Advancing Adoption of Decentralized Clinical Trials: Rationale, Current State, and Policy Recommendations

Initiative to Advance Decentralized Clinical Trials (IADCT)

November 2023

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Foreword and Acknowledgements

Since 2022, the Initiative to Advance Decentralized Clinical Trials (the Initiative) has come together to identify issues and policy opportunities to advance decentralized clinical trials (DCTs). The Initiative is collaborating to improve advancements in health by identifying issues, to identify approaches that will address those issues, and to advocate for policy change that will support greater use of DCTs. The Initiative has engaged a number of health care industry stakeholders, namely patient and cancer advocacy groups, health care associations, pharmaceutical companies, and health technology companies. Through a series of round table meetings, participants have been meeting to discuss policy issues related to DCTs and to develop recommendations to advance widespread adoption of DCTs. The Initiative will continue to discuss issues related to advancing DCT with the goal of advancing policy recommendations, beginning with the ones contained in the attached white paper.

This white paper was discussed and developed through virtual roundtable discussions. While participation in the workgroup does not imply affiliation with or endorsement of the recommendations issued in this white paper, we would like to thank the following organizations for their participation:

- Amazon Web Services
- American Cancer Society Cancer Action Network
- Association of Clinical Research Organizations
- Epic
- Evidation Health
- Genentech
- EMD Group
- National Health Council
- National Partnership for Women & Families
- Thread Research

Executive Summary

Leveraging technology, electronic clinical data, and remote monitoring tools have enabled advancements in clinical trials to drive improvements in clinical and biomedical research. These advancements, primarily driven by developments in digital health technology (DHT), have the potential to improve health care delivery across diverse populations by changing how information is gathered from patients and health care providers.

DCTs are an approach to conducting clinical research in which technologies (including mobile devices) are used to remotely recruit, communicate with study participants, conduct virtual visits, and collect clinical data.[1] Widespread adoption of the electronic health record (EHR) and technological improvements driven by DHT companies have enabled the increased use of decentralized and hybrid clinical trials. DCTs are accomplished using technology and tools such as wearable digital health devices, patient apps, telehealth and smart phones to communicate with patients and collect data.

DCTs exist along a continuum: they include hybrid DCTs where a participant needs to visit the clinician (e.g., primary and specialty care physicians) at some times, and full DCTs where participants complete the entire clinical trial from their home. Some decentralized trials involve the patient's preferred physician administering the majority of standard medical care and data collection, while validating and submitting the details through technology to the physician's team. Most trials are not fully decentralized because of sponsor-mandated in-person interactions for safety and regulatory purposes.[2] DCTs allow for the remote collection of data, including in the home or at the doctor's office, to become integrated into the clinical trial.

Currently, a patchwork of federal laws and regulations outlines requirements for DCT sponsors. In recent months, federal health agencies have also released proposals and frameworks on advancing DCTs. In general, traditional clinical trials and DCTs are subject to regulation by the Food and Drug Administration (FDA). Other DCT-related issues, including incentives for clinicians to recruit patients in clinical trials and DCTs and health information exchange issues, involve the Centers for Medicare & Medicaid Services (CMS) and Office of the National Coordinator for Health Information Technology (ONC). As a result of the COVID-19 pandemic, legislators and policymakers have acknowledged the need to further advance DCT adoption. The COVID-19 pandemic also demonstrated the value of DCTs for patients and supported clinicians' use for certain DHTs (i.e., flexibilities and expanded reimbursement for telehealth remote patient monitoring).

In the Consolidated Appropriations Act, 2023[3], Congress required FDA to issue or revise draft guidance that includes recommendations to clarify and advance the use of decentralized clinical studies. The guidance must include recommendations for several DCT issues such as remote data collection, use of digital health technologies in DCTs, and privacy and security issues. Congress also directed the Department of Health and Human Services (HHS) to evaluate agency practices to ensure that providers and patients have tools to identify and participate in decentralized and remote clinical trials. Congress has directed the HHS Secretary, in collaboration with FDA, ONC, and CMS, to evaluate agency practices across HHS and deliver a report to Congress with its findings and recommendations to accelerate DCTs and increase trial diversity by mid-2024. The policy

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[1] U.S. Department of Health and Human Services, Food and Drug Administration, Digital Health Technologies for Remote Data Acquisition in Clinical Investigations, Guidance for Industry, Investigators, and Other Stakeholders (December 2021) https://www.fda.gov/media/155022/download

[2] Taiwo Adesoye, Matthew H.G. Katz, and Anaeze C. Offodile, "Meeting Trial Participants Where They Are: Decentralized Clinical Trials as a Patient-Centered Paradigm for Enhancing Accrual and Diversity in Surgical and Multidisciplinary Trials in Oncology," JCO Oncology Practice, 2023, https://doi.org/10.1200/op.22.00702.

[3] *Consolidated Appropriations Act, 2023*, Pub. L. No. 117-328 (2022).

recommendations contained in this report are intended to advise on HHS and agencies' upcoming report to Congress.

As explained further in this paper, DCTs offer several advantages over traditional, site-based clinical trials, which often place a significant burden on both patients and family caregivers. Because DCTs reduce the time and financial burden on patients, they can increase patient recruitment and maintain retention rates. DCTs allow access wider to prospective patients and increase the diversity of the patient population.

This paper outlines several policy recommendations to advance widespread adoption of DCTs. It provides an overview of the current environment on decentralized and hybrid clinical trials, including a discussion on benefits and challenges that DCTs may pose. It provides an overview of existing legislation and regulation that have been promulgated by the Administration and various agencies. It also provides background on programs and policies, not specific to DCTs or clinical trials, that can be leveraged to support DCT adoption.

Overview of Policy Recommendations

As outlined in detail later in this report, the Initiative issues the following recommendations to advance DCTs:

- **CMS Incentives**: CMS should incorporate support for DCT in the Merit-based Incentive Payment System (MIPS) Promoting Interoperability Performance Category, such as by providing bonus points for clinicians that identify and enroll patients in DCTs and report data collected during DCTs.

- **CMS Innovation Center Demonstration**: The CMS Innovation Center should create a new payment and service delivery model that incentivizes providers to use DCT to improve health outcomes and increase Medicare beneficiaries' enrollment in clinical trials.

- **Standards***:* ONC should further support interoperability for clinical research exchange purposes by participating in standards development efforts that target clinical trial data and exchange needs and adopting standards for developers of health IT under the ONC Health IT Certification Program. To enable these efforts, Congress should ensure ONC has sufficient funding to support standards efforts that advance clinical trials and DCTs, in particular.

- **TEFCA***:* ONC should include "Research" as an exchange purpose under Trusted Exchange Framework and Common Agreement (TEFCA) to advance clinical research and promote clinical trial participation.

- **FDA Guidance:** FDA should include in final guidance provisions to enable the collection of clinical data and to further enable clinicians to support patients when participating in DCTs. Specifically, FDA should encourage trial sponsors to use ONC adopted data standards, to the greatest extent possible, including United States Core Data for Interoperability (USCDI), for clinical trial recruitment. FDA should retain flexibility for trial sponsors in situations where existing USCDI data elements do not allow for the collection of needed data and work with ONC to develop standards that support DCT.

- **FDA Demonstration Project***:* FDA should conduct a demonstration project on the use of DHTs in DCTs. The project should focus on a number of issues, namely benefits of DHTs, current regulatory and operational barriers of using DHTs, and inter-agency coordination to support DHTs use in DCTs.

- **Protecting Privacy and Security***:* The HHS Office for Civil Rights (OCR), ONC, FDA and the National Institute of Standards and Technology (NIST) should collaborate to provide guidance on privacy and security standards for DCTs. Specifically, agencies can outline privacy and security needs and explain how stakeholders can address such needs when conducting DCTs and hybrid clinical trials.

- **NIH Grants**: The National Institutes of Health (NIH) could promote widespread DCT adoption in the health care community by providing grant funding and/or other incentives to enable use of DHTs and advanced decentralized trials, in general. To support these efforts, Congress should enact legislation or

submit appropriations report language directing NIH to establish a program to advance adoption of DCTs by the health care community.

Overview of Decentralized Clinical Trials

According to NIH data, the U.S. continues to spend billions per year[4] on clinical research and yet our life expectancy is falling[5] and thousands of diseases have no known treatment or cure. Most clinical research is done in a centralized model where data is collected at one or more sites, often academic medical centers.[6] This centralized model has a number of challenges, including:

- Recruitment can be difficult due to limited trial sites and other concerns;
- Patient retention may be challenging in some clinical trials (e.g., studies with long durations)
- Accessibility of patients to participate in clinical trials is limited, including limiting diversity of participants;
- Rising clinical trials costs; and
- Post-market surveillance is "disaggregated and often fails to answer essential questions that must be addressed to provide optimal clinical care."[7]

Federal health agencies, life sciences companies, health care providers, and other health care organizations are looking for ways to advance generation of evidence that can lead to improvements in treatments and health outcomes.[8] They are considering how to leverage real world data to understand how treatments and technologies work in "real" life, rather than in a clinical setting. There is also an increasing drive to improve health care disparities and to understand how the social determinants of health may impact treatment alternatives. Finally, the promise of greater access to electronic data and data analytics can drive precision health care so that patients receive the most effective treatments based on their personal characteristics, biology and environment.

