Decentralized Trials & Research Alliance

Response to Decentralized Clinical Trials for Drugs, Biological Products, and Devices; Draft Guidance for Industry, Investigators, and Other Stakeholders; Availability
(Notice #FDA-2022-D-2870)
Submitted to the Food and Drug Administration (FDA)
Submitted on behalf of the Decentralized Trials & Research Alliance (DTRA)
Submitted August 1, 2023

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.

The FDA draft guidance invites stakeholders throughout the scientific research, advocacy, clinical practice, industry, patient and lay communities, including the general public, to comment on recommendations for sponsors, investigators, and other stakeholders regarding the implementation of decentralized clinical trials (DCTs) for drugs, biological products, and devices. DTRA and its members thank the Agency for issuing this draft guidance, which sends a clear message that FDA is supportive of the adoption of decentralized research methods within existing regulatory frameworks. DTRA is pleased to provide our feedback and constructive suggestions to the Draft Guidance below.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, its branches and offices, and other stakeholders such as the NIH to leverage as they consider the implementation of 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. On January 23, 2023, DTRA responded to an RFI from the White House Office of Science and Technology Policy (OSTP) on Clinical Research Infrastructure and Emergency Clinical Trials by hosting a listening session and offering written comments.

DTRA welcomes this opportunity to share our membership's unique perspective and suggestions regarding federal initiatives to improve the decentralized trial research infrastructure including clarifying regulatory expectations and requirements via this draft guidance.

Clinical trial participation can be a burden to patients and may disproportionately create access barriers which may be mitigated through decentralized methods. As we modernize our clinical research enterprise to make it more patient-friendly, it will require reducing the exclusive reliance on hospitals and medical centers, and enabling broader access to patients , especially for participants from currently underserved and underrepresented communities, to trials. Utilizing decentralized trials and research methodologies offers significant potential to improve access to a greater segment of the population and simultaneously improve diversity in clinical research. Investigational sites remain a cornerstone of our clinical research enterprise, but these institutions may sometimes fail to provide adequate access to traditionally underserved populations. A national plan for a modern clinical trial ecosystem meant to also support diversity and inclusion must include the thoughtful use of decentralized research methods.

General Comments

DTRA would like to thank the Agency for taking this pivotal step in providing clarity and insight into the conduct of decentralized clinical trials, and how the data collected in a decentralized manner can support regulatory submissions in the US. While decentralized research methodologies have been incorporated into drug development for over two decades (Eli Lilly's trial from 2001[1], the Pfizer Remote trial[2], and others[3]), this guidance represents a seminal moment for the field as we focus on the future. Namely, this guidance enables sponsors, CROs and investigators alike to proceed with confidence with a regulatory framework to guide their incorporation of decentralized approaches into clinical trials. DTRA believes this guidance helps elucidate key considerations for trial conduct while maintaining appropriate flexibility for future advancement of decentralized research methodologies.

Site-based clinical trial processes (i.e. operations, data collection, recruitment) are often inaccessible, expensive and burdensome for participants, which may lead to low accrual and

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[1] Eilenberg KL, Hoover AM, Rutherford ML, Melfi CA, Segal S. From Informed Consent through Database Lock: An Interactive Clinical Trial Conducted Using the Internet. Drug Information Journal. 2004;38(3):239-251. doi:10.1177/009286150403800303

[2] Orri M, Lipset CH, Jacobs BP, Costello AJ, Cummings SR. Web-based trial to evaluate the efficacy and safety of tolterodine ER 4 mg in participants with overactive bladder: REMOTE trial. Contemp Clin Trials. 2014 Jul;38(2):190-7. doi: 10.1016/j.cct.2014.04.009. Epub 2014 May 2. PMID: 24792229.

[3] Dolgin, E. Industry embraces virtual trial platforms. Nat Rev Drug Discov 17, 305–306 (2018). https://doi.org/10.1038/nrd.2018.66

retention. These factors often result in study populations that can be non-inclusive and may not reflect the diversity of patients that eventually use the approved medical product. Falling short of trial recruitment targets may lead to under-enrolled clinical trials and trial discontinuation, ultimately hindering timely access to new therapies. DCT's, thus, have the potential to improve accessibility, diversity, and retention in clinical trials. We note the Agency's recent guidance encouraging sponsors to develop diversity plans to improve enrollment of underrepresented patient populations in clinical trials[4] and offer that DCTs can be a powerful approach to achieve that goal.

We commend the Agency for stating that investigations of medical products whether via DCTs or traditional site-based clinical trials must meet the statutory requirements under 21 CFR parts 312 and 812. Having a clear understanding that the Agency views DCTs as equivalent to traditional site-based trials is important for stakeholders to have faith in the results of DCTs and ensures that regulatory expectations for conduct of DCTs are understood.
The agency alludes to the importance of factors such as compliance to Part 11, Digital Health Technologies[5] and diversity plans in a well-designed DCT. We agree and add that another core feature of DCTs is patient-centricity. Therefore, we request the agency to explicitly reference the patient-focused drug development guidances in the final version of this guidance.

DTRA members conduct global clinical studies and therefore request the Agency to consider implications of the revisions to ICH E6(R3) annexe 2[6] which is expected to contain additional considerations for non-traditional interventional clinical trials including decentralized clinical trials and how they may be applicable to FDA's requirements. .

DTRA believes that FDA will serve as an invaluable partner in advancing the decentralized trial ecosystem in the United States. Enclosed in this letter, please comments and suggestions on around the following topics:

- Remote Audits and Cloud-Based Records
- Robustness of Remote Data Collection
- Digital Health Technologies (DHTs)
- PI and Sponsor Oversight
- Patient Centricity
- Next Steps

[4] Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials Guidance for Industry, Draft Guidance issued April 2022, https://www.fda.gov/media/157635/download
[5] Digital Health Technologies (DHTs) for Drug Development, FDA website accessed July 20,2023; https://www.fda.gov/science-research/science-and-research-special-topics/digital-health-technologies-dhts-drug-development
[6] ICH HARMONISED GUIDELINE GOOD CLINICAL PRACTICE (GCP) E6(R3); Draft endorsed May 2023; https://database.ich.org/sites/default/files/ICH_E6%28R3%29_DraftGuideline_2023_0519.pdf

We have provided line edits for the sections contained within the guidance and offer an appendix with schematics for a proposed flow chart of PI-oversight within a decentralized trial.

Remote Audits and Cloud-Based Records

We encourage the Agency to take a forward-looking approach to enable the wide adoption of DCTs. For example, the guidance notes there should be a physical location where all clinical trial-related records are accessible and where trial personnel can be interviewed (Lines 93-95). We request FDA to acknowledge that trial and source records could be cloud-hosted (with appropriate system controls for access, security, privacy and confidentiality) and therefore accessible remotely by the inspector, removing the need for a physical location and/or visit in the final version of this guidance. In addition, it is not entirely clear from this section whether remote trial staff (those listed on FDA 1572) are expected to be available in person for interviews. With advances in video-conferencing technologies allowing for widespread use and familiarity with these tools, we ask the FDA to allow flexibility in the final version of this guidance by giving the option of staff being interviewed remotely.

We point the agency to the approaches taken during the recent Covid-19 public health emergency (PHE) where sponsors exercised considerable flexibility by leveraging tools including video chats with site personnel, scanned document uploads etc to fulfill inspection requirements. During the COVID-19 public health emergency, the FDA expanded its use of alternate tools for assessing facilities named in applications, including exercising its authority to request records and other information in advance of or *in lieu* of an inspection, granted per section 704(a)(4) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 374(a)). While the PHE has ended, there is value in revisiting the many flexibilities offered and assessing their appropriateness as applicable to inspections now and in the future.

Lastly, we note that in the recently passed legislative reauthorization of prescription drugs user fees (PDUFA VII), via the **Continuing Appropriations and Ukraine Supplemental Appropriations Act of 2023**[7]**,** there are commitments for FDA to advance Covid-19 lessons learned, such as increased use of digital technologies and alternatives to in-person visits to assess manufacturing facilities. These could be a valuable source to extrapolate beyond manufacturing and consider in the context of clinical sites as well.

