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Unblinded Monitoring Programs: Design and Education

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Abstract: *Expanded research in biologics and other novel therapies will increase the need for unblinded monitoring programs. This article focuses on the management and monitoring of clinical studies that require unblinded site staff and site monitoring. Consideration of site staffing structure within the study design will be discussed. Appropriate documentation of unblinded staffing delegation, source document requirements, and monitoring considerations will be described. Management of unblinded monitoring at the sponsor and the contract research organization will also be reviewed.*

The Need for Unblinded Monitoring

The first double-blind study was conducted by Benjamin Franklin, when King Louis XVI commissioned him to investigate mesmerism in 1784 and double-blind studies have been fundamental to the scientific validity of clinical trials ever since. For example, an article published in *Headache* noted that many treatment options for headache were effective in open trials but failed in a spectacular way in double-blind trials ("Behavioral Research and the Double-Blind Placebo-Controlled Methodology: Challenges in Applying the Biomedical Standard to Behavioral Headache Research," *Headache*, 2005:45:479-486, quoting Diener, *Cephalagia,* 2003:23:485-486). In science, double-blind studies are our strongest link.

Implementing double-blind studies can present difficulties. Unblinded monitoring can be a solution to blinding difficulties while maintaining the validity of the double-blind study. Table 1 outlines conditions and example indications under which unblinded monitoring may be needed.

TABLE 1
Circumstances Under Which Unblinded Monitoring May Be Needed

- Device insertion and sham surgeries
  - Arthroscopic knee surgery
- Behavioral studies
  - Relaxation method studies
- High mortality studies
  - Septicemia
- Undisguisable differences in study agent appearance or preparation
  - Biologics
- Undisguisable differences in study agent effect upon the subject
  - Antidepressants
- Differences in use of the study agent and care of the subject
  - Antiepileptics

Options other than double-blind studies include unblinded studies; however, unblinded studies reduce the scientific validity of the study in several ways, including the possibility that subjects not assigned to a treatment arm will not complete the study in equal proportion to subjects receiving treatment. Subject compliance theoretically can be bolstered by single-blind studies, but a single-blind creates additional ethical concerns. ("The Ethics of Single Blind Trials," *IRB: Ethics and Human Research*, July-August 2005:12-16)

Who is Unblinded?

According to *The Clinical Research Process in the Pharmaceutical Industry* (Gary M. Matoren, ed., 1984, p. 157):

> "The general rule in a double-blind trial is that as few persons as possible should be unblinded to treatment. These people should be identified and their relationship to other portions of the study should be minimal, if any, and predefined. Obviously, the patients, the treating physicians, and other medical personnel responsible for patient care and evaluation must be blinded throughout the study."

This is important for scientific validity, but it is also important for the many publicly-traded pharmaceutical companies that sponsor research and need to be in compliance with Securities and Exchange Commission regulations in the United States or similar regulations in other countries. It is necessary for sponsors and CROs to protect study staff from any appearance of impropriety in availability and access to study results by ensuring, where possible, that unblinded personnel do not have access to endpoints. In the author's experience, blinded personnel assume unblinded personnel know more than they do; consequently, extra care needs to be taken to protect unblinded personnel from any appearance of impropriety. When unblinded personnel do have access to study endpoints, they should be provided additional training regarding compliance with any applicable financial regulations.

People who are unblinded may include site staff, sponsor/contract research organization (CRO) staff, external staff, and subjects. At the site, pharmacists, nurses, physicians or laboratory or administrative staff members may be unblinded. At the sponsor/CRO, the personnel responsible for the investigational product supply, quality monitoring, and randomization may be unblinded. Monitors and clinical team leads and their administrative staff may be unblinded. External staff such as an independent statistician or members of the data safety monitoring committee and the institutional review board (IRB) may be unblinded. To communicate unblinded information to the IRB, it may be necessary that an unblinded staff member, such as a pharmacist, send the information directly to the IRB in a way that bypasses the principal investigator and the study coordinator.

Subjects may be unblinded through "old-fashioned" unblinding methods such as guessing or the wording of the informed consent form. The wording of the informed consent form can influence the subjects' expectation of being unblinded. When the informed consent form is required to specify that certain side effects are only expected with the investigational product, a subject who does or does not experience those side effects will be influenced to believe that he/she is unblinded (whether the subject has actually been unblinded is another question). The randomization percentages also influence subjects' expectation of being unblinded. There have also been rumors that some subjects take their drugs to independent laboratories to be tested. Subjects in antidepressant studies have unblinded themselves by tasting medications they have previously used. For indications such as hormone replacement, willful unblinding by laboratory analysis is very easy to obtain.

