Protocol Deviations: Characteristics and Consequences

By Elizabeth Tilley Hinkle

Protocol deviations can pose serious risks to clinical trials, including regulatory troubles, study delays and, ultimately, failure to launch an approved investigational product. But despite the importance of following study protocols, deviations remain a consistent problem in the industry, regularly topping the list of problems found during FDA inspections of research sites. Recent figures indicate that the average phase 3 trial has 118.5 deviations per protocol that affect nearly 33 percent of enrolled participants.

A deviation occurs any time a procedure is conducted in a study in a way that doesn't precisely follow protocol instructions. Deviations can be minor, such as missing participant initials on part of a consent form or failure to get a participant survey by the prescribed deadline. They can also be very serious, such as giving participants the wrong dose of a drug or enrolling participants who don't meet inclusion/exclusion criteria.

While any deviation can have consequences, such as an FDA inspection observation that must be corrected before moving forward, the most serious deviations — those that affect participant safety or call into question the integrity of study data — can have significant repercussions. A study plagued with serious deviations could be halted; at best, it is likely to experience serious delays while the issues are corrected. Further, the FDA is more likely to closely scrutinize data after a negative observation,

which could delay or even prevent drug or device approval.

Some experts in the industry consider deviations just part of doing business or even "the new normal."[1]

That does not have to be the case, however. There are steps that clinical researchers and sponsors can take to avoid protocol deviations. For instance, a little extra work done up front can help ensure

> **Learner Outcomes:**
> 1. Define and cite examples of protocol deviations.
> 2. Separate common deviations from harmful violations.
> 3. Explain the consequences of protocol deviations.
> 4. Describe methods to reduce or avoid deviations.

Effective Change Management Can Help Ease Transition and Speed Innovation

By Elizabeth Tilley Hinkle

The word "innovation" is almost synonymous with the word "change," but the former has a positive feel while the latter can have a negative connotation for risk-averse individuals and organizations alike. And few industries are as risk-averse or as in need of innovation as the clinical trials field.

In a report issued earlier this year, the Tufts Center for the Study of Drug Development (CSDD) estimated that it takes an average of 69 months — nearly six years — for clinical researchers to adopt innovations that support clinical trials execution.[1] Companies spend almost 14 months just planning or initiating an innovation and another 16 months evaluating its viability and impact, CSDD found. It takes an additional 16 months to decide whether to move forward with full adoption of an innovation and 23 more months to complete implementation.

> **Learner Outcomes:**
> 1. Explain how technology supports change management.
> 2. Give examples of change management models.
> 3. List examples of change management procedures.
> 4. Describe barriers to successful change management.

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Regulatory Update

Contact hours not offered for these articles

FDA Extends Comment Period on Proposed IRB, Informed Consent Rules

In response to requests for more time to weigh in on a pair of long-awaited proposed rules on IRB review and informed consent requirements, the FDA has extended the comment period to Dec. 28.

The proposed rules would line up the FDA's IRB and informed consent requirements with the Common Rule's provisions and are intended to cut down on administrative burden for sponsors, investigators and IRBs by making IRB reviews more consistent across government- and privately funded research. They were finally published in October after years of delay (CenterWatch, Oct. 3).

"The requests conveyed concern that the current 60-day comment period does not allow sufficient time to develop a meaningful or thoughtful response to the proposed rules," an FDA spokesperson told *Research Practitioner*.

Read the notice here: https://bit.ly/3G4QLKr.

FDA Releases Draft Guidance on Assessing Growth, Puberty in Pediatric Trials

Trials of drugs for pediatric use should train clinical investigators and trial staff to measure and evaluate the drug's potential impact on participants' physical growth and sexual development, according to recent FDA draft guidance.

The recently published 10-page draft guidance recommends that trial protocols include procedures for determining a participant's age, obtaining growth measurements, instrument calibration and evaluation of pubertal development.

"Pediatric clinical trials should include accurate, serial measurements and recordings of growth parameters if an investigational drug has the potential to affect growth or pubertal development," continued the guidance, noting that usually "growth is assessed using measurements of weight and linear growth (length and height), and when appropriate, head circumference."

In addition, said the guidance, sponsors should record growth measurements for a "minimum trial duration" of 12 months or discuss alternative trial durations with the necessary FDA review division.

The guidance also recommended keeping pediatric participants who stop treatment within the trial to collect growth measurements that may be needed to ensure the reliability and interpretability of analyses and results.

Trial sponsors should use a sexual maturity rating to evaluate and document pubertal development at baseline and during "regular intervals based on the potential safety concerns associated with the drug and the pubertal development stage of the pediatric participant," the agency said.

The guidance focuses on data to support a drug's safety and does not address the use of growth or pubertal development data on efficacy in growth disorders, the agency said, adding that sponsors should discuss how to establish efficacy with the appropriate FDA review division.

Comments on the draft guidance should be submitted by Jan. 1, 2023.

Read the draft guidancehere: https://bit.ly/3gZfPrQ.

ICH Publishes M11 Guidelines on Designing Standardized Trial Protocols

With a goal of facilitating the seamless exchange of clinical trial protocols, the International Council for Harmonization (ICH) has published draft recommendations for their structure and content.

The ICH M11 draft guideline provides general protocol design principles for sponsors, investigators, IRBs, regulatory agencies and other stakeholders through a template that promotes "consistency and efficiency in the development, amendment, review, conduct and closeout of a clinical trial and the exchange of protocol information."

Per the guideline, ICH advises designing protocols with an eye for minimizing repetition and including essential information for trial conduct at the top. Similarly, the M11 guideline recommends that sponsors include trial-specific information in the main body of the protocol and reference/general details in an appendix section.

In addition to the template, the M11 guideline comes with a comprehensive technical specification document that goes in depth on the information that should be included for the various components of a protocol.

Access the M11 guideline here: https://bit.ly/3TOKzua.

FDA Addresses Issues with the Use of Multiple Endpoints in Final Guidance

Seeking to help sponsors avoid making false efficacy conclusions in drug and biologic trials that use multiple endpoints, the FDA has published final guidance on grouping and ordering endpoints for analysis and statistical approaches for managing them.

Regulatory Update

Regulatory concerns about multiple endpoints generally come up in trials aimed at showing effectiveness to support drug approval and claims in FDA-approved labeling. "However, this issue is important for trials throughout the drug development process," the agency said.

The guidance includes a detailed section on general principles behind the use of multiple endpoints that sponsors should consider, including the different ways of grouping endpoints, controlling Type I error rates, Type II error rates and sample size, the hierarchical grouping of endpoints in trials and the individual components of composite and multicomponent endpoints.

It also includes an appendix containing a number of common statistical methods that work well with multiple endpoints, as well as a section of general references.

The guidance notes that the FDA's recommendations for multiple endpoints and "multiplicity" generally apply to other areas as well, including the use of multiple doses, time points and study population subgroups, though the guidance does not cover these specifically. It also notes that different considerations may come into play in certain unique situations, such as the evaluation of multiple drugs for a single disease in a master protocol.

Access the full final guidance here: https://bit.ly/3DifjoN.

FDA Issues Final Guidance on Developing Gene Therapies for Neurodegenerative Diseases

Both clinical and surrogate endpoints are acceptable targets for trials investigating gene therapies (GT) for neurodegenerative diseases, according to finalized FDA guidance on developing these products.

The document updates and finalizes draft guidance that was filed last year.

Products advancing through the traditional approval pathway will need to show a significant effect on a clinically meaningful endpoint. But surrogate endpoints can be used to support a marketing approval under the accelerated approval pathway, under some circumstances.

A surrogate endpoint might be the best choice in cases where a GT product "directly targets an underlying, well-understood and well-documented monogenic change that causes a serious neurodegenerative disorder," the guidance says. "In these cases, the GT product could alter the underlying genetic defect and thereby treat or cure the disease."

Sponsors that intend to employ surrogate endpoints need to alert the FDA as early in the development process as possible and well before clinical trials begin.

By the time human studies commence, sponsors should have solid animal data that confirm dosing regimens and a proposed route of administration. These preclinical findings also need to support patient eligibility criteria and identify potential toxicities.

Because of the significant differences between human and rodent neurophysiology, animal studies of GT may be better conducted in larger mammals or non-human primates.