Background on Use of DCT

While trials sponsors have used DCT and virtual trial components in recent years, the COVID-19 pandemic accelerated DCT use due to disruptions to centralized in-person clinical trials that were ongoing and under development. Between travel restrictions, site closures and supply chain disruptions, flexibility was necessary to continue trials. FDA guidance regarding the conduct of trials during the public health emergency considered remote monitoring, remote clinical outcome assessments, remote clinical visits and other alternatives to traditional clinical trials.[9]

Furthermore, advances in DHT, such as remote monitoring and diagnostics, telehealth, digital and mobile health apps, clinical outcomes assessments (COA) conversion to digital (i.e. eCOA), and widespread EHR adoption, has made it easier to conduct DCTs, and the pandemic provided an opportunity to test and refine the approach to using these technologies for clinical care and research on a larger scale. DHTs use computing platforms,

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[4] "Estimates of Funding for Various Research, Condition, and Disease Categories (RCDC)," National Institutes of Health (U.S. Department of Health and Human Services, May 16, 2022), https://report.nih.gov/funding/categorical-spending#/.

[5] Arias, Elizabeth, Betzaida Tejada-Vera, Kenneth Kochanek, and Farida Ahmad. "Provisional Life Expectancy Estimates for 2021." National Center for Health Statistics, 2022. https://doi.org/10.15620/cdc:118999.

[6] Walter De Brouwer et al., "Empowering Clinical Research in a Decentralized World," Npj Digital Medicine 4, no. 1 (January 2021), https://doi.org/10.1038/s41746-021-00473-w.

[7] Robert M Califf, "Now Is the Time to Fix the Evidence Generation System," Clinical Trials, 2023, p. 174077452211476, https://doi.org/10.1177/17407745221147689.

[8] Robert M. Califf et al., "Transforming Evidence Generation to Support Health and Health Care Decisions," New England Journal of Medicine 375, no. 24 (2016): pp. 2395-2400, https://doi.org/10.1056/nejmsb1610128.

[9] U.S. Department of Health and Human Services, Food and Drug Administration, Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency, Guidance for Industry, Investigators, and Institutional Review Boards (March 2020) https://www.fda.gov/media/136238/download.

connectivity, software, and/or sensors, for health care and related uses. DHTs enable trial sponsors to build on traditional clinical trial practices to modernize the performance of trials and improve efficiencies, provide a more convenient and precise way to measure existing features (e.g., sleep exercise, blood pressure), and help improve diverse participation in clinical trials when coupled with other efforts and resourced appropriately. FDA's Oncology Center notes that COVID-19 provided a "proof of concept" and it supports the use of DCTs, noting that it can reduce patient and sponsor burden and increase accrual and retention of a more diverse trial population.[10] DHTs play an integral role in DCTs: they enable remote data collection, more frequent or continuous monitoring compared to traditional clinical trials, provide a longitudinal view of a participant's health status, and improve recruitment and retention of participants (leading to less missing data).

According to a recent analysis highlighting the latest rapid adoption of DCT (Table 1), 673 interventional drug trials mentioned decentralized and virtual components in clinical registry protocols in 2020.[11] The analysis stated that the uptake of DCTs was projected to gain further momentum in 2022 (approximately 1,300 interventional trials were forecasted to be initiated with a virtual and/or decentralized component) representing a 93% increase from 2020. In addition, another updated analysis projects that 5% of clinical trials with an estimated completion date in 2023 have at least one DCT component.[12]

Table 1: Initiated worldwide drug trials identified as involving virtual/decentralized components

Trial categories by start date. Includes interviional drug trials which GlobalData identified as mentioning decentralised/virtual components in clinical registry protocols. 2021 figures include trials scheduled to begin before the end of the year.
Source: GlobalData
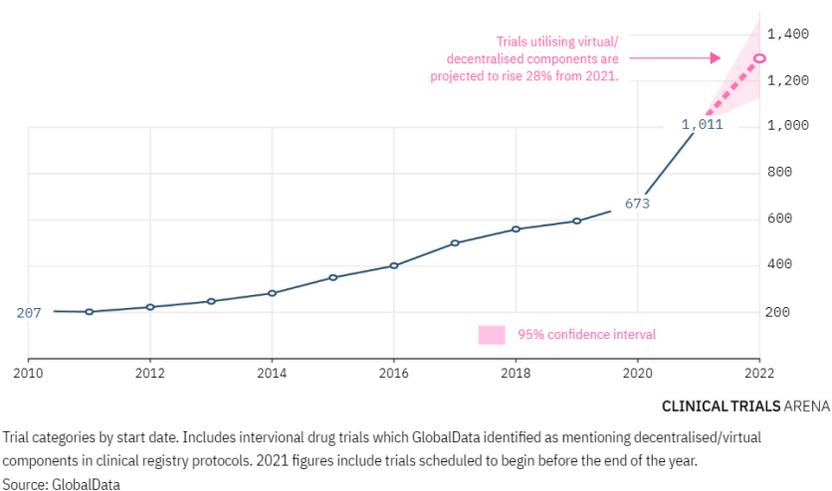
Value of DCT

There are a number of benefits to using decentralized clinical trials that can address issues discussed above.

- **Reduce Burden on Patients**: One of the benefits of using DCTs is the ease of the patient's access to care that may only be available under a clinical trial. DCT reduces burdens in terms of travel and other logistics, which is particularly important with regard to already sick patients and their caregivers and to individuals who may be of lower socio-economic status where the travel may be a barrier to participation.

- **Easier Recruitment**: DCTs lower the barriers to enrollment. When recruiting patients for clinical trials, DCTs allow access to a larger population of individuals by enabling participation of individuals in more

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[10] "Advancing Oncology Decentralized Trials," U.S. Food and Drug Administration (FDA, January 10, 2023), https://www.fda.gov/about-fda/oncology-center-excellence/advancing-oncology-decentralized-trials.

[11] Kezia Parkins, "2022 Forecast: Decentralised Trials to Reach New Heights with 28% Jump," Clinical Trials Arena, July 11, 2022, https://www.clinicaltrialsarena.com/analysis/2022-forecast-decentralised-trials-to-reach-new-heights-with-28-jump/.

[12] Urtė Fultinavičiūtė, "New Year, New Trials: Analysis Reveals Clinical Trial Activity Trends in 2023," Clinical Trials Arena, January 13, 2023, https://www.clinicaltrialsarena.com/news/clinical-trial-activity-2023/.

remote areas or that otherwise may have difficulty travelling to clinical trial sites. There may be a particular value in using DCTs when the disease is rare or widely-dispersed.

- **Retention**: DCTs can eliminate many burdens experienced by patients participating in traditional clinical trials by organizing DCTs around patients' needs. When sponsors incorporate e-diaries and e-consent forms, telehealth visits, and local labs into the trial experience, it eliminates the need for excessive travel and reduces the time patients have to invest in the process.

- **Engage Diverse Participants**: Similarly, by reducing burden on patients that participate in clinical trials and enabling recruitment with broader geographic reach, DCT can support more geographic, racial and ethnic diversity of participants in clinical trials, which can lead to better evidence regarding safety and effectiveness for a broader set of patients.

- **Real World Data**: The data gathered measures "real world" data rather than data only in a clinical setting. If the goal is understanding the impact of treatment on patients, capturing data in the environments where patients live enables a better understanding of how such treatment will affect patients in their day-to-day lives. DCTs can offer a more accurate picture of how a treatment would perform in the general population, rather than in a highly controlled clinical setting.

- **Reduction in Cost**: An additional benefit to DCTs is the reduction in cost.[13] Automatic data gathering, from Continuous Glucose Monitoring (CGM), for example, would not require the use of any trained intermediary. These virtual tools may reduce the number of investigators and other staff needed. It also reduces the workload of the investigators, as much of the work of clinical trials is done by others, including trial participants.[14]

- **Real-time access to clinical data**: Real world data can be collected and analyzed more quickly than data from centralized clinical trials. Through DCTs, effective and instantaneous transfer of data from one location to another enables access to data in real time.

- **Involve Community Physicians**: DCTs can involve the use of community physicians and not just physicians at academic medical centers. This can increase the speed of adoption of innovative treatments as they would be more understood by a broader base of physicians.

DCTs will be more successful when they concern self-administered medication or a disease for which there are remote monitoring tools and outcomes already validated. If the patient population is more familiar with the health technology used (e.g., smart watch) or it is easily accessible, that can make the use of DCTs easier to implement.

