Where and how to act to identify and mitigate the effects of nonadherence

Prior to screening
Screening
Run-in period (post-screening/pre-randomization)
Treatment period (post-randomization)
Data analysis

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Prior to screening

Product formulation

Sustained release implant or injection formulations can address the problem of “real world” medication nonadherence (even in clinical trials).

However, “artifactual” medication nonadherence is just a symptom of a more important, underlying problem.

A subject who feigns depression to gain enrollment in an antidepressant trial is a problem regardless of his/her medication adherence level.
Prior to screening

Decisions regarding financial compensation (for sites and subjects)

Failure to appropriately compensate sites for pre-randomization activities (e.g., obtaining medical records) may incentivize sites to become less stringent.

Eliminating financial compensation for subject time/inconvenience might eliminate the “professional subjects” problem; however, the impact on enrollment rates for legitimate subjects could be devastating.

Avoiding “excessive” compensation is common sense, but there is no “safe” level of compensation.
Concealment and fabrication by experienced research subjects

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\textbf{Background} Subjects who enroll in multiple studies have been found to use deception at times to overcome restrictive screening criteria. Deception undermines subject safety as well as study integrity. Little is known about the extent to which experienced research subjects use deception and what type of information is concealed, withheld, or distorted.

\textbf{Purpose} This study examined the prevalence of deception and types of deception used by subjects enrolling in multiple studies.

\textbf{Methods} Self-report of deceptive behavior used to gain entry into clinical trials was measured among a sample of 100 subjects who had participated in at least two studies in the past year.

\textbf{Results} Three quarters of subjects reported concealing some health information from researchers in their lifetime to avoid exclusion from enrollment in a study. Health problems were concealed by 32\% of the sample, use of prescribed medications by 28\%, and recreational drug use by 20\% of the sample. One quarter of subjects reported exaggerating symptoms in order to qualify for a study and 14\%
75% reported concealing health information to avoid exclusion.

43% reported concealing their participation in another study.

25% reported exaggerating symptoms in order to qualify for a study.

14% reported pretending to have a health condition in order to qualify.

For “deceivers:” Avg. # studies during the prior year = 12.8

Avg. earnings per study during the prior year = $133
Prior to screening

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(for sites and subjects)

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Eliminating financial compensation for subject time/inconvenience might eliminate the “professional subjects” problem; however, the impact on enrollment rates for legitimate subjects could be devastating.

Avoiding “excessive” compensation is common sense, but there is no “safe” level of compensation. ANY financial compensation may be attractive to an unemployed professional subject.
Prior to screening

Protocol design

Increased protocol complexity and/or subject time requirement plays into the hands of “professional subjects.”

From experience, they may know exactly how to respond to complicated questions.

If unemployed, they may equate time requirement with earning potential (“That’s OK – you’re paying for my time”), whereas legitimate, employed subjects may have conflicting outside commitments.

“Need to know” vs. “nice to know” data
Prior to screening

Protocol design

During protocol design, we must decide how to address the problems of “professional subjects” and nonadherence at all stages of a trial.

What can be done during screening?

Should there be a run-in period between screening and randomization?

What can be done after randomization?

Proactive planning appears essential.
Screening

One or more clinical trial participant registries can be used to:

- Prevent enrollment at multiple sites within a trail.
- Prevent simultaneous enrollment in other trials covered by the registries.
- Prevent other types of protocol violations (registry-dependent)

Sponsors may limit public access to inclusion/exclusion criteria (e.g., by listing inclusion but not exclusion criteria on clinicaltrials.gov).

An independent, central review of diagnosis-related ratings may be used to decrease enrollment of inappropriate subjects.
Screening

Site Versus Centralized Raters in a Clinical Depression Trial

Impact on Patient Selection and Placebo Response

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Journal of Clinical Psychopharmacology • Volume 30, Number 2, April 2010

FIGURE 1. Frequency distributions of site and central HDRS ratings at baseline for site eligible subjects.
Run-in period (post-screening, pre-randomization)

“Removing poor compliers identified after randomization is generally not acceptable…”

“Identifying and selecting patients likely to comply with treatment” is a “useful and generally accepted” strategy to decrease variability.

