OPINION

Investigator Selection for Multicenter Clinical Trials:

Remembering Our Ethical Obligations to Clinical Trial Volunteers

PEER REVIEWED
Mark Arquiza, MSc, CCRA
Bohdan Veresh, MD, MSc

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The selection of investigators is one of the first major activities in the conduct of multicenter clinical trials. Based on the requirements of the clinical trial protocol, sponsors may use multiple search strategies such as querying public, private, and/or internal and databases, securing referrals from clinical research colleagues, or performing publication searches.

Sponsors select investigators based on the specifications found in applicable guidelines, laws, and regulations. These specifications include not only an investigator's education, training, experience, and resources, but also his or her availability.[1,2] To verify if an investigator meets the required specifications, the sponsor or its designee would examine the investigator's curriculum vitae and medical license, tour the investigator's facility, and interview relevant site personnel.

These tasks are commonly lumped in an activity designated as a pre-study site visit (PSSV), which is typically performed by a monitor. (The PSSV is also known as a site qualification visit or pre-trial assessment.) After completion of a PSSV, a recommendation on an investigator's suitability to participate in the clinical trial would be made, along with appropriate justification. A designated member of the management staff would either accept or reject the recommendation, and subsequently finalize an investigator list for the clinical trial.

Investigator selection is a critical and fundamental process; it can be very challenging to choose an investigator from a list and, occasionally, sponsors may have few (if any) alternatives. Nonetheless, it is crucial to follow an objective approach that will fulfill all requirements.

Physician versus Investigator

Physicians treat their patients based on the best treatment that can be provided. Typically, they will follow a standard of care as the basis for their prescribed treatments, but they also understand that patients are different; so instituting a minor change to the recognized standard to provide better clinical care is not considered unethical.

In contrast, investigators must ensure that the care provided to clinical trial volunteers is based strictly on the specifications detailed in the clinical trial protocol and the informed consent document, unless there is a serious threat to a volunteer's medical condition.

Since investigators are ultimately responsible for clinical trial conduct at their respective investigative sites, they have additional responsibilities as compared to physicians. These include, but are not limited to, ensuring that only eligible volunteers are enrolled, ensuring the proper and secure storage of the investigational medicinal product, completing required regulatory and trial-related training, meeting with sponsor or contract research organization (CRO) representatives during site visits, completing trial-related documentation such as supplementary documentation in medical charts or other source documents, providing initial and periodic reports to the ethics committee, and reviewing and signing various trial logs. Given these additional responsibilities, an investigator's availability becomes one of the key considerations in the investigator selection process.

Key Opinion Leaders and National Coordinators

There is significant debate in the literature regarding the pharmaceutical industry's use of key opinion leaders (KOLs) as experts who could educate the medical community about sponsors' new and forthcoming products. In our opinion, sponsors must be passionate in their deliberations when deciding whether a KOL should be selected as an investigator for their clinical trials.

KOLs are undoubtedly leaders in their field, and possess superior skills in the type of medicine they primarily practice. Their reputation and political influence in the local medical community are attractive benefits to their selection as investigators of a clinical trial. However, KOL status inherently comes with extra commitments and responsibilities, which would affect availability, and it says little about one's capacity for being a superior investigator.

The fundamental differences between clinical care and clinical research and the competing obligations that KOLs must handle do not allow for the assumption that an excellent clinician would equate to an excellent investigator. Conversely, based on experience, some KOLs have proven themselves as excellent investigators.

Sponsors could also face unique local requirements during investigator selection. The European Union (EU) requires the adoption of a single opinion from each Member State.[3] Implementation of this requirement is left to each member. For some members, sponsors could select a "lead" ethics committee (EC) for a member from one of the ECs affiliated with the investigators selected to participate in the clinical trial. An investigator reporting to the selected EC may become the national coordinator.

For an EU member like Poland, the sponsor selects the national coordinator, which makes the coordinator's EC the lead EC for the country.[4] This further highlights the importance of investigator selection, as national coordinators would be chosen from a list of investigators already selected by the sponsor. National coordinators could therefore have supervisory responsibilities for multiple clinical trials by one or more sponsors, which would challenge any investigator's ability to provide effective oversight.

Basic Ethical Principles and Investigator Availability

Although guidelines, laws, and regulations are crucial in the conduct of clinical trials, investigator selection must also involve basic ethical principles such as respect for persons, beneficence, and nonmaleficence. By demonstrating a deeper appreciation and application of these ethical principles, clinical researchers can change their disposition from one that concentrates on compliance to one of conscience.[5]

Respect for persons most commonly refers to a potential clinical trial volunteer's autonomy. In clinical research, the informed consent process is recognized as a means to provide all relevant information to the potential volunteer to allow him/her to decide whether to participate in the clinical trial.

Once a clinical trial is under way, is the ethical principle of respect for persons violated when the investigator has minimal involvement in the clinical trial? Should a reasonable clinical trial volunteer expect an investigator to be actively involved in his/her care while participating in the clinical trial? These questions must be considered unless the informed consent document and the informed consent discussion specifically noted that the investigator's involvement would be limited.

To verify if an investigator meets the required specifications, the sponsor or its designee would examine the investigator's curriculum vitae and medical license, tour the investigator's facility, and interview relevant site personnel.

LEARNING OBJECTIVE

After reading this article, participants should be able to (a) evaluate investigator selection practices more critically and (b) explain the impact of ethics on investigator selection and clinical trial volunteers.

