*Decentralized Trials & Research Alliance*

**Response to Integrating Randomized Controlled Trials for Drug and Biological Products Into Routine Clinical Practice; Guidance for Industry**
(Notice #FDA-2024-D-2052)
Submitted to the Food and Drug Administration (FDA)
Submitted on behalf of the Decentralized Trials & Research Alliance (DTRA)
Submitted December 17, 2024

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The Decentralized Trials and Research Alliance (DTRA) is a non-profit collaboration with over 100 member organizations working together to ease the global adoption of decentralized research methods. DTRA members represent bio-pharmaceutical companies, technology and service providers, site networks and research centers, advocacy groups, and government agencies.

DTRA and its members thank the Agency for issuing this draft guidance, which sends a clear message that FDA is supportive of the adoption of innovative approaches including decentralized research methods within existing regulatory frameworks to encourage development of novel medicines. DTRA is pleased to provide our feedback and constructive suggestions to the Draft Guidance below.

DTRA workstreams have produced a number of valuable resources in this space which we encourage the FDA, and other stakeholders such as the NIH to leverage as they consider the implementation of trials with decentralized elements (DCTs). Examples include a glossary of DCT terms, best practices handbook, patient journey maps, and evidence of DCT impact. DTRA also remains actively engaged with other Federal agencies and offices who are seeking more information about decentralized clinical trials.

DTRA and its member organizations are encouraged about the FDA's support of modernizing clinical trial designs and conduct paradigms, as evidenced by the publication of this guidance and others (e.g. Use of Decentralized Elements in Clinical Trials). Clinical trial participation can be a burden to patients and may disproportionately create access barriers which may be mitigated through new access approaches, such as integration of trial activities into routine care settings and the use of decentralized elements. Modernizing the clinical research enterprise to make it more patient-friendly, requires reducing the exclusive reliance on hospitals and medical centers. This will enable broader access to patients, especially for participants from currently underserved and underrepresented communities, to trials. Investigational sites remain a cornerstone of our clinical research enterprise, but these institutions may sometimes fail to provide adequate access to traditionally underserved populations. We believe that there is a potentially synergistic access improvement when trial designs integrate routine care and

decentralized elements. It will be critical to ensure that the use of these new approaches is truly fit for purpose, and aligns to current clinical care standards, patient-friendly trial participation, while maintaining the scientific rigor and data reliability.

We applaud FDA's issuance of this draft guidance that aims to enhance trial efficiency by incorporating research into everyday clinical practice. This can accelerate therapy development and patient access to innovative treatments by creating opportunities for non-traditional researchers to participate (HCPs) in clinical trial conduct. However, we believe that the current draft leaves many operational details open for industry concerns and resistance to adoption including expectations regarding trial oversight, data standardization, and patient engagement and follow up during and post trial.

Additional Resources:

As stated in DTRA's mission, we seek to be a preeminent, cross-functional organization that unites stakeholders in promoting the global adoption of clinical trial innovation and the appropriate implementation of decentralized research elements. Given our diverse member base (ranging from CROs, patient groups, pharma and biotechnology sponsors, technology and service providers, etc) and existing resources, we encourage the FDA to contact us for collaboration and dialogue in any future initiatives.

DTRA kindly requests that the FDA reach out to discuss any of our comments and suggestions in greater detail with us.

Kind regards,

DTRA Leadership and Regulatory Affairs Council

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SPECIFIC COMMENTS

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| *Lines/Section/ Text Reference* | *Draft Guidance Text* | *Comment/Recommendation* |
| 17-18 | *The adoption of streamlined protocols that focus on essential data collection, as described in the introduction, may not always facilitate the integration of RCTs into local clinical practice, given the limitations to HCP participation described later in the guidance.* | It would be helpful for the final guidance to specify what considerations might limit HCP participation as these are not always obvious. |
| 57-60 | The text states "As appropriate, sponsors should also obtain agreements from local HCPs to perform these protocol-related tasks, either directly or through the health care institutions in which they work." | Please clarify the relationship of local HCPs to the sponsor and protocol and provide more information as to what 'agreement' is expected. Is the sponsor contracting a fee for service agreement for routine care activities as part of a clinical trial setting? |
| 145-147 | Agreements between sponsors and health care institutions should document the responsibilities that are assumed by the institutions and their employees and the tasks that they will perform as part of the clinical trial. As appropriate, sponsors should also obtain agreements from local HCPs to perform these protocol-related tasks, either directly or through the health care institutions in which they work. | Similar to our earlier comment, we seek clarity on this section.<br>If "local HCPs" are not considered investigators or subinvestigators under 21 CFR 312.3, but sponsors may create agreements with local HCPs to perform tasks, what is the relationship between the "local HCP" and sponsor and protocol?<br>Is there a preference for these agreements to be initiated by the sponsor or by the investigator who would be receiving data from the HCP for trial purposes? |
| 57-59 | In this guidance, the terms investigator and sub investigator will be used for individuals who 56 meet the definitions for those roles under | Definition and clarification of HCP vs site staff: Qualifications/training for non-investigator HCPs. Is there a clear decision framework to consistently determine what is standard of care |