Using larger animals can also allow sponsors to evaluate delivery systems, whether those are surgical or via device. Drug/device compatibility needs to be demonstrated before initiating a phase 1 safety study.

All these requirements contribute to a strong body of preclinical data, which is especially important when the first-in-human clinical trial will be conducted in children.

Ideally, the guidance says, a GT trial should be conducted in an adult population before the product is studied in children. When there are no adult data, sponsors need to explain why adult studies aren't possible.

Read the final guidance here: https://bit.ly/3guoXEP.

EMA Adopts ICH E19 Guidelines on Selective Safety Data Collection

The European Medicines Agency (EMA) has endorsed the International Council on Harmonization's (ICH) guideline on ways to be more selective in collecting safety data in late-stage and postmarket trials.

The guideline, ICH E19, defines selective safety data collection as "the reduced collection of certain types of data in a clinical trial after thorough consideration of factors that would justify such an approach."

The council's recommendations for selectively gathering safety data mainly pertain to postmarket interventional trials, as comprehensive collection is usually expected in preapproval trials, but it does apply to late-stage preapproval trials in certain situations.

E19 presents both general considerations on participant safety, justifying selective safety data collection, data that may be appropriate for selective gathering, benefit-risk considerations and situations in which selective collection should be considered, as well as a section on actually implementing a streamlined safety data collection approach.

Per the guidelines, any selective safety data gathering strategy should be carefully designed and clearly described in the protocol, monitoring plan and statistical analysis plan, and references should be made to ICH E19. And because investigators may be unfamiliar with such an approach, it's important that case report forms are well designed and investigators trained appropriately, the guideline says. The approach(es) should also be described in relevant documents when safety findings are presented.

Regulatory Update

The EMA is the first of the ICH member regulators to adopt the new guideline.

Read the full ICH E19 guidelines here: https://bit.ly/3T1QPOx.

FDA Shares Ethical, Trial Design Considerations for Pediatric Participants

The FDA has published draft guidance outlining an ethical framework for involving children in clinical trials of drugs and devices, as well as trial design considerations.

The guidance offers what the agency deems to be fundamental ethical considerations that come into play when children are involved in trials. For instance, the guidance offers IRBs direction on approving trials that intend to enroll children and ways to assess whether an intervention/procedure offers a prospect of direct benefit to them. It also describes risk categories for interventions/procedures that don't offer a prospect of direct benefit and methods to assess risks for those that do, in addition to other items.

The guidance also delves into trial design for both drugs and devices, covering general factors as well as specifics. Overall, trials that involve children "should be designed to maximize the amount of information gained and minimize the number of subjects involved," the guidance advises.

The guidance distinguishes between the differing challenges of drugs and medical devices, noting that devices come with different hurdles because of their varying applications and the range of technology they use.

For devices, the guidance advises sponsors to consider the available clinical data when putting a trial together and notes that trials for indications involving both adults and children may be able to be designed as a single pivotal trial that enrolls both groups. Doing this can reduce the burden of multiple trials and optimize sample sizes.

The guidance also notes that in certain situations, expected benefit and safety can be derived without separate studies of each pediatric subgroup, although "every effort should be made to gather data that adequately address each targeted pediatric subgroup for the proposed indication."

Read the full draft guidance here: https://bit.ly/3SaRVHB.

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that protocols are worded in a way that is easily understandable with no room for different interpretations among personnel or between one site and another. Inclusion of clinical staff in protocol development can help ensure that the protocol makes sense for the sites that will have to put it into practice.

Similarly, providing the best possible staff training, focusing particularly on procedures unique to a specific protocol, can reduce deviations.

What are protocol deviations?

Generally speaking, a deviation occurs any time an employee at a research site or an enrolled participant deviates from the steps outlined in a protocol. But there is no single definition that is used consistently throughout the industry, particularly when it comes to defining the seriousness of different deviations.

One challenge facing researchers and sponsors is the lack of a regulatory definition. The term "protocol deviation" is not defined by either the HHS or FDA human research subject protection regulations. However, the International Conference on Harmonization (ICH) good clinical practice (GCP) guideline (ICH E6) defines protocol deviations as an unplanned excursion from the protocol that is not implemented or intended as a systemic change.[2]

And that definition forms the backbone of the way most organizations define the term, although some may have slightly different working definitions. The Johns Hopkins Medicine Office of Human Research IRB defines the term as "a departure from the approved protocols procedures made with or without prior IRB approval."[3]

It comes down largely to a "know-it-when-you-see-it" situation. Individual research organizations often have their own definitions for the point at which employee or participant behavior differs enough from what the protocol demands to be considered a deviation.

Protocol deviations can occur at any point during a clinical trial, as well. They can be made by the principal investigator (PI) or other study staff either deliberately or by mistake. Participants may also cause a deviation due to misunderstanding or dismissing study expectations. And these deviations can have a powerful impact on clinical trials.

"All deviations reflect a failure to comply with the approved study and as such are instances of potential noncompliance and must be reported" to the IRB, the University of Nevada,

Reno writes in its *Human Research Protection Policy Manual*.[4] "Protocol deviations have the potential to place participants at risk and can also undermine the scientific integrity of the study, thus jeopardizing the justification for the research."

When does a deviation become a violation?

Some deviations are considered more serious than others. Both regulators and research organizations differentiate in some way between major and minor protocol deviations. The more serious deviations — those with the potential to affect participant health and safety or the integrity of study data — are often referred to as protocol violations.

For instance, although FDA regulations do not specifically mention or define protocol deviations, the FDA's *Compliance Program Guidance Manual*, which provides instructions to agency personnel on inspections and compliance determinations, explains that the difference between the two is a matter of severity.[5] A "deviation" is any noncompliance with the study protocol, no matter how minor, while the term "violation" is reserved for serious noncompliance that could lead to participants being excluded for eligibility. This can include, for instance, simple administrative modifications, such as a change to a participant's or investigator's phone number, a change in monitor or staff additions or losses at a given research site.

"Deviations are classed as a violation if the divergence from the protocol materially reduces the quality or completeness of the data, makes the informed consent form inaccurate or impacts a participant's safety, rights or welfare," explained Arun Bhatt, president of Clininvent Research, in a *Perspectives in Clinical Research* article.[6]

Protocol violations may include failure to obtain informed consent before conducting study procedures, incomplete consent, falsifying records or data, failing to report serious adverse events or enrolling participants that don't meet inclusion/exclusion criteria.

The distinction between violations and deviations can vary from organization to organization. For example, the University of California San Francisco (UCSF) Human Research Protection Program (HRPP) policy states that deviations caused by participant nonadherence are not violations, although nonadherence may affect study data or signal a need for changes in the protocol to improve participant compliance.[7] Some research organizations don't make that distinction.

However, UCSF does require that these be documented, as participant noncompliance can affect study data and may

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signal a need for changes in the protocol or informed consent documents or procedures.

Some IRBs and research organizations may use different terms, as well, such as "significant deviations" or "serious non-compliance," according to ORA Clinical.[8]

A second category of deviations covers those that are unlikely to affect participant safety or data integrity. These usually involve minor or administrative deviations by participants, investigators or other study staff. Examples on the participant side could include participants rescheduling one or more visits outside the windows established in the protocol or not completing scheduled research activities — such as participant diaries, surveys or telemedicine check-ins and in-person visits — on time or at all.