DISCLOSURES

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Perhaps respect for persons includes all research team members appreciating what is valuable to a clinical trial volunteer, and the investigator behaving in a manner consistent with recognition of that knowledge.[6] If this is the case, is it unreasonable to expect that clinical trial volunteers would find it valuable if the investigator is an active participant in the clinical trial? If there is little or no evidence of investigator involvement during the conduct of the clinical trial, would that mean that the ethical principle of respect for persons has been violated?

Meanwhile, beneficence and nonmaleficence refer to maximizing benefits and minimizing harms for clinical trial volunteers. This means an investigator must put the clinical trial volunteer's safety and welfare as the top priority, even above his/her personal interests.[7]

Similar to a physician's relationships with his/her patients, an investigator's ability to establish trust with his/her clinical trial volunteers would be beneficial. Establishing trust will require the investigator to invest time in building a relationship.

If an investigator fails to develop a good relationship with the clinical trial volunteers, it could negatively affect compliance with trial-related procedures,[8] which may increase the safety risk for volunteers. For example, improper use of the investigational medical product or missing protocol-required procedures resulting from a volunteer's lack of education and/or motivation could lead to adverse events. Would this cause-and-effect scenario mean that the ethical principle of beneficence and/or nonmaleficence has been violated?

Investigator selection is a critical and fundamental process; it can be very challenging to choose an investigator from a list and, occasionally, sponsors may have few (if any) alternatives.

When a sponsor selects an investigator to participate in a clinical trial despite knowing the investigator has limited availability (based on previous collaborations or on the information gathered during a PSSV), has the sponsor violated the ethical principle of nonmaleficence? Is making such a decision consistent with the tenet of minimizing harms for clinical trial volunteers?

Potential Solutions

Large companies such as Merck, Eli Lilly, and Quintiles have been using information technology (IT) solutions in their investigator selection process since the mid-2000s.[9] However, it is not clear whether these IT solutions also include information that would allow for an objective assessment of an investigator's level of oversight of a given clinical trial.

Sponsors or CROs could also establish an internal database of investigators to support their investigator selection efforts, but they must ensure that potential legal risks, such as privacy, libel, or tortious interference, are addressed. A close investigation of applicable local and international laws and established operational procedures would be essential in minimizing or eliminating the legal risks and any potential legal challenges.

Some items specified in any operational procedure must include the sources and methods of data collection, procedures for data validation, a list of users who would have access to the data, and data retention time. Other considerations should include investigator notification of the level of information being maintained, and processes to allow updates or follow up on collected information.

For now, both sponsors and ECs should look closely at a potential investigator's workload and availability during the investigator selection process. For ECs falling under the U.S. Food and Drug Administration's (FDA) jurisdiction, the requirement in the *Code of Federal Regulations* of 21 CFR 56.107(a) regarding the EC's responsibility "to ascertain the acceptability of proposed research in terms of institutional commitments"[10] might be expanded to include an investigator's commitments, because the investigator is part of the institution.

ECs could change their application for EC approval and reapproval procedures to require that applicants disclose pertinent information (e.g., number of trials, investigator's role, expected and current number of clinical trial volunteers, trial start and stop dates, etc.) about each investigator's involvement in ongoing clinical trials.

Besides the review of a potential investigator's commitments identical to those suggested for ECs, sponsors could also look at a comparative analysis of selected historical data points related to investigator oversight for potential investigators with which they have previous experience. These data points could include the enrollment of volunteers who did not meet entry criteria, protocol deviations related to missed or improperly performed study-required procedures or erroneous administration of the investigational medical product, and documented involvement of the investigator during visits made by the clinical trial volunteer and monitors.

Sponsors could also adopt strict policies when the recommendation of the individual who conducted the PSSV is disregarded. The FDA has already set precedence by citing a sponsor for using an investigator not recommended by a monitor who conducted the PSSV.[11]

Conclusion

Thinking about our ethical obligations to clinical trial volunteers, investigator selection must go beyond compliance to guidelines, laws, and regulations. We must select only those investigators who have the time and desire to conduct a clinical trial.

An investigator who finds the time to be actively involved in the clinical trial is ideal, because he/she would more likely to interact and develop a relationship with the volunteers, instead of routinely delegating this responsibility to other members of the site staff.[12] It is no exaggeration to say that lack of investigator availability could lead to violations of basic ethical principles.

Further, sponsors must take care when selecting a KOL as an investigator for their clinical trials. They must ensure that they employ the same criteria as they would for non-KOLs during the selection process, and not select a KOL solely on this status or his/her political influences in the industry.

Certainly, potential investigators must realize the importance of honest self-examination when determining if they have enough availability to actively participate in the conduct of a clinical trial.[13]

Finally, for the individual conducting the PSSV and the person approving the selection of an investigator, it might be sufficient to critically answer the following question before recommending or selecting an investigator for a clinical trial: Would you be comfortable in participating, or allowing a family member to participate, in a clinical trial under the care of the investigator being considered?

Disclaimer

The opinions expressed in this manuscript are solely those of the authors, and do not necessarily reflect the opinions of their employers.

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Mark Arquiza, MSc, CCRA, (mark.arquiza@inventivhealth.com) is a senior manager in the Strategic Resourcing Group of inVentiv Health Clinical in Princeton, N.J.

Bohdan Veresh, MD, MSc, (bohdan.veresh@boehringer-ingelheim.com) is a clinical trial manager at Boehringer Ingelheim RCV GmbH & Co KG in Vienna, Austria.