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Monitoring of Clinical Trials—Are Remote Activities Helpful in Controlling Quality?

PEER REVIEWED | Michael R. Hamrell, PhD, RAC, FRAPS, RQAP-GCP, CCRA | Kathleen Mostek, RN, CCRC | Lyn Goldsmith, BSN, RN, MA, CCRC

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The implementation of risk-based monitoring has spawned many forms of remote monitoring activities. This development has the potential to significantly impact how monitoring is accomplished for clinical trials. One question raised is whether remote monitoring activities are beneficial or detrimental to an effective data quality program.

LEARNING OBJECTIVE
After reading this article, participants should be able to define remote monitoring and evaluate its impact on study conduct.

DISCLOSURES
Michael R. Hamrell, PhD, RAC, FRAPS, RQAP-GCP, CCRA;
Kathleen Mostek, RN, CCRC;
Lyn Goldsmith, BSN, RN, MA, CCRC:
Nothing to disclose

A survey was undertaken to assess the utilization and considerations related to remote monitoring activities and their impacts on clinical data quality. The results presented here provide what the authors hope are some useful observations on how remote monitoring is perceived.

Background on Guidance and Regulations

U.S. Food and Drug Administration (FDA) regulations require sponsors to monitor the conduct and progress of their clinical investigations.[1] Similarly, the International Conference on Harmonization's Guideline for Good Clinical Practice (ICH GCP) E6 also requires that a clinical trial be monitored by the sponsor.[2]

FDA regulations are not specific about how sponsors are to conduct such monitoring, and its 2013 "Guidance for Industry: Oversight of Clinical Investigations—A Risk-Based Approach to Monitoring" is therefore compatible with a range of approaches to monitoring (see section III) that will vary depending on multiple factors (see section IV.C).[3] For example, increased use of electronic systems and records and improvements in statistical assessments present opportunities for alternative monitoring approaches (e.g., centralized monitoring) that can improve the quality and efficiency of sponsor oversight of clinical investigations.

The agency encourages sponsors to develop monitoring plans that manage important risks to human subjects and data quality and address the challenges of oversight, in part by taking advantage of the innovations in modern clinical trials.

Monitoring activities include communication with the principal investigator (PI) and study site staff; review of the study site's processes, procedures, and records; and verification of the accuracy of data submitted to the sponsor. Initiatives undertaken by the members of TransCelerate Biopharma Inc. related to monitoring also support the use of remote monitoring and other alternatives to traditional onsite monitoring visits.[4]

The 2013 guidance makes it clear that sponsors can use a variety of approaches to fulfill their responsibilities for monitoring PI conduct and performance in Investigational New Drug studies conducted under FDA's *Code of Federal Regulations* as described in 21 CFR Part 312, or Investigational Device Exemption studies conducted as described in 21 CFR part 812.[1] The guidance describes strategies for monitoring activities that reflect a modern, risk-based approach that focuses on critical study parameters and relies on a combination of monitoring activities to oversee a study effectively. For example, the guidance specifically encourages greater use of centralized and remote monitoring methods where appropriate.

Taking a Closer Look at Monitoring

Periodic, frequent visits to each clinical site to evaluate study conduct and review data for each enrolled subject remains the predominant mechanism by which pharmaceutical, biotechnology, and medical device companies monitor the progress of clinical investigations. However, FDA encourages sponsors to tailor monitoring plans to the needs of the trial.

Centralized monitoring is a remote evaluation carried out by sponsor personnel or representatives (e.g., clinical monitors, data management personnel, or statisticians) at a location other than any of the sites at which the clinical investigation is being conducted. Remote monitoring processes can provide many of the capabilities of onsite monitoring as well as additional capabilities.

Currently, FDA encourages greater use of such centralized monitoring practices where appropriate than has been the case historically, with correspondingly less emphasis on onsite monitoring.

The types of monitoring activities and the extent to which centralized monitoring practices can be employed depend on various factors, including the sponsor's use of electronic systems; the sponsor's access to subjects' electronic records, if applicable; the timeliness of data entry from paper case report forms, if applicable; and communication tools available to the sponsor and the study site.

Sponsors who plan to use centralized monitoring processes should ensure that the processes and expectations for site record keeping, data entry, and reporting are well defined and ensure timely access to clinical trial data and supporting documentation.

Survey Overview

In response to the varied considerations on what role centralized or remote monitoring plays in impacting current quality oversight of clinical trials, we conducted a survey of Association of Clinical Research Professionals (ACRP) members on their experience with remote monitoring. The survey was created by the team of presenters for a session on this topic for the ACRP 2015 Global Conference in Salt Lake City, Utah.

The survey focused on gathering perceptions for gauging the use and acceptability among clinical research staff of remote monitoring practices as part of the new, risk-based approach to clinical monitoring. Based on these initial results, any future studies would delve deeper into the specifics of the concerns identified.

The survey consisted of 15 questions regarding remote monitoring, and was posted on Survey Gizmo for approximately one month. The availability of the survey was posted on the ACRP Online Community and on LinkedIn.

RESPONSES AND LIMITATIONS

A total of 199 responses to the survey were received; however, since its availability was posted for completion and not sent out to individuals, it is not possible to determine a response rate. About 88.9% of the responses were from individuals in the U.S., with most of the responses coming from ACRP members.

Of the respondents, 24% worked for study sponsors and 76% worked for clinical sites. We did not capture any further details on the job title of the responders relative to the specific questions.

No information was collected on the level of experience or exact role of respondents. Also, in most cases the responses were not captured in a manner allowing us to determine differences between the two types (sponsor-based vs. site-based) of respondents.

Finally, this article does not include responses for all questions in the survey. The survey questions not presented relate to additional items about monitoring, types of documents accessed, and country of origin of the responders, and were not considered essential for the present discussion.

Despite these limitations, the survey results describe some important perceptions regarding remote monitoring.

RESULTS

Almost 70% of the site respondents indicated that some of the data collected are monitored remotely, while 20% of the sponsor respondents indicate that they monitor some data remotely. Interestingly, 61% of the respondents indicated that they had experienced a change to a monitoring plan after study initiation by way of the addition of remote monitoring to the plan (see Figure 1).

70%
thought the relationship will be negatively impacted by remote monitoring

FIGURE 1: Have you had a change of monitoring plan that added remote monitoring after study initiation?

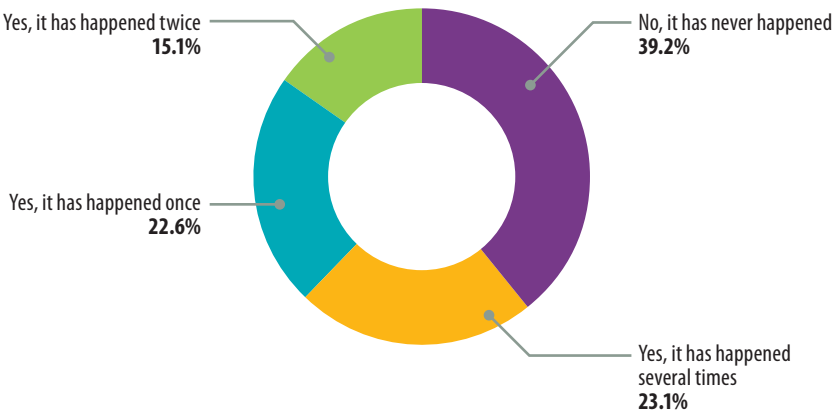


FIGURE 2: What documents are monitored remotely?

FIGURE 3: If source documents are reviewed remotely, how are they accessed?