Figure 1: Examples of Protocol Deviations vs. Violations

Deviations	Violations
Deviations related to the informed consent document or process: • Use of outdated/expired consent form, as long as there has been no impact on participant safety; • Individual obtaining consent not listed on IRB-approved application; • Missing original signed and dated consent form or missing pages from executed consent form; • Missing subject signature, printed name or date; • Missing investigator signature, printed name or date; • Copy not given to the person signing the form; or • Someone other than the subject dated the consent form. Exceeding the approved sample size/enrollment for a study. Failure to follow the approved study procedure, that in the opinion of the PI, does not affect the participant safety or data integrity: • Study procedures conducted out of sequence; • Implementation of unapproved recruitment procedures; • Omission of an approved research activity on a protocol (e.g., mailing out or collecting quality-of-life surveys, evaluating or documenting performance status), unless the omission could affect safety; • Failure to perform a required lab test; or • Missing lab results; Subject visit/procedure falls outside of protocol timeframe due to the following and there is no increased potential for risk to the subject or any damage to the integrity or completeness of the data there is no increased potential for risk to the subject or any damage to the integrity or completeness of the data: • Inclement weather; • Time and burden; • Rescheduling for other reasons that do not involve safety and do not compromise the integrity of the data; or • Procedures not completed at participant's request. Failure of subject to return study medication. Failure to submit continuing review application to the IRB before study expiration. Any lapse in study approval where there is no intervention or interaction with subjects and no analysis of identifiable information during the lapsed period.	Intentional deviation from the protocol or regulations in a nonemergency setting. Deviations related to inclusion/exclusion criteria, informed consent or enrollment: • Enrollment of subjects not meeting the inclusion/exclusion criteria; • Enrollment of a participant after IRB approval of study has expired; • Failure to obtain informed consent prior to initiation of study-related procedures; or • Inadequate or improper informed consent procedures (including no documentation of informed consent process); Performing study procedure not approved by the IRB. Failure to perform a required lab test that, in the opinion of the PI, may affect subject safety or data integrity. Study visit conducted outside of required timeframe that, in the opinion of the PI, may affect subject safety. Failure to withdraw a subject meeting withdrawal criteria. Any medication error involving dosing, administration and/or preparation of the study drugs. Any lapse in study approval where there is a continuation of research activities (i.e., recruitment, enrollment, procedures, data analysis). Inappropriate destruction of study records or inadvertent loss of samples or data. Failure to follow federal and/or local regulations and policies. Failure to follow safety monitoring plan. Failure to report unanticipated problems to the IRB and/or the sponsor. Deviations by the participant: • Participant did not disclose metal and had MRI; • Participant discontinued study meds; or • Participant missed visits involving study drug. Engagement of new study personnel in human subject research without prior approval. Frequent minor deviations. Working under an expired professional license/certification, debarred or disqualified status. Falsifying research or medical records.

Source: Louisiana State University (LSU) Health Sciences Center Office of Research Services[9]

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On the staff side, examples might include failure to collect an ancillary self-report questionnaire from one or more participants.

Figure 1 provides some examples of how the Louisiana State University (LSU) Health Sciences Center Office of Research Services describes deviations and violations.

While it's common to think of protocol deviations as errors, there are cases in which a protocol procedure may be legitimately and deliberately changed in order to protect participant safety.

Some organizations, including the LSU Pennington Biomedical Research Center (PBRC), include another category of deviation used to cover modifications to the protocol made in the interest of a single participant or small group of participants.[10] For example, medications provided as supportive care might be modified for a participant who is allergic to one of the protocol drugs. But deviations that fit into this category must be preapproved by the sponsor or funding agency and the IRB to ensure that the exceptions don't pose a risk to participants or compromise the integrity of study data.

Documentation of sponsor preapproval and IRB approval of a protocol exception should be maintained in the PI's research study file.

Reasons for legitimate and deliberate changes to operations as spelled out in the protocol may include improving participant safety, increasing or improving study data or gaining additional funding. Examples of this type of deviation include increasing the number of enrolled participants, adding new investigators or other key personnel, adding funding sources and changing informed consent documents.

These planned changes, which also must get prior IRB approval, are known as protocol amendments. FDA regulations at 21 CFR 312.30 define when and how to implement protocol amendments.[11]

While researchers may proceed with minor or administrative amendments with prior IRB and sponsor approval and inform the FDA after the fact, study sponsors must submit any substantial amendments to the FDA. These are any changes to a phase 1 protocol that significantly affects participant safety and to any phase 2 or 3 protocol that significantly affects participant safety, the scope of the investigation or the quality of the study. This could include:

- An increase in the dosage or duration of exposure to the investigational product;
- A significant increase in the number of participants enrolled in a study;
- A significant change to the protocol design, such as adding or dropping a control group; or
- Addition or removal of a new test or procedure intended to monitor safety.

These amendments are considered changes to an investigational new drug (IND) application and should include a brief description and reference by data and number to the submission containing the original protocol, the FDA instructs on its website.[12]

Similarly, a protocol amendment must be made when a new investigator is added to a study already underway; the regulation requires that the sponsor notify the FDA within 30 days of adding a new investigator. No investigational product may be shipped to an investigator until that person is included in the protocol.

The regulation requires that any amendments gain IRB approval and be submitted to the FDA before implementation, with a few exceptions. A protocol amendment intended to eliminate an immediate participant hazard may be implemented immediately provided that submissions to the FDA and the reviewing IRB are sent shortly thereafter.

Addition of a new investigator or additional information about investigators may be grouped and submitted at 30-day intervals. If several submissions with minor amendments — those that cover changes that are administrative in nature or otherwise don't affect participant safety or data integrity — are expected in a timely manner, the agency encourages sponsors to provide all the amendments in a single submission.

How common are deviations?

Protocol deviations, running the gamut from simple participant visit scheduling snafus to failure to obtain proper informed consent, have always been common, based on FDA enforcement activity. And the number of deviations that occur annually seems to be trending upward.

In its January/February 2022 Impact Report, the Tufts Center for the Study of Drug Development (CSDD) reported that protocol deviations rose from 2018 to 2020 compared to the 2013-2015 period, with substantial amendments to protocols also seeing an uptick.[13] According to the CSDD report, phase 3 trials had the highest number of deviations per protocol, with an average of 118.5, which affected 32.8 percent of participants enrolled. Phase 2 studies saw an average of 75.3 deviations affecting 30 percent of participants,

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and phase 1 trials had an average of 8.7 deviations affecting 15.3 percent of participants.

FDA data bears out those findings. The agency's Bioresearch Monitoring Program (BIMO) inspectional observations regarding protocol deviations or failure to follow the investigational plan have consistently been the most common Form 483 citation since at least 2015, according to agency reports. For instance, the FDA's analysis of inspectional findings during 2021 put protocol deviations/failure to follow the investigational plan at the top of the list of most common observations listed on Form 483s.[14]

The same observations topped the agency's list of BIMO observations in 2020 and 2019, as well as every year between 2015 and 2018.[15,16]

What are the consequences of deviations?

Noncompliance can pose significant consequences for sites. The top concern is regulatory noncompliance that threatens participant safety, TechSol Life Sciences noted in a post earlier this year.[17] Significant or persistent noncompliance of any type — but especially those issues that affect participant safety or data integrity — may result in penalties, including an FDA warning letter, disqualification, restriction or disbarment, or even criminal prosecution.

At best, noncompliance will cause delays to studies, as researchers must take time to correct the problems to regulators' satisfaction. This could include time spent reconsenting existing participants or even going through another round of participant enrollment.

The ICH GCP guidance states that investigators should not implement any deviation from or changes to the protocol without the sponsor's agreement and the IRB's prior review and documented approval of the amendment. The exception: when changes are necessary to eliminate an immediate hazard to trial subjects or when changes involve only logistical or administrative aspects of the trial.

Basically, that means that any change to the IRB-approved protocol will be flagged during an FDA inspection. Hewing to the letter of the protocol is one of the most important areas of regulatory compliance for clinical research.

If an observation of this type appears on a Form 483 after a BIMO inspection, regulators could issue warning letters or fail to approve an investigational product. Simply implementing the necessary corrective and preventive action plan in response to a deviation — whether identified independently or during an inspection — can take up valuable time and resources. Remediation actions could include remedial training for investigators and staff, more frequent monitoring of the study and voiding data collected during the period of noncompliance.

Nearly as important is the risk of compromising study data quality. The ICH E9 guidance *Statistical Principles for Clinical Trials* states clearly that protocol deviations "always bear the potential of invalidating the trial results."[18]

Deviations that result in incorrect, and therefore unusable, data lead to additional time and resources to replicate that data, Laurie Halloran, president and CEO of Halloran Consulting Group, noted in *Life Science Leader*.[19] And that can extend the length of the study in order to gather that data or correct other problems, she added. In some cases, researchers may need to enroll additional participants to make up for invalidated data.