[7] CONTINUING APPROPRIATIONS AND UKRAINE SUPPLEMENTAL APPROPRIATIONS ACT, 2023 , TITLE 1; https://www.congress.gov/117/plaws/publ180/PLAW-117publ180.pdf

Robustness of Remote Data Collection

We encourage the Agency to consider the advantages a decentralized trial may have over a conventional trial. For example, the FDA states the validity of findings from a non-inferiority study design may be subject to more variability in assessments done remotely and that drug effects, evaluated by traditional clinical studies, may be different from those obtained in a DCT (Lines 98-101). These statements suggest that data obtained remotely have more variability and are less precise than those obtained via traditional methods and further that the main cause of this variability is related to decentralization. This hesitation on the part of the Agency to accept data obtained via remote collection methods may discourage drug developers from conducting a DCT. Even if the Agency wants to include this section in the final version of the guidance (*which we believe warrants qualification*), we suggest more balanced messaging that incorporates some of the benefits to data collection in a DCT such as more continuous data collection, the ability to detect rare adverse events and novel methodologies to study a particular disease/condition. While existing methods and tools may be unvalidated, these will improve, and in fact be more sensitive when compared to current state-of-the-art traditional methods. Thus, the agency should collaborate with vendors, sponsors and other key stakeholders to establish standards and validated methods for remote data collection. Further, the agency should establish a framework whereby both tools and methods can be validated such that novel approaches can be trusted by the agency and the larger clinical trial research community.

With respect to the data flow diagram and associated components of the data management plan (e.g. list of vendors, methods of remote patient data acquisition), we encourage the Agency to consider being less specific as to its suggested location (Lines 198-208). Oftentimes these plans are not shared with site personnel who would benefit from knowing and understanding the sources, vendors and flow of data. This information could be maintained in the sponsor managed DMP, but should be provided to participating research sites as a living document. In summary, DTRA believes these data flow diagrams are a positive development and will ensure the complex nature of data collection in a DCT is well-understood and well-reflected by the sponsor.

Digital Health Technologies

A fundamental facet of certain decentralized trials will be leveraging digital health technologies (DHTs) for remote data capture. We are strongly supportive of the FDA for recognizing the appropriate role of the sponsor in providing DHTs to participants, and how that helps ensure that patients from a wide range of socioeconomic backgrounds are able to participate in clinical trials. Patients may also like a “Bring Your Own Device” or BYOD option and it would be helpful for FDA to address that scenario in the final guidance. When/if allowing patients the option of

BYOD, it would be important for Sponsors to identify criteria for using the BYOD and identify any potential risks around using BYOD vs. provisioned devices. FDA should address any additional concerns with a combination of BYOD and provisioned DHTs and the comparability of data collected with each method.

It would also be beneficial for FDA to address how mixed models would be handled when some participants are willing to use DHTs for remote monitoring while others may prefer traditional site visits and monitoring; or a study-designed to give patients optionality to choose either remote monitoring via telehealth appraisal or an in-person visit a few days before each assessment is to be completed.

An existing challenge with DCT data collection and validity pertains to the standards, terminology, conformance, and interoperability of DHTs. For example, in a DCT, the patient, caregiver or HCP using DHTs should be trained on appropriate usage and understand the conditions and applicable rules to operate the device , to ensure the integrity of data collection. The end-user should also be offered adequate support and help in case of technical difficulties. When such data collection tools are also designed to be interoperable, a greater level of clinical decision support (e.g. real time and remote monitoring of safety events) and quality oversight is achievable. Fast Healthcare Interoperability Resources (FHIR) is an option to facilitate the normalization of these challenges and ensure conformance, and interoperability of remote monitoring tools such as DHTs with existing clinical trial portals. Data acquisition, transmission, quality, and reliability challenges can be reduced or eliminated when such information is collected consistently and in a standardized manner. When HCPs, vendors, and sponsors utilize a consistent and interoperable framework (e.g., FHIR), the risk-based monitoring challenges can become automated in near real-time to detect missing data, inconsistent data, data outliers, and other critical components. [8]

PI and Sponsor Oversight

A longstanding challenge both sponsors and investigators have grappled with in decentralized research is Principal Investigator (PI)-oversight expectations and associated documentation. While the FDA's *Form 1572 Statement of Investigator* is well-suited for conventional, site-based clinical research (with centralized PI and associated institutions), it faces limitations in scenarios where remote assessments and delivery of care are a central feature. DTRA is committed to working with sponsors, PIs, FDA and others to resolve this issue. For example, DTRA's 1572 CoLab is creating resources such as sample 1572 decision trees, suggested documentations by trial activities, and considerations for alternative research sites. We share some of these draft resources in the appendix as illustrative examples of how we envision study documentation elements adapting to the nuances of decentralized research methodologies.

[8] https://www.healthit.gov/topic/interoperability/policy/trusted-exchange-framework-and-common-agreement-tefca

DTRA appreciates the Agency's recommendations on the roles and responsibilities of Sponsors and Investigators as detailed in the guidance. In general, we are aligned with the Agency's threshold for inclusion of trial staff contributing "directly and significantly" (Lines 271-272) for those who should be listed on the Form 1572 and excluding those who "provide trial related services that are part of routine clinical practice" (Lines 274-279). Such a delineation balances the need to ensure oversight while providing sufficient flexibility to allow decentralized models to be effective. However, ambiguity remains as to this specific threshold test, and additional clarity would be welcomed .

For example, it is unclear how to document local HCPs who are conducting activities that contribute to assessments around SAEs/AEs but do not require detailed knowledge of the study protocol. There are many other 'gray areas' regarding PI oversight, the use of local HCPs, and other considerations that warrant the inclusion of a non-exhaustive list of examples and appropriate levels of documentation in the final guidance. PIs are rightfully hesitant to assume oversight accountability when centralized third party service providers, who are selected and contracted by the sponsor, perform significant clinical trial related duties which will have a direct and significant contribution to the data. In this instance, principal investigators may be unwilling to assume accountability for oversight of these third-party service providers. Furthermore, some institution-based sites do not allow contracting for the study with DCT elements or the addition of a non-employee (third party vendor) on the delegation of authority. It would be helpful to clarify PI-oversight expectations in these situations, or to define a different level of accountability for services providers not contracted directly by the PI. We note that the EMA Recommendation Paper on Decentralized Elements of Clinical Trials[9] states an expectation that investigators have an active role in choosing service providers and ensuring they are appropriately trained to complete expected trial duties. As most clinical trial sponsors conduct trials globally, we would find it helpful to have some commonality between the FDA's final guidance and the EU's recommendations on PI-oversight and its relation to third-party selection. As the regulatory framework for DCTs is intended to support adoption, we need to find a way to separate the principal investigator from those parties over which they have little control, i.e. third party service providers contracted by the clinical trial sponsor. We recommend that this be a key consideration for any future guidance on the clinical trial oversight documents (e.g Form 1572).

The risk-based principles of PI-oversight for local HCPs should also be extended to laboratory and imaging services. If such facilities are performing routine exams and testing consistent with activities undertaken at those facilities in a non-clinical trial context, they should not be included

[9] RECOMMENDATION PAPER ON DECENTRALISED ELEMENTS IN CLINICAL TRIALS Version 01, 13 December 2022; Issued jointly by the Heads of Medicines Agency, the European Commision and theEuropean Medicines Agency; https://health.ec.europa.eu/system/files/2023-03/mp_decentralised-elements_clinical-trials_rec_en.pdf

in 1572 forms. Investigators will be challenged with overseeing activities at such facilities, with which they may have little to no contact,connection or privileges. Inclusion of such facilities in the task log would be feasible since the information on the facility should be included within results provided. We would propose that the threshold for when to include such facilities in form 1572 should be whether the testing and imaging performed extends beyond what they might perform on a routine basis. This would exclude for example, standard measurement of lipid profiles, but would include any assessments called for by a protocol which are not part of standard laboratory analysis. We believe such an approach helps to support the adoption of decentralized trials, without compromising the quality of data collection or patient safety.

There remain some basic questions DTRA seeks to have addressed in the final guidance regarding the optimal usage of the task log. We note that the task log is a newly required form, and that it is not currently used in traditional clinical trials. We believe that the purpose of the task log is to provide information on individuals performing clinical trial-related activities under the supervision of the PI. However, we know that not all individuals performing clinical trial activities as part of standard of care in traditional trials are named on the 1572 or in the Delegation of Authority logs. Our concern is that the task log may increase documentation burden and complexity for investigative sites beyond what is required for a conventional clinical trial. This new requirement would necessitate resources including developing training materials, SOPs, dedicated personnel etc. all of which could be a deterrent to sponsors' willingness to adopt DCTs.