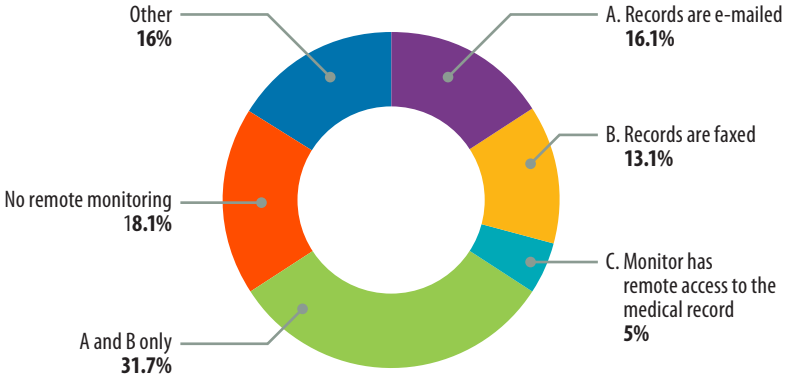
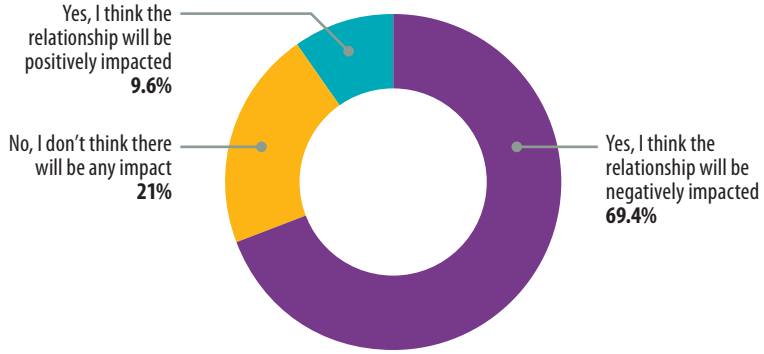


FIGURE 4: Do you believe that remote monitoring can have an impact on the quality of the relationship between site and sponsor?



The type of documents monitored remotely varied, with the largest type consisting of source documents and regulatory documents (see Figure 2).

As far as the method for remote access of source documents, the most common method was either e-mailing (26%) or faxing of the records (13%) for access (see Figure 3).

One of the most important results was the perception of the impact of remote monitoring on quality of the relationship between the site and sponsor. Almost 70% of the respondents indicated that they thought the relationship will be negatively impacted by remote monitoring (see Figure 4). In parallel to this, 62% of the respondents also felt that remote monitoring will have a negative impact on the quality of the data collected for a clinical trial (see Figure 5).

Along with this change in focus on remote monitoring, the change in monitoring approach has the potential for a significant impact on the budget for a study. Site staff are now expected to assume the work of gathering data on items that were previously reviewed by an onsite visit, such as drug/device accountability, and send it to the monitor for remote review.

There can also be costs associated with remote monitoring, including time allocated for repeated telephone calls, copying, maintaining encryption on e-mail correspondence, repeated requests, faxing, scanning to a pdf format, and/or e-mailing documents to the monitor. There are also the costs of maintaining fax, scanner, and copier machines, including paper, ink, phone line charges, and time spent sending and resending documents (see Figure 6).

Although the intent of remote monitoring is to lessen the time monitors spend at sites, it appears to have had a negative effect on the site staff. More than 65% of the site respondents indicated that remote monitoring has added to the time spent on monitoring activities (see Figure 7). From a monitor's perspective, the responses were about equal as to whether it added or lessened the time to monitor a site. This highlights one of the problems in the implementation and success of remote monitoring—the time involved is not even perceived the same by site and sponsor personnel.

Conclusions

The goal of monitoring a study is to assure regulatory compliance, human subject protection, and data integrity. The use of approaches that include remote monitoring in addition to traditional monitoring techniques has the potential to impact the relationship between the site and monitor, and to impact the quality of the data collected. In this survey, more than 69% of the respondents indicated that they think the relationship between the site and sponsor will be negatively impacted, with a correspondingly high potential to impact the quality of the data collected.

This survey, although limited in scope, does provide some interesting perspectives on how clinical research professionals view remote monitoring

FIGURE 5: Do you believe that remote monitoring can have an impact on the quality of data collected for a clinical trial?

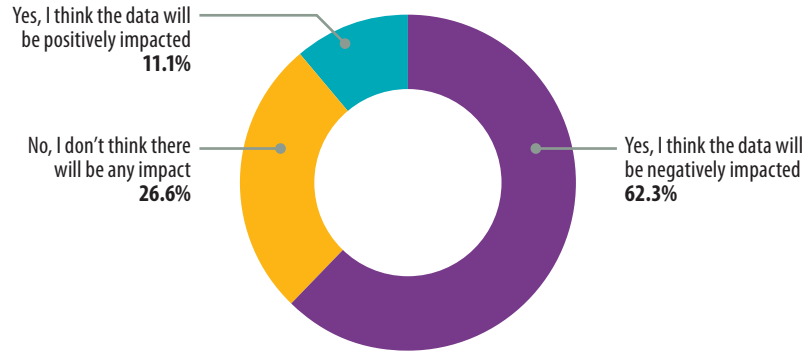


FIGURE 6: Have you added (or, as a sponsor, been asked to pay for) faxing/copying/scanning/redacting as a line item to a study budget?

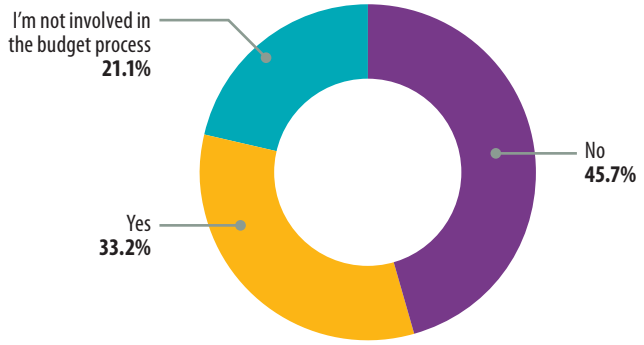
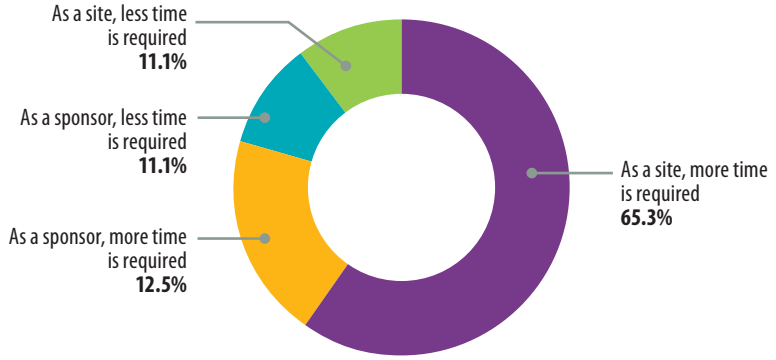


FIGURE 7: Has remote monitoring added to or lessened the time of monitoring by you or your employer?



activities. It is likely that this will change over time as sponsors, contract research organizations, and site personnel become more experienced with remote monitoring and, more importantly, with further advances in technology for remote access.

However, at the present time, not everyone is convinced that remote monitoring aids in efficient use of time or aids in overall data quality. One approach is to further educate sites (and clinical research associates) at the beginning of the study on expectations for data availability and access, in order to avoid the kinds of changes after the study is up and running that lead to some of the concerns raised. The more of these items that are identified and negotiated before the study starts, the better the results and interactions between the staff involved.

Site staff are very busy and focused on completing projects per protocol and on time, but constant change can also negatively impact data quality and sponsor-site relations. The risk-based monitoring guidance suggests that onsite visits can be lessened in favor of remote and central monitoring activities, but it does not appear that industry believes this can happen at the present time.

Risk-based approaches to monitoring, including the use of remote access to documents and data, need to be integrated within a dynamic process. Further changes need to be made to facilitate continuous improvements to the process over time, as the industry gains more experience and expertise with this approach to monitoring.

Electronic solutions for remote data access, such as cloud-based storage, secure websites, fax machines, webportals, or even direct access to site files, provide the potential to facilitate this type of data and information exchange. Concerns over privacy and security weigh heavily into the considerations of any solution.

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Getting the Right Signatures on Informed Consent Documents

PEER REVIEWED | Lindsay McNair, MD, MPH, MSB | Patience Stevens, MD, MPH, CIP | Glenn Veit, JD, CIP

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LEARNING OBJECTIVE
After reading this article, participants should be able to define "impartial witness" and "legally authorized representative" (LAR) as they would be used in the informed consent process; demonstrate understanding of the roles of the impartial witness and the LAR, and in what situations they would participate in the informed consent process; and develop informed consent documents that appropriately specify which persons should sign the informed consent form, consistent with the protocol and the intended study population.

