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In Response to: "Decentralized Clinical Trials for Drugs, Biological Products, and Devices Guidance for Industry, Investigators, and Other Stakeholders - Draft Guidance"

The Society for Clinical Research Sites (SCRS), an advocacy organization for clinical research sites with more than 10,000 members globally, has several comments on the May 2023 draft guidance document entitled "Decentralized Clinical Trials for Drugs, Biological Products, and Devices."

First, we applaud the FDA for preparing this guidance and its intent to foster the extension of the traditional research site via various mechanisms. It is vital that the industry enables patients to have increased access to the necessary items and services required to successfully enter and complete clinical trials. We concur that there are proper ways to extend a clinical trial site/investigators' traditional "brick and mortar" model to one that can be extended by technology, mobile research staff and healthcare providers that are more proximal to the patient at their time of need. Although it challenges the traditional business model of the site industry, the 2022 SCRS Site Landscape Survey results indicated that sites are participating in these kinds of studies in a post-COVID environment, with the top two reasons being "would be beneficial to the participant" and "desire to bring my site into the future".

While we see the investigator/site industry as concurring with the purpose of this draft guidance and with many of FDA's recommendations herein, certain components of the current draft are having the opposite of the intended effect. Some components codify several systems and gaps that are known to contribute to investigator/sites' unwillingness to facilitate decentralized components due to fear of regulatory retribution. Herein we take the approach of highlighting key issues we believe the FDA should address in this guidance to accomplish our shared goal.

We cannot emphasize enough that the erosion of site/investigator oversight and the expected regulatory consequences have a negative effect on the adoption of decentralized/hybrid trials. Based on the 2022 Site Landscape Survey, overwhelmingly the site's answer to the question "what have you experienced to be the biggest challenges for your site in participating in decentralized trials" was "oversight of remote vendors that would interact with the patient, record source data". For sites that refused to conduct trials with the added decentralized components, the second and third most common reasons cited were "not comfortable with this type of trial" and "lack of understanding on how the trial would operationalize".

The great majority of our comments relate to this theme of the site/investigator's eroding control over the operation of the clinical trial, coupled with the reiteration that they remain ultimately responsible from a regulatory perspective. Our community does, although cautiously, embrace the concept that any FDA endorsement of decentralized components that move study operations further away from the investigator's sphere of direct influence should be coupled with backfilling of the investigator's traditional responsibilities to the sponsor (or their selected vendor). Additionally, we encourage those parties, not the investigator, be held directly accountable to the FDA for regulatory compliance.

General Topic 1: HCP Oversight

Some of the greatest anxiety and confusion surrounding this guidance is related to investigator oversight, especially on the issue of the use of HCPs. Conceptually, investigators/sites see a role for HCPs in assisting with the trials; however, the erosion of control and added documentation requirements that the draft guidance puts forth are unfortunately reinforcing their anxiety of regulatory retribution that inhibits investigator/sites from embracing these potential new partners.

- Lines 130-133 state "The trial-related services that they provide should not differ from those that they are qualified to perform in clinical practice (e.g., performing physical examinations, reading radiographs, obtaining vital signs). These services should not require a detailed knowledge of the protocol or the IP." The following sentence (lines 135-137) state "Trial-related activities that are unique to research and/or require a detailed knowledge of the protocol or the IP should be performed by qualified trial personnel who have been appropriately trained." Thus, it seems that the resources and documentation around these individuals pivots on whether they need "detailed knowledge of the protocol or the IP" but "detailed knowledge" is not defined in the draft guidance.

  For example, if an individual performs phlebotomy and vital signs in a manner that does not differ from those that they are qualified to perform in clinical practice, but the protocol requires that the vital signs be done before the phlebotomy procedure, is that sequence of events "detailed knowledge of the protocol" or is it just a simple set of instructions from the referring investigator? Since such significant resources, documentation and regulatory risk to investigators/sites pivot on this issue, the guidance should unambiguously define and provide real-life examples on what is meant by "detailed knowledge".

- The listing of individuals on a Form 1572 as well as the accommodating training documentation requirements of whether an individual is a "trial personnel" or an HCP pivot on what lines 104, 274, 285, 315 and 326 refer to as them providing only "routine

care". However, "routine care" is not defined in the guidance. To our knowledge the FDA has not defined what "routine care" entails outside of referencing it in real-world data as "data not gathered according to a prespecified research protocol".