In some cases, deviations may lead to protocol amendments, which can also delay trials. CSDD noted in an Impact Report earlier this year that timelines for protocols with three or more substantial amendments — which can be a result of widespread deviations — are nearly three weeks longer than the planned treatments and nearly four weeks longer than planned study closeouts. In a 2021 Impact Report, CSDD also reported that mid-study amendments typically delay studies by 30 days.[20]

What are the causes of deviations?

All of the risks and consequences of deviations make avoiding them an important goal for any clinical trial. To do that, researchers must begin with a full understanding of the root causes of deviations. These could include something as basic as a poorly written protocol. If deviations increase as a study progresses, the PI and sponsor would have to consider whether the protocol was clearly written, according to ORA Clinical.

A particularly complex protocol or one that includes one or more novel procedures or expanded eligibility criteria also increases the risk of deviations, Halloran said. CSDD raised this concern in a recent Impact Report, noting that the number of endpoints for phase 2 and phase 3 protocols rose 27 percent from 2009 to 2020, with an average of 20 endpoints and 1.6 primary endpoints.

Additionally, CSDD reported that the mean number of distinct phase 2 and phase 3 protocol procedures rose 44 percent during the same timeframe.[21]

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More procedures, as well as novel procedures that are unfamiliar to investigators, can create more opportunities for mistakes and deviations. Deviations can occur when protocols are difficult to understand or allow for different interpretations at investigational sites, Halloran agreed.

The larger and more global a trial is, the more susceptible it is to deviations. The CSDD report also found that the mean number of countries and sites where phase 2 and phase 3 protocols are conducted has grown substantially since 2009. And deviations may occur because imprecise language leads to different interpretations at different sites, Beth Harper, chief learning officer at Pro-ficiency, said in a recent post.[22]

International differences in culture, language and normal business practices, along with variations in regulatory requirements, can increase the risk for different interpretations, too. Even regional language or cultural differences among countries where English is common can lead to misinterpretations if the protocol isn't carefully crafted.

A study visit schedule that is too rigid, lacking windows of time for participant visits, for example, can also lead to deviations, according to TechSol.

In other cases, deviations — especially repeated deviations — may be the result of lack of oversight by the investigator, sponsor, CRO or IRB, Halloran said.

Staff turnover can also cause deviations if training programs don't ensure knowledge transfer when experienced staff leave and new employees come on board at a site. In fact, Harper suggested, inadequate training in general is a common reason behind protocol deviations.

What are reporting requirements?

Just as researchers must report protocol amendments to the IRB for approval, the deviations that often underlie the need for an amendment have specific reporting requirements. Generally speaking, the PI is responsible for reporting protocol deviations to the study sponsor and the overseeing IRB. Specific requirements may vary among IRBs, so it's important for all sites to understand the requirements for the individual IRBs to which they report.

For instance, the Johns Hopkins Medicine IRB has different requirements for different types of deviations. If a departure from the protocol is needed immediately to protect the life or well-being of a participant, this is classified as an emergency deviation. For these deviations, it is accepted that the study team must act quickly in the best interest of the participant without seeking prior approval from the IRB. For these deviations, the sponsor and IRB must be notified as soon as possible and no later than five days after the emergency situation occurred. In this case, the IRB follows 21 CFR 812.150(a)(4), an investigational device exemption requirement, for all emergency deviations at studies it oversees.[23]

Another category is major, nonemergent deviations that represent a significant change from the approved protocol. Examples include exceptions to eligibility criteria, the form and manner of obtaining informed consent, and the schedule for administering the investigational product. At Johns Hopkins, the PI must submit a "further study action for protocol event" report and get approval from the IRB before implementing changes.

If a deviation occurs without the IRB's approval, the PI must promptly report it to the IRB. Johns Hopkins considers both an unapproved deviation and failure to report it examples of noncompliance.

A third category covers minor or administrative deviations that do not affect the scientific soundness of the research plan or the rights, safety or welfare of human subjects. Follow-up visits that occur outside the protocol-defined timeframe due to participant schedules or blood samples obtained at times close to but not precisely at the points specified in the protocol are among deviations that fit this category.

These minor deviations should be reported to the IRB on the protocol deviation summary sheet when the continuing review application is submitted.

The University of Nevada, Reno specifies in its *Human Research Protection Policy Manual* that PIs also must determine whether immediate corrections are necessary to protect participant safety as soon as they become aware of a protocol deviation. They also must consider what actions should be taken to prevent future occurrences of the same deviation. The deviation report must include a description and justification for all corrective actions taken without prior IRB approval.

Regardless of specifics, all research sites must report deviations internally and to their IRBs. For instance, UC Berkeley's guidelines for reporting protocol deviations states that whatever the cause, researchers must report all protocol deviations and noncompliances to the university's Committee for Protection of Human Subjects (CPHS) for review.[24] "Such reports are considered possible noncompliances until a determination has been made by the Committee," the UC Berkeley guidelines specify.

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Various sources can submit reports of noncompliance at UC Berkeley. For instance, a participant may submit a complaint or a member of the research team may report an incident. The research organization may also discover noncompliance through formal or informal monitoring and auditing.

When an informal report comes from a source other than the PI, the committee may ask the PI to submit a formal one. Research staff who discover a protocol deviation or noncompliance should notify the PI as soon as possible. However, CPHS recognizes that there may be cases in which staff would prefer not to notify the PI directly; in those instances, sources may raise their concerns with the research subject protection director.

The severity of the deviation can impact the reporting schedule. For instance, UC San Francisco policies call for the PI to report deviations that are undertaken deliberately in order to protect participant safety to both the IRB and the internal HRPP within 10 working days; the same deadline applies to other deviations classified as "major" incidents or violations. Deviations affecting participant privacy or confidentiality are deemed especially risky; these must be reported within 48 hours.

Major incidents involving privacy or confidentiality at UC San Francisco include:

- Failure to properly execute a HIPAA research authorization form due to, for instance, a missing participant signature or date, missing initials next to certain information or accessing items not approved for access or release by the participant;
- Failure to collect a participant signature or date on consent form;
- Mailing, emailing or otherwise communicating identifiable participant information to an unauthorized individual (e.g., incorrect participant or wrong mailing or email address); and
- Failing to redact identifiable participant information sent to a study sponsor.

Additionally, sponsor research agreements may require the PI to notify the sponsor of all unplanned deviations; these may differ from FDA or IRB reporting requirements, so the PI must also understand individual research agreements.

What are the best practices for deviation CAPAs?

A correction and preventive action (CAPA) plan must be part of both deviation reports and responses to warning letters or 483 observations. Different root causes of deviations can require different solutions to correct and prevent them. For example, ORA Clinical recommends a careful review of the protocol's participant visit schedule to ensure that expectations are clear and that participants get windows of time — in calendar days versus workdays — to complete required visits.

In fact, experts agree that a focus on the protocol and how it's written is the most important part of deviation prevention. First, Halloran said, the sponsor must provide a clearly written and executable protocol that can be approved by the IRB. Sponsors can further that goal by making sure to consult investigators, along with physicians and participant groups representing the target population, as early in the protocol-writing process as possible. Their input can help ensure that procedures and timelines are realistic in light of available site resources and that sponsors also carefully consider participant burden.

The protocol should also be written with an eye toward including proactive measures to address the human factor that will be involved in enacting the protocol. This includes use of well-qualified staff in all positions, providing comprehensive and continued training of that staff and allowing for regular communication among the sponsor, CRO and research sites, Halloran said.

Another best practice is for the study sponsor or CRO to develop procedures for documenting deviations at the outset of a study, Halloran said. This will ensure they can consistently track and correct deviations, making monitoring and oversight more effective. Common tools to track deviations include monitoring reports, data management systems, study-specific spreadsheets and clinical database reviews.

Tracking deviations should be paired with procedures to assess them, monitor them across research sites and make necessary corrections.

The deviation tracking and evaluation process must be linked to an established CAPA plan to manage any recognized patterns in protocol deviations at individual sites or across multiple sites. This must include accurate identification of the root cause of the deviations.

Finally, many of the common deviations — related to the performance of particular procedures, enrollment and informed consent, and proper handling of investigational product, for example — are often the result of insufficient training. In fact, retraining staff is a common response to observations of protocol deviations on FDA Form 483.