Health Equity

Although mentioned above, it is important to highlight the value of DCTs to further diversity in trial enrollment and reduce health disparities. Racial and ethnic minorities have historically been underrepresented in clinical trials.[15] In the U.S., minority racial and ethnic groups comprise nearly 40% of the population; however, 75% of the 32,000 participants in the trials of 53 novel drugs approved in 2020 by the FDA were white.[16] Overall,

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[13] Gail A. Van Norman, "Decentralized Clinical Trials," JACC: Basic to Translational Science 6, no. 4 (April 27, 2021): pp. 384-387, https://doi.org/10.1016/j.jacbts.2021.01.011.

[14] Gaurav Agrawal et al., "McKinsey & Company," McKinsey & Company (blog) (McKinsey's Pharmaceuticals & Medical Products Practice, June 10, 2021), https://www.mckinsey.com/industries/life-sciences/our-insights/no-place-like-home-stepping-up-the-decentralization-of-clinical-trials.

[15] Luther T. Clark et al., "Increasing Diversity in Clinical Trials: Overcoming Critical Barriers," Current Problems in Cardiology 44, no. 5 (May 2019): pp. 148-172, https://doi.org/10.1016/j.cpcardiol.2018.11.002.

[16] Center for Drug Evaluation and Research (CDER), "2020 Drug Trials Snapshots Summary Report," 2020 Drug Trials Snapshots Summary Report § (0AD).

experts suggest that DCTs can improve trial participation of the most underrepresented patients – the elderly, poor, those living in remote locations and racial/ethnic minorities.[17] Where trials have underrepresented racial/ethnic or socioeconomic groups, genders, or geographic areas, the trial results may not be generalizable to these populations and treatments may not be as effective. Different populations may have different reactions to treatments, based on different genetics, lifestyles, environment, etc. The lack of diversity is an obstacle to understanding the safety and efficacy of novel therapies across population groups, which is crucial to reducing disparities and advancing equity.

DCTs can help improve health equity by increasing access to life saving treatments and supporting knowledge on the impact of treatments across diverse populations. As discussed above, travel can be a barrier to diverse participation in centralized clinical trials, which is limited or eliminated with DCTs. Furthermore, the use of technology and home-based monitoring can lower language barriers for those who are not native English speakers, increasing diverse participation.[18] Digital recruitment can lead to multilingual prescreening and other elements of the DCT process can facilitate communication with non-native language speakers. However, health inequality could be exacerbated by the digital divide, both in terms of access to broadband and familiarity with the tools used.

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[17] Norman, "Decentralized Clinical Trials," 384-386.

[18] Goodson N, Wicks P, Morgan J, Hashem L, Callinan S, Reites J. Opportunities and counterintuitive challenges for decentralized clinical trials to broaden participant inclusion. NPJ Digit Med. 2022 May 5;5(1):58. doi: 10.1038/s41746-022-00603-y. PMID: 35513479; PMCID: PMC9072305.

Challenges

General Challenges

- Digital deserts, while an important issue for the U.S., affects the ability of those in certain places to participate in DCTs. Both United States Department of Agriculture (USDA) and Federal Communications Commission (FCC) are working on increasing access to broadband.

- State licensing laws affect telemedicine and access to specialists, and may have an effect on the ability to deploy DCTs.[19] The interstate medical licensure compact, which more than half of states participate in, creates an expedited pathway for licensed doctors to practice in more than one state. There is also a nurse licensure compact that allows for nurses to have one multistate license with the ability to practice in all compact states.

- Definition of telemedicine and issues regarding scope of practice are determined by federal and state law. The variability creates challenges when providing clinical services in various states with different legal standards.

- Validation of outcomes and measuring tools, already an issue, particularly in rare diseases, may be magnified by the implementation of decentralized clinical trials. The utility of specific tools in a patient's home may be different than in the clinic. While this is generally seen as a benefit of DCTs, it could raise some questions about the way these tools are used.

- Discordance already exists in measuring outcomes. However, any concerns about concordance in evaluation or record-keeping could be exponentially increased with multiple sites, lack of trained recorders and potential for discordance between both patients and between providers.[20]

DCT Specific Challenges

- **IRBs***:* With fewer central research sites, DCTs reduce the number of institutional review boards and redundant applications, decreasing costs and site-specific inconsistencies, but potentially raising intra-site inconsistencies.[21] Despite the challenge, fewer sites also means fewer resubmissions to multiple institutional review boards to institute changes, and better ability to pivot and make across-the-board protocol adjustments to meet evolving study parameters.

- **Distribution of Medicine**: In traditional drug clinical trials, there are a limited number of sites that receive the investigational product*.* Those sites have staff who are responsible for monitoring, storing, dispensing and maintaining supply of that medication. Drug DCTs will have a more diffuse drug distribution chain and will not have the same level of control. Challenges may arise from storing, dispensing and record-keeping around drugs dispensed at a patient's home.[22] FDA guidance allows

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[19] Maria Apostolaros et al., "Legal, Regulatory, and Practical Issues to Consider When Adopting Decentralized Clinical Trials: Recommendations from the Clinical Trials Transformation Initiative," Therapeutic Innovation &Amp; Regulatory Science 54, no. 4 (September 2019): pp. 779-787, https://doi.org/10.1007/s43441-019-00006-4.

[20] Jerry Chapman, "REDICA Systems," REDICA Systems (blog), August 11, 2022, https://redica.com/fda-decentralized-clinical-trials-part-iii/.

[21] Norman, "Decentralized Clinical Trials," 384-386.

[22] Clinical Trials Transformation Initiative, CTTI Recommendations: Decentralized Clinical Trials (September 2018) https://ctti-clinicaltrials.org/wp-content/uploads/2021/06/CTTI_DCT_Recs.pdf

protocol changes to trials that allow drugs to be shipped to a patient's home, but does not discuss any state or federal shipping laws, or other concerns already discussed.[23]

- **Privacy**: Data privacy will continue to be an issue in DCTs.[24] Questions about how to how to protect sensitive data, particularly since data will be transmitted from the patient, is a key consideration. In traditional clinical trials, hospital systems have cybersecurity protections for their data and have trained staff on HIPAA and other privacy rules. Data coming from individual patients, and storing those data on connected devices, provides an additional level of challenge. Further, multiple EHRs may be communicating with a central data repository.

- **Tailoring/Training***: In traditional clinical trials, a team of patient-facing providers are trained on the trial protocol. In DCTs, a dispersed set of providers and/or the patient or caregiver must be trained to accurately capture the appropriate data.[25] Training a dispersed, lay audience provides an additional challenge to the implementation of DCTs.

- **Electronic Record Keeping***: EHRs, medical images, patient reported data, and electronic diaries compiled by study participants are examples of electronic records that may be kept as part of DCTs. Existing regulations, including Part 11, apply to DCTs, but the importance of electronic records is augmented in DCTs. The principles of data integrity (ALCOA+) remain good guidance for records. However, there may be an additional burden place on a trial site to obtain and retrieve information, scan, send, or track, or even facilitate access during a monitoring visit, an audit, or an inspection.[26] Designing these processes and procedures in advance are key.

- **Data Quality and Integrity**: Consistency in collection of data is of critical importance in clinical trials. Where patients are collecting their own data or where data collection is spread over a large number of providers, there are a number of potential issues, such as inconsistent application of the treatment, inconsistent documentation of data, errors in documentation of data, issues regarding transmission of data, etc. There can also be issues regarding accurately linking data from the home and the health care setting.

- **Lack of Standardization**: Similarly, the real-world environment will have fewer controls and less standardization. Each clinician and participant is in a unique site, which may include contaminants or environmental variables, data interruptions due to bandwidth issues, differential use of technology, issues of use of shared devices, etc.

- **Cost of and Familiarity with DHT**: DCTs rely on use of technology, but the digital divide can impact equitable participation. Where individuals in remote areas have limited access to broadband or where individual of lower socio-economic status have less access to, or familiarity with, technology used to capture data and monitor the participant, there may be a hesitation or inability of some individuals to participate. In addition, digital health tools must be both analytically and clinically validated in order to ensure that a tool is measuring and storing data accurately.

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[23] U.S. Department of Health and Human Services, Food and Drug Administration, Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency, Guidance for Industry, Investigators, and Institutional Review Boards (March 2020) https://www.fda.gov/media/136238/download.

[24] Norman, "Decentralized Clinical Trials," 384-386.

[25] Chapman, "REDICA Systems."

[26] U.S. Department of Health and Human Services, Food and Drug Administration, Data Integrity and Compliance With CGMP Guidance for Industry (April 2016) https://www.fda.gov/files/drugs/published/Data-Integrity-and-Compliance-With-Current-Good-Manufacturing-Practice-Guidance-for-Industry.pdf

Policy Recommendations

The purpose of this Initiative is to identify policy opportunities to advance DCT and advise federal policy makers, including for HHS' report to Congress, on findings and recommendations to accelerate DCTs and increase trial diversity. While these recommendations were developed through rigorous discussions, each and every recommendation does not represent the official position of each company or organization that participated. This section includes proposals for federal agencies to create new DCT programs and to build on existing legislation and regulations promulgated by Congress and the Administration, which are further detailed in appendices 1, 2, 3 and 4.