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| | 21 CFR 312.3.5 The use of the term local HCPs will 57 be restricted to health care providers who are involved in the trial but based on the limited tasks 58 they perform are not serving as trial personnel (i.e., investigators, subinvestigators, or their 59 clinical support staff) (see section V.A.3) | for an individual practitioner (HCP role) vs study team member (e.g. included on Delegation of Authority log)? |
| 59-60 & 76 | Sections V.A.3 and IV.C.2 are referenced. However, these section numbers do not exist in the document. It appears these may have been from an earlier version with a different numbering scheme. | Please clarify if these sections have been incorporated elsewhere in the document. Correct the references to the appropriate section number. |
| 113-122 | These two examples, while interesting, are not in today's clinical environment. Specifically, the streptokinase example is over 40 years old, and focused in Italy which would not be representative of the US population. The tocilizumab example pertained to COVID-19 in 2020 where health systems were operating under significantly different conditions as a consequence of a global pandemic. Additionally, the benefit/risk threshold was different in 2020 for a COVID-19 therapy than it is today. The guidance could benefit from FDA providing an example, or hypothetical scenario where a current drug product may benefit from the proposed approaches outlined | Provide an example that would apply to more sponsors under the current environment. If no real examples are able to be shared, we recommend a hypothetical example. This example could also be referenced in a later section to illustrate a more specific point (e.g., in the "choosing suitable investigational drug" section, why the drug in the example was a good fit, etc). |
| 139-144 | The use of EHR systems to capture data for clinical trials integrated into clinical practice may also facilitate the participation of small community health care facilities that have | We request clarification on the following aspects of EHR use in RCT data collection:<br>● Can you offer references to Data standards (e.g., USCDI+) and interoperability requirements to support a |

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| | historically been involved less frequently in FDA-regulated clinical trials. | reliable flow of data between HCPs and Investigator sites?<br>● Consider referencing any sections of the October 2024 guidance, Electronic Systems, Electronic Records, and Electronic Signatures in Clinical Investigations: Questions and Answers pertinent to the reliable integration of study-specific data collection in EHRs |
| 139-144 | The use of EHR systems to capture data for clinical trials integrated into clinical practice may also facilitate the participation of small community health care facilities that have historically been involved less frequently in FDA-regulated clinical trials. | Please provide recommendations and or examples on best practices to manage/ mitigate data variability from different HCPs/systems across trial sites.<br>Is the Agency referring to a similar issue raised in the Conducting Clinical Trials With Decentralized Elements guidance ( Section III, D, i) Is there a common set of recommendations that could be referenced?<br>We would urge a common set of recommendations to address both concerns. |
| 142-143 | Sponsors might consider providing additional resources to participating health care institutions, such as service providers or contract research organizations, to manage specific research requirements. | Are there limitations on support mechanisms offered by sponsors to healthcare institutions to support clinical trial conduct in HCP settings while complying with the Anti-kickback Statute? |
| 145-146 | Agreements between sponsors and health care institutions should document the responsibilities that are assumed by the institutions and their employees and the tasks that they will perform as part of the clinical trial. | Contracts/agreements with health systems for HCP participation. Clarify if the FDA recommends contracts with HCPs be managed by sponsors - or if this is simply an available option. |
| 210 | Trial-specific activities delegated to local HCPs may include, for example:... | Delegation of authority and oversight responsibilities: Please change terminology to request rather than delegate when PI engages |

