A Pragmatic Guide for Migrating Investigator Sites to ICH E6(R3)

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Table of Contents

Introduction

As has been widely publicized, the newly adopted third revision to the International Council for Harmonization Guideline for Good Clinical Practice (GCP), or ICH E6(R3), is a major reworking over the previous R2 version in both structure (rearranging sections) and content (clarifications of previous content and a new section on data management). These changes are not necessarily innovating the clinical trials industry but are largely driven by the need to accommodate the existing evolution of clinical trials—notably in terms of trial designs, the more prevalent use of decentralized and remote elements, and the utilization of advancing technology. Also highly publicized about R3 is the changes in everyday terminology (e.g., shifting to the word "*participants*" instead of "*subjects*" to reflect the more active participation of those enrolling in clinical trials and shifting to the terms "*essential records*" and "*source records*" instead of "*essential documents/source documents*" to reflect that information can be housed in many different settings and not just predetermined documents). Just as R2 was designed for many different types of stakeholders, R3 also includes guidance not germane to the core operations of investigators/sites. These include sections for institutional review boards/institutional ethics committees (IRBs/IECs), sponsors, protocol writers, Investigator Brochure developers, and data managers. This report focuses less on the mile-wide/inch-deep overall analysis of R3 and its impact on all stakeholders. Instead, it focuses more on exactly what investigator sites need to do as their leaders roll up their sleeves and convert their policies, checklists, quality improvement tools, and other materials and operations from R2 to R3.

Under R3's new organization schema, the sections most related to investigators/sites are renumbered from R2; specifically, R3's Section II (Principles of GCP), Section III.2 (Investigator), and Appendix C (Essential Records for the Conduct of a Clinical Trial). While these three sections are most critical to site operations, it remains strongly encouraged for site leaders to read the entire R3 document—not just for awareness of the overall impact, but for pragmatic reasons as well; specifically when requests are made from external stakeholders for new or altered tasks attributed to R3. When faced with confusion over the necessity of a new or altered task, the site's asking for the supporting section number(s) in R3 will help facilitate a more meaningful discussion on validating the requirement as an R3 requirement, how the requested tasks help support that section, and if there are any alternate solutions that can achieve all stakeholder goals.

Fortunately, there is no *major* infrastructure that R2-compliant sites must enact or disassemble to become compliant with R3. Generally speaking, if the site becomes compliant with R3, it remains compliant with R2. Thus, an R3-compliant investigative site can still coexist with sponsors and contract research organizations (CROs) that remain on R2. However, the reverse is not true, as R3 requires additions and clarifications that sites need to be aware of that will likely affect daily work at a more micro-level, and perhaps require changes to one or more local policies and/or quality checklists sites may have developed. Below is a table highlighting the most relevant changes sites should be aware of to effectively transition to R3. By no means is this document 100% comprehensive, but it provides awareness of the most likely changes needed at the site level.

Key Differences Between ICH E6(R2) and ICH E6(R3) Applicable to Investigator Sites

- For full awareness of the requirements put forth by R3, it's advisable to read the full document.
- Although not organized by R3 in such a manner, the elements called out below are grouped thematically for convenience purposes only.

INVESTIGATOR OVERSIGHT AND STUDY MANAGEMENT

R2	R3	COMMENTS
"The investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site." [4.2.5]	Clarified with: "The investigator may be supported by the sponsor in the identification of a suitable service provider(s); however, the *investigator retains the final decision* on whether the service provider intended to support the investigator is appropriate based on *information provided by the sponsor.*" [2.3.1]	For example, if the sponsor/CRO says the investigator must use the sponsor/CRO-contracted home health service to conduct some participant visits, the investigator/site has the right to say "no" to that vendor and provide an alternative solution for protocol compliance. Of course, the sponsor has the ultimate decision in site selection and thus can refuse to select the site as a result of this declination.
Regarding Delegation: "The investigator is responsible for supervising…" [4.2.5] and "The investigator should maintain a list…" [4.1.5]	Added: "Investigator retains the ultimate responsibility…" [2.3.1] "Delegated activities should depend on the nature of the delegated activities and be proportionate to the importance of the data being collected and the risks to trial participant safety and data reliability." [2.3.1] "Documentation of delegation should be proportionate to the significance of the trial site-related activities." [2.3.3] "In situations where the activities are performed as part of clinical practice, delegation documentation may not be required." [2.3.3]	Some countries have already issued guidance on this issue. For example, guidance by the U.S. Food and Drug Administration (FDA) on decentralized trials states that certain local healthcare providers (HCPs) (i) only provide trial-related services that are part of routine clinical practice and (ii) do not require detailed knowledge of the protocol or investigational product. Under those limitations, these HCPs are not sub-investigators, nor do they need to be listed on a delegation of authority log. This is not to say that the investigator is still not ultimately accountable and that the HCPs have obligations (e.g., to report adverse events and the study data they gather), only that HCPs do not need to be listed on any kind of study logs in these situations.