DISCLOSURES
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Patience Stevens, MD, MPH, CIP;
Glenn Veit, JD, CIP:
Nothing to disclose

The process of informed consent to participate in clinical research, and documentation of that conversation, is usually straightforward; the study population includes adults who are capable and competent to make their own decisions, who speak the same language as the investigator and study team, and who can participate fully in the consent discussion and can document their agreement to participate in the study by signing an informed consent document written in the language they speak. Sometimes, though, either the consent process or the documentation of informed consent is more complex.

Complicating Consent

In some settings, the informed consent process may require the involvement of other persons. One example of another involved person is termed a "legally authorized representative" (LAR). Some guidelines use the term "legally acceptable representative,"[1] but the meaning is essentially the same.

An LAR is a person who is "authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research."[2] Increasingly, many protocols consider LARs as including parents and legal guardians of children who have not reached the age of majority to provide consent themselves. This practice can be confusing in studies that enroll both children and adults.

For the purposes of this article, the authors use LAR only in reference to situations in which potential adult study participants lack the capacity to consent.

A second example of an involved person is an impartial witness to the consent process. An impartial witness is defined by the International Conference on Harmonization (ICH) as "a person who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject's [LAR] cannot read, and who reads the informed consent form and any other written information supplied to the subject."[3]

However, there are also regulatory references to witnesses found in U.S. Food and Drug Administration (FDA) and Department of Health and Human Services (HHS) regulations, various state-specific laws (e.g., as found in Virginia) requiring a witness signature in some human subject research, and local uses of a witness signature based on standard procedures. These uses may be very different from ICH, and the U.S. federal regulatory application of witness signatures does not define, nor do consent documents usually define, the purpose of the witness signature.

This article will focus on the ICH and U.S. federal regulatory application of the witness role. Examined in addition will be the fact that informed consent documents might request the signature of someone who is not involved in the consent process. For example, informed consent documents often have a space for the signature of the study's investigator, in addition to the signature of the person who actually conducted the consent discussion.

Whose Line is it, Anyway?

In the process of institutional review board (IRB) review, questions frequently arise when the informed consent document has signature lines for persons who would not be expected to participate in the consent process, based on the protocol information. Delays in IRB review may occur when the protocol and the consent document are apparently inconsistent in their respective intentions regarding the intended informed consent process or the study population. While this may sometimes seem to study sponsors to be a minor clarification, the implications of the potential enrollment of vulnerable subjects in research are significant in the IRB review process.

Ahead, we will take a closer look at the parties who may be involved in the consent process, including those who may be asked to sign the informed consent document, and at the specific settings in which consent should occur. We will also describe the need for careful review of the protocol's description of the intended subject population, the considerations of the IRB for vulnerability, and the informed consent document as part of the development of study-specific consent forms.

When Should LARs Provide Consent?

The inclusion of LARs in the informed consent process implies that potential study participants are expected to be incapable of providing consent on their own behalf. The corollary to this is that someone who would be the LAR (if the subject were not competent) cannot provide a valid consent on behalf of someone who is capable of providing consent for themselves. That is, though a wife would be the LAR for her husband should he become incapacitated, she cannot provide valid consent for her husband to participate in a research study if he is currently capable of making his own decisions about participation.

State laws determine who may serve as an LAR if there is no pre-existing documentation naming an LAR, and in what hierarchy persons should be considered (parent, spouse, adult children, etc.).

As noted previously, it is not uncommon for the signature spaces of a consent document to imply a consent process that is different from that which is described in the study protocol. For example, the eligibility criteria may state that "subjects must be able to agree with the requirements of the study and provide informed consent for participation," but the informed consent document submitted from the sponsor to the IRB with the protocol includes a signature space for an LAR, indicating the expectation that subjects may be enrolled who in fact cannot provide their own informed consent.

In many cases, it is probable that the LAR signature line was present on the template form used to draft the consent, and was never deleted when the consent was made study-specific. In other cases, the protocol eligibility criteria as described in the above example may conflict with other sections of the protocol describing overall quality and compliance standards for the study conduct, which states that "the subject or their Legally Authorized Representative" will sign the consent document. This type of conflict within the protocol must be resolved by the IRB before approving the research and the study documents supporting the consent process.

What Types of Studies Usually Need LARs?

The ICH Guideline for Good Clinical Practice and federal regulations in the United States recognize that decisionally impaired persons are a vulnerable population for whom additional protections are required.[4] As FDA regulations state in the criteria for IRB approval of research, "When some or all of the subjects, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons, are likely to be vulnerable to coercion or undue influence additional safeguards have been included in the study to protect the rights and welfare of these subjects."[5]

Inclusion of such subjects must be made thoughtfully and with specific consideration of the implications for issues pertaining to justice, respect for persons, and the potential benefits of the research. In addition, the IRB is expected to consider "… inclusion of one or more individuals who are knowledgeable about and experienced in working with those subjects…" as part of the review of research involving vulnerable persons.[6] Thus,

In some settings, the informed consent process may require the involvement of other persons. One example of another involved person is termed a "legally authorized representative" (LAR).

The inclusion of LARs in the informed consent process implies that potential study participants are expected to be incapable of providing consent on their own behalf.

consideration of issues pertaining to vulnerable populations requires experience by the IRB reviewing the protocol and attention to the "additional safeguards" that make the research ethical.

Many study protocols refer to the enrollment of decisionally impaired subjects, either intentionally or by implication, by referring to consent by the subject or LAR or by including the LAR signature space on the consent form. IRBs consider the implications of enrolling subjects who do not have the capacity to provide consent themselves very seriously. It is rare to encounter a research proposal that explicitly makes a case for enrolling subjects who lack capacity for consent, unless the disease or condition that causes that lack of capacity is the focus of the study (for example, a new investigational agent for the treatment of acute stroke).

A significant complicating factor in the potential enrollment of decisionally impaired study participants is the wide variety of presentations and etiology of lack of capacity. Conditions such as schizophrenia, brain injury, loss of consciousness due to acute trauma, and dementia such as found in Alzheimer's disease represent very different considerations regarding the prospect for regaining decisional capacity; however, all persons with such conditions deserve the same protections and additional safeguards afforded by the regulations and ethical considerations. IRBs must then consider two core principles that are generally recognized in the ethical literature as supporting the inclusion of this vulnerable population: scientific need and the prospect for direct benefit to those participating in the research.

The concept of *scientific need* asks the question whether the study objectives can reasonably be satisfied by enrolling the less vulnerable population that includes only those who are capable of providing consent. The applicable standard for the IRB's consideration for inclusion can be stated as enrolling those persons with the least degree of impairment that is compatible with the study goals. If there are adequate numbers of competent individuals available, there is little to be gained by including those who lack the ability to consent for themselves, unless the research is specifically intended to treat cognitive impairment.

Consider a large Phase III trial in diabetes comparing add-on therapy with standard of care to standard of care plus placebo. Studies have suggested that type 2 diabetes can increase the risks of Alzheimer's disease, vascular dementia, and other forms of dementia.[7,8] However, there is no scientific need to include those who actually have dementia in the typical diabetes trial—where the endpoints are better glucose control—given the widespread nature of the disease and availability of potential participants. However, if the study drug is intended to treat dementia, the narrative with respect to scientific need would be altered in a positive direction, due to the potential need to try the drug in the population in which it is intended to be used.

The concept of *direct benefit* is an aspect of additional protection for vulnerable populations in that there is justification for the prospect of risk associated with a study that is offset by the potential for direct benefit by participating in the research. The higher the potential risks of the research, the greater the anticipated benefit must be to justify inclusion of vulnerable persons. Thus, a drug with relatively few risks of a transitory nature can be justified by rather modest symptomatic relief. However, a drug with potentially serious and permanent risks must likely meet a higher standard for benefit that might include disease modification rather than mere relief of symptoms.

As an example of how to apply the above concept, a product aimed at treating moderate to severe Alzheimer's disease would likely first be tested in normal, healthy adults for safety, and then in those with less profound loss of mental acuity for reasonable signs of efficacy before being given to more severely ill participants.

What if the Capacity to Provide Consent May Change During the Study?