Further, we request the guidance clarifies that the task log entries can be retrospective or whether timing is critical for capturing full signature/initial date on the log (which may/could result in an inspection finding). DTRA also requests clarification on how to best capture local facilities, and how this approach may differ between inclusion of said facility in Form 1572 and that of the task log. Specifically, DTRA wonders whether local facilities should be identified and /or specified at or around the time the patient is being identified/screened/enrolled. Often, a single large service provider may be contracted to perform services detailed under the task log. In that case, it is highly unlikely that all of the individual HCPs who may eventually provide some non-critical clinical services would be identified at time of patient enrollment. Accordingly, DTRA requests that the Agency confirm that the task log instructions be written to specify an entity and not require named individuals.

We recognize that the conventional methods of PI and sponsor oversight will have to significantly evolve to meet this new paradigm of care delivery. As mentioned, DTRA is supportive of many of the delineations drawn in this initial draft guidance. However, sponsors and PIs alike would benefit from the addition of an appendix to the guidance that depicts

potential scenarios and the appropriate level of oversight required. To this end, DTRA offers potential flow charts, with proposed disposition in Appendix 1.

Patient Centricity

Patient centricity in drug and biological product development, which is sometimes restricted to use of Patient Reported Outcomes (PROs), can be a central feature of the design of a clinical study and if it allows for DCT options it can mitigate barriers imposed by traditional clinical trials that delay or even prevent access to trials for patients who might sometimes not have other options for medical care. Rare disease patients in particular might benefit from the increased use and regulatory acceptance of DCTs which in turn may help address the 93-95% of rare diseases that do not have FDA-approved therapies (source).

Implementing one or more elements of DCTs, spanning the spectrum from hybrid approaches to fully decentralized studies, can: improve and expedite enrollment for rare disease trials with limited patient populations; improve trial population diversity to match disease population demographics more closely; mitigate logistical and financial burden for patients and their families, especially those with difficulty traveling; improve patient safety by reducing unnecessary exposure to infectious disease, especially for immunocompromised patients, improve retention of patients in studies, allow rural and underserved patient populations to get access to cutting edge clinical advances and; potentially lower trials costs for sponsors (source).

However, we note that considerations for the patient voice to be embedded in DCTs do not appear to be adequately-reflected in this guidance compared to other considerations. As for traditional clinical trials, patient-centricity should be a key factor for sponsors employing decentralized research methodologies. For example, the Agency refers to existing guidance around Part 11 and DHTs, however, does not mention how recommendations from the series of patient-focused drug development guidances can be integrated into DCT design and execution.

Additional Resources

We applaud the Agency for developing a glossary as part of this guidance**.** We suggest this glossary be maintained as not merely a reference but as a living document that is revised as appropriate. We point the Agency to an existing tool namely the BEST resource[10] which allows the clinical trial community to use uniform language that in turn enables better communication. A similar approach could be used for a DCT specific glossary and we offer the Agency a glossary

[10] FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource [Internet]. Silver Spring (MD): Food and Drug Administration (US); 2016-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK326791/ Co-published by National Institutes of Health (US), Bethesda (MD).

that we host on our own website as an additional resource[11] to consider as they develop a final version of this guidance.

As stated in DTRA's mission, we seek to be a preeminent, cross-functional organization that unites stakeholders in promoting the global adoption of decentralized research methods. 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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[11] DTRA glossary; https://www.dtra.org/1a-glossary

SPECIFIC COMMENTS

I. BACKGROUND		
Lines/Section/Text Reference	*Draft Guidance Text*	*Comment/Recommendation*
63-65	Fully decentralized trials may be appropriate for investigational products (IPs) that are simple to administer for use, have well-characterized safety profiles (see section III.F), and do not require complex medical assessments."	The association of fully decentralized trials with simple to administer IP could be interpreted as precluding the use of ambulatory infusion suites with pharmacies that prepare the infusion and clinical staff experienced in administering infusions and caring for the participants. Proposed Change: **Fully decentralized trials may be appropriate for investigational products (IPs) that are simple to administer for use (either by the patient themselves or through routine administration routes such as ambulatory infusion centers),** have well-characterized safety profiles (see section III.F), and do not require complex medical assessments It would be helpful if the Agency could provide examples of complex medical assessments in the final guidance via an appendix. While we recognize that the examples will not be exhaustive, we nonetheless request a sampling of scenarios spanning a variety of therapeutic areas as those will help sponsors gain greater understanding of FDA's thinking in this regard.
73	These plans should include, as appropriate, the use of local health care facilities, local HCPs, and local clinical laboratory facilities; visits to trial participants' homes; and direct distribution of the IP to trial participants at their locations.	Suggest that participant direct data capture be included in this list of elements for a plan.
77	Appropriate training, oversight, and up-front risk assessment and management will be key to implementing a DCT successfully	Kindly consider adding effective monitoring, without which it will be difficult to ascertain the success of the DCT or take corrective action during the trial conduct phase

II. RECOMMENDATIONS FOR IMPLEMENTING DCTs		
Lines/Section/Text Reference	*Draft Guidance Text*	*Comment/Recommendation*
A. DCT Design		
93	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	The requirement to have a physical location associated with the clinical trial-related records would prevent implementation of a completely or largely virtual trial. Please clarify FDA's thinking on flexibility to use alternative inspection tools, such as remote records evaluations or virtual inspections, instead of in-person expectations. There may be situations where maintaining a single physical location for inspection purposes only may not be warranted. Consideration should be made for the virtual/online storage of all clinical trial records for participants under the investigator's care and should be noted in this section. It is not clear what it is meant by all trial personnel being accessible at the physical location to be interviewed. We recommend the removal of the concept of a single location where "trial personnel can be interviewed", as it's unlikely all trial personnel will be at one facility Suggested edit: "For inspectional purposes, there should be a ~~physical~~ ~~location~~ **process to securely access** ~~**where**~~ all clinical trial-related records **(including electronic records)**.... ~~are accessible~~ and **interview** trial personnel ~~can be interviewed~~."
103	Assessments performed by local HCPs as part of routine clinical practice (e.g., evaluation of symptoms) may also be more variable and less precise than assessments conducted by dedicated trial personnel.	We urge FDA to consider that local HCPs may often be able to perform assessments appropriately based on their training at a level comparable to trained personnel. Moreover, where testing is more complex or specialized, with appropriate training and educational materials, local HCPs are not necessarily more variable and less precise than dedicated trial personnel. Such language could have the unintended consequence of introducing unwarranted stigma against DCTs.
105-110	In non-inferiority trials, when the effect size of an active control drug, for example, has only been	Comment: Clarify that if the evaluation or measurement is based on a central reader (e.g., central labs, or

	determined in a traditional site-based clinical trial, it may not be reasonable to assume that the same effect size would be seen for the active control drug in a DCT. This may present challenges in calculating a non-inferiority margin. FDA review divisions should be consulted when planning a non-inferiority trial in a DCT setting	through a central adjudication committee), the effect size and non-inferiority margin should not be impacted. Proposed Change: In non-inferiority trials, when the effect size of an active control drug, for example, has only been determined in a traditional site-based clinical trial, it may not be reasonable to assume that the same effect size would be seen for the active control drug in a DCT. This may present challenges in calculating a non-inferiority margin. If the evaluation or measurement is based on a central reader (e.g., central labs or central adjudication committee), the effect size and non-inferiority margin should not be impacted. FDA review divisions should be consulted when planning a non-inferiority trial in a DCT setting.
B. Remote Clinical Trial Visits and Clinical Trial-Related Activities		
119	The protocol should specify when a telehealth visit with a trial participant is appropriate and when a participant should be seen in person.	We agree with the statement and ask that the Agency clarify in the final version of this guidance , that ad hoc telehealth visits or flexible approaches allowing participant choice between telehealth or in-person can also be clarified in the SoA
126-132	Depending on the trial protocol, in-person visits and trial-related activities may also be conducted by HCPs who are located close to trial participants' homes but are not part of the trial personnel. These local HCPs (such as doctors or nurses) may be used by sponsors or investigators to perform certain trial-related activities; for example, on a fee-for-service basis. 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.	We request the agency consider providing further clarity on the utility of the task log (Delegation of Authority log) if the "local" HCPs need signature/initials/date on the log along with identifying their "task". We also ask for more clarity on the training for those local HCPs conducting services that are not different from clinical practice but conduct activities that contribute to the Schedule of Assessments that lend to AEs/SAEs reporting of a patient's condition - to be provided a detailed knowledge of the protocol and IP (also noted for lines 274-279). Please refer to the sample flow chart on page 63 for determining if a study activity is standard of care