R2	R3	COMMENTS
"Each individual involved in conducting a trial should be qualified by education, training and experience to perform his or her respective task(s)." [2.8]	"Trial-related training to persons assisting in the trial *should correspond to what is necessary* to enable them to fulfil their delegated trial *activities that go beyond their usual training and experience*." [2.3.2]	This is a slight clarification to indicate that training should be relevant to the roles of individuals. Specifically, training should be role-based, meaning study personnel should not complete unnecessary training just to check boxes but more importantly, not be undertrained based on their role. External entities that require unnecessary training should have this section called to their attention.
"The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol." [4.5.3]	"The investigator should document all protocol deviations *[noting deviations may be communicated to them by the sponsor]*. In either case, the investigator should review the deviations, *and for those deviations deemed important*, the investigator should explain the deviation and implement appropriate measures to prevent a recurrence, where applicable." [2.5.3]	This addition reflects two things. The first recognizes that the sponsor may be knowledgeable of deviations prior to the investigator becoming aware. These deviations, although discovered by the sponsor, are not immune from documentation at the investigator level. The second and more complex is the reference to the documentation and development of corrective/preventative action plans for protocol deviations. While all deviations still need to be documented, R3 is stating that only "deviations deemed important" necessitate a corrective/preventative action plan. R3 defined an "important deviation" as essentially determined by the sponsor—specifically: "The sponsor should determine necessary trial-specific criteria for classifying protocol deviations as important. Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy and/or reliability of the trial data or that may significantly affect a participant's rights, safety or wellbeing." Thus, although in an ideal world there would be no deviations, should and when they occur, they must be documented and assessed, and the response must be commensurate to the risk/importance.

R2	R3	COMMENTS
"A qualified physician (or dentist, when appropriate), who is an investigator or a sub-investigator for the trial, should be responsible for all trial-related medical (or dental) decisions." [4.3.1]	In addition to physician or dentist, adds "or *other qualified healthcare professionals in accordance with local regulatory requirements*." [2.7.1(a)] In addition to sub-investigators, adds "*Other appropriately qualified healthcare professionals may be involved* in the medical care of trial participants, in line with their normal activities and in accordance with local regulatory requirements." [2.7.1(b)]	This simply expands medical care scenarios to include the involvement of other qualified providers beyond just physicians and dentists (e.g., nurse practitioners, pharmacists, psychologists, etc.). It also clarifies that one does not need to be a sub-investigator to provide medical care (e.g., HCPs).
"It is *recommended* that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed." [4.3.3]	"The investigator *should inform* the participant's primary physician about the participant's involvement in the trial if the participant has a primary physician and agrees to the primary physician being informed." [2.7.1(d)]	This is taking a stronger stance of the investigator notifying the participant's routine care physician(s) of their trial participation by shifting the language from "recommended" to "should." Note that, although "should" is not "must," the reasons not to do so should outweigh the benefits derived from the coordination of care and relationship/trust building between the primary care community and the research site/ investigators.

INFORMED CONSENT CONTENT

R2	R3	COMMENTS
Consent Element: "The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant." [4.8.10(g)]	Adjusted to Read: "The reasonably foreseeable risks or inconveniences to the participant and, when applicable, the participant's *partner*, to an embryo, foetus or nursing infant." [2.8.10(f)]	Adding that the consent risks should also disclose the risks to a participant's partner when applicable. Note that this is technically only describing the risks to the participant for their choice and does not require the partner to co-consent (although an IRB may add that requirement if it chooses).
Consent Element: "…participation is voluntary, and the subject may refuse to participate or withdraw from the trial, at any time…" [4.8.10(m)]	Adjusted to Read: "……participation is voluntary, and the participant may decide to stop taking the investigational *product* or withdraw from the trial at any time…" [2.8.10(l)]	A minor clarification to indicate that, in addition to refusing to participate or withdrawing from the study, the participant can also stop taking the investigational drug. Of course, this may mean that they will have to withdraw from the study, and reasons or procedures for withdrawal are addressed in other consent form areas (see below).
Consent Element: Authorizing direct access to original medical records (e.g., for monitor(s), auditor(s), IRB/IEC, regulatory authority(ies)) without violating confidentiality. [4.8.10(n)]	Adjustment: When allowing direct access to *source records*, confidentiality will be safeguarded and access "*limited for the purpose of reviewing trial activities and/or reviewing or verifying data and records by the regulatory authority(ies) and the sponsor's representatives*." [2.8.10(o)]	This is making a commitment to the participants that, when their medical records are viewed/accessed by monitors, the monitors are limited to monitoring and cannot use the information for other purposes (e.g., to create secondary databases, marketing, etc). Of note, contrary to the opinions of some who put forth otherwise, "direct access to source records" does not require monitors/auditors to have their own log-in IDs, nor does it exempt them from adhering to the site's processes and/or signing required agreements to obtain them. R3 defines "direct access" as "permission to examine, analyse and verify records that are important to the evaluation of a clinical trial and may be performed on-site or remotely," which can be accomplished in many ways beyond providing electronic health record (EHR) log-in IDs to monitors.

