol (with the same medical monitor) at a nearby site.
Sources of Artifactual Nonadherence (2)

- Increasing complexity and longer visits in Ph 2-4 studies (6-10% per year, Getz, 2009) may lead to incr. likelihood of cheating.
- Incr. stringent I/E may give professionals an advantage over bona fide patients
- Studies designed as if subjects are altruists and behave in order to answer the hypotheses being tested?
- They behave like real people: They react to burdens; some have altruistic motives but most want to feel better or support themselves and their families or both
Duplicate and Professional Subjects

- **Duplicate subjects**: participate in multiple studies concurrently or within an exclusionary timeframe (motives vary);
- **Professional subjects**: primary goal to collect stipends (Ph 1 vs 2-4). May be *serially monogamous* or *polygamous*
- Usually protocol or medication nonadherent, deceptive about exclusionary conditions or whether they have the disease (or the severity) in question, previous study participation
- They can adversely affect safety in Ph 1 (violating washout) and efficacy and safety signals in Ph 2-4 studies
Case example (1): safety signal

- A subject screened for a Phase I study in Texas. When he took off his shirt for the ECG, the CRC noted that he still had ECG leads on his chest.
- A call to a nearby Phase I site confirmed that the subject had been at their site earlier in the day.
Case example (2): efficacy signal

- CJL, a 30 y.o. very depressed man enrolled in a DB, placebo-controlled study of recurrent MDD. His MADRS score was 32 at screen and 31 at BL. Score improved to a 2 at end of study
- Subject was on *placebo*
- Later discovered he had recently partic. in a GAD study with initials JCL and had denied any past h/o MDD
Percentage of Duplicates

21,240 CTSdatabase subjects entered, by days between matches, through 12/30/15
Case example (3): safety and efficacy signals

• A 42 y.o. screening for a Schizophrenia study was found to be concurrently in another study. He had denied any previous study participation, but laughed and said “you caught me” when confronted.

• He admitted taking IP “only when it makes my head feel clearer,” while reporting 100% compliance by pill count.

• He was found to have screened / prescreened at a minimum of 7 sites (duplicating 3x) in the last 12 mos.
Change in Indication/Diagnosis
(2,314 CTSDatabase matches, through 12/30/15)

<table>
<thead>
<tr>
<th>Change in Indication</th>
<th># matches crossing indication</th>
<th>% of all matches</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEP ↔ SCZ</td>
<td>189</td>
<td>8.2%</td>
</tr>
<tr>
<td>SCZ ↔ BIP</td>
<td>135</td>
<td>5.8%</td>
</tr>
<tr>
<td>DEP ↔ BIP</td>
<td>125</td>
<td>5.4%</td>
</tr>
<tr>
<td>ANX, INS ↔ DEP, BIP, SCZ</td>
<td>57</td>
<td>2.5%</td>
</tr>
<tr>
<td>HN ↔ MIG, ANX, DEP</td>
<td>45</td>
<td>1.9%</td>
</tr>
<tr>
<td>DM ↔ DEP, BIP, ANX, SCZ, OIC</td>
<td>31</td>
<td>1.3%</td>
</tr>
<tr>
<td>MIG, Pain ↔ DEP, BIP, SCZ, ANX</td>
<td>28</td>
<td>1.2%</td>
</tr>
<tr>
<td>GI, OIC, OA ↔ DEP, BIP, SCZ</td>
<td>26</td>
<td>1.1%</td>
</tr>
<tr>
<td>ADHD ↔ DEP, BIP, ANX, INS</td>
<td>24</td>
<td>1.0%</td>
</tr>
<tr>
<td>AD/MCI ↔ DEP, ANX</td>
<td>7</td>
<td>0.3%</td>
</tr>
<tr>
<td>OTHER</td>
<td>36</td>
<td>1.6%</td>
</tr>
<tr>
<td>Total matches = 2314</td>
<td>703</td>
<td>30.3%</td>
</tr>
</tbody>
</table>
Summary

• Artifactual nonadherence: NA behaviors unique to clinical trials. Covert, misleading
• Along with real-world NA, it can adversely affect patient safety, efficacy/safety signals and study success
• Protocol complexity, perverse incentives, dishonesty (and people being people) contribute to NA in clinical trials.
• Duplicate/professional subjects are a particularly egregious source of artifactual NA
Stay tuned…

• Earle: *Impact of Noninformative Data*
  • Discussion

• Phil: *Compliance Biomarkers, Subject Registries and Medication Adherence Technologies*
  • Discussion, 20 min Break

• Dave: *Where and How to Act To Mitigate the Effects of NA*
  • Discussion

• Tom L: *Regulatory Considerations in NA*
  • Discussion

• Earle: *Recommendations of the Working Group*

• All speakers, Adam: *Panel Discussion, Q&A*
Discussion (10 min)

Next up:
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