A focus on ensuring thorough training customized to each specific protocol and its particular deviation risks could help

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researchers avoid deviations from the start of a clinical trial. When developing training, the protocol must be carefully reviewed with an eye toward identifying situations in which deviations are likely to occur, said Jenna Rouse, chief experience officer at Pro-ficiency.[25] When protocol procedures differ from the usual standard of care, physicians, nurses and other staff members who default to their typical habits could cause deviations.

Thorough, protocol-specific training can help ensure that investigators, coordinators and other research staff fully understand how to perform all tasks included in the protocol, Harper said.

Ideally, that training should allow the research staff to critically think through preventive actions rather than just rote learning of the steps in critical processes and procedures, Harper said. She suggested a simulation-based approach to mimic realistic scenarios and guide research staff through not only the steps of each procedure, but also through common issues that might arise during the course of a trial. Researchers could simulate, for example:

- A participant who takes a restricted medication just before the randomization visit;
- An investigational product temperature excursion; or
- A participant who misses a dose or a visit for a planned procedure.

This approach allows research staff to practice a protocol before applying it to actual participants and data, with the associated real-world risks. And in addition to identifying and addressing protocol deviation risks, the scenarios allow research staff to learn how to prevent the issues that lead to deviations before they arise, thus avoiding the additional cost and effort to fix them.

Halloran also emphasized the value of study-specific tools, such as trackers and checklists to help staff stick to the protocol. Researchers can introduce these during protocol training. Tools such as diaries, regularly scheduled reminders and counseling can serve the same purpose for participants.

In addition to initial protocol training, research sites may need to retrain staff after deviations occur. That can be time-consuming and costly. One solution is to carefully evaluate where the problems are occurring, rather than retraining all staff at all sites involved in a clinical trial. That said, in the face of repeat deviations, sponsors often provide remedial training to all staff throughout the study rather than focusing only on certain sites or the individuals who made the errors.

Using analytics to measure and track how individual research staff and sites are following the protocol can help better target remedial training needs, Rouse said.

Performance metrics can produce analytics that allow sites and sponsors to identify and correct problems. If this tracking is done during training, sponsors can identify areas in which deviations are likely to occur and address weaknesses before the study begins, Rouse said.

If a particular site or coordinator struggles with correctly applying inclusion/exclusion criteria when enrolling participants, for example, or has problems with the dosing regimen under the protocol, retraining can be targeted to those sites or individuals. That leaves other sites and staff free to continue with normal conduct of the study and reduces the time and cost of addressing the deviations on a wider scale.

Determining which metrics to track will depend on the elements of the study most likely to impact its success, as well as those where noncompliance would strike the hardest blow. For instance, deviations such as lack of a signature on a piece of paperwork are easy to fix, while deviations in medication dosing or participant procedures would cause more serious problems. For the latter, researchers would have to investigate whether lab technicians and other staff are handling the investigational product correctly and if participant visits and tests are conducted correctly, Rouse said.

Applying analytics to assess performance during protocol training can identify weak areas in a protocol This gives sponsors an opportunity to submit an amendment before a study begins, thus avoiding the delays and related costs of mid-study amendments.

Protocol deviations are and likely will remain a concern for the clinical research industry. Although deviations and violations are an ongoing problem with a long history, sponsors and research sites alike have plenty of motivations to prevent them and implement protocol amendments to address serious or repeated occurrences.

The good news is that there are clear steps that can be taken toward that goal, beginning with fully understanding the common causes of deviations, such as poorly worded protocols, differences in how sites and staff interpret protocols, burdens on participants that can interrupt protocols and inadequate protocol training. Applying best practices — focused primarily on ensuring that the protocol is written in a way that is thorough and that everyone involved in a study can understand and on providing thorough and meaningful research staff training — will help sponsors and sites complete clinical trials without having their work disrupted by deviations.

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"The timeframe to go through each stage of the process varies by company size, but overall, respondents report the later stages of the process — deciding to adopt the change and implementing it — are the most difficult," CSDD noted.

"Many other professions demonstrate a much higher degree of adaptability and willingness to adopt new technologies and new approaches to getting things done," Jenna Rouse, chief experience officer at the clinical trials software firm Pro-ficiency, wrote earlier this year. "And the clinical research industry likewise demonstrated during the pandemic that it is capable of making swift, agile changes to cope with unusual circumstances."[2]

Time to embrace change

Christine Senn, chief integration officer at Centricity Research, noted in an Association of Clinical Research Professionals (ACRP) post earlier this year that all companies have individual tolerance levels for change. But it's not only the most averse that struggle with new technological or operational methods, according to the post.[3]

"We were early adopters of electronic source documents (eSource)," she said in an ACRP post. "Despite everyone in the industry seeming to recognize that eSource gives sites the opportunity to have quality assurance people on staff reviewing quality in real time and gives monitors the opportunity to review data without traveling and to review data more often, we couldn't get any sponsor or [CRO] to help us mitigate the cost through the budget. It would cost far less than paying a person to fly to us, rent a car and get lodging, but they saw the old way as the acceptable way for several years, despite its drawbacks. We see that still with any innovation we try."

Application of new technologies, such as moving from paper surveys to use of tablets or introducing telemedicine options, is one of the first things that comes to mind when discussing change in the clinical research arena. But change management can apply to myriad modifications, such as new policies or procedures and new forms or updated processes intended to improve regulatory compliance or meet new requirements, said Linda Bunschoten, chief marketing officer at Cyntegrity, which provides risk-based quality management products. Many changes involve combinations of all of these factors, she added.[4]

The need to adapt to new technologies and methods for various reasons means that change management has become increasingly important from a regulatory standpoint, as well, Bunschoten agreed. In fact, regulatory expectations for "continuous improvement" means that change is a regular occurrence. So, both study sponsors and research sites must adopt change management processes and procedures.

"The regulatory landscape has changed from being characterized by meeting prescriptive requirements to one focused on reducing risk, advancing outcomes and improving continuously," she said. "These changes require a holistic and proactive mindset which is seldom found within mature bio-pharma organizations that have for decades focused on 100 percent [source data verification (SDV)], passing audits and implementing corrective actions."

Decentralization drives change

Industry changes may be adaptive or transformational, depending on the situation. Adaptive changes are usually minor and made via incremental adjustments that improve clinical processes and workflows without having significant impact on the facility's existing business model, Christopher Gonzales wrote in an OnPage article earlier this year.[5]

Transformative change, on the other hand, involves substantial — and sometimes sudden, as seen during the COVID pandemic — alterations to normal operations. It involves tools used and the way in which people and processes operate. Transformative change management may lead to a complete overhaul of a site's functions and structure, Gonzales wrote.

The latter is well-illustrated by the rapid shift to decentralized trial (DCT) approaches, an ongoing source of change in the research industry. Change management is such an important part of adapting to DCTs and hybrid trials that the Association of Clinical Research Organizations (ACRO) recently released a new change management resource.[6]

The report, entitled *Navigating change during rapid transformation: a question-and-answer resource for decentralized clinical trials*, aims to facilitate the change management required for greater DCT adoption, particularly among sponsors and sites that may hesitate to adopt novel tools and controls necessary for a decentralized or hybrid approach to research.

"The industry has evolved to offer increasingly sophisticated tools and controls to help protect patient safety and safeguard data integrity in decentralized trials," said Jim Streeter, global vice president of life science customer success at Oracle, in an ACRO press release about the report. "Yet expanded adoption of DCTs is impossible if stakeholders are not ready and comfortable in embracing this paradigm shift in clinical research."[7]

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For instance, when patient safety and data integrity don't require onsite assessments and procedures, off-site or remote approaches may be considered, with an eye toward greater patient flexibility. But change management procedures include considering what the patients prefer, the ACRO report noted. Some may prefer to come to a research site while others may want to use home health providers or go to alternative locations, such as local or mobile facilities. Further, their preference may vary depending on the specific assessment or procedure.

Oversight is a chief concern for sponsors and research sites when it comes to DCTs. Thus, change management procedures would have to make sure to address how principal investigator oversight SOPs would change for remote assessments and procedures versus those done onsite.

Each study needs to have a detailed operational plan that clearly explains everyone's role, according to the ACRO report. This plan should include a protocol for oversight, processes to confirm tasks are completed and documented, and processes for site and home health nurse safety monitoring, among other factors.