Social networking is the new fashion in subject unblinding. If the subjects are from a very motivated, small patient population, they may participate in online discussions sites dedicated to their illness or disease where they discuss the study. The author performed a Google search of a study she was involved with and found detailed chat board discussion of the product, confidential information about the progress of the study, and discussion of the enrollment opinions and temperaments of various investigators and their staff. In the new era of social networking, it is important to discuss with subjects their role in maintaining the blind.

Thus, blinded studies may not be as blinded as researchers think they are. At this point in time, the terms double-blind and single-blind may be outdated. A more nuanced understanding of blinding includes the use of unblinded study staff and personnel. Another innovation in blinding, which will not be discussed in this article, is triple-blinding, where an assessor works on a small part of a study (e.g., assessing a depression scale) without knowing the drugs that are being evaluated or the randomization percentages). Triple-blind has been used in psychiatric studies and epilepsy studies.

Acknowledging and Resolving Problems with Blinding

In order to resolve problems with blinding, the first step is to acknowledge that the problems described previously exist and determine whether researchers are doing enough to assess the blind. As detailed in Table 2, the answer is no.

The second step is to evaluate the blind as part of the study. This is rarely done, although it is becoming more common, especially in psychiatric studies. Evaluating the blind can be as simple as asking the subject and the investigator which arm of the study they thought the subject was on. This type of evaluation often identifies a blinding issue, which is only sometimes statistically significant.

TABLE 2
Literature Reviews of Unblinding Evaluations

Literature Review:	1	2	3
Type of study evaluated:	Placebo-controlled	Antidepressant	Nicotine Replacement Therapy
Number of studies:	97	91	73
Number of studies that evaluated the blind:	7	8	17
Number which noted the blind compromised:	5	4	12

1. "Turning a blind eye: the success of blinding reported in a random sample of randomized, placebo controlled trials," *British Journal of Medicine*, doi:10.1135/bmj.37952.631667.EE published 2004
2. "Critical approach to antidepressant trials: Blindness protection is necessary, feasible and measurable," *The British Journal of Psychiatry*, 2000:177:47:51
3. "The blind spot in the nicotine replacement therapy literature: Assessment of the double-blind in clinical trials," *Addictive Behavior*, 2004:29:673-684

A good example of evaluating the blind was a study of an antibiotic where researchers realized that the antibiotic tablets tasted different from the placebo. The investigators conducted a study to determine if research subjects could differentiate the tablets by taste, and unexpectedly found that the subjects could differentiate the tablets even better by appearance. After evaluating this information, the researchers decided to proceed with their study without modifying the tablets because they felt that study subjects would never see or taste the tablets side-by-side. The evaluation identified an unblinding concern that was thoroughly investigated and determined to be insignificant. ("Pre-trial evaluation of the potential for unblinding in drug trials: A prototype example," *Contemporary Clinical Trials*, 2005:26:459-468)

Acknowledging the existence of blinding issues and continuing to monitor the quality of the blind is essential to scientific integrity. In a study involving different levels of radio waves, a quality auditor found a notebook containing numbers that the researcher didn't want to talk about. The auditor discovered that it was possible to identify the level of radio waves using the numbers from the notebook. Improved blinding of the equipment needed to be implemented, however the auditor also concludes: "...it should be born in mind that fraud is not committed by machines, but by the human beings operating them. The underlying assumption is that everybody works honestly. That notwithstanding, things should not be made too easy for those wishing to cheat the system." ("Security Considerations in Blinded Exposure Experiments Using Electromagnetic Waves," *Bioelectromagnetics*, 2008:29: 659)

If the study blind is carefully evaluated early, issues may be identified in time to develop an appropriate solution. Often, however, issues related to unblinding are not identified until late into study development or after study kickoff. For example, when the study drug is ready to be shipped, someone realizes that there is no way to blind the shipments.

Suddenly, the study needs unblinded monitoring. The unblinded team is brought in late, and the unblinded clinical team leads and staff have the same responsibilities as the blinded clinical team leads and staff, but possibly with reduced budget influence. Another problem is that unblinded monitoring is usually on a different schedule than the main study trajectory. Without being on the critical path and having critical milestones, things that are important to unblinded monitoring can fall by the wayside.

Study Set-up and Start-up

In a study with unblinded monitoring, the set-up for all study arms should be as close in appearance and processing as possible. All processes, including

those for the arrival of product shipments, supply shipments, and sample shipments, should be carefully reviewed for their potential to lead to unblinding. Any small change in a process can and will result in unblinding. For example, if a sample of the study drug is analyzed under a microscope and discarded, a sample of the placebo should also be discarded.

Another example is a case where a quality control sample of the study drug, but not the comparator, is to be evaluated at a central laboratory. One could conceive of some plan for disguising the shipments, such as having unblinded staff ship the boxes from an off-site location, but the removal of the boxes could still be observed by blinded staff. Sending a sample from every preparation, regardless of study arm, creates as little difference in study arms as possible. Incoming shipments of study supplies, which may be needed for one arm and not the other, need to be scrutinized just as carefully for the possibility of unblinding.