R2	R3	COMMENTS
Consent: No real equivalent statement. "Follow-Up" requirement limited to duration only, and not procedures.	New Consent Element: "The follow-up procedure for participants who stopped taking the investigational product, withdrew from the trial or were discontinued from the trial." [2.8.10(m)]	R3 requires more detailed descriptions of what the participant must go through should they withdraw, be discontinued, or stop taking the investigational product. For example, can they stop cold turkey, or do they need to be tapered off? What kinds of visits/procedures will be required for proper closeout?
No real equivalent statement	New Consent Element: "The process by which the participant's data will be handled, including in the event of the withdrawal or discontinuation of participation in accordance with applicable regulatory requirements." [2.8.10(n)	In furthering the impact of withdraw/discontinuation, R3 requires more detail on disclosing what happens to the participant's data after such withdraw/discontinuation.
No real equivalent statement	New Consent Element: "That trial results and information on the participant's actual treatment, if appropriate, will be made available to them should they desire it when this information is available from the sponsor." [2.8.10(v)]	This new element is intended to make commitments to the participant about if/when unblinding will occur for studies where the participant is blinded to the intervention(s) during the study.

INFORMED CONSENT PROCESS AND DOCUMENTATION

R2	R3	COMMENTS
No real guidance on electronic or remote consent	Supports *paper or electronic* means of obtaining and documentation. [2.8.1] Supports obtaining consent *remotely* where appropriate but "the investigator should *assure themselves of the identity of the participant* (or legally acceptable representative)" [2.8.1(e)] Supports "*varied approaches* (e.g., text, images, videos and other interactive methods)" [2.8.1(c)] "When computerised systems are used to obtain informed consent, trial participants *may be given the option to use a paper-based approach* as an alternative." [2.8.1(c)]	Essentially R3 revisions accommodate electronic and remote consent and provide guidelines for its use. Note the statement that if electronic consent is used, the site may (not must) have a paper-based option. Note that a paper-based system is always a good fallback to have in place in the event the technology does not work at the time it is needed for assisting with and/or documenting consent.
"The communication of [new information that may be relevant to willingness to continue] should be documented." [4.8.2]	"The communication of [new information that may be relevant to willingness to continue] *and confirmation of the willingness to continue trial participation* should be documented." [2.8.2]	This puts a new obligation on investigators to not just provide (and document the provision of) the new information that may affect the participant's decision to continue in the study, but to now also confirm (and document such confirmation) that the participant is willing to continue. Many sites were doing this anyway as a best practice, but it is now codified in GCPs.

R2	R3	COMMENTS
[Consent] "should be revised whenever important new information becomes available that may be relevant to the subject's consent." [4.8.2]	"[New information] should be assessed to determine if re-consent is needed (e.g., depending on the stage of the trial, consideration should be given to whether the new information is relevant only to new participants or to existing participants). If re-consent is needed (e.g., information on emerging safety concerns), new information should be clearly identified in the revised informed consent materials." [2.8.2]	This essentially focuses on the content and process of re-consenting participants. As to the content, it is stating that new critical information should not be just buried in a consent form but highlighted in some manner as the new information. As to the process, R3 endorses more pragmatism and flexibility in the need-for and how-to of reconsenting. For example, if (not due to safety concern) a new questionnaire was added in Visit 3, it may not be necessary to reconsent participants that have already passed Visit 3. Another example may be that a change in the contact number of the investigator may not require a full 20-page consent form be signed if that is the only change, but perhaps only a one-page notice. Of course, sites will be subject to IRB oversight of the consent content, forms, and process. Nevertheless, a site can better advocate for more pragmatic and relevant re-consenting based on this provision.
When an impartial witness is required, they "should be present during the entire informed consent discussion." [4.8.9]	When an impartial witness is required, they "should be present (*remotely or in-person*) during the entire informed consent discussion." [2.8.9]	It is rare for most sites to do studies that require an impartial witness, but when doing so, R3 clarifies that the witness can do so remotely.