Technology supports change management

Adoption of new technology is a common impetus for change in clinical research operations. But even for changes that are not tech-focused, technology plays an important role in the change management process.

New DCT technologies driving change include electronic signatures, consent, identity verification, screenings, clinical outcome assessments and patient-reported outcomes in addition to telemedicine, connected devices and digital endpoints.

For example, the Veterans Health Administration (VHA) developed a comprehensive mobile screening technology known as eScreening, which provides a customized and automated self-report health screening via mobile tablet for veterans who receive healthcare in VHA settings, James Pittman and coauthors affiliated with VA San Diego Healthcare System reported in *Implementation Science Communications*.[8] The web-based application that reads from and writes to the VHA electronic medical record (EMR). This allows customized screening and feedback for the veterans using it, real-time alerts for clinicians and EMR data integration.

New telemedicine applications are another common change, especially since the pandemic. However, implementation of telemedicine can pose challenges if insufficient attention is paid to change management, Joanna Kho and her University of Queensland, Australia, colleagues wrote in *BMC Health Services Research*.[9] Despite increasing use of telemedicine, there is little agreement about what specific practices should be involved in changing from an onsite to a telemedicine approach. Rather, a piecemeal approach to the change process seems to be common, based on review by Kho and his coauthors of numerous organizations' reports on telemedicine implementation.

"While digital technology is a necessary prerequisite for DCTs, it is not sufficient for achieving prevalent adoption of DCTs," ACRO said in its report. "To close the gap on DCT adoption, one must examine the human element of change management."

It's essential to address the human aspects of any change, notes Scott Hanlon, editorial director of *Lab Manager* in an article published earlier this year.[10] This requires adequate communication and confirmation that the tools and resources staff need to comply with the change are provided. Management support should also be apparent as employees learn the new technology or process, including some tolerance for mistakes made during the learning process, he wrote.

This approach can also help guide change management decisions to avoid adopting a new software or other technology product just because it's available. Any technology research organizations adopt should provide genuine operational value. For instance, tech tools should improve results, automate tasks or streamline processes, Gonzales wrote.

Existing models help affect change

When a clinical research organization wants to implement new technology or make operational changes, it must focus on managing the change from the old approach to the new. Change management is, in essence, a strategy for evaluating a change to see the expected benefits, as well as possible risks or downsides.

"If your clinical trial organization wants a new technology or workflow to make you more efficient, you need to implement a well-planned change management process from the very beginning," Rachelle Stover, Florence Healthcare solutions engineer, said in an issue of *Clinical Leader* earlier this year.[11]

And these processes don't need to be created from scratch. Many methods already widely used in other industries are readily adaptable to clinical research.

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Additionally, it is rare to find a clinical research organization that does not have at least one employee trained in some of the common management techniques, such as Six Sigma or other processes. These methods can provide guiding principles for change that can be applied to complex and unique contexts, researchers from the University of New South Wales in Australia, led by Reema Harrison, wrote in the *Journal of Healthcare Leadership*.[12]

"Quality improvement methods may offer solutions to overcome barriers related to broad scale implementation of technology in health systems," Pittman et. al wrote.

One such method is a Lean Six Sigma Rapid Process Improvement Workshop (RPIW), which brings together a diverse team to review a problem, propose solutions and develop an approach to implementing changes. Under this practice, preliminary information on current practice is collected prior to a five-day workshop, then analyzed during the workshop by a diverse group of stakeholders. The workshop participants use the information gained to create a future practice — a change that may include new operational procedures, adoption of new technology or other modifications — and a plan to implement that practice, including methods for measurement and ongoing evaluation.

The RPIW typically includes data collection, data analysis, gap analysis, process mapping, factor identification, action planning and cycles of enactment to overcome barriers.

"RPIWs have been used to diminish operational waste, to improve privacy, accuracy of care and efficiency, to standardize processes and to decrease wait times in a variety of healthcare settings," Pittman et al. wrote.

Elliott Liu agreed in a post on the iSixSigma website that applying the Six Sigma method, for instance, could help improve cycle time and reduce errors during the conduct of clinical trials.[13] Three key strategies are necessary to apply Six Sigma within the clinical research arena, he wrote:

- Begin to change traditional ways of conducting clinical trials by campaigning for needed integration initiatives through the use of Six Sigma, with a commitment from top-down leadership;
- Focus on integration of technology and workflow improvement to meet challenges and extend new ventures not possible using conventional isolated implementation of technology or homegrown process improvement methodologies; and
- Provide tested research approaches for quantitative

evaluation of clinical development and process improvement strategies.

One Six Sigma approach that can help achieve lasting change is the ADKAR process, which focuses on:

- Awareness of the nature of the change, why it is needed and what risks are faced without the change;
- Desire to change, centering around how employees perceive the change as beneficial to them or not;
- Knowledge, including training in new processes and tools;
- Ability of the system and personnel available to realistically implement the change; and
- Reinforcement, or actions that will increase the likelihood of sustained change.

A second approach focuses on ongoing communication and collaboration at all levels. The CLARC leadership model assigns responsibility for five key roles that must guide the change management process:

- The communicator, who explains why changes are made and how they impact employees and clients (patients);
- The liaison, who reports to senior executives or other leaders how the change has impacted and is being received by employees and provides employee suggestions regarding ways to improve the change;
- The advocate, a team member or members who demonstrates commitment to the change and promotes a positive attitude;
- The resistance manager, who focuses on understanding and addressing the root causes of change resistance; and
- The coach, who helps employees build the knowledge and skills necessary to master new procedures and/or technology.

Using the ADKAR and CLARC change models, nursing executives in one healthcare system developed a new approach to meeting the demands of increased patient volume as well as decreases in available workforce.[14] Processes varied among individual hospitals, but the core principles and implementation strategies were the same throughout the system. The result was a transition from primary to team nursing, a step needed to better manage large patient volumes due to COVID-19.

Managing the change through the established ADKAR model helped guide the process more smoothly and quickly. And addressing issues that arise promptly is important for sufficient staff engagement with the change. For instance, when some staff exhibited resistance because they didn't feel their roles were clear, nursing leaders worked through those concerns and helped more clearly define staff members' patient care responsibilities within the team nursing model.

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Concrete steps aid change management

Experts differ a great deal on how many strategies or steps are required to achieve change management success.

One often-referenced change management approach is an eight-step process developed by Harvard Business School's John Kotter:

1. Create a sense of urgency within the team, highlighting the consequences of not changing;
2. Form a multidisciplinary guiding coalition that includes key stakeholders to move the change forward;
3. Create a vision statement and strategic initiatives to guide the coalition, allowing for accountability in decision-making;
4. Communicate with all employees, balancing support for and opposition to the change and allowing for feedback, including resistance, debate and even errors;
5. Remove barriers to implementing the change, including any institutional obstacles;
6. Establish achievable goals that can be executed and celebrated as short-term wins as a reward for team contributions and to build momentum towards change adoption;
7. Continue making necessary institutional changes — such as hiring, promotions, new tools, training and other systemic improvements — as the coalition moves forward; and
8. Make recommendations that will boost cultural and institutional change, such as forming new habits and unlearning old ones with help from training and reward systems for employees, while monitoring performance with an eye towards continual improvement.

These steps don't necessarily proceed in order, but the later steps cannot be achieved without the earlier ones, Louise Keogh Weed, program director of the Leadership Strategies for Evolving Health Care Executives program, noted in a 2021 article by Katherine Igoe on the Harvard School of Public Health website.[15]

And two additional core concepts are needed to support those steps and ensure an effective change management program, she added. The first of these she deemed the three dimensions of success: results, process and relationships. It's important to remember that these three are equally important. While there is a tendency to focus on results, how those results are obtained and how team members work together are equally important.

The second is Kurt Lewin's stage theory of change, which involves a circular process of "unfreezing" the status quo, "changing" operations and "refreezing" with the changes in place. This process should repeat as needed whenever an organization identifies a need for change or opportunity for improvement. These concepts tie in with the notion of ongoing improvement and continual monitoring that is prevalent within the biopharma industry.