Examples cited:

- VA CSP hypertension studies (late 1960’s); morbidity & mortality
  Veterans with HBP received placebo tablets containing riboflavin during a run-in period & urine was examined for fluorescence

- The Physicians’ Health Study (1980’s); aspirin to prevent MI
  Patients (all physicians) received placebo during a run-in period and then self-reported adherence.
Run-in period (post-screening, pre-randomization)

In modern-day NME trials, we must consider the potential impact of information contained in ICFs, as well as word-of-mouth communication between study subjects.

If study drug nonadherence will lead to early termination of study participation, it may be impossible to conceal this fact from professional subjects, and they could modify their behavior to remain in the study.
Run-in period (post-screening, pre-randomization)

“Run-in with Adherence Monitoring for Prequalification but Undiminished Participation” (RAMPUP) Design

McCann et al.
Run-in period (post-screening, pre-randomization)

“Run-in with Adherence Monitoring for Prequalification but Undiminished Participation” (RAMPUP) Design

Ongoing NIDA/AZ smoking cessation trial

Required for randomization to Group A or B:
1) MEMS cap opened on at least 6 of 7 days
2) NMT 1 capsule returned on day 8
3) Exhaled CO ≥ 10 ppm (inclusion criterion)
Run-in period (post-screening, pre-randomization)

Advantages to keeping subjects who are nonadherent or apparent early responders:

1) Professional subjects may be more likely to demonstrate nonadherence and/or “placebo response” during the run-in period if there is no threat of early termination.

2) To evaluate the merits of any enrichment strategy, it is critically important to evaluate efficacy in subjects who fail to qualify for the primary endpoint.

3) Evaluation of adverse events in subjects who exhibit both high and low adherence rates may yield a safety profile that is more relevant to the “real world.”

4) Retaining all subjects is responsive to corporate pressure for speed (because safety data from all subjects will contribute to the required safety package for regulatory approval).
Treatment period & data analysis

FDA Guidance:
“Removing poor compliers identified after randomization is generally not acceptable…”

So...why bother measuring medication adherence after randomization?

1) Because “real world nonadherence” occurs in clinical trials (appropriate subjects may simply forget to take their study drug), adherence monitoring and counselling may improve efficacy and safety evaluations.

2) Ignoring post-randomization nonadherence may:
   
   Prevent the detection of efficacy
   (important for go/no go decisions regarding continued development).

   Distort the apparent safety profile
   (perhaps obscuring an important safety signal).
Detection of efficacy based on post-randomization medication adherence data

The Secrets of a Successful Clinical Trial: Compliance, Compliance, and Compliance

Pál Czobor and Phil Skolnick

Molecular Interventions 11: 107-110, 2011

Figure 2. Improvement on the visual analog scale for pain in a twelve-week trial of bicifadone in patients with chronic low back pain. These data represent patients who received either a controlled release form of bicifadone (200 mg, twice daily) or placebo. The visual analog scale (VAS) ranges from 0-100 mm. For patient recruitment in the study reported here, baseline pain severity had to be at least 40 mm. Changes in VAS score was the primary endpoint measure; analysis of plasma bicifadone in this trial arm was a planned pharmacokinetic/pharmacodynamic comparison. VAS change scores as endpoint measures were compared with ANCOVA. Severity at baseline, gender and age were applied as covariates. The pattern of results shown here was largely replicated (data not shown) using the Roland-Morris Disability Questionnaire (15); see text for details. *(p<0.01 vs placebo or noncompliant groups; *p<0.05 vs placebo or noncompliant groups; **p<0.002 vs placebo or noncompliant groups).*
Use of a subject registry should:

1) eliminate the problem of within-study (or within-program) dual enrollment
2) reduce simultaneous subject enrollment in cross-sponsor studies

But…what if the registry reveals that a randomized subject has attempted screening at another site?

Consider site-level action (drop sites where this is common)
Opportunities to identify and mitigate the effects of nonadherence exist throughout the process of conducting clinical trials.

Proactive planning is required.

Acknowledgement of a problem is the first step to a solution.

Embrace the problem!
Discussion (10 min)

Next up:
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