Similarly, CMS (for Medicare reimbursement purposes) excludes from routine costs "items and services provided solely to satisfy data collection and analysis needs and that are not used in the direct clinical management of the patient (e.g., monthly CT scans for a condition usually requiring only a single scan)". A summary of HHS "routine care" definitions could be the items and services the patient would have received absent the protocol. Given that, it may be argued that the HCP is not providing routine care if they are performing an item or service that they would not have done (i.e. out of medical necessity) absent the protocol.

In following that logic, the guidance would be interpreted that even if an HCP provides an item or service in the same manner as they would for routine care, if they are doing it not for conventional care purposes but solely because of the protocol, then they are not providing routine care. Using the CMS example, a provider performing monthly CT scans for a protocol, when absent the protocol, they would only have performed one and would not be performing routine care even if the CT scans were performed in the routine way. In this example, the scans were not done out of medical necessity, but performed only because of the existence of the protocol. We hope that the FDA shifts away from the term "routine care" and simply allows the required technical skills of the individual performing the items and services *as if they were done* for routine care instead of done as part of routine care. This simple change would greatly help to decrease burden on investigator/sites from elevating the classification of these individuals into a class that requires much more paperwork and regulatory risk.

- The issues surrounding training are also not clearly defined in the guidance despite multiple references to additional training and other documents of qualification needed. The issue of training in decentralized trials is already exacerbated in the investigator/site community. The 2022 SCRS Site Landscape Survey noted that for protocols with decentralized components, sites are experiencing/coordinating an additional average of 17.5 hours *per protocol per month* in training alone. The guidance does not indicate what training is needed and how it should be documented. For instance, who will need full GCP training verses only protocol training? Is it expected that the investigator reviews the curriculum vitae of every HCP and mobile health professional to assure they are qualified to perform the procedures? Does the investigator/site need copies and verifications all of their certificates and licenses? Do FDA debarment checks on each HCP

or home health professional need to be performed? This concept is further challenging for the investigator to accomplish in the event that the sponsor/CRO contract directly with the third-party provider of mobile health professionals and/or HCPs, as the site/investigator has no control over this selection yet remains responsible.

In addition to establishing the qualifications of the individual, the guidance is silent on the risk to sites/investigators regarding the physical environment and equipment used at the HCP location. It would be unrealistic to assume the HCPs will all use trial-issued equipment or have calibrated their local equipment (i.e. weight scales) to the standards of the study. While lines 98-99 ("the variability and precision of the data obtained in a DCT may differ from the data in a traditional site-based clinical trial") demonstrate FDA's understanding of this, all other aspects of the guidance do not seem to alleviate the site/investigator from this poorer quality and less verifiable data. The guidance should mention that enforcement discretion will be used in these circumstances.

General Topic 2: Task Log

Many lines (e.g. 126-138, 254-258, 271-272, 278-279, 300-301) reference a "task log" to which has generated significant discussion in the site/investigator community.

The first question is whether this "task log" is the same thing as what is commonly referred to as the "Delegation of Authority Log". It is our hope that the FDA is not suggesting a new kind of form that is not already commonly used that would add burden to the investigator/sites, especially if it is requiring dual entry.

Second, the draft guidance does not bring definitive clarity to the already unclear issue of when an individual crosses the line into being a sub-investigator and thus, among other things, requires being listed on the Form 1572, 21CFR54 disclosures, debarment background checks and other paperwork. Due to fear of regulatory retribution, it is unfortunately a normal occurrence to overreport people to be sub-investigators, which causes significant burden on the investigator/site. While the guidance on completing the Form 1572 is outside the scope of this draft guidance, we hope that the FDA can use the opportunity of this guidance to be more definitive in examples or criteria (instead of the current ambiguous language of "contribute directly and significantly") to diminish the fear that contributes to overreporting.

Finally, the "task log" seems to be related to individuals and not entities. This presents many potential challenges, especially if individuals are to be placed on the log prior to their providing services. For example, an HCP at a community clinic is listed by name to assist with performing and reading an ECG for a protocol. Should the local HCP not be present or available to perform and read the ECG at the date and time of the visit, having to name the HCP individually would preclude another qualified provider at that location (or at a location more convenient to the

participant) from doing the procedure. Being able to name institutions, instead of individuals personally, should be an acceptable alternative to accommodate for the unpredictability of patient schedules and HCP availability/turnover/schedules.

Overall the site community is concerned that, given the encouragement of the multiplicity of new providers with unpredictable schedules and turnover, keeping up with such a log will be impossible and especially burdensome to attempt. Investigators/sites fear regulatory action against them for failure to meet their responsibility in keeping up with the task log as the guidance purports.

