Seeding trials are clinical studies primarily intended to promote use of the study drug by physicians and/or to convert physicians, especially opinion leaders — and study subjects — into advocates for the study drug. Seeding trials seed the market with product samples. The sponsor hopes that physicians and patients will continue using the drug after the trial. Seeding trials are unethical because they exploit study subjects for commercial purposes, create little or no medically useful knowledge, and deceive researchers, subjects and IRBs.

In the interest of protecting human welfare, institutional review boards (IRBs) should not approve seeding trials. A seeding trial can occur only because the sponsor “does not disclose its true purpose to anyone who could say ‘no.’” (p. 279) The question for the IRB thus becomes: Is the study under review a seeding trial?

Inexperienced investigators and IRB members may not be familiar with the characteristics of seeding trials. Table 1 summarizes the six seeding trial criteria of Kessler, et al2 and six additional criteria of Sox and Rennie1. These researchers suggested that clinical trials sharing one or more of these flaws might be seeding trials, although some information may be difficult or impossible for the IRB to obtain. With the criteria in Table 1, IRBs can identify most seeding studies.

**Case Study**

Our IRB reviewed a Phase IIIb rollover trial (“Study A”) using subjects from a Phase III study. Phase III trials are large, multicenter, randomized controlled trials designed to evaluate a drug’s effectiveness in comparison to the standard treatment. The sponsor’s Phase III study met these criteria, comparing two doses of an experimental drug with a comparison drug. Phase IIIb studies are conducted after a drug has been submitted to the FDA, but before the drug is approved for marketing. Phase IIIb studies are done for a variety of reasons, including the collection of additional safety data — one of the sponsor’s two rationales for this study.

Study A (a) compares the safety and efficacy of two drug dosage levels (with no placebo arm) and (b) compares two types of knowledge intervention designed to help subjects change their behaviors to improve their blood pressure, blood sugar, lipids, etc. Because subjects in Study A will receive the same dosage they received in the previous Phase III trial, the risks and safety issues should be the same.

Table 1 summarizes the author’s assessment of Study A. The first column identifies criteria that appear to be consistent with seeding trials. The second column identifies criteria that appear to be inconsistent with seeding trials. The third column identifies criteria that cannot be assessed with the information available to the IRB. Explanations of the assessments follow the table.
Table 1. Study “A” Seeding Trial Review

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
<th>Unk</th>
<th>Criteria (Kessler, et al)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>X</td>
<td></td>
<td>1. Design doesn’t support stated research goals</td>
</tr>
<tr>
<td></td>
<td>X</td>
<td></td>
<td>2. Investigators recruited who often prescribe competing product</td>
</tr>
<tr>
<td></td>
<td>X</td>
<td></td>
<td>3. High payments to investigators</td>
</tr>
<tr>
<td>X</td>
<td></td>
<td></td>
<td>4. Trial sponsorship by company’s sales &amp; marketing division</td>
</tr>
<tr>
<td></td>
<td>X</td>
<td></td>
<td>5. Minimal requirements for data collection</td>
</tr>
<tr>
<td>X</td>
<td></td>
<td></td>
<td>6. Data is of little or no value to the company</td>
</tr>
<tr>
<td>X</td>
<td></td>
<td></td>
<td>Criteria (Sox and Rennie)</td>
</tr>
<tr>
<td>X</td>
<td></td>
<td></td>
<td>7. Study hypothesis addresses a settled research question</td>
</tr>
<tr>
<td>X</td>
<td></td>
<td></td>
<td>8. Open-label design</td>
</tr>
<tr>
<td>X</td>
<td></td>
<td></td>
<td>9. No control group</td>
</tr>
<tr>
<td>X</td>
<td></td>
<td></td>
<td>10. Large enrollment size relative to importance of research</td>
</tr>
<tr>
<td>X</td>
<td></td>
<td></td>
<td>11. Short-term study of chronic disease</td>
</tr>
<tr>
<td>X</td>
<td></td>
<td></td>
<td>12. Study of an already approved drug</td>
</tr>
</tbody>
</table>

1. **Design does not support stated research goals.**

Study A’s first research purpose is to test the long-term safety of two dosages of the experimental drug. Safety studies are completely legitimate. However, although Study A is planned to last two to three years, the sponsor will close the study early if the FDA approves the drug. If closed early, the study probably will be unable to determine the drug’s long-term safety and will not meet the stated research goal. The study subjects will have participated to no scientific purpose. FDA marketing approval *per se* is a commercial, not a scientific, goal. Since there are no comparison drugs, as in the Phase III study, the relative safety of the experimental drug vs. a comparison drug (or placebo) cannot be determined.