Some conditions involving mental capacity are expected to deteriorate over time. If a study is anticipated to run for several years or more in a population including mild-to-moderate Alzheimer's disease, best practices often dictate that individuals asked to take part in such research *identify* an LAR at the beginning of the consenting process in order to reduce unnecessary

withdrawal from the research and the loss of important data. Failure to identify this individual may leave investigators in a position of having to navigate arcane state laws and tricky family dynamics in order to identify an appropriate surrogate for consent. Although the identified LAR would not provide the consent for initial enrollment in the study—when the subject is still competent to make that decision—informed consent is an ongoing process, and the LAR would be asked to provide continuing agreement for participation should the subject become incapable later.

Conversely, some forms of diminished capacity can improve over time. An LAR may be needed for someone to be enrolled in research who may be temporarily incapacitated—for example, in studies involving patients with acute traumatic loss of consciousness or in a medically induced coma. In trials where the intended population may be in this situation, consent by an LAR is appropriate for enrollment, but such subjects must be re-consented in the event that they regain consciousness and the ability to consent.

When Should a Witness be Involved in the Consent Process?

If used, a witness is expected to ensure that the prospective subject was provided sufficient opportunity to consider study participation, that the possibility of coercion or undue influence was minimized, and that the subject or the subject's LAR understood the information provided to them. There are two situations defined in the regulations in which an impartial witness may be required in the informed consent process.

In the first situation, use of an impartial witness is necessary when either the subject or the subject's LAR speaks and understands English, but either cannot read and write, or is visually impaired such that changes to the consent document, such as increasing font size, are insufficient to allow the subject (or LAR) to read the document(s). In this case, the witness is expected to listen to the verbal presentation of the informed consent discussion, which must include all the required regulatory elements of informed consent. The witness is present to ensure that the potential subject appears to understand the information provided to him or her and has the opportunity to ask questions, and that the potential subject is freely consenting to participation in the research. The witness will then sign the consent form on the "witness" line, to document his or her confirmation of these facts.

> In the process of institutional review board review, questions frequently arise when the informed consent document has signature lines for persons who would not be expected to participate in the consent process, based on the protocol information.

In the second situation, a witness is necessary when the informed consent process uses a "short form" informed consent document (a brief document containing the basic statements about the rights of research participants in a language that is understandable to the potential subject).[9] While short form documents are not frequently used in clinical research, they are permissible in situations in which the potential subject does not speak English (or the language in which the study is being conducted, if it is not English) and a full and complete translated informed consent document is not available.

As defined in the regulations,[10] a short form written consent document requires that there is a witness to the oral presentation. The IRB must approve a written summary of what is to be said to the subject or the LAR. Only the short form itself is to be signed by the subject or the LAR; however, the witness will sign both the short form and a copy of the summary, and the person actually obtaining the consent shall sign a copy of the summary. A copy of the summary should be provided to the subject or the LAR in addition to a copy of the short form.

Neither FDA regulations nor HHS regulations define "witness" per se. FDA Guidance (FDA Information Sheets, A Guide to Informed Consent, "Illiterate English Speaking Subjects") indicates the expectation that the witness be an "impartial third party," but does not provide guidance on what constitutes impartiality. It is useful for any institution at which research is conducted to have a written definition or standard operating procedure that covers who may serve as a witness to an informed consent process.

Note that, since the witness should be independent of the trial, the witness cannot be another member of the study team, and should ideally not be someone who works closely with the study team (e.g., office staff). In larger institutions, a person of presumed neutrality, such as a chaplain or someone from another department, would be an appropriate choice.

In many cases, it is probable that the LAR signature line was present on the template form used to draft the consent, and was never deleted when the consent was made study-specific.

Although not prohibited, best practice often dictates that the witness not be a member of the potential subject's family, as it is may be difficult for them to be impartial about the decision regarding study participation. It is also not generally recommended that a family member act as translator when oral translation of informed consent information is needed, since they may not fully understand the medical information and may mistranslate information, and because they may incorporate their own thoughts into the discussion as the information is translated.

Thus, sites should be prepared to have staff who can serve as translators, especially if the need is frequently encountered, or to have a reliable translator service available. This is important as dialogue will continue *after* the initial consent process, or if the subject or LAR has questions that may require site contact outside planned visits.

Having a pre-defined policy will help minimize situations in which a witness has to be chosen quickly, or in which study-related site personnel are pulled in unprepared, or inappropriately, to serve as witnesses.

Further, many protocol inclusion criteria begin with a statement mentioning the "subject who has signed the consent form," or something similar to this. An illiterate or visually impaired subject can usually provide a "signature" (their "mark"—be it an X or thumbprint), and consent forms would also contain impartial witness lines to accommodate these subjects. However, many studies have diaries, dosing instructions, and questionnaires for subjects to complete. Sometimes these documents must be completed by the subject directly, but sometimes completion by someone on behalf of the subject is acceptable.

When no impartial witness lines are present on the consent form, the IRB may anticipate only literate or sighted readers are to be included, even though that is not the sponsor's intent. Therefore, the protocol eligibility criteria should address whether or not nonreaders will be enrolled, to facilitate the IRB's review.

When Should an Investigator's Signature Appear on the Consent Form?

According to the ICH Guideline for Good Clinical Practice, "Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's [LAR], and by the person who conducted the informed consent discussion."[11] The person who conducts the discussion is either the investigator for the study or a study staff member delegated by the investigator to conduct the consent process.

Sometimes, in addition to the space for the signature of the delegated person who conducted the informed consent process, there is also a space for the signature of the investigator. Presumably, a principal investigator is expected to sign the consent form in this space to indicate his or her awareness of the enrollment of the participant in circumstances when he or she was not the person who conducted the consent discussion.

There is no regulatory or best practice requirement for an investigator to sign the informed consent document, unless the investigator was the person who conducted the consent discussion—in which case, he/she would sign the form in that space. Although less frequently seen now, this practice seemed to be a trend for several years, and presumably was intended to document the oversight of the investigators and their knowledge of participants being enrolled in the study. However, asking investigators to provide a signature as verification of a discussion for which they were not present is not good evidence of oversight.

This practice also creates an additional potential issue of noncompliance; what if the study coordinator who conducted the discussion has signed the form but the investigator has not? What if the investigator signature is dated days, weeks, or even months after the consent discussion occurred, and well after the subject's study participation has begun? The routine addition of an investigator signature line seems to add nothing of value to the consenting process. The recommendation, therefore, is that investigators not be asked or required to sign a consent form, unless they were the person who conducted the consent discussion, in which case they would sign in that capacity.

Conclusion

Documentation of informed consent can involve many layers of complexity and is fraught with the potential for errors and confusion. The persons creating the protocol and documents for informed consent should ensure clear descriptions of the eligible population sought for the research, and should carefully review protocol and consent template language to ensure that it is appropriate in that specific setting and that documents are concordant. This requires evaluation of the research proposal's legitimate need to enroll persons who lack capacity to consent for themselves, and when it is neither necessary nor appropriate, to remove protocol language and consent signature lines for LARs.

Of course, in protocols where the intervention is intended to treat the cause of the incapacity to consent, or where there is a robust expectation of benefit for participants, inclusion of those incapable of consent is ethical and just. The issue of allowance of nonreaders is very different, in that these subjects have the capacity to consent for themselves. One can make the case that it is unethical to exclude this population, barring considerations of the necessity for reading to safely administer a study drug or satisfy study endpoints such as self-administered survey instruments.

When these decisions have been reached and the protocol language is clear, the IRB can easily find the correct documentation and the information required to make approval determinations. Adding signature lines that have no regulatory or ethical relevance to the research is an invitation for noncompliance. The result of this careful review is a more ethically sound study, with reduced timelines to initiation.

If used, a witness is expected to ensure that the prospective subject was provided sufficient opportunity to consider study participation, that the possibility of coercion or undue influence was minimized, and that the subject or the subject's LAR understood the information provided to them.

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Addressing Educational Gaps in Biomarker and Pharmacogenomics Research Knowledge Among IRB/IEC Members

PEER REVIEWED
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What is the distinction between biomarker and pharmacogenomic (PGx) research? How are studies conducted in this arena, and what value do they have for patient care? These are just some of the questions that members of institutional review boards and independent ethics committees (IRBs/IECs) may ask themselves when encountering PGx or biomarker research in a clinical protocol.

LEARNING OBJECTIVE
After reading this article, participants should be able to briefly describe biomarker and pharmacogenomic (PGx) research, identify some of the areas of concern for ethics committees and institutional review boards, and locate educational resources available through the I-PWG on biomarker and PGx research.