General Topic 3: Physical Location Of Records and Trial Personnel Interviews
Lines 93-96 state "For inspectional purposes, there should be a physical location where all clinical trial-related records for participants under the investigator's care are accessible and where trial personnel can be interviewed. This location should be listed on Form FDA 1572 or for investigational device exemption (IDE) applications must be included in the IDE application." This statement yields multiple concerns and is seemingly inconsistent with the presumption that the concept of a site is moving away from a single physical location.

Regarding the physical location for records to be accessed, it is appreciated that the draft defines that the location should be where the records can be "accessible" and not "stored" (a challenge in today's status of diminishing or non-existent use of paper-based records in favor of electronic records). However, the guidance does not seem to offer how the realities of the coexistence of paper-based records, locally stored electronic medium and cloud-based records can be accomplished in this "single location" that must be listed on the 1572. Does the phrase "under the investigator's care" mean that only the records related to the items and services directly provided by the investigator are what is needed here? Is it intended to mean all records related to the trial subject's participation while under the investigator's oversight? If it is intended to be the latter, we believe it may be impossible to do this when using contracted mobile health professionals and HCPs, as their source documents are often not under the control of the investigator and cannot be housed in the same location as the site/investigator's files. It will also add significant burden to obtain printed certified copies of every source document from every mobile health professional and HCP.

There is also a similar problem with the ability to have a single location where all trial personnel can be interviewed. With the extension of trial personnel to include mobile health professionals and possibly HCPs not in the nearby community, we believe it will be challenging to have a single location where these trial personnel can be interviewed.

Finally, the site/investigator community is increasingly challenged with record retention given that the regulations were written at a time when study records were almost exclusively on paper. Unlike sponsors and CROs, investigator/sites are generally not equipped with the

expertise or resources to archive records for extended periods. Emerging financial and operational concerns such as technology degradation, technology obsolescence, cybersecurity, password management and similar obstacles germane to the record archiving industry are outside of a site's core competence.

We understand the desire for the need for the site/investigator's records being independent of the study sponsor/CRO, however most technologies are provided by the sponsor/CRO thus it is all-too-often the sponsor/CRO the one sending the investigator/site their records at the end of the study for storage at the site level. While we understand that changing the record retention regulations is outside of the scope of this guidance, we do call to your attention that the growing incapabilities of the site/investigator's ability to adequately keep the records will directly contribute to the inability to adhere to the guidance. The guidance (and perhaps changes in regulations) should call out options in the best interest of record retention such as the investigator/site transferring custody of the records to the sponsor/CRO 2 years after the study is completed instead of being responsible for extended storage, as this may help the FDA achieve their goal of a single location for all trial records.

With that said, while we agree that the identification of a single location for record access and trial personnel interviews brings greater ease for FDA audits, the feedback we are receiving is that it would be extremely impractical and even impossible to see this accomplished in actuality given the very nature of moving trial locations away from a single central physical location foundationally precludes the ability to audit them at a single central physical location.

General Topic 4: Overly Detailed Specifications In The Protocol

There are many statements in this section that suggest the addition of detailed micro-instructions to the written trial protocol. Regarding telehealth, lines 119-121 state "The protocol should specify when a telehealth visit with a trial participant is appropriate and when a participant should be seen in person".

Similarly, regarding in-person trial-related activities performed by HCPs, lines 256-258 state "These procedures may take place at participants' locations or other local health care facilities as specified by the trial protocol".

In the same vein, line 147 states "the trial protocol shall describe how care for urgent AEs will be done" and lines 434-439 speak to how the investigator will track the shipment or IP and how participants must return or dispose of the unused IP. From experience, the more items that are dictated in a written protocol, the greater the risk of protocol deviations. Our experience is that we can have better compliance if the protocol is agnostic or, at most, fully flexible about these issues in a manner that accommodates unexpected circumstances.

Specifically related to the location and methodology of patient visits, we ask that the stakeholders respect the investigators intimate and personal knowledge of their individual trial participants and, unless there is a compelling reason to hardwire something in the protocol, to remain silent on the coordination of the medical care of the participants. We have seen too many attempts, although well intentioned, that actually further limit the flexibility desired to make the decentralization of visits successful. For example, a well-intentioned sponsor may write a protocol stating "this visit may take place at the site or in the patient's home" which would then preclude the patient preference to have the visit done at a different location such as their place of employment.

Similarly, there are many references in the draft guidance to items or services being performed by service providers "close to the trial participant" or "sent to participants' homes or preferred locations" but others reference (specifically lines 127 and 193) "close to the trial participant's home". We read this as a fundamental difference with the latter being potentially problematic (i.e., how far away from home is "close to home" or what about participants that need a simple procedure while on vacation?). It seems that if the intent is to open up the ability for the trial to follow the participant that the "close to home" geography limitation should be eliminated and replaced with the other phrase of "close to the participant" or "at participants' home or preferred locations".