CMS Incentives	
Recommendation	CMS should incorporate support for DCT in the MIPS Promoting Interoperability Performance Category, such as by providing bonus points for clinicians that identify and enroll patients in DCTs and report data collected during DCTs.
Background	The MIPS Promoting Interoperability Performance Category provides bonus points and focuses on the following objectives: e-prescribing; Health Information Exchange (HIE); provider to patient exchange; protecting patient health information; and public health and clinical data exchange.
Problem Addressed	This recommendation allows clinicians who have limited bandwidth to engage in trial-related activities that do not directly increase reimbursement under Medicare. By providing a reimbursement incentive, this recommendation would address payment barriers to participating in DCTs and other clinical trials.
Initiative Action	The Initiative should meet with representatives from CMS to discuss incentives for DCT through changes to the MIPS promoting interoperability performance category and related bonus point criteria. It should also develop a draft measure on the proposed changes to the promoting interoperability performance category and provide feedback to CMS on the Medicare Physician Fee Schedule rule.
CMS Innovation Center Demonstration	
Recommendation	The CMS Innovation Center should create a new payment and service delivery model that incentivizes providers to use DCTs to improve health outcomes and increase Medicare beneficiaries' enrollment in clinical trials.

Background	According to the November 2022 Strategy Refresh, the Innovation Center outlines its commitment to advance health equity and drive care innovations.[27] To date, the Innovation Center has not released a model that focuses on clinical trials or DCT. Under current law and regulations, the federal health programs do not provide sufficient financial reimbursement or incentives for clinicians to identify clinical trials for which their patients are eligible and enroll patients in trials. In order to fully realize the full benefits of DCTs, federal regulators must incentivize identification, enrollment, and data submission from the provider at the point of care to create an ecosystem where patients can enroll in trials regardless of where they are located.
Problem Addressed	This recommendation provides another pathway in which clinicians can receive additional reimbursement under Medicare for performing clinical trial-related activities.
Initiative Action	The Initiative should build out an advocacy strategy that emphasizes how DCT improves health equity and drives person-centered care. Members of the Initiative should meet with CMS Innovation Center representatives and urge them to develop the demonstration model that would advance equity and diversify clinical trial participant populations.
Standards	
Recommendation	ONC should further support interoperability for clinical research exchange purposes by participating in standards development efforts targeting clinical trial data and exchange needs and adopting standards for developers of health IT under the ONC Health IT Certification Program. To enable these efforts, Congress should ensure ONC has sufficient funding to support standards efforts that advance clinical trials and DCTs, in particular.
Background	By leveraging existing standards (e.g. FHIR) and developing implementation guides that facilitate common approaches for collecting, managing, and exchanging data for DCT, ONC can ease some of the challenges of decentralized data collection and data integrity and thereby smooth the way for DCT interoperability and data sharing. In the coming years, ONC should also consider including additional data elements in USCDI to allow collection of detailed clinical data and to address the needs of clinical trial sponsors, including trial recruitment.
Problem Addressed	This recommendation would advance interoperability during the decentralized or hybrid clinical trial. Interoperability simplifies the DCT experience for patients. For clinical trial staff, interoperability allows for a more efficient workflow and data capture. Trial sponsors benefit with improved compliance and increased data quality collected from trial activities.

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[27] U.S. Department of Health and Human Services, Centers for Medicare & Medicaid Services, Innovation Center Strategy Refresh (November 2022) https://innovation.cms.gov/strategic-direction-whitepaper.

Initiative Action	The Initiative can work with ONC and Congressional champions to fund this project. The Initiative can draft language (i.e., both appropriations language and authorizing legislation) that ensures ONC leverages its authority and that the ONC Health IT Certification Program supports decentralized trials.

TEFCA	
Recommendation	ONC should include "Research" as an exchange purpose under TEFCA to advance clinical research and promote clinical trial participation.
Background	The overall goal of TEFCA is to enable nationwide interoperability of electronic health information. TEFCA may offer benefits to a variety of stakeholders, including researchers who can benefit from improved quality and expanded participation in clinical research. [28] While "Research" is included as a future benefit of TEFCA, it is not one of the six exchange purposes authorized under the Common Agreement.
Problem Addressed	This recommendation also improves interoperability during the DCT. If/when TEFCA is fully operationalized, having research already qualified as a permitted exchange purpose would allow clinical researchers to access data without having to experience operational barriers.
Initiative Action	Building on progress made with respect to TEFCA thus far, the Initiative can engage with federal regulators and make recommendations as ONC continues to operationalize TEFCA to maximize clinical research and clinical trial participation.

FDA Guidance	
Recommendation	FDA should include in final guidance provisions to enable the collection of clinical data and to further enable clinicians to support patients when participating in DCTs. Specifically, FDA should encourage trial sponsors to use ONC adopted data standards, to the greatest extent possible, including with USCDI, for clinical trial recruitment. FDA should also retain flexibility for trial sponsors in situations where existing USCDI data elements do not allow for the collection of data and work with ONC to develop standards that support DCT.

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[28] The Sequoia Project, User's Guide to the Trusted Exchange Framework and Common Agreement – TEFCA (January 2022), https://rce.sequoiaproject.org/wp-content/uploads/2022/01/Common-Agreement-Users-Guide.pdf

Background	On May 2, 2023, FDA released draft guidance containing recommendations to implementing DCTs.[29]
Problem Addressed	This recommendation would advise FDA on DCT-related issues, specifically on interoperability and its proposed on the data management plan.
Initiative Action	The Initiative should consider engaging with FDA on future guidance related to DCTs and DHTs.

<div style="background-color: green; text-align: center;">**FDA Demonstration Project**</div>

Recommendation	FDA should conduct a demonstration project on the use of DHTs in DCTs. The project should focus on a number of issues, namely benefits of DHTs, current regulatory and operational barriers of using DHTs, and inter-agency coordination to support DHTs use in DCTs.
Background	The FDA's "Framework for the Use of Digital Health Technologies in Drug and Biological Product Development"[30] stated that the agency will identify at least three issue-focused demonstration projects to inform methodologies for efficient DHT evaluation in drug development. According to FDA, these projects may involve engagement with researchers from academia, the biopharmaceutical industry, patient groups, and other stakeholders to cover key issues to inform regulatory policy development and provide regulatory advice. FDA outlines numerous DHT-related topics that may be the focus on these projects, including the use and limitations of DHTs in DCTs.
Problem Addressed	This recommendation would provide additional details about FDA's priorities for DCTs and hybrid trials and facilitate inter-agency coordination.
Initiative Action	The Initiative should engage with FDA representatives and provide input on a demonstration project on the use of DHTs in DCTs. It can urge FDA to work with other federal health agencies, including CMS, to encourage clinicians to utilize DHTs in patient care and promote clinical trial participation among patients.

<div style="background-color: green; text-align: center;">**Protecting Privacy and Security**</div>

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[29] U.S. Department of Health and Human Services, Food and Drug Administration, *Decentralized Clinical Trials for Drugs, Biological Products, and Devices: Guidance for Industry, Investigators, and Other Stakeholders* (May 2023), https://www.fda.gov/media/167696/download?utm_medium=email&utm_source=govdelivery

[30] U.S. Department of Health and Human Services, Food and Drug Administration, *Framework for the Use of Digital Health Technologies in Drug and Biological Product Development* (March 2023), https://www.fda.gov/media/166396/download?utm_medium=email&utm_source=govdelivery

Recommendation	OCR, ONC, FDA and NIST should collaborate to provide guidance on privacy and security standards for DCTs. Specifically, agencies can outline privacy and security needs and explain how stakeholders can address such needs when conducting DCTs and hybrid clinical trials.
Background	Numerous standards exist and/or are in development for health data, including HIPAA privacy standards, FDA guidance on cybersecurity and connected devices, and NIST standards for digital identity (SP 800-63-3). However, standardizing and implementing existing standards across the industry for the DCT use case can facilitate the use of DCTs.
Problem Addressed	This recommendation would address current gaps and uncertainty on privacy and security issues, particularly with respect to patient data, in DCTs.
Initiative Action	The Initiative should work with industry and government bodies, including Standards Development Organizations, Health Information Technology Advisory Committee (HITAC), [31] OCR, ONC, FDA and NIST, to leveraging existing standards to establish policy and implementation guides regarding privacy and security for DCTs. This can include guidance and/or regulation and may include ONC certification criteria for EHRs to support DCTs.