With the addition of unblinded personnel, the treatment schedule becomes more complicated, and more personnel schedules must be considered in arranging subject visits. Personnel work schedules should be reviewed, and a coordinated plan should be created for visit scheduling. Template communication forms may be created by the sponsor/CRO. Unblinded staff may need to be trained to communicate scheduling issues regarding product supply or preparation time in a blinded manner.

Unblinded case report forms may be needed, which will also require a review of blinded and unblinded roles in data management. There should be separate call-in numbers for blinded and unblinded meetings, secure storage for unblinded documents, and separate and secure electronic systems for unblinded electronic records.

Treatment communication requires clear documentation of the process for the hand-off of records between the blinded and the unblinded sides of a study in a manner which both monitors can review. The process must cover scheduling communication and shared drug compliance and dosing information.

There are three methods for storing these shared study documents. The first is carbon copy forms. A problem with this method is that sometimes updates are made only on one form. Thus, the two monitors would not be looking at the same documents. Another method is a shared communication storage binder that both monitors use. This only works if everybody is under one roof and the components of the study (e.g., the pharmacy and the office for subject visits) are close together.

The author's preferred method for communicating study documents is faxes. Both the blinded monitor and the unblinded monitor will have the original of outgoing communication from their side of the blind and a fax of incoming communication from the other side.

Unblinded staff members may work in a hospital or medical center back-office, the pharmacy, or a laboratory. These staff members may not usually be involved in conversations about clinical research at the site; they may even work for a separate corporation which has been contracted for certain services. It is important to ensure that the unblinded staff members are aware of their participation in the study and are funded for their participation. The author has arrived at a site initiation visit only to find that the pharmacy director did not know that the study was going to occur, had not been funded to perform the study, and refused to attend the training. The sponsor/CRO must insert itself into the relationship with unblinded staff to ensure that this communication has occurred.

Study Documentation

The principal investigator must select a primary unblinded responsible person. Some sponsors require a statement of responsibilities of the primary unblinded responsible person. This might be considered a stand-in for FDA Form 1572; it is a document where the unblinded responsible person signs their obligation to follow the protocol and unblinded process manual for the study.

The principal investigator can either delegate responsibility for this on the main delegation log or have a separate delegation log for the unblinded side of the study. The principal investigator can delegate responsibility for the additional unblinded staff on the main delegation log or have the unblinded responsible person perform that delegation on the separate unblinded delegation log. Training of all unblinded staff members should be documented.

The site should be provided with tools for maintaining the blind, such as template communication forms, door tags (e.g., "Do not enter: Unblinded product being prepared."), and fax machine reminders (e.g., a notice posted on the wall over the fax machine that says, "Do not fax unblinded information.").

The monitor is likely very familiar with clinical standards and practices, but the monitor may be less familiar with pharmacy or biologic laboratory standards and practices. If needed, the monitor should be trained in the standards for source documents specific to the preparation of the study product.

Unblinded Study Staff

Staff members who may not have been involved in clinical research before can be overwhelmed by the

routine processes involved in clinical research studies. They may have little or no clinical study experience. As a back-office of a medical center or hospital, they may be understaffed and overwhelmed. This is especially true of cell laboratories working on biologic therapies, which are in a period of extremely rapid expansion. It can be helpful to remind them that they are only responsible for three things: preparing the product according to the specifications, completing the appropriate documentation, and maintaining the blind.

Site personnel responsible for investigational product preparation are likely to have more expertise in the processes than the monitor. They may also have process standards that deviate from the study standard. For example, they may have better equipment or more training than required by the study. However, the study tries to establish a process that all of the sites can use, as well as sites which may use the marketed product following approval.

It is necessary to explain to site personnel why they need to use what they may consider to be antiquated equipment or an inferior method. The best way to do this is to review their entire process and inform site personnel about where they need to deviate from their normal process and why this is necessary. If this conversation does not occur, site personnel are likely to perform the process in their normal way without being aware of the impact their deviations have on the study integrity.

Basic training on investigational study documentation practices should be provided. The informed consent form and HIPAA authorization should be reviewed so that the staff understands why the monitor has medical record access and that this access is proper. Aside from this training, the unblinded staff may never have access to the informed consent form for the study, especially if the patients are seen in another office or building.

Unblinded personnel, especially biologic preparation and pharmacy personnel, often feel strongly about their responsibility to properly communicate the identification of the prepared product to the administering nurse. This has been part of their training for their clinical role. Consequently, they may resist study blinding and try to insist on using the usual labeling process. The monitor must explain the regulatory body review of the study and its approval of blinding procedures. The differences between blinding procedures and standard product identification requirements should be explained. The monitor should inspect the work area and documents for any sign that unblinding labels are being used contrary to study instructions.