128	The Draft Guidance states: "These local HCPs (such as doctors or nurses) may be used by sponsors or investigators…"	As written, it is unclear whether there is any impact to PI oversight responsibilities based on who directly engages with the local HCP to conduct standard of care clinical assessments.
135-138	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. When applicable, both trial personnel and trial participants should be trained on how to conduct or participate in a telehealth visit.	The distinction between Trial Personnel and "Local HCPs" performing non-interventional activities should be clarified. At a minimum for those performing non-interventional activities, a knowledge of safety aspects of the protocol should be demonstrated.
140	"*During each remote trial visit, investigators should confirm the trial participant's identity'*	While we understand the underlying concern behind this directive, we suggest that there are instances where this may not be necessary. For example, when the same HCP is visiting a participant at their home (or via televisit), there might not be a need to verify participant's identity each time. We therefore recommend the FDA evaluate the extent to which verification of participant identity would be needed.We would recommend FDA consider revising the requirement such that patient identity is verified at the start of the trial or during the first remote visit, if identity is established up front.
144-145	Case report forms and other documentation should be completed for telehealth visits, including the date and time of the visit.	Comment: Why must time of visit be recorded vs. just date? When an activity is time-critical, the date and time should both be recorded. This sentence is unclear on why timing is critical for a telehealth visit and it is not for an on-site visit. Plus time-zones might influence the meaning of the time as recorded. Proposed Change: Please remove documenting time as mandatory as we do not collect time in traditional eCRFs. Also note that the time of data entry is included in data audit trails, so may be available in that digital format, reducing both error and documentation burden.
147	Trial protocol should specify how AEs identified remotely will be evaluated and managed	Comment: This could be outlined in other trial documentation/training vs. protocol only.

		Proposed Change: Trial protocol or other trial documentation or training should specify how AEs identified remotely will be evaluated and managed.
149-152	The Draft Guidance states: "It is the 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."	Suggested edit: "**The entity that is engaging the provider of the telehealth platform is responsible** 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."
182-185	The Draft Guidance states: "…sponsors should ensure proper coordination of the decentralized activities…"	Updated draft or final guidance should clarify what is meant by coordination and clearly state to what degree retain oversight responsibility of trial personnel and local HCPs who are conducting trial-related activities, especially if the PI was not included in selection of these individuals or third parties.
C. Roles and Responsibilities		
210	Sponsors should describe in the trial protocol how operational aspects of the DCT will be implemented.	We welcome FDA allowing sponsors the opportunity to describe operational aspects of DCT. In addition, we request the final version of this guidance allowing sponsors opportunity to discuss these operational aspects with FDA to make corrections; if needed; based on feedback. This may help prevent unnecessary delays in clinical development that would slow patient access to treatments. We also ask the agency to detail in the final version of the document when (e.g. pre-IND, EOP2 etc.) and what meeting type would be best suited for these discussions.
224	"*Case report forms should identify when and **where** data were collected **and by whom**"*	We recommend FDA consider removing the requirement that the CRF capture when, where, and by whom data was collected. We instead recommend that the CRF should identify if the data was collected on-site or remotely, the date of collection, and that the source records identify who collected the data. We note that case report forms (CRFs) do not often capture who conducted the visits and/or collected the data. In many cases sites will have data entry coordinators entering data into the EDC. The source notes (i.e., EMR) would

		capture this level of detail, but it would be uncommon to have this captured in the CRF. In addition, the location or where the data is collected is also not captured in the CRF. In addition, the time of data entry is collected in the CRF or DHT audit trail but outside of certain required assessments (i.e., laboratory assessments) the specific time of data collection is not in the CRF
224	Case report forms should identify when and where data were collected and by whom.	In the current system we leverage CRFs and we aspire to move to an entirely electronic CRF (eCRF) system. As we digitize more and more of the clinical trial ecosystem, we may eventually be able to collect, collate and export data directly into portals or the cloud e.g. real time data collection and deposit via a DHT. Thus, it will be helpful for the agency to expand upon the details of utilizing eCRFs , especially when combined with EMRs, DHTs, integrated lab portals etc. Specifically, will we still need individual eCRFs?
234	"*Specify the frequency with which trial records and source documents will be reviewed*"	We recommend changing this line to read: "*Specify the sampling plan or plans that will be used to identify the specific records and data that will be monitored*" Using the term "frequency" may be not in line with risk-based approaches to monitoring where often there is no fixed frequency of reviews and timing of reviews are driven by predefined triggers. In addition, this will keep consistency with the FDA guidance "*A Risk-Based Approach to Monitoring of Clinical Investigations Questions and Answers Guidance for Industry*", Section Q6
250-252	The decentralized features of the clinical trial may necessitate additional training, coordination and standard operating procedures to ensure consistent implementation.	It would be helpful to include an appendix in the final guidance with suggested training / SOPs specific to DCT implementation,for example: ● documented training to use any data capture platforms and or devices. ● Communication plans to specify expected completion timelines for data entry / review / query resolution (similar to traditional trials) ● A clear safety communication plan to ensure PIs are alerted to changes in

		patient signs / symptoms, and a RACI to document roles and responsibilities in recording, reporting, assessing severity and causality of AEs.
267-279	As for any drug trial subject to 21 CFR 312.53, Form FDA 1572 must be completed by all investigators. The decision to include individuals as sub investigators in a DCT should be based on their assigned responsibilities. - When trial personnel contribute directly and significantly to the trial data, they should be included on Form FDA 1572 as subinvestigators. - Local HCPs contracted to provide trial-related services that are part of routine clinical practice (e.g., performing physical examinations, reading radiographs, obtaining vital signs) and where a detailed knowledge of the protocol, IP, and the investigator's brochure is not necessary should not be listed on Form FDA 1572 as subinvestigators. However, local HCPs should be included in a task log (as described below in this section).	As with the distinction between "Trial Personnel" and "Local HCPs" – further clarity as to FDA 1572 requirements would be appreciated.. A precise definition of "when trial personnel contribute directly and significantly to the trial data" would support appropriate categorization. Whilst a Local HCP would rarely, if ever be regarded as a sub-investigator, a Local HCP considered "Trial Personnel" could, with appropriate training, perform trial related activities that fall outside of routine clinical practice, such as administration of IMP It would be helpful for FDA to provide clarity through examples, such that trial sponsors, contracted service providers and investigational sites are all aligned in their understanding of these terms.. Further, this would help auditors review and document findings using a consistent set of expectations. Please consider adding a table in the final guidance of HCP roles in a clinical trial and HCP roles that interact with a trial participant, from PI to home health nurse to ER staff and indicate whether the role should be on the 1572, the task log or does not need to be documented.
303-305	The task log should include (1) the names and affiliations of the local HCPs, (2) a description of their roles and assigned tasks, (3) the dates these local HCPs are added to the log, and (4) the locations where these activities are conducted.	Often, a single large service provider may be contracted to perform services contemplated under the task log. In that case, it may not be possible to identify all of the individual HCPs who would be involved. If this is the case, we recommend that the overall service provider be named on the 1571 (contracted third party vendors) and the individuals are not named in the task log. If protocol-specific activities are conducted, these individuals are documented on the Delegation of Authority log.
300-309	As part of preparing and maintaining adequate case histories, investigators must maintain a task log of local HCPs	In a DCT, the PI may not have a role in selecting/qualifying local HCPs/facilities, and only be informed of the results. We request the Guidance clarify whether the task log entries can

	who perform trial-related activities. The task log should include…	be retrospective or whether timing is critical for capturing full signature/initial date on the log (which may/could result in an inspection finding). We also request clarification in the guidance on how local "Facilities" are to be captured in a "task log" (vs Form FDA 1572), e.g. should local facilities be identified in the respective sites Form FDA 1572 section #3 (per FAQ #26 of Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs), and can the collection of the accreditation documents be collected after a period of time of when the patient is enrolled into the study, as often times the local facility is identified at or around the time the patient is being identified/screened/ enrolled.
329-330	All clinical laboratory facilities should be listed on Form FDA 1572 or in the investigational plan for device studies under an IDE.	With the expansion of local lab facilities, this will create multiple versions and longer lists for the sites to maintain. We suggest that only the primary laboratory for each institution be listed on the 1572 with information about each local lab listed elsewhere (e.g. task log).
F. Investigational Products in a DCT		
369, 377	"*An investigator must administer an IP only to participants under the investigator's personal supervision or under the supervision of a sub investigator responsible to the investigator*" (Line 369) "*For IPs for which the safety profile is well characterized and that do not involve specialized monitoring during the immediate period following administration it may be appropriate for local HCPs or trial personnel working remotely to administer the IP at local health care facilities or participants' homes*" (Line 377)	We recommend the FDA add an additional scenario in the final guidance for IPs that are well tolerated or have a well classified safety profile *which may be self-administered by the participan*t e.g. oral pill - in which case they may not need any supervision or HCP to administer.
369-393	The Draft Guidance states (Lines 369-370):	"An investigator must administer**, or delegate the administration to an authorized individual, and have oversight of the administration of** ~~an~~ IP