Study A’s second research purpose is to test whether giving subjects and their physicians “personalized feedback” will improve the subjects’ health status. In the Personalized Feedback group, the sponsor periodically sends study doctors reports about the medications their subjects take for hypertension, diabetes, high cholesterol, etc., and compares the study doctor’s treatments to national and international guidelines. The sponsor also periodically sends subjects personalized healthcare information. This information encourages them to talk about treatments with their study doctor and to become more actively involved in their own healthcare. The number and frequency of these communications with physicians and subjects are not defined, so there is no way to know what “periodically” means; this information is crucial because it bears on the intensity of the intervention (e.g., receiving letters every month vs. every six months).

In the Personalized Feedback control group, the sponsor sends study doctors the same current guidelines for managing hypertension, diabetes, high cholesterol, etc., but does not send subjects (or their study doctors) personalized reports about their treatment. There is no non-treatment control group.

If the second research purpose is, in fact, legitimate, it should be treated in a scientifically sound manner consistent with published behavioral studies. Study A’s second research purpose is unlikely to be achieved for the following reasons:
a) Absence of a behavior change rationale

Although the study tests changes to physician and subject behaviors, the study does not include any rationale for an individual's behavior change, although there are at least five well-known behavior change theories\(^3\): 1) Health Belief Model, 2) Stages of Change Model, 3) Consumer Information Processing Model, 4) Theory of Planned Behavior, and 5) Implementation Intentions Model. While a 1992 National Institute of Mental Health consensus meeting on behavior change theories identified eight variables (patients are committed to behavior change, have the skills to carry out new health behaviors, are in environments that do not limit healthy behaviors, etc.) that explain most of the variation in health behaviors\(^3\), nothing in this study specifically addresses any of these relevant variables.

Although Study A assumes that giving information to doctors and patients will ultimately lead to better health outcomes, the study is unlikely to demonstrate a causal relationship and cannot disprove it.

b) No rationale for knowledge intervention methods

The protocol and other study materials offer no insights from the literature on what works — or does not work — to change and maintain health behaviors, or why the proposed interventions should be effective. Information provided to the IRB does not consider proven communication methods between doctors and patients, such as “motivational interviewing\(^4\).” In motivational interviewing physicians 1) collaborate with patients to 2) establish better rapport and reduce their resistance so that patients can 3) make lifestyle changes that 4) will lead to better health outcomes.

c) Healthcare knowledge unknowns

Study A does not measure knowledge, attitudes or behaviors of study doctors or subjects at baseline, during or after the trial. The study collects no data from the study doctors (mostly cardiologists) or subjects about drug information they received prior to the study or received during the study from sources other than the knowledge interventions. In other words, no previous and concomitant treatment data is collected. Since the subjects have already been in the preceding Phase III study, and probably have a primary care physician, they have received and probably will continue to receive healthcare information about their conditions. This other information constitutes confounding variables, especially since the quality and frequency of the information varies considerably.

Subjects may receive information from sources such as:
- Disease management programs through their health plan
- Health plan educational materials
- Disease-specific clinical initiatives, such as Medicare’s Medication Therapy Management Program, described at: http://www.cms.hhs.gov/PrescriptionDrugCovContra/Downloads/MTMFactSheet.PDF
- Counseling with their pharmacist
- Conversations with other physicians they see in addition to the study doctor.

The sponsor has not provided a statistical power calculation to the IRB. In theory, if Study A has enough power, it can overcome the confounding variables. However, because the endpoint (differential change in health status) is indirect and the knowledge intervention is probably only a small fraction of all the highly variable information received by subjects, adequate power may require a subject population much larger than that needed for the safety purpose.

d) Reliance on practice guidelines
The protocol does not justify the use of practice guidelines as a key part of the knowledge intervention. There is evidence that it is not effective. For example, giving physicians practice guidelines for hypertension does not appear to consistently change their practice styles; researchers\(^5\) report that “…conclusions regarding the degree of physician adherence to hypertension guidelines are premature.” (p. 5) Are the “practice guidelines” (undisclosed to the IRB), in fact, marketing literature in disguise?