DISCLOSURES
David J. Pulford, PhD; Linda M. Coleman, JD, CIP, CHC, CHRC, CCEP-I; Kathleen M. Smith, PhD; Jennifer Ribeiro, MBA; Sandra K. Prucka, MS: *Nothing to disclose*

Seeking clarity on how best to help IRB/IEC members, the Industry Pharmacogenomics Working Group (I-PWG), a voluntary collaboration of nearly 20 pharmaceutical companies, conducted a 25-question, global survey, the results of which highlight the educational needs of IRB/IEC members. In particular, the survey's results point to a need to better define biomarker and PGx research and provide tangible examples of its clinical utility. The survey aided in the development of a one-page information sheet to address these educational needs in a format that recognizes the time constraints under which many IRB/IEC members operate.

Understanding Biomarker and (PGx) Research

Biomarker and PGx research as a whole aims to improve the medical field's understanding of drug response (see Sidebar 1) and is an integral part of modern clinical trials. Researchers are required to understand how study participants respond to a drug during the various phases of clinical development, and to evaluate both PGx and non-PGx biomarkers in parallel to enable a better understanding of diseases and responses to medicines (e.g., in terms of safety and efficacy).

There have been numerous successes in biomarker research, a summary of which can be found in the U.S. Food and Drug Administration's (FDA's) Table of Pharmacogenomic Biomarkers in Drug Labeling.[1] For example, research demonstrated that only those patients with metastatic colorectal cancer whose tumors express the EGFR protein and are also negative for a mutation in the K-Ras gene receive a benefit from taking cetuximab.[2] Thus, the FDA has approved a companion diagnostic test for K-Ras to identify colorectal cancer patients best suited to receive cetuximab.[3]

As this example illustrates, the process of research leading to companion diagnostics allows physicians to have individualized information available as they consider the most appropriate treatment recommendations for their patients. PGx and biomarker research can also help streamline drug development through the use of biomarkers as "surrogate" safety/efficacy endpoints, and through lessening the incidence and healthcare burden of adverse drug reactions.

Feedback from IRB/IEC Members

Despite the potential benefits from this research, there have been few, if any, studies examining the comfort of IRB/IEC members in reviewing the ever-growing number of protocols with a PGx and/or biomarker research component. The I-PWG queried IRB/IEC members across 147 countries in an effort to better understand their knowledge of this research, and to aid in developing educational resources that could fill any knowledge gaps identified.

The survey aimed to assess IRB/IEC members':

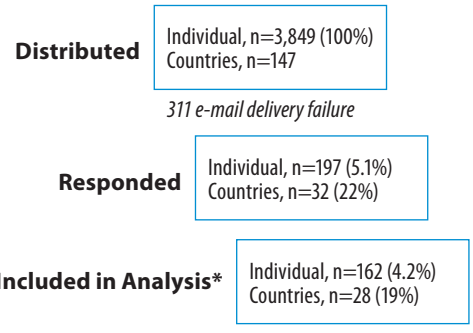
- understanding of the I-PWG;
- use of the current I-PWG educational resources;
- interest in a shortened resource to explain biomarker/PGx research;
- recommended focus areas for educational resources; and
- demographic makeup.

The full survey and other supplemental material related to this article can be found in the Good Clinical Practice & Ethics Interest Group area of the Association of Clinical Research Professionals website at www.acrpnet.org/Interest-Groups/Good-Clinical-Practice-Ethics/Shared-Resources.aspx.

SURVEY RESPONDENT DEMOGRAPHICS

The list of IRB/IEC members used in the present survey was originally compiled for an earlier I-PWG survey conducted in 2011.[5] The current survey was distributed to 3,849 IRB/IEC members, of which 197 (5.1%) responded. (E-mail response rates to surveys of the general public can vary, with some sources reporting 10% to 15% responding [Survey Gizmo][6] and others showing rates as high as 25% [Fluid Surveys].[7])

FIGURE 1: Number and percentage of IRBs/ECs that completed the survey



*Answered at least one survey question which was informative in developing the I-PWG single-page educational brochure.

Sidebar 1: What does biomarker and PGx research involve?

Biomarker and pharmacogenomic (PGx) research aims to provide an understanding of factors that contribute to disease and response to medicines. This research may enable the assignment of patients to specific treatments and may involve, for example, examining DNA, RNA, proteins, or cellular responses (e.g., changes in lipids and metabolites) between patients. Furthermore:

- Biomarker research can involve examining biomolecules (e.g., proteins, changes in lipid/metabolites, hormones) or other measurements (e.g., blood pressure or brain images) to see what the relationship may be between these characteristics and variations in clinical response.
- PGx research is a type of biomarker research that is focused on understanding genetic/genomic contributions to drug response. Pharmacogenetics (PGt) is a subset of PGx research that is specifically focused on the study of DNA sequence variation as it relates to drug response.[4]
- Companion diagnostic tests may be developed for validated PGx and biomarkers with clinical utility. These tests allow for the safe and effective use of the drug when it is available to patients.

Figure 1 and Table 1 show the number of responses received and the breakdown by country for the current survey. While responses were received from IRB/IECs globally—as approximately two-thirds of the responses were from the United States (Table 1)—perspectives of U.S. IRB/IECs are over-represented. The low response rate and overrepresentation of U.S. sites are clear limitations of the current survey; thus, our results may not be representative or generalizable to the global IRB/IEC community.

Of the 91 respondents who answered demographic questions, 85% had participated in an IRB/IEC for at least five years, and 52% had previous experience reviewing protocols that included PGx or biomarker research. Since respondents were predominantly from the U.S., we evaluated whether the U.S. respondents' level of experience differed from those of respondents from other regions of the world. Approximately 56% of U.S. respondents had experience reviewing protocols with biomarker and/or PGx research, which was greater than the 44% observed in non-U.S.

TABLE 1: Distribution of the 162 informative survey responses by country

Country	Number of IRBs/ECs Surveyed	Percentage of Responses
United States	112	69%
Australia	5	3%
Nigeria, Canada	4 each	5%
Brazil, India	3 each	4%
Argentina, China, Germany, Israel, Mexico, Peru, Philippines, Puerto Rico, Thailand	2 each	11%
Belgium, Bulgaria, Egypt, El Salvador, France, Georgia, Ireland, Italy, Namibia, New Zealand, Palestine, Poland, United Kingdom	1 each	8%

Despite the potential benefits from this research, there have been few, if any, studies examining the comfort of IRB/IEC members in reviewing the ever-growing number of protocols with a PGx and/or biomarker research component.

countries. Thus, while the reasons for the low response rate to this survey are unclear, possible contributing factors include the low number of IRB/IEC members with experience in this area of research and limited time to devote to completing this survey.

SURVEY RESPONDENT FEEDBACK

One of the main goals of the survey was to better understand how to create a shortened resource that would have utility for IRB/IEC members. We received helpful feedback to written responses for two questions that asked what information IRB/IEC members felt was most important to communicate about biomarker and PGx research.

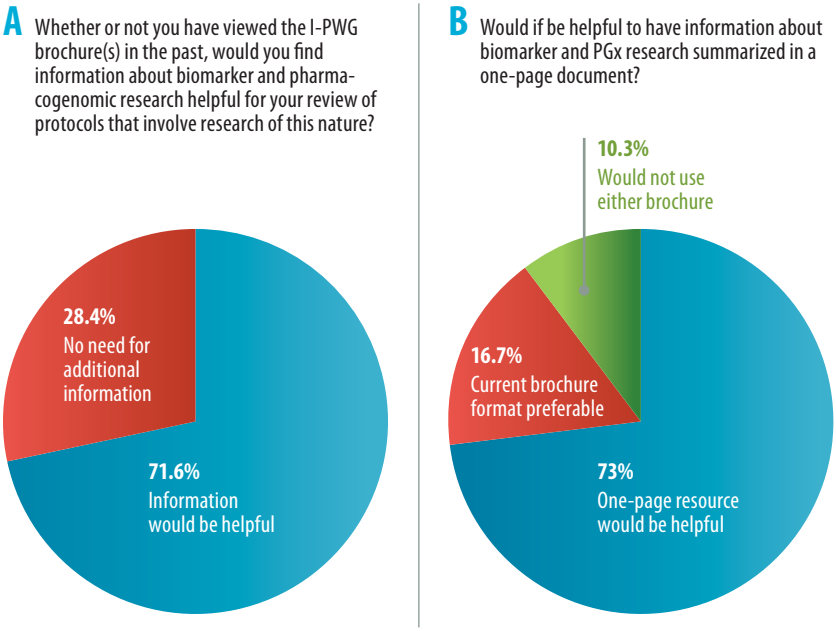
Although the response rate was not robust, there were recurring themes. In particular, multiple survey respondents wrote that they had limited time to commit to further education given life and work demands. The majority of respondents noted that they had not read either of the existing I-PWG brochures, and cited a lack of time as a major contributor.