NIH Grants	
Recommendation	NIH could promote widespread DCT adoption in the health care community by providing grant funding and/or other incentives to enable use of DHTs and advanced decentralized trials, in general. To support these efforts, Congress should enact legislation or submit appropriations report language directing NIH to establish a program to advance adoption of DCTs by the health care community.
Background	On March 1, 2023, the NIH National Center for Advancing Translational Sciences (NCATS) issued a RFI inviting stakeholders to comment on how DCTs may be designed to be more effective, efficient and equitable to bring more interventions to all people. [32] Notably, the RFI highlights the role that enabling tools such as informatics systems, data integration platforms, DHTs, including machine learning or artificial intelligence to integrate disparate data types and linking outcomes, have in advancing DCTs. The RFI requests comment on the following DCT issues: application of research methods; resources, infrastructure, and enabling technologies; community engagement; data integration and quality; and privacy and regulatory considerations.

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[31] "Health Information Technology Advisory Committee (HITAC)," Health Information Technology Advisory Committee (HITAC) | HealthIT.gov, January 5, 2023, https://www.healthit.gov/hitac/committees/health-information-technology-advisory-committee-hitac.

[32] "Not-TR-23-006: Request for Information (RFI): Advancing Clinical and Translational Science through Accelerating the Decentralization of Clinical Trials," National Institutes of Health (U.S. Department of Health and Human Services), accessed April 5, 2023, https://grants.nih.gov/grants/guide/notice-files/NOT-TR-23-006.html.

Problem Addressed	Clinical researchers may not have sufficient funding to execute decentralized or hybrid trials due to a variety of factors (e.g., cost and hesitancy to use non-traditional research methods). A DCT program within NIH would incentivize the research community to use DCTs.
Initiative Action	The Initiative should consider advocating that NIH build on its RFI and provide additional opportunities (i.e., grant funding) to advance DCTs. Specifically, the Initiative can focus on advocating for NIH incentives and programs to train the workforce and facilitate local HCPs to conduct trial-related activities. One option that NIH may consider is to recommend that Congress draft appropriations report language directing NIH to create a program on DCTs.

Appendix 1 – FDA Policies

A patchwork of federal laws, regulations and guidance outlines requirements for DCT sponsors. The following sections focus on the existing DCT regulations that have been promulgated by HHS agencies, including the FDA and CMS. It outlines two requests for information (RFIs) on U.S. clinical trials infrastructure and a provision included in recently enacted legislation that directs the FDA to issue additional guidance on DCTs.

FDA Clinical Trials Regulations

- **General responsibilities of sponsors in drug trials:**[33] Sponsors are responsible for selecting qualified investigators, providing them with the information they need to conduct an investigation properly, ensuring proper monitoring of the investigation, ensuring that the investigation is conducted in accordance with the general investigational plan and protocols contained in the Investigational New Drug (IND) Application, maintaining an effective IND with respect to the investigations, and ensuring that FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug.

- **Recordkeeping and record retention:**[34] Sponsors are responsible for maintaining adequate records showing the receipt, shipment, or other disposition of the investigational drug. These records are required to include, as appropriate, the name of the investigator to whom the drug is shipped, and the date, quantity, and batch or code mark of each such shipment. Sponsors are also responsible for maintaining complete and accurate records showing any financial interest paid to clinical investigators by the sponsor of the covered study, among other provisions.

- **Control of the investigational drug:**[35] An investigator is required to administer the drug only to subjects under the investigator's personal supervision or under the supervision of a sub investigator responsible to the investigator. The investigator should not supply the investigational drug to any person not authorized under this part to receive it.

- **Electronic Records; Electronic Signatures:**[36] Under FDA regulations, sponsors, clinical investigators, IRBs, and others are subject to the electronic records and electronic signatures requirements in clinical trials under Part 11. This part protects public health and privacy while ensuring the authenticity, the reliability, and, when appropriate, the confidentiality of electronic records, and ensuring that the signer cannot readily repudiate the signed record as not being genuine.

- **Protection of Human Subjects:**[37] FDA is charged by statute with ensuring the protection of the rights, safety, and welfare of human subjects who participate in clinical investigations. This section provides the requirements and general elements of informed consent.

- **Investigational Device Exemptions (IDEs):**[38] An IDE allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data. This section covers the procedures for the

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[33] *See* 21 C.F.R. § 312.50.
[34] *See* 21 C.F.R. § 312.57.
[35] *See* 21 C.F.R. § 312.61
[36] *See* 21 C.F.R. Part 11
[37] *See* 21 C.F.R. Part 510
[38] *See* 21 C.F.R. Part 812

conduct of clinical studies with medical devices including application, responsibilities of sponsors and investigators, labeling, records, and reports.

- **Institutional Review Boards (IRBs):**[39] Under FDA regulations, an IRB is group that has been formally designated to review and monitor biomedical research involving human subjects.[40] An IRB has the authority to approve, require modifications in (to secure approval), or disapprove research. The purpose of IRB review is to assure, both in advance and by periodic review, that appropriate steps are taken to protect the rights and welfare of humans participating as subjects in the research. To accomplish this purpose, IRBs use a group process to review research protocols and related materials (e.g., informed consent documents and investigator brochures) to ensure protection of the rights and welfare of human subjects of research. This part contains the general standards for the composition, operation, and responsibility of an IRB that reviews clinical trials regulated by FDA.

FDA Draft Guidance and Other Publications on DCTs and Digital Health Technology

FDA Digital Health Technology Publications

In December 2021, FDA issued draft guidance, "Digital Health Technologies (DHTs) for Remote Data Acquisition in Clinical Investigations", which provides guidance for clinical trial sponsors, investigators and other interested parties on using DHTs to acquire data remotely during clinical trials.[41] In general, the draft guidance includes recommendations intended to address selection of suitable DHTs, verification and validation of DHTs, and use of DHTs to collect data for trial endpoints. The draft guidance also addresses some of the risks associated with the use of DHTs in clinical investigations and their management. Furthermore, the draft guidance highlights DHTs' ability to transmit data remotely, thereby increasing opportunities for patients to participate in DCTs.

In March 2023, the FDA issued the "Framework for the Use of Digital Health Technologies in Drug and Biological Product Development"[42] to guide stakeholders on the use of DHT-derived data in regulatory decision-making for drugs and biological products. According to the framework, FDA will use a multifaceted DHT program for drugs, which will include workshops and demonstration projects; engagement with stakeholders; establishment of internal processes to support the evaluation of DHTs for use in drug development; promotion of shared learning and consistency regarding DHT-based policy, procedure, and analytic tool development; and publication of guidance documents. The framework also highlights the ability of DHTs to enable DCTs and mentions upcoming FDA guidance in 2023 that will issue recommendations to clarify and advance the use of DCTs to support the development of drugs and devices.

FDA "Decentralized Clinical Trials for Drugs, Biological Products, and Devices" Draft Guidance (May 2023)

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[39] *See* 21 C.F.R. Part 56

[40] Center for Drug Evaluation and Research, "Institutional Review Boards (IRBs) and Protection of Human Subjects in Clinical Trials," U.S. Food and Drug Administration (FDA, September 11, 2019), https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/institutional-review-boards-irbs-and-protection-human-subjects-clinical-trials#:~:text=Under%20FDA%20regulations%2C%20an%20Institutional,approval)%2C%20or%20disapprove%20research.

[41] U.S. Department of Health and Human Services, Food and Drug Administration, *Digital Health Technologies for Remote Data Acquisition in Clinical Investigations, Guidance for Industry, Investigators, and Other Stakeholders* (December 2021) https://www.fda.gov/media/155022/download

[42] U.S. Department of Health and Human Services, Food and Drug Administration, *Framework for the Use of Digital Health Technologies in Drug and Biological Product Development* (March 2023), https://www.fda.gov/media/166396/download?utm_medium=email&utm_source=govdelivery

In May 2023, FDA published draft guidance on DCTs[43], as required by the Consolidated Appropriations Act, 2023. FDA made clear, in the guidance, that the same regulations that govern traditional clinical trials also govern DCTs. This includes a physical location for all records, adverse event reporting, IDE application (as necessary), relevant licensing laws, IRB oversight and more.

In the draft guidance, FDA states that DCTs have the potential to expand access to more diverse patient populations and improve efficiencies. FDA also states that enabling remote participation, DCTs may enhance convenience for trial participants, reduce the burden on caregivers, and facilitate research on rare diseases and diseases affecting populations with limited mobility or access to traditional trial sites. This may help improve trial participant engagement, recruitment, enrollment, and retention of a meaningfully diverse clinical population." The guidance also recommends the use of a designated clinical laboratory to reduce variability in results such as blood levels and radiological scans.