	"An investigator must administer an IP only to participants under the investigator's personal supervision..." then proceeds to state (Lines 378-380), "…it may be appropriate for local HCPs or trial personnel working remotely to administer the IP at local health care facilities or participants' homes." Direct shipment to the participant's home is also raised (Line 390-393). As written, lines 369-370 seems to contradict the subsequent statements	~~only~~ to participants under the investigator's ~~personal~~ ~~supervision~~ **oversight**..." Line 132 states services performed by local HCPs "should not require detailed knowledge of the protocol or the IP." What are the expectations regarding knowledge of protocol and IP if a local HCP is administering the IP?
372-374	IPs that involve complex administration procedures; have a high-risk safety profile, especially in the immediate post-administration period; or are in early stages of development such that the safety profile is not well defined may need in-person supervision by the investigator at a trial site.	We suggest that a formal risk assessment that addresses the IP's complexities, storage conditions, and safety profile be taken into account when considering DCT administration of IP. This allows any trial to potentially utilize decentralized shipping/transport methods as long as the risks have been addressed, documented, and appropriately mitigated. Proposed Change: A risk assessment must be conducted reviewing the complexity of administration procedures and the IP's safety profile to document safeguards and provisions to ensure participant safety.
400	"Medical devices suitable for home use (i.e., over-the-counter devices) that do not pose significant risks to trial participants may be appropriate for use by trial participants without the investigator's direct oversight"	We request FDA to note that some medical devices may be prescribed, and not over-the-counter, and still be used by patients at home (i.e., holters or patches that collect temperature or cardia data). Please consider adding a reference to the information Sheet Guidance for Significant Risk and Nonsignificant Risk Medical Device Studies
G. Packaging and Shipping of Investigational Products		
419-420	The protocol should describe how the physical integrity and stability of the IP will be maintained during shipment to trial participants, including appropriate packaging	We recognize the importance of requiring detailed information on IP that will be shipped to participants. However, we recommend that the content of the protocol remain at a high-level when discussing Preparation, Handling, Storage, and Accountability of IP with further details

	materials and methods (e.g., temperature control).	provided in a supplemental document like pharmacy manual if needed. A cross-reference statement could be included in the protocol to point to where more details can be found on this topic. This optionality would allow the sponsor to provide detailed information via the supplemental document to participants, HCPs, local pharmacists etc. without sharing the trial protocol.This will ensure that only pertinent and essential information is shared with individuals. Proposed Change: The protocol, **or supplemental document**, should describe how the physical integrity and stability of the IP will be maintained during shipment to trial participants, including appropriate packaging materials and methods (e.g., temperature control).
425-426	The Draft Guidance states: "When relevant, DCT personnel should be trained on procedures and appropriate documentation for handling, packaging, shipping, and tracking IPs."	Suggested edit: "When relevant, ~~DCT~~ **trial** personnel should be trained on procedures and appropriate documentation for handling, packaging, shipping, and tracking IPs, and trial participants in the correct handling of IMP if IMP is shipped directly to the participant. We also recommend the Agency includes expectations for local HCPs.
428-432	A central distribution service could be used to ship the IP directly to trial participants. 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	Comment: We recommend that the content of the protocol remain at a high-level with further details on IP provided in a supplemental document like a pharmacy manual if needed. A cross-reference statement could be included in the protocol to point to where more details can be found on this topic. Further, additional clarification on the level of detail the Agency is intending by "according to procedures described in the protocol" is welcomed to understand if the Agency is requesting additional detail than has historically been provided for traditional protocols. Proposed Change: A central distribution service could be used to ship the IP directly to trial participants. 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 **or supplemental document**; and monitor the return or disposal of any unused product as directed by the sponsor

434-439	The protocol should describe how investigators will track and document that trial participants (or participants' legally authorized representatives) receive IPs. The protocol should describe procedures that investigators or participants (or participants' legally authorized representatives) should use to return or dispose of unused IPs and how this will be documented.	Comment: This information is not usually included in the protocol, but rather in training or the Manual of Operations/Pharmacy Manual. The Sponsor should provide investigators with instructions to follow for handling and storage of the IP, including receipt, dispensing, retrieval of unused product and return or alternative disposition per Sponsor's instruction.However, this level of operational detail does not need to be described in the protocol. Proposed Change: Change "protocol" to "study-specific manuals."
428-432	A central distribution service could be used to ship the IP directly to trial participants. 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.	Recommendation appears to be to ship directly to participant or legal representatives. Accommodation should be made for receipt by Local HCP.
H. Safety Monitoring Plan		
453-454	The monitoring plan should prespecify if and when telehealth visits or in person visits (e.g., physical examinations) will be scheduled with trial personnel or local HCPs to collect safety data by (see section III.B).	Comment: Requiring the monitoring plan to specify "if and when" the visit type takes place can lead to unnecessary deviations and limit flexibility for clinical trial participants and the PI to enable changes to visit method without deviating from the protocol. Proposed Change: The monitoring plan should prespecify **how** ~~if and when~~ telehealth visits or in person visits (e.g., physical examinations) will be **monitored** ~~scheduled~~ with trial personnel or local HCPs to collect safety data ~~by~~ (see section III.B).
464-465	The Draft Guidance states: "Trial participants should be able to arrange for an unscheduled visit using telehealth or an in-person visit, as appropriate (see section III.B)."	Suggested edit: "Trial participants should be able to arrange for an unscheduled visit using telehealth or an in-person visit, as appropriate (see section III.B)**, and as allowed in or authorized by the protocol**."
I. Software used in Conducting DCTs		

526-531	The Draft Guidance states: “FDA considers real-time video interactions, including telehealth, as a live exchange of information between trial personnel and trial participants. These live interactions are not considered electronic records and, therefore, are not subject to 21 CFR part 11, but local laws governing telehealth may apply. Privacy and security of these real-time visits should be ensured, and the visits must be documented.If this documentation is captured in electronic form, such documentation is subject to 21 CFR part 11. “ As written this section is unclear.	Suggested edit: “FDA considers real-time video interactions, including telehealth, as a live exchange of information between trial personnel and trial participants. **Privacy and security of these real-time visits should be ensured, and the visits must be documented.** ˍThese live interactions are ~~not~~ **only** considered electronic records ~~and, therefore, are not~~, **subject to 21 CFR part 11 if they are recorded and stored**, but local laws governing telehealth may apply. ~~Privacy and security of these real-time visits should be ensured, and the visits must be documented. If this documentation is captured in electronic form, such documentation is subject to 21 CFR part 11~~.
Glossary		
556-557	**Investigational Product** (**IP**): Human drugs, biological products, or devices that are being investigated in a clinical trial	Comment: GCP definition makes specific reference to the product being used as a reference also, e.g., comparator Proposed Change: Change to the ICH GCP definition of IP

Appendix

DTRA has chartered cross-functional teams to create processes and tools to support the adoption of DCT trial design and execution. These teams have created some support materials, based on our best interpretation of the Decentralized Clinical Trials for Drugs, Biological Products, and Devices Draft Guidance, 1 May 2023.