We ask that the FDA take this opportunity to actively encourage more flexibility in this area. The guidance should encourage protocols to be technology and location agnostic, to the extent safety and scientifically possible, as well as not attempting to be the document that coordinates local healthcare care for the trial participants.

General Topic 5: Direct to Participant IP Distribution

We believe the section on direct distribution to participants needs further clarifications. Line 416-417 seems to imply the sponsor's obligations, specifically "The sponsor should consider the following recommendations regarding packaging, shipping, and storage of IPs in a DCT".
We also request a pragmatic change to the lines 429-432 that state "the investigator or delegated trial personnel must control the release of the IP by the distributor; monitor receipt and use by trial participants (or participants' legally authorized representatives), according to procedures described in the protocol; and monitor the return or disposal of any unused product as directed by the sponsor."

First, this would require central inventory systems to change to allow for such authorization, noting that many systems to date have operated independently of the investigator with "auto-refills" unless the allowance of such is considered in the investigator's control. In addition, in line with other sections that are now imposing overly detailed instructions into the trial protocol, we hope line 434-435 can be removed or at least encouraged to not be overly

detailed that the realities of multicenter studies and diverse participant populations are not impeded.

Second, our experience for this overall process is that most of the times that these systems fail, it is not due to the fault of the site/investigator. However, it seems that under this guidance the protocol deviations will be documented as the fault of the site/investigator that likely had no control over the sponsor/CRO or their selected vendor. For example, among the most common failures are the sponsor/CRO or their vendor incorrectly packaging, labeling or shipping the IP, which is something that site/investigator has no line of sight over much less any control over, not the investigator mis-ordering the product to be shipped.

Third, the site/investigator is among the least likely to be able to monitor the return or disposal of the IP unless it is FDA's expectation to now require the investigators to obtain copies of the shipping records to monitor in transit as well as the sponsor/CRO or their vendor's IP accountability logs. While we respect the intent that the investigator be in control over this process, we believe that the investigator should only be accountable for what they have control over (such as if the site/investigator is using their own vendors/couriers to ship the IP) and not what they do not have control over (e.g., a sponsor/CRO or their selected vendor doing this).

General Topic 6: Regulatory Accountability

Finally, a major cause of site/investigator fear of regulatory retribution and a major obstacle for sites/investigators embracing decentralize trials is the disconnect from what the investigator is given control over by the sponsor/CRO. The guidance should clearly indicate what a site/investigator would be accountable for should something go wrong as well as, more importantly, what the site/investigator will not be responsible for. As mentioned, the loss of control – yet no alleviation of accountability – is the leading resistance of investigators/sites in moving forward with trials with decentralized components.

This is exacerbated when the investigator/site is given no choice, other than the choice not to do the trial, in the matter of use and/or selection of vendors that work as site extenders. The guidance is unwavering on the investigator's ultimate accountability. Yet even within the four walls of the guidance it recognizes the sponsor's influence (e.g. Sponsor Roles and Responsibilities lines 183-185 states "because DCTs may involve many contracted services, sponsors should ensure proper coordination of the decentralized activities [e.g., use of mobile nurses for at-home visits, use of local HCPs, direct shipping of IP to participants]; lines 149-152 state it is sponsor and investigator's responsibility to ensure that remote clinical trial visits conducted via telehealth comply with laws governing telehealth in the relevant U.S. States or territories and other countries, as applicable"; lines 170-171 state "Sponsors should ensure that DHTs used in a DCT are available and suitable for use by all trial participants" etc.)].

Overall sites/investigators would have less anxiety about adopting decentralized components if they felt reassured from FDA that the regulatory enforcement system reflected the growing reality that they are in less control of the study and that regulatory risk would be aligned with the party opting for that responsibility. If a sponsor/CRO selects and/or requires the investigators to use of a specific digital health technology (DHT), if that DHT causes protocol deviations or regulatory violations by no fault of the investigator, the sponsor/CRO or DHT vendor, not the site/investigator, should receive the regulatory citation.

Similarly, if the sponsor/CRO selects or requires a specific mobile health provider or HCP for the investigator to use that they (or the healthcare provider) are independently held responsible for regulatory violations and protocol deviations not caused by the investigator/site. We are not meaning to detract that the investigator and the vendor not cooperate with each other for mutual success, only to place the regulatory obligation on the decision-making party and/or the entity that are making the claim(s) that their products and services are appropriate for use in FDA governed activities.