R2	R3	COMMENTS
No real equivalent statement for consenting minors when reaching the age of consent	"A process for consent should be considered if, during the course of the trial, the minor reaches the age of legal consent, in accordance with applicable regulatory requirements." [2.8.12]	When involving research with those not of legal age to consent for themselves, this clarifies the obligation that consent needs to transition to them personally once they reach the age where they consent for themselves. Although R3 states there "should" be a process, legally there must be one based on the site's local laws regarding if/when children can consent for themselves. Of note, although not called out by R3, the same principle may apply to other situations where a participant is not capable of the initial consent but later in the study becomes able to provide consent (e.g., a study in an emergency setting where the participant was unconscious or mentally incapable of providing consent upon arrival, initial consent was provided by their legally authorized representative and the participant later became conscious and/or lucid enough to consent for themselves).
"…the investigator should make a reasonable effort to ascertain the reason(s) [for withdrawal]." [4.3.4]	Elaborates with, without unduly influencing the participant's decision, "to determine if there are ways to address the concerns [i.e. to reconsider]" as well as "should consider explaining to the participant the value of continuing their participation…" [2.9.2]	This one codifies that it is acceptable for investigators (or their delegates) to …in a non-coercing, non-overly influencing and respectful manner… (i) do a little digging into the reasons of the participant wanting to withdraw in an effort to identify and make any reasonable and protocol-compliant attempts to retain them and (ii) provide appropriate and respectful encouragement to the participant in an effort to have them remain in the study.

ELEMENTS RELATED TO RECORDS MANAGEMENT

R2	R3	COMMENTS
"…maintain records of the product's delivery *to the trial site*, the inventory *at the site*, the use by each subject, and the return to the sponsor or alternate disposition…." [4.6.3]	"…maintain records of the product's delivery, the inventory, the use by each participant…and the return to the sponsor *and destruction* or alternative disposition…" [2.10.4] "The investigational product may be shipped to the participant's location or supplied to/dispensed at a location closer to the participant (e.g., at a local pharmacy or a local healthcare center). The investigational product may be administered at the participant's location by investigator site staff, the participant themselves, a caregiver or a healthcare professional." [2.10.8] "Where the investigator has delegated activities related to investigational product management or aspects of these activities have been facilitated by the sponsor, the level of investigator oversight will depend on a number of factors, including the characteristics of the investigational product, route and complexity of administration, level of existing knowledge about the investigational product's safety and marketing status." [2.10.3]	These revisions do two things. First (and evident in the first quote only), they clarify that the site documents destruction of any investigational drug (which it likely already does) and second, more impactfully, they accommodate and provide guidance for shipments of investigational drug not just "to the trial site" but also to locations other than the site (e.g., shipping directly to the participant). The last quote indicates that the investigator still must be involved in this decision to have product shipped to these other locations, even if the sponsor/CRO is handling that.

R2	R3	COMMENTS
No real equivalent statement	"The investigator should define what is considered to be a source record(s), the methods of data capture and their location prior to starting the trial and should update this definition when needed. Unnecessary transcription steps between the source record and the data acquisition tool should be avoided." [2.12.2]	This, among other things, allows the investigator/site to determine what formats constitute their "source records." For example, if a nurse takes a manual blood pressure, writes it on a note, and then enters it into the EHR, it can be confusing as to which is the "source." With an up-front definition, this solves the problem. Some countries may provide additional guidance on this. For example, FDA guidance indicates that when using digital health technologies (DHTs) that gather data directly from participants and transfers that data via a direct, uninterruptable, and secure connection to a durable electronic data repository (including an EHR), they consider the source document as the first database/EHR the data are sent to and not the peripherally feeding DHT itself.