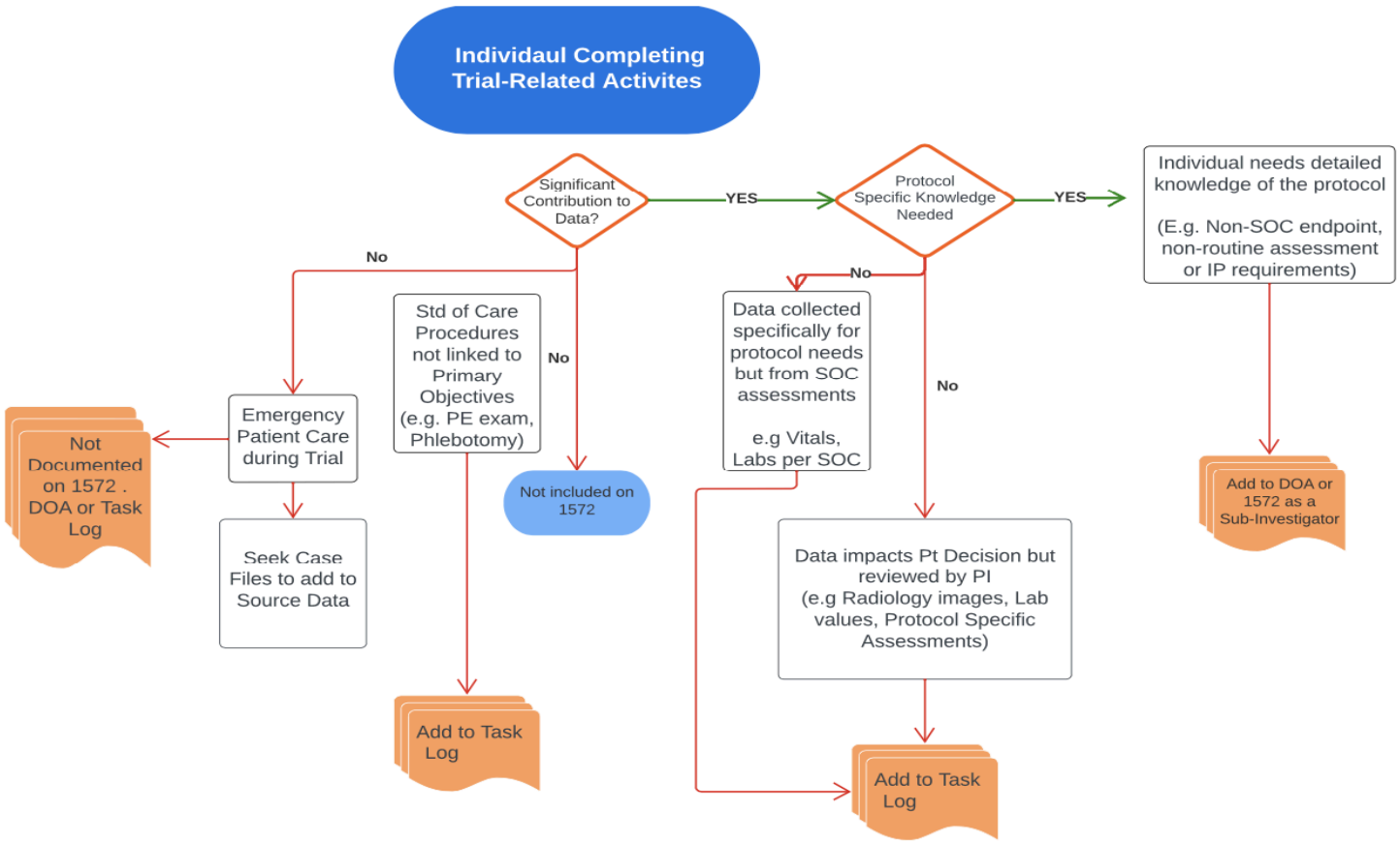
We include these support materials as a basis to illustrate our interpretation of the guidance. We have created two decision trees; the first is Intended to help DCT teams determine which trial assessments might fit the Standard of Care setting. This is not a case-study specific example and is meant to help teams apply common criteria when making these determinations.

The second decision tree is intended to help DCT teams decide who is making a direct and significant contribution to data in the study at a research site. This is not a case-study specific example and is meant to help teams apply common criteria when making these determinations.

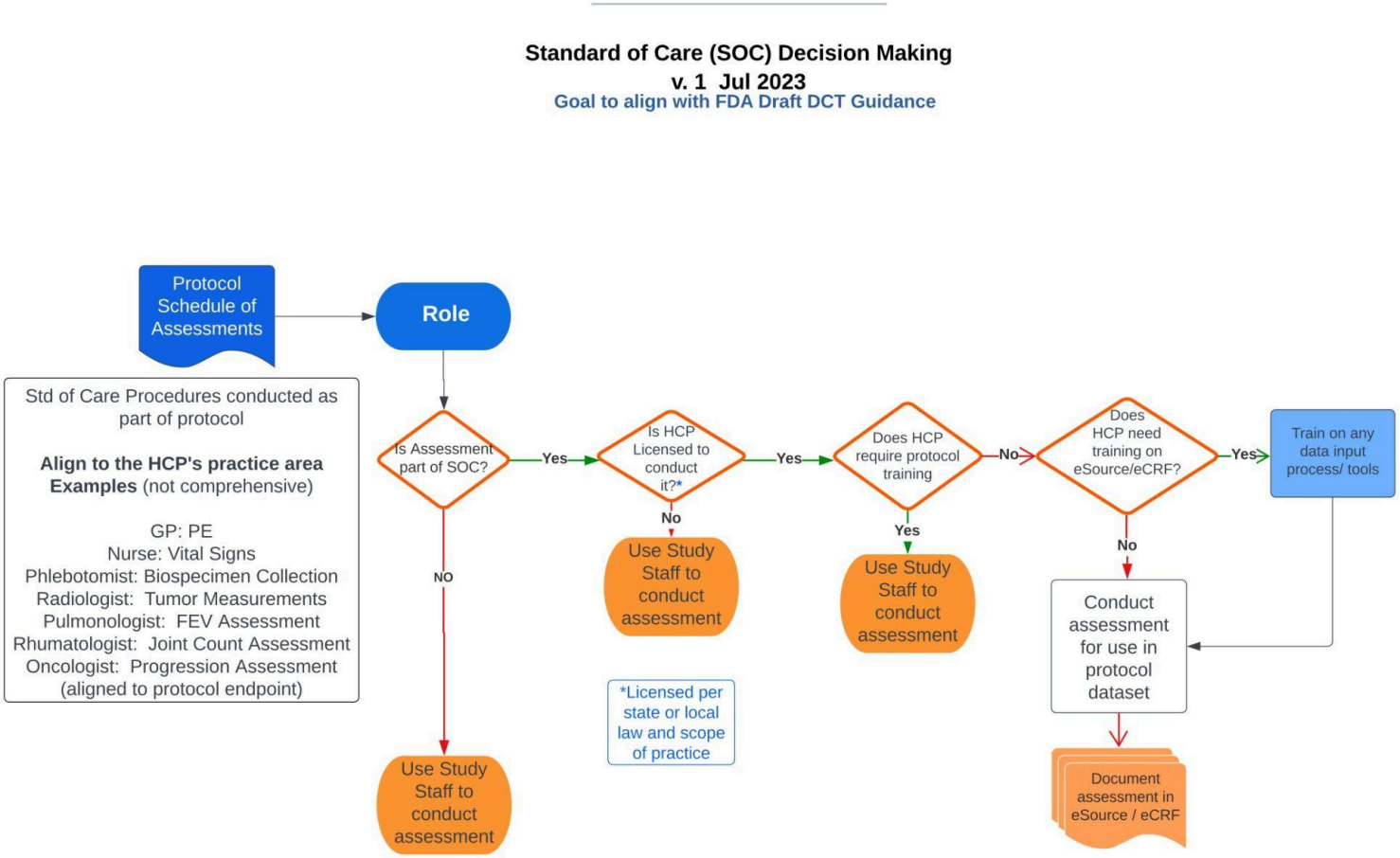
We acknowledge that we may have misinterpreted the Draft Guidance and FDA's intent to provide clarity for DCT implementation. We welcome and encourage the FDA to contact us for collaboration and dialogue on any aspect of these materials to help ensure we support the Agency's guidance.