In the draft guidance, FDA recommends that clinical trial sponsors establish a data management plan (DMP). FDA explains that a DMP is a way for the sponsor to account for multiple sources of data collection. DMPs should include information about the "methods used for remote data acquisition" and transmission of data. Data provenance is also mentioned. Later, the guidance recommends quality control measures to reduce variability of data.[44] FDA also addresses the difference between local health care providers involvement in DCTs and routine care. FDA states that providers who are doing routine care do not need to be listed on the FDA forms as part of the trial;[45] however, this does not address any billing questions regarding these services.

FDA states that informed consent and IRB oversight are requirements of DCTs and recognizes that informed consent may be obtained remotely. FDA states that DCT informed consent should include, in addition to the elements required for traditional clinical trials, information about who will have access to personal health information. FDA recommends the use of a central IRB.

FDA also considers what types of products are well-suited for DCTs, particularly where the investigational product is being remotely administered. The guidance recommends that when the safety profile of the investigational product is well-established and there is little risk of immediate adverse events, remote administration of the product may be acceptable. Some products will be well-suited for self-administration, particularly those who not only meet the above characteristics but also are shelf-stable under normal storage conditions. Packaging and distribution of these products is addressed in the guidance.

As with all trials, FDA requires clinical trial sponsors to outline a safety monitoring plan. DCTs have an additional layer of complexity around monitoring safety, which must be addressed in the plan. FDA addresses the use of software and digital health tools in DCTs. The guidance recommends that sponsors consider a number of factors when selecting these tools, including ensuring that the technologies are suitable for use by all trial participants, that the tools are valid, and meet the recommendations in previous guidances.[46] FDA considers the use of electronic records in DCTs, but allows for remote providers to upload forms or documents securely, rather than directly entering data into the case report forms.

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[43] U.S. Department of Health and Human Services, Food and Drug Administration, Decentralized Clinical Trials for Drugs, Biological Products, and Devices: Guidance for Industry, Investigators, and Other Stakeholders (May 2023), https://www.fda.gov/media/167696/download?utm_medium=email&utm_source=govdelivery

[44] The type and scope of quality control measures should be tailored to the criticality of the data and the complexity of procedures done by the local HCPs.

[45] 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).

[46] Digital Health Technologies for Remote Data Acquisition in Clinical Investigations

FDA addresses telehealth with respect to DCTs and notes that live video or audio interactions are not part of the electronic record and not subject to FDA regulations around electronic records for trials. Privacy and security of these interactions must be protected, and local telehealth laws apply. If these interactions are captured for the record, they must comply with Part 11 requirements.

HHS Human Subject Protection Regulations

The HHS regulations for the protection of human subjects in research[47] include five subparts, including Subpart A, also known as the Common Rule, which provides a set of protections for research subjects.[48] The Common Rule generally requires that researchers get informed consent from those who participate in research. This includes giving them information they would need to make an informed decision about participation in language they would understand. One key protection in the Common Rule is the requirement for appropriate review and approval of research by IRBs.

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[47] 45 C.F.R. Part 46
[48] *See* 45 C.F.R. § 46.101-124

Appendix 2 – Interoperability Policies

ONC Standards and Certification/Interoperability

Although recognized as a leader in advancing cutting edge biomedical research and medical technology, the U.S. continues to rely on multiple, independent healthcare systems and versions that cannot seamlessly communicate with each other.[49] Since DCTs rely heavily on remote collection of clinical data, widespread DCT use requires achieving interoperable and shareable clinical data.

The ONC Health IT Certification Program (Certification Program) is a voluntary certification program.[50] Requirements for certification are established by standards, implementation specifications and certification criteria adopted by ONC. The Certification Program defines the requirements for health IT and the process by which health IT may become evaluated, tested (if required), certified, and maintain its certification and third-parties conduct conformity assessment. The Certification Program was launched in 2010, and while voluntary, links to the CMS Promoting Interoperability (PI) Programs (previously Medicare and Medicaid EHR Incentive Programs), which requires the use of certified health IT.

ONC establishes standards and "certification criteria" through regulation. The ONC Cures Act Final Rule[51] made several changes to the 2015 Edition Health IT Certification Criteria and adopted new Certification Program requirements. Among the changes to the certification criteria are: (1) adoption of the US Core Data for Interoperability (USCDI) standard to establish a set of data classes and constituent data elements required to support interoperability nationwide; and (2) new standardized API criteria for patient and population services. ONC has also adopted Conditions and Maintenance of Certification requirements for health IT developers. One condition is that health IT developers with certified API modules must publish APIs and allow health information from such technology to be accessed, exchanged, and used without special effort.[52]

HL7® FHIR®

The Fast Healthcare Interoperability Resources (FHIR) standard, developed and maintained by the standards development organization Health Level 7 (HL7), is an API-focused standard used to represent and exchange health information.[53] FHIR is based on internet standards widely used by industries outside of healthcare, in particular, the REST approach, which describes how individual packets of information (termed Resources) can be shared easily. By adopting existing standards and technologies already familiar to software developers, FHIR significantly lowers the barriers of entry for new software developers to support healthcare needs.[54] Currently, most health information exchange and data interoperability is based on the transmittal of documents. Using standardized API standards, FHIR allows developers to create apps that transcend this document-based environment. FHIR can support DCT by helping integrate EHRs, electronic data captures, devices and wearables. FHIR data exchange, recent advancements in sensor and wearable devices, and mobile apps and telehealth can

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[49] Ana Szarfman et al., "Recommendations for Achieving Interoperable and Shareable Medical Data in the USA," Communications Medicine 2, no. 1 (2022), https://doi.org/10.1038/s43856-022-00148-x.

[50] ONC's authority was provided by section 3001(c)(5) of the Public Health Service Act (PHSA) and as defined in the Health Information Technology for Economic and Clinical Health (HITECH) Act

[51] 21st Century Cures Act: Interoperability, Information Blocking, and the ONC Health IT Certification Program Final Rule, 85 Fed. Reg. 25642, May 1, 2020. https://www.govinfo.gov/content/pkg/FR-2020-05-01/pdf/2020-07419.pdf

[52] 45 CFR §170.404,

[53] "FHIR Fact Sheets," HealthIT.gov, June 16, 2021, https://www.healthit.gov/topic/standards-technology/standards/fhir-fact-sheets.

[54] Id.

all advance the integration of virtual components and DCTs.[55] Substitute Medical Applications, Reusable Technologies (SMART) on FHIR provides a standard, universal API for accessing EHRs and allows any technology built with SMART works with any EHR database that uses SMART as well.[56]

The ONC Cures Act Final Rule includes the FHIR standard and SMART implementation guide.[57] Moreover, CMS recently released the Interoperability and Prior Authorization Proposed Rule, which is the latest action by the agency to promote adoption of FHIR among providers and payers.

HL7 Project Vulcan and CodeX

In 2019, HL7 announced the launch of its newest FHIR Accelerator, Project Vulcan, which seeks to help health care researchers more effectively acquire, exchange, and use data in translational and clinical research.[58] The goal of the Vulcan project is to fully integrate research into the delivery of health care by streamlining data collection and exchange into a singular process.[59] To accomplish this goal, Vulcan is collaborating with the international research community to align clinical data and clinical research data at the point of collection and developing out the HL7 FHIR standards to support the bidirectional flow of data. According to its website, Vulcan is conducting a number of use case projects, including those related to real world data, adverse event reporting, and electronic patient information. The convening members of Vulcan include representatives from Standards Development Organizations, industry groups, technology vendors, government agencies (i.e., FDA and NIH), patient groups, and research/academia.

An example of an industry initiative to advance clinical trial enrollment, specifically in the oncology space, is the Integrated Clinical Trial Matching use case developed within the CodeX community. Launched in 2021, CodeX is a member-driven HL7 FHIR Accelerator that was formed to enable FHIR-based interoperability.[60] At a high level, this matching use case within CodeX will integrate cancer clinical trial matching capability into existing EHR and patient data management systems using open data standards and APIs.[61] Other CodeX use cases include collection and sharing of patient data for Real-World-Data clinical trials, matching patients with trials, radiation therapy, prior authorization, and registry reporting. This demonstration is achieved through high-quality FHIR standards, implementations in software (commercial or open source products) and tested in new workflows, all piloted in-the-field by various health care stakeholders.

Interoperability Standards Advisory (ISA)

The Interoperability Standards Advisory (ISA) is an ONC process to "coordinate the identification, assessment, and determination of 'recognized' interoperability standards and implementation specifications for industry use to fulfill specific clinical health IT interoperability needs."[62] The ISA is a coordinated catalog of standards and

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[55] Jonathan Andrus, "PharmaVOICE," PharmaVOICE (blog) (PharmaLinx LLC, November 19, 2019), https://www.pharmavoice.com/news/2019-11-decentralized-trials/615831/.

[56] Liz Rivera, "Auth0 Blog by Okta," Auth0 Blog by Okta (blog) (Auth0, September 7, 2021), https://auth0.com/blog/what-smart-on-fhir-means-for-the-future-of-healthcare/.

[57] 85 Fed. Reg. 25642 (May 2020).