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| | | HCPs in SOC data collection.<br>The term delegation may confuse trialists, and lead to the collection of HCPs on the DOA and 1572, in contrast to the draft guidance that specifies they don't need to be included. |
| 225-228 | It may be appropriate to engage local HCPs who are specialists in performing certain procedures (e.g., endoscopy, cardiac catheterization, biopsy) provided these procedures are within the scope of their practice and expertise. Such procedures should be covered by agreements between sponsors or investigators and health care institutions, local HCPs, and medical practices as applicable. | Please clarify if there is a preference for which party creates the agreement (sponsor or investigator) and if there are any additional requirements to assure sponsors are conforming to the Anti-kickback statute if they initiate these agreements. |
| 228-229 | Investigators should ensure that the reports from local HCPs who perform these procedures include the name of the local HCP and the dates that these procedures were performed. | Please confirm that this information is only recorded in source documents, either digitally as part of an audit trail, or manually if the documentation is paper-based. Also, we suggest clarifying in the final guidance that these HCPs are not expected to be part of the 1572 / DOA forms if assessments performed are aligned to standard of care. |
| 265-269 | The sponsor is responsible for monitoring the trial to ensure that it is conducted in accordance with the protocol and FDA regulations, including requirements related to good clinical practice.<br>Remote (including centralized) and/or onsite monitoring should be risk-based and should address the critical-to-quality factors that are needed to generate reliable results | The draft guidance emphasizes using a quality-by-design approach.<br>Further details are requested on:<br>● Expectations for source data verification in HCP settings (as above)<br>● Monitoring responsibilities and processes. Is there an expectation for sponsors to source data verify HCP-generated data?<br>● Please clarify if using EHR data sources changes any of the expectations for data |

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| | and ensure the safety of participants. | review and monitoring.<br>● Inspection scope and focus - what access will be expected to HCP sites? Or is all data expected to be available in some form for review at PI site?<br>● We request clear and consistent expectations regarding SDV and leveraging EHR /EMR such that POC guidance and the many existing guidances on using RWE to demonstrate clinical benefit are aligned. Additionally, expectations for what sponsors should be provided with respect to EHR access and be expected to review should be consistent across guidances. |
| 306 | Informed consent documents for a trial can be embedded in EHRs, akin to how clinical informed consent documents can be embedded in EHRs for patients undergoing surgery or other procedures. | Please clarify whether HCPs are appropriate to conduct consent conversations.<br>The guidance states that the consent may be integrated into the HCP EHR, but not whether HCP can administer consent. Our interpretation is that administering consent is a protocol-specific activity, and thus needs to be conducted by dedicated trial staff. |
| 333-336 | Trials involving approved or unapproved drugs with narrow therapeutic windows requiring therapeutic dose monitoring, those with complex dosing or administration regimens, those requiring special reconstitution processes, or those requiring specialized storage conditions <u>might not be suitable for integration into clinical practice.</u> | Comment: This statement implies that local HCPs (i.e., who don't have the requisite expertise or facilities) will store and administer the medication. That may not always be an accurate assumption, especially if the medication has previously been approved for use in the same /similar patient population.Sponsors could (unintentionally) interpret this language as 'do not attempt' to integrate trials with specialized dosing, administration, or storage needs in routine care.<br><br>Proposed Change: Suggest an additional sentence that clarifies such scenarios... "may require sponsors to consider additional |

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| | | specialized expertise or facilities needed to manage storage or administration of study medication." Also, the DCT guidance issued in Sept has more to say on this topic that suggests there are ways to manage this even in DCTs (see section on investigational products in DCT). Recommend that the Agency reference the DCT final guidance in this context to help sponsors be aware of strategies to address such challenges. |
| 370-372 | *If there is a significant concern about managing concomitant medications, then the study may not be appropriate for integration with routine practice.* | Comment: We acknowledge the Agency's hypothetical concerns that where significant concerns exist about HCPs managing concomitant medications, they believe such approaches may not be appropriate for routine practice. However, it's not clear from the current draft guidance how managing concomitant medications is better handled better in a traditional clinical trial vs a trial integrated in routine care.<br><br>Proposed Change: Encourage the Agency to provide an example(s) of how traditional clinical trials better enable managing patients' concomitant medications than routine care, or if this is not an appropriate blanket statement, then remove or revise with additional considerations stated. |
| 461-463 | The sponsor must ensure that source records (or certified copies of source records) to support clinical trial data submitted to FDA are available for review by FDA upon request. Records must be maintained and retained in compliance with FDA regulations. | Clarify access to source records generated by HCPs as part of the clinical data collection for the trial. Is this simply access to a copy of source generated by the HCP (digitally or paper-based)? Or is there an expectation that an FDA inspection might take place at the HCP's facility / office? |

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| No section | Patient management and long term follow up. | We suggest adding content to the guidance document to clarify expectations regarding<br>○ Tracking patients across different healthcare providers/systems<br>○ Aligning data capture timeframes to clinical trial visit / follow up timelines. Participant data collection must align to the trial parameters and not continue indefinitely.<br>○ Ensuring adherence to protocol assessment and visit timelines in routine care settings |