USE OF ELECTRONIC SYSTEMS

R2	R3	COMMENTS
No real equivalent statement (for systems deployed by the investigator/site)	"For systems deployed by the investigator/institution, ensure that appropriate individuals have secure and attributable access." [2.12.10(a)] "For systems deployed by the investigator/institution that maintain and retain trial data/information, the investigator/institution should ensure that such data are protected from unauthorised access, disclosure, dissemination or alteration and from inappropriate destruction or accidental loss." [2.12.9]	Cybersecurity is of growing importance. For sites that are part of larger organizations with robust cybersecurity resources, it is encouraged that the site leadership be an active member of that infrastructure. For those that do not have such an infrastructure, it is recommended to read SCRS's "A Site Manager's Non-Technical Guiden to Cybersecurity on a Budget" located at myscrs.org/digital-innovation-initiative/.
No real equivalent statement (for oversight of systems deployed by the sponsor)	"The investigator should ensure that data acquisition tools and other systems deployed by the sponsor are used as specified in the protocol or trial-related instructions." [2.12.4] "For systems deployed by the sponsor, [the investigator/institution] should notify the sponsor when access permissions need to be changed or revoked from an individual." [2.12.10(b)]	In this case, although the investigator/site does not incur R3's obligations of the technology's deployers (see related obligations under R3's Sections 2 and 4), they do have some minimal obligations as end-users of the technology.

R2	R3	COMMENTS
No real equivalent statement (for systems deployed by the investigator/site)	"For systems deployed by the investigator/institution specifically for the purposes of clinical trials, ensure that the requirements for computerised systems in Section 4 are addressed proportionate to the risks to participants and to the importance of the data." [2.12.10(c)]	The new Section 4 (entitled "Data Governance – Investigator and Sponsor") obligates the responsible party deplo ying the technology (to which the responsible party is the site if the site is deploying) to, among many other things, do the following related not only to the study data but also to the metadata and audit trails supporting the study data: (i) ensuring that "those developing computerised systems for clinical trials on their behalf are aware of the intended purpose and the regulatory requirements that apply to them" [4.3]; (ii) that "those using computerised systems are appropriately trained in their use" [4.3.2]; (iii) that security controls (i.e., user management and ongoing measures to prevent, detect and/or mitigate security breaches such as user authentication requirements and password management, firewall settings, antivirus software, security patching, system monitoring, and penetration testing) are implemented and maintained [4.3.3(b)]; (iv) "maintain adequate backup of the data" [4.3.3(c)]; (v) validate systems, including those developed by other parties, as fit for purpose for use in the trial, "based on a risk assessment that considers the intended use of the system; the purpose and importance of the data/record that are collected/generated, maintained and retained in the system; and the potential of the system to affect the well-being, rights and safety of trial participants and the reliability of trial results" and such "validation documentation is maintained and retained" [4.3.4]; (vi) "Ensuring that the automatic capture of date and time of data entries or transfer are unambiguous (e.g., coordinated universal time (UTC))" [4.2.2(d); (vii) "systems are designed to permit data changes in such a way that the initial data entry and any subsequent changes or deletions are documented, including, where appropriate, the reason for the change" [4.2.2(a)(2)]; and (viii) ensuring that audit trails, reports, and logs are (a) "not disabled"; (b) "not modified except in rare circumstances (e.g., when a participant's personal information is inadvertently included in the data) and only if a log of such action and justification is maintained; and (c) "interpretable and can support review" (i.e., human readable) [4.2.1(b)-(c)]. As voluminous as this is, Section 4 has many more process requirements as well as how these processes are documented. Any investigator/site deploying its own technology yet not familiar with technology assessments will be challenged to meet these obligations.

R2	R3	COMMENTS
No real equivalent statement	"Where equipment for data acquisition is provided to trial participants by the investigator, ensure that traceability is maintained and that participants are provided with appropriate training." [2.12.10(d)]	Of note, this obligation applies regardless of whether the equipment was procured by the sponsor or the investigator/institution. Discretion is allowed on the content and documentation of this training.
No real equivalent statement	"Ensure that incidents in the use and operation of computerised systems, which in the investigator's/institution's judgement may have a significant and/or persistent impact on the trial data or system security, are reported to the sponsor and, where applicable, to the IRB/IEC." [2.12.10(e)]	Unfortunately, many sites do not report such incidents for a variety of reasons (e.g., fear of retribution from the sponsor/CRO). In many cases, the site may have created a workaround to an issue but also does not share that information with the sponsor, vendor, and/or other sites using the system. Failure to report is not only detrimental to the local site and its participants, it also extends risk to other sites and their participants. Such incidents often result in screen failures, protocol deviations, participant dropout, loss of data integrity, and, most critically, participant safety issues. Of note, there is a corollary obligation of the sponsor to provide a mechanism to be informed of such incidents—see below description of 3.16.1(x)(ix).

Changes Indirectly Affecting Sites/Investigators

On the following pages, grouped thematically, are some additional changes in R3 that directly affect other stakeholders but are tangential to site operations. These are highlighted for site/investigator awareness and may be necessary for policy revisions, contract/budget negotiations, monitor management, and/or other purposes.