[58] Amy Cramer, "HL7 Launches Project Vulcan Fhir Accelerator Program," HL7 Launches Project Vulcan FHIR Accelerator Program, August 17, 2020, https://blog.hl7.org/hl7-launches-project-vulcan-fhir-accelerator-program.

[59] "Vulcan Accelerator Home," Confluence, accessed May 30, 2023, https://confluence.hl7.org/display/VA.

[60] "Codex Home," Confluence, accessed June 9, 2023, https://confluence.hl7.org/display/COD.

[61] "ACS CAN and CodeX Lead Project to Expand Cancer Clinical Trial Enrollment Through Improved Technology," Press Release (blog) (American Cancer Society Cancer Action Network, May 18, 2021), https://www.fightcancer.org/releases/acs-can-and-codex-lead-project-expand-cancer-clinical-trial-enrollment-through-improved.

[62] "Interoperability Standards Advisory (ISA)," HealthIT.gov (Office of the National Coordinator for Health Information Technology), accessed February 14, 2023, https://www.healthit.gov/isa/.

implementation specifications that can be used by different stakeholders to consistently address a specific interoperability need. It may also inform policymaking.

Standards and implementation specifications are advisory in nature. ONC encourages stakeholders (specifically those who administer government programs, procurements, and testing or certification programs) to implement and use the standards and implementation specifications identified in the ISA as applicable to the specific interoperability needs they seek to address. Starting with the 2017 ISA, the ISA's focus expanded to more explicitly include public health and health research interoperability.

Comments on the ISA are accepted year-round, and changes are made to the web version of the ISA frequently throughout the year, based on comments and other changes to the health IT standards environment. An annual Review and Comment period also occurs each summer-fall, when a majority of comments are received.

TEFCA

The 21st Century Cures Act required the ONC to develop a trusted exchange framework, including a common agreement among health information networks (HINs) nationally.[63] The stated goal was to scale health information exchange nationwide and ensure that HINs, health care providers, health plans, individuals, and other stakeholders can access real time, interoperable health information. The Trusted Exchange Framework (TEF) describes high-level common principles that networks should adhere to for trusted exchange of electronic health information (EHI).[64] The Common Agreement (CA) is a legal agreement between the Recognized Coordinating Entity (RCE) and Qualified HINs (QHINs) that advances those principles and enables network-to-network data sharing.[65] Together, the two parts are known as "TEFCA."

The TEF describes a common set of seven nonbinding, foundational principles for trust policies and practices to facilitate data sharing among HINs. The concept behind these principles is to create broad industry alignment to facilitate entities' entering into effective contractual relationships for the secure electronic flow of digital health information. According to ONC, the TEF principles also support the ability of patients, their health care providers, and other authorized health care stakeholders to electronically access digital health information when and where it is needed most to improve care coordination and quality improvement.

The Common Agreement authorizes "exchange purposes" for which information may be requested or shared on the TEFCA network (QHIN to QHIN). Authorized exchange purposes include the following: Treatment, Payment, Health Care Operations, Public Health, Government Benefits Determination, and Individual Access Services (definitions outlined below).

- **Treatment**: the provision, coordination, or management of health care by one or more health care providers. It also includes the coordination or management of healthcare by a third-party provider, a

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[63] "ONC Completes Critical 21st Century Cures Act Requirement, Publishes the Trusted Exchange Framework and the Common Agreement for Health Information Networks." HHS.gov, January 18, 2022. Department of Health and Human Services (HHS). https://www.hhs.gov/about/news/2022/01/18/onc-completes-critical-21st-century-cures-act-requirement-publishes-trusted-exchange-framework-common-agreement-health-information-networks.html.

[64] U.S. Department of Health and Human Services, Office of the National Coordinator for Health Information Technology, The Trusted Exchange Framework (TEF): Principles for Trusted Exchange (January 2022) https://www.healthit.gov/sites/default/files/page/2022-01/Trusted_Exchange_Framework_0122.pdf.

[65] U.S. Department of Health and Human Services, Office of the National Coordinator for Health Information Technology, Common Agreement for Nationwide Health Information Interoperability (January 2022) https://www.healthit.gov/sites/default/files/page/2022-01/Common_Agreement_for_Nationwide_Health_Information_Interoperability_Version_1.pdf.

consultation between providers treating a common patient, or the referral of a patient from one provider to another.

- **Public Health**: any request, use, disclosure, or response authorized under HIPAA regulations or other applicable laws regulating public health activities.

- **Payment**: the various activities that healthcare organizations use to obtain payment or a reimbursement fee correlated with healthcare services. It also encompasses health plans acquiring premiums to satisfy their coverage responsibilities.

- **Benefits Determination**: refers to federal or state government agencies deciding whether a person is eligible for federal or state benefits for any reason other than health care.

- **Healthcare Operations**: certain administrative, financial, legal, and quality improvement functions of a covered entity (CE) essential to running its business and supporting treatment and payment activities.

- **Individual Access Services**: outline the rules and regulations that allow patients to receive a copy of their EHRs. They also ensure that patients have the ability to direct a copy of their records to another provider or entity authorized by the individual.

Notably, clinical research is not included as a permitted exchange purpose in the Common Agreement. A document published by the Sequoia Project, which was awarded a cooperative agreement by ONC to serve as an RCE, lists research as a future benefit on TEFCA.[66]

TEFCA is voluntary, although HHS may tie policies (e.g., CMS Incentive Programs) to participation in TEFCA data exchange. In February 2023, ONC and HHS announced that the following six organizations were approved to implement TEFCA as prospective QHINs: CommonWell Health Alliance, eHealth Exchange, Epic TEFCA Interoperability Services, Health Gorilla, Kno2, and KONZA National Network.[67] Now that the initial QHINs have been selected, ONC and the RCE, the Sequoia Project, will begin to onboard the QHINs and continue to operationalize TEFCA.

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[66] The Sequoia Project, User's Guide to the Trusted Exchange Framework and Common Agreement – TEFCA," (January 2022), https://rce.sequoiaproject.org/wp-content/uploads/2022/01/Common-Agreement-Users-Guide.pdf

[67] Micky Tripathi and Mariann Yeager, "HealthITbuzz," HealthITbuzz (blog) (Office of the National Coordinator for Health Information Technology, February 13, 2023), https://www.healthit.gov/buzz-blog/electronic-health-and-medical-records/interoperability-electronic-health-and-medical-records/building-tefca.

Appendix 3 - CMS Clinical Trials Regulations and Reimbursement Policies

Medicare Coverage Policies

In general, Medicare covers and provides payment only for healthcare items and services that are reasonable and necessary for the diagnosis or treatment of an illness or injury and within the scope of a Medicare benefit category. CMS makes national coverage determinations (NCDs) through an evidence-based process with opportunities for public participation.[68] NCDs are coverage policies that apply nationwide to all Medicare beneficiaries and can grant, limit or exclude Medicare coverage for specific medical items or services. NCD policies are based upon authority found in Section 1862(a)(1)(E) of the Social Security Act.

NCD for Clinical Trials

Effective July 2007, Medicare covers the routine costs of qualifying clinical trials as well as reasonable and necessary items and services used to diagnose and treat complications arising from participation in all clinical trials.[69] Routine costs of a clinical trial include all items and services that are otherwise generally available to Medicare beneficiaries that are provided in either the experimental or the control arms of a clinical trial, with certain exceptions. Any clinical trial receiving Medicare coverage of routine costs must meet the following three requirements:

- The subject or purpose of the trial must be the evaluation of an item or service that falls within a Medicare benefit category (e.g., physicians' service, durable medical equipment, diagnostic test) and is not statutorily excluded from coverage (e.g., cosmetic surgery, hearing aids).
- The trial must not be designed exclusively to test toxicity or disease pathophysiology. It must have therapeutic intent.
- Trials of therapeutic interventions must enroll patients with diagnosed disease rather than healthy volunteers. Trials of diagnostic interventions may enroll healthy patients in order to have a proper control group.

According to CMS, the three requirements above are insufficient by themselves to qualify a clinical trial for Medicare coverage of routine costs.[70] Clinical trials also should have the following desirable characteristics; however, some trials, as described below, are presumed to meet these characteristics and are automatically qualified to receive Medicare coverage:

1. The principal purpose of the trial is to test whether the intervention potentially improves the participants' health outcomes;
2. The trial is well-supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use;
3. The trial does not unjustifiably duplicate existing studies;
4. The trial design is appropriate to answer the research question being asked in the trial;
5. The trial is sponsored by a credible organization or individual capable of executing the proposed trial successfully;

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[68] "Medicare Coverage Determination Process," CMS, accessed February 23, 2023, https://www.cms.gov/Medicare/Coverage/DeterminationProcess.

[69] "Routine Costs in Clinical Trials," CMS.gov Centers for Medicare & Medicaid Services, accessed January 26, 2023, https://www.cms.gov/medicare-coverage-database/view/ncd.aspx?NCDId=1&ncdver=2&fromdb=true.