Contents:

1. **a. Decision elements to determine appropriate documentation of delegated trial-related activities**



1. b. Decision Elements re Standard of Care Practice



2. Resource Table - Traditional and DCT Roles and Documentation Recommendations

	Traditional Documentation	DCT Trial Related Role / Activity	DCT Recommendation
Investigator	1572 Field 1: Name of Investigator	Investigator	1572 Field 1: Name of Investigator
Virtual Investigator	1572 Field 1: Name of Investigator	Virtual Investigator	1572 Field 1: Name of Investigator
Central lab	1572 Field 4 (Clinical Labs)	Central lab	1572 Field 4 (Clincial Labs)
Local Lab	1572 Field 4 (Clinical Labs)	Local Lab	Task Log (DCT Guidance)
Local Radiolgy Lab	Other (Comment)	Local Radiolgy Lab	Task Log (DCT Guidance)
eCOA raters	Delegation of Authority Log	eCOA raters (not HCP Providers)	Delgation of Authority Log
Sub-investigators	1572 Field 6 (Sub-Investigators)	Virtual Investigators	1572 Field 6 (Sub-Investigators)
Network sites	1572 Field 3 (Facilities where research will be conducted_	Network Sites	1572 Field 3 (Facilities where research will be conducted)
		Mobile research sites	1572 Field 3 (Facilities where research will be conducted)
		Pharmacy research sites : SOC Assessment/ HCP Activities asacting as another location for Traditional Research Site	Task Log (DCT Guidance)
		Pharmacy research Site acting as full site	1572 Field 1: Name of Investigator
		Pharmcy research site acting as another location for Traditional Research Site Conducting Protocol Specific Activites	Delgation of Authority Log
		Pharmacy Research Site: Low Risk IP Admin (SOC Tasks)	Task Log (DCT Guidance)
		Pharmacy Research Site: High Risk IP Admin	Delgation of Authority Log
Primary Care MD	Other (Comment)	Primary Care MD/ HCP acting as another location for traitional site: SOC Assessment	Task Log (DCT Guidance)
		Primary Care MD/ HCP acting as another location for traitional site: : Protocol Specific Assessment	Delgation of Authority Log
		Primary Care MD/ HCP acting as the PI	1572 Field 1: Name of Investigator
CRC (Clinical Research Coordinator)	Delegation of Authority Log	Virtual CRC	Delgation of Authority Log
Home Health Nurses - SOC Procdures (signs and symptoms)	Delegation of Authority Log	Home Health Nurses - SOC Assessment (signs and symptoms)	Task Log (DCT Guidance)
Home Health Nurses - IP admin	Delegation of Authority Log	Home Health Nurses - Low Risk IP Admin	Task Log (DCT Guidance)
		Home Health Nurses - High Risk IP admin	Delgation of Authority Log
		Hone Healh nursse conducting SOC activities.	Task Log (DCT Guidance)
Home Health Nurses - Protocol Specific Assessment (not SOC)	Delegation of Authority Log	Home Health Nurses - Protocol Specific Assessment (not SOC)	Delgation of Authority Log
Pharmacy	1572 Field 3 (Facilities where research will be conducted_	Direct to Patient Pharmacy Depot	1571: Sponsor ID of CROs
Pharmacist	Delegation of Authority Log	Direct to Patient Pharmacist	Delgation of Authority Log
Phlebotomist	Delegation of Authority Log	Mobile / in home phlebotomist - SOC Procedure	Task Log (DCT Guidance)
		Mobile / in home phlebotomist - Protocol Specific Procedure	Delgation of Authority Log
Study Research Staff (Nurse, Fellow, etc)	Delegation of Authority Log	Mobile Research Unit Nurses: SOC procedures	Task Log (DCT Guidance)
Study Research Staff (Nurse, Fellow, etc)	Delegation of Authority Log	Mobile Research Unit Nurses: Low Risk IP admin	Task Log (DCT Guidance)
		Mobile Research Unit Nurses: High Risk IP Admin	Delgation of Authority Log
Study Research Staff (Nurse, Fellow, etc)	Delegation of Authority Log	Mobile Research Unit Nurses: Protocol Specific Assessments	Delgation of Authority Log
Wearable Provider	1571: Sponsor ID of CROs	Wearable Provider	1571: Sponsor ID of CROs
Provider support service and technical needs for the software/ equipment	Other (Comment): Identify services in operational study plans and contracts, not regulatory documents	Provider support service and technical needs for the software/ equipment	Other (Comment): Identify services in operational study plans and contracts, not regulatory documents

3. Scenarios for PI Oversight and Delegation of Trial-Related Activities

b. RSV Vaccine Trial

i. Briefing document - Study Execution Model

1572 Annotation Example

1. Vaccine Study Based on RSV Patient Journey Map:

Protocol Title: **Vaccine trial to prevent Respiratory Syncytial Virus (RSV)**

Study Execution Plan:
Hybrid model with Traditional Brick and mortar site and Pharmacy based adjunct site

Direct to patient outreach, as well as site to patient outreach and referral
Visit 0: eConsent. Informed consent conversation with site staff. Screening.
Visit 1: Initial Visit in clinic, with initial RSV Vaccine dose, labs collected at site.
Visit 2: Follow up lab at pharmacy site. Labs collected at pharmacy.
Visit 3: Telehealth AE Follow up with Study Coordinator
Visit 4: RSV Vaccine Dose at Pharmacy Based Research Site (Year 2)
Visit 5: Follow up lab at pharmacy site. Labs collected at pharmacy.
Visit 6: Telehealth follow up with Study Coordinator (pharmacy)
RSV event: HCP involvement - SOC PE / Labs and RX

For this annotation example:
Traditional research site: Perfection Clinical Research Inc.
123 Main Street, Sunrise FL 33351
PI Name: Dr. Tom Pretty
Research Coordinator: Lena Love, RN (DOA Log)
SubInvestigator: : Dr. Steve Ferrone, MD

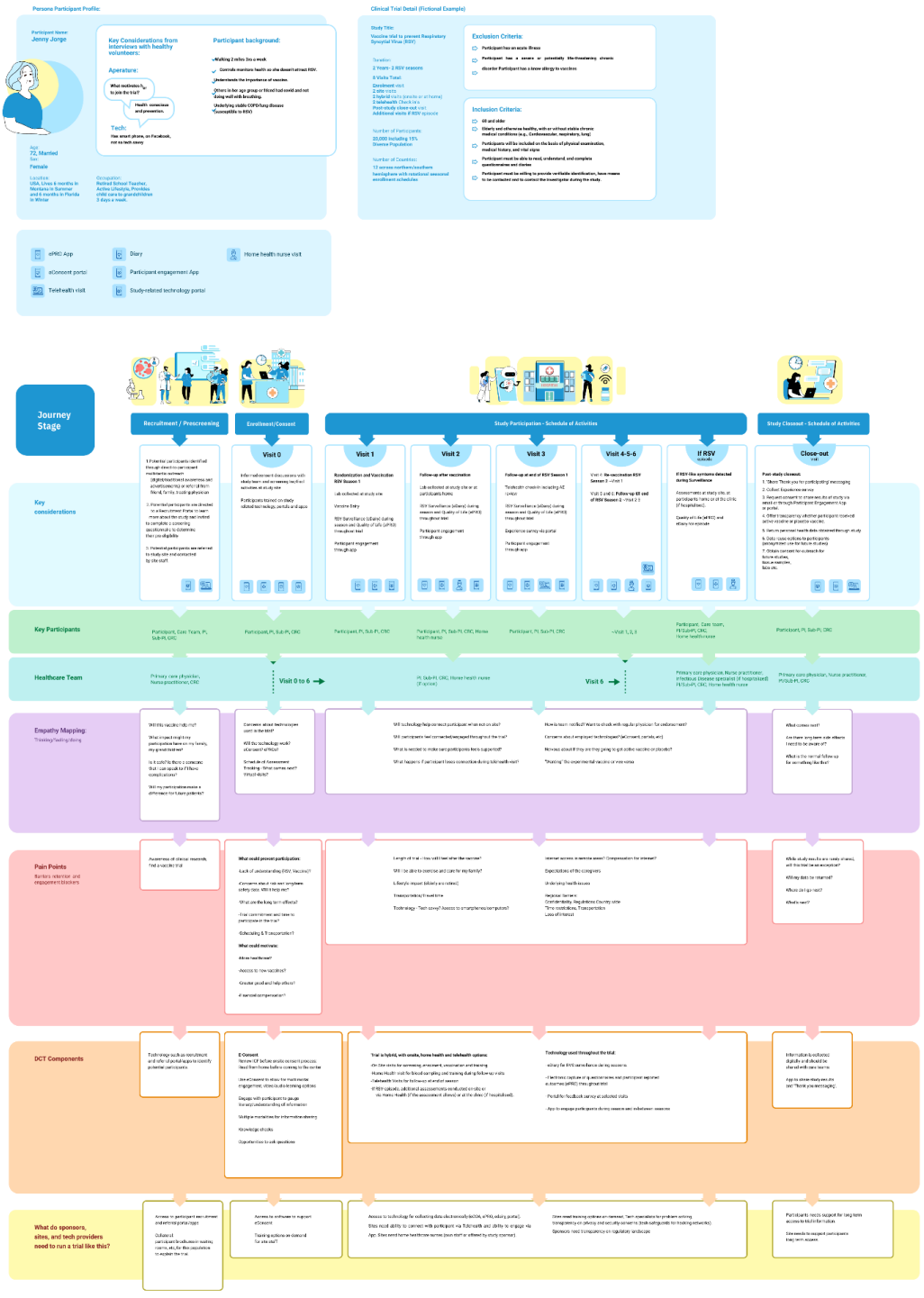
Sub-investigator Pharmacy location:
Walgreens
6401 W Commercial Blvd, Tamarac, FL,
Pharmacist: Michael Campbell
Study Nurse: Marilyn Martin, RN

Patient's Primary Care Physician: Dr Stevie Nicks,
12651 W Sunrise Blvd Suite 202, Sunrise, FL 33323
(Not part of the study staff)

IRB: Advarra
6100 Merriweather Drive, Suite 600, Columbia, Maryland 21044

Central Labs: LabCorp
Labcorp Central Laboratory Services Limited Partnership
8211 SciCor Drive
Indianapolis, IN

3. c. ii. Patient Journey Map - Illustrative of an RSV Vaccine DCT Design and Implementation



3.c. iii. Example: Completed 1572 Form and Additional Page for RSV Trial Site per Briefing Document.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

STATEMENT OF INVESTIGATOR

(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)

(See instructions on reverse side.)