1) **Site Input, Burden, and Budgeting**
    a. R3's Section 3.1.3 (along with references in the Principles of ICH GCP and Appendix B: Clinical Trial Protocol And Protocol Amendments sections) state sponsors "should consider inputs from a wide variety of interested parties, for example, healthcare professionals and patients, to support the development plan and clinical trial protocols as described in ICH E8(R1) and when developing the informed consent materials and any other participant-facing information." Unfortunately, investigator sites did not get a call-out as an example here; however, more sponsors are recognizing the importance of site input in protocol design and operations.

    b. R3's Principles of ICH GCP 7.4 states *[emphasis added]* "Trial processes should be operationally feasible and avoid unnecessary complexity, procedures and data collection. Trial processes should support the key trial objectives. **The sponsor should not place unnecessary burden on participants and investigators**." Similarly, R3's Section 3.1.4 states *[emphasis added]* "the sponsor should ensure that all aspects of the trial are operationally feasible and should avoid unnecessary complexity, procedures and data collection. Protocols, data acquisition tools and other operational documents should be fit for purpose, clear, concise and consistent. **The sponsor should not place unnecessary burden on participants and investigators**."

    c. R3 Section 3.2 states *[emphasis added]* "**the sponsor should ensure that sufficient resources are available to appropriately conduct the trial**." Sites are often faced with resistance to proposed budgeting amounts with statements akin to "this study has limited funds." Under this new GCP requirement, sponsors should not begin studies until such time as they have sufficient resources. Of note, while this new GCP requirement does not explicitly state that "sufficient resources" includes the extension into the site/investigator budget, one may imply that in order to be compliant with GCPs, the sponsor must also extend the necessary resources to the sites as needed to appropriately conduct the trial. Note, however, that R3 twice references that selected investigators should demonstrate they also have adequate resources and facilities to conduct the trials safely and properly (3.7.1 and 3.11.4.5.2(a)).

2) **Study Monitoring**
    a. R3 Section 3.11.4.5.4(b) modified R2's Section 5.18.4(m)'s monitor obligations of "checking the accuracy and completeness of the [case report form] entries, source documents and other trial-related records against each other" to *[emphasis added]* "checking the accuracy, completeness **and consistency** of the reported trial data against the source records and other trial-related records **and whether these were reported in a timely manner**." Of note, while R3 does not define "timely," it likely may be defined in the protocol, contract, or elsewhere.

    b. R3's Section 3.11.4.5.1 addresses the communication between sites and monitors, specifically noting that the monitoring plan should include [emphasis added] "establishing and maintaining a line of communication between the sponsor and the investigator and other parties and individuals involved in the trial conduct (e.g., centrally performed activities). **In general, each site should have an assigned monitor as their contact point.**"

3) **Protocol Deviations**
    a. R2 Section 5.0.7 references the concept of "important deviations" but R2 does not define them or provide any instructions related to them. R3 elaborates on the concept of "important deviations" as being protocol-specific and defined

by the sponsor. Specifically, R3's Section 3.9.3 states "the sponsor should determine necessary trial-specific criteria for classifying protocol deviations as important. Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy and/or reliability of the trial data or that may significantly affect a participant's rights, safety or well-being." The difference is critical as investigator obligations diverge between required action for *important deviations* versus just documenting (i.e., no required corrective or preventative action plans) *deviations that are not deemed important*. Specifically, R3's Section 2.5.3 states "the investigator should document all protocol deviations… the investigator should review the deviations, and for those deviations deemed important, the investigator should explain the deviation and implement appropriate measures to prevent a recurrence, where applicable."

b. R3 Section 3.11.4.5.1(b) obligates the sponsor to report to the investigator any protocol and other deviations the sponsor discovered occurring at the site (e.g., through centralized monitoring). Specifically, "informing the investigator or other parties and individuals involved in the trial conduct of relevant deviations from the protocol, GCP and the applicable regulatory requirements and, if necessary, taking appropriate action designed to prevent recurrence of the detected deviations."