Site personnel must be provided with peer support in maintaining the blind. There should be at least two unblinded staff members at each site. This is necessary in order to ensure that subject visits are covered, but also because it can be extremely stressful to be the unblinded person in the case of serious diseases or conditions. The unblinded staff member needs someone with whom to talk. The monitor can provide an outlet for the discussion of individual cases while continuing to support the study rationale and the importance of maintaining the blind.

Sites that maintain the blind can be identified by an attitude of ownership for the blind. They may use additional signs and binder notes that support maintaining the blind. Any discussion of unblinded information should start with the question, "Are you unblinded on this protocol?" The author has worked on one study for three years where she knew all of the unblinded laboratory personnel extremely well. Yet some of these personnel started every conversation with her by asking if she was unblinded on the protocol. This behavior indicates a strong ownership of the blind.

The sponsor/CRO should develop an unblinding procedure that removes responsibility from unblinded site personnel and places it on the central sponsor/CRO personnel. Investigators can put tremendous pressure on site personnel to unblind subjects, and it is an undue burden on the unblinded personnel to be placed in that position.

The same person should not be assigned a blinded and an unblinded role at the site. Although this seems obvious, the author has encountered this problem frequently. Generally, the individual states that he did not look at information which unblinded him; however, this places the integrity of the study at risk.

It is also important to ensure that the unblinded personnel understand which information has the potential to be unblinded. This includes drug shipment and use, supply shipment and use, photocopying and use of template study documents, preparation or procedure time, and testing sample shipment. If the proper study set-up has occurred, the sponsor/CRO has already identified these issues and prepared training for the unblinded personnel.

Unblinded Monitoring

Table 3 provides an overview of unblinded monitoring. Monitoring visits may be short and infrequent because there are few documents to review. The monitor may supplement these visits by performing more remote monitoring of faxed source documents. When visiting the site, the monitor should look for signs of additional unauthorized labeling of the investigational product or unnecessary references to unblinding information.

TABLE 3
Unblinded Monitoring Best Practices

- Add remote monitoring if visits are infrequent
- Monitor for signs of additional unauthorized labeling
- Monitor for unnecessary references to unblinding information
- Avoid unnecessary references to unblinding information
- Clearly identify unblinded follow-up letters and documents on the outside of the envelope
- Provide the investigator with enough information for oversight in the blinded follow-up letter
- Avoid unblinded paper; unblinded secure electronic systems are best
- Do not copy blinded personnel and unblinded personnel on the same email; use separate emails
- Use the question, "Are you unblinded on this protocol?" in internal sponsor and/or CRO conversations and with the sites
- Even more than usual, take care with conversations and computer use in public areas, especially when traveling to/from major medical centers

The monitor should avoid unnecessary references to unblinding in the follow-up letter to the unblinded responsible person because somebody else at the site could end up with the letter. In the follow-up letter, the monitor should only refer to the study arm if it is necessary to describe the finding; in the author's experience, it is rarely necessary to make an unblinding statement in an unblinded follow-up letter. Unblinded follow-up letters and documents should be clearly identified on the outside of the envelope when sent to the site. One good practice is to place colored stickers that say "Unblinding information" on the outside of envelopes; this is a reminder to the blinded staff not to open the envelope.

At the same time, the monitor must provide the investigator with enough information in a blinded follow-up letter to properly oversee the study. For example, the letter could state:

> "A blinded protocol violation occurred in the preparation of IP for subject 123/ABC on 12 January 2010, performed by Mr. Smith. This issue was reported to the IRB on 14 January 2010. Mr. Jones, unblinded responsible person, re-trained Mr. Smith regarding IP preparation and a training log was completed."

Avoiding unnecessary paper is helpful in unblinded monitoring. Secure electronic systems are best for unblinded communication and less likely than paper to end up in the hands of blinded personnel. The monitor should not copy blinded and unblinded personnel on the same email. Inevitably, an unblinded person will answer "Reply all" in an email that contains unblinded information. The monitor should write one email to personnel on the unblinded side of the study and then a second email to personnel on the blinded part of the study.

Using the question, "Are you unblinded on this protocol?" in internal sponsor/CRO conversations and with the sites is important. The monitor should also take even more care than usual having conversations and using computers in public areas, especially when traveling to or from major medical centers. Blinded staff, patients, and patient loved ones may be using the same modes of transportation and be present in the same locations.

Conclusion

In conclusion, with new biologics and novel therapies, increased evidence-based review of old surgeries, which is likely to increase (especially as the United States undergoes insurance reform), and improved understanding of the limits of blinding, more variations of blinded and unblinded personnel can be expected in the future. Unblinded personnel hold a special trust regarding the ethical, scientific, and financial integrity of medical research. The proper processes must be used so that unblinded personnel can be equal to that trust.

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