Form Approved: OMB No. 0910-0014
Expiration Date: March 31, 2025
See OMB Statement on Reverse.

NOTE: No investigator may participate in an investigation until he/she provides the sponsor with a completed, signed Statement of Investigator, Form FDA 1572 (21 CFR 312.53(c)).

1. NAME AND ADDRESS OF INVESTIGATOR

Name of Clinical Investigator			
Dr. Tom Petty			
Address 1		Address 2	
Perfection Clinical Research Inc.		123 Main Street	
City	State/Province/Region	Country	ZIP or Postal Code
Sunrise	FL	USA	33351

2. EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFY THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THE DRUG FOR THE USE UNDER INVESTIGATION. ONE OF THE FOLLOWING IS PROVIDED *(Select one of the following.)*

☒ Curriculum Vitae ☐ Other Statement of Qualifications

3. NAME AND ADDRESS OF ANY MEDICAL SCHOOL, HOSPITAL, OR OTHER RESEARCH FACILITY WHERE THE CLINICAL INVESTIGATION(S) WILL BE CONDUCTED — CONTINUATION PAGE for Item 3

Name of Medical School, Hospital, or Other Research Facility			
Perfection Clinical Research Inc.			
Address 1		Address 2	
123 Main Street			
City	State/Province/Region	Country	ZIP or Postal Code
Sunrise	FL	USA	33351

4. NAME AND ADDRESS OF ANY CLINICAL LABORATORY FACILITIES TO BE USED IN THE STUDY — CONTINUATION PAGE for Item 4

Name of Clinical Laboratory Facility			
Labcorp Central Laboratory Services Limited			
Address 1		Address 2	
8211 SciCor Drive			
City	State/Province/Region	Country	ZIP or Postal Code
Indianaopolis	IN	USA	46214

5. NAME AND ADDRESS OF THE INSTITUTIONAL REVIEW BOARD (IRB) THAT IS RESPONSIBLE FOR REVIEW AND APPROVAL OF THE STUDY(IES) — CONTINUATION PAGE for Item 5

Name of IRB			
Advarra			
Address 1		Address 2	
6100 Merriweather Drive		Suite 60046214	
City	State/Province/Region	Country	ZIP or Postal Code
Columbia	MD	USA	46214

6. NAMES OF SUBINVESTIGATORS *(If not applicable, enter "None")*

Steven Ferrone, MD

CONTINUATION PAGE – for Item 6

7. NAME AND CODE NUMBER, IF ANY, OF THE PROTOCOL(S) IN THE IND FOR THE STUDY(IES) TO BE CONDUCTED BY THE INVESTIGATOR

Vaccine trial to prevent Respiratory Syncytial Virus (RSV)

PSC Publishing Services (301) 443-6740 EF

3.c. iii. Example: Completed 1572 Form and Additional Page for RSV Trial Site per Briefing Document continued

8. PROVIDE THE FOLLOWING CLINICAL PROTOCOL INFORMATION. *(Select **one** of the following.)*

☐ For Phase 1 investigations, a general outline of the planned investigation including the estimated duration of the study and the maximum number of subjects that will be involved.

☐ For Phase 2 or 3 investigations, an outline of the study protocol including an approximation of the number of subjects to be treated with the drug and the number to be employed as controls, if any; the clinical uses to be investigated; characteristics of subjects by age, sex, and condition; the kind of clinical observations and laboratory tests to be conducted; the estimated duration of the study; and copies or a description of case report forms to be used.

9. COMMITMENTS

I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.

I agree to personally conduct or supervise the described investigation(s).

I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.

I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64. I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

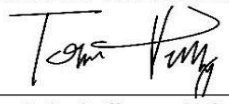
I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.

I 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. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

INSTRUCTIONS FOR COMPLETING FORM FDA 1572
STATEMENT OF INVESTIGATOR

1. Complete all sections. Provide a separate page if additional space is needed.
2. Provide curriculum vitae or other statement of qualifications as described in Section 2.
3. Provide protocol outline as described in Section 8.
4. Sign and date below.
5. FORWARD THE COMPLETED FORM AND OTHER DOCUMENTS BEING PROVIDED TO THE SPONSOR. The sponsor will incorporate this information along with other technical data into an Investigational New Drug Application (IND). INVESTIGATORS SHOULD NOT SEND THIS FORM DIRECTLY TO THE FOOD AND DRUG ADMINISTRATION.

10. DATE *(mm/dd/yyyy)*	11. SIGNATURE OF INVESTIGATOR	Sign
		

(**WARNING**: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

The information below applies only to requirements of the Paperwork Reduction Act of 1995.

The burden time for this collection of information is estimated to average 100 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden to the address to the right:

Department of Health and Human Services
Food and Drug Administration
Office of Operations
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

DO NOT SEND YOUR COMPLETED FORM TO THIS PRA STAFF EMAIL ADDRESS.

FORM FDA 1572 (3/22) **PREVIOUS EDITION IS OBSOLETE.** **Page 2 of**

3.c. iii. Example: Completed 1572 Form and Additional Page for RSV Trial Site per Briefing Document continued

1572 Continuation Page
3. NAME AND ADDRESS OF ANY MEDICAL SCHOOL, HOSPITAL, OR OTHER RESEARCH FACILITY WHERE THE CLINICAL INVESTIGATION(S) WILL BE CONDUCTED

Walgreens
6401 W Commercial Blvd.
Tamarac, FL, USA 33319-2110

3. c. iv. Example of a combined Delegation of Authority and Task Log for RSV Trial Site per Briefing Document

Delegation of Authority and Task Log

Protocol Title: Vaccine trial to prevent Respiratory Syncytial Virus (RSV)

Name		Protocol Training Needed	Is Assessment SOC?	Study Role Designation	Location of Clincial Trial Activites	Start Date	End Date	Delegated Responsibilities	Tasks Completed
Lena Love, RN	Study Coordinator	Yes	NA	Study Site Team Member	Perfection Clinical Research Inc. 123 Main Street, Sunrise FL 33351	6/1/2023		Patient Pre-Screening Patient Informed Consent Patient Screening Med Hx / Con Med RSV Vax Administration AE / SAE Reporting	NA
Dr. Steve Ferrone, MD	Sub-Investigator	Yes	NA	Study Site Team Member	Perfection Clinical Research Inc. 123 Main Street, Sunrise FL 33351	6/1/2023		Patient Informed Consent Patient Screening Med Hx / Con Med RSV Vax Administration All Study Visit procedures	NA
Marilyn Martin, RN	Study Nurse (Pharmacy Based)	Yes	NA	Pharmacy Site Team Mer	Walgreens 6401 W Commercial Blvd. Tamarac, FL 33319	6/1/2023		Med Hx / Con Med RSV Vax Administration Study Assessments for V2,3,4,5,6	NA
Michael Campbell, PharmD	Study Pharmacist (Pharmacy Based)	Yes	NA	Pharmacy Site Team Mer	Walgreens 6401 W Commercial Blvd. Tamarac, FL 33319	6/1/2023		Med Hx / Con Med RSV Vax Administration Study Assessments for V2,3,4,5,6	NA
Dr. Stevie Nicks, MD	HCP	No	Yes	HCP treating patient	12651 W Sunrise Blvd Suite 202, Sui	7/23/2023	7/30/2023	NA	PE, Labs, Rx for RSV

PI Signature *Tom Petty* **Date** 7/23/2023