These data underscore the very real constraints experienced by IRB/IEC members, and served as a motivator for the I-PWG to create a shorter brochure, which may be more accessible to IRB/IECs and healthcare professionals conducting clinical trials. Furthermore, the responses received helped us conceptualize how the information from our more lengthy resources could be condensed into a one-page resource focused on the areas felt to be the most important to those responding.

Although this feedback was helpful, we also wanted to be certain this type of resource is needed before taking this project on as a group. To that end, survey participants were first asked a series of three questions about the availability and usefulness of the current I-PWG educational brochures. Results from two of the questions demonstrated that the majority of IRB/IEC members felt that information about biomarker and PGx research would be helpful as they review protocols (see Figure 2).

The majority (66%) indicated that the current length of the brochures is sufficient, with 11% of respondents feeling more detail could be added and 22.2% saying the current brochures are too long to be useful. Regardless, when asked directly if it would be helpful to have a shorter brochure to complement existing resources, the majority (73%) said yes.

FIGURE 2: Interest in I-PWG educational resources



Translating Feedback to the Development of a One-Page Resource

To create a concise, educational brochure, we used survey responses to focus on what our target audience found to be the most helpful information. This was primarily driven by the responses to seven survey questions that allowed for open-ended answers.

INFORMATION OF MOST INTEREST TO IRB/IEC MEMBERS

As described above, the two open-ended questions leading to the most numerous and informative responses were: "What information do you think would be most important and helpful to communicate regarding biomarker research?" and "What information do you think would be most important and helpful to communicate regarding pharmacogenomic research?" We categorized responses as displayed in Figure 3.

To ensure all feedback from each IRB/IEC member was represented, we assigned a category to each concept. Thus, a single respondent could provide information that was scored into more than one category. For example, if a respondent indicated he or she felt both clinical utility and privacy were important to communicate when discussing PGx research, the answer was counted in both categories. A total of 48 respondents answered the question regarding biomarker research, and 47 responded to the question regarding PGx research. A total of 66 biomarker and 55 PGx topics were tabulated.

As we analyzed responses to these two questions, two areas emerged as most important to include in our resource: better scientific explanations of biomarker and PGx research, and explanations and examples of its clinical utility. The majority of those expressing a desire for "better scientific explanation" articulated a basic need for "definition of terms—biomarker, etc." and "basic definitions, functions, and examples of use."

NEED FOR INCREASED GENETICS EDUCATION

This desire for better understanding of basic definitions highlights the disparity between the knowledge base of ethics communities who review protocols containing this research and the expectations of regulators (such as the FDA and the European Medicines Agency [EMA]). These regulatory bodies have increased expectations for integrating biomarker research in general, and PGx research specifically, into drug discovery and development.

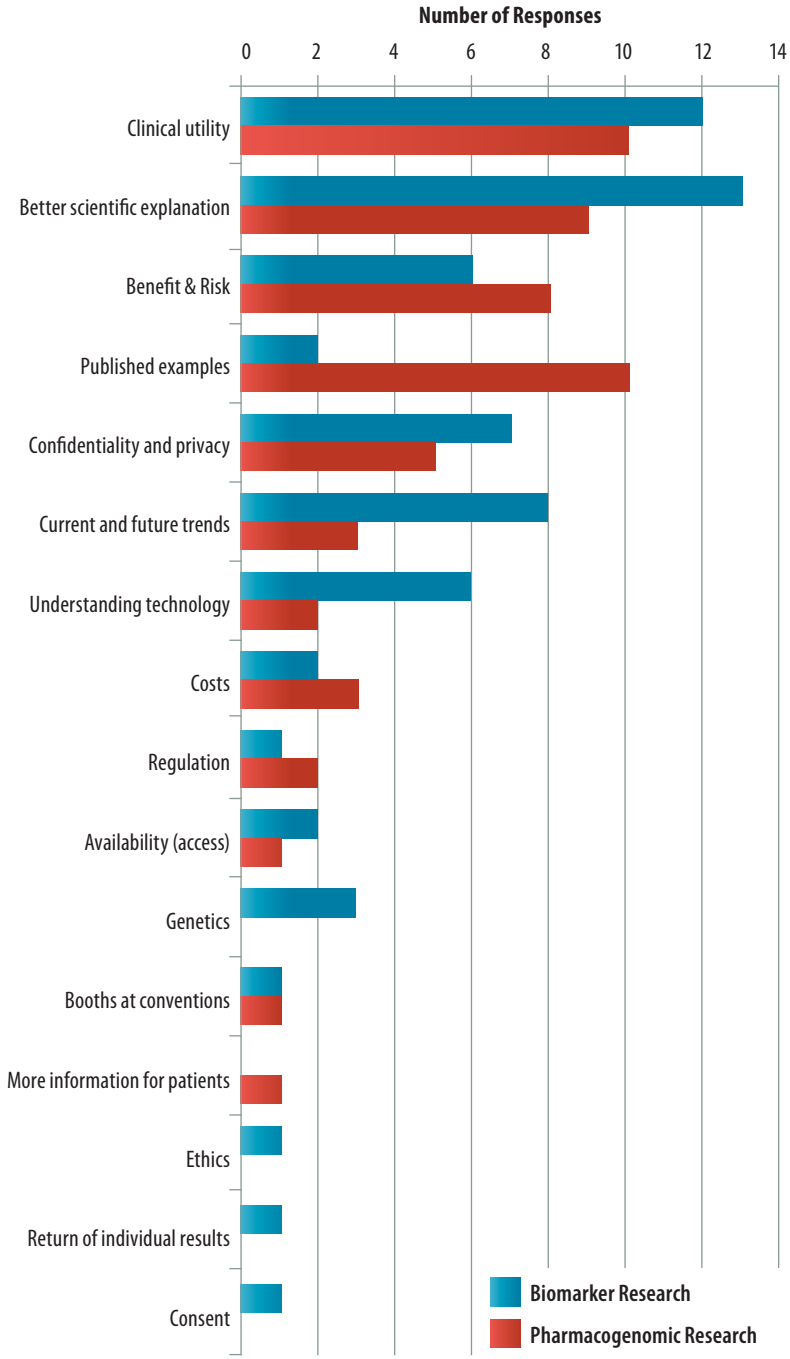
There have been multiple position papers and guidance documents published that support PGx and biomarker sample collection and research. A FDA report entitled "Paving the Way for Personalized Medicine" states that "[a]dvances in PGx have opened new possibilities in drug discovery and development. PGx has allowed for more tailored treatment of a wide range of health problems, including cardiovascular disease, cancer and HIV/AIDS."[8] Quotations from additional guidance documents are listed in Sidebar 2.

Thus, the pharmaceutical industry, through the I-PWG and other consortia, is working to bridge the gap between regulator expectations and the ethics community's obligation to stay apprised of the current science relevant to human subject research.