4) Record Retention

a. For many reasons, post-study record retention is a growing challenge for sites—especially as the industry moves into electronic records. Sponsors are increasingly recognizing and reducing their long-term risk by contracting with central professional archiving vendors for transfer of the records after the site's regulatory retention period is over. However, sites do have a period of regulatory retention that must be adhered to, which may extend into longer contractual obligations if jointly agreed to between the site and sponsor.

b. Although applicable to paper records as well, the increasing use of electronic records and their cybersecurity is relevant to R3's Section 4.2.7, which states that, for any stakeholder (including sites) housing such, "the trial data and relevant metadata should be archived in a way that allows for their retrieval and readability and should be protected from unauthorised access and alterations throughout the retention period."

c. The use of vendors is more prevalent during and after the study. R3's Appendix C.2.2 states "for activities that are transferred or delegated to service providers by the sponsor or investigator/institution, respectively, arrangements should be made for the access and management of the essential records throughout the trial and for their retention following completion of the trial." Part of the challenge of post-regulatory voluntary record retention at the sites is the obligation to not only secure these vendors' archiving timeframes, but also to accommodate for hardware obsolescence, software obsolescence, and backup plans if the vendor no longer functions in that capacity (i.e., they went out of business, discontinued the product, or the technology merged with another company's pursuant to an acquisition). Vendor contracts and affiliated cybersecurity insurance are increasing in costs and sites require more sophisticated operational planning and budgeting, especially if the site wants to serve as a record archiving vendor for the sponsor after the legal obligation of its role as a site has expired.

d. Similar to R2's section 5.5.12, R3's Section 3.6.3(c) states "the sponsor should inform the investigator(s)/institution(s) and service providers, when appropriate, in writing of the requirements for the retention of essential records." However, R3 takes an additional step in Section 3.11.4.5.2 obligating the sponsor's "confirming the arrangement for the retention of the essential records and the final accountability of the investigational product (e.g., return and destruction or

alternative disposition, if appropriate) during site close-out activity." This means both sponsor and site must be aware of the obligations of retention and how they will evolve over time. Such conversations may lead to revisiting the original contractual arrangement of the site retaining the records for the sponsor after the site's regulatory obligation has expired.

e. R2's Section 5.5.12 states the sponsor "should notify the investigator(s)/institution(s) in writing when the trial related records are no longer needed." R3's Section 3.16.3(b) states the same thing but appends at the end the clause [emphasis added] "in accordance with applicable regulatory requirements." Whether this was intended to tie to a site's legally obligated record retention period (as opposed to the contractually obligated period) or tie to cases in which a sponsor is legally required to report this to the sites unfortunately remains ambiguous. Nevertheless, although historically required by R2, the apparent lack of adherence to this requirement by many sponsors has been frustrating to sites, especially if sponsors are unable to be reached or not responding to requests. Even with R3 continuing this requirement, sites may still desire to include language in clinical trial agreements akin to "Institution will give Sponsor a thirty (30) days written notice to the correspondence address indicated in this Agreement prior to intent to destroy records to allow Sponsor to either a) provide verification that the Investigator's regulatory retention obligation under applicable law has not expired; and/or b) provide the shipping information necessary for Institution to transfer records into Sponsor's custody at Sponsor's sole expense. Failure to respond within thirty (30) days of the notice shall constitute the Sponsor's waiver of the Sponsor's option to have records shipped to them in lieu of destruction."

5) Protocols and Amendments

a. For protocols, R2's Section 6.8.4 requirement for "the type and duration of the follow-up of subjects after adverse events" was modified in R3, renumbered as B.9.4, stating *[emphasis added]* "the type and duration of the follow-up of participants after adverse events **and other events such as pregnancies**."

b. Likely in an effort to decrease protocol amendments for such minor changes, R3 removes R2's obligation to identify (by name/address/phone) the sponsor's medical/dental expert, investigator, sites, labs, etc. in the protocol itself as well as R2's requirement for specifying in the protocol "the numbers of enrolled subjects projected for each trial site."

6) For Essential Records

a. With the conceptual change from Essential Documents to Essential Records, R2's tables of Essential Documents and who is to retain them (in R2's Section 8) is removed and replaced in R3 with a definition of Essential Records being "*documents and data (and relevant metadata), in any format*, associated with a clinical trial that facilitate the ongoing management of the trial and collectively allow the evaluation of the methods used, the factors affecting a trial and the actions taken during the trial conduct to determine the reliability of the trial results produced and the verification that the trial was conducted in accordance with GCP and applicable regulatory requirements." In its own table, R3 essentially codifies that all of the documents listed in R2's table of Essential Documents meet, by default, the R3 definition of an Essential Record. Any other record will have the criteria applied to it in order to be deemed essential. In removing R2's delineation of whether the investigator/institution, sponsor, or both must retain the

specific records, R3's C.2.7 states "the sponsor and investigator/institution should ensure the retention of the essential records required to fulfill their responsibility. The original records should generally be retained by the responsible party who generated them."