[70] "Routine Costs in Clinical Trials," CMS.gov Centers for Medicare & Medicaid Services, accessed January 26, 2023, https://www.cms.gov/medicare-coverage-database/view/ncd.aspx?NCDId=1&ncdver=2&fromdb=true.

6. The trial is in compliance with Federal regulations relating to the protection of human subjects; and
7. All aspects of the trial are conducted according to the appropriate standards of scientific integrity.

CMS Innovation Center

The Center for Medicare and Medicaid Innovation (CMMI), also known as the "Innovation Center," was authorized under the Affordable Care Act (ACA) and tasked with designing, implementing, and testing new health care payment models to address growing concerns about rising costs, quality of care, and inefficient spending.[71] Congress specifically directed the Innovation Center to focus on models that could potentially lower health care spending for Medicare, Medicaid, and the Children's Health Insurance Program (CHIP) while maintaining or enhancing the quality of care furnished under these programs.

The Innovation Center can waive requirements in Medicare and, to a more limited extent, Medicaid.[72] This waiver authority allows the Center to test promising payment and service delivery changes. If models are deemed successful in that they reduce or do not increase federal health expenditures while maintaining or improving quality for beneficiaries, and certain other requirements are met, CMS has the authority to expand the duration and scope of the model test. To date, the Innovation Center has launched over 50 model tests.

The Innovation Center's models are alternative payment models (APMs) which reward health care providers for delivering high-quality and cost-efficient care. APMs can apply to a specific health conditions, care episodes, provider types, communities, and innovation on specific areas of Medicare coverage.[73] The Innovation Center leverages expertise from across the health care industry, including clinicians, analysts and beneficiary groups, and other federal agencies in the development of new payment and service delivery models. The Innovation Center solicits and selects model participants through open competition.

CMS Incentive Programs

The HITECH Act[74] authorized incentive payments under Medicare and Medicaid for the adoption and meaningful use of certified electronic health record technology (CEHRT). Incentive payments under Medicare were available to eligible professionals, eligible hospitals and critical access hospitals (CAHs) for certain payment years if they successfully demonstrated meaningful use of certified electronic health record technology (CEHRT), which included reporting on clinical quality measures using CEHRT.

The CMS Merit-based Incentive Payment System (MIPS) is a program established to incentivize health care providers to use technology and data to improve patient outcomes and experience, reduce costs, and advance care coordination. MIPS is part of the Quality Payment Program (QPP), which was created under the Medicare Access and CHIP Reauthorization Act of 2015 (MACRA).[75] MIPS performance is measured across four areas— quality, improvement activities, promoting interoperability, and cost—which cumulatively determines the payment adjustment applied to Medicare Part B claims. The promoting interoperability performance category, which comprises of 25% of the final MIPS score, promotes patient engagement and electronic exchange of

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[71] "What is CMMI? and 11 other FAQs about the CMS Innovation Center," KFF Filling the Need for Trusted Information on National Health Issues (blog) (KAISER FAMILY FOUNDATION, February 27, 2018), https://www.kff.org/medicare/fact-sheet/what-is-cmmi-and-11-other-faqs-about-the-cms-innovation-center/.

[72] Centers for Medicare & Medicaid Services, Innovation Center Strategy Refresh (November 2022) https://innovation.cms.gov/strategic-direction-whitepaper

[73] Centers for Medicare & Medicaid Services, Innovation Center Strategy Refresh (November 2022) https://innovation.cms.gov/strategic-direction-whitepaper

[74] Title IV of Division B of the American Recovery and Reinvestment Act (ARRA), together with Title XIII of Division A of the ARRA.

[75] "MACRA: MIPS and APMS," CMS, accessed January 27, 2023, https://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/Value-Based-Programs/MACRA-MIPS-and-APMs/MACRA-MIPS-and-APMs.

information using CEHRT and provides the opportunity for eligible clinicians to earn additional bonus points. Beginning with the 2023 performance year, the Promoting Interoperability performance category is 25% of the MIPS score for individual, group, virtual group, and subgroup participation and 30% for alternative payment model (APM) entity participation.[76] The Promoting Interoperability performance category provides bonus points and focuses on the following objectives: e-prescribing; Health Information Exchange (HIE); provider to patient exchange; and public health and clinical data exchange. Requirements are updated in the Medicare Physician Fee Schedule rule. CMS uses these requirements to promote data exchange policies.

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[76] "Promoting Interoperability: Traditional MIPS Requirements," Quality Payment Program (Centers for Medicare & Medicaid Services), accessed February 14, 2023, https://qpp.cms.gov/mips/promoting-interoperability?py=2023.

Appendix 4 – Additional Federal Activities

2022 White House National Biodefense Strategy and Implementation Plan

In October 2022, the White House released a framework to prepare and respond to biological threats and bolster pandemic preparedness capabilities.[77] As part of the implementation plan, the Office of Science and Technology (OSTP) issued a RFI[78] on strategies to build and maintain a U.S. clinical trials infrastructure that is capable of responding to outbreaks of disease and other biological incidents on an emergency basis. Specifically, the RFI requests input on use of decentralized clinical trial design elements, or other innovative approaches such as trials conducted at the point of care. OSTP, in collaboration with the ONC, also issued an RFI[79] to seek input on how best to operationalize clinical trial data capture and protocol distribution from a technical perspective within the current health care and research data ecosystem.

Consolidated Appropriations Act, 2023 (CAA 2023)

Section 3606 of the CAA 2023 requires FDA to issue draft guidance that addresses considerations for decentralized clinical studies, among other clinical trial modernization provisions.[80] FDA is required to finalize this guidance no later than one year after the public comment for the draft guidance ends. Congress directs FDA to include the following recommendations:

- Recommendations related to digital health technology or other assessment options (e.g., telehealth, local laboratories, local health care providers, or other options for remote data collection) that could support DCT, including guidance on considerations for selecting technological platforms and mediums, data collection and use, data integrity and security, and communication to study participants through digital technology;
- Recommendations for subject recruitment and engagement, including considerations for sponsors to minimize or reduce burdens for clinical study participants through the use of digital health technology;
- Recommendations with respect to the evaluation of data collected within a decentralized clinical study setting;
- Recommendations regarding conducting DCTs to facilitate and encourage meaningful diversity among clinical trial participants, including with respect to race, ethnicity, age, sex, and geographic location, as appropriate; and
- Considerations for review and oversight by sponsors and IRBs, including remote trial oversight, among other provisions.

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[77] White House, National Biodefense Strategy and Implementation Plan for Countering Biological Threats, Enhancing Pandemic Preparedness, and Achieving Global Health Security (October 2022) https://www.whitehouse.gov/wp-content/uploads/2022/10/National-Biodefense-Strategy-and-Implementation-Plan-Final.pdf

[78] Office of Science and Technology Policy, "Notice of Request for Information (RFI) on clinical research infrastructure and emergency clinical trials," Federal Register 87, no. 64821 (October 26, 2022): 23110, https://www.govinfo.gov/content/pkg/FR-2022-10-26/pdf/2022-23110.pdf

[79] Office of Science and Technology Policy, "Notice of Request for Information (RFI) on Data Collection for Emergency Clinical Trials and Interoperability Pilot," Federal Register 87, no. 65259 (October 28, 2022): 23489, https://www.govinfo.gov/content/pkg/FR-2022-10-28/pdf/2022-23489.pdf

[80] *Consolidated Appropriations Act, 2023*, Pub. L. No. 117-328 (2022).

In the explanatory statement[81] that accompanies the statute, Congress notes that the COVID-19 pandemic demonstrated the possibility of conducting DCT.[82] It states that DCT can foster greater clinical trials participation, including by promoting increased diversity in participants. Congress directs the HHS Secretary, in collaboration with FDA, ONC, and CMS, to evaluate agency practices across HHS to ensure that providers and patients have tools to identify and participate in decentralized and remote clinical trials. It also directs HHS to deliver a report to the House and Senate Appropriations Committee with findings and recommendations to accelerate decentralized clinical trials and increase trial diversity, including recommendations to foster greater data sharing, including of EHRs, genomics, and imaging information.

As mentioned earlier, the Initiative is acting in response to the upcoming report to Congress on DCTs that was included in the CAA 2023. The policy recommendations included in this document are intended to advise HHS and agencies on its findings and recommendations.

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[81] *The joint explanatory statement explains the various elements of the conferees' agreement in relation to the positions that the House and Senate had committed to the conference committee.*

[82] United States. Congress. Conference Committees 2022. Joint Explanatory Statement of the Committee of Conference on H.R. 2617: Consolidated Appropriations Act, 2023, One Hundred Seventeenth Congress. Washington: U.S. Govt. Print. Off., 2022. https://www.appropriations.senate.gov/imo/media/doc/LHHSFY23REPT.pdf