Other approaches are also available. OnPage's Gonzales outlined five key steps specific to change management in the research arena:

- Define the change, including identifying areas that require minor or significant alterations;
- Develop a plan that details the objectives of the change, any new roles and responsibilities, and key performance indicators (KPI) to measure success;
- Implement the plan, including providing training to employees, as well as anticipating obstacles and generating solutions to overcome them;
- Stick to the plan, even in the face of expected or unexpected obstacles or personnel resistance, including offering rewards, if necessary, for welcoming changes; and
- Analyze the outcomes and results by using the pre-established KPIs to determine if objectives have been met.

Similarly, the *Lab Manager* article describes a change management process focused on laboratory operations that can also be applicable to clinical research sites:

- Define the opportunity, which is something that must be highly likely to improve operations in some way;
- Communicate the envisioned change with the rest of the organization, including directly affected employees and line management;
- Build support for and commitment to the coming change;
- Implement the change, with a plan to monitor results and course-correct as necessary; and
- Sustain the change with ongoing monitoring using KPIs and a continual improvement philosophy.

Regardless of how many specific steps an organization opts to include in its change management procedure, the overall process can be viewed as occurring in three phases, Kho et al. suggested. The first phase involves preparing for change. This phase would include establishing plans for implementing the change and gaining leadership/management support and commitment to the change. Also part of the planning phase is

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identification of "champions" — enthusiastic individuals who initiate and promote the new procedures or technology — for the change. These people will be important in engaging partners and stakeholders.

In the case of new technology, the planning phase should yield a clear and well-articulated vision of how the technology will work within the organization and how the switchover will be accomplished. According to Kho et al., for instance, four operational practices must be included for optimal implementation of telemedicine. These include a needs assessment, equipment and application compatibility assessment, assignment of coordinating roles and confirmation of adequate resources.

The second phase should focus on managing the change. Several key strategic practices are necessary for this phase, starting with clear communication of changes and ensuring that affected stakeholders fully understand the new technology or methods. Change leaders need to gain stakeholder trust and acceptance and continue engaging them throughout implementation of the change, otherwise resistance is likely to develop. Leaders also need to facilitate a sense of ownership of the new service, such as giving facilities some discretion in when and how a new approach or technology is used.

Finally, the change must be monitored for success even after it is fully implemented, with flexibility maintained to respond to feedback from affected employees and stakeholders.

And two operational practices are especially crucial for the second phase, Kho et al. said: providing adequate training and education, and developing new work protocols and processes to work with the changed operations.

The final phase involves reinforcing the change by continuing to engage partners and stakeholders and providing procedures for the ongoing evaluation of changes, with flexibility to allow modifications if problems develop or improved ways of operating are identified.

People, process and technology at the core of change

For clinical research, it's important that improvement procedures be both process-based, focused on how people work, and data-based, looking at how data must move among participants. But improvement efforts should mostly focus on improvement of the procedures that projects follow, not the projects themselves, Liu advised.

There is a common tendency within the industry to manage the process first and then consider its effects on people.

This is particularly evident when an organization faces firm deadlines for applying a new technology, such as a clinical trial management system that reorders existing workflows as part of a larger change process, Pam Weppler, a process and change program leader at Rho Inc., told *Clinical Researcher*.[16]

Staff must fully understand what a change means to them personally, especially when change management programs redefine risk management or make other radical adjustments in an organization, Weppler added.

Clinician engagement has proven crucial to successful, sustained change in the general healthcare industry; this is likely true for the clinical research niche, as well.

"Change is naturally challenging for humans, particularly when it is rapid and ongoing," Harrison et al. said. "Those directly and indirectly affected by change are more likely to commit to and embrace change when they contribute to the decision-making about the change and understand why and how the change is going to improve patient and/or staff experiences or the healthcare environment."

But successful change management may mean reducing hierarchy to ensure stakeholder input, Igoe wrote in the Harvard School of Public Health article. That might mean including physicians and medical assistants in solution development and "having both perspectives matter equally in the context of problem-solving."

"Adept organizations give people room to adjust by starting early and introducing the impact gradually when possible," she wrote, adding that gradual implementation isn't always an option.

During changes related to a clinical trial program consolidation at Rho, for instance, company leaders introduced the change by hanging process maps on hallway walls. They invited internal stakeholders to write suggestions and concerns on them.

"The maps first appeared as a curiosity, attracting a few passersby who scanned a list of questions about the new process," Igoe wrote. "The crowds grew as people gathered to offer feedback, attracting others who wanted to express their opinions, too."

Other participants are also important to change management. IT vendors, for instance, can help by providing technology that supports seamless communication among all parties, thus allowing easier adaptation to change.

Centricity's Senn, likewise, emphasized the importance of people in change management strategies. The first strategy is forming a change management team. Key players on the team should include a change management leader who is knowledgeable and

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passionate about the proposed change, a member of the executive leadership team, employees who embrace the change and "super users," or employees already comfortable with the technology or procedures involved in the change, she told ACRP.

These individuals should have a concrete understanding of the change and why it should occur. They also need to be willing to share this information with other employees and executives.

The second strategy is to obtain buy-in from the organization's leadership. This means someone from upper management must be involved in every step of change implementation. These executives can set a positive tone for adoption of the change and keep the process moving forward as well as making sure that the necessary resources are available to implement the change.

And the final strategy is to engage all potential stakeholders, including research staff, patients and study sponsors. A stakeholder should be considered any individual impacted by the change. If a change involves technology, for instance, any end users of that technology would be considered stakeholders. Having these people actively engaged in the change management process will help with early identification of potential stumbling blocks.

Outside help can also support the change management process. If a research organization aims to adopt new software, for instance, an experienced software vendor can help evaluate the best options for that organization as part of the change management process.

Pitfalls and barriers can hamper change

Regardless of how it's achieved, any change management process must be designed to avoid common pitfalls that can trip up planned changes.

One such pitfall to avoid, Igoe noted, is the sense that everything is urgent. A sense of urgency is the first of Kotter's steps, but in healthcare and clinical research, the stakes are high. Moving fast is not always necessary.

A related challenge is the temptation to skip the earlier steps in the process and jump straight to execution in order to act more quickly, described in steps five and six. Doing this can increase resistance from employees who feel left out of the process, making them more likely to resist change.

But excessive rigidity is also a potential pitfall. For example, if a change coalition tackles a particular problem and

while doing so realizes that its focus is on the wrong issue, it may need to back up and realign the vision statement or change the goal to reflect the new information. Forcing the team to stick with the same approach without flexibility means that the intervention ultimately won't be as effective in meeting the intended goals.

Rouse pointed to three additional barriers to change in the clinical research industry. The first is regulatory uncertainty. The heavily regulated industry tends to fear that any changes, even those with potential benefits, could lead to problems with the FDA. The results of the CSDD survey also listed lack of regulatory clarity as a major barrier to adoption of innovations. Regulatory and legal departments at research sites and sponsor companies, for instance, may resist new technology or methods due to vagueness in current regulations and guidance.

"Even if a new technology or approach could make part of an operation cheaper, any uncertainty or risk or even lack of proven effectiveness can be enough to prevent a research site or other organization from even considering adoption of new technologies or other changes," Rouse said.

However, the FDA and other global regulators were flexible during the COVID-19 pandemic, Rouse noted. The FDA even issued several guidance documents explaining how new technologies and decentralized approaches would fit into the existing regulatory environment.

In fact, change management procedures are an important part of the risk-based management approach that the FDA and other regulators expect, the nonprofit Transcelerate Bio-Pharma noted in a paper on its website.[17]

Each element of the protocol, including those that allow for patient flexibility, must face a rigorous risk assessment, including mitigation measures when a risk to patient safety, data integrity or protocol compliance may arise, ACRO noted in its report.

A second barrier is concern about the workloads imposed on research staff. Many employees already face enormous workloads as clinical trials become more complex and new technology is adopted. Technology burnout, especially, is a complaint heard at research sites, CROs and sponsors alike. With that in mind, organizations have become more reluctant to add yet another login, password and training to their staff's workload.

Addition of operational burden to research sites is a concern common to many types of change, including those related to incorporation of decentralized research approaches. For instance, technology overload for already-busy staff and

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the time and resources needed for training in new technology could add burdens and must be considered and managed.