b. R3 recognizes that some records may extend across multiple studies and thus allows for storing them centrally instead of in all-inclusive, study-specific storage. R3's Appendix C.2.12 reads "certain essential records may not be specific to a trial but may be related to the systems and processes involved in running multiple trials and retained outside the trial-specific repositories (e.g., standard operating procedures, validation records, master services agreements)." Although this may be a welcome option for sites to not have to duplicate documents for storage in multiple study repositories, it may introduce other inventory challenges if duplicate documents/information are stored separately. Nothing therein alleviates the site's accountability to reproduce the entirety of essential records during the retention period, and site leaders must make their risk- and cost-based business decisions analyzing the balance between burden and complexity.

c. R3 strengthens the integrity of the data and the site's (or participant's) ability to make corrections. R2's Section 4.9.3 simply states "sponsors should have written procedures to assure that changes or corrections in [case report forms] made by sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator." R3's Sections 3.16.1(i)-(j), however, state *[emphasis added]* "the sponsor **should not make changes to data entered by the investigator** or trial participants **unless justified**, agreed upon in advance by the investigator and documented" and "the sponsor should allow correction of errors to data, including data entered by participants, where requested by the investigators/participants. Such data corrections should be justified and supported by source records around the time of original entry."

7) IRB/IEC Related

a. More than one section (e.g., 2.4.5, 3.13.3) refers to the fact that the sponsor may also submit documents to the IRB/IEC in accordance with applicable regulatory requirements.

b. R3's Section 1.2.8 clarifies for IRBs/IECs that "reasonable reimbursement of expenses incurred by participants, such as for travel and lodging, is not coercive."

8) Electronic Systems

a. The site should be aware of sponsor obligations regarding systems deployed by the investigator/site. Specifically before being used in the trial (i.e., site selection) and in a manner proportionate to the importance of the data managed in the system deployed by the site, the sponsor must document an assessment of the site's systems (i) that "if identified as containing source records in the trial, (e.g., electronic health records, other record keeping systems for source data collection and investigator site files) are fit for purpose or whether the risks from a known issue(s) can be appropriately mitigated"; (ii) that "clinical practice computerised systems are being considered for use in clinical trials (e.g., electronic health records or imaging systems used or deployed by the investigator/institution), these systems should be assessed for their fitness for purpose in the context of the trial"; and (iii) "factors such as data security (including measures for backup), user management and audit trails, which help ensure the protection of confidentiality and integrity of the trial data, should be considered as appropriate." [3.16.1(x)(vi-viii)]

b. The sponsor must "ensure that there is a process in place for service providers and investigator(s)/institution(s) to inform the sponsor of incidents that could potentially constitute a serious noncompliance with the clinical trial protocol, trial procedures, applicable regulatory requirements or [GCP] [3.16.1(x)(ix)]. Of note, R3 does not specifically state how this must be done (e.g., sites contacting the monitor or project manager? notifying the vendor helpdesk?) nor does it require obligations and/or timeliness for correcting and/or preventing future incidents. The sponsor must make its own determinations here based on its risk assessment. However, the sponsor's decisions herein have a clear impact on the site's ability to conduct the trial and a participant's willingness to continue in the trial.

Conclusion

Sponsors, CROs, regulatory authorities, other stakeholders and sites are all independently migrating to R3 at different pacing. Unfortunately, there will be times when R3 must coexist with R2 during the fragmented global transition noting that, generally speaking, compliance with R3 is not incompatible with compliance with R2 (whereas the opposite is not true). To keep pace and remain competitive, investigative sites are encouraged to ensure a steadfast and determined transition to R3. Although major infrastructure changes are not required, many micro-level changes in items like policies, practices, documentation requirements, quality assurance/improvement tools, and others are called for. A site's adoption of R3 for its internal operations, as well as being knowledgeable enough to speak intelligently about it to cooperate with and/or educate external customers and other stakeholders, will be of critical importance for site success in the near future.

Acknowledgements

About the Author: David Vulcano is a well-known thought leader and change agent in the clinical research industry through numerous associations, boards, initiatives, publications, and presentations. His primary employment is as the Vice President for Research Compliance & Integrity at HCA Healthcare, providing research-related support to its portfolio of hospitals, physician practices, healthcare technology and other operations. He has held numerous influential leadership positions in the industry both in the United States and internationally, including as Fellow and former Chair of the Board of Trustees for the Association of Clinical Research Professionals (ACRP), Honorary President for the Society for Clinical Research Sites (SCRS), and Advisory Board member for the Society for Clinical Data Management.

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For additional resources to support the transition to ICH E6(R3), please visit ACRP's Guidelines and Regulations Resource Center.

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