Despite a growing focus on genomics in biomedical research, genetic education for healthcare professionals is lagging. The need for more genetic education is not an entirely new concept; a 2008 Canadian study involving family medicine residents found that "medical school educational experiences may not be preparing future primary care physicians to address genetic issues with patients. A change and a broadening of the teaching of genetics are required to fulfill this need."[12] In addition, a 2013–14 study examining trends in genetics curricula in U.S. and Canadian medical schools similarly found that most respondents felt that the amount of time spent on genetics was insufficient to prepare them for clinical practice.[13]

The need for more genetic education for the general public was noted in a 2004 study that found many adults lacked a basic understanding

FIGURE 3: Most important information for a resource to include



Sidebar 2: PGx Sample Collection Recommendations from Regulatory Bodies and ICH

- EMA 2011: Prospective DNA sampling and banking for pharmacogenomic/pharmacogenetics-related genotyping analysis are highly recommended.[9]
- FDA 2013: Ideally, baseline DNA samples should be collected from all patients in all arms of clinical trials in all phases of drug development.[10]
- ICH 2014: Genomic sample collection for future use...to enable retrospective analysis when new scientific evidence emerges or when additional analyses of genomic samples become necessary.[11]

Despite a growing focus on genomics in biomedical research, genetic education for healthcare professionals is lagging.

of genetic terms. This lack of understanding impacts genetic literacy, public health practices, and routine healthcare, and can be problematic when individuals are asked to take more responsibility for the management of their own health.[14] Furthermore, lack of genetic education amongst physicians and subjects in clinical trials may negatively impact participation in biomarker and PGx research, thus limiting research opportunities.

It is difficult to predict what the experiences of IRB/IEC members may be, since IRBs/IECs typically are composed of a diverse group of individuals (including nonscientific members) who collectively have expertise and experience to review research from a scientific, ethical, and community perspective.[15,16] Therefore, in order to effectively translate genomics into the promise of personalized medicine, more education and practical training opportunities are essential for the general public, healthcare professionals, and IRB/IEC members.[17]

INTEREST IN CLINICAL UTILITY

The second most commonly expressed need was for examples demonstrating the utility and application of biomarker/PGx research in clinical practice, and a better understanding of how this research contributes to developing tests for routine medical practice.

Despite numerous examples (nearly 166 drug labels in the U.S., or about 10% of all FDA-approved drugs since 1938, include genomic information), there is an understandable frustration that more clinically actionable biomarkers have not been identified to date.[18] This frustration was articulated by one respondent, who noted: "There is a critical lack of specific, reliable, quantifiable, and easily measured biomarkers that correlate well with early disease progression."

While regulators, such as the FDA, are advising pharmaceutical companies to take a more objective stance toward PGx research, there is still considerable effort needed to make these tests applicable to clinical practice.[19] In addition, there is a pressing need for the research community to better communicate the complexities of achieving actionable results from biomarker/PGx research.

Increased communication, which could be achieved in part through the sharing of published examples, would provide better education of the research process, successes to date, challenges ahead, and expectations for the future.

BENEFITS AND RISKS

One of the complexities requiring increased communication is an understanding of the research process and the difficulties in reporting individual results. In the "benefit/risk" category, one respondent asked: "What is the impact on an individual human subject? What is the impact of this research on communities from which the subject is drawn?" Utility in this category was articulated not only as a need for information on individual benefits, but also on societal benefits.

Before clinical utility is established, scientific hypotheses must be replicated in additional patient cohorts, and an association between the marker(s) and outcome of interest must be validated. This research is often done in parallel to development of therapeutics, or analyzed retrospectively on samples banked from previous clinical trials. Therefore, it can take years before the clinical utility of an individual biomarker is established and is ready to be used in medical decision making.[20] Any direct benefits of research to individuals enrolled in such studies are thus limited, though eventual benefits may be experienced by future patients.

The survey results suggest a strong need for researchers to demonstrate the value of biomarker and PGx research through successful examples of such work, and to ensure that these are provided to the members of IRB/IECs, so that they can determine the added benefit of the research for potential study participants and the public at large. Clearly providing examples from the literature and drug labels also provides evidence of the benefits of this research to society as a whole.

PATIENT PRIVACY CONCERNS

As would be expected, another area of great interest was a need for information regarding patient protections, as evidenced by the categories on "benefit/risk," "confidentiality/privacy," "consent," and "ethics." Concerns over patient privacy pointed

specifically to concerns regarding "whole genome sequencing or analysis of many alleles." Due to the sensitivity and personal nature of these data and expressed concerns over privacy, we chose to make this one of the focal points of the I-PWG one-page information resource.

It is worth noting that privacy concerns with this research are often directed specifically at germline PGx/genetic research (genetic changes that are passed from one generation to the next), as release of this information may have consequences for individuals and their families. In contrast, oncology research that focuses on understanding genetic variation in the tumor (somatic genetics) does not provide information that is passed down generationally.

Researchers must be aware of legal and regulatory requirements that are in place to provide data protection, and should communicate steps taken to protect research subject confidentiality.

Conclusions

The I-PWG undertook a survey of IRB/IEC members that provided feedback for the generation of additional education materials that meet the needs of this global community. Despite the recognized limitations of the survey, there was an underlying theme that more information is required by IRB/IEC members on biomarker and PGx research. As a result, we created a concise educational resource to better prepare IRB/IEC members and investigators and their site staff for reviewing and implementing protocols with biomarker and PGx research (see the online supplemental materials in the ACRP interest group referred to earlier). Survey results highlighted the need for increased education and communication to keep these individuals and the general public aware of the progress being made toward making personalized medicine a reality.

Resources

The I-PWG aims to promote better understanding of PGx and biomarker research by providing educational materials for use by ethics review boards, healthcare professionals, scientists, and the public. It engages regulators to identify noncompetitive issues about which the group can provide information or support. The I-PWG has produced several informational brochures to explain biomarker and PGx research targeted toward IRBs/IECs and investigational site staff (available at www.i-pwg.org), and continues to examine ways to increase education and communication about this research.

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HOME STUDY HS

Is Your Site Up to Speed?

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This test expires on October 31, 2017

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Monitoring of Clinical Trials—Are Remote Activities Helpful in Controlling Quality?

1. **Monitoring of clinical trials can involve a number of techniques described in which source(s)?**

- **A.** Only in U.S. Food and Drug Administration (FDA) regulations
- **B.** In regulations and guidelines from multiple sources
- **C.** Only in the protocol for a specific clinical trial
- **D.** Only in the official Good Clinical Practice (GCP) guideline

2. **Which of the following is true of the FDA's risk-based monitoring guidance on "Oversight of Clinical Investigations"?**

- **A.** It is in conflict with all advice from the International Conference on Harmonization (ICH)
- **B.** It is only of value to principal investigators (PIs) as a reference during monitoring visits
- **C.** It allows for many different approaches to monitoring to be followed according to different circumstances
- **D.** It advises against the use of electronic systems and records in support of centralized monitoring

3. **Monitoring activities include which of the following?**

1. Verification of study-related data
2. Surveys of patients' health status
3. Review of study-related activities at the site
4. Communication with site study team members

- **A.** 1, 2, and 3 only
- **B.** 1, 2, and 4 only
- **C.** 1, 3, and 4 only
- **D.** 2, 3, and 4 only

4. **Centralized monitoring involves which of the following practices?**

- **A.** Remote evaluation of how a site is conducting a study
- **B.** Asking the site staff to review their own documents
- **C.** Reviewing databases without verifying the contents against the sources
- **D.** Only reviewing key documents that are submitted to the sponsor

5. **Use of centralized monitoring may depend on which one of the following factors?**

- **A.** State laws limiting access to sites by monitors for out-of-state sponsors
- **B.** Conflicts of interest between PIs and contract research organizations
- **C.** Demands for records to retained at the site for years following study completion
- **D.** The timely sharing of data from paper case report forms with sponsors

6. **What percentage of survey respondents indicated some data collected at their sites are being monitored remotely?**

- **A.** 30%
- **B.** 50%
- **C.** 70%
- **D.** 90%

7. **What documents did the largest percentage of survey respondents indicate are monitored remotely?**

- **A.** Source and Regulatory only
- **B.** Source, Regulatory, and Drug/Device Accountability
- **C.** Source and Drug/Device Accountability only
- **D.** Regulatory and Drug/Device Accountability only

8. **What percentage of survey respondents felt that remote monitoring would negatively impact the relationship between sites and sponsors?**

- **A.** Almost 10%
- **B.** Almost 30%
- **C.** Almost 50%
- **D.** Almost 70%

9. **How did the largest percentage of respondents feel that remote monitoring had affected workload time devoted to monitoring?**

- **A.** Less time required for sites
- **B.** More time required for sites
- **C.** Less time required for sponsors
- **D.** More time required for sponsors

10. **The authors suggest which of the following approaches to avoid changes in monitoring after a study has started?**