The materials given to the IRB do not review the relevant behavioral literature. For example, other researchers conclude\(^6\) that “Physician practice behavior often produces poor clinical outcomes in the management of cardiovascular disease risk factors in spite of effective treatments and guidelines” (p. 394). However, these researchers produced significant improvements in patient systolic blood pressure and LDL cholesterol via “academic detailing,” using a multidisciplinary team (a physician champion, project coordinator, and data analyst) to (a) give physicians patient data, (b) review that data with the physicians, and (c) advise physicians on how to improve patient outcomes.

2. **Investigators recruited who often prescribe competing product**

Information on this criterion is not available.

3. **High payments to investigators**

Information on this criterion is not available.

4. **Trial sponsorship by company’s sales & marketing division**

Information on this criterion is not available.

5. **Minimal requirements for data collection**

The research hypothesis assumes that providing information will affect health status, but this cause and effect is very indirect: the information must include the right content and be provided in a suitable form at the right frequency; the physicians and subjects must read and understand it; the subjects must then alter their behavior; and the alterations must then impact measurable health status during the term of the study. Materials provided to the IRB do not discuss the literature on these intermediate factors, nor does the study collect information about them. Although psychologists would be very interested in how the intervention affects subject and physician knowledge, attitudes and behaviors, the study does not collect any data on these key factors. The study does not collect data on whether the subjects read the information or even care about it. The protocol does not characterize even the reading level of the information. If the knowledge intervention leads to improved health outcomes — or poorer health outcomes — the sponsor has no way of knowing which factors contributed to these changes.

6. **Data is of little value to the company**

If the study closes early, the interim data may have no value. Because only endpoint data is collected about the knowledge intervention, it is unlikely to have value to the sponsor.

7. **Study hypothesis addresses a settled research question.**

Study A, if completed, may answer unsettled questions about the safety of the drug at the two dosages. The knowledge intervention question is not settled, but is posed in such a manner that it probably cannot be answered by this study. (See criterion 1 above.)

8. **Open-label design**

Study A is partly open-label. The subjects receive one of two dosages of the experimental drug, but neither the subject nor the researcher knows the dosage. There is no comparison drug. The personalized feedback component is open label.
9. No control group

Neither component of the study has a placebo, non-treatment or active drug control group. There may be a serious ethical dilemma in the Control Group, in which neither study doctors nor subjects receive any information about medications taken for health conditions. Since this is a safety trial, is it ethical to withhold lab test results from study doctors, especially if subjects have some abnormal lab values? The consent form notes that drug dosages will be made available to study doctors in an emergency, and that additional tests may be run if subjects have “very abnormal” liver or kidney functions. But what about other results for hypertension, diabetes, cholesterol, etc.? For subjects and study doctors in the control condition, will this procedure invalidate the “control,” so that subjects experiencing these problems should be dropped from the “control group?”

10. Large projected enrollment

Although Study A plans to enroll thousands of subjects worldwide, the protocol and other study materials do not include a power analysis; the sponsor offers no statistical justification for the sample size.

11. Short-term study of chronic disease

Given Study A’s focus on long-term health problems of hypertension, diabetes, high cholesterol, etc., the length of the study may be insufficient to determine long-term health changes attributable to personalized feedback.

12. Study of an already approved drug

The FDA has not approved the drug for marketing, but the application is pending.

Conclusion

When an IRB suspects a seeding study, it can use the criteria in Table 1 for a thorough assessment. Study A meets several criteria of seeding trials, although the evidence is not conclusive. The legitimacy of closing the study upon FDA marketing approval is problematic. There may not be an ulterior motive behind the poor design of the knowledge intervention component of the study. Unfortunately, the sponsor did not provide substantive answers to the questions posed by the IRB on the issues raised above.

Nevertheless, the IRB approved the study, largely because risk to the subjects is modest and physicians on the IRB believed that it would improve the doctor-patient relationship, even if the study is not scientifically sound.

References


Author

Mark Hochhauser, Ph.D. is a readability consultant and IRB member. Contact him at 1.763.521.4672 or MarkH38514@aol.com.