In a parallel example, if an individual desiring to have a house built hires a general contractor for a house but separately contracts with a company to build the patio and deck, although the general contractor must work in conjunction with the patio/deck provider, the general contractor (the "PI") would not be held liable for fault by the patio/deck construction vendor. Although informally done, this is arguably similar to what OCR did with HIPAA when they altered the regulation to hold the subcontracted Business Associates undependably liable for breaches they caused with the covered entity's data.

The FDA could go so far as to recognize a growing practice by investigator/sites in keeping separate deviation logs, one for deviations that were under their control (where they would be wholly responsible for corrective and preventative action plans) and another for deviations outside of their control (where they do not have control over the corrective and preventative action plans). Even in FDA regulated studies, we see that investigators must sign Form 1572s or device agreements indicating that they will "ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation". However, when an IRB fails to meet 21CFR56, the FDA issues the 483 and subsequent regulatory actions upon the IRB itself and not the investigator(s) who signed the 1572.

We firmly believe that it would go a long way in decreasing the fear that investigators/sites have in adopting decentralized components if the FDA can clearly state in this guidance that they will align regulatory actions with the entities in control. The guidance should indicate that the FDA will hold investigators/sites harmless should it be determined that the protocol deviation or other regulatory violation was not within their control. This also seems to be good policy as it holds the entities that hold out their shingle of capabilities of doing FDA-governed

work accountable for their actions, not only at the one site, but across all sites. For example, if a Digital Health Technology caused a protocol deviation at one site, it arguably caused protocol deviations at multiple sites. The regulatory action and its accommodating corrective and preventative action (CAPA) plan would best come from the DHT vendor (or the sponsor/CRO selecting the vendor) to ensure multicenter quality improvement. Requiring the regulatory action and the CAPA plan to be from the investigator level misaligns the CAPA and isolates the solution to the single center leaving risk at the multiple other centers.

General Topic 7: Miscellaneous

A few items that are often discussed at the site/investigator level are not addressed in this guidance:

- When data is gathered by sponsor/CRO-issued DHTs or mobile health providers, the trial participants may not be aware that the data may (i) not be read in real time by a clinician or (ii) may be read by the trial sponsor/CRO first prior to it being forwarded to the investigator for clinical considerations. This may cause actual or perceived risk and arguably should be disclosed in the informed consent document. We know that the European Union has weighed heavily on this issue in their guidance.
- There is chatter among all stakeholders that should an investigator/site be desired for the acute portion of a trial but unable or unwilling to participate in the remaining decentralized components of a given study, that the option to transfer the trial participants to another investigator who is capable should be explored. For example, a traditional site/investigator may be engaged as the principal investigator for the acute care portion of a study and then when the participant gets to the point that all remaining aspects are fully decentralized (i.e. all conducted by mobile health professionals and DHTs) that the initial investigator can transition the patient(s) to the subsequent sites/investigators (or the mobile health agency or to the sponsor/CRO) who would then take all responsibility for the protocol conduct of the decentralized components. Although not common, such transitions happen today when trial participants move their residence permanently or spend time in multiple locations. To our knowledge, FDA has not yet offered guidance on how an investigator/site can transfer care to another investigator/site. Under the prediction that this may be desired, perhaps this is an opportunity to do so.
- Lines 170-174 reference that the “Sponsors should ensure that DHTs used in a DCT are available and suitable for use by all trial participants. When a trial permits participants to use their own DHTs, sponsor-provided DHTs should be available as an option to ensure that participants who do not have a protocol-specified DHT are not excluded from the DCT for that reason (e.g., lower socioeconomic groups who cannot afford the

DHT)". We believe this to be incomplete and that the FDA should also officially recognize that investigator/sites are also able to provide the technology. We also encourage the FDA to recognize that technology fails and that sponsors should also have a "downtime" plan for investigator/sites if their supplied technology fails. Finally, we encourage FDA to elaborate that by "all trial participants" that they perhaps mean "all prospective trial participants in accordance with the any Diversity Action Plan" to more fully embrace their efforts to improve trial participant diversity and not only cater to those that made it into the trial.

In conclusion, we appreciate the opportunity to present the collective voice of investigative sites in the development of this guidance. As the individuals most affected by the decentralization of trials, sites believe we have the strongest voice to contribute to this dialogue for the success of the purpose.

We always welcome further dialogue with FDA on this and other topics that directly or indirectly involve the research sites. As we say, to be successful in clinical research, there should be nothing built for sites without sites. Please do not hesitate to contact us for further dialogue on this or other topics by reaching out to the Society for Clinical Research Sites (SCRS) at info@myscrs.org.