- **A.** Educate site staff about expectations regarding data availability and access
- **B.** Establish legally binding contracts regarding data availability and access
- **C.** Withhold payments to sites until all data availability and access expectations are met
- **D.** Terminate studies before completion if data availability and access expectations are not being met

Getting the Right Signatures on Informed Consent Documents

11. **Which of the following additional persons may, in certain circumstances, be needed to participate in an informed consent process?**

1. Impartial witness
2. Legally authorized representative
3. Participant's primary care physician
4. Site's regulatory compliance officer

- **A.** 1 and 2 only
- **B.** 1 and 4 only
- **C.** 2 and 3 only
- **D.** 3 and 4 only

12. **Why do signature blanks on an informed consent document frequently cause delays in the process of institutional review board (IRB) review?**

- **A.** Because the labels are misspelled
- **B.** Because the signature blanks are inconsistent with the protocol information regarding the study population
- **C.** Because the only signature blank should be one for the study participant
- **D.** Because the only signature blank should be one for the principal investigator (PI)

13. **The term "legally authorized representative" should be used in which of the following settings?**

- **A.** When referring to the parent or guardian of a child who is being asked to participate in a clinical study
- **B.** When referring to the person who is legally empowered to make healthcare decisions for someone who does not have the capacity to make these decisions for themselves
- **C.** When referring to someone who is visually impaired
- **D.** When referring to someone who is a prisoner

14. **Which of the following are qualifications of an impartial witness per the Good Clinical Practice guideline of the International Conference on Harmonization?**

1. That they are independent of and cannot be influenced by people involved in the trial
2. That they can pass a quiz about the goals of the study
3. That they attend the informed consent process
4. That they can read

- **A.** 1, 2, and 3 only
- **B.** 1, 2, and 4 only
- **C.** 1, 3, and 4 only
- **D.** 2, 3, and 4 only

15. **If there is signed documentation that makes Person A the legally authorized representative for Person B, Person A can do which of the following?**

- **A.** Give consent on behalf of Person B, even if Person B currently has the capacity to make his or her own decisions
- **B.** Give consent on behalf of Person B, only when Person B does not have the capacity to make his or her own decisions
- **C.** Appoint a different person to make decisions for Person B
- **D.** Veto any medical decisions made by Person B, even if Person B has the capacity to make his or her own decisions at the time

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16. **Decisionally impaired persons are considered to be a vulnerable population; therefore, which of the following is not true?**

A. The IRB must consider whether inclusion of these participants requires additional protections for them.

B. The protocol should provide a rationale for why the study cannot be conducted by only including a less vulnerable population, such as persons who can provide consent themselves.

C. The sample size should be increased to allow for additional attrition.

D. The IRB will consider the prospect of direct benefit to potential participants in relationship to the risks of participation.

17. **If the capacity of a participant to provide consent may be lost over the course of the study, and the study anticipates this and allows continued participation, which of the following is a best practice?**

A. Have the person who would be the legally authorized representative give consent at the start of the study, even if the potential subject has the capacity to give consent at that time

B. Do not enroll that potential subject in the study

C. Have an impartial witness participate in the informed consent process

D. Identify the participant's legally authorized representative at the start of the study, as he or she may need to provide continuing consent as the study progresses

18. **Which of the following situations may require an impartial witness to participate in the informed consent process?**

1. The participant (or his or her legally authorized representative) is able to read and understand English but unable to write

2. The participant (or his or her legally authorized representative) is visually impaired to the degree of being unable to read consent documents

3. A "short form" consent document is being used

4. An IRB member is present to observe the consent process

A. 1, 2, and 3 only **C.** 2, 3, and 4 only

B. 1, 3, and 4 only **D.** 1, 2, and 4 only

19. **An impartial witness should be which of the following?**

A. The study coordinator

B. A family member of the potential study participant

C. A person of neutrality, such as someone from another department

D. The PI for the study

20. **Why should the PI not sign the informed consent document if he or she was not the person who conducted the informed consent discussion?**

1. If not present, he or she cannot attest by signature that the consent discussion occurred.

2. Compliance issues are likely if the date or time of signature is after the study participation began.

3. There is no requirement for them to do so.

4. The study coordinator can sign the PI's name if he or she was not present.

A. 1, 2, and 3 only **C.** 1, 3, and 4 only

B. 1, 2, and 4 only **D.** 2, 3, and 4 only

Addressing Educational Gaps in Biomarker and Pharmacogenomics Research Knowledge Among IRB/IEC Members

21. **The Industry Pharmacogenomics Working Group (I-PWG) is a voluntary organization that does which of the following?**

1. Promotes a better understanding of biomarker and pharmacogenomic (PGx) research

2. Engages in information sharing with regulators to identify noncompetitive issues that the group can provide support and information on

3. Provides educational materials to healthcare professionals, ethics review boards, scientists, and the public regarding relevant ethical, legal, and regulatory issues on biomarker and PGx research

4. Funds potential breakthrough biomarker and PGx research at startup pharmaceutical companies internationally

A. 1, 2, and 3 only **C.** 1, 3, and 4 only

B. 1, 2, and 4 only **D.** 2, 3, and 4 only

22. **Biomarker research examines characteristics that are which of the following?**

1. Indicators of normal biological processes

2. Pathological processes

3. Evidence of patients' noncompliance

4. Pharmacological responses to medication

A. 1, 2, and 3 only **C.** 1, 3, and 4 only

B. 1, 2, and 4 only **D.** 2, 3, and 4 only

23. **PGx research is focused on which of the following?**

A. Examining protein biomarkers to understand pathogenic processes

B. Understanding protein and cellular responses between patients

C. Understanding genetic and genomic contributions to drug response

D. Identifying and validating novel molecular targets for the treatment of disease

24. **The I-PWG survey revealed what key consideration as most important to respondents?**

A. The need for better explanations of biomarker and PGx research and examples of clinical utility

B. The need for more geneticists to sit on ethics committees

C. The need for more regulation in biomarker and PGx research

D. The fact that there are already sufficient educational tools and resources for ethics committees, clinicians, and patients in biomarker and PGx research

25. **Which of the following is true about how the members of ethics committees (ECs) feel regarding having adequate information about biomarker and PGx research to understand it?**

A. ECs have all the information they need to evaluate protocols

B. Only U.S. ECs need education on pharmacogenomics

C. Educational materials would help the majority of ECs

D. Biomarker and particularly PGx research is irrelevant

26. **Why do pharmaceutical companies want to bank samples for future biomarker and PGx research?**

1. They have unlimited money to spend.

2. It supports retrospective analysis when new scientific evidence emerges.

3. Research on these samples facilitates personalized medicine.

4. International regulatory bodies recommend it.

A. 1, 2, and 3 only **C.** 1, 3, and 4 only

B. 1, 2, and 4 only **D.** 2, 3, and 4 only

27. **Which of the following agencies have increased expectations for integrating biomarker research in general, and PGx research specifically, into drug discovery and development?**

1. U.S. Food and Drug Administration

2. Office for Human Research Protections

3. Centers for Medicare & Medicaid Services

4. European Medicines Agency

A. 1 and 3 only **C.** 2 and 3 only

B. 1 and 4 only **D.** 2 and 4 only

28. **Which of the following best describe the benefits of biomarker and PGx research?**

1. There are limited direct benefits to individual study participants.

2. Individual study participants should expect immediate return of research results.

3. It can take many years before the clinical utility of a biomarker is established.

4. The benefits to this research are mainly in terms of cutting study costs.

A. 1 and 2 only **C.** 2 and 4 only

B. 1 and 3 only **D.** 3 and 4 only

29. **Which of the following were presented in the article as being true of establishing clinical utility of an individual biomarker?**

1. Scientific hypotheses must be replicated in additional patient cohorts.

2. An association between the marker and outcome of interest must be validated.

3. The research is often done in parallel to the development of a therapeutic, which in and of itself can take years.

4. Establishing clinical utility is only a secondary or tertiary goal in the majority of studies.

A. 1, 2, and 3 only **C.** 1, 3, and 4 only

B. 1, 2, and 4 only **D.** 2, 3, and 4 only

30. **What did the survey reveal was related to the greatest privacy concern in biomarker research?**

A. The wide variation in coding practices across the industry

B. Whole genome sequencing or analysis of many alleles

C. Cyber security is particularly lax in this kind of research

D. Insecure storage of paper case report forms with study results