Similar concerns can exist for patient burden, especially when patients must learn to use specific technologies for self-reported outcomes or e-diaries or wearable devices that automatically track and report key health indicators.

The training needed for new systems, technologies and approaches can be seen as a burden itself. But training and other educational measures are critical for both risk-based management generally and the change management component specifically. Open communication among site staff and management, sponsors and CROs is also necessary for effective change management. In particular, when a change is sponsor-initiated, the sponsor company needs to be willing to modify its methods to meaningfully address concerns raised by sites, Transcelerate recommended.

Appropriate training is also important, *Lab Manager*'s Hanlon said, because it will help staff be confident that they can successfully execute the new approach. Lacking that confidence, they could be more likely to revert to more familiar approaches.

Simulation-based training that generates immediate information about staff performance in real-life scenarios, for instance, could reduce the amount of time research staff have to spend on training, Rouse said. This type of training could be tailored to the needs of individual jobs and allow research staff to whip quickly through skills in which they are already proficient and focus on new procedures or technologies where they need more guidance, she said.

And the third barrier lies with uncertainty about the potential benefits and impacts of adopting innovations, according to Rouse. The CSDD survey also pointed to the challenge of return-on-investment assessments as a barrier to innovation in the industry. Sponsors and sites alike want to see any changes have some sort of defined benefit and a strong assurance that they will not cause negative consequences.

It's well-established that changes in one aspect of a clinical trial can impact other aspects. This can be costly not only from the standpoint of money and time but also from potential regulatory or legal consequences. And this ties back into the overall risk-averse nature of the clinical research industry.

"If something has been done the same way and there were no serious problems — e.g., there was no regulatory fallout, no patients were harmed, no one got fired — organizations may be [loath] to take a chance with a new technology or approach," Rouse wrote.

And some specific technologies or methods may face unique barriers, as well, Kho noted. For instance, when looking at telemedicine, limited reimbursement and current licensing laws may pose barriers to its use at some organizations. Common barriers include lack of technological compatibility, resistance to change, lack of adequate reimbursement, lack of usability and medical, legal and liability concerns, Kho et al. said.

All of these concerns relate to change management. An effective change management system must account for the various barriers as it lays out a step-by-step process to identify a challenge, decide on changes and execute them successfully.

But many research sites lack efficient, established procedures for evaluating and implementing change. That also means that the mere process of moving to adopt new technology or operational approaches could improve change management processes for many organizations, making it both simpler and safer for them to adopt future innovations.

And just as there are barriers to innovation in clinical research, there are enabling factors as well, Kho et al. said. For instance, enablers of telemedicine may include development of organizational protocols, adequate funding and support, user training plans and change management plans.

Change is an eventuality that all clinical research organizations must be ready to handle. Whether change comes in response to societal, business or regulatory demands, researchers will be expected to embrace new technologies or approaches while still maintaining risk-based quality assurance in their clinical trials.

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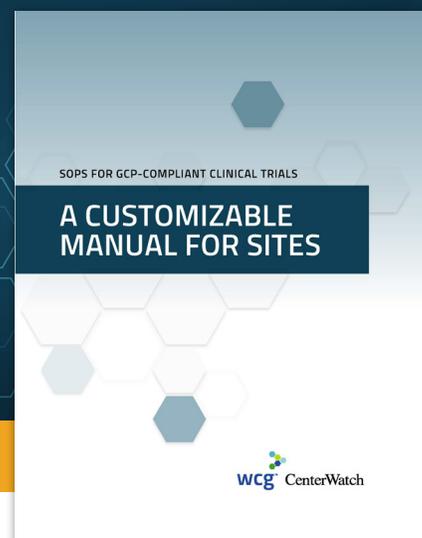
Exam for Continuing Education

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Protocol Deviations

1. Which of the following is the most accurate description of a protocol deviation?
   a. Any change that puts patients at risk of death or serious injury.
   b. Any unplanned deviation that is not intentional systemic change.
   c. Information that is not adequate to support a proposed clinical trial.
   d. Failure to follow ethical standards while conducting clinical research.

2. Which of the following statements about protocol deviations is true?
   a. They are typically caused by patients.
   b. They can cause costly delays to trials.
   c. They are typically minor.
   d. They are rarely intentional.

3. Under what circumstance is a protocol change typically categorized as a protocol violation rather than a deviation?
   a. When the change results in an FDA citation.
   b. When it threatens patient health and safety.
   c. When it fails to follow good clinical practice.
   d. When it is not reviewed and approved by an IRB.

4. Which of the following is an example of an appropriate operational change?
   a. Changing out-of-date enrollment criteria.
   b. Changing out-of-date consent forms.
   c. Enrolling new patients.
   d. Dropping a control group.

5. True or false: Protocol amendments are considered changes to an investigational new drug (IND) application and must be reported to the FDA.
   a. True.
   b. False.

6. Which of the following trial phases are most likely to see substantial protocol amendments?
   a. Phase 1.
   b. Phase 2.
   c. Phase 3.
   d. Change is consistent across trial phases.

7. Which of the following is a consequence of "significant or persistent" protocol deviations?
   a. They may result in federal penalties.
   b. They may require enrolling more patients.
   c. They may result in criminal prosecution.
   d. All of the above.

8. Which of the following increases the likelihood of protocol deviations?
   a. A particularly complex study protocol.
   b. Failure to document protocol deviations.
   c. A decrease in the number of study endpoints.
   d. Failure to report deviations to the IRB or FDA.

9. Which of the following statements about protocols is true?
   a. A clearly written and executable protocol must have IRB approval.
   b. Separate protocols should be written for sites in other countries.
   c. Protocols should not include the use of novel procedures.
   d. All of the above.

10. Which of the following tactics is most effective for protocol deviation reduction?

   a. Conduct training after a protocol deviation observation on FDA Form 483.

   b. Customize training to each specific protocol and its particular deviation risks.

   c. Conduct daily protocol deviation training.

   d. Conduct self-guided protocol training.

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11. On average, how long does it take for clinical research organizations to adopt clinical trial innovations?

   a. One year.

   b. Three years.

   c. Four years.

   d. Six years.

12. Why is change management important from a regulatory standpoint?

   a. Regulatory agencies require researchers to use change management during trials.

   b. Regulatory agencies focus on data verification, audits and corrective actions.

   c. Regulatory agencies expect continuous improvement from both sites and sponsors.

   d. Regulatory agencies expect researchers to meet prescriptive requirements.

13. Which of the following is an example of a transformative change?

   a. An overhaul of a research site's functions and structure.

   b. An adjustment to improve clinical processes and workflows.

   c. An assessment or procedure that requires an onsite visit.

   d. A new hire arrives or an existing employee departs the study.

14. How can change management help researchers make decisions about adopting new technology?

   a. It identifies the maximum number of tools and software that a site can adopt.

   b. It identifies tools and software that can provide operational value.

   c. It identifies gaps in training on new tools and technologies.

   d. It identifies sources of funding for new tools and technologies.

15. True or false: Training staff on change management is important because it is rare to find employees who are already trained in common techniques.

   a. True.

   b. False.

16. ADKAR is an acronym for:

   a. Adoption, dignity, knowledge, adaptability and research.

   b. Authorship, desire, knowledge, adaptability and research.

   c. Awareness, desire, knowledge, ability and reinforcement.

   d. Academia, decentralization, knowledge, ability and reinforcement.

17. Key roles in the CLARC leadership model include which of the following?

   a. Researchers.

   b. Clerical staff.

   c. Advocates.

   d. Leaders.

18. What step must be taken after a change has been implemented?

   a. Develop a vision of how the change will work in the organization.

   b. Define the opportunity to improve operational efficiency.

   c. Create a plan to monitor the results of the change.

   d. Conduct ongoing monitoring of results of the change.

19. Which of the following describes how to engage stakeholders in a proposed change?

   a. Involve them after the proposed change has been implemented.

   b. Explain how the proposed change will impact them personally.

   c. Engage only people who are directly affected by the change.

   d. Increase emphasis on hierarchy to simplify stakeholder input.

20. Which of the following best describes a tactic to overcome barriers to change?

   a. Emphasize urgency and move quickly.

   b. Begin with the execution of the change.

   c. Focus exclusively on a single problem.

   d. Conduct a rigorous risk assessment.